Diagnosis, mechanisms and treatment of complex regional pain syndrome

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Purpose of review
The incidence and disease course of complex regional pain syndrome (CRPS) has been unclear until recently. This was due to inconsistent diagnostic criteria used in previous studies and a lack of large-scale prospective datasets. Multiple mechanisms of CRPS have been suggested, and recent research has begun to explain how inflammation, the immune system and the autonomic nervous system may interact with aberrant central neuroplasticity to produce the clinical picture. This review summarizes progress in these fields.

Recent findings
National registries of patients with CRPS have provided us with an invaluable insight into the epidemiology of the disorder. We now have a better understanding of the disease course and expected outcome. Widespread sensory abnormalities, not limited to the CRPS limb, have been found suggesting that systemic changes may occur. Parietal lobe dysfunction and problems with sensory-motor integration have also been revealed. Abnormalities in the immune system in CRPS have also been demonstrated.

Summary
Recent findings in diverse research fields suggest novel treatment options for CRPS: from targeting autoimmunity to correcting abnormal body image. Many of the advances in our understanding of CRPS have arisen from the development of collaborative research efforts, such as the TREND group in the Netherlands.

Keywords
autoimmunity, autonomic nervous system, complex regional pain syndrome, inflammation

INTRODUCTION

Complex regional pain syndrome (CRPS) is a peripherally limited pain syndrome. It is characterized by intense pain, inflammation, altered autonomic function, abnormal motor function and trophic changes. Although most individuals recover rapidly from mild to moderate injury to the distal limbs, a small proportion will develop CRPS, and in some it may occur spontaneously [1]. The disorder was first described by Mitchell [2] following battlefield injuries. Numerous terms have been used to describe the condition, from causalgia to reflex sympathetic dystrophy and algodystrophy. Currently, CRPS is the accepted terminology, and is divided into two subtypes: CRPS type I occurs without nerve injury and CRPS II in which significant nerve injury can be demonstrated. Although the majority of individuals recover within 12 months, CRPS may result in severe long-term pain, and sufferers report a very low quality of life [3,4]. As there is no gold-standard test for CRPS, clinical diagnostic criteria have been developed. The most often accepted diagnostic criteria are based on the Bruehl and Harden 1999 criteria, modified at a consensus meeting in 2003 and subsequently validated and termed the Budapest Criteria in 2010 [5]. The Budapest clinical criteria are as follows:

(1) continuing pain disproportionate to any inciting event;
(2) must report at least one symptom in three of the four following categories:
  (a) sensory: hyperalgesia and/or allodynia,
  (b) vasomotor: temperature asymmetry and/or skin colour changes and/or skin colour asymmetry,

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> (c) sudomotor or oedema: oedema and/or sweating asymmetry,
> (d) motor or trophic: decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (nail, hair, skin);

(3) must display at least one sign at time of evaluation in two or more of the following categories:
> (a) sensory: hyperalgesia (to pin-prick) and/or allodynia (to light touch, deep somatic pressure, joint movement),
> (b) vasomotor: temperature asymmetry and/or skin colour changes and/or skin colour asymmetry,
> (c) sudomotor or oedema: oedema and/or sweating changes and/or sweating asymmetry,
> (d) motor or trophic: decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (nail, hair, skin);

(4) there is no other diagnosis that better explains the signs and symptoms.

CLINICAL FINDINGS AND DIAGNOSIS

In the acute phase of CRPS (<6 months), there are marked inflammatory changes; the limb is painful, discoloured, often sweaty, hot, swollen and held immobile, reflecting both autonomic dysfunction, and inflammation or neurogenic inflammation. Bone metabolism is abnormal leading to patchy osteoporosis in up to 50%. The diagnostic utility of X-rays or bone-scanning for CRPS appears limited [6].

Utilizing a criterion-based diagnostic model has led to difficulties in defining CRPS for clinical and research purposes [7■]. Features suggestive of CRPS may be present following recent trauma, even if the inflammatory response to injury is entirely normal.

An additional problem is defining recovery from CRPS, as some symptoms commonly resolve with time, but the individual cannot be said to have recovered their quality of life. The term CRPS not otherwise specified has been suggested for patients in this group. Differential diagnoses for CRPS are listed as follows:

(1) common conditions:
> (a) arterial insufficiency,
> (b) arthritis or arthrosis,
> (c) bony or soft tissue injury,
> (d) compartment syndrome,
> (e) complications of orthopaedic surgery,
> (f) infection (bony, soft tissue, joint),
> (g) lymphatic or venous obstruction,
> (h) Raynaud's disease;
(2) rare conditions:
> (a) erythromelalgia (may include all limbs),
> (b) Gardner–Diamond syndrome,
> (c) self harm,
> (d) thoracic outlet syndrome.

