Complex Regional Pain Syndrome

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KEY POINTS

- Complex regional pain syndrome is a chronic pain condition characterized by pain out of proportion to any inciting event.
- Complex regional pain syndrome can occur in the presence or absence of significant injury.
- The exact pathophysiology is not clearly understood, and several possible mechanisms are postulated.
- Treatment involves a multidisciplinary approach involving the 4 Ps: patient education, physical therapy, pain management, and psychological treatment.

INTRODUCTION

Complex regional pain syndrome (CRPS) is a painful and disabling disorder affecting one or more extremities with vasomotor changes (colour or temperature changes relating to vasoconstriction or dilation of blood vessels), sudomotor changes (oedema and/or sweating), inflammatory changes, trophic changes (changes in nails or skin) and motor changes (weakness, tremor, dystonia) in the affected extremity. CRPS can occur even after trivial injury or even in the absence of any injury.

History

Cases of CRPS have been documented as early as the 16th century. Ambroise Paré, a French barber and surgeon who was involved in treating King Charles IX for his endless pain and contracture following a surgery, referred to a persistent pain syndrome after limb phlebotomy (‘bloodletting’). In 1864, Silas Weir Mitchell published a paper ‘Gunshot wounds and other injuries of nerve’ where he characterised a specific type of pain following gunshot wounds during the American Civil War as ‘causalgia’—patients described this as severe burning pain and shining red skin. In 1946, James Evans from Massachusetts described a similar condition and referred to it as ‘reflex sympathetic dystrophy’. Other names coined have been ‘algodystrophy’, ‘algoneurodystrophy’, ‘Sudeck’s dystrophy’, and ‘reflex neurovascular dystrophy’.[1]

Definition

Lack of a clear definition of CRPS led to underreporting of the incidence of CRPS. In 1994, the International Association for the Study of Pain (IASP) came up with the first set of diagnostic criteria (Table 1).[2,3] However, it was soon found to have low specificity and often led to misdiagnosis. In 2003, the Budapest Criteria was developed (Table 2).[2,3] In 2010, Harden and colleagues developed the CRPS severity score.[2,3] It included 17 different symptoms with 1 point for the presence of each

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TAKE ONLINE TEST

- Presence of an initial inciting event
- Allodynia or hyperalgesia out of proportion for the inciting event
- Evidence of skin changes, sudomotor dysfunction, or oedema
- The absence of any other syndrome that would otherwise explain the presenting syndromes

Table 1. IASP Diagnostic Criteria

symptom. Higher scores had greater correlation with increased pain and functional limitation and better measure of response to treatment (Table 3).

Two distinctive forms of CRPS are currently described. CRPS type I has no demonstrable nerve lesion and Type II has demonstrable nerve injury. Additionally, not-otherwise-specified CRPS has been proposed for patients who failed to fit into either type 1 or 2. Nevertheless, the types of CRPS do not differ in clinical presentation or treatment.

The IASP CRPS Special Interest Group convened a workshop of CRPS experts in Valencia, Spain, in September 2019 to review the perceived ambiguities in the diagnostic text and issues identified in applying these criteria in both research and clinical contexts. Following the workshop, adaptations were made to the diagnostic taxonomy. The wording of diagnostic criteria themselves was not altered to avoid invalidating the criteria.[11] Some of the recommendations proposed are summarised in Figure 1.

Epidemiology

Though the first diagnostic criteria were put forward in 1994, the first extensive population-based study was done in 2003 by Sandroni et al. with very limited data available before 2000.[9] This study revealed an incidence of 5.46 per 10 000 for type I and 0.82 per 10 000 for type II. In a subsequent study, surgery and presence of a fracture seemed to be significant 'inciting' causes. The incidence was higher in age groups 61 to 70 years, with higher female predilection (3:1). Increased upper limb incidence (3:2) was also found. Risk factors include menopause, osteoporosis, asthma, smoking, and angiotensin-converting-enzyme inhibitor treatment.

