

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, bisphosphonates). 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

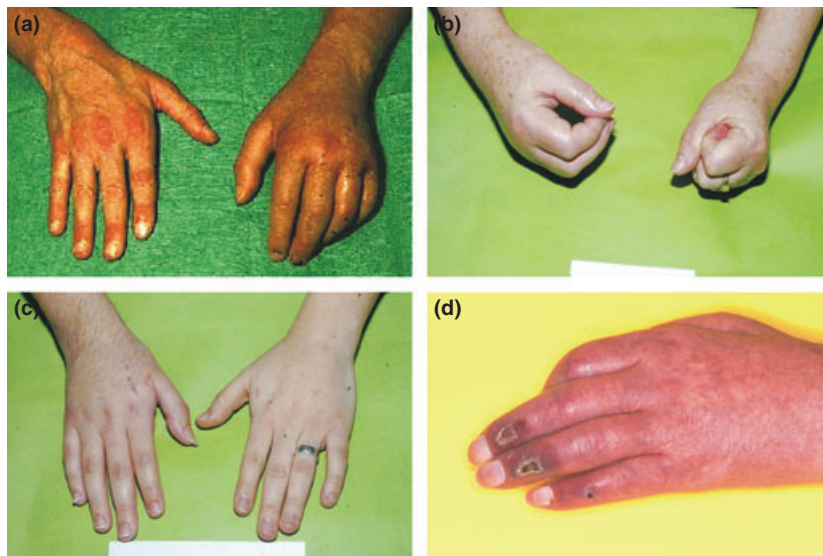


Figure 1 Clinical symptoms in complex regional pain syndrome (CRPS). Color descriptions refer to the online version of this article. (a) Acute stage of CRPS I with swelling, discoloration and function impairment of the left hand following distal radius fracture. (b) Swelling and impaired mobility at 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. hypoaesthesia 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, C-M_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 C-M_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

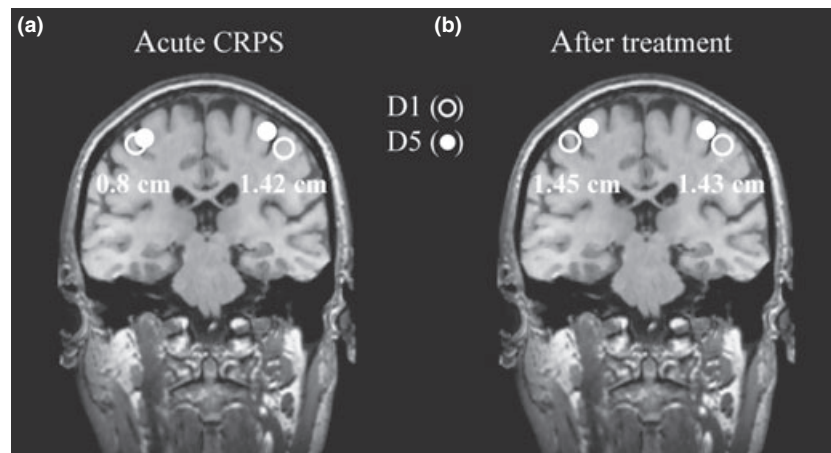
The distinct autonomic disturbances in CRPS point to an involvement of the sympathetic nervous system. Several studies showed that these disturbances depend on the stage of the disease [23,25,61]. The initial warming of the affected limb may not only result from neurogenic inflammation, but also from 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 somatotopic 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-organization 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 aberrations 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].

