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Complex Regional Pain Syndrome

Synonyms: reflex sympathetic dystrophy (RSD), causalgia. Earlier synonyms no longer used: algodystrophy, algoneurodystrophy, Sudeck's atrophy, shoulder-hand syndrome, reflex neurovascular dystrophy, fracture disease

Complex regional pain syndrome (CRPS) is a poorly understood painful condition. There is pain in a limb, usually associated with sensory, motor, autonomic, skin and bone abnormalities. The symptoms are severe and have a debilitating effect. Often there is a history of trauma but the effects are disproportionate to the severity of the injury. It usually only affects one limb but in 7% of people it spreads to affect other limbs.^[1]

Occasionally, it affects parts of the body other than the limbs.^[2] It may also arise in the absence of injury.

The exact pathophysiology is unclear but CRPS is not a psychological disorder. It appears to result from an individual's abnormal response to injury involving neural inflammation, vasomotor dysfunction and maladaptive neuroplasticity.^[3]

CRPS has in the past been divided into two disease entities of differing aetiologies:

- **CRPS I** - pain which develops in the absence of **identifiable** nerve injury (previously called reflex sympathetic dystrophy).
- **CRPS II** - pain in the presence of damage to a major nerve (previously called causalgia).

However, these types do not alter management, although they may still be important in medico-legal cases.^[1]

Epidemiology

Incidence

Incidence rates of 26 per 100,000 patient years are reported in Europe.^[1]

CRPS can affect any age but it is more common with increasing age up to age 70. It is 3-4 times more common in women, in whom it is also more likely to be of a severe type, than in men. In about 60% of the cases it is the arm that is affected, with the leg being affected in 40%. The most frequently reported triggering events are fractures (45%), sprain (18%) and elective surgery (12%). CRPS occurring spontaneously is uncommon (<10%).^[3]

In children CRPS typically peaks in early adolescence and is rare before the age of 6.^[4] It is much more likely to affect the lower limb in children and has an even greater female-to-male preponderance.^[5]

Risk factors^[3]

- Immobilisation of the affected limb: healthy volunteers will show signs of CRPS (although no pain) after four weeks of limb immobilisation.
- Use of angiotensin-converting enzyme (ACE) inhibitors at the time of trauma.
- History of migraine.
- History of asthma.
- Being the sibling of a young-onset case.

There is no evidence of psychological risk factors for developing CRPS. Although there is evidence that patients with CRPS are more depressed and anxious than control groups, it isn't clear whether CRPS patients are more depressed and anxious than patients with other causes of chronic pain. A retrospective review of children with CRPS has not found any increased incidence of anxiety or depressive symptoms compared with other children with chronic pain syndromes.^[5]

Presentation

The word 'complex' reflects the variety of symptoms and signs that these patients can present with, in addition to pain. Symptoms usually begin within one month following the inciting event or immobilisation. As the signs and symptoms vary widely, patients can present to various specialities:

- Orthopaedics - up to 25% of cases follow limb fractures and orthopaedic surgery. Patients may have been discharged but it may be necessary to re-refer to rule out organic pathology - eg, compression of nerves by scar tissue.
- Rheumatology, neurology and neurosurgery - having been referred to rule out other potential causes of pain.
- Dermatologists - precipitating factors can be skin conditions, such as herpes zoster, vasculitis and leg ulcers. CRPS may also present with skin changes (see 'Signs', below).

Delay in diagnosis is common; thus, a thorough history and examination are crucial from the initial consultation.^[1]

Symptoms

The symptoms of CRPS vary in severity and duration. The characteristic symptom is that of pain - typically burning in nature and out of proportion to the severity of any injury. The affected area, which is not confined to a specific nerve distribution or dermatome, may have other features such as:

- Sensitivity to touch.
- Allodynia - perception of pain from a non-painful stimulus.
- Hyperalgesia - painful stimuli provoke more pain than usual; mechanical and thermal hyperalgesia are especially common.
- Swelling.
- Abnormal vasomotor activity - spontaneous temperature changes, either warmer or cooler than the contralateral limb.
- Abnormal sudomotor activity - spontaneous sweating.
- Abnormal pilomotor activity - 'goosebumps'.

