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Complex Regional Pain Syndrome I (Reflex Sympathetic Dystrophy)

Srinivasa N. Raja, M.D.,* Theodore S. Grabow, M.D.†

*COMPLEX regional pain syndrome (CRPS) type I, formerly known as reflex sympathetic dystrophy (RSD), and CRPS type II, formerly known as causalgia, are debilitating pain syndromes that have been recognized for more than a century. Despite the long history of these disorders, the natural course and pathophysiology of CRPS types I and II are elusive, and hence, their therapies remain controversial. The following overview highlights the clinically relevant aspects of CRPS type I in adults to guide practitioners in treating these patients. The reader is referred to recent reviews for discussions about the proposed pathophysiologic mechanisms of this syndrome.*¹⁻³

Terminology

Several terms have been used to describe RSD and causalgia-like syndromes. In recent years, the traditional concept of the involvement of the sympathetic nervous system in RSD has been questioned because only a subset of patients with presumed RSD respond to sympathetic blockade. In addition, the lack of evidence for a reflex mechanism and the presence of dystrophy in only a subgroup of patients implied that RSD is a misnomer. Hence, a new terminology has been adapted by the International Association for the Study of Pain to improve recognition of the disease and facilitate treatment outcomes research. The term complex regional pain syndrome was recommended by a Special Consensus Group.⁴

Historical reports suggested that sympathetic blockade alleviated the symptoms in patients with RSD, and hence, the term sympathetically maintained pain (SMP) has been used interchangeably with RSD. Because pain is maintained by sympathetic efferent innervation or by

circulating catecholamines in only a subset of patients with CRPS, the term SMP should be restricted to that aspect of pain that is relieved by specific sympatholytic procedures. Clinically, a patient with CRPS may have varying components of SMP or sympathetically independent pain throughout the course of disease.

Epidemiology

Complex regional pain syndrome frequently occurs in young adults and is more frequent in females than in males (2.3-3:1). The onset of CRPS is usually linked to a history of trauma, immobilization, or a procedure such as venipuncture, intramuscular injection, or surgery. There is no correlation between the severity of the initial injury and the ensuing painful syndrome.

Little epidemiologic data are available on the incidence of CRPS. Many types of surgeries on the extremities have been associated with the development of CRPS. The incidence varies from 7% to 37% for wrist fractures. A CRPS-like syndrome may be observed in patients with certain neoplasms, *e.g.*, lung, breast, central nervous system, and ovarian cancers, and in patients after myocardial infarction or strokes. A precipitating event may not be identified in approximately 10% of cases.

Psychologic factors, such as stressful life events and inadequate coping mechanisms, are potential risk factors that influence the development or severity of symptoms in CRPS. Eighty percent of patients with upper extremity CRPS of less than 3 months had a stressful social life event within the 2 months before or the month after a trauma compared with a 20% incidence in control patients. Nevertheless, no specific personality trait or psychologic factor has been identified that predisposes an individual to development of CRPS.⁵

Clinical Features

According to the International Association for the Study of Pain criteria, the characteristic features required to establish the diagnosis of CRPS type I are as follows: (1) the presence of an initiating noxious event or a cause of immobilization; (2) continuing pain, allodynia, or hyperalgesia with pain disproportionate to any inciting event; (3) evidence at some time of edema, changes in

* Professor of Anesthesiology and Critical Care Medicine, † Assistant Professor of Anesthesiology and Critical Care Medicine.

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Address reprint requests to Dr. Raja: The Johns Hopkins Hospital-Osler 292, 600 North Wolfe Street, Baltimore, Maryland 21287. Address electronic mail to: srnaja@jhmi.edu.

The illustrations for this section are prepared by Dmitri Karetnikov, 7 Tennyson Drive, Plainsboro, New Jersey 08536.

