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Practical Management of Complex Regional Pain Syndrome

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Complex regional pain syndrome (CRPS) describes a diversity of painful conditions following trauma, coupled with abnormal regulation of blood flow and sweating, trophic changes, and edema of skin. The excruciating pain and diverse autonomic dysfunctions in CRPS are disproportionate to any inciting and recovering event. CRPS type I is formerly identified as "reflex sympathetic dystrophy." CRPS type II is the new term for "causalgia" that always coexists with documented nerve injury. The present diagnostic criteria of CRPS I and II depend solely on meticulous history and physical examination without any confirmation by specific test procedure (or gold standard). There are only few clinical studies with large-scale randomized trials of pharmacologic agents on the treatment of CRPS. Bisphosphonates have been studied in multiple controlled trials, based on theoretical benefit of bone resorption, to offer pain relief and functional improvement in patients with CRPS. Many current rationales in treatment of CRPS (such as topical agents, antiepileptic drugs, tricyclic antidepressants, and opioids) are mainly dependent on efficacy originate in other common conditions of neuropathic pain. There are additional innovative therapies on CRPS that are still in infancy. No wonder all the treatment of individual CRPS case nowadays is pragmatic at best. Although the interventional therapies in CRPS (such as nerve blockade, sympathetic block, spinal cord and peripheral nerve stimulation, implantable spinal medication pumps, and chemical and surgical sympathectomy) may offer more rapid response, yet it is still controversial with unpredictable outcome. Nevertheless, we need to start pain management immediately with the ambition to restore function in every probable case of CRPS. An interdisciplinary setting with comprehensive approach (pharmacologic, interventional, and psychological in conjunction with rehabilitation pathway) has been proposed as protocol in the practical management of CRPS. It is crucial to have a high sensitivity value combined with a fair specificity in revising diagnostic criteria of CRPS. The validation and consensus for new rationalized diagnostic criteria of CRPS could facilitate further research to enhance clinical outcome including quality of life. These endeavors to minimize suffering from CRPS would certainly be appreciated by many patients and their loved ones.

keywords: complex regional pain syndrome, reflex sympathetic dystrophy, causalgia, pharmacologic therapy, interventional therapy

INTRODUCTION

Complex regional pain syndrome (CRPS) is one of the most challenging pain conditions for health care providers and patients. CRPS describes a severe painful condition following trauma, manifesting regionally with predominantly distal location over the extremities.[1] The common scenario is someone who suffered from an inciting event but kept on experiencing progressive pain despite recovering from the original trauma. The sympathetic dysfunction became apparent based on the abnormal changes in skin color, temperature, hair and nail growth, and abnormal sweating function. There were multiple terminologies such as "reflex sympathetic dystrophy" (RSD) and "causalgia" being applied to these mysterious and painful conditions for years.[2]

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DIAGNOSTIC CRITERIA

There was a consensus meeting that led to the current diagnostic criteria included in "Taxonomy of Pain" by International Association for the Study of Pain (IASP) in 1994. CRPS type I is the new name for RSD, and CRPS type II is now used to replace the previous term "causalgia."[3] The nonspecific history of minor injury is usually the prelude to the development of CRPS I. While in CRPS II, there is always a well-documented nerve injury accompanied by the clinical manifestation of pain and diverse sympathetic dysfunction.

The intractable pain in CRPS I and II could be spontaneous or induced by light touch (allodynia) and exaggerated by pinprick stimulation (hyperalgesia). The pain complaint is not limited to the territory of a single peripheral nerve. The striking feature "severe pain" is disproportionate to the inciting and recovering event. There is evidence of edema and vasomotor and sudomotor abnormalities in the region of pain since the inciting event. These are the common presentations of symptoms and signs in both CRPS I and II.

TIME COURSE AND STAGES

There used to be a description of 3 stages in the sequential progression of untreated cases of CRPS. It is uncertain whether the staging of CRPS offers practical implication to clinical management. The abnormalities of processing noxious, tactile, and thermal information in the somatosensory systems may be present to different degrees, that is, mild, moderate, or severe, in patients with CRPS.[4]

The clinical presentation of CRPS has significant variation among different settings. It is easier to diagnose a full-blown picture of classic case that fulfills the diagnostic criteria. However, there are more patients who meet only partial criteria and cause confusion and controversy for clinical management of CRPS. The current diagnostic criteria for CRPS I and CRPS II are dependent on a thorough history and physical examination.[5] The primary goal in evaluation and treatment of CRPS I and II is to start physiotherapy and occupational therapy in addition to pain management to achieve functional restoration as soon as possible.