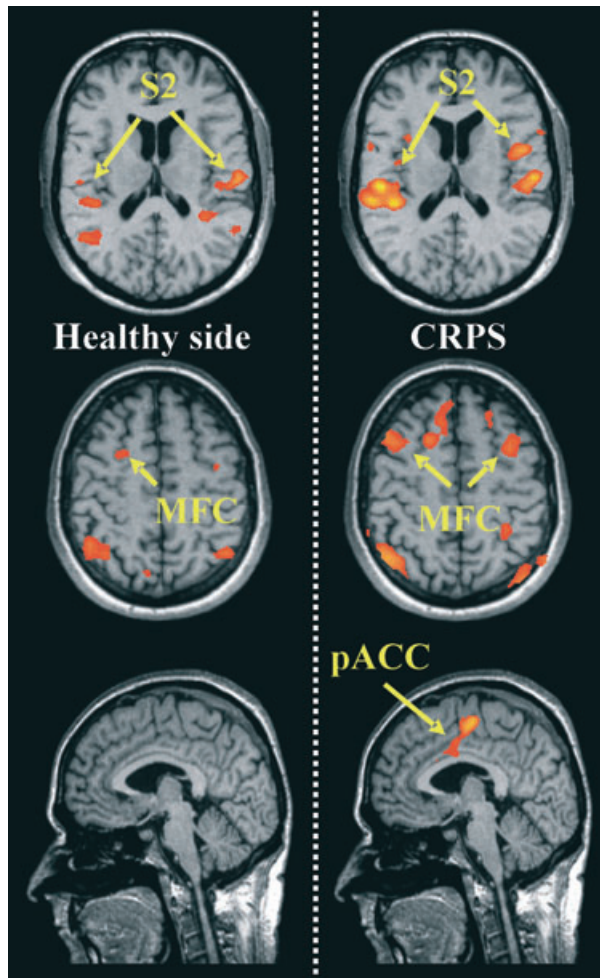


Figure 3 Brain activations (fMRI) during non-painful mechanical stimulation of the healthy side (a) and the hyperalgetic complex regional pain syndrome-affected side (b). Higher activation of secondary somatosensory cortices (S2), middle frontal cortices and the posterior part of the anterior cingulate 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 \times 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 μ g 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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References

- Mitchell SW, Morehouse GR, Keen WW. *Gunshot Wounds and Other Injuries of Nerves*. New York: Lippincott JP, 1864.
- Leriche R. De la causalgie envisagée comme une névrite du sympathique et de son traitement par la dénudation et l'excision des plexus nerveux périartériels. *Presse Med* 1916; **24**: 178–180.
- Evans JA. Reflex sympathetic dystrophy. *Surg Clin North Am* 1946; **26**: 435–448.
- Sudeck P. Über die akute entzündliche Knochenatrophie. *Arch Klin Chir* 1900; **62**: 147–156.
- Stanton-Hicks M, Janig W, Hassenbusch S, Haddox JD, Boas R, Wilson P. Reflex sympathetic dystrophy: changing concepts and taxonomy. *Pain* 1995; **63**: 127–133.
- Sandroni P, Benrud-Larson LM, McClelland RL, Low PA. Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. *Pain* 2003; **103**: 199–207.
- de Mos M, de Bruijn AG, Huygen FJ, Dieleman JP, Stricker BH, Sturkenboom MC. The incidence of complex regional pain syndrome: a population-based study. *Pain* 2007; **129**: 12–20.
- Atkins RM, Duckworth T, Kanis JA. Features of algodystrophy after Colles' fracture. *J Bone Joint Surg Br* 1990; **72**: 105–110.
- Atkins RM, Duckworth T, Kanis JA. Algodystrophy following Colles' fracture. *J Hand Surg [Br]* 1989; **14**: 161–164.
- Bickerstaff DR, Kanis JA. Algodystrophy: an under-recognized complication of minor trauma. *Br J Rheumatol* 1994; **33**: 240–248.
- Dijkstra PU, Groothoff JW, ten Duis HJ, Geertzen JH. Incidence of complex regional pain syndrome type I after fractures of the distal radius. *Eur J Pain* 2003; **7**: 457–462.
- Field J, Atkins RM. Algodystrophy is an early complication of Colles' fracture. What are the implications? *J Hand Surg [Br]* 1997; **22**: 178–182.
- Raja SN, Grabow TS. Complex regional pain syndrome I (reflex sympathetic dystrophy). *Anesthesiology* 2002; **96**: 1254–1260.
- Sarangi PP, Ward AJ, Smith EJ, Staddon GE, Atkins RM. Algodystrophy and osteoporosis after tibial fractures. *J Bone Joint Surg Br* 1993; **75**: 450–452.