Signs

There are not always any objective findings in these patients. However, the following may occur:

- About 80% of cases have temperature differences between opposite sides. They may be warmer or cooler and this may be a fluctuating sign (sometimes occurring within a few minutes) depending on room temperature, local temperature of the skin and emotional state. Occasionally, it may occur spontaneously. This may be associated with a change in skin colour.
- Other skin changes include a shiny, dry or scaly appearance. Hair may be coarse initially, then become thin; nails become brittle and grow faster (initially), then slower; there may be associated rashes, ulcers or pustules which may become infected. Abnormal and spontaneous vasomotor, sudomotor and pilomotor activity also occur.
- Hard, pitting oedema may occur diffusely over the painful region. There is often a well-demarcated boundary along the skin line - almost diagnostic of the condition, although similar findings occur when patients tie a band around the limb for comfort.
- Movement may be limited, both because of the pain and because joints are often described as stiff (particularly with difficulty in initiating movements) or muscles weak. Disuse atrophy can ensue. Other muscular disorders include sudden and severe spasms, tremors and involuntary severe jerking and dystonia.

It is also important to look for psychological symptoms which may need to be treated.

Diagnosis

The diagnosis is clinical and may be difficult, particularly in the early stages of the syndrome where there may be little, if any, objective evidence of a problem. The Royal College of Physicians recommends that doctors and other trained therapists use the 'Budapest criteria' to make a diagnosis.^[1] The clinical diagnosis requires all of the following four to be present:

- Presence of pain which is disproportionate to the initial causative event.
- Presence of at least one symptom in three of the four following categories:
 - Sensory - reports hyperalgesia and/or allodynia.
 - Vasomotor - symptoms of temperature differences and/or skin colour changes and/or skin colour asymmetry.
 - Sudomotor/oedema - complains of swelling and/or sweating changes and/or sweating asymmetry.
 - Motor/trophic category - reports reduced range of motion and/or motor dysfunction (including weakness, tremor or dystonia) and/or trophic changes (of the hair, nail or skin).
- Presence of at least one sign in two or more of the following categories:
 - Sensory - allodynia (to light touch, temperature, deep somatic pressure or joint movement) and/or hyperalgesia (to pinprick).
 - Vasomotor category - signs of temperature differences ($>1^{\circ}\text{C}$) and/or skin colour changes and/or skin colour asymmetry.
 - Sudomotor/oedema category - oedema and/or sweating and/or sweating asymmetry.
 - Motor/trophic category - evidence of reduced range of motion and/or motor dysfunction (including weakness, tremor or dystonia) and/or trophic changes (of the hair, nail or skin).
- No other diagnosis would better explain the signs and symptoms.

This classification means that CRPS can only be diagnosed if there are objective signs in the limb at the time the patient is seen. Many patients experience a delay in diagnosis and some changes (eg, swelling and sweating) may abate over time. In those patients who still have pain and who would have fulfilled the criteria in the past, a diagnosis of CRPS-NOS (not otherwise specified) is made.^[1]

Contrary to what was previously believed, CRPS is not a progressive disease. However, there would appear to be three distinct subtypes:^[6]

1. A relatively limited syndrome with predominant vasomotor signs.
2. A relatively limited syndrome with predominant neuropathic pain/sensory abnormalities.
3. A florid CRPS which, despite having the shortest pain duration, shows the greatest level of motor and trophic signs and disuse changes.

Prompt diagnosis and early intervention help management and aid recovery. Complications which occur from limb disuse and the psychological effects of living with an undiagnosed chronic pain are also prevented by prompt diagnosis.

