Updates in Complex Regional Pain Syndrome
Atualizações em Síndrome Dolorosa Regional Complexa

Paulo Henrique Pires de Aguiar1,2,3
Bruno Camporeze4
Caroline Zapelini2
Ricardo Hiroshi Murashita Fujiki2
Jonathan Watanabe Rodriguez2
Pedro Henrique Simm Aguiar2
Giovan Cassia de Almeida Motta5

ABSTRACT
Background: The Complex Regional Pain Syndrome (CRPS), known as reflex sympathetic dystrophy, Sudeck atrophy, causalgia or post-traumatic pain has been described as an important cause of chronic morbidity, which acknowledge of clinical limits, pathophysiology and implications of pathogenesis is still little elucidated. Therefore a great dissatisfaction for patients and health professionals has been described regarding to the currently available therapeutic methods. Objectives: The goal of this paper is to discuss the current perspectives of physiopathology, diagnosis and treatment in CRPS. Methods: A review of the literature was carried out using the MEDLINE, LILACS, and SciELO databases, with preference to articles in English, Portuguese and Spanish. Results: The diagnosis is predominantly based in clinical evidences of signs and symptoms. Although it has been described in the literature in many studies and guidelines about the treatment of CRPS, there is no consensus of procedure indications. Between the surgical methods, the use of spinal cord stimulation and others neuromodulators approaches has been described associated to significant rates of success in the management of CRPS. Conclusion: According to the literature and authors experience, the successful treatment of CRPS is based in early diagnosis associated to experienced interdisciplinary team aiming the functional restoration and psychological aspect monitoring.

Keywords: Complex Regional Pain Syndrome, Chronic Pain, Physiopathology, Diagnosis, Treatment

RESUMO
Introdução: A Síndrome Dolorosa Regional Complexa (SDRC), conhecida como distrofia simpático-reflexa, atrofia de Sudeck, causalgia ou dor pós-traumática tem sido descrita como importante causa de morbidade crônica cujo conhecimento clínico, fisiopatológico e das implicações da patogênese é ainda pouco elucidada. Nesse sentido, há uma grande insatisfação dos pacientes e profissionais de saúde em relação aos métodos terapêuticos atualmente disponíveis. Objetivo: Discutir as perspectivas atuais de fisiopatologia, diagnóstico e tratamento na Síndrome Dolorosa Regional Complexa. Método: Foi realizada uma revisão da literatura nas bases de dados MEDLINE, LILACS e SciELO, com preferência por artigos em inglês, português e espanhol. Resultados: O diagnóstico é predominantemente baseado em evidências clínicas de sinais e sintomas. Embora tenha sido descrito na literatura em muitos estudos e diretrizes sobre o tratamento da SDRC, não há consenso sobre as indicações de procedimentos. Entre os métodos cirúrgicos, o uso de estimulação da medula espinhal e outras abordagens neuromoduladoras é apontado com taxas significativas de sucesso no manejo da SDRC. Conclusão: De acordo com a literatura e a experiência dos autores, o sucesso do tratamento da SDRC baseia-se no diagnóstico precoce associado ao equipe interdisciplinar experiente visando a restauração funcional e o acompanhamento do aspecto psicológico do paciente.

Palavras-chave: Síndrome Dolorosa Regional Complexa; Dor Crônica; Fisiopatologia; Diagnóstico; Tratamento

1Department of Neurosurgery, Santa Paula Hospital, São Paulo, Brazil
2Department of Medicine, Division of Neurology Pontifical Catholic University of São Paulo, Sorocaba, Brazil
3Department of Neurosurgery, Public Servant Hospital of São Paulo, SP, Brazil
4Medical School of São Francisco University, Bragança Paulista, SP, Brazil
5Department of Neurology, Santa Paula Hospital, São Paulo, Brazil

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INTRODUCTION

Historically known as reflex sympathetic dystrophy, causalgia or Sudeck dystrophy, the complex regional pain syndrome (CRPS) describes a diversity of chronic painful conditions with a disproportionate pain to the seriousness of the early injury or trauma and not limited to a nerve area or a specific dermatoma. The CRPS can develop following an injury, a trauma, after a surgery, a stroke or a heart attack, usually affecting one of the upper or lower limbs. The CRPS terminology includes Type I and Type II modalities, with no nerve injury established and with a nerve damage found, respectively. Although the CRPS has been described widely in the literature in retrospective and prospective studies, until the moment the etiology of this syndrome remains unclearly understood. It has been reported an incidence rate of 5.46/100,000 person/year, affecting mainly females around the third decade of life.