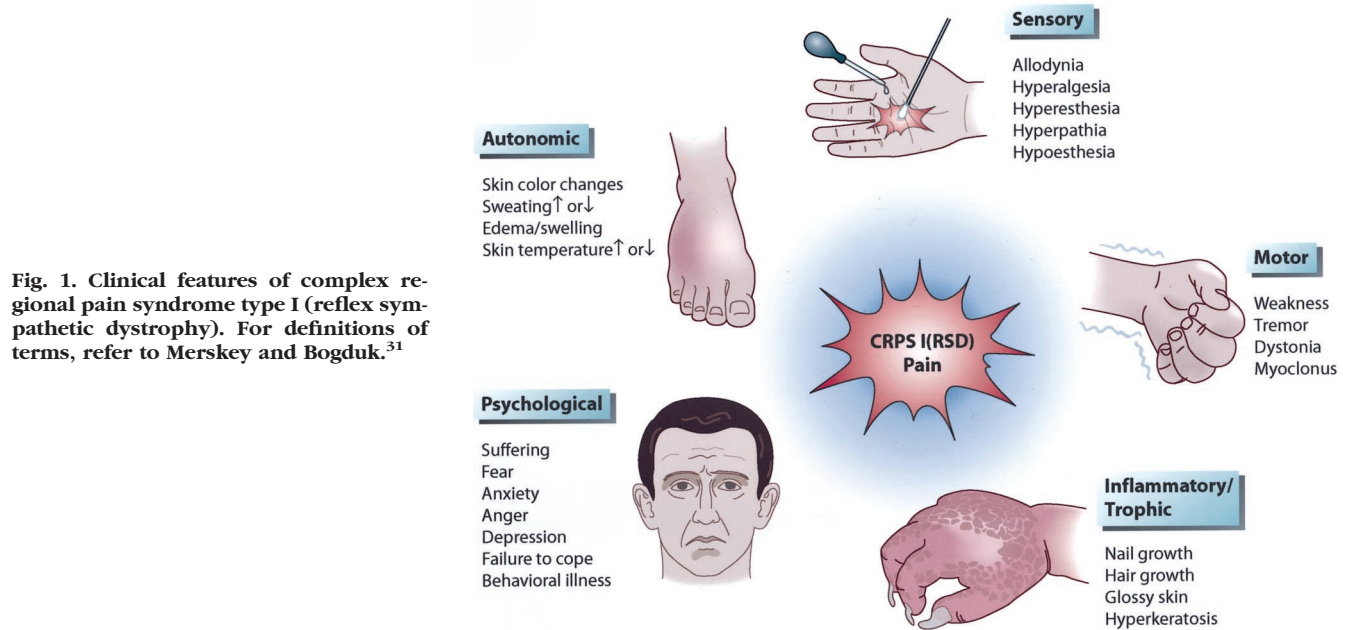


Fig. 1. Clinical features of complex regional pain syndrome type I (reflex sympathetic dystrophy). For definitions of terms, refer to Merskey and Bogduk.³¹

skin blood flow, or abnormal sudomotor activity in the region of the pain; and (4) the exclusion of medical conditions that would otherwise account for the degree of pain and dysfunction. Motor disturbances and trophic changes, such as altered nail and hair growth, may be observed in some cases. CRPS type II has the same clinical features as CRPS type I except for the presence of clinical signs and history consistent with a nerve injury.

The clinical presentation consists of a triad of sensory, autonomic, and motor signs and symptoms (fig. 1).^{3,6,7} Pain in CRPS varies in quality from a deep ache to a sharp stinging or burning sensation. Often, patients report that the pain is worsened by environmental (cold, humidity) and emotional (anxiety, stress) factors. Cutaneous hypersensitivity presents as pain on contact with clothing or exposure to a cool breeze. The involved extremity is often guarded, even from the examining physician. Patients frequently experience pain from innocuous tactile stimuli (allodynia) and have an increased response to painful stimuli (hyperalgesia). A cooling stimulus, such as a drop of alcohol or acetone in the painful region, may be perceived as painful, especially in the subset of patients with predominantly SMP. Neglect of hygiene is not unusual in the affected limb.

