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Clinical diagnostic criteria for complex regional pain syndrome

A-D must apply
A The patient has continuing pain which is disproportionate to any inciting event ☐
B The patient has at least one sign in two or more of the categories ☐
C The patient reports at least one symptom in three or more of the categories ☐
D No other diagnosis can better explain the signs and symptoms ☐

Category		Sign (you can see or feel a problem)	Symptom (the patient reports a problem)
1 Sensory	Allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement) and/or hyperalgesia (to pinprick)	☐	Hyperaesthesia also qualifies as a symptom ☐
2 Vasomotor	Temperature asymmetry and/or skin colour changes and/or skin colour asymmetry	If you notice temperature asymmetry: must be > 1°C ☐	☐
3 Sudomotor/oedema	Oedema and/or sweating changes and/or sweating asymmetry	☐	☐
4 Motor/trophic	Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair/nail/skin)	☐	☐

BOX 1
Budapest clinical criteria for complex regional pain syndrome[1]

How do patients present in primary care?

COMPLEX REGIONAL PAIN SYNDROME (CRPS) IS A CHRONIC DEBILITATING PAINFUL CONDITION comprising unremitting pain, sensory, sudomotor, vasomotor and motor abnormalities in the affected extremity.[1] In the past decade, standardisation of the taxonomy and the formation of the International Research Consortium for CRPS have led to improvement in our understanding and management of this often poorly understood condition.[2]

Although the pathophysiology has not yet been fully elucidated, the concept of CRPS as a clinical entity is not a new one. During the American Civil War, a young army physician named Silus Weir Mitchell treated many patients with gunshot wounds who went on to develop an intense burning pain and subsequent loss of function which he attributed to nerve injury and termed causalgia.[3] Over the subsequent 150 years a variety of terms reflecting the proposed pathophysiology have been used such as Sudek's atrophy and reflex sympathetic dystrophy (RSD).

What are the diagnostic criteria?

In the 1990s Stanton-Hicks proposed the current taxonomy in an attempt to change conventional thinking to a more descriptive terminology.[4] The word complex was chosen to reflect the wide diversity of presentations; regional to signify the non-dermatomal distribution, pain which is a prerequisite of the diagnosis, and syndrome to describe the associated symptoms and signs.

This is further subdivided into subtypes CRPS I and CRPS II. The former generally occurs following trauma but without evidence of nerve injury and was previously known as RSD. The latter is the classic causalgia that can develop following nerve injury. CRPS I can occur following local injuries such as fracture, sprains, surgery or even remote insults such as myocardial infarction or cerebrovascular accident.[5] In as many as a quarter of cases, no clear precipitant or inciting event is discovered.[5]

What are the treatment approaches?

Following a large European epidemiological study, we now know that CRPS is more common than previously thought with an incidence of 26 per 100,000 population per annum.[6] This is a similar incidence to trigeminal neuralgia and more common than, for example, multiple sclerosis. A GP with a list of 2,000 patients might expect to see a case once every two years. It has a peak incidence in the 55-75 age group and there is an association with asthma and migraine.[7] CRPS is three times more common in women than men.

CLINICAL PRESENTATION

The diagnosis of CRPS should be suspected in any patient presenting with persistent pain in an extremity beyond the expected period of tissue healing following an acute injury, sprain, fracture or surgical procedure.

Severe pain in a glove or stocking distribution is the predominant »

Table 1

Differential diagnosis of complex regional pain syndrome[10]

Neuropathic pain	Vascular disease	Inflammation	Myofascial pain
● Peripheral neuropathy	● Thrombosis	● Bursitis	● Repetitive strain injury
● Nerve entrapment	● Acrocyanosis	● Seronegative arthritis	● Overuse/disuse syndromes
● Radiculopathy	● Atherosclerosis	● Rheumatological diseases	● Fibromyalgia
● Post-herpetic neuralgia	● Raynaud's disease	● Erysipelas	
● Post-stroke pain	● Erythromelalgia		
● Plexopathy			
● Motor neurone disease			

symptom in more than 90% of cases.[8] In adults, the upper limb is more commonly affected, whereas in children and adolescents the lower limb is the most common site of presentation.[9]

Unfortunately, the differential diagnosis is wide (see table 1, above) and there is no single test or investigation that can conclusively confirm what is essentially a clinical diagnosis. Instead, over time various diagnostic criteria have been created and subsequently revised as our understanding of the condition has improved.

