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Mini-review

Algodystrophy: recent insight into the pathogenic framework

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Summary

Algodystrophy, nowadays called CRPS I, is a painful syndrome characterized by sensory and vasomotor disturbance, edema and functional impairment. Significant progress in knowledge about the pathogenic mechanisms of the disease have been recently achieved, but they are not yet fully understood and some clinical aspects are still lacking of a whole pathogenetic comprehension. The local release of pro-inflammatory neuropeptides and some cytokines may be the event that triggers and maintains the disease, causing hyperalgnesia and allodynia. In the following phases, the impaired capillary permeability, the interstitial edema and the consequent hypoxia and local acidosis have been proposed as possible pathophysiological pathways. The local hyperactivity of the sympathetic nervous system supposed in the past have not been confirmed and the hypothesis of an altered nociceptive processing at CNS level has limited evidences in acute phases of the disease. The steady bone involvement could be confirmed by the efficacy of bisphosphonates in the treatment of early disease.

KEY WORDS: algodystrophy; CRPS; pathophysiology; microcirculation; inflammation.

Introduction

More than 110 years ago the German surgeon Paul Sudeck described the clinical case of a patient suffering from “acute inflammatory bone atrophy” remarking the presence of all the clinical signs of inflammation (tumor, dolor, calor, rubor and functo laesa) in association with a “patchy” osteoporosis (1). This is considered the first report of Algodystrophy and the disease has been called for several decades, at least in Europe, “Sudeck disease”. In the following years, many troubles have been found in the full understanding the pathophysiological mechanisms responsible for the disease. The main misleading problem was the observation of an alleged therapeutic efficacy of the surgical and pharmacological sympathectomy that supported the hypothesis of a local hyperactivity of the sympathetic nervous system in the genesis and maintenance of the disease. Accordingly, the disease was called “reflex sympathetic dystrophy” for several decades, mainly in the USA. Afterwards, the evidence of the ineffectiveness of the sympathetic blocks (2) and the biochemical assessment of a reduced sympathetic activity rather than enhanced, especially in the early stages of the disease, lead to an unavoidable review of the denomination conuding to the nowadays internationally recognized term of Complex Regional Pain Syndrome type I or II, regarding respectively the absence or presence of an overt neurological lesion (3). This change was also neccessful because of significant progress in the knowledge about the pathogenic mechanisms as the result of more recent studies. First, the use of highly sensitive biochemical methods helped to identify some local and systemic factors responsible for the beginning and the maintenance of the inflammatory process (neuromodulators and cytokines). Secondly, some animal models allow to obtain a disease showing features similar to those observed in patient suffering from CRPS-I, despite the obvious limitations existing in comparing animal behaviors to the characteristic and entity of human pain. On the basis of these results, the most convincing pathogenic hypotheses have shifted to a local process of neuroinflammation, probably associated with the clinical features occurring in the first stage of the disease (edema, eritrosis, increased local temperature and sweating); later, in the following phases, the microcirculation impairment and the microvascular damage appear to be the pathophysiologic mechanism responsible for the clinical evolution that can be observed in most patients (“dystrophic” or “cold” phase), characterized by the reduction of edema, the presence of subcianosis and a decrease of the local temperature (4). The role of the hypoxia or ischemia and sympathetic fibers as well as the functional changes at the level of the central nervous system still remain only hypotheses that need more strong demonstrations. In spite of these new findings, it is very difficult to combine old and new different pathogenic theories which trigger and maintain CRPS-I, mainly for the possible interaction between them, the entity of each of them and changes in time when they are present. These issues are possibly related to the well-known variety of clinical aspects that can be present in different stages of the disease in the same patient and among patients (5), irrespective of the trigger causal event.

