

Review

Complex regional pain syndrome in adults

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Abstract

Complex regional pain syndrome (CRPS) is a highly painful, limb-confined condition, which arises usually after trauma. It is associated with a particularly poor quality of life, and large health-care and societal costs. The causes of CRPS remain unknown. The condition's distinct combination of abnormalities includes limb-confined inflammation and tissue hypoxia, sympathetic dysregulation, small fibre damage, serum autoantibodies, central sensitization and cortical reorganization. These features place CRPS at a crossroads of interests of several disciplines including rheumatology, pain medicine and neurology. Significant scientific and clinical advances over the past 10 years hold promise both for an improved understanding of the causes of CRPS, and for more effective treatments. This review summarizes current concepts of our understanding of CRPS in adults. Based on the results from systematic reviews, treatment approaches are discussed within the context of these concepts. The treatment of CRPS is multidisciplinary and aims to educate about the condition, sustain or restore limb function, reduce pain and provide psychological intervention. Results from recent randomized controlled trials suggest that it is possible that some patients whose condition was considered refractory in the past can now be effectively treated, but confirmatory trials are required. The review concludes with a discussion of the need for additional research.

Key words: Complex regional pain syndrome, Neuropathic pain, Chronic pain, Pain, Intravenous immunoglobulin.

Introduction

Complex regional pain syndrome (CRPS) is a painful condition that develops after trauma to a limb (Fig. 1). About 10% of patients report minor trauma or cannot remember any trauma. These patients are on average 9 years younger at disease onset, but there are no differences in signs or symptoms [1–3]. CRPS is characterized by limb-confined sensory, autonomic, motor, skin and bone changes, but the lead symptom is pain. Earlier names include reflex sympathetic dystrophy (RSD), algodystrophy, algoneurodystrophy, Sudeck's atrophy and causalgia. The diagnosis is clinical; the diagnostic Budapest Criteria (Fig. 2) have recently been updated and are widely accepted [4]. These criteria, in a prior version also termed Bruehl-Harden criteria replace earlier criteria that were not specific. Over the past 10 years, scientists and clinicians have jointly achieved remarkable

progress in understanding and treating CRPS. In this review both scientific and therapeutic advances are summarized.

CRPS epidemiology, course and recovery, health economics, clinical presentation and delayed diagnosis

Epidemiology

From the first ever population representative European epidemiological study, we know that CRPS is more common (incidence: 26/100 000 life-years, female male ratio 3.5:1) than previously thought (for comparison, the incidence of RA is 30/100 000, that of multiple sclerosis 4/100 000) [1]. The peak incidence is in people aged 55–75 years, but CRPS may take a more benign course in this group than in many younger, adult patients [1, 5]. CRPS in children is probably rare; it has its own specific diagnostic and management requirements and will not be discussed in this review [6, 7].

Course

Similar to postherpetic neuralgia, but unlike lower back pain and FM almost all CRPS is monophasic, with only 2% relapsing-remitting cases [2]. Recently, CRPS experts

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Fig. 1 Clinical presentation of CRPS. Early CRPS of the right hand; clearly visible signs include swelling, red colour and a shiny skin. As the disease progresses some of these visible signs can partially or completely disappear while pain may persist unabated.



have suggested a scoring system, designed to quantify the CRPS disease severity; however, epidemiological studies using that system have not yet been performed [8]. By 6 years after disease onset, 30% of patients consider themselves completely recovered, and 54% of patients consider their disease as stable. Most patients in this latter group take up some kind of gainful employment. There is also a group of ~15% of patients who experience no improvement, and overall 30% of those who worked before CRPS onset remain completely unable to work [9].

Most cases improve or stabilize early after disease onset, while later improvement is less common [9]. It can, therefore, make sense to consider the efficacy of clinical interventions specifically in long-standing CRPS (which usually does not spontaneously get better). Not much is known about the typical course and duration of long-standing CRPS; for health economic calculations, the UK National Institute for Clinical Excellence (NICE) has assumed a 15-year estimated average CRPS duration for those cases of long-standing CRPS that require spinal cord stimulation (SCS) (<http://www.nice.org.uk/nicemedia/live/12082/42367/42367.pdf>, p. 21).

