

# Complex regional pain syndrome: recent updates



Praveen Ganty DA FRCA FFPMRCA  
Rajiv Chawla FRCA FFPMRCA

## Key points

Complex regional pain syndrome (CRPS) is a disabling condition that needs timely recognition by the clinician for effective therapy.

The Budapest criteria have more specificity than the International Association for the Study of Pain criteria.

There are multiple theories on the pathogenesis of CRPS—it probably is a result of multimodal pathogenesis.

CRPS diagnosis is essentially clinical although some investigations may be useful.

The four pillars of treatment of CRPS are patient education, physical rehabilitation, pain management, and psychological interventions.

Complex regional pain syndrome (CRPS) may be defined as a painful and disabling disorder affecting one or more extremities showing signs of vasomotor (relating to the constriction and dilatation of blood vessels), sudomotor (stimulation of sweat glands), inflammatory, and trophic changes (changes brought about in tissues from interruption or destruction of nerve, blood supply or both) in the affected extremity. CRPS can occur after even trivial injury and, on occasion, can develop spontaneously. It was first described as a spectrum of symptoms during the American Civil War by Silas Weir Mitchell and colleagues in their book entitled *Gunshot Wounds and Other Injuries of Nerves*, and named it *causalgia*. The gamut of symptoms stretches from a self-limiting mild condition to a severe, debilitating condition affecting the quality of life and having a high impact on activity. Owing to the varied manifestation, the patient can present to any specialty be it orthopaedics, rheumatology, neurology, dermatology, or pain medicine. Pain is an early presenting feature and can be the most prominent of symptoms. A high index of suspicion is needed as early diagnosis and treatment may prevent the progression of symptoms and prevent disability. It has been known by many names in the past, including reflex sympathetic dystrophy, algodystrophy, algoneurodystrophy, Sudeck's dystrophy, and causalgia.

In 1994, the International Association for the Study of Pain (IASP) came up with a standardized set of criteria to diagnose CRPS. Until then, numerous different diagnostic and clinical criteria were used. As IASP criteria lacked specificity, a new set of diagnostic criteria were adapted at a closed conference of leading experts from around the world in the Fall of 2004 in Budapest, Hungary—these were called the 'Budapest criteria' (Table 1). The Budapest criteria were compared with the former IASP criteria and found to have a higher specificity while maintaining sensitivity, and were validated.<sup>1</sup>

## Clinical presentation

The patient presentation varies from only sudomotor symptoms with an erythematous or cyanotic-looking limb with or without oedema, to a completely atrophic limb with or without radiological evidence of osteoporosis. Less than 10% of patients may present without pain but have other typical features of CRPS. There could be associated joint immobility and stiffness and some patients have a fine tremor. Dystonia, myoclonus and chronic lymphoedema and severe atrophy could also be encountered. Skin blistering and secondary bacterial infection could result in ulceration in the affected limb. As the presentation is varied, there is a danger that a clinician unfamiliar with the condition could diagnose CRPS late, thus affecting recovery.

## Theories on pathophysiology of CRPS

Although numerous theories abound regarding the origin and maintenance of CRPS, none of them can completely explain all the clinical features seen in this syndrome. There is a possibility that multimodal factors play a role in the development of CRPS.

The following are the current concepts about the aetiology in CRPS.<sup>2</sup>

(a) CRPS arises because of an inflammatory process

This was originally proposed by Sudeck, and hence the synonym 'Sudeck's dystrophy'. Inflammatory markers such as interleukin-8 (IL-8) and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) are elevated in the local tissues in the limb showing signs of CRPS, but not systemically. There is also a suppression of anti-inflammatory cytokines like IL-4 and IL-10. Neuroinflammatory mediators like Substance P are also raised in the affected limb. Substance P is known to have

### Praveen Ganty DA FRCA FFPMRCA

Consultant in Pain Medicine  
The Walton Centre for Neurology  
Neurosurgery & Pain NHS Foundation  
Trust  
Lower Lane  
Liverpool L9 7LJ  
UK  
Tel: +44 015 152 95750  
Fax: +44 015 152 95486  
Email: p.ganty@gmail.com  
(for correspondence)

### Rajiv Chawla FRCA FFPMRCA

Consultant in Pain Medicine  
The Walton Centre for Neurology  
Neurosurgery & Pain NHS Foundation  
Trust  
Liverpool  
UK

