Review Article

The complex regional pain syndrome: Diagnosis and management strategies

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ABSTRACT

متلازمة الألم الناحي المعقد هو مرض مزمن يصيب أحد الأطراف بعد الإصابة أو الصدمة. يرتبط بهذا المرض العديد من الأعراض بما في ذلك الألم الشديد والتورم في الطرف المصاب، وكذلك التغيرات في لون الجلد ودرجة حرارته. يتطلب علاج متلازمة الألم الناحي المعقد نهجا متعدد الجوانب، مع التركيز على خطط العلاج الشخصية ومعالجة العوامل النفسية. في هذه المراجعة نقدم نظرة عامة على التحديثات في التشخيص والعلاج بالإضافة الى المعايير السريرية للتشخيص، بما في ذلك الألم المستمر والتورم. يمكن أيضا تشخيص هذا المرض عن طريق التصوير الاشعاعي والاختبارات المعملية. يوجد هنا رؤى جديدة حول مناهج العلاج وفهم الفيزيولوجيا المرضية. يشمل علاج متلازمة الألم الناحي المعقد التدخلات الدوائية وغير الدوائية. تؤكد أحدث الإرشادات الخاصة بالعلاج على أهمية التشخيص والتدخل المبكرين، وخطط العلاج الشخصية، ومعالجة العوامل النفسية في إدارة المرض.

Complex regional pain syndrome (CRPS) is a chronic disease that affects a limb following an injury or trauma. The CRPS associated with symptoms, including severe pain, swelling, as well as changes in skin color and temperature. Treatment of CRPS requires a multidisciplinary approach, with a focus on personalized treatment plans and addressing psychological factors. This review provides an overview of updates in the diagnosis and treatment of CRPS. There are clinical criteria for diagnosing CRPS, including persistent pain and swelling. The CRPS can also be diagnosed with imaging and laboratory tests. Novel insights into treatment approaches for CRPS have been gained from advances in understanding its pathophysiology. Treatment of CRPS includes both pharmacological and non-pharmacological interventions. The latest guidelines for CRPS treatment emphasize the importance of early diagnosis and intervention, personalized treatment plans, and addressing psychological factors in managing CRPS.

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Complex regional pain syndrome is a poorly understood and challenging chronic pain condition that can occur at any age.[1,2] There is usually a trigger associated with an injury or surgery, although it may appear for no apparent reason in some cases.[3] Pain that is unrelated to any known injury is a characteristic feature of the condition, along with swelling, stiffness, changes in skin color and temperature, and reduced mobility.[1] Other body parts can be affected by CRPS, causing significant disability. The pathophysiology of CRPS is complex, involving a combination of neurological, vascular, and immune system dysfunctions.[4] Several studies have suggested the underlying mechanisms of CRPS, including an abnormal neurotransmission of pain signals to the brain, as well as activation of the sympathetic nervous system.[5] However, the exact cause of CRPS remains unclear, and much is still to be learned about the condition.

Despite the challenges in diagnosis and treatment, the understanding and management of CRPS have improved dramatically in recent years. The development of diagnostic criteria, such as the Budapest criteria, has improved the accuracy and consistency of CRPS diagnosis.[6] Furthermore, advances in imaging and laboratory tests have enabled clinicians to exclude other conditions and identify bone and soft tissue changes.[7] Treatment for CRPS is multidisciplinary and involves a combination of pharmacological and non-pharmacological interventions, including physical therapy, occupational therapy, cognitive-behavioral therapy, and pain management medications.[8]

The goal of CRPS treatment is to reduce pain and improve function. Therefore, it can be challenging to achieve these outcomes, and many patients continue to experience chronic pain and disability despite treatment.[9] As a result, in recent years, researchers have developed novel therapies that target CRPS, such as ketamine infusion therapy,[10] neuromodulation,[11] and stem cell therapy.[12] These emerging treatments could improve patient outcomes. This review demonstrates the latest advances in the diagnosis and treatment that could benefit patients suffering from CRPS.