The original International Association for the Study of Pain diagnostic criteria created in 1994 were deemed to lack specificity and so were replaced with the current Budapest criteria in 2004.

'Severe pain in a glove or stocking distribution is the predominant symptom in more than 90% of cases'

There are two types of diagnostic criteria within the Budapest criteria; clinical criteria,[1] which are most commonly used in everyday practice (see box 1, p17) and research criteria, with improved specificity at the expense of reduced sensitivity, for use in the field of research.

The criteria are split into four domains.

- First, there must be continuing pain which is disproportionate to the inciting event
- Second, the patient must report symptoms in three out of four categories
- On examination, there must be evidence of signs in two of the same four categories
- Finally, there must be no other diagnosis that could account for the presentation.

SYMPTOMS AND SIGNS

Pain

The pain is generally described using neuropathic descriptors such as burning, shooting or lancinating. It can be severely debilitating with the individual hesitant to move the affected limb or reluctant to be examined for fear of exacerbating discomfort.

Vasomotor

It was formerly suspected that patients underwent a transformation following injury with an acute 'warm' CRPS characterised by hyperaemia and swelling which would then be followed by a 'cold' CRPS phase comprising pallor, cyanosis and ischaemia.[5] It is now recognised that these changes in colour and temperature of the affected limb in relation to altered vasomotor tone can occur at any stage of the illness.

Sudomotor

In severe cases, there may be quite obvious swelling and distortion of the affected limb to the extent that alternative diagnoses such as venous thrombosis are considered before CRPS is ultimately diagnosed. Sweating can be either decreased or increased.

Motor and trophic changes

Immobility, dystonia and a fine tremor have all been observed in patients with CRPS.[8] Alterations in hair and nail growth (increased or decreased) and a waxy atrophic appearance to the skin are also seen.[6,11]

INVESTIGATIONS

In the domain of research the use of radiographs, triple-phase bone scans, sweat testing, diagnostic sympathetic blocks and quantitative sensory testing have all been described.[6] Radiographs may show osteopaenia or patchy osteoporosis in the early stages. Vasomotor asymmetry and abnormal blood flow patterns may be seen in radiolabelled bone scans.

None of these changes are specific and the role of investigations in CRPS is principally to exclude other diagnoses.

PATHOPHYSIOLOGY

Despite a number of proposed theories, there is still considerable controversy about the mechanisms of CRPS. It may be that, as in neuropathic pain syndromes, there is involvement of both peripheral and central mechanisms.[12]

Chronic inflammation, neurogenic inflammation and autoimmune mechanisms have been suggested. These are supported by findings of elevated pro-inflammatory cytokines in the serum, plasma and cerebrospinal fluid of patients with CRPS.[13-15]

Microvascular ischaemia-reperfusion injury, genetic factors and cortical reorganisation (akin to phantom limb pain) have all received attention in the published literature.[16,17,18] This has led some authors to propose that treatment is aimed at whichever underlying mechanism is thought to be most prominent, i.e. anti-inflammatories for inflammation, muscle relaxants for motor disorder, anti-neuropathics for neuropathic pain and so on.[19]

In reality, it can be difficult to distinguish between these sub-types and a rational approach to management and treatment is offered below.

MANAGEMENT

The approach to managing patients with CRPS is multifaceted and a multidisciplinary approach is required. The overall goal is to reduce painful symptoms and improve function. Prompt and aggressive treatment is advocated to prevent a deteriorating spiral of disuse, loss of function and the psychological distress associated with persistent pain.[20]

The key criteria for referral to specialist services are: [21]

- To confirm the diagnosis or exclude alternatives (pain clinic, neurology, rheumatology)
- To exclude ongoing pathology warranting intervention (e.g. orthopaedics

key points

SELECTED BY

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Complex regional pain syndrome (CRPS) is a chronic debilitating painful condition comprising unremitting pain, sensory, sudomotor, vasomotor and motor abnormalities in the affected extremity. The incidence is 26 per 100,000 population per annum. This is similar to trigeminal neuralgia and more common than multiple sclerosis. It has a peak incidence in the 55-75 age group and there is an association with asthma and migraine. CRPS is three times more common in women than men.