**Table 1** Budapest clinical diagnosis criteria for CRPS

A. The patient has continuing pain which is disproportionate to the inciting event		<input type="checkbox"/>		
B. The patient has at least one sign in two or more categories		<input type="checkbox"/>		
C. The patient reports at least one symptom in three or more categories		<input type="checkbox"/>		
Category		Sign (you can see or feel a problem)	Symptom (the patient reports a problem)	
1	Sensory	Allodynia (to light touch, temperature sensation and/or deep somatic pressure and/or joint movement)* and/or hyperalgesia (to pinprick) <sup>†</sup>	<input type="checkbox"/>	Hyperaesthesia does also qualify as a symptom <input type="checkbox"/>
2	Vasomotor	Temperature asymmetry and/or skin colour changes and/or skin colour asymmetry	If you notice temperature asymmetry: must be >1°C <input type="checkbox"/>	
3	Sudomotor/oedema	Oedema and/or sweating changes and/or sweating asymmetry	<input type="checkbox"/>	<input type="checkbox"/>
4	Motor/trophic	Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair/nail/skin)	<input type="checkbox"/>	<input type="checkbox"/>
D. No other diagnosis can better explain the signs and symptoms <sup>‡</sup>		<input type="checkbox"/>		

All the points A to D must apply for diagnosing CRPS using the Budapest diagnostic criteria. Although it is possible to distinguish between CRPS-1 (without damage to major nerves) and CRPS-2 (associated with damage to a major nerve), this distinction does not have any consequence for treatment. \*The 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). <sup>†</sup>Hyperalgesia is exaggerated pain to a painful stimulus such as a pinprick. <sup>‡</sup>Common investigations, for example, raised systemic inflammatory markers are not associated with CRPS, even in the initial inflammatory phase and such a finding of raised markers should 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 as CRPS, by definition is always secondary, and its presence cannot explain major nerve damage. Table adapted from Goebel<sup>2</sup> with permission.

both neuromodulatory and immunomodulatory effects. Substance P has been implicated in other immunomodulatory diseases like asthma, atopic dermatitis, and inflammatory bowel disease. It is interesting that there is no correlation between the titres of these mediators and the presence of pain, and even if the pain disappears, the patient continues to have high titres of these inflammatory markers.

(b) CRPS as a sympathetically mediated condition

Sympathetic dysregulation is partly responsible for the colour and temperature changes seen in CRPS-affected limbs, when compared with the unaffected limb. A cold and blue limb could be caused by an up-regulation or hypersensitive adrenoceptors in the affected limb. Endothelial dysfunction in chronic CRPS has also been implicated. Many researchers doubt the importance of the sympathetic nervous system as a primary source of imbalance causing CRPS especially in long-standing cases. This has been substantiated by the lack of efficacy of guanethidine in alleviating symptoms of CRPS in four randomized controlled trials (RCTs).<sup>3</sup> It is debateable as to the clinical effect seen is because of the guanethidine or because of the application of a tourniquet.

(c) CRPS is facilitated by central sensitization

Central sensitization is the concept wherein constant nociceptive afferent inputs result in even a non-noxious afferent input to be misrecognized by the brain as noxious. The N-methyl D-aspartate (NMDA) receptor is considered to be the primary target at the receptor level to prevent central sensitization, and infusions of ketamine at low dose have shown a reduction in pain in the CRPS-affected limb but without an improvement in function. Magnesium, an

NMDA antagonist, also shows promise in the treatment of CRPS but the results from larger studies are awaited.

(d) CRPS resultant of an ischaemia–reperfusion injury

Some researchers consider CRPS to be the result of a tissue hypoxia and reperfusion injury. It has been suggested that tissue hypoxia releases free radicals and cytokines that damage the endothelium leading to further release of cytokines. This leads to continuing damage of the endothelium and excitation of nociceptors. Local vasoconstriction could explain the colour change of the affected limb along with a feeling of cold. Theoretically, sympathetic blocks could contribute to pain relief by causing vasodilation.