II. Diagnosis of CRPS. Diagnosing CRPS can be challenging as no single test can confirm or rule out the condition. Therefore, the diagnosis is based on a combination of clinical criteria, imaging, and laboratory tests, ruling out other conditions with similar symptoms. The International Association for the Study of Pain (IASP) established the clinical criteria for the diagnosis of CRPS in 1994, and those criteria were updated in 2003 and 2013 respectively.[6,13] The Budapest criteria, the most recent version, is based on pain that is disproportionate to any known injury, along with 2 or more signs in at least 3 of 4 categories: sensory, vasomotor, sudomotor/edema, and motor/trophic.[6] These signs include changes in skin color, temperature, texture, swelling, decreased range of motion, and abnormal hair or nail growth.

Additionally, imaging and laboratory tests can help diagnose CRPS and rule out other conditions. It is possible to detect changes in bone and soft tissue caused by CRPS by imaging tests such as X-rays, CT scans, and MRIs, including bone demineralization and soft tissue edema, through imaging tests.[14] However, these tests are not specific to CRPS and may also be present in other conditions with similar symptoms, such as arthritis or osteoporosis. Laboratory tests, such as blood tests and skin biopsies, can also help diagnose CRPS and rule out other conditions. For example, blood tests can detect changes in inflammatory markers and associated with CRPS, while skin biopsies can identify nerve fiber abnormalities characteristic of the condition.[15] However, these tests are not specific to CRPS and may also be present in other conditions.

The CRPS can be misdiagnosed as other pain conditions, such as diabetic neuropathy or postherpetic neuralgia, or as neuropathic pain syndromes such as diabetic neuropathy or postherpetic neuralgia.[16] Therefore, additional tests, such as nerve conduction studies or electromyography might be needed.[17] Diagnosing CRPS requires thoroughly evaluating the patient's symptoms, medical history, and imaging and laboratory results.[6]

III. Pathophysiology of CRPS. Recent research studies have advanced our understanding of the complex pathophysiology causing CRPS.[4,18] One major cause of CRPS is inflammation, which can occur in response to injury or tissue damage, **Figure 1**. TNF-alpha, interleukin-1 beta, and other pro-inflammatory cytokines are released during inflammation.[19,20] These cytokines promote neuroinflammation and central sensitization, contributing to developing and maintaining chronic pain in CRPS patients.[21] It has been shown that elevated levels of proinflammatory cytokines are associated with an increase in the severity of CRPS pain.[22]

On the other hand, autonomic dysregulation is another major cause of CRPS, which can result from nerve damage or inflammation.[23] There are several physiological processes controlled by the autonomic nervous system, such as blood pressure, heart rate and hidrosis. Thus, in CRPS patients, autonomic dysregulation leads to changes in blood flow and skin temperature and symptoms such as swelling and hypersensitivity to touch.[24]

Moreover, other causes of CRPS can include brain and spinal cord changes, such as altered neural activity between different nervous system regions.[25] Patients with CRPS have functional connectivity changes between their primary somatosensory cortex and other brain regions.[26] All these pathophysiological findings could have implications for developing potential new treatment strategies that target each mechanism of CRPS.

Treatment options for CRPS. A. Pharmacological interventions: 1-Non-steroidal anti-inflammatory drugs. In terms of pain relief and anti-inflammatory effects, non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most common used medications.[27,28] NSAIDs inhibit the production of prostaglandins through Cyclooxygenase (COX) enzyme and reduce inflammatory mediators that play a significant role in pain and inflammation.[27,28] In CRPS, inflammation is believed to be a key factor in the development and persistence of symptoms, which include pain, swelling, and skin changes. Therefore, NSAIDs might be beneficial in managing CRPS in order to reduce pain and inflammation and improve overall function. However, most studies have demonstrated little or no benefit

