Complex regional pain syndrome (reflex sympathetic dystrophy)

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Chronic pain from complex regional pain syndrome (CRPS) or reflex sympathetic dystrophy (RSD) of the foot and ankle presents a myriad of diagnostic and therapeutic challenges to the foot and ankle surgeon. The disease involves multiple organ systems, including neural, vascular, bony, and soft tissue structures [1–5]. CRPS is a descriptive term defining a complex disorder or group of disorders that may develop as a consequence of trauma affecting the limbs, with or without an identifiable nerve lesion. To differentiate the presence or absence of nerve trauma, the two categories of CRPS type 1, with no identifiable nerve injury, and CRPS type 2, with identifiable nerve injury, have been proposed. CRPS consists of pain and related sensory abnormalities, abnormal blood flow and sweating, abnormalities in the motor system, changes in structure in both superficial and deep tissues (trophic changes), or functional impairment. It does not exist in the absence of pain.

CRPS may be sympathetically independent (SIP) or sympathetically maintained (SMP) [6,7]. Sympathetically maintained pain is defined as significant pain decreased or relief after sympathetic intervention by oral medications (eg, amitriptyline) or parenteral intervention (eg, IV phentolamine, stellate ganglion block). SMP is more completely characterized than SIP, is more responsive to treatment, and has a better prognosis. A hallmark feature of SMP is thermoregulatory and vasomotor instability responding to sympatholytic intervention. A mechanical or neural precipitating or exacerbating event is termed nociceptive.
Because the single best prediction of success in the management of CRPS is early treatment, the prompt diagnosis of CRPS, identification of the nociceptive focus, determination of physiologic staging (hot/cold, SMP versus SIP), and prompt treatment provide palliation and allow recovery.

**Anatomic/physiologic considerations**

Perception of pain is complex and is dependent upon the initiating event, afferent input, efferent modulation, and cortical interpretation. Nociceptive or painful events secondary to cellular damage produce a secondary inflammatory cascade, which includes the activation of polymodal afferent neurons (pain receptors) that input through the dorsal horn of the spinal cord to higher cortical centers (Fig. 1). If nociceptive signals are inappropriately intense or ineffectively modulated by descending pathways, symptoms may escalate beyond the magnitude of the cellular insult. In the extremity, increased receptor-neurotransmitter activity potentiates sympathetically maintained pain through one or more of the following: microvascular control, direct neural input, or central sensitization [8–11]. Following trauma, lower-extremity physiology is altered by the magnitude of the insult, subsequent internal responses, and external occurrences. How

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**Fig. 1.** Nociceptive (painful) information is relayed through the dorsal horn of the spinal cord for processing and modulation before cortical evaluation. (From Koman LA, editor. Bowman Gray orthopaedic manual 1996. Winston-Salem [NC]: Orthopaedic Press; 1996; with permission.)
an individual perceives pain depends upon a complex interplay of physiological occurrences and psychological adaptations. In the majority of cases, return to “normal,” or a premorbid functional steady state, occurs in a predictable manner [1,12].

The persistence of abnormal extremity physiology beyond normal time frames, with concomitant pain and functional impairment, is pathologic. The presence of transient dystrophic pain is normal, but the abnormally prolonged persistence of that dystrophic pain is pathologic and is termed causalgia, reflex sympathetic dystrophy, algodystrophy, or complex regional pain syndrome (Fig. 2). Persistence of pathologic responses can result in permanent structural or functional damage within the extremity, the central nervous system, or both. Because of individual variability in the natural history of the dystrophic process, time frames for staging CRPS often are inappropriate. Physiologic responses are influenced by the magnitude of damage from the initiating injury, the structures damaged, variability in premorbid physiology, existing extremity adaptability, and the effects of partial treatment [1,12–16].

Clinical definition

Reflex sympathetic dystrophy, a series of complex physiologic events, must include pain in combination with impaired function, trophic change, and auto-
nomically dysfunction [17]. The distinction between sympathetically maintained pain and sympathetically independent pain is important [7,10,11]. Because early recognition and treatment of RSD is the single most important predictor of functional recovery and pain relief, objective techniques to diagnose the syndrome are crucial [12,18].

Pain

Pain is manifest in a variety of presentations. Hyperalgesia, increased intensity of pain, is common and may be primary, affecting the area of injury, or secondary, affecting nontraumatized surrounding regions. Allodynia, pain produced by normally nonpainful stimuli, is frequently a characteristic of SMP. The use of standardized questionnaires or scales such as the Visual Analog Scale [19], the McGill Pain Questionnaire [20], the Rand Corporation short form (SF-36) [21–23], or a self-administered questionnaire for assessment of symptom severity and functional status are useful tests for conversion of subjective complaints of pain into objective scores [19].

Trophic changes

Trophic changes are common in the dystrophic process and include stiffness, edema, osteopenia, and atrophy of hair, nails, and skin. Edema may be followed with volumetric studies; however, most trophic changes are difficult to qualify. Osteopenia, unless severe, may not be documented by plain roentgenograms and, for quantitative analysis, must be analyzed by dual photon absorptiometry or quantitative scintigraphy [24,25]. Endurance testing using computerized equipment may detect subtle functional changes that may reflex extremity stiffness or atrophy [12,18].

