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REVIEW ARTICLE

Complex regional pain syndromes: new pathophysiological concepts and therapies

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Complex regional pain syndrome (CRPS), formerly known as Sudeck's dystrophy and causalgia, is a disabling and distressing pain syndrome. We here provide a review based on the current literature concerning the epidemiology, etiology, pathophysiology, diagnosis, and therapy of CRPS. CRPS may develop following fractures, limb trauma or lesions of the peripheral or CNS. The clinical picture comprises a characteristic clinical triad of symptoms including autonomic (disturbances of skin temperature, color, presence of sweating abnormalities), sensory (pain and hyperalgesia), and motor (paresis, tremor, dystonia) disturbances. Diagnosis is mainly based on clinical signs. Several pathophysiological concepts have been proposed to explain the complex symptoms of CRPS: (i) facilitated neurogenic inflammation; (ii) pathological sympatho-afferent coupling; and (iii) neuroplastic changes within the CNS. Furthermore, there is accumulating evidence that genetic factors may predispose for CRPS. Therapy is based on a multidisciplinary approach. Non-pharmacological approaches include physiotherapy and occupational therapy. Pharmacotherapy is based on individual symptoms and includes steroids, free radical scavengers, treatment of neuropathic pain, and finally agents interfering with bone metabolism (calcitonin, biphosphonates). Invasive therapeutic concepts include implantation of spinal cord stimulators. This review covers new aspects of pathophysiology and therapy of CRPS.

Introduction and historical background

The first description of symptoms suggesting complex regional pain syndrome (CRPS) probably dates back to 1864, when Silas Weir Mitchell reports his impressions during the American Civil War [1]. He observed a puzzling constellation of symptoms in soldiers with injuries of the peripheral nervous system: constant burning pain in combination with substantial trophic changes. He named this syndrome 'causalgia', derived from the Greek words 'burning' ('καυσισ', kausis) and 'pain' ('αλγοσ', algos). During the First World War, Rene Leriche successfully treated such syndromes by surgical sympathectomy. Accordingly, he presumed already an involvement of the sympathetic nervous system in this condition [2]. During the 1950s, John Bonica (who later founded the International Association for the Study of Pain; IASP) developed invasive techniques allowing temporary blockade of the sympathetic nervous system. Impressed by the efficacy of these techniques, Evans coined the term 'reflex sympathetic dystrophy' [3]. In 1900, the surgeon Paul Sudeck gave a lecture at the 24th meeting of the German Society of Surgery on patients with 'acute inflammatory bone atrophy' [4]. Sudeck observed that the syndrome was accompanied by key symptoms of inflammation and that symptoms may spread beyond the region of initial damage. In his honor, the disease was, mainly by traumatologists, temporarily called 'Sudeck's dystrophy'.

The pathophysiology of this pain syndrome is still controversially discussed. In the following years, there was growing evidence for an 'inflammatory' as well as for a 'sympathetic' pathogenesis. Finally, the term 'reflex sympathetic dystrophy' was abandoned at a consensus conference held in Orlando, Florida, in 1993, and the strictly descriptive term 'CRPS' was introduced [5]. This is still the IASP's official term. CRPS is subdivided into CRPS type I and CRPS type II. CRPS type I is diagnosed when there is no obvious nerve injury, whereas CRPS type II refers to cases with nerve injury.