Neurogenic inflammation

The development of animal models showing clinical manifestations very similar to human CRPS-I with a same time evolution to what can be observed more frequently in clinical practice, has been the main research tool by which some pathophysiological pathways have been proposed and then confirmed in subsequent clinical studies on patients. Both the model of chronic pain obtained in rats by inducing a close fracture of the distal tibia and the model of ischemia and subsequent reperfusion of a limb have provided bio-
Chemical information sustaining the hypothesis that the local release of pro-inflammatory neuropeptides and some cytokines may be the event that triggers and maintains the disease in the first phases, causing hyperalgesia (increased nociceptive sensitivity) and allodynia (pain for non-painful stimulation), edema and local warmth (6). In the early stage of the inflammatory process, the nerve growth factor (NGF) present in injured tissues seems to play a central role (7). Polimorfonucleated cells, leukocytes, macrophages and activated mast cells, which the local presence is documented by an increased radiolabeled leukocyte uptake, are able to produce NGF which, by binding to specific receptors on sensitive afferent fibers C and Aδ, induces NGF which, by binding to specific receptors on sensitive afferent fibers C and Aδ, determines the retrodromic release of neuropeptides as substance P (SP) and calcitonin gene-related peptide (CGRP). These two neuropeptides are able to induce meaningful changes in the local microcirculation causing vasodilatation, increased permeability of the plasmatic proteins and interstitial edema. In patients with CRPS-I local and systemic increased levels of SP and CGRP have been found (6). Some other pro-inflammatory cytokines such as tumor necrosis factor-α (TNFα), interleukin-1 (IL-1) and interleukin-6 (IL-6) seem to be involved because higher plasmatic levels have been found in patient suffering from CRPS-I. TNFα seems to be the link between the inflammatory process triggered by the injury responsible for the onset of the disease, the subsequent synthesis and release of other cytokines (IL-1β and IL-6) and the release of SP and CGRP, with a consequent impairment of the microcirculation (9). Finally, TNFα and IL-1β themselves are able to influence the local release of NGF; moreover NFkB, a nuclear transcription factor, could represent the link between the local release of proinflammatory neuropeptides and the local production of cytokines. These processes seem to have a reduction in time, as demonstrated by studies that have not been able to found a local increase of cytokines in chronic CRPS-I.

The altered microcirculation

In the cascade of events responsible for the subsequent phases of the disease, the metabolic alterations due to the disrupted capillary exchange maintain and exacerbate the clinical manifestations of CRPS-I. On the basis of results obtained with different studies in patient suffering from CRPS-I, the altered capillary permeability, the interstitial edema and the consequent hypoxia and local acidosis due to the anaerobic metabolism have been proposed as a possible pathophysiological pathway (Figure 1). In this regard, recent investigations are addressed to the genesis of some particular clinical manifestations, for example the induction and maintenance of hyperalgesia and allodynia, hallmarks of nociceptive alterations of the disease, the origin of which may be not due to a process of central sensitization and/or induction of nociceptive circuits that nowadays are not confirmed in research studies. Tissue ischemia involving not only the skin and subcutaneous tissues, but also the deep structures (muscles, joints and bone) has been demonstrated in the rare histological studies both in muscles samples (deposit of lipofuscin pigment, atrophy of muscles fibers) and in the endothelium of small vessels of different tissues. The endothelial damage observed in human biopsies of patient suffering from CRPS-1 is very similar to that observed in animal models of ischemia/reperfusion injury experimental studies (10). The endothelial cells appear swollen, with polymorfonucleated cells attached to the capillary wall; the vessel lumen is often occluded with consequent formation of arteriovenous shunts that worse the metabolic exchanges and compromise the blood flow. Such alterations are very similar to those found in the so called “compartment syndrome” where, following an injury or surgery, interstitial plasma extravasation exceeds the drainage capability of the lymphatic system, leading to an increase of hydrostatic tissue pressure and an altered dynamics capillary exchanges (slow-flow/no-reflow phenomenon) (11). In this occurrence, the production of oxygen free radical deriving from hypoxic stress induces a further capillary damage and supports the inflammatory process. The compensatory response is the production of antioxidant factors, which are increased in CRPS-I patients both in serum and salivary fluid. This pathogenic pathway (“slow-flow/no-reflow”) could be related to the clinical evolution of the disease toward the cold phase in which the clinical signs of ischemia are prevalent. Further experimental evidences allow to suppose that the local tissue acidosis and the free radicals production are the events associated to the

![Figure 1 - Consequences of the impaired microcirculation found in patients with CRPS-I.](image)
nociceptive sensitization typical of CRPS-I. Afferent nociceptors show activated H+ receptors (TRPV1 and ASIC) and the decrease of pH can be the main factor responsible for the maintenance of pain in CRPS-I as well as in reverberating the painful stimulus by the release of neurotransmitters responsible for the altered dynamics of capillary exchange (CGRP and SP). A further pathogenic step related to the microcirculation impairment is now identified in the endothelial damage and the consequent altered balance of the local factors concentration that physiologically control the blood flow, such as endothelin-1 (ET-1) with its specific vasoconstrictor action and nitric oxide (NO) with vasodilating action. Clinical studies on patients have demonstrated an increased local concentration of ET-1 with a possible increase in vasoconstriction and decrease levels of NO with a lowered vasodilating action. The low local levels of NO are thought to be secondary to the inactivating action of free radicals; instead the increased levels of ET-1 are possibly supported by more complex mechanisms. Pro-inflammatory cytokines such as TNF-α and IL-6 are able to increase endothelial production of ET-1 which in turn seems to be able to increase the production of the same inflammatory cytokines, generating a self-maintaining circle from an inflammatory process to the microcirculation damage (12). Factors responsible for the onset and maintenance of CRPS-I are schematically shown in Figure 2.

