Reflex Sympathetic Dystrophy
Complex Regional Pain Syndrome (CRPS)

Recognition and Management for the Physician

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ABSTRACT

Reflex Sympathetic Dystrophy is a dysfunctional pain response to a noxious stimulus. It is characterized by pain out of proportion to the inciting event, which may be quite insignificant but can be severe. In its earliest stages reflex sympathetic dystrophy is responsive to sympathetic blockade, pharmacologic agents, other modalities, and physical therapy. Early recognition and treatment is critical, because unrecognized reflex sympathetic dystrophy left untreated can result in irreversible neurologic and functional deterioration. A new nomenclature is presented, Complex Regional Pain syndrome, (CRPS) Type I, and for the similar entity causalgia Complex Regional Pain Syndrome, Type II.

INTRODUCTION

Reflex Sympathetic Dystrophy (RSD), now known as Complex Regional Pain Syndrome, Type I (CRPS I), is a pain syndrome characterized by an exaggerated response to a painful stimulus. It is a diagnosis often overlooked by the busy physician. The character of the injury may be severe as in acute trauma or surgery, low grade as in chronic overuse, or quite insignificant. The result, however, which is the hallmark of CRPS I, is pain out of proportion to the noxious stimulus. This pain not only long outlasts the healing phase of the acute event, but may spread within an extremity or to other extremities, causing significant neurological, functional, and psychological impairment. This often leads to frustration for both the treating physician and the patient. Their relationship can easily become adversarial when the painful mechanical source has been eliminated but the pain persists. An understanding of the signs, symptoms, and pathophysiology of CRPS I enables early recognition. Early referral to a qualified expert in pain management is critical. Prompt treatment is necessary to reverse the dysfunctional pain, arrest the functional deterioration, and salvage patient satisfaction and the doctor-patient relationship.

DESCRIPTION, DEFINITIONS, AND HISTORICAL PERSPECTIVE

Evans in 1946 (1) is credited with referring to reflex sympathetic dystrophy (RSD) as a disorder which was dependant upon abnormal sympathetic hyperactivity at the periphery. The first true proponent of the concept of RSD as a disease entity was John J. Bonica 1953 (2). Many names have been used to describe the same clinical entity, e.g. Sudeck’s atrophy, traumatic arthritis, minor causalgia, post-traumatic osteoporosis, post-traumatic pain syndrome, post-traumatic edema, post-traumatic angiospasm, shoulder-hand syndrome, and many others (3). It has been defined by the International Association for the Study of Pain as continuous pain in a portion of an extremity after trauma, which may include fracture but does not involve major nerves. It is associated with sympathetic hyperactivity (4), but this is not universally present. Causalgia in contradistinction, is a similar but separate syndrome describing the residual pain from damage to a major nerve trunk (5).

Disease Stages

In 1947, 3 stages of RSD were defined by deTakats (6), and later modified by Bonica in 1953 (2). Causalgia may present in the identical three stages. These stages may not always occur sequentially, and are presented for historical perspective only. They are no longer used to describe the disease, since we now understand that RSD can present in variable and unpredictable forms.

Stage I: Beginning within a few days or weeks of the precipitating event, this stage is characterized by pain, and often by burning, in the area of the injury. There is frequently hyperesthesia. Movement worsens pain; therefore, the limb is held immobile. There is usually accompanying edema, tenderness of the distal joints of the limb, and often local muscle spasm.
The limb may be warm, red, and dry, or cool and pale. This phase may resolve spontaneously and should respond rapidly to the appropriate treatment modality. The clinical course varies from a few days to a few months.

Stage II: As the RSD progresses, pain can increase, decrease or remain unchanged. There may be local hyperesthesia, paraesthesia, or alldynia, which is pain produced from a normally non-noxious stimulus such as light touch to the involved area. Edema spreads, adjacent joints become stiff, muscle wasting in the region of the injury begins, and the skin may become cold, pale, cyanotic, and moist. The hair of the affected limb may become thickened and coarse., the nails may become brittle. Diffuse osteoporosis may occur. Increased blood flow on scintigraphy is seen. Appropriate therapy can still be effective, but patients in this stage will be more difficult to cure.

