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Complex Regional Pain Syndrome

Maria A. Hendrix
Otterbein University, maria.hendrix@otterbein.edu

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Maria Hendrix BSN, RN

Otterbein University, Westerville, Ohio

Introduction

Complex regional pain syndrome (CRPS) is a chronic and often disabling condition that is seen in many patients seeking pain management. The condition leaves patients in excruciating pain that is disproportionate to the inciting injury. In addition, patients with this pain disorder experience abnormal sensations such as cold and heat allodynia, hyperalgesia, edema, abnormal sudomotor activity and trophic changes (Lee et al., 2015). CRPS disproportionally affects four times as many women as men (Alexander, Peterlin, Perreault, Grothusen, & Schwartzman, 2012). There are two types of CRPS: type 1, often referred to as reflex sympathetic dystrophy (RSD), is not evident of nerve damage while type 2 does indicate nerve damage. Figure 1 provided by Marinus et al. (2011) depicts the appearance of CRPS in the acute state; figure 2 depicts the appearance of CRPS in the chronic state. The pathophysiology of CRPS remains unproven: however, many hypotheses exist due to this disorder's multiple system dysfunction and the evidence is continuing to progress. As the pathophysiologic mechanisms of CRPS further advance, treatment modalities will continue to emerge in order for health care providers to improve the outcomes for patients suffering from CRPS.

Complex regional pain syndrome, formerly known as RSD or causalgia, requires more education and knowledge pertaining to the disease and the underlying processes that are involved. The completed research is presented to educate other medical professionals on the pathophysiological hypotheses behind CRPS, as well as individuals that are subject to this pain disorder.

Implications for Care

Treatment of CRPS involves a combination of modalities for both psychological and pain symptoms. Interventional therapies include peripheral nerve blocks, spinal cord stimulator, pump implantation, chemical and surgical sympathectomy and deep brain stimulation. Pharmacological therapies consist of bisphosphonate compounds, phentolamine, systemic steroids, antidepressants, opioids, benzodiazepines and membrane stabilizers in order to treat the symptoms of this syndrome.

Signs & Symptoms

CRPS may be caused spontaneously or by an inciting injury that causes an abnormal response to tissue injury. The signs and symptoms of this multifactorial disorder include:

- severe pain,
- Hyperalgesia
- Hyperesthesia
- atypical sudomotor activity
- swelling of the affected limb
- changes in skin color
- cold and heat allodynia
- motor or tropic changes which may involve weakness, tremor, dystonia, changes of the hair, skin and nails, wasting away of tissue, skin or muscle and bone thinning.
- Patients with CRPS also present with anxiety and depression when compared to healthy individuals.
- The pain is neuropathic in nature and is not limited to certain dermatomes (Alexander et al., 2014).
- The pain caused by CRPS spreads proximally over time and may even develop on the opposite limb.
- Patients with longstanding CRPS tend to perceive their affected limb as larger than in reality and report feelings of hostility toward the limb, feeling as though the limb is a separate entity and causing the patient to desire amputation of the affected limb (Marinus et al. 2011).

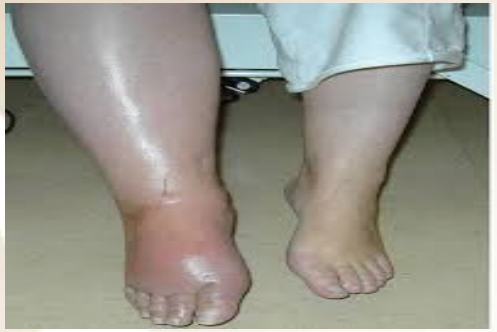


Figure 1 Acute CRPS (Marinus et al., 2011)

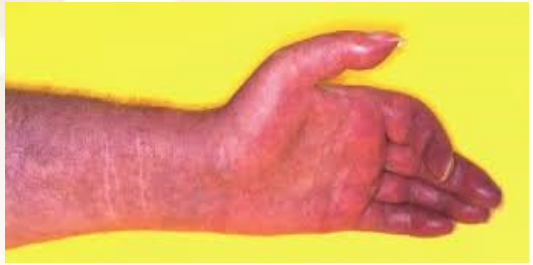


Figure 2 Chronic CRPS (Marinus et al., 2011)

Underlying Pathophysiology

Genetic association does appear to play a role in the pain disorder. CRPS phenotypes are correlated with the human leukocyte antigen (HLA) system when two HLA alleles are present at the loci (Watts & Kremer, 2011), associating CRPS with a genetic disposition.

The pathophysiology of CRPS remains elusive, but with multiple hypotheses. CRPS involves interactions between the immune system and nervous system. CRPS also involves both the peripheral and central nervous systems. The traumas usually identified in the etiology of CRPS most likely begin with peripheral nociceptive overstimulation and can eventually create and sustain the central sensitization that is indicated by the sensory factors of the pain disorder (Hardin et al, 2013). Marinus et al. (2011) has identified three major pathophysiological pathways: abnormal inflammatory mechanisms, vasomotor dysfunction and maladaptive neuroplasticity.

