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Overview on Complex Regional Pain Syndrome: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Complex regional pain syndrome (CRPS) is a neuropathic pain disease characterized by the presence of allodynia, hyperalgesia, sudomotor and vasomotor abnormalities, and trophic alterations. CRPS can be caused by a variety of degrees or types of tissue damage, but it has also been reported in the absence of injury or after lengthy periods of immobility. A fracture is the most prevalent injury linked to the development of CRPS. CRPS is thought to be caused by a complex process involving both the peripheral and central nerve systems, according to a recent acceptance. Patients with CRPS are said to have all of the symptoms of inflammation, including heat, discomfort, redness, and swelling. CRPS symptoms have been greatly reduced by corticosteroids in several clinical studies. The diagnosis of CRPS is mostly dependent on a patient's medical history and clinical examination, which includes a variety of tests that can help rule out other diseases. Given the syndrome's complexity, it's doubtful that focusing on a single mechanism will be successful. Combination therapy, like with other chronic conditions, may be the future of CRPS treatment. In this review we will be looking at disease definition, pathophysiology, and treatment.

Keywords: Complex regional pain syndrome; neuropathic pain; injury.

1. INTRODUCTION [1,2]

Complex regional pain syndrome (CRPS) is a neuropathic pain disease characterized by the presence of allodynia, hyperalgesia, sudomotor and vasomotor abnormalities, and trophic alterations. The pain is disproportionate to the severity of the tissue injury and lasts longer than the typical time for tissue repair. The pathogenesis is complex, involving pain dysregulation in the sympathetic and central nerve systems, as well as hereditary, inflammatory, and psychosocial factors. Type I, formerly known as reflex sympathetic dystrophy, and type II, formerly known as causalgia, is one of the two sorts of disease. Type I occurs when there is no evidence of nerve trauma, but type II occurs when there is evidence of nerve trauma. They are clinically indistinguishable and have a regional distribution rather than a dermatomal or peripheral nerve distribution. CPRS favours the distal extremities, while it can sometimes migrate to the proximal or contralateral limb. Warm CRPS differs from cold CRPS, and sympathetically-maintained CRPS differs from sympathetically-independent CRPS, which might alter prognosis and treatment choices [1].

CRPS refers to a group of painful disorders marked by persistent (spontaneous and/or evoked) limb pain that seems to be disproportionately long or severe in comparison to the typical course of any known trauma or other injury. There is a distal prevalence of dysfunctional sensory, motor, sudomotor, vasomotor, and/or trophic abnormalities, and the pain is regional (not in a specific nerve area or dermatome).Based on the length of time that symptoms have been present, CRPS has been classified into three phases of progression. Although it is not required for each patient to advance through all phases or in a chronological order, knowing the stage and the prevailing complaint might aid in patient care [2].

AmbroiseParé described the first examples of CRPS-like symptoms that emerged following phlebotomy in the 16th century. Silas Mitchell first noticed this condition following gunshot wounds in 1864. In 1872, he coined the word "causalgia" to characterise the illness. In 1946, James A. Evans used the term'reflex sympathetic dystrophy' to describe a similar illness in which sympathetically mediated pain was hypothesized. Finally, in 1994, the International Association for the Study of Pain coined the term "Complex Regional Pain Syndrome" and presented a diagnostic definition for the illness. Because of the poor specificity, a generally recognized new criterion, known as the "Budapest Criteria," was suggested in 2010 [1].

1.1 Etiology [1]

CRPS can be caused by a variety of degrees or types of tissue damage, but it has also been reported in the absence of injury or after lengthy periods of immobility. A fracture is the most prevalent injury linked to the development of CRPS. Another typical cause is surgery. Sprains, contusions, crush injuries, and surgeries are all frequent triggering traumas or insults. Even seemingly harmless treatments like intravenous line installation have been found to cause CPRS. Increased psychological stress linked with the

development of CRPS may have an impact on the severity and prognosis of the condition [1].

