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Review Article

Complex Regional Pain Syndrome Classification, Damage, Mechanisms, and Treatment: A Narrative Review

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ABSTRACT

Complex regional pain syndrome (CRPS), previously known as reflex sympathetic dystrophy syndrome, is a situation specified by persistent regional pain. The aberrant functioning of the neurological system is believed to be the root cause of an exaggerated reactivity to pain signals that are unable to switch off the sensation of pain. It is characterized by such symptoms as swelling, alterations in the color of the skin and tissues, along with edema. Although it most commonly affects the limbs, such as the arm, leg, hand, or foot, these symptoms can manifest themselves in any part of the body. The existence or nonexistence of nerve injury is used to classify patients into one of two subgroups, I or II, when referring to this illness. Since many medical professionals are unfamiliar with the diagnosis of CRPS and its etiology is not fully elucidated, the condition is frequently incorrectly diagnosed. The treatments available for CRPS focus on alleviating symptoms, regaining organ function, and cosseting a person's quality of life, despite the fact that no cure for the condition has been identified.

Introduction

Complex regional pain syndrome (CRPS) is an uncommon clinical situation identified by persistent regional pain (not in a particular dermatome) that is excessive in intensity and duration compared to the underlying cause. It is typically along with sensorimotor, vasomotor, sudomotor, and trophic changes in the affected site [1-2]. This pain is usually more intense or long-lasting than typical after similar tissue traumas, especially in the distal extremity [3]. Symptoms are localized to the affected limb but may spread to other areas [4]. This disorder was first described by Ambroise Paré, the father of modern surgery, almost 465 years ago, in 1557. An acute and constant pain syndrome happened to the French King Charles IX of Valois after limb phlebotomy and was successfully relieved [5-6].

It is proven that notable autonomic and inflammatory changes in the site of pain distinguish CRPS from other chronic pain conditions (Pain lasting longer than three months is considered chronic [7]). This condition manifests as extreme hyperalgesia and allodynia in the limbs (ordinarily non-painful stimuli, like touch and cold, are perceived as painful), changes in skin color, temperature, and sweating in comparison with the noninvolved side, edema, altered patterns of hair, skin, or nail growth in the affected areas, decreased strength, tremors, and dystonia [8]. It is worth noting that scientists arranged CRPS as type I or type II based on the absence or presence of clinical signs of peripheral nerve injury [3].

There is an urgent need for early and aggressive therapeutic interventions, in addition to comprehensive

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diagnostic evaluation [9]. Although CRPS was explained decades ago, its epidemiology has not yet been well surveyed, and compelling epidemiological data on this abnormality are still missing, along with meager incidence statistics [10]. Nonetheless, between 5.5 and 26.2 per 100,000 person-years have been reported as the incidence of CRPS, and women are reported to be more frequently affected than men [11]. Furthermore, based on the literature, the course of CRPS and its prognosis are exceedingly unpredictable. Only approximately 5% of symptoms resolve [12], although they frequently become much better over the course of the first year, and many people have continuing CRPS with considerable functional impairment and low quality of life [13-14].

In order to find a suitable treatment for these patients, researchers suggested pain alleviation as one of the main aim of CRPS treatment, which is followed by an increase in the patient's overall satisfaction with life. Physiotherapy and cognitive behavioral therapy (CBT) are also part of the treatment plan [15]. Moreover, the trophic alterations of the afflicted extremity are hypothesized to be influenced by catecholamines and autoimmune processes [16]. They mainly stimulate nociceptors of deep tissues, resulting in motion-associated pain. Some of these mediators also activate second-order neurons in the spinal cord, which are in charge of deep tissue or skin mechanical hyperalgesia. If CRPS is not properly managed during this inflammatory stage, susceptible patients experience cortical remodeling over time due to the constant input of nociceptive activity to the brain [17]. Due to the importance of this disease among neurologists and pain specialists, the current survey discusses the characteristics, treatment methods, and mechanisms of pain transmission.

Clinical criteria in patients with CRPS

The CRPS patients exhibit various clinical features in different stages of the disease. To confirm the diagnosis of this syndrome, there must be a certain number of symptoms described below. Researchers refer to these diagnostic criteria as Budapest criteria [18].

1) There is continuous pain in the patient, often disproportionate to the cause of the pain.

2) At least one symptom from three of the four categories below must be reported by the patient:

a. Sensory manifestations: The patient mentions allodynia or hyperesthesia.

b. Vasomotor symptoms include temperature asymmetry, skin color variations, and/or color asymmetry, according to the patient.

c. Motor or trophic symptoms: The patient reports a reduced range of motion and/or motor dysfunction, such as weakness, tremor, dystonia, and/or trophic modifications in hair, nails, and skin.

d. Sudomotor or edema manifestations: The patient describes edema, sweating abnormalities, and/or sweating asymmetry.

