CHAPTER 26

Complex Regional Pain Syndrome

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- Complex regional pain syndrome is an uncommon but long recognized and high-impact regional musculoskeletal pain disorder.
- Current emphasis on pain sensitization mechanisms and earlier clinical recognition is facilitating management and improving outcomes.

Complex regional pain syndrome (CRPS) is a disorder of the musculoskeletal system that primarily relates to abnormal functioning of the sensory, sympathetic, and motor nerves. The clinical picture is varied, but the main components are those of regional pain and tenderness disproportionate to any inciting event and commonly coupled with vasomotor (swelling and color change), sudomotor (sweating), or motor abnormality (stiffness, weakness, tremor, or dystonia). There are a number of clinical presentations of CRPS, with milder forms being fairly common and having a good prognosis, but less common and more severe CRPS often responding poorly to treatment and being more persistent. Pain, emotional distress, and disability characterize this disorder.

EPIDEMIOLOGY

Criteria to define CRPS continue to evolve (1). Currently, most CRPS may be subclassified as CRPS type I, formerly called *reflex sympathetic dystrophy*, but when major nerve damage triggers the syndrome (around 10% of cases) it is subclassified as CRPS type II, formerly called *causalgia*. Both types are clinically identical. CRPS occurs in all races and geographical regions. It affects both sexes and may occur at any age, but most commonly between 40 and 60 years. In the adult presentation men slightly outnumber women but in the adolescent age group females predominate. Triggering factors associate with different age and sex distribution. For instance, CRPS following fall and fracture of the distal radius often occurs in osteoporotic women in the sixth decade.

The prevalence of CRPS is unclear (2). Minor forms are common after injury and might blend with clinical features which are part of the normal response to injury. Of 109 unselected patients with Colles' fracture, 25% had two or more features of CRPS at 9 weeks and 62% still had residual features at 6 months (3). Between 1 in 20 and 1 in 200 people presenting to a trauma unit develop CRPS. Before intense mobilization of patients with myocardial infarction and hemiplegia became standard treatment, it was estimated that between 5% and 20% would develop CRPS (4,5).

CLINICAL FEATURES

Trauma precedes CRPS in around 50% of cases. Another 25% is associated with a variety of miscellaneous medical disorders. These include diseases of the central nervous system, such as hemiplegia, cerebral tumor, or meningitis, or disorders of the peripheral nerves, such as nerve injury from herpes zoster, nerve root impingement, or peripheral neuropathy. Medications, particularly barbiturates and isoniazide, as well as pregnancy, metastatic tumors, and prolonged immobilization of a limb, are also associated with CRPS. About 25% of CRPS occurs for no apparent reason. In this setting there may be a background history of overt or subtle psychosocial distress (6). Distress-associated psychological factors are also seen in individuals with the specific triggering factors named above. The link between psychological distress and the onset of CRPS remains unclear as the persistent pain of the disorder may result in emotional distress as part of the individual's adjustment to the disorder. Whether cause or effect, emotional distress is a characteristic clinical feature of CRPS.

Chronic regional pain syndrome usually affects a distal limb component, for example, patella, digit, hand, or foot, with the key symptom of being pain out of proportion to any tissue damage in the region (7). The majority have persistent spontaneous pain often described as tearing or burning in quality. Lancinating pain occurs in one third and activity-induced pain is