Clinical Presentation

Patients present with severe constant pain, often disproportionate to the initial injury, with associated hyperalgesia (abnormally increased sensation to a normal painful stimulus), allodynia (pain sensation to a nonpainful stimulus), and/or hyperaesthesia (extremely increased sensitivity to any stimulus). The pain is usually described as stabbing, penetrating, throbbing, nagging, and burning in nature. The pain is accompanied by vasomotor, sudomotor, and trophic changes. Difference in skin temperature, sweating pattern, colour, swelling or dystrophy, and changes in nail or hair growth can be seen on physical examination of the affected limb compared to the healthy limb. Tremor and dystonia may also be observed.

INVESTIGATIONS

CRPS has a wide differential diagnosis (Table 4). The diagnosis is essentially a clinical diagnosis based on the diagnostic criteria (Table 2) with additional tests done to exclude other differential conditions. Additional tests may include the following:

- Continued pain that is disproportionate to any inciting event
- Patient must report one symptom in 3 of the following 4 categories:
  1. Sensory: allodynia or hyperalgesia
  2. Vasomotor: temperature asymmetry, skin colour changes
  3. Sudomotor: oedema, changes in sweating
  4. Motor or trophic: decreased range of motion, motor dysfunction, changes in hair and nail growth
- Must display 1 sign at the time of evaluation in at least 2 of the following categories:
  1. Sensory: evidence of allodynia or hyperalgesia
  2. Vasomotor: evidence of temperature asymmetry or skin colour changes
  3. Sudomotor: evidence of oedema or swelling
  4. Motor: motor weakness or dysfunction
- No other diagnosis explains the patient's signs or symptoms

CRPS 1 – without evidence of major nerve damage.
CRPS 2 – with evidence of major nerve damage.

Table 2. Budapest Criteria for CRPS

Symptoms that were self-reported: • Allodynia • Temperature asymmetry • Skin colour asymmetry • Sweating asymmetry • Trophic changes • Motor changes • Decreased range of motion • Asymmetric oedema
Symptoms observed at the time of examination: • Hyperpathia to pinprick • Allodynia • Temperature asymmetry on palpation • Skin colour asymmetry • Sweating asymmetry • Asymmetric oedema • Trophic changes • Motor changes • Decreased active range of motion

Table 3. CRPS Severity Score

- X-ray: Osteopenia and patchy osteoporosis can be seen as early as 2 weeks after the onset of pain.
- Sweat test: Colour-changing indicator powder is applied on the affected limb. Sweating is measured at basal level and on cholinergic stimulation and difference in output is measured.
- Sympathetic blocks: Sympathetic ganglion blocks (eg, stellate ganglion block for upper limb) relieves pain in affected limb without improvement in function. However, placebo effect by injecting saline produces similar pain relief.
- Three-phase bone scan: Technetium 99–labelled bisphosphonates used to detect early bone changes have been found to be more sensitive than plain radiograph.[4]

PATHOPHYSIOLOGY

The exact pathophysiology of CRPS is still unknown. It is thought to be a combination of inflammatory changes, autonomic dysfunction, and neuronal desensitisation along with genetic and psychological factors at both peripheral and central levels.

Inflammatory Process

This was originally proposed by Sudeck (hence named Sudeck dystrophy) as an exaggerated response to trauma or surgery. However, this was long debated as general markers of inflammation like C-reactive protein, leucocyte count, and Erythrocyte Sedimentation Rate were not elevated, though classical signs of inflammation—pain, swelling, redness, and/or increased temperature—were present. Further studies have found increased levels of proinflammatory markers IL-6, TNFα, IL-8 raised

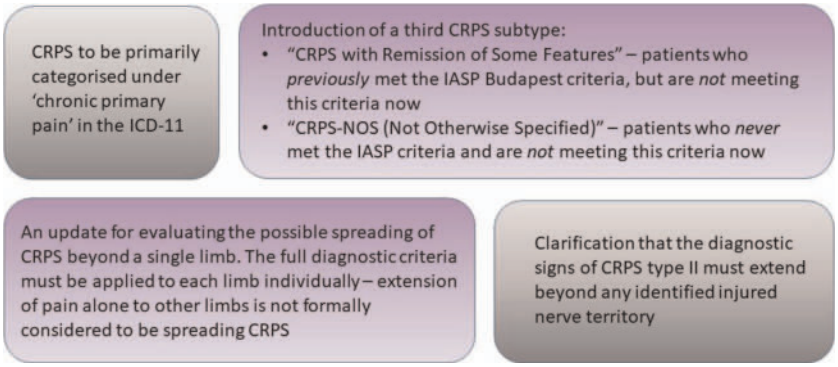

Figure 1. Proposed IASP adaptations to CRPS diagnostic taxonomy.[11]