Recovery

A definition of recovery from CRPS has not yet been achieved, which can pose problems for the diagnosis of some long-standing cases. This is because certain limb signs, including swelling, sweating and discolouration often reduce with time, while pain persists [10]. Without these signs, a diagnosis of CRPS can often not be made (Fig. 2), so that patients may lose their initial diagnosis after some years, but continue to suffer from pain. It is likely that separate terms, such as post-Budapest CRPS and/or post-CRPS syndrome will in the future define such patients who have fulfilled the Budapest criteria in the past.

Health economics

Similar to other chronic pain conditions [11], CRPS is expensive. Average annual health-care costs (excluding physiotherapy) in the Netherlands were €5700 in 1998. Since patients with ongoing significant pain from CRPS almost never work [12], and as additional patients reduce their work commitments or retrain, overall costs are higher. The return to work rate remains low even where patients undergo SCS treatment with good pain relief and improvement in the quality of life (personal communication: Prof. MA Kemler, Maastricht University Hospital [13]). The reason may be related to residual pain and poor functional improvement. The average quality of life reported by those with long-standing CRPS requiring SCS is poor, an EQ-5D score of 0.2 to 1 [12]. For comparison, average scores in RA are 0.5–0.6 to 1 and in FM 0.4–0.5 to 1 [14].

Clinical presentation and delayed diagnosis

Patients with CRPS can present in many different ways. For example, limbs can be hot or cold, shiny, swollen or thin, red or blue (Fig. 1), with scaling or clammy skin, bones may or may not appear with localized osteoporosis on X-ray. Some patients cannot tolerate slight air movement on their skin, while others have completely lost the ability to feel any stimulus to the limb (with normal nerve conduction studies). Joints usually feel stiff with reduced range and weakness; often limb parts cannot be moved at all, and there is a fine tremor. Up to 7% of patients present with typical CRPS signs, but without pain [2]. In addition, there are some presentations that even pain specialists may encounter only every few years. These include CRPS in the shoulder—with autonomic signs only in the ipsilateral but non-painful hand, spreading of symptoms to another limb, chronic lymphoedema, blister formation, skin ulcerations (often with secondary infections [15]), severe atrophy, joint ankylosis, dystonia and myoclonus [2, 5]. Some of these complications are more common in young women [5]. The CRPS signs and symptoms mimic a range of other health conditions; this may be one reason why CRPS is often diagnosed late [16]. In addition, the wide variety of circumstances under which CRPS can occur (none, mild to severe injuries of all kinds), means that patients are seen by a wide range of health-care

Fig. 2 Budapest diagnostic criteria (A–D must apply). Note that it is possible to distinguish between CRPS-1 (without damage to major nerves) and CRPS-2 [associated with (yet not causing) damage to a major nerve, a very rare presentation], but there is currently no RCT-derived evidence that this distinction has any consequence for treatment. ^aThe reflected understanding of allodynia as painful sensation to a number of normally non-painful stimuli is under review by the IASP taxonomy group. Some experts suggest that the term allodynia should be reserved only for brush-stroke evoked pain (dynamic mechanical allodynia). ^bHyperalgesia is exaggerated pain to a painful stimulus such as a pinprick. ^cFor example, raised systemic inflammatory markers are not associated with CRPS, even in the initial inflammatory phase; such a finding of raised markers would lead to a search for an alternative or concomitant cause. Abnormal nerve conduction studies do not exclude CRPS, but the primary cause of the observed abnormality must be clarified: CRPS, by definition is always secondary, its presence cannot explain major nerve damage. Figure adapted from Ref. [4].

A The patient has continuing pain which is disproportionate to the inciting event

Category	Sign (you can see or feel a problem)	Symptom (the patient reports a problem)
1 Sensory	Allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement) ^a and/or hyperalgesia (to pinprick) ^b	Hyperaesthesia does also qualify as a symptom
2 Vasomotor	Temperature asymmetry and/or skin colour changes and/or skin colour asymmetry	
3 Sudomotor/edema	Oedema and/or sweating changes and/or sweating asymmetry	
4 Motor/trophic	Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair/nail/skin)	

B The patient has at least one sign in two or more of the categories

C The patient reports at least one symptom in three or more of the categories

D No other diagnosis can better explain the signs and symptoms^c

professionals (Fig. 3); since CRPS is not common, some practitioners are unfamiliar with the clinical presentation.