(e) Cortical reorganization and CRPS

It is a well-known fact that a patient with CRPS would have an altered perception of the affected limb. The patient may perceive the limb to be longer or shorter and associate it with disfigurement. This has been shown in many studies using functional magnetic resonance imaging (fMRI) that the sensory homunculus (the Penfield homunculus) is altered in these patients. There are associated motor cortex changes as well, but it is difficult to ascertain if these changes are the cause of the condition or are a result of intense and chronic afferent stimuli stimulating the sensory and motor cortices. Indeed, the changes seen on fMRI are related to the severity and intensity of the patient’s pain.

(f) CRPS resultant of a small-fibre neuropathy

Some small-fibre polyneuropathies can have similar presentation to CRPS with auto-dysregulation and limb oedema in the affected limb. This has led to the concept that CRPS could be because of

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small-fibre neurone damage. End-organ damage by partial denervation of the blood vessels and sweat glands in the affected limb with a lowered threshold of firing of adjacent nociceptors results in the symptoms and signs of CRPS, with resultant cortical changes. This theory cannot explain the almost ubiquitous presence of pain in CRPS although pain is not always present in other small-fibre polyneuropathies.

(g) CRPS as a result of sensitivity to neuropeptides

CRPS could occur because of 'facilitated neurogenic inflammation'.<sup>4</sup> This theory states that the actions of neuropeptides are exaggerated in the affected limb of a patient with CRPS, and that accounts for the dermal changes in colour and the development of oedema. This theory is supported by the recent findings that there is an association between angiotensin-converting enzyme inhibitors therapy for hypertension (ACE-inhibitors), and the development of CRPS.<sup>5</sup> ACE is responsible for the metabolism of the neuropeptides bradykinin and Substance P, and inhibiting this enzyme leads to higher tissue levels of these neuropeptides.

(h) CRPS and psychological stress

There is some evidence that a significant life event or stressor sometimes precedes the development of CRPS and it has been proposed that there is a psychological cause for the condition and that the clinical findings are secondary. This theory has been refuted in recent reviews.<sup>2</sup> Although there are no RCTs on cognitive behavioural therapy (CBT) and CRPS, CBT has been shown to be effective in many patients with CRPS.

(i) Genetics and CRPS

There could be a possible link between human leucocyte antigen (HLA) system and the development of CRPS with dystonia. There seems to be an association between HLA-B62 and HLA-DQ8 and CRPS in a subset of patients with dystonia, attributed to alteration in the regulation of inflammation and neuroplasticity.

(j) CRPS as an auto-immune disorder

Auto-antibodies have been demonstrated in many patients with CRPS. These auto-antibodies are in response to an inducible autonomic nervous system auto-antigen. Although most clinical changes are confined to the affected limb, these patients can have an abnormal response to the tilt-table test, and the unaffected limb can also show enhanced neurogenic inflammation.

## Investigations in CRPS

The diagnosis of CRPS is essentially clinical, which is secured after ruling out other causes of the patient's symptoms. There is no definitive investigation available, but the following investigations, which are predominantly available in research laboratories, could be carried out to augment the diagnosis. Osteopenia and patchy osteoporosis can be seen in the early stages. These changes can be seen on the radiographs as early as 2 weeks from the onset.

**Three-phase bone scans:** This is a more sensitive investigation than plain radiography and involves the use of technetium-99 (Tc-99m)-labelled bisphosphonates to detect early bone changes. The scan has three phases; a blood pool phase, a blood phase and a scan phase—hence the name. Findings include increased periarticular uptake in the third phase (scan phase) and evidence of vasomotor instability and abnormal patterns of flow distribution in the first and second phase (blood pool and blood phase).

**Sweat testing:** An indicator powder that changes colour when it comes in contact with sweat is used in this test. The powder is applied to the affected limb, and change of colour noted. Sweating is measured at rest (basal levels) and on stimulation of the sudorimotor axonal reflex by inducing a cholinergic challenge, and the difference in output is measured quantitatively.

**Diagnostic sympathetic blocks:** These have been used to relieve pain by injecting local anaesthetics, or performing a sympathetic ganglion block (e.g. stellate ganglion block for upper limb). The pain is relieved in the affected limb, but function may not be regained. The large placebo effect of the procedure itself should not be discounted, and it has been shown that injection of saline into the stellate ganglion produced pain relief similar to injection of local anaesthetic although the effect lasted longer when local anaesthetic was injected. A Cochrane review would not recommend the use of local anaesthetic blocks (Bier blocks) as a gold standard for the treatment of CRPS.<sup>6</sup> Sympathetic ganglion blocks (Stellate or lumbar sympathetic blocks) may relieve pain for the short term in selected patients.