3) At least one indication in two or more of the four categories listed below

a. Sensory symptoms, such as hyperalgesia to pinpricks, allodynia to light touches, or stiffness in the joints

b. Vasomotor symptoms, such as asymmetry in skin color or temperature

c. Motor or trophic symptoms: reduced movement range and/or muscle weakness, tremor, dystonia, and/or trophic changes of hair, nails, and skin.

d. Sudomotor or edema signs: edema and/or sweating asymmetry

4) No alternative explanation for the symptoms and indications is more accurate [19-20].

Nevertheless, it is noteworthy that it is not yet apparent how or to what extent any of these pathways contribute to the development and maintenance of this disease [11].

Type of complex regional pain syndrome

There are different subtypes and/or stages of CRPS, and the phenomena are not consistent among individuals [18]. For example, in 1994, at a conference organized by the International Association for the Study of Pain (IASP), the "officially approved" term "complex regional pain syndrome" was coined to describe the disease in general. The disease was later classified into "CRPS 2" in the presence of nerve damage (replacing the term causalgia) and "CRPS 1" if there was no evidence of nerve damage (replacing the term reflex sympathetic dystrophy) [21]. Based on previously conducted studies, despite a low frequency, CRPS 1 imposes s heavy burden on patients and is associated with significant direct medical and social expenditures (such as lost productivity, disability, and social security payments) [14, 16, 22] Nevertheless, one-third of CRPS 1 patients will not respond to treatment and will instead develop a long-term condition with severe pain, disability, and diminished quality of life [22]. Chronic CRPS 1 is more likely to develop if proper diagnosis and therapy are delayed; however, early treatment is associated with better outcomes [16].

There is another different classification with two distinct subtypes: "warm" and "cold," the former of which is linked to acute inflammation, and the latter is primarily present in chronic CRPS [23]. Patients with warm CRPS demonstrate an extremity that is warm, red, dry, and edematous, while cold CRPS patients are characterized by an extremity that is cold, blue, sweating, and less edematous. In accordance with clinical data, the mean CRPS duration was significantly shorter in the warm CRPS subtype (4.7 months) compared to that in the cold CRPS subtype (20 months), with similar pain intensity in both subtypes [23].

Mechanisms involved in the development of complex regional pain syndrome

As expected, several underlying mechanisms are involved in the forming and persistence of this disease, leading to the development of pathological conditions in the patient. The pathophysiology of CRPS has long been associated with peripheral neurogenic inflammation [24]. Studies have pointed to several molecular mechanisms in the creation of these conditions. For instance, uncontrolled blood sugar can make CRPS after stroke more common [25]. Even in cold CRPS, inflammatory mechanisms appear to be crucial [26]. Direct evidence has been presented regarding decreased tissue oxygen saturation [27]. and autoantibody-mediated autoimmune processes [28]. Increased amounts of proteobacteria and lower amounts of firmicutes in the gut microbiome have been hypothesized as autoimmune mechanisms through which the gut microbiome may contribute to CRPS [29].

Primary afferent sensory neurons release neuropeptides during peripheral neurogenic inflammation, leading to cutaneous vasodilation (primarily via substance P [S.P.]), changes in vascular permeability (primarily via calcitonin gene-related peptide [CGRP]), increased protein efflux, and improved leukocyte recruitment [30, 31]. Therefore, the symptoms of CRPS patients, including allodynia, hyperalgesia, edema, vasodilation, and trophic abnormalities, may also be resulted from this elevated neuropeptide release [32, 33]. In addition to neurogenic inflammation, some other surveys have given Evidence regarding the role of neuroinflammation (i.e., glial cell activation leading to increased production of proinflammatory cytokines and chemokines) in CRPS [34-36].

Apart from being brought on by different types of trauma and surgery, primary afferent nerve fibers and/or higher-order neurons have also been theorized to have a role in neuroinflammation [36, 37]. A change from acute to chronic pain and the maintenance of chronic pain are just two negative consequences of Neuroinflammation. Central cytokines, chemokines, and mediators released by glia are what cause and maintain the central sensitization that leads to this chronic pain [36]. Clinical manifestations of dynamic tactile allodynia, secondary punctate and/or pressure hyperalgesia, temporal summation, and pain after touching are all signs of central sensitization, which is specified by pain hypersensitivity [38].

Central sensitization symptoms reported in CRPS patients [11] have been linked to the sensitization of the nociceptive system as a result of chronic pain and, thus, continuous nociceptive input [39, 40]. In addition, it is noteworthy that for a long period, the disruption of the immune system was not considered a probable pathophysiological mechanism in CRPS since there was no objective evidence, such as C-reactive protein and white blood cells that are generally within the normal range in these patients, pointing to immune system involvement [41-43]. Nonetheless, in recent years, substantial advances in study methodologies and Knowledge of the disease have made it possible to pinpoint the function of the immune system in CRPS.

There is growing evidence that dysregulated immune activation and consequent inflammation have a duty to play in CRPS, including the enhancement of the levels of Tumor necrosis factor (TNF-α), the incidence of different autoantibodies, and T lymphocyte activation [11]. Increased serum concentration of neuropeptides [43-45], mast cell tryptase, and interleukin (IL)-6 (also in cerebrospinal fluid) have also been determined, while anti-inflammatory cytokines have been discovered to be decreased [46].