Causes of CRPS

CRPS is associated with migraines, osteoporosis, asthma and angiotension-converting enzyme (ACE) inhibitor therapy [17, 18]. There are currently eight major concepts about CRPS aetiology. These concepts, which also explain the rationale behind most clinical treatments, are described here. The clinical trial evidence cited in this section is derived from at least one randomized controlled

trial (RCT) in each case with no conflicting published results, unless specifically noted. Evaluation of the evidence is based on systematic reviews by Forouzanfar *et al.* ([19], until June 2000), and the UK CRPS guideline group (from June 2000 to April 2010, Cossins *et al.*, 2011, data not published).

CRPS is the result of an inflammatory process

This was originally proposed by Peter Sudeck ('Sudeck's atrophy') [20]. The painful CRPS-affected limb is often red, hot and swollen, with reduced function, the five cardinal signs of inflammation [21]. Indeed, recent research has

Fig. 3 Health-care services involved in the care of patients with CRPS. The management of patients with CRPS in primary and secondary care involves specialists from a wide range of health-care professions. Many specialists see patients with CRPS only rarely and are, therefore, relatively unfamiliar with the clinical presentation. Further, CRPS mimics a range of other health conditions encountered by these health-care professionals; these factors may contribute to causing delay in confirming the correct diagnosis.



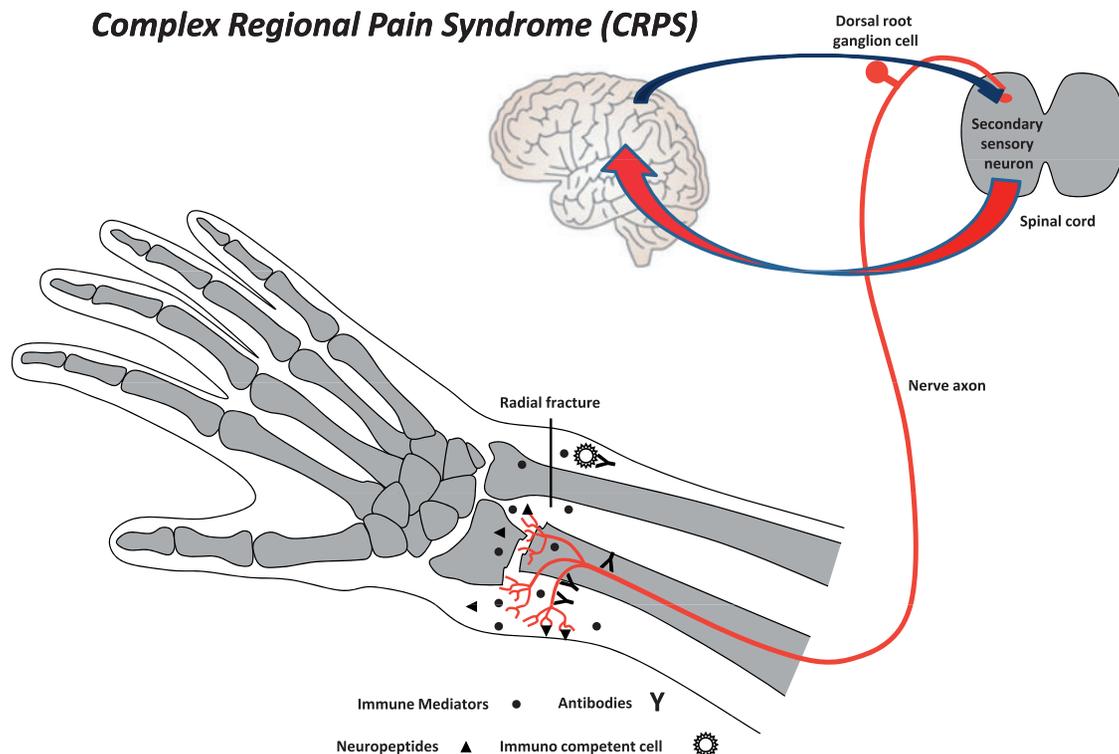
shown that inflammatory mediators, including TNF- α , are elevated in blister fluid taken from CRPS-affected limbs [22]. Similar observations were reported in a rodent rat (tibia fracture) CRPS model [23]. The titre of these mediators, however, is not related to the pain intensity and can remain high even if the pain disappears [24]. The cellular sources of most mediators are unknown. An integrative model of CRPS pathophysiology including inflammatory changes is presented in Fig. 4. Since local inflammation has a role, anti-inflammatory treatment may be effective. One small RCT has suggested that steroid treatment is effective in very early CRPS [25]. Regional i.v. blocks (Bier blocks) with steroids [26] are likely not effective in early CRPS, and intrathecal steroids are not effective in CRPS of >6 months duration [27]. No RCT has assessed high-dose oral or i.v. steroid treatment, or the recently proposed anti-inflammatory anti-TNF- α therapy [28]. The recently reported efficacy of low-dose IVIGs could be due to an anti-inflammatory effect [29]. Bisphosphonates, which have immune modulatory properties, were effective in four small and heterogeneous RCTs in CRPS of <6 months duration [30–34]. Three of these trials included only patients with local osteoporosis, confirmed on X-ray, or by increased bone-scan uptake; however, bone changes are not a requirement for the diagnosis of CRPS, and many patients will not have bone changes. In the fourth study, a direct comparison of outcomes between patients with versus without bone changes was