1.2 Epidemiology [1- 6]

The prevalence of CRPS appears to vary depending on where you live. Sandroni et al. identified an incidence of 5.46 per 100,000 person-years for CRPS type I and 0.82 per 100,000 person-years for CRPS type II in Olmsted County, Minnesota, in research published in 2003. However, research published in 2006 by Mos et al. in the Netherlands found the incidence to be substantially higher, at 26.2 instances per 100,000 person-years. Females were shown to be more typically afflicted in both trials. Females were shown to be four times more likely than men to be impacted in the first research, while the second study confirmed that females were at least three times more likely to be afflicted. The Netherlands study indicated that the highest incidence occurred between the ages of 61 and 70, whereas the American study found that the median age of initiation was 46. In both research, the upper extremities were shown to be more typically affected than the lower. For diagnosis, both studies followed the IASP CRPS criteria. A fracture was shown to be the most prevalent cause of the disease, accounting for 44 to 46 percent of all cases. Vasomotor signs such as edoema, warmth, and colour changes were the most often reported clinical symptoms [1- 4].

Three-phase bone scans were determined to be the most useful diagnostic test in reaching a diagnosis (85 percent). Autonomic testing, on the other hand, was useful in identifying in 80% of instances. Asthma, usage of angiotensin-converting enzyme inhibitors (ACE inhibitors), menopause, osteoporosis, and migraine history are all risk factors for CRPS. Tobacco use appears to enhance the likelihood of getting CRPS [1,5,6].

1.3 Pathophysiology [7-9]

CRPS is thought to be caused by a complex process involving both the peripheral and central nerve systems, according to a recent consensus. Although there is evidence of each of the processes that have a role in the development of CRPS, there is limited experimental data on how these mechanisms collaborated to cause this disease. The diversity of symptoms experienced in CRPS is determined by the relative contributions of several processes, which might vary over time and within people. For example, fracture or sprain causes account for around 60% of CRPS patients, and the symptoms are wide-ranging and severe. Many clinical trials have been classified, but the remaining reported events that make up the remaining estimated 40% are considerably more ambiguous, and in certain CRPS instances, causes are unknown.

1.4 Inflammatory Mechanism [10-12]

Patients with CRPS are said to have all of the symptoms of inflammation, including heat, discomfort, redness, and swelling. CRPS symptoms have been greatly reduced by corticosteroids in several clinical studies, showing that inflammatory pathways have a role in CRPS, particularly in the acute phase. Langerhans cells have been seen in skin biopsies from CRPS patients in some investigations, and cellular infiltration, primarily lymphocytes, has been found in synovial biopsy specimens in another. In addition, two inflammatory cascades may be involved in the inflammatory process that leads to CRPS.To begin, there are the traditional inflammatory pathways involving immune cells such as mast cells and lymphocytes. Mast cells and lymphocytes release proinflammatory cytokines such as tumour necrosis factor (TNF)-, interleukin-1, -2, and 6 after a traumatic soft tissue injury. As a result, these chemicals promote localized edoema by increasing plasma extravasation.

Second, neurogenic inflammation pathways contribute to CRPS in response to various stimuli, such as nerve damage, by the direct release of neuropeptides and proinflammatory cytokines from nociceptive fibres. Neuropeptide mediators (calcitonin gene-related peptide (CGRP), substance P, and bradykinin) produce vasodilation and increased plasma extravasation, resulting in a warm, red, and edematous appearance. Furthermore, separate classes of C-fibers have an afferent mediation function for pain and itch, as well as an efferent neuro-secretory function, according to the idea of neurogenic inflammation.Significantly, silent nociceptors are mechano-heat-insensitive C-fibers (C-MiHi), which do not respond to a physiological or mechanical stimuli. Inflammatory mediators excite these chemoreceptors and released neuropeptides, causing C-MiHi to activate central sensitization (e.g. secondary mechanical hyperalgesia development). Several studies have demonstrated an increase in neuropeptide release in CRPS patients, with the degree of release returning to baseline following adequate treatment [7,13-18].