Vasomotor changes cause diverse skin discoloration, including various hues of red and purple to mottled, ashen, and gray. The presence of edema in the painful region gives a glossy and smooth appearance to the skin (fig. 1). A difference in skin temperature (either higher or lower of 1°C) is found in only 42% of patients with CRPS, and detectable differences are influenced heavily by ambient temperature. Sudomotor abnormalities range from hyperhidrosis to bone-dry skin. The vasomotor and

sudomotor changes are variable not only between patients, but also within individual patients over time.^{8,9}

Motor disturbances in the affected limb may present as tremors, weakness, muscular incoordination, decreased range of movement, muscle spasms, and dystonia. Dystonia in the upper extremity is typified by fingers fixed in flexion, or the clenched-fist syndrome (fig. 1). Dystonia in the lower extremity often presents as an equinovarus position of the foot. Range of movement may be compromised on the affected side, and contractures may develop in severe cases.

Considerable variability is observed in the intensity of symptoms, the rapidity of progression of the syndrome, and the response to standard therapies. In a retrospective analysis of more than 1,000 patients, severe complications, such as infection, ulcers, chronic edema, dystonia, and myoclonus, occurred in 7% of patients.¹⁰ These complications were more frequent in the lower extremity (65%), in younger female patients, and in patients in whom the acute phase of CRPS was associated with a decreased skin temperature. Infections were usually preceded by ulcerations, edema, or both, and infection was severe enough in one third of patients to require limb amputation.

The progression and recurrence of symptoms in CRPS have not been studied prospectively. A recent retrospective analysis of patients with CRPS I identified three different patterns of spread: *contiguous* spread in all patients, characterized by the gradual enlargement of the area affected from distal to more proximal regions of the limb; *independent* spread in 70% of patients, depicted by appearance of signs and symptoms at sites distant and noncontiguous from the initial site; and *mirror-image* spread (15%), typified by appearance of symptoms in the

opposite limb in a region similar to the site of initial presentation.¹¹ Studies suggest a 4-10% recurrence of CRPS in the same or another limb between 3 months and 20 yr after the first event. Although most cases occurred after trauma (56%) or surgery (20%), there was no clear etiology in approximately 20% of patients. These observations suggest that the spread of CRPS is not uncommon and raise the issue of whether there is a generalized susceptibility to this condition after CRPS develops.

Earlier reports suggested that CRPS may progress through distinct, sequential stages with an early, an intermediate (dystrophic), and a late (atrophic) stage. The latter stage, presumed irreversible, is characterized by trophic changes in skin, nail, and hair (fig. 1) and motor dysfunction resulting from prolonged disuse of the affected region. In a recent multicenter study, a cluster analysis was used to identify relatively homogenous subgroups of patients with CRPS based on their signs and symptoms and the duration of the disease.¹² Three subgroups of patients with CRPS were identified. However, these subgroups were not significantly different regarding the duration of CRPS, refuting the traditional view of progressive stages of the disease. The subgroup of patients who exhibited florid CRPS features, including motor or trophic changes and osteopenia, had the briefest disease duration of the three groups. The presumed stages hence may represent subtypes of the disease that are independent of the duration of CRPS.

Staging of the disease implies a critical window of opportunity after the development of CRPS for optimal therapeutic results. Therefore, it is commonly advocated that a limited trial of interventions that interrupt sympathetic function should be instituted early in the course of CRPS. However, direct evidence in support of these concepts is lacking.

Most patients with CRPS have associated symptoms of psychologic distress. Anxiety, depression, fear, anger, and other psychologic symptoms are considered to be the result and not the cause of CRPS. The signs and symptoms of CRPS may be worsened by illness behaviors, such as disuse and immobilization, or by maladaptive coping skills.

