Complex regional pain syndrome (CRPS) is a clinical disorder that is characterized by severe, continuous pain in the affected extremity, which is accompanied by sensory, vasomotor, sudomotor, and trophic changes. The pain is regionally restricted (i.e. cannot be related to a specific dermatome) and disproportionate to the inciting event.

CRPS is usually precipitated by trauma (mostly fractures) or surgery. The upper extremity is affected more often than the lower extremity. CRPS is usually limited to one extremity, though cases of CRPS simultaneously affecting multiple extremities have been described.

The incidence of CRPS has been reported to range from 5.5 to 26.2 per 100,000 person-years. Women are more frequently affected than men, with studies reporting a three- to four-fold higher incidence in women. The highest incidence was found in women aged 61–70 yr.

Two distinctive forms of CRPS are currently described in the literature: CRPS type I where there is no demonstrable nerve lesion and CRPS type II where there is demonstrable nerve lesion. CRPS types I and II do not differ in clinical presentation and the choice of treatment. Consequently, CRPS will be used as a general term in this article referring to both CRPS type I and CRPS type II.

CRPS can have a severe impact on the quality of life of patients and can lead to substantial physical and social disability. It is therefore important for clinicians to recognize and diagnose this disorder in order to provide appropriate care and guidance to patients suffering from this debilitating disease.
The purpose of this educational article is to provide clinicians with concise information regarding the pathophysiology, diagnosis, and treatment of CRPS.

Clinical presentation

Patients generally present themselves with severe, continuous pain that typically takes on a glove- or stocking-like distribution. Injuries or surgery usually precede the symptoms. The pain is often accompanied by sensory, vasomotor, sudomotor/oedema, and motor/trophic symptoms. These signs and symptoms can vary during the course of the disease.

Patients may report (hyper)sensitivity to painful and non-painful stimuli (hyperaesthesia and/or allodynia). Differences in skin temperature between the affected and contralateral limb may be reported.

Sweating patterns between the affected and contralateral limb may be altered. Swelling of the affected limb can be reported. Symptoms of motor dysfunction, such as loss of range of motion, tremor, and dystonia, can be described. Patients may also report changes in hair and nail growth of the affected limb. Patients may further report increase of symptoms after exercise.

Findings during physical examination include, but are not limited to, allodynia and/or hyperalgesia, differences in colour and skin temperature between the affected and contralateral limb, and oedema of the affected limb. Functional tests may reveal a reduction in the range of motion of the affected limb in comparison with the contralateral limb. Tremor, dystonia, and altered nail and hair growth of the affected limb can also be observed.

CRPS patients are often described as having warm, intermediate, or cold CRPS based on reported and measured skin temperature differences between the affected and contralateral limb.

Current research suggests the existence of different phenotypes of CRPS based on the signs and symptoms deemed most prominent during history taking and physical examination. These signs and symptoms could reflect the underlying pathophysiological mechanism (i.e. inflammation, pain/sensory disturbances, vasomotor disturbances, motor disturbances, and psychological disturbances). When assessing signs and symptoms of CRPS patients, it is important for physicians to recognize which pathophysiological mechanism is most prominent. By determining the most prominent mechanism, physicians can use specific therapies to target these mechanisms.

It is our hypothesis that in the majority of patients, especially patients with warm (acute) CRPS, inflammation is the most prominent mechanism. All the other mechanisms are a result of the ongoing inflammation. During the course of the disease, inflammation disappears in some of the patients, resulting in different forms of rest damage.

Diagnosis

There is currently no gold standard for the diagnosis and treatment of CRPS. History and physical examination are the cornerstones for appropriate diagnosis and management. Various criteria exist for the diagnosis of CRPS. Currently, the most commonly used criteria for the diagnosis of CRPS are the new International Association for the Study of Pain (IASP) clinical diagnostic criteria (Table 1). These criteria are based on observed and patient-reported signs and symptoms.