Regarding the symptoms of CRPS, associated symptoms such as sensory and autonomic disturbances have been described: disturbance of sudomotor function, allodynia or hyperalgesia, edema, changes in skin blood flow or furthermore, changings in autoregulation of blood flow and trophic changes, stressing the fact that, the syndrome shows many facets according to the time progression.

In the complex regional pain syndrome, the management seems to be more effective when started early, looking for partial or total recovery of symptoms. The objective of this paper is to prospect the various approaches developed within few years for the diagnosis of this condition and present some of the new treatments developed for these patients.

METHODS

Bibliographical consultation was performed from 1940 to 2017 using as keywords “Complex Regional Pain Syndrome”, “Physiopathology”, “Diagnosis”, “Treatment” in MEDLINE, LILACS, and SciELO databases, with preference to papers in English, Portuguese and Spanish and only based on human studies. Also, authors reviewed the references aiming the selection of relevant papers to be included in this critical review.

DISCUSSION

Symptoms and signs are variable and changing individually, justifying the significant challenge regarding to the diagnosis and treatment of this pathology. The CRPS is associated to several symptoms and signs summarized in Table 1. The most common and early showed are the inflammatory signs and symptoms such as redness, swelling, noticeable changes in temperature, pain and sensitivity.

Specific signs and symptoms show that situation can be irreversible, and the most important are spasms, pale skin, spasms and tightening, nail trophic changings. Emotional stress can be the cause of worsening of pain in this disease. A study demonstrated that 9-49% of the patients may develop movement disorders (MDs), including involuntary movements, bradykinesia, dystonia, myoclonus, and tremor occurring early, occasionally may be anterior the onset of typical signs and symptoms.

The prevalence of MDs is proportional to the length of duration of this disease. Several cases of CRPS may occur just after a local traumatic injury to one of upper or lower limb. Crush injury, fracture or amputation are the main causes of this phenomenon.

Emotional stress, surgery procedures, acute heart disease, infections and ankle sprain may culminate in the syndrome.
The physiopathological mechanism of trauma as a trigger is controversial and still unknown, but a disconnection between peripheral and central nervous system and amplified inflammatory reactions might be involved.

The grade of sequelae related to delayed treatment may be identified by the following signs: atrophy of muscles, weakness of bones and muscles, contracture, and rupture of ligaments, fixed position of hands and fingers, and feet and toes. Specific tests developed can identify early the disease and with statistical significance, the following items have being described early: pain sensation, vasomotor disturbance, sudomotor, edema, motor and trophic (Table 2, Box 1). Harden et al. and Bruehl et al. demonstrated that specific signs on examination and patient-reported symptoms could give important and decision data.