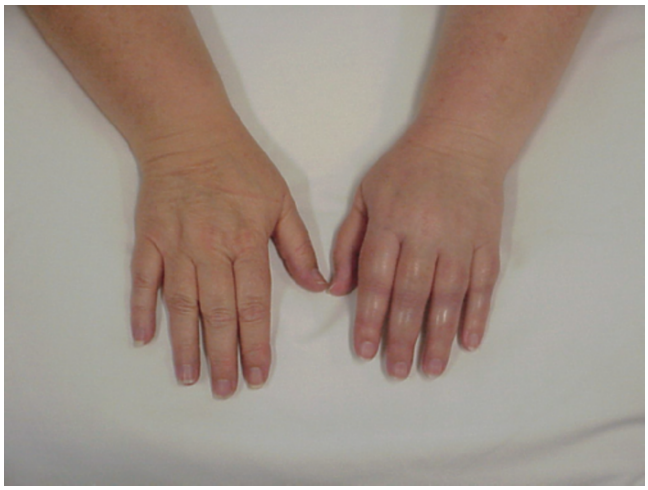

FIGURE 26-1

Chronic regional pain syndrome (CRPS) affecting left hand showing diffuse swelling, dusky discoloration, and shiny skin.

present in all. Many describe the painful area as "numb." Pain is associated with abnormal cutaneous sensitivity, manifesting as allodynia (whereby otherwise innocuous stimuli, such as touch, induce pain), and hyperalgesia (whereby pain perception is increased to a given painful stimulus, such as a pinprick). Unless there is a triggering nerve lesion, neurological examination of the painful and abnormally tender region will only show variable dysesthesia in a non-neuroanatomical distribution.

The most severe discomfort and allodynia is present distally, but the majority have abnormal tenderness present in the entire quadrant of the involved limb, including the low back or neck, as the case may be. The relevant spinal region is often stiff. Frozen shoulder may be a CRPS variant. In around 25% of cases, the opposite limb also develops similar but less marked clinical features.

Swelling of the involved area is common, usually diffuse and often associated with reticular or lividoid appearance over the skin of the involved part (Figure 26-1). Alteration in peripheral sympathetic tone may lead to other changes in skin color (cyanotic, pale, or red). Temperature may be decreased or increased, as may be sweating—there is no specific pattern. The distal involved limb of adolescents with CRPS tends to be cooler and those of adults warmer, but both may have temperature fluctuation over days and weeks. Finally, many patients have disorders of muscle function that might include peripheral weakness, proximal co-contraction and tightness, dystonia, spasm, tremor, or myoclonus. Tendon reflexes are usually normal or brisk. As time passes trophic changes may occur, but they are uncommon. Changes include unilateral differences in growth (more or less) of hair or nails and thinning of skin. A staging system for the progress of CRPS is now little used due to poor correlation with mechanisms and outcomes (8).

Variants of CRPS include transient regional osteoporosis, which often affects the hip. Fairly rapid onset of pain and restricted movement, without cutaneous features, are characteristic and a combination of appropriate clinical assessment, plain x-ray, bone scan, and magnetic resonance imaging (MRI) are usually diagnostic (9). The duration of symptoms is shorter, possibly because mobilization is easier, and there is usually an absence of precipitating trauma. Good outcome is expected but there is a propensity for recurrent episodes as well as involvement of multiple regions, often termed *regional migrating osteoporosis*.

LABORATORY FEATURES

There are no specific abnormal features on investigation and clinical features remain the most important contributors to diagnosis (10). Acute-phase reactants are not elevated. Routine radiological imaging in the first weeks to months may show patchy osteopenia affecting adjacent bones in the involved region or diffuse osteopenia later. This has only moderate diagnostic predictive value. Fine-detailed radiography will show some degree of cortical bone resorption in around 80%. MRI shows more clear-cut abnormality with regional or diffuse bone loss and increased T2 bone signal affecting many adjacent bony areas. Three-phase technetium bone scans are abnormal in around 75% of patients with established CRPS, with regional change in blood flow in the early phase and increase in bone uptake in the late phase (Figure 26-2) (11). Diminished flow and uptake