CRPS should be suspected in any patient presenting with persistent pain in an extremity beyond the expected period of tissue healing following an acute injury, sprain, fracture or surgical procedure. Severe pain in a glove or stocking distribution is the predominant symptom in more than 90% of cases. The differential diagnosis is wide and there is no single test or investigation that can conclusively confirm what is essentially a clinical diagnosis.

The International Association for the Study of Pain diagnostic criteria were deemed to lack specificity and were replaced by the current Budapest criteria in 2004. First, there must be continuing pain disproportionate to the inciting event. Second, the patient must report symptoms in three out of four categories. On examination, there must be evidence of signs in two of the same four categories. Finally, there must be no other diagnosis that could account for the presentation.

The approach to managing patients with CRPS is multifaceted and a multidisciplinary approach is required. Criteria for referral to specialist services are: to confirm the diagnosis or exclude alternatives (pain clinic, neurology, rheumatology); to exclude ongoing pathology warranting intervention (e.g. orthopaedics for non-union or suspected infection); when symptoms are proving difficult to manage (pain clinic); to address functional rehabilitation (pain clinic, specialist pain physiotherapist). Patients should be referred urgently to the local pain service to allow prioritisation before a downward spiral of loss of function, depression and worsening pain ensues.

For symptom control, paracetamol and anti-inflammatories are recommended in the first instance, with the addition of a first-line antineuropathic agent (e.g. duloxetine, amitriptyline, gabapentinoids) if this fails. Topical agents have the advantage of localised action with reduced systemic side effects and are an attractive option in those intolerant of first-line antineuropathic agents or those vulnerable to side effects (the elderly; those with co-existing renal or hepatic impairment). Topical lidocaine 5% plasters and capsaicin 0.075% cream have both been used successfully in CRPS, although the evidence is limited to case reports. They are worth trialling while awaiting specialist input and generally well tolerated. It is prudent to warn patients regarding the initial burning and pruritus that can occur with capsaicin and to reassure them that this generally subsides after several days' use.

for non-union or suspected infection)
- When symptoms are proving difficult to manage (pain clinic)
- To address functional rehabilitation (pain clinic, specialist pain physiotherapist)

The authors recommend that patients should be referred urgently to the local pain service to allow prioritisation before a downward spiral of loss of function, depression and worsening pain ensues. It is recognised that the wait for specialist services can be several months and resources vary throughout the UK.[22] This means that (with the exception of mild cases, which may be managed entirely in the community) treatment will need to be started while waiting for specialist input. Ultimately the aims of treatment are functional rehabilitation and symptom control. If a patient fulfils the criteria for CRPS but the impact on psychosocial function is minimal, and symptoms are controlled with first-line analgesia, then the patient would not need to be referred unless the situation changes.

A four-pronged approach to the management has been suggested in a previous article,[8] consisting of patient education, physical rehabilitation, pain relief (analgesia and procedures), and psychological interventions. It is important to explain to the patient what is meant by the diagnostic term CRPS, our current understanding of the disease process and the management options available. This offers reassurance that they are being taken seriously and that potentially alarming symptoms such as swelling and colour changes are a common feature of the condition.

'Patients should be referred urgently to the local pain service to allow prioritisation before a downward spiral of loss of function, depression and worsening pain ensues'

Prompt referral to a physiotherapist can begin the process of desensitisation, stretching, gradual weight bearing and graded motor imagery. Depending on the resources available, some of the treatment modalities employed can be quite specialised, highlighting the importance of urgent referral to pain services where specialist pain physiotherapy input can be arranged. Occupational therapy and physiotherapy have the dual benefit of reducing pain and improving function in the treatment of CRPS.[23]

'Occupational therapy and physiotherapy have the dual benefit of reducing pain and improving function'

For symptom control, the authors would suggest starting with paracetamol and anti-inflammatories in the first instance, with the addition of a first-line antineuropathic agent (e.g. duloxetine, amitriptyline, gabapentinoids) if this fails. There is a paucity of evidence beyond clinical experience for the latter in the context of CRPS, although gabapentin has been shown to reduce pain and sensory deficits in a randomised controlled trial.[24] Tramadol on a short-term basis can be useful. We would limit this to four weeks for a trial period to assess if the opioid was having a positive effect. However, caution is required with stronger opioids in the context of chronic non-malignant pain in accordance with national guidance.[25]