PATHOPHYSIOLOGICAL MECHANISM

The significant parts of CRPS pathophysiology are evidently located within the central nervous system. It might be appropriate to illustrate the CRPS as a neurological disease. There are autonomic, sensory, and motor systems and cortical areas that are implicated in the processing of cognitive and affective information in CRPS. Inflammatory component and the neurological disease may play a vital role in the acute phase of CRPS.[6]

EPIDEMIOLOGY

The incidence of CRPS I was reported by Sandroni et al[7] to be 5.46 per 100,000 person-years at risk and an occurrence of 20.57 per 100,000 person-years. Female to male ratio was 4:1, with a median age of 46 years at onset. Upper limb was affected twice as commonly as lower limb. All cases reported some kind of antecedent event, and fracture was the most common trigger (46%).

Dijkstra et al[8] reported that the incidence of CRPS I after fractures of the distal radius might be low (1%). The incidences rate for CRPS II after peripheral nerve injury varies from 2% to 14% in different series, with a mean around 4% according to Veldman et al.[9]

The diagnosis of CRPS in pediatric population was often delayed as compared with the counterpart in adult. There is a higher incidence of CRPS I at or just before puberty (mean 12.5 years) with female to male ratio of 4:1. In contrast to adult, the lower limb is more affected than the upper limb with a ratio of about 5:1. CRPS II is found with roughly equal incidence in both boys and girls. Although the recurrence rate of CRPS in children may be higher than that in adults, response to reinitiating of treatment seems to proceed efficiently according to the article by Wilder.[10]

DIAGNOSTIC TESTS

There is no gold standard for confirmation of CRPS by any specific test procedure.

Three-phase bone scintigraphy may provide important information for the common osseous changes in CRPS. A pathological uptake in the metacarpophalangeal or metacarpal bones was proposed to be a highly sensitive and specific marker of CRPS. It would only be useful to rule out other pain syndromes due to the lack of gold standard to compare with bone scintigraphy. The best timing to use bone scintigraphy is the subacute (up to 1 year) phase of CRPS. Plain radiographs, x-ray bone densitometry, and magnetic resonance imaging have not shown to offer sensitive and specific values in the work up toward CRPS.[1,11]

There are research tests that may offer additional measurement in clinical study on CRPS. Quantitative sensory testing may reveal impairment of warm and cold sensation and heat pain in patients with CRPS. Autonomic function testing comprises infrared thermometry, infrared thermography, the quantitative

sudomotor axon reflex test, and thermoregulatory sweat test and laser Doppler flowmetry.[1] It is not the standard of practice to incorporate any research tests to the diagnosis and treatment of CRPS. However, these are certainly important research tools to facilitate the clinical study on CRPS.

CLINICAL MANAGEMENT OF CRPS

These patients often present to primary care providers due to persistent pain of unclear etiology. The referral process may start with orthopedics or neurology and end up with pain consultant. The list of pain medications usually continue to grow but with unsatisfactory progress. Timely diagnosis and validation of clinical presentation for CRPS may result in a better outcome. Pain relief is a major factor that determines patient's willingness and cooperation to participate in the multidisciplinary approach on CRPS. Pharmacotherapy and nonpharmacological pain coping skills, for example, relaxation and biofeedback, may have synergistic benefit toward the management of CRPS I and II. Interventional therapies may help to provide additional benefit toward functional restoration in CRPS.

PHARMACOLOGIC THERAPY ON CRPS

It is hard to conduct any clinical trial on the pharmacotherapy of CRPS due to deficiency and controversy in objective diagnostic criteria and underlying pathophysiology. The paucity of available randomized trials of pharmacotherapy specifically on CRPS resulted in pragmatic approach for all health care providers.

Antiepileptic drugs

Although there are abundant pharmacotherapy trials on other naturopathic pain entities, for example, diabetic neuropathy and postherpetic neuralgia, we cannot truly extrapolate these results to the treatment of CRPS due to the dissimilar pathophysiology and variable clinical course.