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Epidemiology and etiology

Based on epidemiological data of a regional North American population (Olmsted County, Minnesota), an incidence rate of 5.46/100 000/year and a prevalence rate of 20.57/100 000 has been calculated [6]. A recent population-based study from the Netherlands found an incidence rate of 26.2/100 000/year [7]. Retrospective follow-up studies revealed prevalence of CRPS following fractures between 0.03% and 37% [8–14]. The age pattern shows an almost normal distribution with a maximum in the 5th–7th decade [7,15–17]. The overall female to male ratio is 2–3:1, and the upper limbs are twice as frequently affected as the lower limbs [6,7,15–17]. Most of the patients have experienced preceding trauma, in about 40% of the cases fracture or surgery. Thirty percent of the patients had a decompression of the median nerve, 9% radicular lesions, and 6% spinal cord injury. In approximately 10% of cases, there is a minor trauma like distortion and in 5–10%, CRPS develops spontaneously [6,7,15–17]. Notably, there is no distinct correlation between the severity of trauma and the degree of CRPS symptoms [5]. The role of psychological factors, e.g. critical life events or inadequate coping strategies (i.e. difficulties with dealing with post-trauma consequences) in the development or aggravation of CRPS is controversially discussed. Geertzen *et al.* [18] observed 'stressful life events' in approximately 80% of patients suffering from CRPS of the upper limb 2 months before or 1 month after the development of CRPS, compared with 20% in a control group. However, similar findings can be obtained in other diseases, e.g. carcinoma or cardiovascular disorders. So far no psychological factor or personality structure predisposing for CRPS has been identified [18–21], apart from avoidant or anxious personality disorders [22].

Clinical presentation

The symptoms of CRPS are various, but close inspection reveals a relatively characteristic triad comprising autonomic, sensory, and motor disturbances. However, this triad can individually differ and change of symptoms over time is a rule rather than an exception.

Autonomic and trophic disorders

An impressive symptom of CRPS is the presence of a distal edema (Fig. 1a), which occurs in 80% of all cases [16,17]. Orthostasis or physical strain, as well as overzealous physiotherapy, can lead to a dramatic increase of edema. The incidence of skin temperature changes at the affected body part is 80% [16,23–25]. As the skin temperature strongly depends on ambient temperature, the patient should acclimatize themselves prior to the measurement. Most studies consider a temperature difference of 1°C to be significant. Initially the affected limb is mostly warm. In approximately 40% of patients, the skin temperature decreases over the course of the disease [16,23]. Initially, skin color often looks red, but rather pale or livid in chronic stages (Fig. 1d). Fifty-five percent of patients with CRPS present altered sweating of the affected limb with hyperhidrosis being more common than hypohidrosis [26].

In addition to trophic disturbances in the skin, nails, and hair are also affected. Hair and nail growth can be increased in early stages (Fig. 1c). In chronic stages

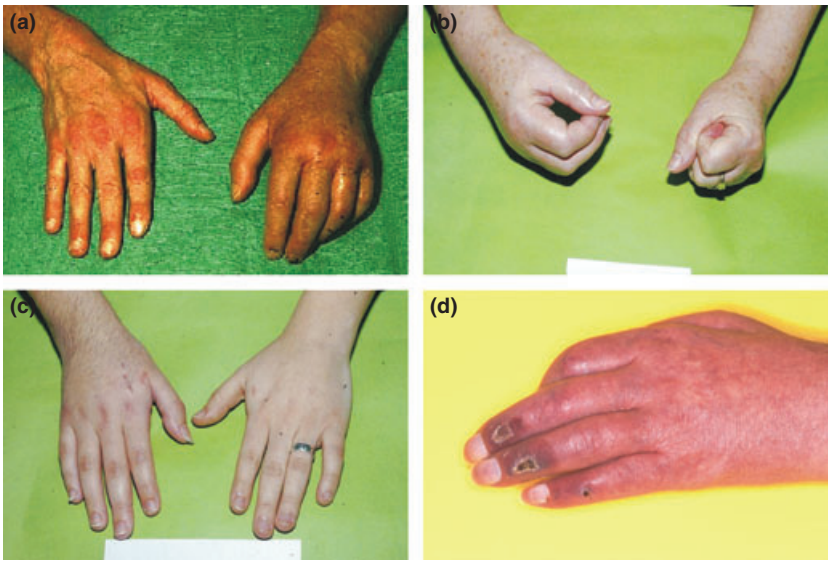

Figure 1 Clinical symptoms in complex regional pain syndrome (CRPS). Color descriptions refer to the online version of this article. (a) Acute stage of CRPS I with swelling, discoloration and function impairment of the left hand following distal radius fracture. (b) Swelling and impaired mobility at the attempt to clench the fist. CRPS type II after carpal tunnel release surgery. (c) Hypertrichosis of the right hand (CRPS I). (d) Contractures, bluish-livid discoloration and trophic skin disturbances in chronic CRPS I.

atrophy of skin and muscles as well as contractures severely restricting movement can appear (Fig. 1d) [16,17,27].