In some centres bisphosphonate therapy is commenced early on specialist advice although this is not widespread practice. There is some evidence of reduced levels of pain and improved mobility with its use.[26]

Topical agents have the advantage of localised action with reduced systemic side effects and are an attractive option in those intolerant of first-line antineuropathic agents or those vulnerable to side effects (the elderly; those with co-existing renal or hepatic impairment).[27] Topical lidocaine 5% plasters and capsaicin 0.075% cream have both been used successfully in CRPS, although the evidence is limited to case reports.[28] They are worth trialling while awaiting specialist input and generally well tolerated. It is prudent to warn patients regarding the initial burning and pruritus that can occur with capsaicin and to reassure them that this generally subsides after several days' use.

Where there is evidence of vasomotor instability and 'cold' CRPS, »

short-term treatment with nifedipine or phenoxybenzamine (a calcium channel blocker and alpha-adrenergic blocker respectively) have been shown to be effective.[29]

If the above measures are ineffective for pain reduction, a pain specialist will consider more invasive interventions such as intravenous ketamine or lidocaine, or sympathetic blockade such as stellate ganglion block for upper limb CRPS. In our centre, we would consider neuromodulation in the form of spinal cord stimulation or dorsal root ganglion stimulation for refractory cases. The evidence from randomised trials and guidance from NICE supports the cost-effectiveness of this treatment, with a cost per QALY of £3,562.[30,31]

It is imperative to mention that these interventions are only undertaken as part of a multidisciplinary package of care with the emphasis on allowing patients to engage with self-management, physiotherapy and psychology through the benefit conferred by these treatments. In the case of neuromodulation therapies, all patients locally are assessed by a pain physician, specialist physiotherapist, and psychologist prior to embarking on such an invasive intervention.

There is an interesting interplay between chronic pain and depression that has been well summarised in a recent article.[32] Essentially patients with CRPS should be screened for co-existing depression and anxiety with pharmacotherapy and psychological support instigated where appropriate.

We screen all patients for significant mood disturbance, whether pre-existing or secondary to pain as part of a biopsychosocial assessment process when they are first seen in the clinic.

The aim is to identify patients who warrant treatment of significant depression or anxiety, whether that be pharmacological or through the specialist pain psychology team who work within the pain service.

For anyone with a significant primary psychiatric disorder we involve the psychiatry team, whether that be for simple advice or directly asking them to see the patient for complex cases. If a patient is already seeing a consultant psychiatrist, we do not change their antidepressant medication to antidepressants with neuropathic benefit such as duloxetine without directly consulting them. Some patients, for example with bipolar disorder, will be at increased risk of mania with certain antineuropathic medications, so we would always consult with their psychiatry team before changing medication.

A psychogenic cause for CRPS has been refuted in the literature.[33]

DISCUSSION

The diagnosis of CRPS can be challenging, with patients often having multiple consultations and investigations beforehand to exclude other pathology.

It is important that once recognised, treatment is begun on an urgent basis to prevent poor outcomes. With an aggressive approach, 85% of patients will receive significant improvement in pain and level of function within the first two years following diagnosis.[34] Unfortunately, CRPS which has not improved within this timeframe is less likely to improve thereafter,[34] highlighting the importance of prompt recognition, explanation to the patient, and initiation of the multidisciplinary management strategies required.

Finally, the evidence base for treatment of CRPS to date is limited due to the poor quality of study methodology, compounded by the confusion and inconsistency of diagnosis (which has now been rectified by the Budapest criteria).

The primary aim of treatment is to improve physical function with specialised physiotherapy techniques, aided by whatever analgesia or intervention proves effective. Case reports abound, but the strongest evidence available supports pharmacological treatments such as bisphosphonates, neuropathic analgesics and ketamine.[21]

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Useful information

CRPS-UK
https://crps-uk.org

Arthritis Research UK
www.arthritisresearchuk.org/arthritis-information/conditions/complex-regional-pain-syndrome.aspx

Pain Concern
http://painconcern.org.uk