Abnormal Inflammatory Mechanisms

Alexander et al. (2012) identified significant changes in the plasma cytokines, chemokines, and soluble receptors in individuals with CRPS that contribute to the inflammatory process. Cytokines most likely act not only in the affected limb, but also in the spinal cord. Neurologic inflammation is most likely the mechanism of post-junction signaling caused by weak inactivation of neuropeptides and increased receptor availability (Marinus et al. 2011). The pro-inflammatory cytokines are liable for the initiation and facilitation of inflammatory and neuropathic pain and directly contribute to the extravasation of the limb, edema and increased cytokine expression in CRPS.

Vasomotor Dysfunction

Vasomotor changes and hyperalgesia have been associated with sympathetic dysfunction. In CRPS, the affected limb is initially warm due to vasoconstrictor neurons and further progresses to become cold and a blue-like color. The up-regulation of alpha-adrenoreceptors in cutaneous microvasculature has been identified as the mechanism of hypersensitivity (Watts & Kremer, 2011). Watts and Kremer (2011) report that the vasoconstrictor adrenoreceptors produce cool and pale skin and the adrenoreceptors on afferent nociceptive fibers cause spontaneous pain. The result of this process is increased circulating catecholamines that exacerbate sympathetically mediated symptoms. Furthermore, the sustained vasoconstriction may be caused by changes in the endothelium that cause a decreased ability to release endothelial nitric oxide (Marinus et al., 2011).

Maladaptive Neuroplasticity

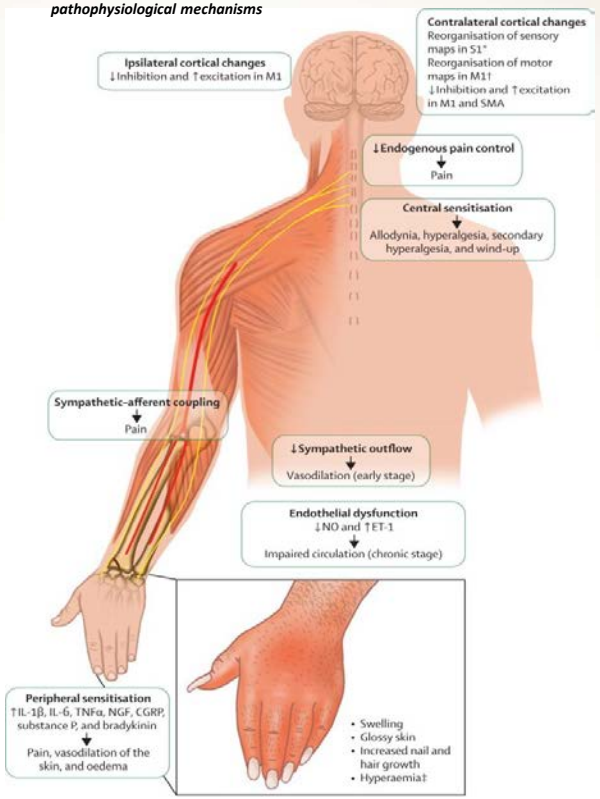
Maladaptive neuroplasticity could be explained by evidence of structural brain changes. D. Lee et al. (2015) reported that CRPS patients revealed significantly decreased cortical thickness in the right dorsolateral prefrontal cortex, implying that CRPS is accompanied by cerebral atrophy that may contribute to the pathophysiology. In addition, Pleger et al. (2014) found that CRPS patients have an increase in gray matter density in the dorsomedial prefrontal cortex which is involved in coding emotional correlates of pain. This evidence demonstrates that brain structure alterations in patients with CRPS are involved in regulating cognitive processes including emotional behavior and pain perception.

The central nervous system (CNS) is affected by CRPS. Although not completely understood, central sensitization may occur from lack of restraint of spinal and trigeminal nociceptive neurons or enablement of nociceptive activity by excitatory neurons (Marinus et al. 2011). Sensitization of the CNS can cause symptoms such as chronic pain, hyperalgesia, allodynia and spreading of pain to nearby non-injured areas.

Conclusion

CRPS is a painful disorder that effects more than 50,000 new cases every year in the United States (Watts & Kremer, 2011). The research continues to progress for this disorder as the pathophysiology continues to unfold. Current evidence of multiple mechanisms interconnected in the pathophysiology of CRPS should provide for additional discovery and more targeted therapeutic interventions for the future.

- ***Figure 3 below, provided by Marinus et al. (2011), represents clinical features and proposed CRPS pathophysiological mechanisms***



M1=primary motor cortex. S1=primary somatosensory cortex. SMA=supplementary motor cortex. IL=interleukin. TNF=tumor necrosis factor. NGF=nerve growth factor. CGRP=calcitonin-gene-related peptide. SP=substance P. NO=nitric oxide. ET=endothelin.

Additional Sources

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