### Table 1. Signs and Symptoms of CRPS

<table>
<thead>
<tr>
<th>Sensitive:</th>
<th>Musculoskeletal:</th>
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<tbody>
<tr>
<td>Continuous burning or throbbing pain, usually in arm, leg, hand or foot;</td>
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<tr>
<td>Sensitivity to touch or cold;</td>
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<tr>
<td>Allodynia or hyperalgesia.</td>
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<td></td>
<td>Swelling of the painful area;</td>
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<tr>
<td></td>
<td>Joint stiffness;</td>
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<tr>
<td></td>
<td>Swelling and damage;</td>
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<tr>
<td></td>
<td>Muscle spasms;</td>
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<tr>
<td></td>
<td>Weakness and loss (atrophy);</td>
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<tr>
<td></td>
<td>Osteoporosis.</td>
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</tbody>
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<table>
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<tr>
<th>Dermatologic/Autonomic disorders:</th>
<th>Movement disorders:</th>
</tr>
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<tbody>
<tr>
<td>Changes in skin temperature (can range from sweaty to cold);</td>
<td></td>
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<tr>
<td>Changes in skin color (can range from white and mottled to red or blue);</td>
<td></td>
</tr>
<tr>
<td>Changes in skin texture (can range from tender to thin or shiny);</td>
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<tr>
<td>Changes in hair and nail growth;</td>
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<tr>
<td>Vasomotor instability.</td>
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<td>Reduction in functional capacity of affected limb;</td>
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<td></td>
<td>Loss of voluntary control;</td>
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<td></td>
<td>Bradykinesia;</td>
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<td>Dystonia;</td>
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<td>Myoclonus;</td>
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<td>Tremor.</td>
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**Box 1. Original International Association for the Study of Pain (Orlando) diagnostic criteria for complex regional pain syndrome.**

1- The presence of an initiating noxious event or a cause of immobilization;

2- Continuing pain, allodynia, 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 pain;

4- This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.
Table 2. Clinical diagnostic criteria for complex regional pain syndrome.

1- Continuing pain, which is disproportionate to any inciting event;

2- Must report at least one symptom in three of the four following categories:
   - Sensory: Reports of hyperalgesia and/or allodynia
   - Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   - Sudomotor/Edema: Reports of edema and/or sweating changes and/or sweating asymmetry
   - Motor/Trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin);

3- Must display at least one sign* at time of evaluation in two or more of the following categories:
   - Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)
   - Vasomotor: Evidence of temperature asymmetry and/or skin color changes and/or asymmetry
   - Sudomotor/Edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
   - Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin);

4- There is no other diagnosis.

Physiopathology

The perception of pain may be involved in a system of direct transmission of certain somatic receptors to the encephalon according to the main theory 14. The cortical and thalamic involvement are supposed to be related to patients with chronic pain diseases and fibromyalgia syndromes with somatosensory effects 15. The amount of pain perceived, moreover, is thought as consequence of direct trauma and intensity of noxious stimuli as well as related to the extent of injury; however, we currently denote that a differentiated complex physiopathological process regulates the pain.

Phantom limb is an important physiopathological model, showing that patients, who received analgesia blockage, developed an autonomic picture less intense after the amputation of the limb, meaning that a central pain can have its effect diminished with blockage of afferences 14.

When we understand the central changes induced by peripheral injury or noxious stimulation, we can identify a complete treatment for the relief and prevention of pathological pain. Different mechanisms may play a role. But inflammation is the most important agent developing the clinical picture of this syndrome 16,17. Tissue lesion activates C and A delta fibers of sensory nerves, which cause the delivery of P substance and Calcitonin-gene-related-peptide from the afferent nerve endings 18.

Local increased capillary permeability and vasodilatation are demonstrated causing oedema and an increase of skin blood flow, a process named neurogenic inflammation (Figure 1) 5,13,19. The mechanisms of MDs in CRPS are still nuclear, but it may be also explained by the inflammation initiated after injury in the area of peripheral sensory nerves, sensitization of nociceptive neurons in dorsal horns of the spinal cord (central sensitization) despite a lack of change of afferent input 20.
This theory explains the chronicity of pain and hyperalgesia, and allodynia. Other neurotransmitters and γ1 aspartate receptors must be involved. Two lines of research show that central sensitization may influence spinal motor circuitry. Fergusson et al. found that the induction of central sensitization might cause a spinal learning deficit with respect to simple motor responses to shock. Floeter et al. showed that the interneuronal circuits of the spinal column between nociceptive withdrawal reflexes (NWR) are also linked to the afferent neurons of the skin that intervene in the neurogenic inflammation. In animal models with neural inflammation, the release of the dorsal horn of the spinal cord alters the sensory response after nociceptive stimulation reducing its excitability.

Involvement of the central nervous system has an important characteristic: the central disinhibition, present in patients both with and without dystonia, indicated by studies of neurophysiology.