Neuropathic pain syndromes: • Peripheral polyneuropathy • Nerve entrapment • Radiculopathy • Postherpetic neuralgia • Deafferentation pain post–cerebrovascular accident • Plexopathy • Motor neuron disease
Vascular diseases • Thrombosis • Acrocyanosis • Atherosclerosis • Raynaud phenomenon • Erythromelagia
Inflammation • Erysipelas • Inflammation not otherwise mentioned • Bursitis • Seronegative arthritis • Rheumatological arthritis
Myofascial pain syndromes • Overuse • Disuse • Tennis elbow • Repetitive strain injury • Fibromyalgia
Psychiatric syndromes • Somatoform pain • Munchausen

Table 4. Differential Diagnosis for CRPS

locally in affected limb with suppression of anti-inflammatory IL-4, IL-10. Neuro- and immunomodulatory Substance P and CGRP are also raised in local tissue and intrathecally.

Sympathetic Dysregulation

Distinct aspects of CRPS symptoms are thought to be due to dysregulation of adrenergic and nociceptive receptors. Increased expression of $\alpha 1$ adrenergic receptors and decrease in circulating norepinephrine can explain changes in temperature and colour of limbs. However, this has been debated to be due to lack of efficacy of guanethidine in relieving symptoms.[2,4]

Ischaemia-Reperfusion Injury

It has been suggested that deep tissue hypoxia and reperfusion injury resulting in release of free radicals and cytokines result in endothelial damage and nociceptor excitation.

Central Sensitisation

Continuous peripheral activation increases firing frequency in synapses in the dorsal horn resulting in decreasing threshold of responses to mechanical and thermal stimuli, causing symptoms of allodynia and hyperpathia. Glutamate and Substance P are thought to be the main mediators at the NMDA receptor level. The efficacy of ketamine and magnesium in treatment substantiates this theory.[2]

Cortical Reorganisation

Functional magnetic resonance imaging studies have shown structural changes in motor cortex areas and the sensory homunculus resulting in smaller representation of an affected limb than an unaffected limb, resulting in patients having altered perception and movement of the affected limb.

Small-Fibre Neuropathy

Due to similarities to generalised small-fibre-predominant polyneuropathic conditions, there is thought to be a small-fibre neuropathy aspect, which could explain the trophic changes (decreased number of sweat glands and epidural nerve fibres).

Psychological Stress

Evidence suggests a link between psychological stress and CRPS disease development and progress. Post-traumatic stress disorder patients have significantly increased incidence compared to controls. Patients with higher levels of anxiety, depression, and pain-related fear are found to have a worsened disease course. This has been explained by stress-induced increase in systemic catecholamine release. Cognitive behavioural therapy has been shown to be effective in this group of patients.

Genetics

A Dutch study showed HLA (Human Leucocyte Antigen) DQ1, HLA B62, and HLADQ8 to be associated with CRPS with fixed dystonia.[4]

Autoimmune Disease

A small group of patients showed relief of symptoms following low-dose intravenous immunoglobulins. A small subgroup of patients has been shown to have increased levels of antineutrophil cytoplasmic antibodies in the blood. These findings have postulated that CRPS can be autoimmune in origin. However, to define CRPS as an autoimmune disease, the Witebsky criteria must be met, which is not the case.

PREVENTION

Studies have shown that supplementation with vitamin C $>$500 mg/d for 50 to 60 days immediately after the injury or surgery helps reduce the risk of developing CRPS.[2]

MANAGEMENT

Comprehensive management of CRPS patients involves a multidisciplinary approach. The 4 pillars of treatment can be referred to as 4 Ps:

- Patient education and information
- Physical therapy
- Pain management (drugs and interventions)
- Psychological therapy

Patient Education and Information

It is crucial to take time with the patient and family to provide information in simple language and ensure they have understanding of the condition and outcome of the disease. Salient points of discussion should revolve around the following:

- CRPS is usually preceded by injury but persists well after completion of the healing process. It can also occur without any significant preceding injury.
- It is not hereditary, and the cause of the disease is not clearly understood.
- There is no specific cure.
- Pain can lead to psychological complications, and these can worsen pain in a vicious cycle.
- A multidisciplinary approach in treatment reduces severity of the disease process.