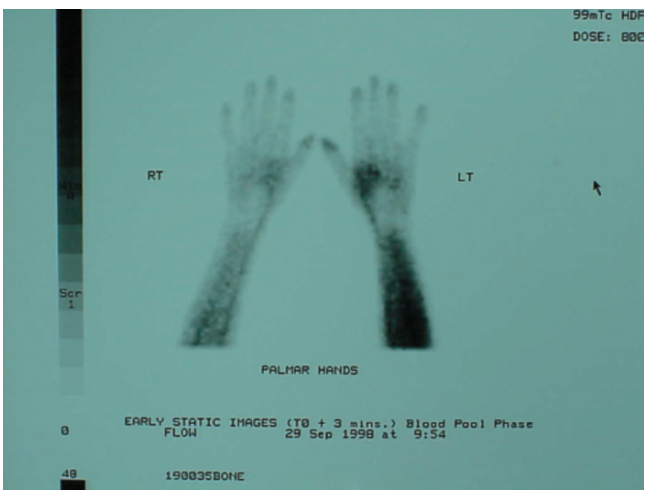

FIGURE 26-2

Technetium bone scan of patient with left forearm/hand chronic regional pain syndrome (CRPS) showing altered (increased) blood flow into involved part in early phase of study.

are more commonly seen in children and adolescents than in adults. Thermography may show significant changes compared to the unaffected side.

PATHOPHYSIOLOGY

The exact cause of CRPS remains unclear. However, the key pathophysiological abnormality lies in the change in function of peripheral sensory, autonomic, and motor nerves in the symptomatic region. This relates to both peripheral and central mechanisms. Increased activity in the two afferent nociceptor fiber types (the small diameter nonmyelinated C-fibers and myelinated A-delta fibers), the proprioception afferents (the large myelinated A-beta-fibers), and the sympathetic efferents appear to be mediators of many of the peripheral features (Table 26-1).

Enhanced sympathetic fiber activity, likely through release of norepinephrine will promote sensitization of peripheral nociceptors, decreasing threshold to mechanical and chemical stimuli. This may result in the hyperalgesia. In a minority subset of patients with CRPS, blockage of sympathetic nervous system inputs to the painful area will significantly modify clinical features, including pain. Release of proinflammatory neuropeptides, such as substance P, by activated C-fibers will likely contribute to regional neurogenic inflammation with increase in blood flow, edema, and other features such as synovitis and regional osteoporosis. The sensory peripheral nerves link to deeply placed pain transmission neurones located in the dorsal horn. In CRPS there is increased spontaneous activity of these neurones, called *central sensitization*. As a result of this process the large myelinated afferent A-beta fibers, which can also access these neurons, will now translate sensory mechanoreceptor function inputs into pain sensation.

TABLE 26-1. MECHANISMS OF CHRONIC REGIONAL PAIN SYNDROME CLINICAL FEATURES.

FEATURE	MECHANISM
Spontaneous pain	Peripheral nociceptor sensitization
Allodynia, movement	Mechanoreceptor input to sensitized dorsal horn transmission neuron
Swelling	Neuropeptide release from C-fibers, sympathetic neural effects
Sudomotor changes	
Vasomotor changes	
Bone, synovial changes	Neuropeptide and sympathetic effects
Dystrophy	Altered neural input to dermal structures

Thus, movement and touch, which otherwise would be innocuous, activate pain and account for the key feature of allodynia. The pain transmission neurons are modulated by other inputs, including descending pathways from the mid-brain which involve the neurotransmitters norepinenephrine and serotonin. These pathways link in turn to higher cortical centers, including those that relate to the emotional part of the brain. Other brain changes in CRPS include expansion of pain-related limb areas, implying plasticity and significant functional changes within the cerebral cortex (12,13).

Where there is a painful triggering cause for the CRPS it is likely that the nociceptive pain input to the dorsal horn will activate the sensitization process. The resultant emotional response to the pain and the injury predicament may both increase sympathetic tone and also impact on spinal cord sensitization through a change in spinal cord pain modulation, as described above. Thus, a mixture of peripheral and central interactions, of differing degrees in different patients, may sensitize the spinal cord. The resultant cascade of downstream events leads to the typical clinical features.