In addition, nerve damage causes plastic changes in neurons and post-ganglionic sympathetic afferents with reorganization of these neurons and of the somatosensory cortex. This central sensitization is related to spinal changes. In CRPS, it is possible that dystonia spreads to other extremities of the body. In this context, two studies revealed that 37% and 67% of the patients had two or more affected extremities.

Current studies on neuropathic pain in animals and humans have demonstrated a relationship between abnormal thalamic

Figure 1. Scheme proposed by the authors to explain the pathophysiology of Complex Regional Pain Syndrome.
rhythmicity associated to Thalamocortical Dysrhythmia (TCD) and the presence of central pain. The evaluation form used to compose this relationship was using magnetoencephalographic (MEG) imaging in CRPS Type I, in which there is no absence of nerve lesions 30.

With the use of independent component analysis (ICA) of the sensor, it was possible to reveal activity of the delta and / or theta range located in the somatosensory cortex and also in the orbitofrontal-temporal cortices associated to the realization of affective pain perception. Actually, the patients with Type I CRPS showed abnormal brain activity typical of TCD, whose diagnostic value indicates central origin for the disease and a treatment interest involving pharmacological and electrical neurostimulation therapies 30.

Neuropathic pain as well as other symptoms of CRPS may cause changes in motor cortical plasticity beyond the somatosensory cortex 24,31.

In this sense, motor cortical asymmetry can be understood as an effect of alteration of sensorimotor plasticity. In this way, the use of the unaffected hand and the presence of pain as a variable of cortical influence should be considered. The physiopathology remains controversial and speculative.

However, studies with transcranial electrostimulation and electroneuromyography propose that the pathophysiological mechanisms of the disorder do not disturb the neural circuitry that connects sensory and motor cortex 32.

The classification is divided in two types 33,34. In type 1, the reflex sympathetic dystrophy syndrome appears when there is no damage to the nerves of the affected limb after injury or illness. Ninety percent of people with complex regional pain syndrome have reflex sympathetic dystrophy syndrome. In type 2, a direct damage to the nerve occurs. Coronary catheterization using a transradial approach is an example of type I because of the risks of local complications. There have been reports in the literature of complications such as radial artery spasm, hematoma formation and compartmental syndrome at the site of access, but it is rare in cases of complex regional syndrome (CRPS) of the hand 33,34.

Diagnosis is done with a detailed medical history and physical examination. The Budapest Criteria is used when pain should be disproportionate to the inciting event in time and intensity, and the findings of sensory, motor, vasomotor and/or trophic changes. Besides not being explained by other pathology, such criteria reduce the misdiagnosis. Imaging tests are not specific. Physiological maps or neuropathic brain activity related to magnetic resonance imaging (MRI) could now be produced 35.

Patients with neuropathic pain, angina, and facial pain may present PET abnormalities which results are inconclusive. However, they are located in the thalamus and anterior cortex, demonstrating that the distribution is not random, at the same time as the discriminative responses in the insula and remains detectable 35. It is believed that functional activation of brain regions is reflected by increased regional cerebral blood flow (rCBF) in PET and blood oxygen level dependent (BOLD) in fMRI. Noxious stimuli normally cause increases in rCBF in the second somatic regions (SII), insular and in the anterior cingulate cortex (ACC) 36.

In general, pain caused by innocent stimuli has been associated with increased thalamic, insular and SII responses, together with a decrease in CBF in ACC 36. Imaging studies in allodynia cases should be encouraged to better understand the abnormal processing of cortical pain and central reorganizations. During analgesia, there is an increase in rCBF in areas of the brain activated by acute pain, mainly the thalamus and anterior cingulate 36.

The evaluation of responses, neurochemical correlates (PET), time course, individual strategies are needed together with the results of LEP and fMRI and this assessment are still challenges for the researchers 35. Electromyography may show any abnormality in CRPS regarding nerve conduction. However, thermography could be used. In the literature, a case of a man with difference of temperature on both forearms, confirmed the diagnosis of CRPS 37.