Sensory disturbances

In almost 90% of patients with CRPS sensory symptoms can be found [16,17]. These disturbances are not limited to the innervation territory of a single nerve root or a single peripheral nerve. A glove or stocking-like distribution is typical. Pain and hyperalgesia are key symptoms of CRPS. About 75% of the patients report spontaneous pain. It is often described as burning, dragging or stinging. The pain is more frequently located in deep structures (muscles and bones; 68%) than in the skin (32%). Spontaneous pain often persists with fluctuating intensity (77%). Less frequently, shooting pain attacks are also reported. Pain can be increased by orthostasis, anxiety, exercise or temperature changes. In many cases, pain is more pronounced at night. Mechanical hyperalgesia (increased sensation of pain for lightly painful stimuli) or allodynia (pain for light touch) are common findings [28–30]. These symptoms represent 'sensory gain'. In contrast, there may be also 'sensory loss', i.e. hypaesthesia and hypalgesia.

Motor dysfunction

Most of the patients report motor weakness [16,17,31]. Particularly, complex movements like finger tapping are severely impaired (Fig. 1d). Initially, the range of motion may be additionally impaired by concomitant edema, in later stages by contractures and fibroses. In some patients, neglect-like symptoms have been reported [32,33], and grasping of objects is only possible under visual control. A recently published study showed that there is no classic neglect or extinction in patients with CRPS [34], but 54% of the patients reported that their hand felt 'foreign'. Moreover, the ability to identify fingers after tactile stimulation was impaired [34]. About half of the patients developed an enhanced physiological tremor [35]. Especially, patients with CRPS type II (approximately 30%) show myoclonus or dystonia [36–38].

Pathophysiological concepts

Basically, there are three main pathophysiological concepts for the development of CRPS: facilitated neurogenic inflammation, autonomic dysfunction, and neuroplastic changes within the CNS. Notably, these concepts rather support than exclude each other.

CRPS – an inflammatory disease

Paul Sudeck noticed that the syndrome goes along with classic inflammatory signs [4,39]: pain, swelling, erythema, hyperthermia, and impaired function. However, evaluation of clinical chemistry parameters for inflammation did not reveal any differences between patients and controls [40,41]. These findings rather suggest neurogenic inflammation. The concept of neurogenic inflammation includes the fact that distinct classes of C-fibers do not only have an afferent function in the mediation of pain (and itch), but also an efferent neurosecretory function [42]. Of particular importance are mechano-heat-insensitive C-fibers (C-M_iH_i), belonging to the chemoreceptors [43,44]. These nociceptors release neuropeptides via axon reflex [45]. Mechano-heat-insensitive C-fiber units have been termed 'silent nociceptors', because of their non-excitability by physiological heat or mechanical stimuli. Nevertheless, CM_iH_i units are activated and sensitized by inflammatory mediators [43,46]. Also central sensitization, e.g. the development of secondary mechanical hyperalgesia, is induced by CM_iH_i units [47,48]. In neurogenic inflammation, action potentials are conducted retrogradely to terminal branches via axon collaterals after distal activation of nociceptors. Neuropeptides, mainly substance P and calcitonin-gene-related peptide (CGRP) are consecutively released. Substance P provokes plasma protein extravasation (development of edema), whereas CGRP induces vasodilation (hyperthermia and erythema) [42]. Experiments employing intradermal microdialysis capillaries showed that electrically induced protein extravasation providing information about the amount of released substance P can be provoked in patients with CRPS, but not in healthy controls [49]. Similar results could be obtained for electrically induced axon reflex vasodilation, an indicator of CGRP release [49,50]. Finally, another experiment demonstrated a significant increase of CGRP serum levels in patients with CRPS [51], which was normalized after sufficient therapy. In summary, there is convincing evidence for facilitated neurogenic inflammation in CRPS. As increasingly recognized the effects of neuropeptides might particularly explain trophic and autonomic symptoms such as swelling, erythema, and hyperhidrosis [52]. Elevated CGRP levels were also associated with autonomic disturbances, mainly with increased sweating (hyperhidrosis) [51]. Hyperhidrosis in CRPS has been shown to be based on alterations of the peripheral nervous system [26], and CGRP amplifies sweating by a peripheral mechanism [53]. Also, a role for CGRP in hair growth is suggested [54,55], and substance P seems to be involved in the regulation of osteoclastic activity [56]. Interestingly, not