Stage III: This stage is marked by severe trophic changes and resistance to treatment. The pain is variable, with increased and more diffuse alldynia and dysesthesia. The pain is usually burning in character, and may also be aching or throbbing. Exposure to cold, a draft, or damp weather may aggravate the pain. The limb is held extremely immobile, disuse muscle atrophy and contractures result, and joints may actually become ankylosed. Often the edema is resolved and the subcutaneous tissues atrophy. The skin is smooth, shiny, cold and often damp. The nails and hair are thickened and brittle. These patients are often anxious, tentitive, and depressed, experiencing all the vegetative symptoms of that state. Radiographs may show diffuse osteoporosis. More advanced and aggressive forms of treatment are required to help patients with this sort of problem.

Pain Categories

Sympathetically maintained pain (7): In CRPS I, sympathetically maintained pain occurs together with swelling, hyperesthesia, alldynia, burning dysesthesia, and temperature, color, and trophic changes to the extremity. These signs and symptoms may be inconsistent, presenting not at all, alone or in any combination. However, any pain which is relieved by and is responsive to sympathetic blockade is by definition sympathetically maintained pain.

Sympathetically independent pain: Some patients will present with symptoms and signs classic for RSD but will be unresponsive to sympathetic blockade. this is called sympathetically independent pain. Although not entirely understood, a potential explanation for this phenomenon is that the disease process has become so advanced that the pain becomes centrally maintained only. Accordingly, this situation is seen more frequently in chronic CRPS and only extremely rarely in the early stages of the disease.

Nomenclature

There has been dissatisfaction with the term reflex sympathetic dystrophy, because it is non-specific and imprecise. Furthermore, the entity is not a reflex; it is not specifically a disease of the sympathetic nervous system; and it is not a dystrophy. Therefore, in 1995 a new taxonomy (8) was formulated to include the terms, complex regional pain syndrome Type I (formerly reflex sympathetic dystrophy), and complex regional pain syndrome Type II (formerly causalgia).

Complex regional pain syndrome (CRPS) is a term that describes a variety of painful conditions which can follow injury, appearing regionally and having distal predominance of abnormal findings that exceed in both magnitude and duration the expected clinical course of the inciting event. Such conditions often result in significant impairment of motor function. The syndrome has been split into two clinical entities, defined by the presence or absence of an associated nerve injury. CRPS I is defined as a syndrome which develops after an initiating noxious event, in which continuing pain, alldynia, and hyperalgesia occur, associated with vasomotor, sudomotor, and
trophic changes to the extremity. The details of the entity will be described below. CRPS II can present in an identical manner but develops after a nerve injury.

Pathophysiology

The most accepted theory was proposed by Roberts (9). It incorporates many of the observations noted in CRPS I and suggests that the allodynia and spontaneous ongoing pain is the result of a chronic maladaptive sensitization of wide dynamic range neurones in the dorsal horn of the spinal cord, and is not due to heightened sympathetic tone. There is, however, a connection between the sympathetic nervous system and these wide dynamic range neurones.

One theory which explains much of the evidence is as follows. The output from skin mechanoreceptors is via large diameter Ab fibers. This output is influenced by efferent sympathetic activity, i.e., local norepinephrine levels. The touch receptors discharge afferent impulses at a rate proportional to the sympathetic tone. Under normal circumstances these sensory invoked impulses from touch fibers have insufficient magnitude to provoke a response from the wide dynamic range cells. However, when a wide dynamic range cell becomes sensitized following peripheral injury, referred to as “wind up”, the threshold of stimulation falls sufficiently so that it responds to the sympathetically maintained impulses from the touch receptors. The wide dynamic range neurones then convert this information into noxious impulses destined for the brain. If the level of norepinephrine circulating in the area of the mechanoreceptors is reduced, then their output is reduced and the pain disappears.

Sympathetic blockade relieves the pain of CRPS I and sympathetically maintained pain syndromes by reducing circulating norepinephrine and in turn the tone and output of the mechanoreceptors. However, if left untreated, and if the barrage of impulses bombarding the dorsal horn of the spinal cord from the periphery continues unchecked, neurone death occurs. A chronic pain state develops that may no longer respond to sympathetic blockade. The pain now becomes sympathetically independent pain. Although it does not explain all of the phenomena observed in CRPS I, this theory is a useful framework in which to consider these sympathetically related pain syndromes.