Treatment

In order to avoid physical problems related to the disuse of the limb and the psychological consequences of a life with chronic
pain, a quick and early diagnosis should be considered. According to the practical management protocol of CRPS, the treatment should be performed in a multidisciplinary manner, with pharmacological, psychological and interventionist approach allied to a good job of rehabilitation. Early treatment leads to improvement and even remission of CRPS.

Initially, the proposed treatment will be conservative with medication and physiotherapy. Combinations of drugs should be combined for each case. Treatment options include: physiotherapy and support for the return of the movement as soon as possible, in order to avoid the progression of the symptoms. We emphasize the importance of the multidisciplinary approach.

Several drugs can be used to treat CRPS:

Pain relievers: the use of painkillers, such as aspirin, ibuprofen and naproxen can ease pain and inflammation. Another option are opioids, which when administered in appropriate doses can provide good pain control.

Antidepressants and anticonvulsants: some antidepressants, for example amitriptyline and anticonvulsants, like gabapentin, may be used to control neuropathic pain resulting from CRPS.

Corticosteroids: steroid medications, such as prednisone, have immunosuppressive action and thus decrease inflammation and allow mobility in the affected limb.

Sympathetic blockade: another alternative for the treatment of neuropathic pain, such as CRPS, but its effects are short-term. In addition, there is little evidence of high quality to conclude regarding the use of local anesthetic sympathetic blockade (LASB). But the available evidence does not suggest so many benefits of LASB to reduce pain in CRPS. Kim et al. consider that a sympathetic continuous blockage is an acceptable option before performing neurolysis or rhizotomy by radiofrequency and even after implantation of spinal cord stimulation. In case of CRPS of the upper limb, for instance, we should seek an immediate treatment. In this context, star-crossed lymph node block is superior to intravenous regional anesthetic blockage of the upper limbs for pain in the refractory finger or associated hand. Cold reduces oedema and sweating and heat helps to relieve pain when the affected area is cool. In cases of sciatric causalgia, the combination of local therapies produces good results.

Physical therapy: the earlier the illness is diagnosed, the better the results obtained. Exercising affected limbs can help to reduce pain and improve the range of motion and strength.

Transcutaneous electrical nerve stimulation (TENS): in this approach, neuropathic pain is alleviated by stimulation of nerve endings. Neurostimulation applied directly to a single peripheral nerve can lead to pain relief, improve patient well-being, improve lasting sleep, and reduce the dose of analgesic medications that may cause dependence. Neuroma, direct injury of the peripheral nerve or a peripheral nerve that underwent surgeries due to compressive neuropathy is usually treated with neurostimulation in cases of refractoriness to treatment.

Biofeedback: the patient learns to become more conscious of his/her body. With this, it becomes possible to make the patient relax the body and relieve the pain.

Invasive Therapies

In epidural catheter with anesthetics agents for upper and inferior limb pain, an epidural catheter and two infracavitricular catheters are used to infuse the local anesthesia continually. A solution with 0.1% ropivacaine, preservative-free morphine (20 µg/mL) at 8 mL/h and ropivacaine 0.1% 6 mL/h is used in each infracavitricular catheter.

In spinal cord stimulation (SCS), ascending Aβ fibers are stimulated with electrodes inserted along the spinal cord, which results in nociceptive signal inhibition. Majority of patients with FBSS and CRPS Type I had an effective improvement of neuropathic pain.

Furthermore, the patients with stimulation experiment improvement of quality of life, as well as a greater possibility of returning to work when compared to others with no spinal stimulation. The SCS is also beneficial to patients.
with refractory angina pectoris, reducing their pain and hospitalization, and Failed Back Surgery Syndrome (FBSS) and CRPS type I and II. This device has multiple utilizations and can be used also in the treatment of neuropathic pain or subgroups of ischemic pain.

For neuropathic pain due to several etiologies in upper and lower limb, even caused by infectious diseases as Lyme, we found an ideal indication. Preoperative or intraoperative somatosensory evoked potential (SSEP) provide an objective prediction of patient outcome after SCS. According with Sindou et al., the SCS is just indicated to patients with preserved central conduction time (CCT).