only signs of inflammation but also symptoms related to the chronic stage of CRPS, thus decreased limb temperature and trophic changes, might be related to aberrant neuropeptide signaling. The vasoconstrictive neuropeptide endothelin-1 was found to be significantly increased in blister fluid in patients with early chronic CRPS when compared to the contralateral extremity, whereas nitric oxide levels were decreased [57].

Recent studies hint at a trauma-induced release of inflammatory cytokines possibly being involved in facilitated neurogenic inflammation [58]. Cytokines, such as interleukines or tumor necrosis factor-α (TNF-α) enhance synthesis and release of neuropeptides from C-fibers [59]. The soluble TNF-α-receptor type I turned out to be predictive for hyperalgesia. Also, increased blood concentrations of proinflammatory cytokine IL-2 and decreased blood concentration of anti-inflammatory cytokines IL-4 and IL-10 were reported [60].

Autonomic dysfunction

The distinct autonomic disturbances in CRPS point to an involvement of the sympathetic nervous system. Several studies showed that these disturbances depend on the stage of the disease [23,25,61]. The initial warming of the affected limb may not only result from neurogenic inflammation, but also from a functional inhibition of sympathetic vasoconstrictor neurons and consecutive vasodilation. Correspondingly, venous noradrenaline levels are lower on the affected side [25,61]. In the acute stage of CRPS sympathetic vasoconstrictor reflexes (induced by forced breathing, mental stress or whole-body cooling) are inhibited [62,63]. Chronification of the disease leads to cold skin and vasoconstriction. Furthermore, a supersensitivity of the innervated vascular structures in the affected limb as a consequence of the initially decreased sympathetic activity might play a role. Accordingly, autoradiographic measurements in skin samples from patients with CRPS have provided evidence for an increased density of alpha-adrenoceptors in the epidermis [64]. Nevertheless, how the efferent sympathetic nervous system might connect with the afferent nociceptive system is still controversially discussed. Such pathological sympatho-afferent coupling would be an essential condition for sympathetically maintained pain. Animal studies have shown the existence of a coupling between sympathetic efferences and nociceptive afferences; however, it is limited to certain pathophysiological conditions. After nerve injury, alpha-adrenoceptors (mainly alpha 2b) are expressed on primary nociceptive afferences, allowing direct adrenergic excitation [65]. There is also evidence for the existence of sympatho-afferent coupling in humans. In patients successfully treated with sympathetic blockade, cutaneous injection of noradrenaline can provoke a pain sensation equal to the one they experienced prior to the intervention [66]. In another study, electric stimulation of the sympathetic trunk in sympathectomized patients led to recurrence of pain and hyperalgesia [67]. Finally, massive activation of skin vasoconstrictor neurons by whole-body cooling in CRPS resulted in a notable increase of pain and hyperalgesia [62]. These results show that enhanced sympathetic activity might contribute to an excitation of nociceptive fibers and thus directly to the development of pain. Besides direct coupling mediated by adrenoceptors also indirect sympatho-afferent coupling is possible. Therefore, long-term sympathetic disturbances in CRPS lead to redistribution of the blood flow in arterioles and consequently to impaired capillary nourishment [68]. Another important mechanism leading to alterations in local microcirculation in chronic CRPS is impaired endothelial function with reduced acetylcholine-induced vasodilation [69]. These alterations finally result in tissue hypoxaemia and acidosis [70,71]. The emerging protons are again potent pain-inducing agents causing pain and hyperalgesia in skin and muscles [72]. These abnormalities may result in production of free radicals, which could induce histopathologic changes by oxidative stress [73].

