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A MEDICAL MYSTERY OF COMPLEX REGIONAL PAIN SYNDROME (CRPS)

Orthopaedics

Dr. Sameer Mohammad Zargar* PG Scholar Orthopaedics, GMC Srinagar *Corresponding Author

Dr. Uroosa Fayaz Mir PG Scholar, Department of Anatomy

Dr. Rajkumar Prasad Assistant Professor, Department of Orthopaedics, JNUIMSRC, Jaipur

ABSTRACT

Complex regional pain syndrome (CRPS) is a condition of neuropathic pain, which is characterized by significant autonomic and inflammatory features. CRPS occurs in patients who have limb surgery, limb fractures, or trauma. Many patients may have pain resolve within twelve months of the inciting incident; however, a small subset progresses to the chronic form. This transitional process often happens by changing from warm CRPS with dominant inflammatory phase to cold CRPS, in which autonomic characteristics or manifestations dominate. Several peripheral and central mechanisms are involved, which might vary among individuals over a period of time. Other contributors include peripheral and central sensitization, autonomic alterations, inflammatory and immune changes, neurochemical changes, and psychological and genetic factors. Although effective management of the chronic CRPS form is often challenging, there are a few high quality randomized controlled trials that support the efficacy of the most commonly used therapeutic approaches.

KEYWORDS

Neuroscience, Health sciences, Neurology, Surgery, Pain research, Pain management, CRPS, Pain, Pathophysiology, Treatment, Future therapy

1. INRODUCTION

Complex regional pain syndrome (CRPS) is a chronic neuropathic pain condition generally affects an extremity and can potentially spread to other extremities, and become disabling. CRPS is characterized by severe prolonged pain, changes in skin color and temperature, swelling, and bone loss in the affected limb [1, 2]. The disorder involves autonomic and inflammatory abnormalities. With CRPS, the afflicted person experiences pain that is greater in magnitude and/or duration than would be typically expected from the surgery or traumatic inciting event [3-5]. Complex regional pain syndrome (CRPS) is a form of spontaneous or stimulus-induced chronic pain that most often affects one limb (arm, leg, hand, foot) usually after an injury and lasting over six months [1].

Complex regional pain syndrome (CRPS) was first described by Mitchell [6] in 1864 as a "burning pain" experienced by injured soldiers in a Civil War. Currently, it is known as a neuropathic pain syndrome that can occur postoperatively as a complication of surgery. CRPS was previously known as Sudeck's atrophy (or dystrophy), algoneurodystrophy, algodystrophy, reflex neurovascular dystrophy, and reflex sympathetic dystrophy (RSD).

CRPS is divided into two types: I and II. Patients who have reflex sympathetic dystrophy syndrome without confirmed nerve injury are categorized as having CRPS-I [7]. However, CRPS-II, which is known as causalgia, occurs when there is associated and established nerve damage. As there is no golden test for CRPS, there are many diagnostic criteria [8]. Also, the heterogeneity of patients' signs and symptoms makes it difficult to compare the studies to explain pathophysiological mechanisms or to evaluate treatment outcomes [9]. Consequently, this review aimed to reveal the updated therapeutic strategies based on the recent understanding of the pathophysiology of CRPS and to discuss novel approaches and techniques for managing this condition.

2. Pathophysiology

The pathophysiologic mechanism underlying CRPS is not fully known, but it is believed that the inciting event considered an injury triggers abnormal processes in both the peripheral and central nervous systems, causing dysfunctional neuroplasticity and an excessive immune and inflammatory response [10-12]. There is a recent universal agreement that CRPS is caused by a multifactorial process that involves both the peripheral and central nervous systems [13]. There is evidence of each of the mechanisms that have a role in the development of CRPS, although there is little experimental data about how these mechanisms may have interacted to produce this syndrome [14]. The variety of manifestations seen in CRPS depends on the relative contributions of different processes that can differ among patients over time. For instance, fracture or sprain causes have represented approximately 60% of CRPS patients, and the symptoms are extensive wide and severe. Many clinical trials have been categorized the remaining alleged events that comprise the other estimated 40% are even more imprecise, and in some CRPS cases, causes are not recognized. Therefore, we will discuss the pathophysiological mechanisms that are involved in the development of CRPS.