Quantitative sensory testing has been used to document the warm and cold detection thresholds, and heat and cold pain thresholds along with paradoxical heat sensation. The changes in the affected limb are thought to be attributable to initial excitation of the A delta and C-fibres in the early phase of the disease, followed by their degeneration which accounts for the hypoesthesia.

## Prevention

Only one prospective, double-blind study published in 1999 showed that vitamin C was associated with a lower risk of reflex sympathetic dystrophy after wrist fractures. This study supported the use of vitamin C 500 mg daily for 50 days to prevent the development of CRPS.<sup>7</sup> This study has not been replicated since.

## Comprehensive management

There is a paucity of controlled trials in the treatment of CRPS and hence, results have to be extrapolated from other non-CRPS neuropathic pain conditions.

Patients must be educated about CRPS and given information on self-management.

The four pillars of treatment<sup>8</sup> (each of them being equally important) are:

Patient information and education to support self-management  
Physical and vocational rehabilitation

Pain relief (medication and procedures)  
Psychological interventions

## Patient information

It is crucial that adequate time is spent with the patient, and the patient's family, to ensure that the patient has a thorough understanding of the condition and what needs to be done regarding the treatment options. Concise patient information material, written in an unambiguous and simple language, should be offered to the patient at the earliest opportunity. Table 2 highlights the key areas of information to be delivered to the patient with CRPS.

Commonly used physical therapy/occupational therapy methods include desensitization, gradual weight bearing, stretching, and fine motor exercises. This also involves isotonic strengthening, general aerobic conditioning, and helping the patient in regaining and maintaining a normal posture.

Most patients require specialized physiotherapy/occupational therapy delivered by specialist pain physiotherapists or occupational therapists. An early referral to specialist centres, if not available locally, could prevent the development of many chronic complications associated with CRPS.

Multidisciplinary pain management treatment guided by principles of CBT should be considered early, especially for patients who show signs of distress.

Mirror therapy is an approach wherein the patient hides the affected limb behind a mirror that is positioned perpendicular to his/her body midline. When looking into the mirror and performing bilateral synchronized gentle movements, the reflection of the unaffected limb in the mirror has a normal appearance and also moves normally. This visual feedback substitutes the inapt proprioception in the diseased limb and improves the pain.<sup>9 10</sup> Graded motor imagery is a computer based program which involves an exercise to train the brain in better recognizing the affected limb, and can reduce pain and swelling in some patients.<sup>11</sup>

## Medications and interventions

### Anti-neuropathic agents

Although many patients are commenced on anti-neuropathic agents, there is a lack of evidence about their efficacy in CRPS. Only

gabapentin at a dose of 1800 mg day<sup>-1</sup> has yet been assessed in CRPS, and was not shown to be efficacious. The empiric anti-neuropathic pain treatment is often started for symptom relief which may augment the rehabilitation process. This treatment can be initiated as per NICE CG96 starting with either tricyclic antidepressant amitriptyline starting at a dose of 10 mg day<sup>-1</sup> titrated up to 75 mg day<sup>-1</sup> or pregabalin starting at 75 mg b.d. to 300 mg b.d. If either of the medication fails to give an effective pain relief it can be given in a combination or supplemented with tramadol (<http://www.nice.org.uk/guidance/CG96>).

### 5% Lidocaine medicated plasters

The majority of the evidence has been extrapolated from non-CRPS neuropathic pain conditions and only some patients with CRPS have been shown to have benefited from a topical application of 5% medicated lidocaine plasters.

### Bisphosphonates

Bisphosphonates (pamidronate and alendronate) inhibit bone resorption and improve levels of spontaneous pain, pressure tolerance, and joint mobility. Bisphosphonates also have immune-modulatory properties and though shown to be effective in CRPS in some studies, currently, there is insufficient evidence for their routine use in clinical practice.

### Ketamine

Ketamine acts as an NMDA receptor antagonist. I.V. ketamine can reduce CRPS pain and is specifically useful for NMDA-mediated central sensitization. Not only the logistics of delivering i.v. ketamine therapy can be challenging like needing an inpatient monitored bed, but also the side-effects from repeated infusions are poorly understood, and can include neurotoxicity and liver failure. Topical ketamine has been shown to decrease allodynia and hyperalgesia, but does not help with pain. In our centre, i.v. ketamine has been used successfully to treat patients with CRPS.