Autonomic dysfunction

Autonomic function controls sweating, piloerection, and microvascular perfusion in the digits. It may be evaluated by an assessment of: (1) total digital blood flow, which is composed of both thermoregulatory and nutritional components; and (2) sudomotor activity (sweating). Total digital perfusion and its components can be analyzed by indirect measures such as temperature, laser Doppler fluxmetry, and plethysmography, and by direct techniques such as vital capillaroscopy (Figs. 3, 4) [26]. Sweating may be analyzed by changes in galvanic skin response, which measures skin resistance using Ag/AgCl (silver/silver chloride) electrodes. Changes in electrical conductance/resistance (galvanic skin response) are related to the rate of sweating, which in turn is under sympathetic control [12,20]. Quantitative analysis of thermoregulatory and nutritional microvascular flow allows physiologic staging of RSD and provides a mechanism to evaluate the effects of interventions and time upon the process (see Figs. 3, 4) [12,15,18,26–28]. Use of physiologic stress in some form is a
necessary component of extremity testing for reproducible analysis of dynamic physiologic events [12,15].

Physiologic staging

The inability to classify or stage CRPS with consistency has been a problem. CRPS may progress rapidly or slowly, so chronologic staging may confound the clinical picture. By using existing objective instruments and tests, it is possible to stage pain patients using physiologic and functional criteria. The following discussion assumes that patients fulfill the clinical criteria for CRPS as defined previously.

Sympathetically maintained pain versus sympathetically independent pain

Differentiation of SIP from SMP is important diagnostically. The former implies a more central process, often with irreversible end-organ adaptations and the presence of central pain. Prognosis for recovery in SIP is guarded.

SMP is diagnosed in patients who experience an improvement during or after treatment with sympathetic medications. Classically, SMP must respond to a epidural, intrathecal, or lumbar plexus block or peripheral nerve block. Rapid response to such blocks supports the concept of receptor-mediated CRPS and has led to the suggestion that pain relief following intravenous phentolamine, a mixed
α₁ and α₂ antagonist, is pathognomonic for SMP [29,30]. Not all patients with clinical SMP who respond to other forms of sympathetic intervention report relief with phentolamine, however. Although clinical signs and symptoms of RSD and pain relief following pharmacologic interventions that affect sympathetic controls can combine to support the diagnosis of SMP, it must be stressed that there is no single pathognomonic test for SMP.

Once a sympathetic component of pain is verified, it is important to determine the presence or absence of a mechanical or a neurologic focal trigger or nociceptive event. If an identifiable focus can be corrected, surgical treatment should be performed once optimal nonoperative relief has been obtained (Fig. 5). In the foot, ankle, and lower extremity, posterior tibial nerve entrapment or compression, contusion of superficial sensory nerves in the dorsum of the foot, peroneal nerve entrapment, or injury to the intrapatellar branch of the saphenous nerve are common nerve irritants. Mechanical nociceptive conditions include entrapment of the peroneal tendons, intra-articular abnormalities such as cartilage flaps, arthrofibrosis, and others. In general, these conditions require pharmacologic palliation preoperatively and pharmacologic protection postoperatively. Identifiable peripheral nerve lesions include neuroma, neuroma-in-continuity, and compression neuropathy. Neural involvement may have been primary (ie, part of an initiating injury), or secondary (ie, caused by altered extremity physiology). In either situation, the compromised and irritated nerve serves as a nociceptive focus. Surgical intervention is indicated if symptoms persist after nonoperative
intervention. Although surgery can precipitate a dystrophic flare, it still can be performed safely in patients with active or latent RSD [12,18,31].

Two major microvascularly mediated pathophysiologic stages associated with lower extremity CRPS are identifiable (Table 1): (1) the “hot swollen” stage—increased total flow with decreased nutritional flow, and (2) the “cold-stiff”

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**Table 1**

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<th>Symptoms</th>
<th>Increased total flow, decreased nutritional flow</th>
<th>Decreased total flow, decreased nutritional flow</th>
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<tr>
<td>Signs</td>
<td>Hot, swollen</td>
<td>Cold, stiff</td>
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<td></td>
<td>Edema</td>
<td>Atrophic</td>
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<td></td>
<td>Increased sweating</td>
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<td>Pain</td>
<td>Pain with hyperalgesia</td>
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stage—decreased total flow with decreased nutritional flow [8]. In addition, the presence or absence of edema, with or without hyperalgesia, provides two clinical subgroups within the increased total flow group. Treatment modalities can be selected based on specific physiologic states and the overall clinical condition. In general, the more simple techniques and drugs should be used before trying more complex modalities.

Management

Management alternatives of patients with CRPS include physical therapy, medication, and surgery.