TREATMENT

Appropriate management of CRPS requires early diagnosis. The key clinical predictors for the problem are regional pain occurring in an emotional context, particularly after injury. Pain which seems out of keeping with the original injury, particularly where it becomes more diffuse and persistent, coupled with swelling and vasomotor change are the usual early features. Not all people get all components of the syndrome. In others, the original injury triggering the problem may still be present and might require independent treatment and investigation. Preventive strategies thus include identification of clinical situations where this syndrome has been shown to be common. Early mobilization after myocardial infarction, cerebrovascular accident, hand surgery, or mild peripheral injury is essential. Appropriate reassurance and explanation of all patients in the post-traumatic setting is a part of routine treatment. Addressing anxiety and sleep disturbance with explanation, physical therapy, or medication is essential (14).

Chronic regional pain syndrome is a pain syndrome and hence holistic management is required. This should include a team of individuals, including relevant family members and health professionals, which could include an occupational therapist, physiotherapist, psychologist, and doctor, among others. Patient education about the nature of the problem and the expected good prognosis is essential.

In milder CRPS, particularly in children, exercise programs that include hydrotherapy can be very helpful. To achieve good exercise, adequate analgesia may be

TABLE 26-2. MANAGEMENT PRINCIPLES OF CHRONIC REGIONAL PAIN SYNDROME.

Anticipate high-risk situations
Ensure accurate diagnosis and careful explanation
Indicate expected good outcome
Identify and manage psychosocial stressors Seek psychological advice
Encourage activity Involve physical therapist
Plan resumption of normal activities
Provide analgesia (acetaminophen, NSAIDs, opioids)
Consider transcutaneous nerve stimulation, hydrotherapy
Consider topical agents (capsaicin, DMSO)
Use tricyclic drugs early (e.g., low-dose mid-evening amitriptyline)
Trial of other drugs, more so in adults Oral corticosteroids, pregabalin, clonidine, bisphosphonates, many others
Review response each 2 to 4 weeks; adjust therapy if not improving
Consult anesthesiologist/pain management team Sympathetic nerve blocks Other strategies
Use various combinations of above according to response

ABBREVIATIONS: DMSO, dimethylsulfoxide; NSAIDs, nonsteriodal anti-inflammatory drugs.

required with the use of oral analgesics ranging from acetaminophen to more potent opioid medication at appropriate dosage for the patient's age. Where CRPS occurs in the context of medicolegal and similar safety-net deliberations, these need to be addressed as quickly as possible as they may act as significant stressors and negate response to otherwise appropriate therapy.

The role of sympathetic blocks remains unclear (15). In some patients temporary interruption of the sympathetic efferent nerve supply to the symptomatic region gives benefit. There are many ways to produce nerve block and an anesthesiologist or pain management team approach is required.

Medication approaches include the use of low-dose tricyclic medications, such as amitriptyline in doses of 25 to 50 mg. These drugs appear to act through modulation of descending influences on the central sensitization process in the spinal cord. Oral corticosteroids, such as prednisone 25 to 50 mg per day over a few weeks and tapering thereafter, may be effective in early CRPS (16).

Membrane-stabilizing drugs, such as gabapentin or pregabalin, may have benefit, but controlled trials are inconsistent or lacking. There is little evidence to suggest specific benefits from NMDA-receptor antagonists, opioids, or nonsteroidal anti-inflammatory agents, although these and other potentially neuromodulating drugs are often used empirically (17). Bisphosphonates may help prevent bone loss and help pain (18,19). Calcitonin, alpha blockers (prazocin), beta blockers (propanolol), or calcium channel blockers (nifedipine) may sometimes help. Appropriate trials for all these agents are lacking. In severe cases of this disorder, advice from a pain management center may be required and, rarely, more invasive neuromodulation therapies, such as dorsal horn stimulation, have been used (20).

Response to treatment in CRPS is unpredictable. Generally, earlier diagnosis and intervention result in better outcomes. Most patients have CRPS of mild-to-moderate severity that responds well to treatments. Adolescents are typical of this group (14). Some patients have more severe and persistent symptoms with resultant high impact on activities of daily living. A positive approach to treatment outcomes is appropriate for the majority (Table 26-2).

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