DIAGNOSIS

Incidence and epidemiology

The upper extremity seems to be involved more than the lower extremity, although lower extremity CRPS I is becoming much more frequently recognized. Females are affected more than males (2 & 4). The majority of cases occur between the ages of 40 and 60, but CRPS I has been reported in all age groups including infants (17). There is not a typical patient personality; however, CRPS I seems to occur more often in patients with a Type-A psychological profile (10).

Blunt trauma and fractures are cited as the leading causes (11-15). Surgery for carpal tunnel syndrome has been strongly associated with CRPS I (16). CRPS I can also be caused by crush injuries, burns, amputations, and other extremity surgery including arthroscopy (17) and arthroplasty (18). It is frequently seen related to chronic overuse injuries or repetitive low grade trauma (2). It may also be associated with a variety of other diseases including myocardial infarction, (5) neurologic disorders, infection, and vascular disease(2).

Causalagia occurs in 26% of peripheral nerve injuries, but is short lived in up to 20% of cases (2). Eighty-two percent of cases involve the brachial plexus, medial, sciatic or tibial nerves (2).
Clinical features and findings

The onset of CRPS I is normally preceded by some noxious stimulus, but this may be quite trivial, indeed. The clinical presentation may be variable. A high index of suspicion is necessary in order to avoid overlooking the diagnosis. Pain out to proportion to the clinical settings is really the hallmark of the diagnosis, and CRPS I should be suspected whenever this disproportionate pain is present. The pain may vary with barometric changes, worsening preceding foul weather, and it is rarely controllable with systemic narcotics. Sleep disturbances are prominent.

The primary clinical findings are pain of a burning, aching or shooting character, often worse at night, and may include, swelling and edema of the extremity. Disturbances in autonomic regulation can cause vasomotor (alterations in blood flow) changes, and sudomotor (alteration in temperature, color, and sweating) changes, as well as trophic changes to the skin, hair and nails. Sensory abnormalities can include intolerance to cold, hyper- or hypo-esthesia, hyperpathia (exaggerated response to painful stimuli), allodynia, and burning dysesthesias. Motor weakness and tremor can occur. Disuse because of the pain can cause joint stiffness, contractures, and disuse osteopenia. Psychological reactive disturbances, including anxiety, depression, and hopelessness are seen late, as the chronic pain erodes the usual coping mechanisms. The location of symptoms is non-anatomic and does not follow dermatomes, but occurs in a glove or stocking distribution, usually affecting the distal extremity worse and diminishing in a proximal gradient. Despite this long list of potential findings, there are no pathognomonic signs or symptoms of CRPS I. In addition, as noted previously, the stages of the disease, described above for historical completeness only, may not occur sequentially or even recognizably as distinct stages.

The clinical features may spread distally or proximally, independent of both source and site of the precipitating event in as many as 25% of patients (19). Seemingly unrelated areas may become affected. CRPS I of the lower extremity may spread up the spine to an ipsilateral upper extremity, or to the contralateral upper and lower extremities. Upper extremity CRPS I may spread proximally, causing headaches, sinus problems, occular dysfunction, and even cardiac arrhythmia's and anginal syndromes, and may also spread to the contralateral upper extremity or to the lower extremities. (20).

Complications from CRPS I can include phlebitis, drug dependence, inability to perform occupational and recreational activities, and activities of daily living. Suicide can result if psychological decompensation is not recognized and treated.

Diagnostic testing

It is crucial to identify an untreated stimulus for the sympathetically maintained pain. A thorough evaluation of the pain and its potential somatic etiologies by conventional methods is critical. Sympathetically maintained pain may be quite resistant to treatment, and any successful progress will not be sustained if a nociceptive or neuropathic stimulus persists untreated.

Sympathetic block is the diagnostic and therapeutic modality of choice for suspected CRPS I (21,22). In over 95% of patients with sympathetically maintained pain, sympathetic blockade will take away their pain. Other tests with some diagnostic value are thermography (23), the quantitative sweat test (24), triple phase bone scans (25,26), and IV phentolamine test (27). Although these may be confirmatory or suggestive of CRPS I, only formal sympathetic blockade correctly performed is diagnostic. There may be only a small percentage reduction of pain since some of the pain may have become sympathetically independent pain or there may be some residual a percentage of noicioceptive pain.
CRPS II, formerly known as causalgia, can present in a manner identical to CRPS I. The main differentiating feature is prior partial injury to a nerve or one of its major branches. Unrecognized local pathology such as a fracture, sprain, or strain must be sought, although CRPS I can coexist with such pathology. Traumatic vasospasm, cellulitis, Raynaud’s disease, thromboangiitis obliterans, and thrombosis can all present with some symptoms similar to CRPS I; however, these entities should not respond to sympathetic blockade, and normally have distinctive features to aid in the differential diagnosis.