Therapeutic interventions

Physical therapy is important in the management of patients with SMP. Motion of the lower extremity is crucial to provide cartilage nutrition and periarticular circulation to joints in order to decrease hypersensitivity and to prevent contractures. It is important for the therapy to involve the entire limb, because decreased ankle motion is a common complication in patients with CRPS of the knee. In addition, active and passive range of motion is recommended. Transcutaneous nerve stimulator (TENS), contrast baths, hydrotherapy, and continuous passive motion also may be helpful. It is theorized that the use of a TENS unit decreases symptoms by increasing nutritional flow and inhibiting smaller nociceptive fibers [32–34]. The use of contrast baths—alternating hot and cold therapy—can provide clinical palliation by overloading nonpainful larger fibers, and thereby blocking painful sensations.

Oral and parenteral pharmacologic treatment

The prompt use of pharmacologic management is integral to optimal outcome. Narcotic medications are less effective in managing dystrophic symptoms than sympatholytic interventions that: (1) decrease nerve hyperexcitability (eg, membrane stabilizers such as steroids or anticonvulsives); (2) diminish receptor upregulations (eg, phenolamines, \(\alpha_2\) agonists, tricyclic antidepressants); (3) block or decrease neural transmission (eg, peripheral nerve blocks, intrathecal medications); or (4) improve nutritional flow (eg, calcium channel blockers). Oral medications should be initiated early in the presence of “burning,” “tearing,” or “searing” pain that does not respond to analgesic medications (non-narcotic or narcotic). First-line agents include nonsteroidal anti-inflammatory drugs (NSAIDS), tricyclic antidepressants, (eg, low-dose amitriptyline), anticonvulsant (eg, phenytoin or gabapentin), or steroids. Because of concerns over the development of avascular necrosis, steroids are often avoided by orthopaedic surgeons but are commonly employed by internists. The judicious use of steroids is appropriate.
Surgery

If identifiable and manageable by surgery, dystrophic foci should be corrected after optimal pharmacologic protection has been obtained. Injury to peripheral nerves is the most common source of nociceptive (dystrophic) irritation; it may be associated with osseous and nonosseous derangements. Nerves may require neurolysis, neurorrhaphy, neuroma resection, and if necessary, environmental modification of the nerve bed [12,31].

When CRPS is suspected, a combination of NSAIDS may be combined with combination sympatholetics. For example, burning dysesthetic hyperpathic foot pain after a sprain associated with swelling would be treated with physical therapy, contrast baths, COX-2 nonsteroidal medication, low dose amitriptyline (25 mg tid or 50 gtts); and either phenytoin (100 mg tid) or gabapentin (starting at 100 mg tid), or a calcium channel blocker (eg, Norvasc at 5mg qd) may be employed. Drugs are tapered or actively increased depending on the patient’s response. If symptoms are not alleviated, a short course of high-dose steroid or continuous blocks should be considered.

In the presence of edema and localized hyperalgesia, an alpha2 agonist (eg, clonidine, 0.1 mg patch) may be applied to the hyperalgesic area. If the extremity is painful, cool, and early trophic changes are present, physical therapy, physical modalities (eg, contrast baths), a tricyclic antidepressant, and a calcium channel blocker may be effective.

If the patient shows no appropriate response, intermittent or continuous autonomic blocks should be considered. We prefer continuous epidural blocks for 5 to 7 days, combined with outpatient therapy. Optimal management of CRPS

<table>
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<th>Oral and parenteral drugs used in treatment of CRPS</th>
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<td><strong>Oral</strong></td>
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<td>Nonsteroidal anti-inflammatory</td>
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<td>Steroids</td>
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<td>Antidepressants</td>
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<td>Tricyclic</td>
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<td>Serotonin reuptake inhibitors</td>
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<td>Anticonvulsants</td>
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<td>Calcium channel blockers</td>
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<td>Alpha2 agonists</td>
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<td><strong>Parenteral</strong></td>
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<td>Steroids</td>
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<td>Alpha2 agonists</td>
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in the lower extremity is multimodal and requires titration of interventions and drugs, modifications of intervention based upon response, and art as well as science. General principles of treatment include: (1) use of physical modalities such as range of motion, intermittent stress (eg, weight bearing, impact), or contrast baths (should be initiated early); (2) oral medications based upon staging (hot/cold, edema/trophic) and adjusted depending on response; (3) use of the least invasive, least expensive, and safest interventions first, with an increase in complexity of treatment until adequate response occurs; (4) identification of any nociceptive foci and surgical intervention if necessary; and (5) the use of pain consultants for intermittent or continuous autonomic blocks in refractory patients. Oral and parenteral drugs used in treatment of CRPS are listed in Box 1.

Summary

The management of CRPS can be approached using objective criteria in a logical and systematic fashion. Frustration during treatment is common because: (1) the pathophysiology of CRPS is incompletely understood, (2) there is significant variation in presentation due to disparate premorbid anatomy and physiology, and (3) the natural history may be affected by incomplete treatment. Therapeutic efforts that should be effective may fail, and a trial-and-error approach to treatment is often mandatory. Early recognition of CRPS and prompt intervention, however, provide the best opportunity for clinical improvement.

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