Gabapentin and pregabalin are γ-aminobutyric acid (GABA) analog by structure. The mechanism of pain control may be attributed to modulating calcium channels at the alpha-2–delta ligand. Mellick and Mellick[12] presented a successful treatment of RSD using gabapentin in a case study of 6 patients. The reduction of verbal pain scale was 60%–100% with dose range of 300–800 mg 3 times a day. Tan et al[13] enrolled 21 RSD patients and treated them with gabapentin 900–1800 mg/day. There were significant improvements in spontaneous and provoked pain intensities. No statistically significant difference was obtained in parameters on functional improvement.

van de Vusse et al[14] enrolled 58 patients in a randomized double-blind, placebo-controlled, crossover study with two 3-week treatment periods with gabapentin and placebo separated by a 2-week washout period. Gabapentin had a mild effect on pain in CRPS I and significantly reduced the sensory deficit in the affected limb. It was concluded that a subpopulation of CRPS patients may benefit from gabapentin with vigilant assessment of frequent side effects, that is, dizziness, somnolence, and lethargy. Pregabalin has obtained the Food and Drug Administration label for postherpetic neuralgia and painful diabetic neuropathy. Pregabalin offers more linear pharmacokinetic profile over gabapentin and may result in a shorter course of titration and quicker response. However, there is no available study of pregabalin in the treatment of CRPS I or CRPS II.

Sodium channel blocking agents

Lidocaine is a sodium channel blocking agent and may have clinical implication in management of neuropathic pain. Wallace et al[15] has demonstrated that intravenous lidocaine affects pain in response to cool stimuli more than mechanical pain in 16 patients with neuropathic pain due to CRPS I and II. There was a lesser effect of lidocaine on spontaneous pain and pain induced by stroking stimuli. Lidocaine infusion had no effects on the pain induced by punctuate stimuli. Intravenous lidocaine may offer both diagnostic and therapeutic benefit in the treatment of neuropathic pain in CRPS.

Antidepressants

The clinical efficacy of tricyclic antidepressants (TCAs) has been well documented in multiple trials of neuropathic pain management except in CRPS. The main concern with TCA in neuropathic pain management is the varied anticholinergic and cardiac side effect. Morbidity and mortality associated with overdose is very concerning.[16]

Serotonin and norepinephrine reuptake inhibitors (SNRIs), for example, duloxetine, have been approved by the Food and Drug Administration for treatment of painful diabetic neuropathy and depression.[17] However, there is no clinical study of SNRI on the treatment of CRPS so far. Antidepressants are popular adjutants in the management of CRPS despite lack in clinical literatures. Selective serotonin reuptake inhibitors have not been shown to be as beneficial as TCA for neuropathic pain management. Citalopram, paroxetine, and bupropion had shown limited evidence of efficacy in diabetic polyneuropathy. Selective serotonin reuptake

inhibitors may only be considered in refractory case after exhausting the trial of TCA and SNRI in neuropathic pain and CRPS.[18]

Systemic steroids

There is evidence indicating that neurogenic inflammatory processes may contribute to the pathogenesis of early phase in CRPS. Hence, different nonsteroidal anti-inflammatory drugs have been used for anti-inflammation and pain management in the treatment of CRPS. COX-2–specific inhibitors may inhibit cyclooxygenase, preventing the prostaglandin production and the consequent hyperalgesia. However, the clinical study of nonsteroidal anti-inflammatory drugs or COX-2 inhibitor in the treatment of CRPS has not been available yet.

Oral prednisone (10 mg 3 times a day) provided improvement in the clinical course of 23 patients compared with placebo according to Christensen et al.[19] A short course of corticosteroid may be considered if there are prominent symptoms and signs of inflammation in the early phase of CRPS I and II.

Bisphosphonates

Bisphosphonates compounds (eg, pamidronate, alendronate, clodronate) may inhibit the process of bone resorption and have been studied in CRPS patients. Hence, a number of controlled studies on bisphosphonates in CRPS have been published. There were some improvements in joint movement and decrease in pain level. Robinson et al[20] studied a single dose of intravenous pamidronate 60 mg or placebo in 27 patients with CRPS I. The treatment response was variable but the majority improved.