not reported [30], consequently the response of patients without such bone changes is unknown. Lenalidomide, a highly toxic, anti-inflammatory thalidomide derivative was tested in one of the largest ever RCTs conducted in long-standing CRPS, but unfortunately the sponsoring company (Celgene Corporation, Summit, NJ, USA) has not published the results.

CRPS is a sympathetically mediated disorder

Sweating and colour/temperature differences between CRPS-affected and unaffected limbs are in part mediated by a complex sympathetic dysregulation. There is a low, rather than high, centrally mediated sympathetic outflow to cutaneous vasoconstrictors in the CRPS-affected extremity, which likely contributes to produce red and warm extremities [35]; other vasomotor signs such as cold temperature and bluish discoloration may be caused by reactive adrenoceptor up-regulation and/or supersensitivity, rather than by a dysregulation of the sympathetic outflow [36, 37]. Vaso- and sudomotor signs often diminish with time. The permanent cold temperature in some cases of late CRPS may be due to endothelial rather than sympathetic dysfunction [38]. Evans [39] had introduced the, now superseded term RSD to indicate that regional autonomic dysregulation actually causes the patients' pain. Hannington-Kiff [40] later suggested that agents that deplete the limb autonomic nerve endings of noradrenaline, such as regional guanethidine should, therefore, be

Fig. 4 Integrative conceptual model of CRPS. In the affected limb after trauma, enhanced anti-dromic secretion of neuropeptides from sensory nerve endings [77], enhanced release of immune mediators from various cells [22] and surface binding autoantibodies [54] may contribute both to change regional sensory nerve function, and elicit sensory axonal degeneration; resulting functional and structural changes may then elicit further changes creating a vicious cycle [70]. Some of these changes may be enhanced by tissue ischaemia ([59], data not shown). The long-lasting response of patients with long-standing CRPS to the—likely centrally acting—NMDA-receptor antagonist ketamine [47, 48] also suggests that, at least in chronic cases these regional factors do not sufficiently activate nociceptors (otherwise pain intensity would return as the ketamine plasma level declines); these factor may rather create a low-level activation of sensory nerves sustaining central sensitization in the dorsal horn (see main text). Certain methods of brain training, and spinal cord stimulator treatment can, through yet unknown mechanisms alter regional factors in the affected limb, as evidenced by their reported efficacy to reduce limb swelling [13, 66, 92]. The model does not account for the presumed role of sympathetic dysfunction in some patients.



effective. Unfortunately, all four RCTs conducted to assess this treatment have been negative [19]. Given the experience shared by many clinicians that this method, termed i.v. regional sympathetic block (IVRSB), actually does reduce pain in some patients, one wonders whether it is perhaps the application of tourniquet that conveys that effect. Indeed, IVRSB with saline may be more effective than IVRSB with guanethidine [41]. Local anaesthetic application to the sympathetic ganglia (i.e. stellate or lumbar sympathetic blocks) can relieve pain for the short term in selected patients [42], but repeat application does not prolong that effect [43]. Sympathetically maintained pain (SMP), that is pain that can be reduced by sympathetic blockade, although common in early CRPS, is rare in long-standing CRPS [44]. While there clearly is autonomic dysregulation [45], both the discussed rarity of SMP in those clinically particularly problematic long-standing cases, and the emergence of novel aetiological concepts have contributed to prompting CRPS

experts to de-emphasize the importance of the concept of sympathetic dysfunction for advancing patient treatment.