The role of the Sympathetic Nervous System

The pivotal role of the sympathetic nervous system (SNS) in the pathogenesis of CRPS-I has not been confirmed on the basis of studies that document only a limited participation mostly in the first phases of the disease. The evidence of a decreased instead that increased sympathetic activity in the first stages of the disease has been independently demonstrated by different research approaches and is thought to possibly have a sharing role in vasodilatation, due to a functional inhibition of sympathetic terminations having a vasoconstriction action. The subsequent vasoconstrictive cold phase is possibly acknowledged as hypersensitivity consequent to an initial reduced sympathetic activity. According to this hypothesis, same autoradiographic studies have shown high levels of α-adrenoreceptors at skin level only in CRPS-I lasting more than several months. Even without a sympathetic hyperactivity, the excessive sensitivity to the circulating catecholamines consequent to the initial reduced sympathetic input may be involved in the microcirculation impairment, contributing to the pathogenesis of hypoxia and ischemic changes typical of advanced stages of the disease. The hypothesis of a SNS role in stimulating the afferent nociceptors is linked to the appearance of α-adrenoreceptors on primary nociceptive afferences showed in some animal models after an injury. On this basis, the nociceptive stimulus could be the consequence on an adrenergic activation with a possible short circuit where a nociceptive stimulus follows an adrenergic activation. This assumption needs further evidence in patients with CRPS-I.

The role of Central Nervous System

While the hypothesis of an altered nociceptive pathway in the spinal cord have limited experimental evidences, some studies published in recent years seem to point out a possible role of the central nervous system (CNS) in the pathogenesis of CRPS-I. The non-metameric hyposensitivity and some movement disorders (muscle weakness, tremor) would be the clinical findings related to a CNS involvement. Functional magnetic resonance studies have demonstrated a reorganization (reduction) of the somatosensory areas in the cortex of the corresponding affected sites compared to the contralateral side with a return to normality with the regression of the disease. The major limitation about a pathogenic role of these findings, mainly in the late stage of the disease, is that the reorganization of cortical projections areas is not a
specific remark of CRPS-I with similar findings showed in other diseases characterized by a chronic neuropathic pain.

Conclusions

The new research tools available in the last decades have deeply modified the conception about the pathogenic framework of CRPS-I. Although some clinical aspects are still lacking of a full comprehension, the identification of several biochemical mechanisms involved in the local neuroinflammation and the blood peripheral flow disorder are now considered the cornerstone of the first pathogenic steps of the disease. However, these mechanisms recently discovered do not allow a satisfactory interpretation of CRPS-I cases that develop without a local trauma (for example related to a hemiplegic syndrome or a myocardial ischemia) or in patients who do not report any detectable predisposing local event. Finally, on the basis of the new proposed pathogenic mechanisms, CRPS-I defined as “cold at onset”, such as a disease without the clinical manifestation of the first stages related to a local inflammation, has still an incomplete knowledge about the possible causes able to trigger the disease. Another limitation of the available data is that all the studies are addressed to the superficial tissues of the affected limb (skin and subcutaneous tissues) disregarding changes at deep level (muscles, joints and bone). The technical difficulties in exploring deep tissues do not justify a seeming paradox: epidemiological studies show that the bone injury (fracture, sprain, and surgery) is the most frequent predisposing factor for CRPS-I and the incidence of the disease is higher in patients with a reduced bone mechanical strength and a consequent increased risk of fracture. Finally, the few histopathological studies performed in human and in animal models have demonstrated that deep tissues are steadily involved. The evaluation of involved bones with magnetic resonance imaging often shows changes suggesting the presence of an increased fluid content in the bone marrow, very similar to the interstitial edema found in the skin and in muscles, consistently with the distribution at these levels of sensory afferents expressing CGRP and with membrane receptors sensitive to acid pH (TRPV1 and ASIC) that innervate both the bone marrow and the mineralized bone and probably related to bone pain. Regardless the still unknown fields, the current theories about the pathogenic steps of CRPS-I are supported by evidence in some therapeutic approaches able to interfere with the pathogenic steps of the disease. The preventive and therapeutic results of drugs able to hinder the production of free radicals such as dimethylsulfoxide or high doses of vitamin C seem to confirm the more recent pathogenic theories casting doubts on expensive and invasive approaches, for example spinal cord stimulation or intratechal drug infusion that have showed only a palliative effect in most cases. Finally, the pivotal role of the bone involvement is supported by the evidence that bisphosphonates represent nowadays the most effective strategy for the treatment of CRPS-I in the early stage.

References