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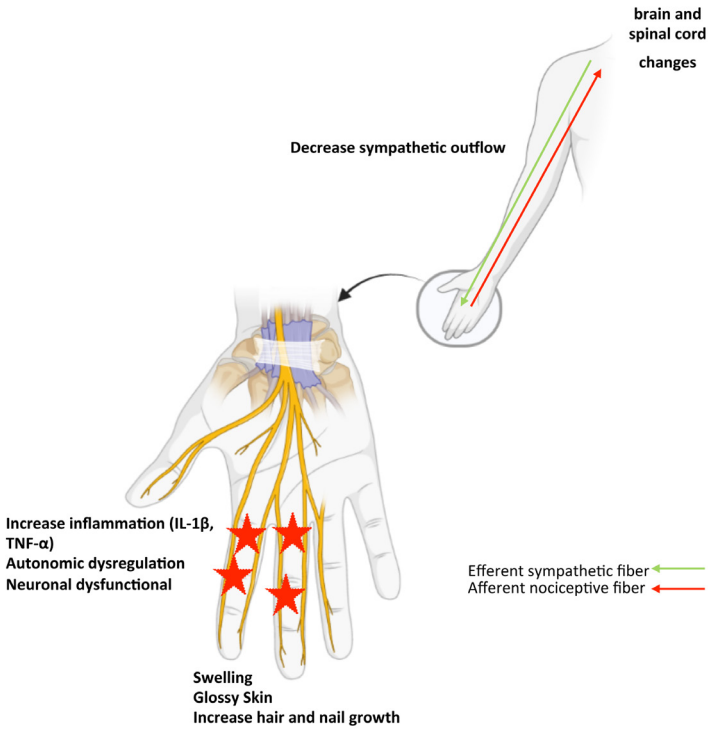

Figure 1 - The clinical manifestations and pathophysiology of CRPS

in pain reduction or functional improvement with NSAID.[29-31] Some studies have suggested that NSAIDs may be more effective in patients with early-stage CRPS or those with a predominantly inflammatory component to their pain,[29,32] while others have suggested that NSAIDs are ineffective in patients with long-standing or more severe cases.[29,31] Although, NSAIDs remain the least effective treatment option for CRPS, their efficacy and safety profile might be considered depending on patient-specific factors and disease characteristics. The NSAIDs need further research to be used optimally in CRPS and to identify which patients will most likely benefit from this treatment.

2. Opioids. Opioid drugs are commonly used for pain management, including treating CRPS.[33,34] However, the use of opioids in CRPS management is debated due to their potential for addiction and abuse and their limited effectiveness in treating chronic pain.[35-38] However, the use of opioids can be beneficial, particularly in acute pain situations.[39] The most commonly used opioids for CRPS treatment include morphine, oxycodone, fentanyl, and hydromorphone.[40-43] In spite of this, opioids should be carefully considered on a case-by-case basis in the treatment of CRPS. As a result, opioids should be used in conjunction with comprehensive treatment plans.

3.Antidepressants. Antidepressants are used in CRPS pain management as they improve both mood and quality of patient life.[44,45] Antidepressants modulate the activity of neurotransmitters, including serotonin and norepinephrine, in the brain.[46] Amitriptyline and nortriptyline are tricyclic antidepressants (TCA) that have been shown to be effective in managing pain associated with CRPS. Thus, it increases the availability of these neurotransmitters in the brain and helps alleviate pain. Reports have suggested that amitriptyline and nortriptyline were effective in reducing pain.[45,47] The potential efficacy of serotonin-norepinephrine reuptake inhibitors (SNRIs), such as duloxetine and venlafaxine, in the management of neuropathic pain in CRPS has also been investigated. These drugs increase the levels of catecholamine neurotransmitters serotonin and norepinephrine in the brain, which can help to reduce pain sensitivity.[48-50]

The use of antidepressants in treating CRPS remains controversial, with few studies suggesting that these drugs might effectively reduce pain and improve functional outcomes, while others have poor tolerability

or negative results.[51,52] However, given the low risk of adverse effects associated with these drugs, they may be considered a potential treatment option for patients with CRPS.