Differential diagnosis

- Poorly placed splint or cast.
- Nerve entrapment.
- [Deep vein thrombosis](#).
- [Thrombophlebitis](#).
- [Thoracic outlet syndrome](#).
- [Carpal tunnel syndrome](#).

Investigations

- No blood tests support or exclude the diagnosis.
- The diagnosis is clinical and over-reliance on investigations is unnecessary.^[1]
- It is worth noting that X-rays, electromyography (EMG), nerve conduction studies, CT scans and MRI studies may all be entirely normal.
- Definitive tests of nerve damage, such as EMG, needed to differentiate between CRPS I and CRPS II, are considered unnecessarily painful to CRPS patients.^[6]
- Thermography may confirm changes in body temperature that are common in CRPS.

Management

For the purposes of management, assessment of severity is divided as follows:^[1]

- Mild CRPS: few signs of pain-related disability or distress. Pain can be managed with simple analgesics or neuropathic medications.
- Moderate-to-severe CRPS:
 - Moderate-to-severe signs and/or symptoms at presentation.
 - Dystonia.
 - Failure of response to treatment.
 - Continued deterioration or only short-lived improvements.

General principles

The Royal College of Physicians provides four 'pillars' of therapy: education, pain reduction, physical rehabilitation and attention to psychological needs, with the aim being to improve the quality of life.^[1]

- Restoring function is pivotal.
- The key approach is a multidisciplinary one but should be centred around the GP and pain teams.
- Pain-related fear may be more disabling than pain itself.
- Ensure the patient's care does not become fragmented; they may end up seeing several different specialities.

Referral

Referral from primary care is necessary for the following:^[1]

- Confirmation of CRPS.
- Exclusion of other causes of the symptoms/signs.
- Functional rehabilitation.
- Helping to control difficult symptoms including pain, distress and associated disability.

Mild confirmed cases can be managed in primary care provided symptoms are responding to treatment, although referral to a multidisciplinary pain clinic may be necessary.

Moderate-to-severe CRPS should be referred to either a multidisciplinary pain clinic or specialist unit.^[1]

Education

Patient information and education about CRPS is fundamental.

- Only with a correct diagnosis and information about the condition can a patient be actively engaged in self-management, goal setting and pacing and ultimately take control of their condition.
- Patients need to understand that they will experience pain both when they exercise too much but also when they exercise too little; they need to be taught how to find the middle ground.^[6]
- A survey of people with CRPS stressed the significance of telling those with CRPS that it can become a chronic condition, so that the importance of rehabilitation is emphasised.^[7]

Pain reduction^[1, 6]

- No medications are specifically licensed for CRPS

- Simple analgesics to begin with - eg, non-steroidal anti-inflammatory drugs (NSAIDs) and gradually up-titrate, such that limb use can be encouraged with gentle exercise.
- If pain is not reduced to a mild level by 3-4 weeks then use medication for neuropathic pain (tricyclic antidepressants or gabapentin).
- Pain flares are normal but usually settle over a few days or weeks. Medications should be continued with a *temporary* reduction in intensity of physical therapy.
- Medications may also be needed for associated depression if present.
- Bisphosphonates: some patients with CRPS have evidence of active bone resorption which can be painful. Inhibiting bone resorption may thus reduce bony pain. Pamidronate, as a one-off treatment, can be used with CRPS of less than six months' duration. Other bisphosphonates have also been shown to reduce pain significantly.
- Baclofen may be needed for dystonia.
- Capsaicin is not recommended as it can be intolerably painful.