On the other hand, intranasal calcitonin did not contribute any additional benefit to simple analgesic (paracetamol) in 35 patients with CRPS I while getting physical therapy during the course of treatment.[21]

Free radical scavengers

Free radical scavengers such as dimethylsulfoxide (DMSO) and N-acetylcysteine (NAC) are popular in the treatment of CRPS I in the Netherlands. Perez et al[22] reported that DMSO and NAC were equally effective in the treatment of CRPS I. DMSO appears to be more favorable for warm CRPS I, and NAC is more effective for cold CRPS I in clinical application.

Zollinger et al[23] have demonstrated a lower risk of developing RSD after wrist fracture when vitamin C 500 mg was given for 50 days in a prospective double-blind study.

Topical agents

Topical agents could be considered as an intuitive approach for the hyperalgesia and allodynia frequently associated with CRPS. Capsaicin activates the vanilloid receptor-1, provokes burning pain, and then desensitizes the localized area afterward. Ribbers and Stam[24] published a case report using 0.075% topical capsaicin successfully in a patient with CRPS I. There was also a preliminary report by Robbins et al[25] using topical large dose of capsaicin with significant efficacy in patients with CRPS.

Topical application of the alpha-2 adrenergic agonist clonidine was studied to relieve the localized hyperalgesia in patients with sympathetically maintained pain (SMP) by Davis et al.[26] Topical agents are good adjuvants in the treatment of CRPS thanks to easy application and minimal systemic side effect.

N-methyl-D-aspartate antagonists

The increase in expression of N-methyl-d-aspartate (NMDA) receptors was demonstrated in an animal model of neuropathic pain. Antagonists of NMDA receptor were studied in experimental and clinical settings of neuropathic pain.

Ketamine is a potent NMDA antagonist and has been used as a dissociate anesthetic. Correll et al[27] reported a retrospective analysis of 33 inpatients with CRPS I who received subanesthetic ketamine infusion (10–40 mg/h) for the range of 0.75–20 days. There was favorable pain relief with prolonged duration after the infusions of ketamine.

Koffler et al[28] demonstrated the reduction in acute and overall pain after 5 days of ketamine infusion (3–7 mg/h) in 9 patients with intractable pain due to CRPS I. There was no report of adverse neurocognitive effect except a mild decline in motor strength.

GABA agonist

Zuniga et al[29] presented 2 case reports that illustrate the efficacy of chronic intrathecal infusion of baclofen in the treatment of CRPS I. Both patients had intractable CRPS and had failed multiple treatment modalities, including intrathecal morphine.

van Hilten et al[30] have reported that intrathecal baclofen, a GABA-B agonist, provided effective treatment of dystonia in patients with CRPS. There is no other clinical study available for systemic application of GABA-B agonist in the treatment of CRPS.

Opioids

The use of opioids may be considered as second and third step in the World Health Organization analgesic ladders in cancer pain management. The indication for opioids in noncancer pain has been more controversial especially in the management of neuropathic pain and CRPS.

Watson et al[31] demonstrated that controlled-release oxycodone is effective and safe for the management of painful diabetic neuropathy and improves quality of life.

Gilron et al[32] enrolled 57 patients (35 with diabetic neuropathy and 22 with postherpetic neuralgia) in a randomized, double-blind, placebo-controlled trial. The combination of gabapentin and morphine offered better analgesia at lower doses of each drug than either as a single agent. They reported that constipation, sedation, and dry mouth were the most frequent adverse side effects with the combination of gabapentin and morphine in this study.

It is a common scenario in pain management of CRPS when opioids are being prescribed to provide immediate analgesia and to encourage participation in physical therapy and functional restoration. The risk and benefit ratio needs to be discussed thoroughly and then patients being consented for opioids management as part of the regimen on CRPS.

Methadone has a unique antagonistic action on NMDA receptors in addition to affinity for opioids receptors. Altier et al[33] reported a case study of 13 patients with neuropathic pain. Methadone was effective at relieving pain and ameliorating quality of life and sleep in 62% of the patients during a follow-up period up to 12 months. However, methadone should be considered only in opioid-tolerant patients because of high potency and long elimination half-life. The conversion from other opioids to methadone also requires vigilant titration and follow-up.