Central sensitization is the driving factor for CRPS

Central sensitization is the molecular process that corresponds to the clinical observation that after a period of intense or repeated noxious stimulation (a noxious stimulus actually or potentially causes tissue damage), innocuous (non-noxious) stimuli become painful and remain painful (for a while at least) even if the initial noxious stimulation has subsided. This mechanism is important in most chronic pain [46]. Since *N*-methyl *D*-aspartate (NMDA) receptors play a critical role in central sensitization, the recent observation in two RCTs that low-dose i.v. ketamine (an NMDA antagonist) can dramatically reduce CRPS pain, indicates an important role for such central sensitization [47, 48]. There is currently no RCT evidence for high-dose ketamine coma under

intensive care conditions, which has sometimes been discussed in the media [49]. In the two published low-dose RCTs, ketamine strongly reduced average pain intensity for several weeks independently of the CRPS disease duration, but without improving function. It is uncertain how these research findings will translate into clinical practice. Side effects from repeated ketamine infusions are poorly understood, and some experts have expressed concern about potential neurotoxicity [50]. Current protocols for ketamine treatment are expensive and cumbersome. In the published protocols, either a 5-day hospital inpatient stay, or 10 consecutive working-day outpatient treatments are required to achieve pain relief lasting several weeks. Recently, a small pilot trial suggested efficacy of i.v. magnesium which, similar to ketamine, may work to reduce central sensitization [51].

CRPS is an autoimmune condition

This is a novel concept that has recently been further advanced by our and Franz Blaes's groups. Both groups found evidence for anti-neuronal autoantibodies, in between 30 and 90% of patients [52–54]. Further, we have shown that the passive transfer of patient serum immunoglobulin G (IgG) antibodies elicits abnormal behaviour and motor function in mice, suggesting a functional effect [55, 56]. We have also demonstrated in a corresponding RCT, that a single infusion of low-dose (0.5 g/kg) IVIG effectively reduces pain in patients with long-standing disease [29]. The pain relief lasted 5 weeks on average. Response to IVIG is considered circumstantial evidence for an autoimmune aetiology [57]. If autoantibodies are involved (Fig. 4), then novel therapeutic strategies, such as plasmapheresis and reverse vaccination may hold promise for the future [58].

CRPS is the result of limb ischaemia or ischaemia reperfusion injury

This concept is related to the inflammatory hypothesis. The idea is that in CRPS I, an abnormal inflammatory response to a deep tissue injury produces a compartment syndrome-like picture with resultant, oxygen-free radical-induced microvascular damage/dysfunction and, in a vicious cycle, further ischaemia and inflammation and nociceptor excitation [59]. In animal models, transient application of limb ischaemia produces a syndrome that resembles CRPS [60]. There is some evidence for low oxygen tension in the superficial skin layers of CRPS-affected limbs [61] potentially strengthening the idea that ischaemia may also be present in deeper tissues. The efficacy of vitamin C in preventing the development of CRPS after dorsal radius fracture has been suggested to be due to the scavenging of free oxygen radicals, a mechanism that would prevent microvascular damage [59, 62]. If ongoing deep tissue ischaemia was important, then vasodilation might improve CRPS. A recent pilot trial showed that tadalafil, a phosphodiesterase inhibitor, reduces pain in some patients, in a subgroup of CRPS with cold limbs [63]. Tadalafil is a vasodilator and it may be that the vasodilatory property of this

drug is responsible for pain relief; however, the affected limbs did not get warmer with treatment (limb temperature was the primary outcome). No other trial has to date demonstrated the success of a treatment that improves limb blood flow, although the working mechanism of sympathetic blocks could be explained that way.