Role of the Sympathetic Nervous System

There is considerable evidence suggesting that the sympathetic nervous system has a role in chronic neuropathic and inflammatory pain states in both animals and humans (table 1; for details, see Baron *et al.*²). Preclinical models of neuropathic and inflammatory pain show up-regulation of α -adrenergic receptors, adrenergic receptor supersensitivity, and functional coupling between sympathetic efferent and sensory afferent fibers. Clinically, patients with CRPS type I have significant impairment of sympathetic nervous system func-

Table 1. Sympathetic Nervous System Involvement after Nerve Injury and Inflammation

Animal	Sympathetic sprouting in neuroma and dorsal root ganglia Up-regulation of adrenoceptors in neuroma and DRG Sympathetic fiber migration into denervated skin Increase afferent, neuroma, and DRG sensitivity to norepinephrine sympathetic stimulation and stress; effects are decreased by α -adrenergic antagonists Decrease in allodynia or hyperalgesia after chemical or surgical sympathectomy NE rekindles pain behavior after sympathectomy Increase in pain behaviors with NE injection or during stress
Human	Increase in adrenoceptors in skin Topical α_2 -adrenoceptor agonists (presynaptic decrease in NE) decrease pain in the affected region Chemical or surgical sympathectomy decreases pain Subcutaneous injection of NE or sympathetic stimulation rekindles pain after sympathectomy Increase in reported pain with stress Chemically-mediated allodynia and hyperalgesia are decreased by adrenergic antagonists and increased by NE

DRG = dorsal root ganglia; NE = norepinephrine.

tion¹³ characterized by decreased sympathetic outflow and increased adrenergic responsiveness in target tissues that may be reversible over time. This alteration of sympathetic function can be generalized (not necessarily limited to the affected extremity),¹⁴ which suggests aberrant processing in the central nervous system. Recently, patients with CRPS have been shown to have an increased density of α_1 adrenoceptors in hyperalgesic skin.¹⁵

Diagnosis

Clinical Presentation

There is no consensus with regard to how many of the different signs and symptoms described in the International Association for the Study of Pain criteria need to be present for an accurate diagnosis. However, CRPS should be suspected if the regional pain and sensory changes after a trauma exceed in magnitude or duration the anticipated healing period. Recent studies on the external and internal validity of the International Association for the Study of Pain criteria suggest that patients should have (1) at least one symptom in each of the following general categories: sensory (hyperesthesia = increased sensitivity to a sensory stimulation), vasomotor (temperature abnormalities or skin color abnormalities), sudomotor-fluid balance (edema or sweating abnormalities), or motor (decreased range of movement, weakness, tremor, or neglect); and (2) at least one sign within

two or more of the following categories: sensory (allo-dynia or hyperalgesia), vasomotor (objective temperature abnormalities or skin color abnormalities), sudomotor-fluid balance (objective edema or sweating abnormalities), or motor (objective decreased range of motion, weakness, tremor or neglect).^{16,17}

Vascular and neurologic examinations will help to detect the presence of conditions that may mimic CRPS. However, currently, there is no test that is easy to perform in the clinical setting to differentiate CRPS from similar pain states of separate origin. Neurologic conditions, such as diabetic and small-fiber peripheral neuropathies, entrapment neuropathies, thoracic outlet syndrome, and discogenic disease, should be excluded. Other differential diagnoses include deep vein thrombosis, cellulitis, vascular insufficiency, lymphedema, and erythromelalgia.

Additional Tests

Laboratory tests are not essential for the diagnosis of CRPS, but certain additional tests may help to confirm clinical impressions, determine the component of SMP, and design a therapeutic strategy. Tests of sensory (quantitative sensory tests to examine small-fiber function), motor (electromyogram and nerve conduction studies), autonomic (quantitative sudomotor axon-reflex test, thermography, sympathetic block, Doppler flowmetry), and trophic dysfunction (radiograph, bone scintigraphy) have been advocated to reinforce the diagnosis. A recent study suggests that diagnostic accuracy can be improved by incorporating information from laboratory tests into a disease probability scoring system.¹⁸ Currently, the prognostic or therapeutic value of any of these tests has not been substantiated by outcomes research. Increased periarticular uptake in delayed bone scintigraphy and demineralization on fine-detail radiography have been used to reinforce disease in the subacute (< 1 yr) and chronic stages, respectively. Nevertheless, the diagnostic use of these tests has been questioned because of the lack of differentiation between characteristic findings in patients with CRPS and patients with posttraumatic syndromes in general.