- Allen G, Galer BS, Schwartz L. Epidemiology of complex regional pain syndrome: a retrospective chart review of 134 patients. *Pain* 1999; **80**: 539–544.
- Birklein F, Riedl B, Sieweke N, Weber M, Neundorfer B. Neurological findings in complex regional pain syndromes – analysis of 145 cases. *Acta Neurol Scand* 2000; **101**: 262–269.
- Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. *Lancet* 1993; **342**: 1012–1016.
- Geertzen JH, de Bruijn-Kofman AT, de Bruijn HP, van de Wiel HB, Dijkstra PU. Stressful life events and psychological dysfunction in Complex Regional Pain Syndrome type I. *Clin J Pain* 1998; **14**: 143–147.
- de Mos M, Huygen FJ, Dieleman JP, Koopman JS, Stricker BH, Sturkenboom MC. Medical history and the

- onset of complex regional pain syndrome (CRPS). *Pain* 2008; **139**: 458–466.
20. Lynch ME. Psychological aspects of reflex sympathetic dystrophy: a review of the adult and paediatric literature. *Pain* 1992; **49**: 337–347.
 21. van der Laan L, van Spaendonck K, Horstink MW, Goris RJ. The Symptom Checklist-90 Revised questionnaire: no psychological profiles in complex regional pain syndrome-dystonia. *J Pain Symptom Manage* 1999; **17**: 357–362.
 22. Harden RN, Bruchl S, Stanos S, *et al.* Prospective examination of pain-related and psychological predictors of CRPS-like phenomena following total knee arthroplasty: a preliminary study. *Pain* 2003; **106**: 393–400.
 23. Birklein F, Riedl B, Claus D, Neundorfer B. Pattern of autonomic dysfunction in time course of complex regional pain syndrome. *Clin Auton Res* 1998; **8**: 79–85.
 24. Wasner G, Schattschneider J, Baron R. Skin temperature side differences – a diagnostic tool for CRPS? *Pain* 2002; **98**: 19–26.
 25. Wasner G, Schattschneider J, Heckmann K, Maier C, Baron R. Vascular abnormalities in reflex sympathetic dystrophy (CRPS I): mechanisms and diagnostic value. *Brain* 2001; **124**: 587–599.
 26. Birklein F, Sittl R, Spitzer A, Claus D, Neundorfer B, Handwerker HO. Sudomotor function in sympathetic reflex dystrophy. *Pain* 1997; **69**: 49–54.
 27. Geertzen JH, Dijkstra PU, Groothoff JW, ten Duis HJ, Eisma WH. Reflex sympathetic dystrophy of the upper extremity – a 5.5-year follow-up. Part II. Social life events, general health and changes in occupation. *Acta Orthop Scand Suppl* 1998; **279**: 19–23.
 28. Maihofner C, Forster C, Birklein F, Neundorfer B, Handwerker HO. Brain processing during mechanical hyperalgesia in complex regional pain syndrome: a functional MRI study. *Pain* 2005; **114**: 93–103.
 29. Maihofner C, Handwerker HO, Neundorfer B, Birklein F. Patterns of cortical reorganization in complex regional pain syndrome. *Neurology* 2003; **61**: 1707–1715.
 30. Sieweke N, Birklein F, Riedl B, Neundorfer B, Handwerker HO. Patterns of hyperalgesia in complex regional pain syndrome. *Pain* 1999; **80**: 171–177.
 31. Maihofner C, Baron R, DeCol R, *et al.* The motor system shows adaptive changes in complex regional pain syndrome. *Brain* 2007; **130**: 2671–2687.
 32. Galer BS, Butler S, Jensen MP. Case reports and hypothesis: a neglect-like syndrome may be responsible for the motor disturbance in reflex sympathetic dystrophy (complex regional pain syndrome-1). *J Pain Symptom Manage* 1995; **10**: 385–391.
 33. Galer BS, Jensen M. Neglect-like symptoms in complex regional pain syndrome: results of a self-administered survey. *J Pain Symptom Manage* 1999; **18**: 213–217.