Sensory findings

Altered skin sensitivity to noxious and innocuous stimulation is commonly found in a CRPS limb. Both hyperalgesia (an increased response to a painful stimulus) and allodynia (a painful response to an innocuous stimulus) occur. Using quantitative sensory testing, both sensory gain and sensory loss have been demonstrated in CRPS I and II, with sensory loss more common in the latter [8,9■■]. Interestingly, recent studies have demonstrated bilateral sensory abnormalities in patients with unilateral CRPS, including increased pain response to capsaicin and widespread muscle sensitivity [10,11]. This suggests a generalized disturbance of pain processing, which may reflect a process of central sensitization within the spinal cord and brain.

Motor function findings

Weakness and a limited range of movement develop in 80% of cases. There are also impairments in voluntary control, sense of force production and proprioception. Dystonia occurs in 25–30% and there is emerging evidence that this may have a genetic basis in some cases [12].

EPIDEMIOLOGY

The absence of a gold-standard diagnostic test has resulted in slow progress in researching the epidemiology of the disorder. However, retrospective cohort studies, longitudinal observational studies, and

recently national registries of patients with CRPS, such as the Dutch TREND (trauma related neuronal dysfunction) consortium, have rapidly increased our knowledge base (http://www.trend-consortium.nl).

The incidence of CRPS varies with diagnostic criteria and has been quoted as 18.1–26.2 per 100 000 person years in Europe. The first large-scale retrospective cohort study was based on primary care data in the Netherlands and revealed that the disorder occurs most commonly in women (sex ratio 3–4 : 1), between 50 and 70 years of age. Most cases involve trauma (45% fracture, 18% ligamentous injury and 12% surgery) [13].

Risk factors for onset and persistence of complex regional pain syndrome

The frequency of CRPS following fracture is approximately 7%. CRPS occurred more frequently after intra-articular fractures and was more common in patients with rheumatoid arthritis or other musculoskeletal conditions, such as chronic back pain [14■■]. Additionally, a pain score of 5 or above on a 0–10 verbal rating scale in the first week following wrist fracture was predictive of the development of CRPS at 4 months [15■■]. Immobility may be an independent risk factor. In fact, immobilizing the limbs of healthy volunteers produces sensory abnormalities similar to CRPS (although not pain) [16]. The small proportion of spontaneous cases of CRPS (< 10%) occur mostly in women at a younger age and more commonly follow a chronic course (12 : 1 F : M) [1]. CRPS tends to run a more chronic course in younger adults. Further risk factors include asthma, migraine, osteoporosis and the use of angiotensin-converting enzyme (ACE) inhibitor drugs (but not other antihypertensives) [13,17]. ACE inhibitors prevent the breakdown of the peptide neurotransmitters – potentially leading to increased inflammation. The co-occurrence of migraine and asthma with CRPS may reflect a common neuroinflammatory mechanism of these disorders.

It is likely that genetic factors play a role in the development of CRPS, as there is an increased incidence in siblings with an odds ratio varying between 1.5 and 9.8 [18,19]. CRPS is also associated with specific human leukocyte antigen (HLA) system haplotypes. HLA-DQ8 was associated with CRPS in general, whereas HLA-B62 was associated with CRPS with dystonia [20]. This suggests that the dystonia associated with CRPS in 25–30% of cases may have a separate mechanism to CRPS without dystonia.

Psychological factors play a role in determining the impact of any chronic painful condition on patients' functioning and quality of life. However, there is currently little evidence for the involvement of psychological factors in the onset of CRPS other than perhaps the number of life events, and no clear evidence for such factors playing a role in the maintenance of the disorder [21,22].

MECHANISMS

Explanatory models of CRPS must account for abnormal inflammation, nociceptive sensitization, autonomic dysfunction and maladaptive neuroplasticity. It has been debated as to whether CRPS I can be defined as a neuropathic pain syndrome, on the basis of the most recent diagnostic criteria for neuropathic pain [23,24]. Symptoms and signs suggestive of neuropathic pain are present in CRPS I [25]. Some studies have demonstrated a mild loss of small nerve fibres, providing support for a neuropathic mechanism [26,27].

Inflammation

There is evidence for abnormal immune activation in CRPS [28], but most proinflammatory cytokine markers found in blood and blister fluid return to normal levels after 6 months [29].

Nociceptors release peptide neurotransmitters including substance P and calcitonin gene-related peptide (CGRP), which may activate immune cells in peripheral tissues. Levels of substance P and its receptor neurokinin-1 are elevated following fracture in a rat model of CRPS, and mast cell degranulation may consequently be triggered via a substance P pathway [30]. Numerous substances are released from mast cells, including tryptase, histamine and cytokines. Binding of histamine, substance P and CGRP to receptors on small blood vessels results in oedema, vasodilation and pain – characteristic of both early CRPS and neurogenic inflammation.