Physical Therapy

Due to the extremity pain, CRPS patients tend to avoid using the limb (kinesiophobia). Physical therapy aims to increase range of motion and functionality of the limb and reduce pain. Commonly used therapies are gradual weight-bearing, fine-motor exercises, isotonic strengthening, aerobic conditioning, graded motor imagery and mirror therapy. Early involvement of specialised physiotherapists and occupational therapists has shown to be beneficial in various studies through specialised programmes.

Pharmacological Pain Management

Several medications used in the treatment of neuropathic and nonneuropathic pain conditions have been trialled with varying degrees of success.

- Gabapentinoids or tricyclic antidepressants: There has been a lack of evidence of efficacy of these groups of drugs. Gabapentin has been used with very limited success.[7] Tricyclic antidepressants such as amitriptyline have been based on clinician's preference and experience[8].
- Anti-inflammatories: There has been some evidence of efficacy of nonsteroidal anti-inflammatory drugs in CRPS pain, especially in the early part of the disease. Corticosteroids have also been studied. Short pulse therapy of methylprednisolone 100 mg/d reducing by 25 mg/d every week was found to be useful in small subgroup of patients.[9]
- Bisphosphonates: Meta-analysis of all randomized clinical trials, which included 4 studies, showed statistically significant pain reduction in patients with CRPS following 8 weeks of treatment.[10] The proposed mechanism of action is that the medication modulates inflammation, thereby reducing bone micro-environment acidity and reduces bone resorption, helping in improving pain and mobility.
- Lidocaine plasters: A small group of patients has been shown to benefit from 5% lidocaine plasters. However, larger studies are needed to establish this treatment.
- Ketamine: Topical application of the NMDA antagonist ketamine has been shown to reduce allodynia and hyperalgesia. Intravenous ketamine can reduce CRPS pain, and is specifically used for NMDA central sensitisation. However, side effects from repeated use can be serious (neurotoxicity and liver failure).
- Capsaicin: Topical capsaicin (5-10%) was found to be useful in some studies with some others resulting in worsening of pain.
- α-2 Agonists: Sympathetically mediated pain in CRPS led to use of phenoxybenzamine and clonidine in treatment. Several case reports have shown efficacy in reducing pain with both drugs' use.
- Antispasmodics: Research studies have shown positive effect with intrathecal baclofen on CRPS dysfunction. However, due to side effects and the invasiveness of the procedure, the number of studies has been limited.

Nonpharmacological Interventions Interventional Procedures

- Acupuncture: A small amount of conflicting evidence about the use of acupuncture in CRPS showed minimal benefit.
- Spinal cord stimulation (SCS): This involves a process of sending signals to the dorsal column of the spinal cord using leads with electrodes placed in the epidural space using an implantable pulse generator. Systematic review in 2017 [14]evaluated 19 studies showing good evidence of improvement in perceived pain relief, pain score, and quality of life in patients with type 1 CRPS who received SCS treatment. The National Institute for Health and Care Excellence [7]recommends SCS for patients experiencing pain for 6 months or more despite adequate conventional management. Nevertheless, the evidence of effectiveness of SCS for type 2 CRPS is still weak.

Psychological Treatment

CRPS has significant emotional effects. Patients trend to avoid use of the affected limb due to pain, leading to progressive dysfunction of the limb. This then affects their professional and social life causing significant emotional stress for patients and their family. Cognitive behavioural therapy is useful in these patients and sometimes can even be extended to family members. Underlying psychiatric conditions (such as post-traumatic stress disorder or depression) should be actively identified and additional support provided. These treatments should work synergistically with other therapies.

CONCLUSION

CRPS is a life-altering condition. Due to unclear pathophysiology, treatment is driven by available evidence and clinician experience in a multidisciplinary fashion based on the 4 pillars of management. As research continues to reveal more about the involved mechanisms, future treatment will presumably shift to more novel mechanism-based treatments.

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