4.Anticonvulsants. Anticonvulsants are a group of drugs used to treat epilepsy; however, studies have suggested they are also effective in treating neuropathic pain conditions such as CRPS.[53,54] Anticonvulsant drugs block the voltage-gated ion channels in the brain and spinal cord, stopping the neurotransmission of pain signals.[55] Several anticonvulsant drugs have been used including gabapentin, pregabalin, and carbamazepine in CRPS patients. Gabapentin and pregabalin are both anticonvulsant medications that are effective in reducing neuropathic pain associated with CRPS. Several clinical studies have shown that gabapentin and pregabalin can effectively reduce pain, improve function, and improve the sensory deficit in the affected limb in patients with CRPS.[56,57] However, the mechanism is not fully understood, and some patients may not respond to treatment or could experience several side effects such as dizziness, drowsiness, or weight gain.[58] Carbamazepine, on the other hand, is an anticonvulsant medication that is often used to treat trigeminal neuralgia.[59] Some studies have also suggested that carbamazepine may effectively lower patients pain with CRPS.[60] Like gabapentin and pregabalin. Carbamazepine inhibits voltage-gated sodium channels (VGSC) leading to the inhibition of synaptic transmission. Nevertheless, anticonvulsants are considered a useful option in the treatment of CRPS and are often prescribed as part of a multimodal approach to pain management.

5.Sympathetic nerve blocks. It has been shown that sympathetic nerve blocks can treat CRPS in some cases.[61] Sympathetic blocks are performed by injecting lidocaine or bupivacaine into a targeted area. During this procedure, the lidocaine or bupivacaine is injected into the sympathetic ganglia within the affected limb or into the nerves that supply it. This procedure modulates the abnormal sympathetic activity that is believed to contribute to the pain and other symptoms associated with CRPS.[62] A sympathetic block's effectiveness, however, depends on several factors, such as its timing, location, severity, and duration of the condition. In some cases, sympathetic blocks may not be effective, or the pain relief may only be temporary. One potential benefit of sympathetic nerve blocks is that they can be used to confirm the diagnosis of CRPS. If the patient experiences significant pain relief following the block, it may provide evidence that sympathetic dysfunction contributes to their symptoms.[63]

6.Ketamine. One emerging treatment for CRPS is ketamine infusion therapy.[64] Ketamine is a dissociative anesthetic with analgesic properties.[65] It has been reported that ketamine is effective in relieving postoperative pain at doses lower than those required for anesthesia.[66] Ketamine block N-methyl-D-aspartate (NMDA) receptors involved in pain transmission.[65] It has been reported that ketamine infusion therapy can reduce pain and improve motion function in CRPS patients.[64] Study results indicate that patients with CRPS who received an escalating dose of ketamine infusion experienced an improvement in pain thresholds and a significant reduction in overall pain.[67]

B. Non-pharmacological interventions. A critical aspect of the overall management of CRPS is the addition of non-pharmacological interventions as part of the overall management strategy. The treatment of these conditions involves a variety of physical interventions, including mirror therapy, physical therapy, transcutaneous electrical nerve stimulation (TENS), acupuncture, and spinal cord stimulation. For individuals with CRPS, these interventions may help alleviate their pain and improve their function as well as improve their quality of life. Therefore, non-pharmacological interventions can be combined with pharmacological therapies to provide a more comprehensive treatment plan.