 34. Forderreuther S, Sailer U, Straube A. Impaired self-perception of the hand in complex regional pain syndrome (CRPS). *Pain* 2004; **110**: 756–761.
 35. Deuschl G, Blumberg H, Lucking CH. Tremor in reflex sympathetic dystrophy. *Arch Neurol* 1991; **48**: 1247–1252.
 36. Schwartzman RJ, Kerrigan J. The movement disorder of reflex sympathetic dystrophy. *Neurology* 1990; **40**: 57–61.
 37. van Hilten BJ, van de Beek WJ, Hoff JI, Voormolen JH, Delhaas EM. Intrathecal baclofen for the treatment of dystonia in patients with reflex sympathetic dystrophy. *N Engl J Med* 2000; **343**: 625–630.
 38. van Hilten JJ, van de Beek WJ, Roep BO. Multifocal or generalized tonic dystonia of complex regional pain syndrome: a distinct clinical entity associated with HLA-DR13. *Ann Neurol* 2000; **48**: 113–116.
 39. Sudeck P. Die sogenannte akute Knochenatrophie als Entzündungsvorgang. *Der Chirurg* 1942; **15**: 449–457.
 40. Ribbers GM, Oosterhuis WP, van Limbeek J, de Metz M. Reflex sympathetic dystrophy: is the immune system involved? *Arch Phys Med Rehabil* 1998; **79**: 1549–1552.
 41. van de Beek WJ, Remarque EJ, Westendorp RG, van Hilten JJ. Innate cytokine profile in patients with complex regional pain syndrome is normal. *Pain* 2001; **91**: 259–261.
 42. Herbert MK, Holzer P. [Neurogenic inflammation. I. Basic mechanisms, physiology and pharmacology]. *Anesthesiol Intensivmed Notfallmed Schmerzther* 2002; **37**: 314–325.
 43. Schmidt R, Schmelz M, Forster C, Ringkamp M, Torebjork E, Handwerker H. Novel classes of responsive and unresponsive C nociceptors in human skin. *J Neurosci* 1995; **15**: 333–341.
 44. Weidner C, Schmelz M, Schmidt R, Hansson B, Handwerker HO, Torebjork HE. Functional attributes discriminating mechano-insensitive and mechano-responsive C nociceptors in human skin. *J Neurosci* 1999; **19**: 10184–10190.
 45. Schmelz M, Michael K, Weidner C, Schmidt R, Torebjork HE, Handwerker HO. Which nerve fibers mediate the axon reflex flare in human skin? *Neuroreport* 2000; **11**: 645–648.
 46. Schmelz M, Schmidt R, Weidner C, Hilliges M, Torebjork HE, Handwerker HO. Chemical response pattern of different classes of C-nociceptors to pruritogens and algogens. *J Neurophysiol* 2003; **89**: 2441–2448.
 47. Klede M, Handwerker HO, Schmelz M. Central origin of secondary mechanical hyperalgesia. *J Neurophysiol* 2003; **90**: 353–359.
 48. Ziegler EA, Magerl W, Meyer RA, Treede RD. Secondary hyperalgesia to punctate mechanical stimuli. Central sensitization to A-fibre nociceptor input. *Brain* 1999; **122**(Pt 12): 2245–2257.
 49. Weber M, Birklein F, Neundorfer B, Schmelz M. Facilitated neurogenic inflammation in complex regional pain syndrome. *Pain* 2001; **91**: 251–257.
 50. Leis S, Weber M, Schmelz M, Birklein F. Facilitated neurogenic inflammation in unaffected limbs of patients with complex regional pain syndrome. *Neurosci Lett* 2004; **359**: 163–166.
 51. Birklein F, Schmelz M, Schifter S, Weber M. The important role of neuropeptides in complex regional pain syndrome. *Neurology* 2001; **57**: 2179–2184.
 52. Birklein F, Schmelz M. Neuropeptides, neurogenic inflammation and complex regional pain syndrome (CRPS). *Neurosci Lett* 2008; **437**: 199–202.
 53. Schlereth T, Dittmar JO, Seewald B, Birklein F. Peripheral amplification of sweating – a role for calcitonin gene-related peptide. *J Physiol* 2006; **576**: 823–832.