The clinical presentation of CRPS does not help to predict whether the sympathetic nervous system is involved in the generation or maintenance of the pain in a given patient. Selective and specific local anesthetic sympathetic blocks, such as cervicothoracic (stellate) ganglion block for the upper extremity and lumbar sympathetic block for the lower extremity, help to determine the involvement of the sympathetic nervous system. However, the potential for false-positive and false-negative tests and complications associated with these procedures have led to the introduction of an additional placebo-controlled test, the phentolamine infusion test. The rationale for this test is that sympathetic efferents release norepinephrine that is considered to be involved

in the generation or maintenance of the pain state. Phentolamine, a nonspecific α -adrenergic receptor antagonist, is infused intravenously (1 mg/kg over 10 min) while the patient is blinded to the time of drug administration.¹⁹ A significant reduction in pain that is coincident with the time of drug administration implies a role of adrenergic mechanisms in the pain state.

Therapy

General Strategies

Therapies for CRPS types I and II are similar and are guided by the recognition of the complex interaction between psychosocial and biophysical disease and the need for a multidisciplinary approach. In general, there is an incremental incorporation of therapeutic measures that combine aspects of physiotherapeutic, pharmacotherapeutic, and psychotherapeutic modalities (fig. 2). Ultimately, the treatment goal is pain relief, functional recovery, and psychologic improvement. No one therapeutic modality achieves this goal in all patients, and a scientifically proven cure for CRPS does not exist.

Numerous treatment modalities have been purported to be useful in the management of CRPS. These include pharmacologic therapies, physiotherapy, behavioral modification and psychotherapy, neuromodulation, surgical procedures, and miscellaneous complementary and alternative therapies. Studies on the role of different treatment strategies for CRPS are difficult to compare because of heterogenous inclusion criteria, inappropriate or absence of adequate controls, lack of adequate power because of small sample sizes, and lack of blinding or randomization. In addition, long-term follow-up studies are scarce.

Because the pathophysiologic mechanisms of CRPS are poorly understood, therapy has been directed at managing the signs and symptoms of the disease. Because no single drug has proven to be efficacious for all patients with CRPS, the continual reassessment of the adequacy of pain relief and the careful attention to the side effect profile of drugs are required to make meaningful decisions regarding the initiation or continuation of medications.

Medical Therapies (Oral, Topical, Intravenous, Infusion Therapy)

Few placebo-controlled trials have determined the therapeutic efficacy of analgesics for patients with CRPS, irrespective of route of injection or technique of drug delivery. Most of the adjuvant drugs currently used for the treatment of neuropathic pain have been used for the treatment of CRPS (see Kingery²⁰ for review). Recently, intravenous infusion of alendronate (bisphosphonate), a powerful inhibitor of bone resorption, was shown to be effective in a randomized, controlled trial in