1.Mirror therapy. Mirror therapy is a relatively new rehabilitation technique that has shown promising results in treating CRPS.[68] This technique involves using a mirror to create a visual illusion of movement in the affected limb, which can help reduce pain and improve motor function.[69] Several studies have considered the effectiveness of mirror therapy in CRPS patients, with varying results. One study found that mirror therapy effectively reduced pain and improved the range of motion in CRPS patients.[70] The study included 8 patients who received mirror therapy for 15 minutes twice a day for 6 weeks. Mirror therapy showed a significant reduction in pain scores and improvements in hand function and range of motion. Another similar study found that mirror therapy significantly improved pain, function, and quality of life in CRPS patients.[71] However, not all studies have reported positive results with mirror therapy in CRPS patients.[72] Despite these mixed results, mirror therapy remains a promising treatment option for CRPS patients, particularly in those with upper limb involvement. It is inexpensive, non-invasive, and easy to administer, a pleasant option for clinicians and patients. However, more research is still warranted to determine the optimal duration and frequency of mirror therapy sessions and their long-term effectiveness in CRPS patients.

2.Physical therapy: Physical therapy is an important treatment modality for CRPS.[73] It reduces pain, improves joint mobility, and promotes functional independence.[74] Therapeutic exercises may include range-of-motion exercises, strengthening exercises, and proprioceptive training. Recent studies support the evidence of using physical therapy for CRPS, particularly in the early stages of the condition.[75,76] One of the primary goals of physical therapy in CRPS is to improve joint mobility and reduce muscle stiffness through manual therapy techniques, such as joint and soft tissue mobilization, and therapeutic exercises.[77] Desensitization training is another essential component of physical therapy for CRPS that should not be overlooked.[78] This involves exposing the patient to various sensory stimuli, such as light touch, vibration, and temperature changes, to reduce hypersensitivity and promote habituation.[78] Desensitization training can be challenging and uncomfortable for patients, but it has effectively reduced pain and improved functional outcomes in CRPS patients.[79]

3.Transcutaneous electrical nerve stimulation (TENS): TENS is a non-invasive treatment used to manage various types of pain, including chronic pain conditions such as CRPS.[80] The TENS involves an electrical current connected to the skin via electrodes, to stimulate the sensory nerves and reduce pain perception.[80] Growing scientific evidence supports the use of TENS in CRPS patients.[81,82] A randomized controlled trial investigated the efficacy of TENS in pain and disability in patients with CRPS.[83] The TENS therapy in addition to physical therapy significantly improved pain scores, edema, range of motion, and functional capacity compared to physical therapy alone.[83]

As well, another study evaluated the effectiveness of TENS in reducing pain and improving function in patients with CRPS of the upper limb.[82] The results showed that active TENS significantly reduced pain intensity and improved function compared to the control treatment.[82]

Furthermore, TENS is a safe and non-invasive treatment option that may be used alone or in combination with other treatments for CRPS. Further research is warranted to understand the effectiveness of TENS in CRPS, and to optimize the parameters of TENS application for optimal pain relief.

4. Acupuncture: There are a number of conditions that can be treated with acupuncture, including chronic pain. Acupuncture involves the insertion of fine needles into specific points on the body as part of a traditional Chinese medicine practice.[84,85] In recent years, there has been growing interest in the potential therapeutic benefits of acupuncture for CRPS.[86] A number of clinical trials have investigated the effectiveness of acupuncture in treating CRPS. The CRPS patients after stroke were treated with Jingu three-needle therapy along with Xingnao Kaiqiao acupuncture for a period of 6 months to observe the clinical therapeutic effects. The study involved 96 patients with CRPS after stroke. The study showed that both groups had significant improvements in visual analogue scale (VAS) score and hand swelling level.[87]

Electroacupuncture is still in the preclinical research phase on CRPS-related pain and disability.[88] A study investigated the efficacy of electroacupuncture in managing chronic postischemic pain (CPIP), which is used to simulate CRPS in animals.[88] Electroacupuncture at 100Hz provided a significant and long-lasting antiallodynic effect. It has been found that electroacupuncture can suppress the overexpression of chemokines in the dorsal horn of the spinal cord as well as significantly decrease the activity of neurons and glia in the area, as revealed by the study. Therefore, further research is needed to understand acupuncture's underlying mechanisms in CRPS better and optimize treatment protocols for maximum efficacy.