This therapy is an effective way to manage the patients with CRPS type I (Level A evidence) and type II (Level D evidence), but a significant negative prognosis is the development of allodynia in patients with chronic CRPS. A high level of pain in CRPS-I is not a contraindication for SCS treatment. The treatment is better, according to evidences in the literature if the patient receives a SCS device associated to physiotherapy.

In the therapy of intrathecal clonidine, hydromorphone and morphine, CRPS is through catheter or pump. Some important considerations before the use of intrathecal drug needs to be observed, such as properly patients selection, delivery systems, and medications, as well as potential complications of therapy as infection, lesion of nerve roots and the measures of quality of assurance needed to ensure the patient safety.

We prefer to use the intrathecal drugs when direct nerve stimulation on spine cord fails, since there is efficacy reduction of the results of neuromodulation after a chronic use of opioid, and the patient will became dependent on such drugs, even with the stimulation relieving the pain. However, we prefer the central neurostimulation after such intrathecal devices delivering opioids.

The techniques of deep brain stimulation (DBS), motor cortex immobilization (MCS) and spinal cord stimulation (SCS) were indicated for patients with phantom limb pain and CRPS type II and, with still doubtful results, the results with MSCs appear to be superior to DBS. For deafferentation pain, the MCS has good outcomes minimizing the pain.

In spite of controversial results on the literature, in refractory cases of CRPS type II, a dual stimulation with spinal and motor cortex stimulation would be used. Deep brain stimulation with the implantation of electrodes in the somatosensory thalamus and the periventricular gray region demonstrated good results in the Failure Surgery Syndrome, as well as in patients with peripheral neuropathic pain.

The results in the central pain syndromes were not encouraging, for example in spinal cord injury pain and postpartum pain. One study performed direct stimulation of the median nerve for the treatment of iatrogenic complex regional pain syndrome (CRPS type II) in a patient with causalgia after many surgeries of carpal.

It was observed through the Visual Analogue Scale (VAS) a score 8 to 10 of a total score of 10 after a 15-day experimental study with median nerve stimulation by means of a quadripolar lead in the right carpal tunnel space. The pulse generator was implanted in the right inflatable bladder space. It was concluded that, by analyzing the VAS, there was an improvement in the capacity to sleep.

The interesting fact about their report is that after 36 months of follow-up, the patient was still experiencing good pain relief without other treatment. Therefore, the stimulation is a valid treatment and easy option to manage the iatrogenic CRPS type II. The permanent implant, such as StimRouter System, can be safe and effective in the treatment of chronic peripheral neuropathic pain.

In the University of Regina, Canada, a few devices were implanted direct in the sciatic nerve rami of L4 and S2 with good results using low voltage. The parameters of stimulation were less than 1 milliampere, <1 volt, pulse width between 30-60 millisecond and frequency of 60 and 120 Hz. The emotional
status (denial, anger and frustration) is a problem during the treatment and appropriated management may be used for that with psychiatry protocols and psychotherapy in our opinion. After the discharge from the hospital, psychological support is also needed.

For the treatment of dystonia and in patients with CRPS-I, benzodiazepines, high-dose baclofen and botulinum toxin may be used. In one study, intrathecal baclofen was used in a limited number of patients with dystonia and CRPS-I and demonstrated good results.

CRPS has a complex origin and is difficult to handle. Although many guidelines have been described regarding the clinical picture, pathophysiology, diagnosis and treatment of CRPS, there is still no consensus. The current treatment, due to the lack of more consistent scientific evidence, is based on empirical evidence or with unclear description. The result is due to the small number of patients surveyed.

Based on the literature and experience of the authors, the successful treatment is one in which there is an early diagnosis associated to the performance of an experienced interdisciplinary team aiming at monitoring the psychological aspect and functional restoration as a way to prevent long or permanent disability.

REFERENCES


CORRESPONDING AUTHOR

Paulo Henrique Pires de Aguiar, MD, PhD
Rua David Ben Gurion, 1077, apto 11
Morumbi, São Paulo
05634-001, São Paulo - Brazil
E-mail: phpaneurocir@gmail.com

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