The diagnostic criteria for CRPS I include (28):

1. The presence of an initiating noxious event, or a cause of immobilization.

2. Continuing pain, alldynia, or hyperalgesia with which the pain is disproportionate to any inciting event.

3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain.

4. No evidence of other conditions that would otherwise account for the degree of pain and dysfunction. (Criteria 2-4 must be satisfied)

TREATMENT

The primary goal of treatment is to reduce the tone of the local sympathetic nerves in order to rest the wide dynamic range neurons and allow them to return to their previous condition (plasticity of the spinal cord). Simultaneously, the extremity and joints which are not functioning properly need to be rehabilitated. Manipulation of contracted joints may be necessary with careful control of nociceptive pain in order to avoid a flare of sympathetically maintained pain, followed by careful management of the sympathetic nervous system and aggressive physical therapy.

Sympathetic Blockade and Physical Therapy

The primary treatment modalities for CRPS I and sympathetically maintained pain syndromes are sympathetic blockade and physiotherapy. In the upper extremity, sympathetic blockade can be achieved with injection of the Stellate ganglion, (29,30) the cervical epidural space (31), the interscalene area, and the brachial plexus (32), or by intravenous regional (Bier) (33) blocks. In the lower extremity, sympathetic blockade is achieved by injection of the lumbar ganglia (34), the lumbar epidural space (35-36) the femoral (37) or sciatic nerves (38), and also by intravenous regional (Bier) blocks (33). Other methodologies include intravenous phentolamine (39) or lidocaine infusions (40).

Commonly, oral medications will be administered, a sympathetic block will be performed and the patient will be sent immediately for physical therapy. The therapy should be done while the sympathetic block is in effect, if at all possible. Although passive manipulation and range of motion is important, they can cause nociceptive pain and a flare in the sympathetically maintained pain. Isometric strengthening and active and active-assisted range of motion should be emphasized. Ice must be vigilantly avoided, because of the cold intolerance associated with CRPS I. Provided the patient progresses and improves, this modality of treatment is continued. If
this program fails, more aggressive management with the use of more pharmacologic agents and interventional techniques may become necessary.

Pharmacologic Agents

Medications are important adjuncts to the primary treatment modalities. Analgesics, muscle relaxants, antidepressants, hypnotics, non-steroidal anti-inflammatory medications, steroids, adrenergic alpha blocking drugs (e.g., phentolamine, yohimbine), calcium channel blockers (e.g., Nifedipine), oral local anesthetics (e.g., mexilitene), and anticonvulsant (e.g., neurontin) may all have a role in treating the disease. In addition, intrathecal narcotics administered from an implantable pump may be necessary for intractable pain unresponsive to any other modality (41). This is an option of last resort, but unlike orally administered narcotics which seem to have little effect on the pain of CRPS I intrathecal narcotics are more efficacious (42).

Invasive Modalities

Acupuncture (43): This seems to be effective only during the treatment itself and lacks any sustained effects.

Removal of trigger areas: Local trigger areas, such as a neuromas, are an increasingly recognized cause of the disease(44). These areas may need to be removed for successful treatment of the CRPS I. Injection of phenol or alcohol, or application of radio frequency can be effective. Cryoneurolysis is felt by many to be the best treatment for these neuromas. Open surgery and excision may be necessary, but can be complicated by failure and recurrence.

Epidural injections/infusions: Dilute local anesthetics can be placed into the epidural space either with single injections of infused via in-dwelling catheters for weeks at a time. These provide effective sympathetic blockade and can be used prior to more invasive techniques (45).

Non-surgical sympathectomy: Chemical sympathectomy (46) or radio frequency applied to sympathetic ganglia (47), can temporarily decrease sympathetic tone, alleviate sympathetically maintained pain, and allow the wide dynamic range neurons to rest and recover normal function. Unfortunately the targets usually re-grow within three to four months; nevertheless, the unpleasant sequelae of a surgical intervention are avoided. (48).