INTERDISCIPLINARY PROGRAM IN CRPS

Singh et al[34] reported improvement in function capacity and decrease in pain and anxiety levels in a prospective outcome study on CRPS. There were 12 patients with CRPS I who participated in 4 weeks of interdisciplinary program (physical and occupation therapy, psychotherapy, stellate ganglion blocks, and drug therapy) with a follow-up of 2 years.

Lee et al[35] also conducted a prospective, randomized trial in 28 children (8–17 years old) with CRPS. The treatment consisted of physical therapy and cognitive–behavioral treatment with 10 patients eventually receiving sympathetic blockade after recurrent episodes of CRPS. However, most children with CRPS showed reduced pain and improved function with a noninvasive rehabilitative treatment approach according to this study.

Complementary and alternative medicine

Acupuncture is one of the popular modality in complementary and alternative medicine for pain management. There are evolving studies on acupuncture for treatment of various painful conditions. Korpan et al[36] reported a double-blind, placebo-controlled prospective trial on 14 patients with history of CRPS for 1–6 months. There was no difference in clinical outcome between sham acupuncture and classical acupuncture group. Both groups underwent standard treatments of five times a week for three weeks. However, the number of patients of this study was small, so further study was planned. Acupuncture could be incorporated as part of an interdisciplinary program in CRPS because of the noninvasive nature and relatively easy access.

INTERVENTIONAL THERAPY

Nerve blockade

The clinical presentation of CRPS I or CRPS II may be caused by SMP with expected reduction of pain after sympatholysis. Sympathetic nerve blockade could serve as both diagnostic and therapeutic approach for SMP. However, there is no definite protocol on selecting candidate for lumbar sympathetic and stellate ganglion block in CRPS. It is also unpredictable for the effectiveness of repeated sympathetic blocks performed in patients with CRPS.[37]

Whenever patients reach the plateau in responding to nerve blocks, then it is time to consider more advanced interventional therapies, that is, peripheral nerve stimulation (PNS), spinal cord stimulation (SCS), chemical and surgical sympathectomy, implantable spinal infusion pumps, and deep brain stimulation. These interventional therapies could facilitate physiotherapy and occupational therapy and achieve functional rehabilitation in CRPS.

Intravenous regional anesthesia

Intravenous regional anesthesia (IVRA) has been use to provide anesthesia for surgery in extremity especially the hand. IVRAs with different medications have been studied in the management of CRPS.

Reuben and Skalr[38] conducted a prospective, nonblinded study in 7 patients with CRPS of the knee. Five patients received complete pain relief after a course of 4–6 sessions of IVRA with clonidine 1 μg/kg in 50 mL of 0.5% lidocaine.

Reuben et al[39] also reported a prospective, randomized, double-blind study in 84 patients with previous history of CRPS undergoing surgery on the affected upper extremity. All signs and symptoms had resolved before the time of surgery. Patients were randomized to receive IVRA with 0.5% lidocaine with either 1 mL normal saline or clonidine 1 μg/kg. The recurrence rate

of CRPS was significantly lower (10%) in those patients receiving IVRA with lidocaine and clonidine as compared with those receiving IVRA lidocaine alone (74%).

CRPS may develop frequently after fasciectomy for Dupuytren's contracture. Reuben et al[40] published a prospective observational study of 4 anesthetic techniques (general anesthesia, axillary block, and IVRA with lidocaine with or without clonidine). Axillary block and IVRA with clonidine offered a significant advantage for decreasing the incidence of CRPS compared with either IVRA with lidocaine alone or straight general anesthesia.

SCS and PNS

Kemler et al[41] published a randomized controlled study on SCS in patients with refractory RSD. Those patients in the SCS and physical therapy group experienced significant reduction in level of pain as compared with the physical therapy group.

Harke et al[42] conducted a prospective trial on 29 patients with CRPS I with documented responsiveness to sympathetic block as prerequisite. When SCS was combined with concurrent physiotherapy, there was a reduction in the level of both deep pain and allodynia in addition to the improvement in functional status and quality of life.