CRPS has an extensive differential diagnosis, which can be summarized into the following categories: neuropathic pain syndromes, myofascial pain syndromes, inflammation, vascular diseases, and psychological disorders (Table 2). Most of these disorders have similar presentations, occasionally making the diagnosis of CRPS a challenge.

As the pathophysiology of CRPS is still not completely understood, there is limited use for additional clinical and laboratory tests in the diagnosis of CRPS. Diagnostic tests can, however, be used to exclude other disorders that could explain the observed signs and symptoms or to monitor the signs and symptoms of CRPS. An example of the latter is quantitative sensory testing, which is mostly used in research settings to quantify sensory disturbances found during physical examination.

Pathophysiology of CRPS

The exact pathophysiology of CRPS is still unknown. Both peripheral and central mechanisms are thought to play a role in the initiation and maintenance of CRPS.

Inflammation in CRPS

Various studies point towards CRPS being an exaggerated inflammatory response as a result of trauma or surgery. This inflammatory response has long been a topic of debate, as general markers of inflammation, such as C-reactive protein, white blood cell count, interleukin 6 (IL-6), and erythrocyte sedimentation rate, are usually not elevated in plasma of CRPS patients. However, when considering the symptoms of (acute) CRPS, ‘classic signs of inflammation’, such as pain, redness, increase in temperature, swelling, and loss of function, are often displayed.

Recent studies focusing on inflammatory processes in CRPS have found higher levels of pro-inflammatory cytokines in blister fluid [IL-6, tumor necrosis factor alpha (TNF-α)] of the affected extremity compared with the unaffected extremity. This suggests a role for local inflammatory processes in CRPS. Elevated levels of pro-inflammatory cytokines have further been found in serum, plasma, and cerebrospinal fluid of patients with CRPS.

Pro-inflammatory cytokines have been suggested to be involved in peripheral nociceptor activation and sensitization, which in turn could cause symptoms such as pain and hyperalgesia that are experienced in CRPS.

Neurogenic inflammation in CRPS

Apart from the ‘classic’ form of inflammation, studies have proposed neurogenic inflammation as an underlying mechanism for symptoms such as oedema, vasodilatation, and increased sweating that are observed in CRPS. Studies have found increased levels of calcitonin-gene-related peptide (CGRP) and substance P (SP) in serum of patients with CRPS versus healthy controls. These neuropeptides have been shown to lead to neurogenic dilatation of arterioles (CGRP) and plasma protein extravasation (SP). This in turn could explain the redness and swelling that are observed in CRPS.

CRPS as an autoimmune disease

CRPS has previously been described as an autoantibody-mediated autoimmune disease. Passive transfer of CRPS patient serum–immunoglobin G has been shown to induce behavioural changes in mice, and serum from CRPS patients has been shown...
to stain rodent sympathetic ganglia. 20,22 Furthermore, a small group of CRPS patients experienced pain relief after treatment with low-dose intravenous immunoglobulin. 21 A study conducted by Dirckx et al. 23 showed a significantly higher proportion of CRPS patients with positive anti-nuclear antibody test results as compared to a population of healthy blood bank donors. There are thus many findings supporting this theory of autoimmunity. 20,23

However, to define a disease as an autoimmune disorder certain criteria (Witebsky’s criteria) must be met. 24 These criteria have not yet been fulfilled in the case of CRPS which gives rise to the question whether CRPS is more an auto-inflammatory than an autoimmune disease. 23

Deep-tissue microvascular ischaemia–reperfusion injury in CRPS

Another hypothesis on the pathophysiology of CRPS is that of deep-tissue microvascular ischaemia–reperfusion injury. 25 This hypothesis, which was tested in a chronic post-ischaemia pain animal model, proposes a state of deep-tissue ischaemia and inflammation caused by a microvascular ischaemia–reperfusion injury as the cause for abnormal pain sensations, such as allodynia, in CRPS. 25,26