 54. Hagner S, Haberberger RV, Overkamp D, Hoffmann R, Voigt KH, McGregor GP. Expression and distribution of calcitonin receptor-like receptor in human hairy skin. *Peptides* 2002; **23**: 109–116.
 55. Kruger L, Silverman JD, Mantyh PW, Sternini C, Brecha NC. Peripheral patterns of calcitonin-gene-related peptide

- general somatic sensory innervation: cutaneous and deep terminations. *J Comp Neurol* 1989; **280**: 291–302.
56. Goto T, Tanaka T. Tachykinins and tachykinin receptors in bone. *Microsc Res Tech* 2002; **58**: 91–97.
 57. Groeneweg JG, Huygen FJ, Heijmans-Antonissen C, Niehof S, Zijlstra FJ. Increased endothelin-1 and diminished nitric oxide levels in blister fluids of patients with intermediate cold type complex regional pain syndrome type 1. *BMC Musculoskelet Disord* 2006; **7**: 91.
 58. Huygen FJ, De Bruijn AG, De Bruin MT, Groeneweg JG, Klein J, Zijlstra FJ. Evidence for local inflammation in complex regional pain syndrome type 1. *Mediators Inflamm* 2002; **11**: 47–51.
 59. Oprea A, Kress M. Involvement of the proinflammatory cytokines tumor necrosis factor-alpha, IL-1 beta, and IL-6 but not IL-8 in the development of heat hyperalgesia: effects on heat-evoked calcitonin gene-related peptide release from rat skin. *J Neurosci* 2000; **20**: 6289–6293.
 60. Uceyler N, Eberle T, Rolke R, Birklein F, Sommer C. Differential expression patterns of cytokines in complex regional pain syndrome. *Pain* 2007; **132**: 195–205.
 61. Wasner G, Heckmann K, Maier C, Baron R. Vascular abnormalities in acute reflex sympathetic dystrophy (CRPS I): complete inhibition of sympathetic nerve activity with recovery. *Arch Neurol* 1999; **56**: 613–620.
 62. Baron R, Schattschneider J, Binder A, Siebrecht D, Wasner G. Relation between sympathetic vasoconstrictor activity and pain and hyperalgesia in complex regional pain syndromes: a case-control study. *Lancet* 2002; **359**: 1655–1660.
 63. Birklein F, Riedl B, Neundorfer B, Handwerker HO. Sympathetic vasoconstrictor reflex pattern in patients with complex regional pain syndrome. *Pain* 1998; **75**: 93–100.
 64. Drummond PD, Skipworth S, Finch PM. Alpha 1-adrenoceptors in normal and hyperalgesic human skin. *Clin Sci (Lond)* 1996; **91**: 73–77.
 65. Sato J, Perl ER. Adrenergic excitation of cutaneous pain receptors induced by peripheral nerve injury. *Science* 1991; **251**: 1608–1610.
 66. Torebjork E, Wahren L, Wallin G, Hallin R, Koltzenburg M. Noradrenaline-evoked pain in neuralgia. *Pain* 1995; **63**: 11–20.
 67. Walker AE, Nulsen F. Electrical stimulation of the upper thoracic portion of the sympathetic chain in man. *Arch Neurol Psychiatry* 1948; **59**: 559–560.
 68. Kurvers HA, Jacobs MJ, Beuk RJ, *et al.* Reflex sympathetic dystrophy: evolution of microcirculatory disturbances in time. *Pain* 1995; **60**: 333–340.
 69. Schattschneider J, Hartung K, Stengel M, *et al.* Endothelial dysfunction in cold type complex regional pain syndrome. *Neurology* 2006; **67**: 673–675.
 70. Birklein F, Weber M, Neundorfer B. Increased skin lactate in complex regional pain syndrome: evidence for tissue hypoxia? *Neurology* 2000; **55**: 1213–1215.
 71. Koban M, Leis S, Schultze-Mosgau S, Birklein F. Tissue hypoxia in complex regional pain syndrome. *Pain* 2003; **104**: 149–157.