In early CRPS, keratinocyte proliferation occurs, resulting in epidermal thickening. Increased numbers of mast cells were found in the skin and there was upregulation of interleukin-6 and tumor necrosis factors. Later, keratinocytes were reduced, leading to epidermal thinning [31]. This suggests that early CRPS involves activation of the cutaneous immune system, resulting in increased production of inflammatory mediators. Interestingly, similar changes in inflammatory mediators were found in the skin biopsied from the operated arm of patients who did not develop CRPS following hand surgery. This suggests that such inflammatory changes do not exclusively occur in CRPS and may be part of a normal response to injury [32].

Oxidative stress is also a potential contributor to the abnormal inflammatory state seen in CRPS. As part of the chronic inflammatory process, activated

immune cells produce reactive oxygen species (ROS), which may cause oxidative damage to cells. In the healthy individual, ROS are inactivated by anti-oxidant pathways. However, it has been suggested that excessive production of ROS in CRPS results in an imbalance in the redox pathway, affecting cell function and resulting in pain, ongoing inflammation and cell damage [33].

Finally, macrovascular changes suggestive of ongoing inflammation have been found in patients with chronic CRPS [34].

Autoimmunity

It has recently been suggested that autoantibodies may play a role in CRPS. Autoantibodies found in the plasma of patients with CRPS are active at the muscarinic cholinergic receptor and the β_2 adrenoceptor [35]. An autoimmune mechanism for CRPS is also suggested by the finding that transfer of serum IgG from patients to mice elicits signs similar to CRPS in the recipient animals [36■■].

Autonomic dysregulation

Autonomic dysregulation is a key clinical feature of CRPS. The sympathetic outflow to skin vasoconstrictors is inhibited, resulting in the warm, swollen limb seen in the acute phase. The cold limbs seen in chronic CRPS may reflect increased sympathetic nervous system (SNS) receptor sensitivity rather than an increase in sympathetic outflow [37]. In addition to marked peripheral abnormalities in autonomic function, there are also mild abnormalities in systemic autonomic function in CRPS; haemodynamic instability increased with CRPS duration but not pain severity [38].

Animal studies support a role for the SNS in CRPS. In a rat tibial fracture model, noradrenaline released from sympathetic nerve terminals triggers the production of inflammatory mediators (interleukin-6) by epidermal keratinocytes, via noradrenaline binding to β_2-adrenoreceptors [39]. Independently, α_1-adrenoreceptors are upregulated in the skin of CRPS II-affected limbs in humans, potentially increasing the effects of sympathetic activation [40].

Interestingly, some autonomic features of CRPS (skin temperature) seem to be under marked cortical control as they change with the perceived position of the limb related to the body, rather than its actual position or anatomical location [41].

Maladaptive neuroplasticity

Maladaptive neuroplastic changes occur throughout the neuraxis in CRPS, resulting in sensory and motor abnormalities. Imbalanced reflex sensitivity in agonist and antagonist muscles has been implicated in generating the flexion deformities seen in CRPS with dystonia [42]. Abnormal processing of proprioceptive information results in impairment in arm position sense [43]. Perceptual changes in body shape and position also involve sensory cortex processing abnormalities, but meta-analysis of available studies has revealed limited consistent findings. The spatial representation of the CRPS limb in the primary somatosensory cortex is reduced [44■]. There is limited evidence for bilateral disinhibition within the motor cortex, but no change in spatial representation, reactivity or glucose metabolism [45]. [The first sentence refers to the somatosensory cortex (reduced representation), and the second to the motor cortex (no reduction in representation area)].

There may also be altered functional connectivity between brain regions in CRPS. In the resting state patients with CRPS had decreased functional connectivity within sensory and motor regions of the cortex and greater diffuse connectivity with other brain regions [46].

These functional abnormalities are mirrored by structural changes in grey matter volumes of several brain areas. MRI scanning of the brains of patients with right upper limb CRPS revealed altered morphology within not only sensory and affective regions, but also motor and autonomic centres [47].

PREVENTION AND TREATMENT

Longstanding CRPS is difficult to manage, and therefore prevention of progression to chronic disease is a priority. Acute CRPS presents relatively commonly to the anesthetist, potentially providing an opportunity to influence disease progression within his or her practice [4]. Originally, CRPS was thought to pass through predictable clinical stages, but this has not been substantiated by cluster analysis studies [48■]. Nonetheless, the management of CRPS may be usefully divided into prevention, early CRPS (< 6 months) and established CRPS.

Recently, a Cochrane review [49] of interventional treatment for CRPS reached limited conclusions based on a lack of good quality evidence. Practical guidelines based partly on expert opinion have been produced in the UK, USA and the Netherlands [48■,50,51].