Genetics and CRPS

Genetics seems to play a role in the predisposition to CRPS. A Dutch cohort study showed the frequency of human leucocyte antigen (HLA)-DQ1 to be significantly higher in CRPS patients than in the controls. 27 There is evidence that HLA-B62 and HLA-DQ8 are associated with CRPS with fixed dystonia. 28 Another study showed HLA-DR13 to be associated with multifocal or generalized tonic dystonia of CRPS. 29 These findings indicate that certain HLA loci may be involved in the susceptibility to certain phenotypes of CRPS. 28,29

Cortical reorganization in CRPS

Central processes, such as cortical reorganization and changes in pain processing, may also play a role in CRPS. 30–33 Cortical reorganization has been shown to take place in both the primary somatosensory cortex (S1) and the motor cortex. 30,32 Maihofner et al. 30 showed changes in S1 to be correlated with the intensity of pain and mechanical hyperalgesia in CRPS. In a later study, this group showed reversal of cortical reorganization in S1 to be correlated with pain reduction in CRPS. 31

Cortical reorganization could thus explain some sensory features in CRPS. An example is the distribution of pain and

Fig 1. Treatment algorithm for CRPS.
Peripheral (poly) neuropathy

Neuropathic pain syndromes

• Neuropathy has been proposed to be a small-fibre neuropathy because of its similarity to generalized small-fibre-predominant polyneuropathies.34 Studies have found a decrease in epidermal nerve fibres and a decrease in sweat gland and vascular innervation in patients with CRPS.35 This could explain not only the (neuropathic) pain experienced in CRPS but also the trophic and vasomotor dysfunctions that are observed.34 The latter could be caused by antidromic release of neuropeptides, such as CGRP and SP, by these small fibres in response to trauma and inflammation.36 It is still not completely understood whether this small-fibre loss is a result of CRPS rather than a cause of this disease.

Psychological factors in CRPS

Physicians often consider CRPS patients to be psychologically different from other groups of patients. This is mostly because of the complexity and the poorly understood pathophysiology of this disease.

However, most studies show no association between the onset of CRPS and psychological factors, such as depression, anxiety, paranoia, and hostility/anger.37–39 There is some evidence for the influence of stressful life events before the onset of the disease.40 Although these factors may not play a role in the onset of CRPS, the probability still remains that these factors play a role in the maintenance of this disease.39,41

Taking the above into account, CRPS seems to be a multifactorial disease with a multi-mechanism pathophysiology requiring a multimodal workup and treatment.

Treatment

Effective treatment options in CRPS are limited and consist of both non-invasive and invasive therapies.

Physical rehabilitation and physiotherapy have been shown to reduce pain and improve function in patients with CRPS. Physicians are therefore advised to start with active physical therapy in the treatment of CRPS.42 Medication can be started in addition to physiotherapy. The choice of medication should be based on the mechanism deemed most prominent in a specific CRPS case (Fig. 1).

Anti-inflammatory drugs

In the Netherlands, free-radical scavengers (dimethyl sulphoxide or acetylcysteine) are advised for inflammatory symptoms.42 However, these drugs have not gained general international acceptance.

Immunomodulating medication reduces the manifestation of inflammation by influencing mediators of inflammation, such as cytokines, neuropeptides, eicosanoids, and amino
Acids. Standard use of immunomodulating medication in CRPS is not common, although there is strong evidence for the use of bisphosphonates. For other immunomodulating medications, i.e. glucocorticoids, TNF-α antagonists, thalidomide, and immunoglobulin, evidence is often conflicting and not sufficient to advise standard use.

**Analgetics/co-analgetics**

Although there is insufficient evidence available on the treatment of nociceptive pain in CRPS, it seems wise to treat nociceptive pain according to the World Health Organization analgesic ladder, bar strong opioids.

The little evidence available on the treatment of neuropathic pain in CRPS supports the use of co-analgetics in the management of this disease. Gabapentin has been shown to lead to a reduction in pain symptoms in CRPS and can be used in the treatment of neuropathic pain.