CRPS: a central nervous disease

Recent studies point to a crucial role of the CNS in the pathophysiology of CRPS. Not only the complex patterns of autonomic dysfunction but also motor and sensory symptoms imply CNS alterations. Almost all patients have paretic muscles in the affected limb [36]. Paresis cannot be explained through edema or contractures. Typically, active range of movement is restricted, whereas passive movement is often possible. Myoclonus or dystonia can occur [36–38,74]. About 50% of the patients have an enhanced physiological tremor [35]. Furthermore, the pattern of sensory deficits (a glove or stocking-like distribution) is not limited to the territory of a single peripheral nerve [5]. Also hemisensory loss has been reported [75,76]. These findings served as a starting point for several studies of our group using functional imaging. We examined the extension of the cortical hand representation in primary somatosensory cortex comparing the healthy and CRPS-affected side [29,77]. Astonishingly, the region of the CRPS hand within the contralateral S1 cortex was dramatically decreased (Fig. 2a). The amount of reorganization was positively correlated with the extent of mechanical hyperalgesia and pain intensity of CRPS. In a second study, we could demonstrate that the plastic cortical changes are reversible under sufficient

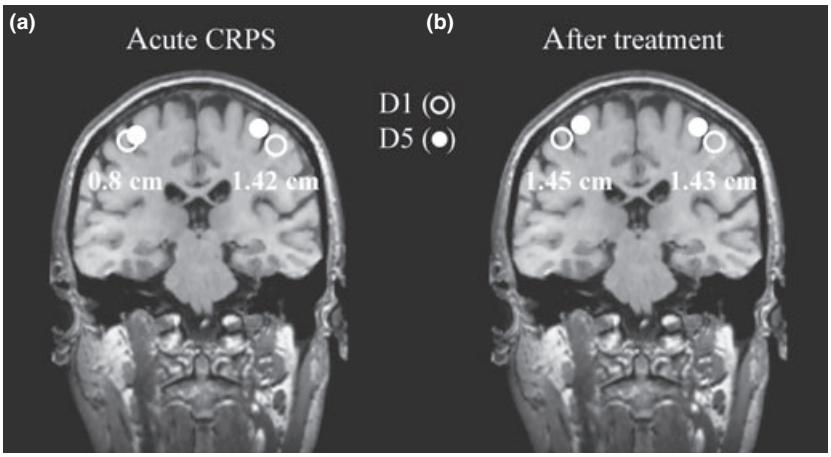

Figure 2 Cortical reorganization in complex regional pain syndrome (CRPS). In this case, the left hand was affected. (a) The cortical extension of the hand (distance between the first and fifth finger, D1 and D5) was in the acute stage decreased from 1.42 cm in the healthy side to 0.8 cm in the affected side. Somatotopic alterations correlated with the painfulness of the disease. (b) Normalization of the somatotopy in the gyrus post-centralis 1 year after successful therapy (modified after [77]).

treatment (Fig. 2b) [77]. Similar findings have also been published by other groups [78,79]. Central reorganization is reminiscent of the somatotopical aberrations observed in patients with phantom limb pain [80]. Plastic CNS alterations might explain the complex sensory symptoms (e.g. glove-stocking sensory loss, 'foreign-hand' sensation, mislocalization after tactile stimulation, impaired perceptual learning ability [81]). A lack of re-reorganization could be an important factor for pain chronification. Moreover, we could show in a study using fMRI that the cortical processing of mechanical stimuli on the hyperalgetic CRPS-side is substantially different from activation during identical stimulation in the healthy side [28]. We could particularly demonstrate an increased activation in brain areas related to affective-motivational pain processing, i.e. mainly the cingulate and frontal cortices (Fig. 3). Another study that investigated cerebral pain processing in children with CRPS found similar underlying mechanisms as in adults [82] with persisting abberations of pain processing even after recovery. Finally, patients with CRPS show a significant reorganization of central motor circuits, with an increased activation of primary motor, parietal and supplementary motor cortices during finger tapping [31]. In addition to these fMRI-studies, there are psychophysical studies showing that many patients with CRPS suffer from cognitive and motor neglect-like symptoms [32–34]. Summarizing these results, there is growing evidence that CNS alterations play an important role in the development of CRPS.