Cortical reorganization sustains CRPS

Functional MRI studies over the past 10 years have clearly shown that the sensory representation of the CRPS-affected limb, as part of the Penfield homunculus is altered (shrunk and shifted), that the degree of this alteration corresponds to the patient's pain intensity and that pain reduction is associated with normalization [64, 65]. There are also important changes in the motor cortex. We do not know whether these changes are secondary or linked to the CRPS cause. Clinically, patients often feel alienation with their affected limb; the limb can feel strange and disfigured and out of place [16]. These feelings are often not communicated to health-care professional, perhaps to avoid the suspected danger of not being believed. Some patients cannot stop thinking about amputating their affected limb. Such features may be associated with an altered cortical limb representation, although this has yet to be confirmed. Clinician's anticipation and reflection of his/her patient's strange limb feelings may well support a better understanding and acceptance of the condition. Computer-based graded motor imagery (GMI), which involves an exercise to train the brain in better recognizing the affected limb, can reduce pain and swelling in some patients [66]. Mirror therapy was first applied to the treatment of CRPS by Candy McCabe's group [67]. This method requires that the patient hides the affected limb behind a mirror that is positioned perpendicular to his body midline. When looking into the mirror and performing bilateral synchronized gentle movements, the virtual affected limb (=the reflection of the unaffected limb in the mirror) has a normal appearance and also moves normally. Mirror therapy has been shown to reduce pain in CRPS (both early and late) after stroke [68]. These positive research results also strongly suggest that in some patients limb signs such as swelling are in part under cortical control (Fig. 4), although the biological correlates of such control remain unknown. The described therapeutic advances appear particularly exciting since these treatments are cheap and have few adverse effects [2]. We and others were recently unable to reproduce the published GMI findings in prospective clinical audits, suggesting that their translation into clinical practice will require more work (Johnson *et al.*, 2011, data not published). GMI and mirror treatment are now widely practised, and clinicians should be aware that many patients may not respond.

CRPS may be due to nerve damage

This concept states that persistent dysfunction of small-diameter primary afferent nociceptor axons distal to the trauma is causal to CRPS. Similarity of CRPS to

small-fibre-predominant polyneuropathies (which can be associated with mild distal limb oedema, vasodysregulation and disordered sweating [69]), first stimulated the idea that regionally restricted small nerve fibre damage may also occur in CRPS, and that it, rather than sympathetic dysfunction, may be responsible for CRPS signs [70]. Studies in CRPS-amputated limbs and skin biopsies later indeed showed small-fibre loss [71–73]. Thus, it is postulated that CRPS-I may represent a neuropathic pain syndrome. Neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system [74], and CRPS is then considered a small-fibre-predominant mono- or oligoneuropathy, initiated by limb trauma or its treatment [70]. This concept, which shares some arguments with that of neurogenic inflammation (see next section) demands that CRPS signs, symptoms and associated tissue inflammation are caused by the consequences of end-organ (including sweat glands and small vessels) partial denervation, by malfunctioning of neighbouring survivors to the dead small fibres (irritable nociceptors) and by resulting central changes [70]. The cause of the first step in the proposed cascade of events, the post-traumatic death of small fibres in some patients, is currently unknown. It is also not yet clear why pain is almost universal in CRPS, while it is only variably present in established small-fibre neuropathies. Of the recommended first- or second-line treatments for neuropathic pain [75], only gabapentin at a submaximal dose of 1800 mg/day has yet been assessed in CRPS, with negative result [76].

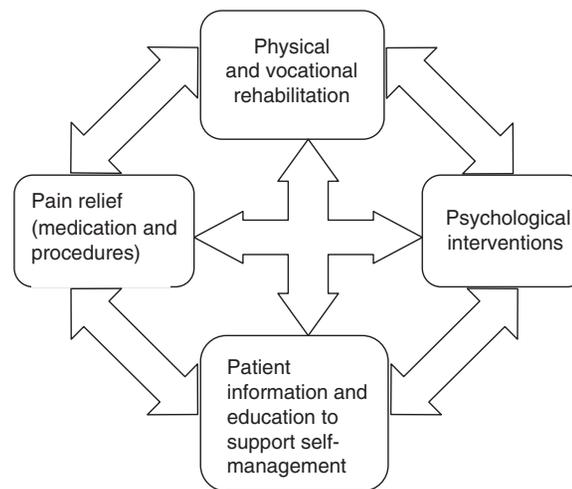
Neurogenic inflammation can explain clinical CRPS signs

Neuropeptides, anti-dromically released from sensory neurons, cause skin reddening and swelling, thus producing signs as are seen in CRPS. Frank Birklein's team [77] has described an abnormality of neuropeptide handling in CRPS, and termed this 'facilitated neurogenic inflammation'. When c-fibres in affected, and to a lesser degree also unaffected [78], limbs are experimentally activated, CRPS patients respond with much stronger (neuropeptide-mediated) skin reddening and swelling than control patients. The cause of the facilitation is unclear. The importance of neuropeptides for CRPS pathophysiology is further underlined by the recent finding that CRPS is associated with ACE-inhibitor therapy [18]. ACE metabolizes the neuropeptides substance P and bradykinin to inactive forms, thus ACE inhibitors may lead to higher tissue levels of both neuropeptides. Up until now, these findings have not yet translated into clinical treatments.