### Spinal cord stimulation

Spinal cord stimulation (SCS) is a recognized treatment for neuropathic chronic pain. NICE recommends SCS for patients who experience pain for 6 months or more despite conventional medical management (<http://publications.nice.org.uk/spinal-cord-stimulation-for-chronic-pain-of-neuropathic-or-ischaemic-origin-ta159>). The long-term follow-up analysis has demonstrated that the pain-alleviating effect of SCS in CRPS diminishes with time, when compared with that in a control group, and is no longer statistically significant after 3 years.<sup>12</sup>

**Table 2** Key patient information

CRPS is an infrequent nerve pain disorder of arm or leg
CRPS is generally preceded by injury but the cause is inadequately understood
Pain continues after the original injury has healed
Unlike some other medical conditions, there is no specific cure
This pain can lead to anxiety, depression, lack of sleep, disability and distress
CRPS pain cannot be prevented; it is not hereditary
It can get better by itself or may be helped with specialized treatment and antiepileptic or antidepressant medication
The doctor may refer the patient to a multidisciplinary team for specialized treatment
Aim to improve the function of the limb with help from physiotherapists and occupational therapists

## Oral steroids

Short-pulsed steroid therapy in the acute phase has shown benefits. A commonly used steroid is methylprednisolone 100 mg day<sup>-1</sup>, which is reduced by 25 mg every 4 days.

## I.V. regional sympathetic blocks

An i.v. regional sympathetic block (IVRSB) with guanethedine, which acts by depleting norepinephrine in the limb autonomic nerve endings, is supposed to reduce the regional autonomic dysfunction. However, the evidence behind this treatment is negative.<sup>13</sup> One study has demonstrated that an IVRSB with saline may be more effective than IVRSB with guanethidine.<sup>14</sup>

## Acupuncture

There is conflicting evidence regarding the use of acupuncture in CRPS with minimal benefit described and that was not statistically significant.

## Psychological interventions

The psychological effect of CRPS on a patient should not be underestimated. It is paramount that patients and their family receive early education on the perils of disuse of the affected limb. Fear of movement is quite common as movement could trigger pain in a patient with CRPS. This could lead to disuse atrophy and could hamper physical rehabilitation. CBT is helpful in these patients and can even be offered to family members. Other stressors in life and potential psychiatric conditions should be identified and dealt with by offering additional psychological support, especially in those patients who do not make adequate progress with treatment. CBT works in a synergistic fashion along with physical rehabilitation and medical management of CRPS.<sup>15</sup>

## Experimental therapy

The following therapeutic modalities are being considered as treatment options and evidence is still being actively gathered through research for their use in CRPS.

### I.V. immunoglobulins

It has been demonstrated in an RCT that a single infusion of low-dose (0.5 g kg<sup>-1</sup>) i.v. immunoglobulins effectively reduces pain in patients with long-standing disease. The pain relief lasted 5 weeks on average in the study.<sup>16</sup> The cost-effectiveness of this treatment is yet to be determined.

### Capsaicin

Capsaicin has been tried in a concentration of 5–10% as a topical application, but the results have not been encouraging. Pain was found to get worse after capsaicin application.

## Amputation

Some authors have suggested amputation of the affected limb to treat severe pain and disability. Some patients even desire amputation to get rid of suffering. Amputation is only indicated if there is a severe infection in the affected limb not responding to treatment.

## Topical dimethylsulfoxide (DMSO 50%), N-acetylcysteine (NAC)

These free radical scavengers have shown some reduction in pain in patients with early CRPS-I. The postulated mechanism is decreasing the excessive production of toxic oxygen free radicals and hence the inflammatory response.<sup>17</sup>

## Conclusion

CRPS is a disabling condition that probably has a multimodal aetiology. Since the diagnosis is essentially clinical, a high degree of suspicion is required to recognize the symptoms as that of CRPS. The latest Budapest criteria have higher specificity for the diagnosis of CRPS. The aggressive management based on the four pillars of treatment should be commenced as early as possible aiming for functional restoration and to stem the progression of the disease.

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Please see multiple choice questions 25–28.