Changes in brain structure and function in patients with complex regional pain syndrome

Researchers have pointed to significant alterations in brain structure and function in CRPS; nonetheless, these changes may occur before or during the disease. For more explanation, neuroimaging studies demonstrating decreased gray matter (GM) volume and cortical thickness in the prefrontal cortex (PFC), insular cortex (IC), and basal ganglia provided Evidence of brain plasticity [47]. The anterior IC and orbitofrontal cortex showed CRPS-specific GM volume reductions when collated to other chronic pain disorders [48]. Clearly, CRPS is frequently attributed to pain processing and is connected to functional connectivity alterations in the default mode network (DMN) [49-50].

Several investigations have explained a reduction in GM volume/density in the anterior IC and areas of the PFC; although, it is not known whether these structural and functional brain changes emerge quickly after diagnosis or gradually over time. This is related to the length of CRPS and the pain severity; therefore, it is suggested that professionals think of it as a series of minor slow changes that decrease with the patient's pain intensity [51-52]. Moreover, it has been discovered that contralateral thalamic perfusion is increased within the first year of disease but comes back to normal levels for prolonged illness durations [52-53]. Therefore, understanding the variations in the brain across CRPS stages may help explain the variety of therapy responses.

Clinical diagnosis methods of complex regional pain syndrome

The updated International Association for the Study of Pain (IASP) clinical diagnostic criteria for CRPS are presently used to identify the condition [1]. Both primary care physicians and hospital specialists tend to miss the diagnosis of CRPS. The consequences include a delay in

the identification of CRPS cases and initiation of effective treatment. The noteworthy point is that long-term CRPS-related pain becomes more difficult to manage without effective treatment [54]. Therefore, the detection of CRPS is still a challenge in daily clinical practice due to the wide range of clinical symptoms [55] This disease may be accompanied by other diseases or have symptoms similar to other diseases.

Nonetheless, only other disorders, like rheumatic diseases, are excluded from the differential diagnosis by further testing, like blood tests and radiography [56]. The average time between injury and CRPS diagnosis ranged from 0.5-10 years, according to a study [57]. When the diagnosis is postponed, treatment effectiveness suffers even more. Some researchers have proposed the use of bone scintigraphy (BS) to confirm the detection of CRPS 1, even though this diagnosis is based on the Budapest criteria [58]. It is not known if the percentage of positive BS results is affected by patient variables [55]. Furthermore, a meta-analysis looked at the sensitivity and specificity of both BS and magnetic resonance imaging (MRI) for the detection of CRPS 1 [59].

Methods

It is generally stated that CRPS is an incurable pain disorder without any specific therapeutic strategy; therefore, it requires a multimodal treatment strategy [18]. In a study on three patients who touch the Budapest criteria for CRPS, Thor used perineural injection therapy as a treatment to reduce their pain [60]. One of the most recent developments in the field of regenerative medicine is perineural injection treatment (PIT) which targets cutaneous nerves as a potential source of pain [61-62]. Moreover, sympathetic blocks are a well-known technique for the reduction of pain and enhancement of motor and autonomic nervous system activities [63].

In this method, in individuals with CRPS in their lower extremities, a nerve block with local anesthetics is typically performed on the lumbar sympathetic chain. The blocking effects in most patients are transient; therefore, one or more of the further procedures, such as repeated sympathetic blocks with local anesthetics, radiofrequency thermocoagulation, or neurodestructive procedures using alcohol or phenol, are required to exert a more lasting effect [64]. For instance, botulinum toxin can block the sympathetic ganglion and inhibit acetylcholine release at cholinergic nerve endings via the antagonistic effect of botulinum toxin [65].

Literature is filled with studies reporting the Use of different clinical treatments for CRPS; however, the level of protective evidence is largely inadequate for most [66]. Bisphosphonates, for example, have been proposed as a treatment for CRPS-related pain. Furthermore, dimethyl sulfoxide, steroids, epidural clonidine, intrathecal baclofen, spinal cord stimulation, and motor imagery programs have demonstrated pain relief, although additional research is needed [67]. Anticonvulsants and antidepressants, which are often administered by specialists and thought to help with sensory-associated symptoms in CRPS, have not created clear effects, according to a review of the research [67-68]. In addition, anticonvulsants, such as gabapentin, are widely used to treat neuropathic pain and CRPS 1; although, it is not well established whether anticonvulsants or antidepressants, included due to similarity in mechanism, are helpful in the relief of CRPS-related pain [69-70]. It should be mentioned that physical therapy is advised for CRPS patients by American, U.K., and more recent Dutch recommendations [20,69]. The U.K. guidelines specifically suggest education as another therapeutic pillar [20].

Conclusions

In general, the observations obtained from various studies have pointed out that there is still no definitive and effective treatment method for CRPS patients. Considering numerus physical, psychological, and social problems posed to the affected patients, it is suggested that more clinical studies be conducted to find a suitable and unified treatment method.

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