Alternative concepts on CRPS pathophysiology

Several groups have investigated whether genetic associations can provide novel clues to CRPS pathophysiology. Most of these studies have examined HLA associations, but to date no robust finding has been reported [79].

Fig. 5 The four pillars of treatment in CRPS. Information/education, physical rehabilitation, psychological intervention and drug/procedural interventions have equal importance for the treatment of CRPS. Emphasis is on an individualized, integrated interdisciplinary approach.



Genome-wide association studies have not yet been accomplished.

Some authors have placed CRPS broadly into the context of somatoform disorders or malingering. A few authors have also taken the fact that CRPS 1 (Fig. 2) is not associated with any major structural lesion, as evidence that this problem should be, at least in part, of psychological origin [80]. Recent more systematic investigations were not corroborative [17, 81]. There is preliminary evidence, however, that major life events may be more common in patients before development of the condition [81]. Independently, some people self-induce injuries to resemble CRPS [82].

Although this has not been systematically assessed, in my experience some patients report feeling stigmatized by health professionals who did not believe that their condition is real. In common with other chronic pain, CRPS should best be seen as a biopsychosocial condition [83], which requires multidisciplinary treatment [84]. Randomized controlled trials of cognitive behavioural therapy in CRPS are still missing; behavioural graded-exposure therapy showed promise in a subgroup of patients with high fear of movement, in a small trial with a non-RCT experimental design [85]. Based on results in chronic pain conditions in general, the UK guideline group will recommend cognitive behavioural therapy as one of the four pillars of treatment (Fig. 5).

Recommendations for the treatment of CRPS

- (i) Patients should be educated about CRPS and be given simple information on self-management such as advice to direct attention to the limb and to stroke and use it frequently and gently.

- (ii) Most patients require specialized physiotherapy/occupational therapy delivered by physiotherapists or occupational therapists experienced in the treatment of patients with chronic pain (Fig. 5). Both physiotherapy and occupational therapy have been shown to be more effective in reducing pain and improving function in patients with <1 year disease duration than social work [86], but treatment should also be offered to patients with long-standing CRPS. Important methods include desensitization (rubbing the affected limb gently with cloth), gradual weight bearing, stretching and functional and fine motor exercises. The mechanism through which the pain reduction is achieved is unknown. Since the required expertise to deliver these treatments is not universally available, the development of a network approach appears useful, where stakeholders in a region know to locate the regional expert centre(s). It is possible that overall increased awareness of the need for early and continuous treatment has already reduced the number of patients who unnecessarily develop certain complications; severe muscle atrophy, contracture and joint ankylosis have frequently been reported in the past, but seem to be a less common problem now; however, more research is needed to better understand the relationship between early physiotherapy/occupational therapy treatment and prevention of these complications.
- (iii) Multidisciplinary pain management treatment guided by principles of cognitive behavioural therapy should be considered early for those patients who do not improve, and who show signs of distress. Here, again stakeholders should know of the nearest centre that offers such a service.
- (iv) A number of novel drug or interventional treatments that may provide pain relief have been described; however, confirmatory trials are still required for most before recommendations can be given. It is reasonable to initially treat patients with drugs developed for neuropathic pain [75], although there is no CRPS-specific evidence for any of these treatments (1800 mg gabapentin/day is not effective [76]). In addition, bisphosphonate treatment should be considered for those with <6 months duration. In some countries, low-dose ketamine outpatient treatment is now common practice. Efficacy of this treatment has been reported in two positive RCTs [47, 48]; long-term and pharmacoeconomical data are currently not available. SCS is the application of an electrical current to the spinal cord dorsal column through a catheter inserted into the epidural space. The electronic equipment and battery are implanted under a muscle and device activity can be controlled with an external magnet. Its working principles are unclear. The (only) large RCT found a response rate of 50% for >50% pain relief in patients with >6 months, disease duration [13]. Limb function did not improve. In the UK, SCS treatment is the only NICE-approved method to treat CRPS.