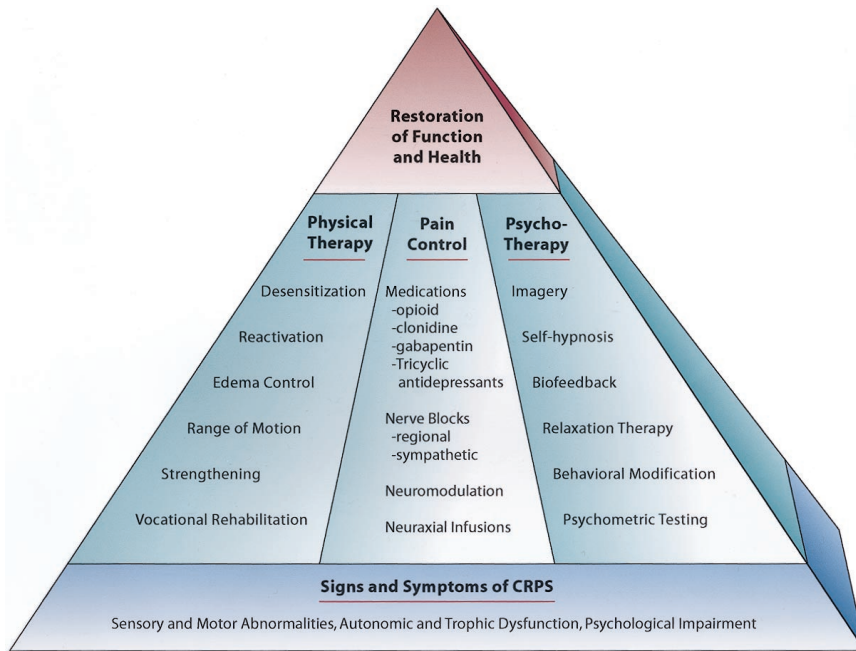


Fig. 2. Therapeutic goals and strategies for the management of complex regional pain syndrome (CRPS) type I (reflex sympathetic dystrophy). (Adapted from Stanton-Hicks *et al.*²⁷)

decreasing pain and swelling, and increasing range of motion in patients with CRPS. Other therapies reported to be effective in CRPS include topical dimethyl sulfoxide (a free radical scavenger), topical clonidine, oral corticosteroids, intravenous bretylium, intravenous ketanserin, intravenous phentolamine, intravenous lidocaine, and intranasal calcitonin.²⁰ Systemic α blockers (phenoxybenzamine, prazosin, doxazosin, and terazosin) may be useful in improving peripheral blood flow and tissue perfusion as well as reducing pain in patients with SMP. However, a recent meta-analysis of medical therapies aimed at inhibiting sympathetic function failed to establish the utility of sympathetic blockade.²¹ Despite controlling for effect size by weighting the methodologic quality of the studies, the variability in diagnostic inclusion criteria between the studies is a confounding factor in this analysis. Finally, the prophylactic administration of high-dose vitamin C in the perioperative period reportedly can decrease the recurrence of symptoms in patients with a previous history of CRPS.

Role of Nerve Blocks

Historically, interventions that interrupt sympathetic nervous system or adrenergic receptor function were advocated as treatments for CRPS. Despite popular opinion, there is little evidence-based information regarding the proper timing, number, necessity, or appropriateness of nerve blocks for the diagnosis or treatment of CRPS. Scientific progress regarding disease concept and taxonomy has led to a reappraisal of the role of sympathetic ganglionic blockade in CRPS management.²² Nerve blocks are recommended primarily to reduce pain and facilitate physiotherapy and functional rehabilitation. Nevertheless, a retrospective study showed that the

prophylactic use of stellate ganglion blocks in patients with a previous history of CRPS decreased recurrence rate of disease from 72% to 10% after reoperation on the affected extremity.²³

Neuromodulation

Implantable devices, such as spinal cord stimulators, are being increasingly used in intractable CRPS to produce symptomatic relief. Neuromodulatory modalities include peripheral nerve, spinal cord, and thalamic stimulation. The efficacy of most of these therapies has not been shown by placebo-controlled trials in CRPS patients. In a recent prospective, randomized, controlled study, patients with CRPS who received spinal cord stimulation combined with physiotherapy obtained greater pain relief and improvement in health-related quality of life compared with patients who received physiotherapy alone.²⁴ Spinal cord stimulation produced analgesia in patients with CRPS who had undergone previous sympathectomy. This observation suggests that spinal cord stimulation-mediated analgesia can be produced without inhibition of sympathetic function in patients with CRPS.²⁵ Although spinal cord stimulation does produce inhibition of sympathetic outflow, its mechanism of action is diverse and likely involves neurochemical changes at both spinal and supraspinal targets. In particular, spinal cord stimulation may have an inhibitory effect on A- β fiber-mediated hyperexcitability of dorsal horn neurons through a γ -aminobutyric acid (GABA)-mediated mechanism. The observation that patients can receive analgesia without alteration of sympathetic function suggests that pain and sympathetic function are not interdependent in all patients. This is supported by the finding that impairment of sympathetic function shows no correlation with clin-

ical symptoms of disease, such as pain, edema, or temperature differences, in patients with CRPS.¹³