2.1 Inflammation

CRPS is characterized by both a pro-inflammatory immune response and impaired neuropeptide signaling [15]. Inflammation is an expected outcome after stroke, surgery, or tissue trauma; however, the activation of the innate immune system is amplified and persistent in CRPS patients. This innate immune system activation triggers the proliferation of keratinocytes and the release of proinflammatory cytokines including interleukin-6 (IL-6), IL-1b and tumor necrosis factor-a (TNF-a) [16]. These cytokines trigger an immune cascade that results in histamine-induced vasodilation, causing the redness, swelling, pain, and warmth that is characteristic of the acute phase of CRPS [17]. Pro-inflammatory cytokines also activate osteoblasts and osteoclasts, resulting in the rapid bone turnover and osteoporotic changes that are characteristic of the chronic phase of CRPS [18]. Expanded populations of CD4 and CD8 lymphocytes in CRPS patients were documented in multiple studies, suggesting an antigen- mediated T lymphocyte response [12, 19]. A recent study examining serum levels of pro- and anti-inflammatory cytokines in the serum of CRPS patients also identified IL-37 and GM-CSF as novel biomarkers in the immune response [19]. Decreased serum levels of IL-37 were found, indicating a suppression of the immune response through the activation of IL-10 and regulatory T lymphocytes. In contrast, an increase of GM-CSF was noted, highlighting a balance between pro- and anti-inflammatory cytokines in the pathogenesis of CRPS, with a predominantly pro-inflammatory state. Neuropathic inflammation is also believed to play a central part in the development of CRPS.

2.2. Autonomic Nervous System

An imbalance in the autonomic nervous system of CRPS patients often leads to clinical manifestations such as skin color changes, increased heart rate, decreased heart rate variability, low cardiac output, and excessive sweating [20]. Subsequent studies noted that the autonomic

imbalance of CRPS is explained by the increased expression of a-1 adrenergic receptors on keratinocytes and nociceptors [21]. Under normal circumstances, sympathetic activation results in the release of catecholamines such as norepinephrine, which bind a-1 adrenergic receptors causing vasoconstriction [21]. CRPS patients, however, were found to have decreased norepinephrine levels in their affected limb but increased overall systemic catecholamine expression.

In the acute phase of CRPS, sympathetic nervous system activity is decreased, leading to lower circulating levels of norepinephrine. As a result, peripheral a-1 adrenergic receptors are upregulated and sensitized. This results in vasodilation and increased blood flow to the CRPS affected limb, leading to warmth and erythema [21]. Similarly, during the chronic cold phase of CRPS, the prolonged release of proinflammatory cytokines, including endothelin-1, results in excessive sympathetic nervous system outflow leading to increased norepinephrine levels and decreased a-1 adrenergic receptor expression, culminating in vasoconstriction and the development of a cold, blue, clammy limb [21].

2.3. Autoimmunity

The evidence for autoimmunity in CRPS comes from both prior studies which have observed elevated levels of autoantibodies in the serum, skin, and tissues of CRPS patients, as well as from animal models [2]. It is believed that autoantibodies produce pain in CRPS by sensitizing nociceptors [23].

Recent mice models studied the effects of transferring serum IgG from CRPS patients into mice with hind paw incisions [23]. It was found that mice who received serum IgG from CRPS patients displayed increased hypersensitivity to painful mechanical stimuli like cold and heat, but not too painful tactile stimulation [23].

Additionally, it was found that CRPS patients who endorsed greater pain had higher IgG antibody titers than patients who endorsed lower pain levels [23]. These studies illustrated that the IgG antibodies found in the serum of CRPS patients sensitize A and C nociceptors, maintaining the painful hypersensitivity that is characteristic of persistent CRPS [23].