Is there a predisposition for CRPS?

Distal radius fracture is one of the most common fractures, but only a fraction of patients develops CRPS. On the other hand, there is evidence for familial occurrence of CRPS [83]. This raises the question whether there are predisposing factors for CRPS. Microdialysis experiments suggest a bilaterally increased plasma extravasation induced by substance P in patients with CRPS compared to controls [84]. Neurogenic vasodilation is generally more intensive in patients with CRPS than in healthy subjects – independent of the side affected [50]. This suggests that there is a predisposition for increased neurogenic inflammation in CRPS. However, no correlation between polymorphisms in genes coding for neuropeptide-degrading enzymes (e.g. angiotensin-converting enzyme) and the manifestation of CRPS has been proved so far [85]. Other genetic researches indicate an association with the HLA II loci DR15 and DQ1 [86]. A significant elevation of HLA DR13 was found in patients with multifocal or generalized tonic dystonia [38]. Although the exact relations between HLA features and CRPS are not clear yet, these findings suggest possible genetic factors for the manifestation of CRPS.

Diagnosis

The diagnosis of CRPS is mainly made clinically. Thus, a detailed clinical examination is crucial in establishing the diagnosis. There are different diagnostic criteria sets that are currently available. In absence of a biomarker, a gold standard for the external validation is still lacking. Revised operational criteria for the clinical diagnosis of CRPS have been published by the IASP 2007 (the 'Budapest criteria') [87], see Table 1. They are proposed criteria and have not been validated. Employing these criteria, it should be possible to make a diagnosis with satisfactory sensitivity (0.85) and specificity (0.69).

Other diagnostic criteria available are the 'Veldman criteria' [17], the 'IASP criteria' [88], and the 'Bruehl criteria' [89].

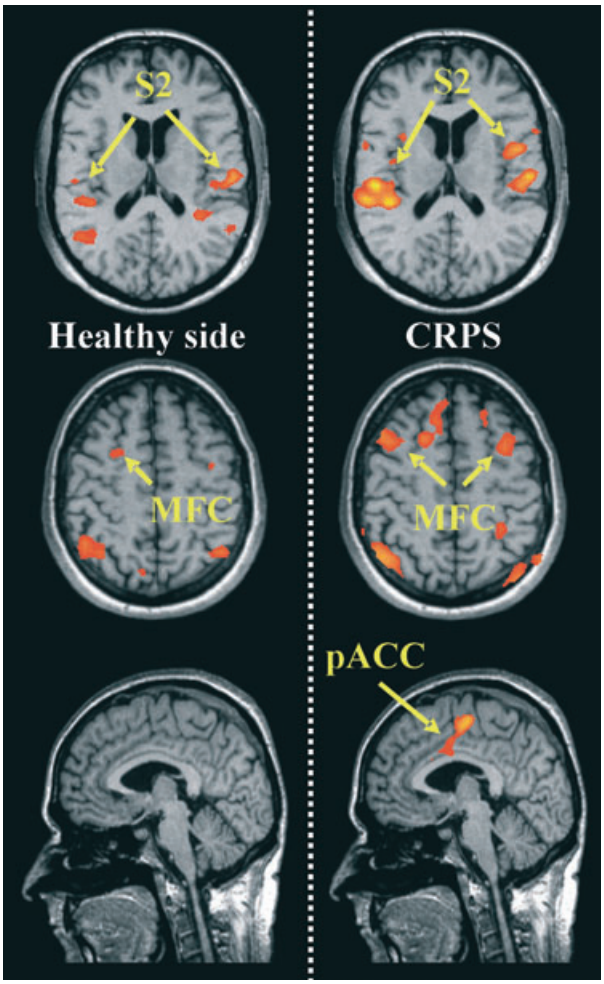

Figure 3 Brain activations (fMRI) during non-painful mechanical stimulation of the healthy side (a) and the hyperalgetic complex regional pain syndrome-affected side (b). Higher activation of secondary somatosensory cortices (S2), middle frontal cortices and the posterior part of the anterior cingulate cortex during mechanical hyperalgesia (b) (modified after [28]).

