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REVIEW ARTICLE

Complex regional pain syndrome (CRPS), a review

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Abstract Complex regional pain syndrome is a chronic and painful condition that affects the quality of life of patients. It is usually triggered by a traumatic event of the soft tissues involving the nervous tissue. Although the factors that cause the syndrome are varied and not well known, different etiopathologic concepts have been proposed to explain the presence of this syndrome, such as autonomic dysfunction and changes in CNS plasticity, among others. The patient characteristically presents pain, sensory abnormalities, vasomotor disturbances in the skin, edema, changes in sweating, and motor alterations. The pain is associated with changes in the autonomic nervous system and has a distal predominance. Since there is no definitive diagnostic test, diagnosis is mainly based on a complete medical history and physical examination. Treatment is multidisciplinary and based on pain relief. Although in most cases evolution is favorable, rapid diagnosis and treatment are recommended to avoid dystrophic stage as much as possible.

Introduction

The first description of complex regional pain syndrome (CRPS) dates from the seventeenth century and was reported by the French surgeon Ambroise Paré to describe persistent pain and contractures of the arm suffered by King Charles IX after the bloodletting to which he was subjected. During the American Civil War, Mitchell described cases in which the soldiers suffered from burning pain secondary to gunshot wounds. This was described as causalgia. In 1900 Sudeck described traumatic complications in the extremities characterized by intractable pain, edema, and limitations in motor function. Lerich in 1916, suggested that causalgia was caused by excessive activity of the sympathetic nervous system. It was

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not until 1946 when Evans proposed reflex sympathetic dystrophy.[1]

In 1979 the International Association for the Study of Pain (IASP) defined causalgia as ''a syndrome of sustained, burning pain after a traumatic nerve injury, combined with vasomotor and sudomotor and later trophic changes'' and reflex sympathetic dystrophy as ''similar, but from other causes.''[1]

The term proposed by the IASP in 1994, which differentiates complex regional pain syndrome into type 1 and 2, is currently used with the dissimilarity that type 1 is caused by an injury or trauma to tissue and in type 2 there is prior and obvious neurological damage.

Since the characteristics of these two types of disease are essentially the same and treatment is not different, the rest of this text will not distinguish between them with respect to pathophysiology, diagnosis or treatment.

Epidemiology

Worldwide, the incidence and prevalence of CRPS is unknown. Some studies have reported an incidence rate that ranges from 5.46 to 26.2 per 100,000 persons year.[2,3] In addition, the prevalence subsequent to trauma ranges from 0.03 to 37%, based on retrospective studies. In 40% of cases it is associated with a fracture or surgery, with compression of the median nerve being the most common, although it can also appear after a sprain (10%), root lesions (9%), lesions of the spinal cord (6%), and spontaneously (5–10%). It was found that it more frequently affects women (2–3:1) with a peak between 50 and 70 years of age, with a predominance in the arms.[4]

It is noteworthy that the severity of the original injury is not correlated with the severity of the symptoms of CRPS, although psychological factors such as stress are risk factors that worsen symptomatology.[5]

CRPS is also associated with other diseases and conditions such as stroke, mastectomy, pregnancy, and the use of drugs such as phenobarbital and isoniazid. There are predisposing factors for the development of this syndrome in addition to trauma and diabetes mellitus.[6]

The main feature of the history is a fracture, and immobilization has been proposed as a possible predisposing factor for CRPS. Immobilization studies in animals have found increased sensitivity to stimuli, and changes at the spinal level. In humans it was found that plaster splint immobilization results in an increase in cerebral blood flow in areas related to sensory, motor, and emotional processing.[7]

It is believed that psychogenic or hysterical factors, mainly associated with depressive symptoms, may contribute to CRPS. Any psychological factor can interact with catecholamine release and thus interfere with the pathophysiological mechanisms mentioned; however this is only a hypothesis.[8] The success of psychotherapy and occupational and cognitive therapy in CRPS patients shows that the symptoms of dystonia and myoclonus are of a psychogenic origin in some patients. It is not always easy to distinguish these symptoms from simulation.[9]

CRPS often occurs in several family members and at younger ages, which may indicate a genetic predisposition. Accordingly, HLA has been proposed to have a role in CRPS. Genetic studies have also identified polymorphisms in the TNF-α gene and the angiotensin converting enzyme gene, but no contrasting results have been found with the latter.[10]

Studies have shown that the use of ACE inhibitors at the time when the causal trauma is suffered, as well as a medical history of asthma or migraines, is associated with an increased risk of developing CRPS. It is noteworthy that these factors imply underlying inflammation, since ACE inhibitors increase the availability of substance P, and both migraines and asthma share neurogenic inflammation mechanisms.[10]

Pathophysiology

CRPS is a chronic pain condition that usually arises after a traumatic event of the soft tissues. The ''definitive'' cause still remains unknown, although different pathogenetic concepts have been proposed; three of the most studied are: autonomic dysfunction, neurogenic inflammation, and changes in CNS neuroplasticity, all of which are still in dispute. However, current evidence shows that this problem could have a multifactorial origin.

Autonomic dysfunction

Refers to an alteration of the sympathetic nervous system. It has been suggested that its degree depends on the stage in which the syndrome is found. This suggests the existence of inhibition of sympathetic vasoconstrictor neurons, expressing lower levels of norepinephrine in the affected limb compared to its counterpart. This triggers vasodilation, and chronicity of this condition allows vasoconstriction. This chronicity contributes to a redistribution of blood flow through arterioles, causing inadequate capillary nutrition, which results in hypoxemia and acidosis. These alterations can produce free radicals, which cause histopathological changes by oxidative stress.

There is evidence of an increase in the number of α-adrenergic receptors in the skin of patients with CRPS. Their activation would trigger an increase in noradrenaline release, which in turn produces hyperstimulation of nociceptive fibers causing pain and hyperalgesia, even in sympathectomized patients.

Cutaneous injection of norepinephrine induces pain via these adrenoreceptors in patients who respond to sympathetic blockade, whereas there is no reaction in patients who showed no response to the blockade. These data imply that CRPS may involve abnormal adrenoreceptors expressed in nociceptors which, when stimulated by circulating catecholamines, are activated and cause hyperalgesia and possibly alodinia.[11]

Another group of researchers found that in CRPS II, nerve damage causes an upward regulation of catecholamine receptors (Fig. 1).

Catecholamine levels

Plasma norepinephrine levels were lower in the affected limb compared to its healthy counterpart. However adrenaline levels were similar in both extremities.[6]