2.4. Genetic Factors

The relationship between genetic factors and CRPS has been studied for many years with no concrete genetic link found. There is a suspected link due to familial aggregation and similar findings among CRPS patients. The human leukocyte antigen system (HLA) was the primary focus of studies because the genes in that system were found to be the most significantly upregulated (HLA-DRB1) and downregulated (HLA-DQB1) [24]. The abnormal regulation of these genes suggests that the immunes system, and more specifically the adaptive immune response, is a driving factor behind the development of CRPS. Among the HLA family, the expression of HLA-DQB1 was increased among CRPS patients [24, 25]. HLADQB1 is expressed by a subgroup of immune cells which includes B cells, activated T cells and macrophages. One study theorizes that this genetic association between HLA-DQB1 and CRPS can be compared to that of the association between HLA-DQ8 and celiac disease. The HLA gene fulfills the role of binding gluten-peptides on antigen-presenting cells. Gluten-specific CD4 T-cells in the lamina propria respond to these peptides and enhance cytotoxicity of the locally present lymphocytes. Gluten peptides gain an enhanced affinity to bind to gliadin T-cell epitopes, which promotes a downstream inflammatory effect. The proposed mechanism of celiac disease is that once the threshold of gluten on T-cells has been reached, a self-amplifying loop that causes a continuous inflammatory response is established. The exact nature of the inflammatory response in CRPS is unknown, but this offers an interesting avenue that can be pursued [26]. A recent study explored the correlation behind CRPS and exosomes. The study found changes in gene expression among human cells following the uptake of exosomes enriched in miR-939 [27]. There are many gaps in our knowledge about exosomes and their relationship to pain and more specifically CRPS. As more studies on the subject are published, we hope to fill in some of those gaps.

2.5. Epigenetic Factors

The study of how epigenetics influences pain and more specifically CRPS is very young with limited sources. A study of post-war amputee victims was conducted in which DNA methylation was the epigenetic factor that was observed. CpG sites which contain the DNA sequence cytosine–phosphate–guanine nucleotides were the sites of interest, these sites are known to be affected by genetic and environmental factors such as trauma, smoking, and diet. The sites also suppress transcriptional activity [25]. The study revealed that 48 CpG sites were statistically significant in how they were methylated. All but seven of the 48 sites were hypomethylated compared to the non- CRPS patients and a substantial amount of the 48 sites were related to immune function. Over one-third of the CRPS patients exhibited a higher-than-normal level of antineuronal antibodies [25]. The apparent commonalities among both genetic and epigenetic factors are found within the characteristics of the immune system. Based on the current findings, it would suggest that a focus on the immune system and inflammatory system and their relationship to CRPS would be the best approach for further understanding.

2.6. Psychological factors

The results of studies concerning the role of psychological factors in the development of CRPS are inconclusive. More dated studies have suggested the association does not exist; however, more recent studies have suggested that there is a connection between psychological factors and pain outcomes in patients with CRPS [28]. Few studies have been conducted on this topic and for us to truly under the relationship more research is needed.

2.6.1. Depression

It has been suggested that psychological disorders, such as depression, may contribute to the development of CRPS. A study conducted comparing CRPS patients, major depressive disorder (MDD) patients, and a control group suggested that psychological profiles do not predispose the individual to the development of CRPS. The psychological profile may be secondary to the pain or contribute to the chronicity of the pain however [28]. The anxiety and depression that MDD patients were experiencing involved emotional dysregulation but this differed from the mechanism of depression in CRPS patients. This difference between CRPS and MDD patients may suggest that CRPS patients have an intact emotional regulation and that their depression is not the same as the mental disorder depression [28]. Though the causal relationship remains unclear, it is known that depression is one of the most common psychiatric diagnoses among CRPS patients and thus each patient should be observed for depressive symptoms.

2.6.2. Post-traumatic stress disorders (PTSD)

It has been suggested that there may be a link between post-traumatic stress disorder (PTSD) and CRPS. A study was conducted where 152 patients with CRPS, 55 control with chronic pain and 55 age- and sex-matched healthy individuals were evaluated for PTSD; 38% of the CRPS patients (58), 10% of the non-CRPS pain patients (six), and 4% of the healthy individuals (four) met the criteria for PTSD. Of the 58 CRPS patients who met the PTSD criteria, 86% (50) had PTSD symptoms prior to the CRPS diagnosis; 14% of the patients (eight) developed PTSD during the course of CRPS [29]. From the limited scope of this study, we can infer that PTSD is more prevalent in CRPS patients. It should be noted this was one of the few studies of its kind that we could find. More research into this subject would allow us to yield a more concrete conclusion.