The differential diagnoses comprise rheumatic diseases, inflammatory diseases (arthritis, infections following bone surgery, neuritides), thromboembolic diseases, compartment syndromes, and (mainly in CRPS II) nerve injury syndromes.

Therapeutic concepts

Only a few controlled studies on the therapy of CRPS have been conducted so far. Frequently, results of studies on neuropathic pain syndromes have been 'transferred'. Thus, there is a great need for randomized controlled studies. Generally, there is the need for a multidisciplinary therapeutic approach in CRPS. Therapy should be supervised by an experienced pain therapist [90] or a case manager familiar with treatment of CRPS. Besides pain therapy, improvement and restoration of limb function is also an integral part of treatment.

Non-pharmacological therapies

Non-drug therapeutic strategies require an active role on the part of the patient within the treatment concept. They especially aim at improving and restoring function of the involved limb. Early physiotherapy is essential to avoid atrophy and contractures. The efficacy of physiotherapy could be demonstrated in studies [91] in which it was able to reduce pain as well as motor impairment, especially when initiated early. Regression of edema can be facilitated by lymphatic drainage. Also occupational therapy plays an important role to improve function and coordination ability of the limb. Recent studies suggest that CRPS may be improved by mirror therapy. A mirror is positioned perpendicular to the patient's midline, so that only the unaffected limb, and its reflected image in the mirror, can be seen during the following exercises, creating an illusion of normal movement of the CRPS-limb. This strategy is based on concepts developed in patients with phantom limb pain [92]. Probably, mirror neuron systems of the frontal cortex are being activated [93]. In acute stages, the use of mirror images of the unaffected extremity whilst moving is very effective [94]. A graded motor learning concept is required in chronic cases, which contains a limb recognition task, then imagination of movements and in the last step, use of the aforementioned mirror therapy [95,96]. Transcutaneous electric nerve stimulation (TENS) can support analgetic therapy. A small case series could show a reduction of pain in patients with CRPS [97]. It is necessary to meet the patient's individual needs, as especially patients suffering from allodynia and hyperalgesia often do not tolerate TENS.

Pharmacological therapy – pathophysiologically oriented therapeutic approaches

Glucocorticoids

The positive effect of glucocorticoids in CRPS has been demonstrated in controlled studies. Glucocorticoids inhibit the expression of proinflammatory cytokines (e.g. TNF-α, interleukine 1 beta), interfere with the production of inflammatory mediators (e.g. prostaglandines), can reduce the expression of neuropeptides in afferent neurons and accelerate degradation of peripheral neuropeptides [98–101]. Application of cortisone is especially approved in the initial phase which is often accompanied by excessive edema and hyperthermia. Our standard dosage scheme is methylprednisolone 100 mg/day, which is reduced by 25 mg every 4 days.

Table 1 Proposed clinical diagnostic criteria for CRPS (the 'Budapest criteria' [87])

General definition of the syndrome
CRPS describes an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time
To make the *clinical* diagnosis, the following criteria must be met
1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one *symptom in three of the four* following categories
   - Sensory: reports of hypaesthesia and/or allodynia
   - Vasomotor: reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   - Sudomotor/edema: reports of edema and/or sweating changes and/or sweating asymmetry
   - Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one *sign* at time of evaluation in two or more of the following categories
   - Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
   - Vasomotor: evidence of temperature asymmetry (> 1°C) and/or skin color changes and/or asymmetry
   - Sudomotor/edema: evidence of edema and/or sweating changes and/or sweating asymmetry
   - Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms

For *research* purposes, diagnostic decision rule should be at least one symptom *in all four* categories and at least one sign (observed at evaluation) in two or more sign categories.
CRPS, complex regional pain syndrome.