1.5 Autonomic Nervous System [19-22]

Clinical indications of an imbalance in the autonomic nervous system in CRPS patients include skin colour changes, increased heart rate, reduced heart rate variability, poor cardiac output, and excessive perspiration. Increased expression of -1 adrenergic receptors on keratinocytes and nociceptors was shown to explain the autonomic imbalance of CRPS in later research. Sympathetic activity normally leads in the production of catecholamines like norepinephrine, which bind to -1 adrenergic receptors and cause vasoconstriction.Patients with CRPS, on the other hand, had lower norepinephrine levels in the afflicted leg but higher total systemic catecholamine expression [19-21].

Sympathetic nervous system activity is reduced in the acute phase of CRPS, resulting in lower norepinephrine levels in the bloodstream. As a result, peripheral -1 adrenergic receptors become more sensitive and activated. This causes vasodilation and increased blood flow to the limb with CRPS, resulting in warmth and erythema.Similarly, during the chronic cold phase of CRPS, prolonged release of proinflammatory cytokines, such as endothelin-1, causes excessive sympathetic nervous system outflow, which leads to increased norepinephrine levels and decreased -1 adrenergic receptor expression, resulting in vasoconstriction and the development of a cold, blue, clammy limb [19-21].

In CRPS patients, elevated expression of -1 adrenergic receptors was revealed to be a cause of pain after phenylephrine, a -1 analogue, was injected intradermally, which is consistent with the preceding findings. Patients who had hyperalgesia after receiving phenylephrine injections had more cutaneous -1adrenergic receptors. Patients with CRPS II, as well as those with acute CRPS, have higher levels of -1 adrenergic receptor expression than those with chronic CRPS [19,22].

1.6 Peripheral Nervous System [23-26]

The onset of CRPS is thought to occur after a triggering or stressful event, resulting in unique alterations in the peripheral nervous system. The production of pro-inflammatory mediators such as tumour necrosis factor-alpha (TNF-) and prostaglandin E2 causes nociceptive sensitisation to begin early on. This sensitization causes a local drop in the depolarization threshold, which is thought to contribute to hyperalgesia in these individuals [23,24].

It's also thought that with time, a connection between the sympathetic and peripheral nociceptive nerve systems develops, resulting in the characteristic CRPS symptomatology.After sustained synaptic firing, A and C afferent neurons are hypothesised to activate the autonomic nervous system, connecting the two. In CRPS, nociceptive neurons in the periphery have also been demonstrated to acquire catecholamine sensitivity after damage [23,25].

The anatomy of the peripheral nervous system is also likely to have changed through time. Transmission electron microscopy was used to analyse the peripheral nerve fibres of a persistent CRPS patient in a recent case study. Large somatomotor A nerve fibres degenerated significantly, while A nerve fibres were spared, according to a study.They theorised that a peripheral imbalance of nerve signalling may increase A nociceptive activity and enhance pain. Regardless, long-term modifications in the peripheral nervous system appear to have a significant influence [23,26].

1.7 Evaluation [1,7,27,28]

CRPS has yet to be linked to a specific pathophysiologic mechanism. As a result, there is no gold standard diagnostic test for CRPS. The diagnosis is clinical and based on the Budapest criteria, which are universally recognised. The Budapest criteria have a similar sensitivity (0.99) to the old IASP criteria, but a better specificity (0.68) [1,27,28].

The diagnosis of CRPS is mostly dependent on a patient's medical history and clinical examination, which includes a variety of tests that can help rule out other diseases. Indeed, neurological examinations, such as conduction velocity investigations to rule out nerve diseases, are particularly important. Electromyography treatments, on the other hand, may be unneeded due to their excruciating discomfort and the fact that their results have little bearing on therapy. Small fibre impairment can also be detected via quantitative sensory testing (QST) or bedside sensory testing.The preceding producers should be combined with transcranial magnetic stimulation of motor circuits and somatosensory evoked potential experiments to examine central pathways. Furthermore, physicians and pain specialists should be aware that conducting

studies might rule out other medical disorders such as severe skin infections and persistent rheumatic illnesses [7].