 72. Birklein F, Weber M, Ernst M, Riedl B, Neundorfer B, Handwerker HO. Experimental tissue acidosis leads to increased pain in complex regional pain syndrome (CRPS). *Pain* 2000; **87**: 227–234.
 73. van der Laan L, ter Laak HJ, Gabreels-Festen A, Gabreels F, Goris RJ. Complex regional pain syndrome type I (RSD): pathology of skeletal muscle and peripheral nerve. *Neurology* 1998; **51**: 20–25.
 74. van Rijn MA, Marinus J, Putter H, van Hilten JJ. Onset and progression of dystonia in complex regional pain syndrome. *Pain* 2007; **130**: 287–293.
 75. Rommel O, Gehling M, Dertwinkel R, *et al.* Hemisensory impairment in patients with complex regional pain syndrome. *Pain* 1999; **80**: 95–101.
 76. Rommel O, Malin JP, Zenz M, Janig W. Quantitative sensory testing, neurophysiological and psychological examination in patients with complex regional pain syndrome and hemisensory deficits. *Pain* 2001; **93**: 279–293.
 77. Maihöfner C, Handwerker HO, Neundorfer B, Birklein F. Cortical reorganization during recovery from complex regional pain syndrome. *Neurology* 2004; **63**: 693–701.
 78. Pleger B, Tegenthoff M, Ragert P, *et al.* Sensorimotor retuning [corrected] in complex regional pain syndrome parallels pain reduction. *Ann Neurol* 2005; **57**: 425–429.
 79. Pleger B, Tegenthoff M, Schwenkreis P, *et al.* Mean sustained pain levels are linked to hemispherical side-to-side differences of primary somatosensory cortex in the complex regional pain syndrome I. *Exp Brain Res* 2004; **155**: 115–119.
 80. Flor H, Elbert T, Knecht S, *et al.* Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature* 1995; **375**: 482–484.
 81. Maihöfner C, DeCol R. Decreased perceptual learning ability in complex regional pain syndrome. *Eur J Pain* 2007; **11**: 903–909.
 82. Lebel A, Becerra L, Wallin D, *et al.* fMRI reveals distinct CNS processing during symptomatic and recovered complex regional pain syndrome in children. *Brain* 2008; **131**: 1854–1879.
 83. de Rooij AM, de Mos M, Sturkenboom MC, Marinus J, van den Maagdenberg AM, van Hilten JJ. Familial occurrence of complex regional pain syndrome. *Eur J Pain* 2009; **13**: 171–177.
 84. Leis S, Weber M, Isselmann A, Schmelz M, Birklein F. Substance-P-induced protein extravasation is bilaterally increased in complex regional pain syndrome. *Exp Neurol* 2003; **183**: 197–204.
 85. Huhne K, Leis S, Schmelz M, Rautenstrauss B, Birklein F. A polymorphic locus in the intron 16 of the human angiotensin-converting enzyme (ACE) gene is not correlated with complex regional pain syndrome I (CRPS I). *Eur J Pain* 2004; **8**: 221–225.
 86. van de Beek WJ, Roep BO, van der Slik AR, Giphart MJ, van Hilten BJ. Susceptibility loci for complex regional pain syndrome. *Pain* 2003; **103**: 93–97.
 87. Harden RN, Bruhl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. *Pain Med* 2007; **8**: 326–331.
 88. Merskey H, Bogduk N. *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definition of Pain Terms*, 2nd edn. Seattle: IASP Press, 1994.
 89. Bruhl S, Harden RN, Galer BS, *et al.* External validation of IASP diagnostic criteria for complex regional pain syndrome and proposed research diagnostic criteria. International Association for the Study of Pain. *Pain* 1999; **81**: 147–154.
 90. Stanton-Hicks M, Baron R, Boas R, *et al.* Complex regional pain syndromes: guidelines for therapy. *Clin J Pain* 1998; **14**: 155–166.

91. Oerlemans HM, Oostendorp RA, de Boo T, Goris RJ. Pain and reduced mobility in complex regional pain syndrome I: outcome of a prospective randomised controlled clinical trial of adjuvant physical therapy versus occupational therapy. *Pain* 1999; **83**: 77–83.