TNF-α-antibodies
There have been several promising case reports on the use of TNF-α antibodies [102,103] with a great need for randomized controlled studies.

Free radical scavengers
In a randomized controlled trial, treatment with a fatty cream with 50% dimethyl sulfoxide (DMSO) applied four times daily led to an improvement of pain and inflammatory signs [104]. Another two randomized clinical trials indicated a prophylactic effect of vitamin C on the development of CRPS following wrist fracture [105,106]. Furthermore, a positive effect of *N*-acetylcysteine (3 × 200 mg) has been reported [107]; however, the effects were limited to moderate and acute stages of CRPS type I.

Sympathetic blockade
Sympathetic blockade has been established in the treatment of CRPS for years, despite the fact that the few controlled studies existing could not show a convincing positive effect of sympathetic intervention compared to placebo [108]. Thus, sympathetic blockade can not be advised.

Pharmacological therapy – symptomatic therapy of neuropathic pain

Little data exists for treatment of neuropathic pain in CRPS. Most drugs (i.e. anticonvulsants, antidepressants and opioids) are used in analogy to other neuropathic pain syndromes [109]. So far, positive effects on neuropathic pain symptoms could be shown for gabapentin in CRPS [110,111]. Opioids have also been shown to be effective in neuropathic pain [112].

Non-steroidal anti-inflammatory drugs (NSAIDs)
Efficacy of NSAIDs in CRPS has not been systematically evaluated so far; however, this class of drugs often represents the primary therapy, i.e. prior to referral to a specialized institution. From our experience, most of the patients report a mild pain relief.

Gamma-aminobutyric acid-agonists (Baclofen)
A controlled trial examined the efficacy of intrathecally administered baclofen on dystonia in patients with CRPS [37]. In six of seven patients, bolus injections of 50 and 75 μg of baclofen resulted in complete or partial resolution of focal dystonia. In a second phase of the study, a long-term-efficacy of a subcutaneous pump for continuous intrathecal administration of baclofen could be shown. Thus, baclofen may be a potential therapeutic option in dystonia associated with CRPS.

Other therapeutic approaches – inhibition of osteoclastic activity

Calcitonin
The evidence relating to calcitonin is conflicting. In randomized controlled trials calcitonin had a positive effect on pain [113–115], but not on CRPS-associated osteoporotic bone alterations [116]. A meta-analysis reports conflicting findings as to the effects of calcitonin [117].

Bisphosphonates
In randomized controlled trials, the efficacy of bisphosphonates on pain, swelling, and mobility in CRPS has been demonstrated [118,119].

Mannitol
In a randomized controlled trial, no beneficial effect of 10% mannitol has been shown [120].

Vasodilating drugs
There is no evidence for the use of oral vasodilating drugs (e.g. verapamil, ketanserin) although they are prescribed widely [121].

Invasive therapy

Sympathectomy
Despite the theoretical reasonableness in sympathetically maintained pain, definite reports on the efficacy of this method are still lacking. Several open studies report a positive effect on the reduction of pain in patients with CRPS [122,123]. However, there is a considerable risk of developing a post-sympathectomy pain syndrome that perhaps results from a denervation supersensitivity of alpha-adrenoceptors [124,125].

Spinal cord stimulation (SCS)
Long-term effects of cervical and lumbar SCS have been investigated in a case series of 36 patients with CRPS type I. Pain intensity was significantly reduced at 6, 12, and 24 months after implantation. There was no difference in pain relief and complications between cervical and lumbar SCS [126]. A follow-up study evaluated long-term effects of SCS in these patients over 2 years. The authors report a constant pain reduction and health-related quality of life improvement [127]. Also peripheral nerve stimulation had a positive impact on CRPS pain in several studies [128].

Conclusion

Regarding treatment of CRPS, there is a great need for randomized controlled studies. Considering the available published data, an evidence-based advice can be currently given for (i) the administration of 50% DMSO [104], (ii) *N*-acetylcysteine 600 mg [107], and (iii) in prophylaxis after wrist fracture vitamin C 500 mg daily during 50 days [105,106].

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