Surgical sympathectomy: Surgical sympathectomies are generally discouraged in the treatment of CRPS I. 30-50% of patients develop a very resistant, sympathetically independent pain following surgical sympathectomy (48). In addition, the result may be incomplete, because of contralateral sympathetic innervation crossing the midline or regrowth of the sympathetic ganglion. Hypersensitivity to circulating catecholamines in the area may also cause return of pain.

Spinal cord stimulators: Spinal cord stimulators (49, 50) can be extremely effective in treating sympathetically maintained pain. Initially, there is a trial period with the stimulator lead in place and the stimulator external to the body. If satisfactory pain control is obtained, an internal stimulator is implanted subcutaneously. This functions similarly to a TENS unit placed directly over the dorsal column of the spinal cord, and has as its underlying theory the gate theory of Melzak and Wall (51). There is in increased use of stimulators in the earlier stages of the disease which allows physiotherapy to be carried out with much less pain and it is believed that the stimulator has a beneficial effect on calming the wide dynamic range neurons.

Intrathecal narcotics: For intractable pain not amenable to any of the above, intrathecal infusion of narcotics may be needed, (52) and the implantation of a narcotic pump may be necessary. It should be noted that narcotics do not work well peripherally on patients with sympathetically
maintained pain. However, given intrathecally, the medications do seem to have a more beneficial effect and there is less mental obtundation for the patient. (52).

Adjunctive Modalities

TENS Unit: These units will often help, particularly for nociceptive pain or calm a local pain trigger. The technology is entirely non-invasive, but has unpredictable results (53).

Biofeedback and Psychotherapy: Biofeedback has been shown to help patients with chronic pain (54, 55). Although not normally used as an early treatment of CRPS I, it may be helpful if the pain is resistant to management. In addition, many patients with CRPS I are depressed, and can exhibit any or all of the classic signs of depression. This is generally an understandable response to the chronic and debilitating pain. Usual coping mechanisms are exhausted as patients become sleep-deprived. Nevertheless, too many patients become labeled as malingerers, psychotic, or otherwise psychologically impaired. In fact, the changes in personality are a byproduct of the chronic pain and not the cause of it. Behavioral aberrations usually abate and psychological disturbances revert to normal once the sympathetically maintained pain is successfully treated (3). Short-term counseling and participation in local support groups available in many cities may be helpful.

ROLE OF PHYSICIAN

The most critical role of the physician is to suspect CRPS I and identify the process as early as possible. It is imperative that an underlying, chronically painful noxious stimulus must be excluded. A thorough search for a neuroma in the area of an incision, a persistent mechanical lesion in a joint or extremity, a hidden chondral lesion, or infection must be undertaken. Such a somatic pain focus will prevent successful treatment of sympathetically maintained pain. When and if surgery is necessary in the presence of sympathetically maintained pain, it should be done under epidural or other block anesthetic in order to control both the nociceptive and sympathetic pain, and this anesthetic should be continued in the postoperative period to decrease the potential for exacerbating the sympathetically maintained pain, (45).

Once the CRPS I is suspected or identified, early referral to a qualified pain management specialist is critical. This pain specialist should have available a wide variety of treatment options, and should be facile with sympathetic blockade. Early aggressive treatment is essential to prevent the often irreversible neurologic and functional sequelae of chronically untreated CRPS I. Close consultation regarding appropriate rehabilitative goals and techniques will be critical. The duration of treatment will vary with the extent and duration of the disease, but clearly a straightforward and successful outcome is much more achievable when treatment commences early.

SUMMARY

Physicians should maintain a high index of suspicion of the diagnosis of CRPS I. Pain out of proportion to the inciting noxious stimulus is its hallmark. A large array or paucity of other signs and symptoms may accompany this disproportionate pain. Once other causes of pain have been excluded, early referral to an expert pain management specialist is essential to insure its timely treatment in its earliest stages when it is most amendable to successful intervention. Left untreated or unrecognized, it can compromise the functional result of an otherwise successful surgery, and it can adversely impact patient behavior and personality with a corresponding negative impact on the physician-patient relationship.
REFERENCES


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