Physical and vocational rehabilitation^[1]

- Physical therapy is the cornerstone of treatment and should be considered in everyone. It should be started early, regardless of which speciality the patient is seeing when the initial diagnosis is made.
- Frequent attention to the affected limb and desensitisation by stroking the affected limb, using various fabric modalities whilst observing the limb, is a pragmatic initial approach.
- Multidisciplinary pain management programmes, which are run in groups, are available in specialised settings.
- Intensive exercise therapy may be particularly effective in children, especially when combined with cognitive psychological approaches.^[8] This has been shown to be practicable in an outpatient setting.^[4]
- Psychosocial factors may lead to reduced response to rehabilitation and should be actively looked for and corrected. This includes previous negative experiences, poor coping and depression.
- Treatment approaches used in rehabilitation for CRPS are wide and include education and support, desensitisation, postural control and stress loading of the affected limb.
- Specialised units may also undertake the following more therapeutic strategies, which are thought may reset abnormal, central, sensory processing.^[6] There is some low-quality evidence to support their use:^[9]
 - Mirror visual feedback involves the patient describing their affected and unaffected limbs with their eyes closed, followed by imagined movements and then looking at their arm or leg in a mirror, without moving it, while trying to establish ownership of the mirrored limb.
 - Graded motor imagery involves the patient imagining moving their affected limb into the position demonstrated first in pictures and then in a reflected image of their unaffected limb moving.

Other treatments^[1]

- Spinal cord stimulation is used in specialist centres for patients who have not responded to a multidisciplinary approach. There is some evidence that the effects of this treatment reduce over time.
- Specialist centres may also use clonidine and local anaesthesia injection into the epidura, local anaesthetic injection into the sympathetic chain, intravenous regional sympathetic blocks or interscalene indwelling catheters. The evidence for their use is inconclusive but if they reduce pain (as opposed to simply producing a sympathetic block) they can provide a less painful 'window of opportunity' for rehabilitation techniques.^[6]
- The N-methyl-D-aspartate (NMDA) receptor antagonist ketamine has been used in intractable CRPS but has to be given in anaesthetic doses.
- There is evidence that intravenous regional blockade with guanethidine is ineffective.^[10]

Psychological support

Integration of psychological methods, including cognitive behavioural therapy, relaxation techniques, counseling and psychotherapy, alongside medical and intensive physical and occupational therapy, may be particularly helpful in CRPS.

A psychological evaluation by an expert in chronic pain may be necessary to identify factors which might be contributing to poor progress. Patients with CRPS commonly report the following psychological issues:

- Difficulty relaxing.
- Low self-esteem.
- Inappropriate/ineffective coping strategies.
- Difficulty accessing/accepting social support.
- Suicidal ideation.

Unfortunately, a Cochrane review concluded that although there is a wide range of therapies used to treat CRPS, there is little evidence of their effectiveness and very few large controlled trials have been undertaken; further well-designed trials are needed.^[10] The interventions thought to hold most promise are bisphosphonates, ketamine and graded motor imagery.^[11]

Complications

- [Depression](#) is common.
- Immobilisation may aggravate pain and stiffness.
- Skin infections can occur and occasionally may be very severe.

Prognosis^[1]

There is no cure for CRPS but the majority of patients will get better. Pain flares are common and not a sign that the condition is worsening. The duration of CRPS varies. Resolution rates in studies have varied widely from 74% in the first year to 36% within six years.^[3] CRPS developing following a fracture appears to have a more favourable outcome than when it follows a soft-tissue injury, as does 'warm' CRPS (in which impaired thermoregulation leaves the affected limb warmer than normal).

If undiagnosed and untreated, CRPS can spread to all extremities such that the patient is completely incapacitated by the disease. Rehabilitation is subsequently much more difficult and potentially complicated by opiate dependency. The treatment of patients with advanced CRPS is a challenging and time-consuming task. However, if diagnosed early and treated aggressively, prognosis is improved.

Prevention

Investigators are studying new approaches to treat CRPS and intervene more aggressively after traumatic injury to lower the patient's chances of developing the disorder. Researchers hope to discover the mechanisms that cause the spontaneous pain of CRPS; that discovery may lead to new ways of blocking pain. There is some evidence the use of vitamin C in patients who have a fractured wrist may reduce their chances of developing CRPS.^[12]

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