PNS may offer support for patients with CRPS II after exhausting other conservative modalities. In contrast to SCS in CRPS I, there is only limited literature regarding the efficacy of PNS in the treatment of CRPS II.[43]

Sympathectomy

Sympathectomy was proposed as the treatment for more "permanent" interruption of the sympathetic system to control the SMP in CRPS. Furlan et al[44] published a case report and systemic literature review on chemical sympathectomy for neuropathic pain. The chemical sympathectomy provided at best a temporary effect, limited to cutaneous allodynia. Only 44% of 66 patients in 13 studies that met the authors' inclusion criteria experienced meaningful pain relief, 19% reported no relief, and the remaining 37% reached no conclusion due to poor reporting of outcomes. How effective is surgical sympathectomy in CRPS? Bandyk et al[45] conducted a study on 73 patients with RSD who underwent 46 video-assisted thoracoscopic and 37 surgical lumbar sympathetic chain resections. Overall, patient satisfaction was 77%, and it was not significantly influenced by patient age, duration/stage of RSD, or extremity involvement (lumbar 84%; cervicodorsal 72%). The incidence rate of "new" complex regional pain or disabling compensatory sweating syndromes was reported as 7%. Nevertheless, there were other reports that raised the concern regarding the "post-sympathectomy neuralgia" that may complicate the clinical outcome of the CRPS.

CONCLUSION

The current treatment of CRPS is mainly empirical at best. The consensus is using interdisciplinary approach on CRPS to achieve pain relief and functional restoration. Pharmacotherapy only offers some symptomatic relief to facilitate progress in management of CRPS. It is common practice to prescribe conventional therapies for neuropathic pain, although not specifically studied in CRPS. The only systemic therapy evaluated in multiple controlled trials has been those drugs affecting bone absorption, such as the bisphosphonates.[46]

We may start with nonopioid medications such as TCAs and SNRIs and add on certain antiepileptic drugs. Opioids may be considered, in addition to other agents, only for intractable pain in CRPS due to the ongoing controversy. The long-term benefit of various pharmacotherapies in CRPS and the impact on the clinical course are still unclear at this time.[47]

Interventional therapies have always gone hand in hand on the treatment of CRPS. Nerve blocks may be indicated when patients present with mechanical allodynia, burning pain, and temperature and color changes associated with difficulty with progression in physiotherapy and occupational therapy despite adequate trials of pain medications.

SCS and PNS would be the next approach for patients with favorable yet only temporary response to nerve blocks and still not making progress in rehabilitation. Implantable medication pump and even chemical or surgical sympathectomy could be the invasive and destructive procedure to offer in those cases that are refractory to other treatments.[48]

There is a consensus report in the treatment algorithm that proposes an interdisciplinary pathway for CRPS.[1,49] The treatment should start as early as possible upon the clinical impression of CRPS. The concurrent rehabilitation and psychological pathways emphasize conservative approach while interventional procedures (sympathetic block) are being contemplated for SMP. The corticosteroids may alleviate the inflammatory component (edema) in acute stage of CRPS. The ongoing treatment plan may adapt to the severity of CRPS. If a patient experiences intense pain at rest and during movement, then immobilization and contralateral physiotherapy may be started with the aide of aggressive pain management. Sympathetic block may provide pain relief and facilitate the treatment in SMP. If a patient complains of pain only during the movement, physiotherapy and occupational

therapy may proceed up to pain threshold. Intensive physiotherapy and occupational therapy will help patients with mild severity of CRPS to achieve maximal progress soon.

Meanwhile, ongoing synchronized psychological pathway with pain coping skills, biofeedback and relaxation training, and cognitive–behavioral therapy would eliminate any obstacle against rehabilitation pathway. The frequency and intensity of psychotherapy can be adjusted closely according to the progress of treatment on CRPS.

In case of relapse, repeat pathway and consider advanced treatment such as epidural clonidine,[50] SCS, or PNS. The risk and benefit ratio of pharmacotherapy (especially polypharmacy) needs to be reviewed and updated on a regular basis.

There are few medical conditions that take as devastating a toll as CRPS on a patient and their loved ones. Future large-scale clinical trials of new treatment, whether single modality or combination treatment, need to base on the new ''statistically derived revisions of the IASP criteria for CRPS.'' Although the current IASP diagnostic criteria[3] were adequately sensitive, the validation research suggested the overdiagnosis of CRPS. It is crucial to have a high sensitivity value combined with a fair specificity in clinical management of CRPS. As far as research goes, we need high specificity to conduct studies in a more precisely diagnosed population of CRPS.[51]

Whenever the major breakthrough in basic science and clinical medicine happens, it is hoped that these patients who suffer from CRPS may see the light at end of tunnel.

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