92. Ramachandran VS, Hirstein W. The perception of phantom limbs. The D. O. Hebb lecture. *Brain* 1998; **121**(Pt 9): 1603–1630.
93. Pomeroy VM, Clark CA, Miller JS, Baron JC, Markus HS, Tallis RC. The potential for utilizing the “mirror neurone system” to enhance recovery of the severely affected upper limb early after stroke: a review and hypothesis. *Neurorehabil Neural Repair* 2005; **19**: 4–13.
94. McCabe CS, Haigh RC, Ring EF, Halligan PW, Wall PD, Blake DR. A controlled pilot study of the utility of mirror visual feedback in the treatment of complex regional pain syndrome (type 1). *Rheumatology (Oxford)* 2003; **42**: 97–101.
95. Moseley GL. Graded motor imagery is effective for long-standing complex regional pain syndrome: a randomised controlled trial. *Pain* 2004; **108**: 192–198.
96. Moseley GL. Graded motor imagery for pathologic pain: a randomized controlled trial. *Neurology* 2006; **67**: 2129–2134.
97. Robaina FJ, Rodriguez JL, de Vera JA, Martin MA. Transcutaneous electrical nerve stimulation and spinal cord stimulation for pain relief in reflex sympathetic dystrophy. *Stereotact Funct Neurosurg* 1989; **52**: 53–62.
98. Guo TZ, Wei T, Kingery WS. Glucocorticoid inhibition of vascular abnormalities in a tibia fracture rat model of complex regional pain syndrome type I. *Pain* 2006; **121**: 158–167.
99. Kingery WS, Agashe GS, Sawamura S, Davies MF, Clark JD, Maze M. Glucocorticoid inhibition of neuropathic hyperalgesia and spinal Fos expression. *Anesth Analg* 2001; **92**: 476–482.
100. Kingery WS, Guo T, Agashe GS, Davies MF, Clark JD, Maze M. Glucocorticoid inhibition of neuropathic limb edema and cutaneous neurogenic extravasation. *Brain Res* 2001; **913**: 140–148.
101. Piedimonte G, McDonald DM, Nadel JA. Neutral endopeptidase and kininase II mediate glucocorticoid inhibition of neurogenic inflammation in the rat trachea. *J Clin Invest* 1991; **88**: 40–44.
102. Huygen FJ, Niehof S, Zijlstra FJ, van Hagen PM, van Daele PL. Successful treatment of CRPS I with anti-TNF. *J Pain Symptom Manage* 2004; **27**: 101–103.
103. Bernateck M, Rolke R, Birklein F, Treede RD, Fink M, Karst M. Successful intravenous regional block with low-dose tumor necrosis factor- α antibody infliximab for treatment of complex regional pain syndrome I. *Anesth Analg* 2007; **105**: 1148–1151. Table of contents.
104. Zuurmond WW, Langendijk PN, Bezemer PD, Brink HE, de Lange JJ, van loenen AC. Treatment of acute reflex sympathetic dystrophy with DMSO 50% in a fatty cream. *Acta Anaesthesiol Scand* 1996; **40**: 364–367.
105. Zollinger PE, Tuinebreijer WE, Breederveld RS, Kreis RW. Can vitamin C prevent complex regional pain syndrome in patients with wrist fractures? A randomized, controlled, multicenter dose–response study. *J Bone Joint Surg Am* 2007; **89**: 1424–1431.
106. Zollinger PE, Tuinebreijer WE, Kreis RW, Breederveld RS. Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomised trial. *Lancet* 1999; **354**: 2025–2028.
107. Perez RS, Zuurmond WW, Bezemer PD, et al. The treatment of complex regional pain syndrome type I with free radical scavengers: a randomized controlled study. *Pain* 2003; **102**: 297–307.
108. Cepeda MS, Lau J, Carr DB. Defining the therapeutic role of local anesthetic sympathetic blockade in complex regional pain syndrome: a narrative and systematic review. *Clin J Pain* 2002; **18**: 216–233.
109. Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch Neurol* 2003; **60**: 1524–1534.
110. van de Vusse AC, Stomp-van den Berg SG, Kessels AH, Weber WE. Randomised controlled trial of gabapentin in complex regional pain syndrome type 1 [ISRCTN84121379]. *BMC Neurol* 2004; **4**: 13.
111. Mellick LB, Mellick GA. Successful treatment of reflex sympathetic dystrophy with gabapentin. *Am J Emerg Med* 1995; **13**: 96.
112. Rowbotham MC, Twilling L, Davies PS, Reisner L, Taylor K, Mohr D. Oral opioid therapy for chronic peripheral and central neuropathic pain. *N Engl J Med* 2003; **348**: 1223–1232.
113. Perez RS, Kwakkel G, Zuurmond WW, de Lange JJ. Treatment of reflex sympathetic dystrophy (CRPS type 1): a research synthesis of 21 randomized clinical trials. *J Pain Symptom Manage* 2001; **21**: 511–526.
114. Gobelet C, Waldburger M, Meier JL. The effect of adding calcitonin to physical treatment on reflex sympathetic dystrophy. *Pain* 1992; **48**: 171–175.
115. Forouzanfar T, Koke AJ, van Kleef M, Weber WE. Treatment of complex regional pain syndrome type I. *Eur J Pain* 2002; **6**: 105–122.
116. Bickerstaff DR, Kanis JA. The use of nasal calcitonin in the treatment of post-traumatic algodystrophy. *Br J Rheumatol* 1991; **30**: 291–294.
117. Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. *Pain* 1997; **73**: 123–139.
118. Adami S, Fossaluzza V, Gatti D, Fracassi E, Braga V. Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. *Ann Rheum Dis* 1997; **56**: 201–204.
119. Varenna M, Zucchi F, Binelli L, Failoni S, Gallazzi M, Sinigaglia L. Intravenous pamidronate in the treatment of transient osteoporosis of the hip. *Bone* 2002; **31**: 96–101.
120. Perez RS, Pragt E, Geurts J, Zuurmond WW, Patijn J, van Kleef M. Treatment of patients with complex regional pain syndrome type I with mannitol: a prospective, randomized, placebo-controlled, double-blinded study. *J Pain* 2008; **9**: 678–686.
121. DE Moss M, Huygen FJ, VDH-B M, Dieleman JP, Stricker BH, Sturkenboom MC. Referral and treatment patterns for complex regional pain syndrome in the Netherlands. *Acta Anaesthesiol Scand* 2009; **53**: 816–825.
122. AbuRahma AF, Robinson PA, Powell M, Bastug D, Boland JP. Sympathectomy for reflex sympathetic dystrophy: factors affecting outcome. *Ann Vasc Surg* 1994; **8**: 372–379.
123. Schwartzman RJ, Liu JE, Smullens SN, Hyslop T, Tahmouh AJ. Long-term outcome following

- sympathectomy for complex regional pain syndrome type 1 (RSD). *J Neurol Sci* 1997; **150**: 149–152.
124. Furlan AD, Lui PW, Mailis A. Chemical sympathectomy for neuropathic pain: does it work? Case report and systematic literature review. *Clin J Pain* 2001; **17**: 327–336.
125. Furlan AD, Mailis A, Papagapiou M. Are we paying a high price for surgical sympathectomy? A systematic literature review of late complications. *Pain* 2000; **1**: 245–257.
126. Forouzanfar T, Kemler MA, Weber WE, Kessels AG, van Kleef M. Spinal cord stimulation in complex regional pain syndrome: cervical and lumbar devices are comparably effective. *Br J Anaesth* 2004; **92**: 348–353.
127. Kemler MA, De Vet HC, Barendse GA, Van Den Wildenberg FA, Van Kleef M. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial. *Ann Neurol* 2004; **55**: 13–18.
128. Hassenbusch SJ, Stanton-Hicks M, Schoppa D, Walsh JG, Covington EC. Long-term results of peripheral nerve stimulation for reflex sympathetic dystrophy. *J Neurosurg* 1996; **84**: 415–423.