2.7. Neuropsychological

CRPS seems to cause complex neurological changes that can affect a patient's way of life similar to that of a brain lesion. These changes include ownership of the affected body part, distortion of size, negative feelings toward the affected body part, and deficits in both lateralized spatial and non-spatial-lateralized cognitive functions [30].

3. Diagnosis Criteria

The diagnosis of CRPS is made clinically, and no diagnostic tests are available. Little information is available in published studies regarding the types of patients who develop CRPS. This study aimed to reveal the updated therapeutic strategies based on the recent understanding of the pathophysiology of CRPS and to discuss novel approaches and techniques for managing this condition.

4. Current Treatment

As symptoms of CRPS exhibit a variable progression over time, early initiation of therapy is integral to patient prognosis, with the goals of restoring limb functionality, decreasing pain, and improving quality of life [31, 32]. This often requires a multidisciplinary approach involving patient education, physical and occupational therapy,

psychiatry, and pain medicine specialists, along with pharmacological and surgicalinterventions.

4.1. Physical and Occupational Therapy

Physical and occupational therapies are key initial components of treatment to help CRPS patients overcome their fear of pain and kinesophobia. Several therapeutic modalities have been studied such as massage, electrotherapy, acupuncture, contrast baths, biofeedback, isometric strengthening exercise, counter strain, and gentle range of motion. Among various physiotherapy interventions, a Cochrane review of 18 RCTs identified graded motor imagery and mirror therapy as providing the greatest rehabilitation benefit, significantly improving pain and quality of life, although the quality of evidence was very low [33, 34]. A recent randomized comparative effectiveness trial evaluated the use of a modified graded motor imagery program in women at risk for developing CRPS after distal radius fracture treated with cast immobilization [35]. However, larger and higher-quality RCTs are still needed.

4.2. Pharmacotherapy

A variety of medications have been utilized for symptomatic pain management of CRPS, with the primary goal to enable patients to participate in rehabilitation regimens. Traditionally, non-steroidal anti-inflammatory drugs (NSAID) and corticosteroids have been used to target the pain and inflammation underlying CRPS in both adults and pediatric patients [36].

Bisphosphonates are commonly used in the treatment of CRPS, largely due to evidence from several small RCTs that have shown significant positive effects [37]. Although the exact mechanism is not well understood, current research suggests bisphosphonates play a role in modulating inflammatory mediators, as well as the proliferation and migration of bone marrow cells.

Gabapentin has also shown efficacy in reducing pain in patients with CRPS, although there are limited recent studies [38]. A small RCT compared the use of gabapentin to amitriptyline in children with CRPS-I or a neuropathic pain condition and found a significant reduction in pain score that did not differ between the medications [39]. With its favorable safety profile, the use of gabapentin for treating CRPS is largely dependent on provider preference and clinical experience [40].

The use of ketamine in the treatment of CRPS targets the sensitization of N-methyl-Daspartic acid (NMDA) nociceptive pathways as a result of the upregulated inflammatory response [41, 42]. By using an NMDA receptor antagonist, topical and intravenous ketamine have been shown in multiple placebo-controlled studies to be effective at providing pain relief and even inducing remission in treatment-resistant patients, although systematic reviews have concluded to be low-quality evidence overall [43].

Many antioxidants have been proposed for the treatment of CRPS based on the concept that local inflammation in CRPS generates oxygen free radicals [44]. However, vitamin C is the only antioxidant therapy supported by current evidence and is commonly used perioperatively for the prevention of CRPS following extremity surgery [45].

Recent advancements in the understanding of the autoimmune pathophysiology of CRPS have highlighted the potential benefits of plasma exchange therapy, which has historically treated other autoimmune conditions. A 2015 retrospective case series demonstrated that out of 33 patients who received plasma exchange therapy, 91% reported a significant reduction in pain, with 45% reporting sustained pain relief with additional weekly treatment [46]. These preliminary findings support the need for larger RCTs to be performed in the future to further elucidate the efficacy of plasma exchange therapy.