Epidural and Intrathecal Drug Administration

Epidural clonidine has been reported to be beneficial in patients with CRPS in a double-blind controlled trial. Intrathecal drug therapy has been advocated for patients with CRPS refractory to conventional modalities based predominantly on case reports. A recent controlled study in seven patients with CRPS showed the efficacy of intrathecal baclofen for the treatment of dystonia.²⁶ A reduction in pain, autonomic, and sensory symptoms was observed in a subset of these patients after chronic infusion of intrathecal baclofen. These preliminary findings are particularly important given the fact that the treatment of severe dystonia with physiotherapy or surgery (tenotomy, tenoplasty) has been unsatisfactory.

Neuroablative Therapies

Surgical or chemical sympathectomy and radiofrequency ablation of sympathetic ganglia are options when conservative therapies have failed. The diagnosis of SMP should be confirmed with placebo-controlled tests before considering sympathectomy as a therapeutic option. However, a potential risk of sympathectomy is the development of postsympathectomy neuralgia, which may represent denervation supersensitivity of adrenoceptors. Amputations of the affected limb have been performed for pain refractory to medical therapy, for limbs with recurrent infections, and to improve residual function. Unfortunately, relief of pain is achieved only in a minority of patients after amputation.

Functional Rehabilitation with Physiotherapy

The primary objective of physiotherapeutic modalities is goal-oriented functional restoration. The algorithm for physiotherapy can be divided into four general steps that should be customized to individual needs: (1) desensitization of the affected region; (2) mobilization, edema control, and isometric strengthening; (3) stress loading, isotonic strengthening, range of motion, postural normalization, and aerobic conditioning; and (4) vocational and functional rehabilitation as well as ergonomic reconditioning.²⁷ In general, progression through physiotherapy will require concurrent application of psychological and pharmacological modalities. Despite the widespread conviction that physiotherapeutic modalities are beneficial for patients with CRPS, the effect of physiotherapy on the natural course of disease is unknown. To date, only the short-term efficacy of physical therapy compared with placebo therapy has been shown for patients with CRPS.²⁸

Behavioral Modification and Psychiatric Consultation

The recent International Association for the Study of Pain consensus report recommends that patients with

pain less than 2 months in duration generally do not require formal psychological intervention.²⁷ The panel of experts recommended that after 2 months, patients with CRPS should receive psychological evaluation, including psychometric testing, to identify and treat psychological disease, such as anxiety, depression, or personality disorder. All factors that contribute to patient disability should be determined. Counseling, behavioral modification, biofeedback, relaxation therapy, group therapy, and self-hypnosis should be considered. Therapies aimed at improving patient motivation and coping skills are necessary. For patients with pain longer than 6 months in duration, additional psychological testing may be warranted. Despite the fact that principles derived from cognitive behavioral theory are effective for treatment of chronic pain in general,²⁹ the value of cognitive-behavioral psychotherapy and psychometric testing specifically for patients with CRPS has not been fully determined.

Prognosis

The World Health Organization acknowledges the existence of a sequence between disease—impairment—disability, and handicap. A 5-yr follow-up study of patients with upper extremity CRPS revealed that patients continue to have impairments and disabilities in activities of daily living. Severe cases of CRPS may lead to marked limitation of function and even amputation of the affected limb. A 5-yr follow-up study in The Netherlands of patients with CRPS of the upper extremity indicated that 26% of patients had to change their jobs, and nearly 30% of patients had to stop work for more than a year. However, 72% continued to work full time.³⁰ Although most experts agree that the prognosis is poor when symptoms become chronic, the prognostic implications regarding the occurrence, timing, or intensity of the variety of sensory, motor, trophic, or autonomic disturbances that occur throughout the course of the disease are unknown.

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