5.Spinal cord stimulation (SCS). The SCS has emerged as a promising treatment option for patients with CRPS.[89] The SCS involves the use of electrical stimulation to the dorsal columns of the spinal cord, which can modulate the transmission of pain signals and provide relief from chronic pain.[90] In CRPS, the mechanism of action of SCS is unclear, but it is believed to involve a complex interaction between immune and neural pathways.[91] The SCS may modulate the transmission of pain signals by stimulating inhibitory pathways in the dorsal columns of the spinal cord, which could reduce the sensitivity of peripheral nerves.[92] As a result of SCS, there may also be an anti-inflammatory effect, since it can reduce the release of pro-inflammatory cytokines in the spinal cord, as well as modulate the activity of immune cells in the spinal cord.[93]

There is evidence that SCS can reduce pain in patients with CRPS and improve their quality of life as well.[94] The SCS might be a better alternative for patients with refractory CRPS, that is resistant to conventional treatments. A systematic study investigated the SCS in CRPS, an evaluation of the medical records of 35 CRPS patients who underwent SCS trials has been conducted, and the data on opioid and neuropathic pain medication purchases were retrieved from national registries.[94] The SCS was found to reduce pain, improve

physical function, and enhance the quality of life of CRPS patients.

6. Other treatments for CRPS. Botulinum toxin injections, commonly known as Botox, have been investigated as a potential treatment for CRPS due to their ability to modulate pain pathways in the nervous system.[95] Botox has been suggested as a treatment for CRPS and dystonia by preventing the release of acetylcholine, which play an role in pain signalling.[96] Botox has been explored in several studies for its efficacy and safety in reducing pain and improving function in CRPS patients.[97]

Stem cell therapy is an emerging treatment option for complex regional pain syndrome (CRPS).[98] Stem cells can differentiate into various cell types and release factors that promote tissue repair and regeneration.[99] In the context of CRPS, stem cells can potentially repair damaged nerves, reduce inflammation, and improve blood flow to the affected area.[100] Although research on stem cell therapy for CRPS is still in its early stages, there have been some promising results. A study has shown that stem cell therapy can lead to significant pain reduction, improved range of motion, and increased function in a patient with CRPS.[12] However, stem cells used in CRPS is still under investigation and need to time to examine its safety and effectiveness for CRPS, as well as the optimal dosage and delivery method.

Conclusion. In conclusion, the current state of CRPS treatment highlights the importance of a multidisciplinary approach to care tailored to each patient's individual needs. Physical therapy and mirror therapy, as well as pharmacological interventions such as bisphosphonates, calcitonin, and ketamine, have been shown to reduce pain and improve function in patients with CRPS. The latest guidelines for CRPS treatment emphasize the importance of early diagnosis and intervention, personalized treatment plans, and addressing psychological factors in managing CRPS. Advances in understanding the pathophysiology of CRPS have led to new insights into potential treatment approaches, such as immunomodulatory agents and anti-inflammatory drugs. However, further research is needed to fully clarify the underlying mechanisms of CRPS and identify new treatment targets. Additionally, more studies are needed to compare the effectiveness of different treatment modalities, particularly in different subgroups of CRPS patients. In terms of clinical practice, healthcare providers should remain up-to-date with the latest guidelines for CRPS treatment and provide a multidisciplinary approach to care, addressing the condition's physical and psychological aspects. Patients with CRPS should be encouraged to participate in their care by setting personalized goals and actively engaging in their treatment plans. Future research should focus on developing more targeted and personalized treatment approaches, with a particular emphasis on understanding the pathophysiology of CRPS and identifying new therapeutic targets.

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