With time, the SCS effect does slowly diminish, so that in the RCT the SCS results did not exceed those in the physical therapy control group from 3 years after implantation [87]. The authors of the seminal RCT conclude that, although patient satisfaction was generally high, the unknown working mechanisms of the (SCS) treatment apparently do not function indefinitely [88]. Spinal cord stimulator treatment may be appropriate where other treatments do not provide benefit. Unfortunately, even with the best current treatment approaches some patients may not experience sufficient pain relief.

- (v) Perioperative care: the risk of surgery causing a severe new CRPS episode in someone who had CRPS in the past is probably neither high, nor zero [89]. It seems common sense to defer operating in an early case of CRPS until acute symptoms have subsided, if at all possible, to reduce the risk of aggravating the condition, though even for such recommendation no RCT-derived evidence exists. There is no evidence for the superiority of any anaesthetic technique to prevent re-igniting or aggravating CRPS.
- (vi) Long-term care: not a single publication to date has described how we should care for those who have trialed available physical, behavioural and pain relief treatments, but who still have ongoing pain and a reduced quality of life. Any long-term approach should be patient centred and include facilitated ways for the patient to request top-up support (e.g. by way of accelerated occasional on-demand consultation with a named specialist physiotherapist, psychologist or doctor), attendance of self-support groups under the umbrella of, or with some link to, the medical treatment centre, and access to information about available support for developing adapted work, leisure and social activities. In a recent series of CRPS focus group discussion at our centre, patients named the education of health-care professionals, particularly their general practitioners, about CRPS a top priority (Poole *et al.*, 2011, data not published).

Initiatives to enhance the care of patients with CRPS

As with many other conditions, there is a problem with the timely diagnosis of CRPS. Jenny Lewis [16] found in her cohort at the UK Royal National Hospital for Rheumatic Diseases in Bath, UK, that while ~50% of patients were diagnosed relatively early, the others had a median onset to diagnosis time of 2 years. Late diagnosis may lead in some patients to unnecessary suffering from not understanding what is wrong, high-pain intensity, poor limb function and, in some cases, inappropriate treatment. Possible ways to ensure earlier diagnosis are currently being tested in the UK and include the training of community-allied health professionals in diagnosing

CRPS (Fig. 3), and the introduction of diagnostic reminders into GP's electronic database systems. There are currently two published national guidelines [90, 91], UK guidance will be published later this year.

Gaps in current knowledge, and future research

Although a lot has been achieved over the past 10 years, we still cannot answer even simple questions about CRPS response to medication with opioids, gabapentoids and antidepressants. When compared with more common rheumatological and neurological disorders, our knowledge about the aetiology and the treatment of CRPS is limited, yet at the same time this disorder so profoundly impacts on patients' quality of life that further research is urgently needed. It is difficult to predict advances around the corner; in my field of interest, autoimmunity in CRPS, it should be possible to develop serum tests that would allow us to predict those at high risk from elective operations, after trauma, or who may respond to certain treatments. Promising new treatment approaches with tadalafil in cold CRPS, NMDA antagonists, immunoglobulins and brain-training methods require both refinement and confirmation in long-term trials. Each method may only benefit a fraction of patients, and ways to predict a beneficial response are required. Finally, several routes of non-RCT evidence suggest that early intervention with physiotherapeutic methods and simple medications can reduce the incidence or duration of CRPS; therefore, RCTs in this area are also needed. Preventative interventions may provide a realistic cost-benefit ratio, even more so in developing countries, where having CRPS may be an even more devastating experience.

Summary

We have learned much about CRPS in the past 10 years, and we have been given a glimpse into some treatments that for the first time, promise effective pain reduction for those with long-standing disease. The quality of clinical trials has much improved and the quantity of research into this condition has skyrocketed. While we still do not know what causes CRPS, one has the sense that efforts to tackle this fascinating, debilitating condition are exemplary for the progress of the new field of Pain Medicine to come into its own.

Rheumatology key messages

- CRPS can now be diagnosed with high sensitivity and specificity using the Budapest criteria.
- A multidisciplinary treatment approach is essential for successful rehabilitation.

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