Criteria of Budapest: [1]

1. They should describe persistent discomfort that is unrelated to the triggering event.
2. They must report at least one symptom from each of the four categories below:
   - Sensory: Hyperalgesia and/or allodynia were reported.
   - Temperature asymmetry and/or skin colour fluctuations and/or skin colour asymmetry are reported as vasomotor symptoms.
   - Sudomotor/edema: Edema, sweating alterations, and/or sweating asymmetry have been reported.
   - Reduced range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic alterations have been reported (hair, skin, nails).

3. They must also exhibit at least one indicator from two or more of the following categories at the time of evaluation:

   - Sensory: Hyperalgesia (to pinprick) and/or allodynia are present (to light touch or deep somatic pressure),
   - Evidence of temperature asymmetry and/or skin colour alterations and/or asymmetry in the vasomotor system.
   - Edema and/or sweating alterations and/or sweating asymmetry are examples of sudomotor/edema.
   - Evidence of reduced range of motion and/or motor dysfunction (weakness, tremor, dystonia) as well as trophic alterations (motor/trophic) (hair, skin, nails).

4. Finally, no alternative diagnosis describes the signs and symptoms as well as this one.

The quantitative sudomotor axon reflex test, thermography, and a triple-phase bone scan were among the objective testing methods used. While these investigations add to the picture, they aren't required for a CRPS diagnosis. The majority of CRPS diagnoses are clinical and based on exclusion. Small or large fibre sensorimotor neuropathy, cellulitis, erythromelalgia, vasculitis, vascular insufficiency, lymphedema, deep vein thrombosis, and Reynaud's phenomenon are among the differential diagnoses. In the case of CRPS, diagnostic tests are largely used to rule out other possible diagnoses.

1.8 Treatment [1]

Because CRPS is a complex illness, it requires a multidisciplinary approach that includes patient education and information, pharmaceutical therapies, physical and occupational therapy, and psychological support. The goal of therapy is to alleviate discomfort and restore the damaged limb's functioning. Despite the fact that the course of the disease is varied and there is no clear evidence that treatment changes it, treatment should not be postponed since individuals with a more chronic course have a worse prognosis.

1.9 Patient Education and Information [1]

Patients and their family should be informed about their illness, as with any chronic disease, in order to understand the nature of their symptoms and the progression of the ailment.Patients will be able to take a more active role in the management of their disease through education, which will allow them to develop their own understanding of the therapeutic strategy proposed by the physician, build the knowledge and skills required for the rehabilitation process, and gain trust in the process, ultimately improving their adherence to the treatment plan.

1.10 Occupational and Physical Therapy [29]

In individuals with CRPS, physical and occupational therapy is an important part of the recovery process and is suggested as the first-line treatment. Patients can develop kinesophobia, and the goal of therapy is to help the patient overcome their fear of pain and obtain the most functional use of their limb. This programme is individualised to each individual and may include a variety of modalities. Elevation, massage, contrast baths, transcutaneous electrical nerve stimulation, moderate range of motion, isometric strengthening training, and stress loading of the afflicted limb, as well as sufficient analgesia, are some of the treatments available.Occupational therapy promotes the use of the injured limb in daily tasks. The use of specialised garments or wrappings on the damaged limb can help to minimiseoedema and sensory overload. Mirror

box therapy has been demonstrated to enhance two-point sensation and lessen neuropathic pain in the afflicted limb [29].

1.11 Psychological Therapy [29]

Chronic pain has a negative impact on patients' health-related quality of life and puts a significant emotional and psychological strain on them. As a result, it is critical for newly diagnosed CRPS patients to speak with a psychosocial care provider about their disease and how it is progressing, as well as the need of active self-management and involvement in a treatment plan. To aid rehabilitation, lessen pain intensity, and give patients more control, patients can get cognitive behavioural therapy, acquire relaxation methods, and receive biofeedback.Concomitant axis I illnesses, such as severe depression, generalised anxiety disorder, and post-traumatic stress disorder, must be assessed and treated, since they might hinder the recovery process. [29].