Prevention

No specific technique has been shown to prevent CRPS following surgery, but avoidance of prolonged immobilization may be important [32]; the latter

constitutes a key argument for initiating early physiotherapy after operations, where possible. There is limited evidence for vitamin C reducing the incidence of CRPS following lower limb injury and wrist fracture [52,53]. However there is no evidence that vitamin C is useful for the treatment of CRPS.

Early complex regional pain syndrome

The key to management of early CRPS is the return of normal limb function, which may be facilitated by adequate analgesia. Physiotherapy or occupational therapy should be instituted and immobilization avoided. Although multidisciplinary management is usually considered in the context of long-term CRPS, it is nevertheless important to consider aspects of this approach (such as patient education) early in the disease process.

Analgesia should be provided following the WHO analgesic ladder. Given the large number of proposed mechanisms for CRPS, it is not surprising that numerous pharmacological treatments have been proposed. Pain with neuropathic characteristics is treated following guidelines developed for neuropathic pain such as the National Institute for Health and Care Excellence guidelines (guidance. nice.org.uk/cg173). However, there is no strong evidence to support the use of one antineuropathic drug over another. First-line medications for neuropathic pain (and by extension CRPS) include tricyclic antidepressants, such as amitriptyline, nortriptyline or imipramine. Gabapentin and pregabalin are also listed as first line. However, there have been negative trials of gabapentin in CRPS. Selective serotonin and norepinephrine reuptake inhibitors, such as duloxetine and venlafaxine, are also included in this group [54].

Early CRPS often involves marked inflammation. Corticosteroids, given orally as a short tapering course, could be considered in early CRPS, in which inflammation is prominent, but may be associated with significant side-effects [55]. The use of cyclooxygenase inhibitors has also been studied, with generally negative or weakly positive outcomes [56]. Bisphosphonates, acting to inhibit osteoclastic bone resorption, have shown some promise [57].

Guidelines for the interventional management of neuropathic pain have been produced [58]. SNS blockade with local anesthetic has short-term analgesic effects in CRPS. Intravenous regional anesthesia (IVRA) with guanethidine is no longer recommended and recent reviews emphasize the risk of significant adverse effects [49]. Most controlled trials are confounded in that the control arm usually involves IVRA with lidocaine or the application of a tourniquet. It is, therefore, possible that positive effects of IVRA found in these studies may be due to lidocaine or tourniquet pressure.

Established complex regional pain syndrome

Approximately 15% of patients will continue to suffer from significant symptoms beyond 12 months. Multidisciplinary management, addressing the four pillars of treatment, includes patient education, pain relief, physical rehabilitation and psychological intervention [59].

Education

Education plays an important role in developing concordance between the patient and therapists [60].

Pain relief

Putative neuroplastic changes in CRPS have led to the use of ketamine as a potential treatment at both high and low doses. In two trials, low dose ketamine infusion over several days resulted in improvements in pain but not function. In one study ($n = 19$), ketamine was infused at 0.35 mg/kg/hr with clonidine for 4 h daily for 10 days. Pain scores averaged over 2 weeks reduced from $7.51 +/- 0.4$ to $6.01 +/- 0.6$ ($P < 0.01$) after treatment in the active group. No such change in scores was seen in the placebo group, who received clonidine and a saline infusion [61,62].

Spinal cord stimulation, a neuromodulation technique, has a moderate quality evidence base. Long-term reduction in pain has been demonstrated in CRPS I, but the effect reduces with time, disease progression is unaffected and reoperation rates for complications are high [49].

In general, evidence for pharmacological and interventional treatment in chronic CRPS is weak, and nonpharmacological options predominate.

Physical rehabilitation

General physiotherapy or occupational therapy with gradual desensitization of hyperalgesic skin encourages normalization of function [63]. Physical therapies and psychological therapies often overlap in CRPS treatment, as aberrant neuroplasticity may respond to both approaches.

Psychological intervention

Specific treatments for CRPS, including mirror visual feedback and graded motor imagery, may

be offered in more specialist settings [64,65,66■]. It may also be helpful to assess and treat disturbed body perception [67]. These treatments may be combined and tailored to the individual in specialist CRPS pain management programmes [68–70].

CONCLUSION

Our knowledge of the epidemiology and mechanisms of CRPS has advanced significantly in recent years. National registries and well designed studies show promise for assessing the effects of potential new treatments for CRPS. Prospective studies may point to strategies, which may be delivered by anesthetists to prevent the progression of CRPS to a chronic disease. In the absence of a strong evidence base, recent guidelines for the management of CRPS in various settings provide a valuable resource for clinicians involved in managing this multifaceted condition. As a multidisciplinary approach would seem to be optimal, the effects of combining pharmacological or interventional treatment with CRPS-specific pain management programmes should be one target for future research.

Conflicts of interest

There are no conflicts of interest.

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