If intractable pain persists, treatment with low-dose i.v. ketamine in long-standing CRPS can be considered. However, which dose and the length of treatment is still unclear. Liver function should be monitored frequently during treatment with i.v. ketamine. If liver enzymes increase, i.v. ketamine should be stopped immediately.

**Vasodilators**

If vasomotor disturbance, leading to ‘cold’ CRPS, is the most prominent mechanism, a short-term treatment with a calcium channel blocker, an alpha-sympathetic blocker, or phosphodiesterase-5 inhibitor can be considered. The medication should be stopped if no effect is achieved.

**Muscle relaxants/spasmolytics**

With regard to the use of muscle relaxants in CRPS, research has mainly been focused on the intrathecal use of these drugs. Intrathecal baclofen is likely to have a positive effect on dystonia in CRPS patients. However, given the side effects associated with intrathecal baclofen and the invasiveness of this treatment, it seems justified to try oral muscle relaxants first.

**Psychological intervention**

When there are indications for psychological problems, signs of chronic pain behavior, or inability to cope with the disease, referral to a multidisciplinary team including a psychologist should be considered.

**Invasive treatments**

Invasive treatments can be considered if the aforementioned therapies are insufficient, despite adequate treatment of the underlying pathophysiological mechanism.

‘Evidence-based Guidelines Development (EBGD) Guidelines on Complex Regional Pain Syndrome Type I’ (updated in 2014) give a negative recommendation on the use of sympathetic blocks, such as stellate ganglion blocks, thoracic sympathetic nerve blocks, and lumbar sympathetic nerve blocks, in the treatment of CRPS. Spinal cord stimulation (SCS) may be considered if patients do not respond to pharmacological treatments or rehabilitation therapies.

The effect of this treatment on (neuropathic) pain and health-related quality of life in CRPS has been demonstrated in a randomized controlled trial. SCS is currently the only therapy with a multi-mechanism mechanism of action in CRPS. It has been shown to have a positive effect on both the somatosensory system and the vasomotor disturbances.

**Prevention**

As treatment options for CRPS are limited, prevention of the disease would be the best medicine. Studies have shown supplementation with vitamin C (>500 mg day−1), initiated immediately after injury or surgery and continued for 45–50 days, helped to reduce the risk of developing CRPS.

**Prognosis**

The prognosis and outcome of CRPS is still difficult to predict. Resolution rates range between 74% in the 1st year to 36% after 6 years.

The social impact of CRPS is significant. Return-to-work rates vary, with one CRPS population study describing a permanent inability-to-work rate of 31% and a partial inability-to-work rate (i.e. work adaptations) of 28% in patients.

**Future perspectives**

The current treatment of CRPS is based on observed and reported signs and symptoms.

The present thinking is that these signs and symptoms reflect the underlying pathophysiological mechanism leading to the different CRPS phenotypes. Consequently, it can be derived that patients with a warm, oedematous extremity suffer from inflammation, while in patients with a cold, atrophic extremity, the role of inflammation diminishes and vasomotor disturbance becomes the predominant process.

However, it has recently been shown that (a subgroup of) cold CRPS patients can still suffer from inflammation. Therefore, the question arises whether the current diagnostic methods are sufficient. Perhaps the presence or absence of inflammation might be a better distinction for choosing the appropriate therapy.

It is now possible to determine whether there is an ongoing inflammation in CRPS-affected extremities by determining the levels of pro-inflammatory cytokines in fluid from artificially induced skin blisters. However, this a time-consuming procedure that limits its use to the field of research and is therefore not easily available for use in daily clinical practice.

It is likely that multiple mechanisms simultaneously can play a role in the pathophysiology of CRPS in an individual patient. As research continues to reveal more about the mechanisms involved in CRPS, future treatment will presumably shift from a symptomatic approach to a more mechanism-based treatment approach.

**Declaration of interest**

None declared.

**MCQs**

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to BJA Education.
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