1.12 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) [30]

Pain and inflammation have traditionally been treated with nonsteroidal anti-inflammatory medications (NSAIDs). However, only 20 patients with CRPS 1 and 2 of the upper limb were included in a randomised double-blind placebo-controlled study with pare-coxib, 80mg on two consecutive days, which found no benefit of parecoxib on pain or edoema. A randomised study with 60 patients with CRPS after a stroke evaluated the efficacy of a one-month therapy with either a tapering dosage of prednisolone starting at 40 mg daily or piroxicam 20 mg daily.At the end of treatment there was a significant improvement of the CRPS score in patients on prednisolone, but no improvement in those on piroxicam. Hence, currently there is no evidence supporting the use of NSAIDs for the treatment of CRPS. [30].

1.13 Glucocorticoids [30]

Glucocorticoids may be useful since typical inflammation is likely implicated at least in the early stages of the illness. Relevant studies, on the other hand, are diverse in terms of CRPS diagnosis, patient characteristics, glucocorticoid formulations and doses used, and almost all of them involved small numbers of patients. In a randomised placebo-controlled trial including 23 patients with CRPS type 1, oral prednisone 10 mg three times daily for up to 12 weeks was found to be more efficacious than placebo in causing clinical improvement.In another prospective trial, patients with post-stroke shoulder-hand syndrome were treated with 32 mg of oral methylprednisolone daily for 14 days, followed by a 14-day taper, and 31 out of 36 patients were nearly symptom-free after 10 days. [30].

1.14 Bisphosphonates [30]

Bisphosphonates were recently approved for the treatment of CRPS, though the specific mechanism of action is yet unknown. Many theories have been offered, the most prominent being the modulation of inflammatory mediators and the suppression of bone marrow cell growth and migration. More crucially, a number of small-scale trials have shown that bisphosphonates are beneficial in the treatment of CRPS. The first was a randomised double-blind experiment that found a substantial improvement in pain, soreness, edoema, and mobility when intravenous alendronate (7.5mg daily for 3 days) or placebo was given. [30].

1.15 Anticonvulsants and Antidepressants 1

Gabapentin is the most extensively researched drug in this category. The alpha 2-delta subunit of voltage-gated calcium channels is inhibited. Gabapentin, despite its widespread usage in the treatment of CRPS, appears to be unsuccessful in the treatment of CRPS I, according to extremely low-quality data. A research comparing amitriptyline and gabapentin for CRPS I and juvenile neuropathic pain was published in 2016. Both drugs were shown to considerably lower pain intensity and impairment. However, there was no discernible difference in impact between the two. [1].

1.16 Antioxidants [19,31-34]

Many antioxidants have been recommended for the treatment of CRPS, based on the idea that CRPS causes local inflammation, which causes oxygen free radicals to form. Vitamin C, on the other hand, is the only antioxidant treatment that is currently supported by data and is widely administered perioperatively to prevent CRPS after extremities surgery. The most recent meta-analysis, which included three RCTs with a total of 875 participants, found that patients taking daily 500 mg vitamin C supplements for 50 days

had a significantly lower 1-year incidence of CRPS following wrist fracture [19,31-34].

2. CONCLUSION

The biology of CRPS is complicated, making it difficult for doctors and researchers to create effective therapies for this severe, life-threatening disorder. Despite the fact that there has yet to be a good therapy for CRPS, years of study have helped us to know, and our understanding of the disorder is still growing. In comparison to CRPS type I, the evidence basis for CRPS type II is still limited. As a result, further research is needed to determine which patient subgroups might benefit the most from currently available treatments.

Given the syndrome's complexity, it's doubtful that focusing on a single mechanism will be successful. Combination therapy, like with other chronic conditions, may be the future of CRPS treatment. Animal models that may imitate the illness process are inadequate due to the complexities of this ailment. This has slowed the discovery of new treatments, forcing physicians to rely on trial and error to treat the disease. We hope in the future for better understanding of the disease and emerging of new and more effective treatment options.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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