4.3. Minimally Invasive/Interventional Therapy Treatments

Sympathetic Block

A routinely used minimally invasive treatment for CRPS is a sympathetic block. Though routinely used, there is not a large amount of evidence on the short- and long-term analgesic effects of sympathetic blocks. The role of sympathetic blocks and epidural catheters and continuous sympathetic blocks has been described by Weissman et al., but Zernikow et al. concluded that there is a weak level of evidence for use of invasive treatments for CRPS in pediatric patients [47].

Transcranial magnetic stimulation (TMS)

Another treatment that has seen success and may have a clinical application is transcranial magnetic stimulation (TMS). It is a safe and non-invasive technique that produces a brief magnetic pulse into the brain and can induce cortical excitability [48]. The research showed that this high-frequency stimulation had effect 30 seconds after treatment and continued to reduce pain beyond 1 week [48]. More research on the long-term pain relief is needed to be able to make a conclusive statement on the efficacy of TMS.

4.4. Surgical Management

Several options have been used as surgical treatment for CRPS in effort to avoid excessive use of opioids and improve quality of life. One such therapy is spinal cord stimulation, which has been used for over 50 years as the most common treatment for chronic pain globally [49]. This approach traditionally involves tonic electrical stimulation of the dorsal columns avoiding ablation and in theory utilizing the 'gate-control' theory of Melzack and Wall [50]. Other explanations for effectiveness include modulating neuronal hyperexcitability and neurotransmitter concentration [49].

Another surgical treatment that exists for patients with CRPS is implantable peripheral nerve stimulation (PNS). This exists as a more focal approach to specific nerves that have presented problematically with regards to response. One study utilized a surgical procedure that addressed specific neuropathy in upper and lower extremity nerves with the sciatic nerve being the most commonly affected in this cohort [51]. Significant improvements were seen in visual analog scale (VAS) pain rating, reduction of patients on concurrent opioid therapy, and improved functional outcomes [51].

Amputation has long been employed and is among the most controversial surgical treatments for CRPS. A systematic review found that although prominent risks of phantom limb pain (PLP) and recurrence are of consideration, there exist many studies showing possible improvement of symptoms with amputation [52]. Stoehr et al. in their 2020 article in Microsurgery treated four patients ranging in age from 38 to 71 years with targeted muscle reinnervation [53]. Two of the subjects developed residual limb pain (RLP) and PLP, one only had RLP, and one only had PLP [53]. Due to the conflicting results and historical avoidance, some of the most important aspects of care that improve surgical outcomes include pre-, peri-, and postoperative care irrespective of procedure performed [54].

4.5. Future therapy

With the expanding knowledge base of medicine, the future holds many novel and promising treatments. One such treatment includes use of mycophenolate, which has historical use as an immuno suppressant and anecdotal evidence that it improves neuropathic pain [55].

A study showed intriguing results, prompting additional studies on immune suppressant based treatment for analgesic effects. However, considerations exist due to the unknown mechanism, inconsistent results, and possible side-effect profiles [55]. Similarly, a different study examined use of another substance, polydeoxyribonucleotide (PDRN), which has anti-inflammatory and regenerative effects [56]. Results did show some allodynia reduction effects along with activation of astrocytes in animal models. Finally, as perhaps the most novel of applications, immersive virtual reality has been applied to reduce neuropathic pain in CRPS [57]. This pilot study of eight participants used kitchen simulation software and discovered that patients with upper-extremity CRPS who completed at least ten sessions showed some improvement [57]. Chau et al. reported that participants described pain relief and functional improvement possibly using a similar mechanism of effect as mirror therapy stimulating mirror neurons and neuroplasticity [57]. These innovative future therapies need more examination to prove effectiveness and longevity, but all are encouraging at this juncture.

CONCLUSION

CRPS is a complex and multifactorial condition. While our current understanding of CRPS has come a long way since those early definitions, it is still not complete. Larger and higher-quality clinical studies are needed to further elucidate the underlying mechanisms of

this condition, which will enable the development of more precisely targeted therapies. Although advances in novel treatments have expanded the range of therapy options, no successful therapeutic intervention exists. Therefore, continued research efforts are needed to investigate combinations of medical and surgical therapies for the future of CRPS treatment.

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