Algodystrophy in major orthopaedic surgery

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Summary

Complex Regional Pain Syndrome (CRPS) describes a diversity of painful conditions following trauma, associated with abnormal regulation of blood flow and sweating, trophic changes, and edema of skin. Epidemiology of this disease is not convincing because of the difficulties and inaccuracies in the diagnosis. Several mechanisms are involved in the genesis of CRPS. The higher incidence of CRPS in women over 65 suggests that some changes involving natural and pathologic processes of aging predispose to onset of CRPS. Many features of the orthopaedic management (surgical time, immobilization, surgical incision, fracture osteosynthesis or prosthetic implants) might influence inflammation status in different way. It is mandatory to improve the understanding of both the pathogenesis of CRPS and the conditions that play a decisive role in its genesis. Furthermore it is important to find some biomarkers that allow early diagnosis before the onset of typical clinical signs.

KEY WORDS: CRPS; orthopaedic surgery; fracture; fracture healing.

Background

Complex Regional Pain Syndrome (CRPS) is characterized by a large spectrum of symptoms and clinical signs. Symptoms include severe and disabling pain that may occur from a few weeks to several months from a triggering event. This condition develops generally within 4-6 weeks following a fracture or surgery to an extremity (the arm is more involved than the leg). About 3-5% of patients with distal radius fracture showed a CRPS that resolves spontaneously in most of cases. In some cases pain, along with the typical pattern of CRPS I, is likely to persist even for years, with an incidence ranging from 5.5 (2) to 26.2 (3) per 100,000 persons/years. The variability of clinical presentation of CRPS comes from the combination of several pathophysiologic mechanisms probably with a predisposing genetic susceptibility (4-6). It is well known that the main pathogenic mechanism underlying acute phases of CRPS is an abnormal inflammatory responsiveness to injury. It was demonstrated a significant increase of proinflammatory cytokines, particularly TNF-α, in patients with acute CRPS. Furthermore, the increased production of Nerve Growth Factor (NGF) and other neuropeptides, such as substance P and Calcitonin-Gene-Related Peptide (CGRP) might play a key role in the pathogenesis of hyperalgesia and allodynia (6). It was also demonstrated an imbalance between the production of Endothelin 1 (ET 1) and Nitric Oxide (NO) in favor of the first one, especially in patients affected by cold CRPS. When the acute pain syndrome is not treated early and appropriately, it is likely to evolve towards a persistent pain until to the chronic stage of CRPS. These changes are related to the involvement of new biological pathways leading to neuronal, synaptic and even cerebral plasticity, similarly to what happens in other chronic pain conditions. It was hypothesized also a role of the Sympathetic Nervous System (SNS) in the pathogenesis of CRPS, as suggested by the historical experience of Leriche by performing sympathectomy in the treatment of algodystrophy. Supporting this hypothesis, increased receptor sensitivity to catecholamines in some cases of chronic CRPS have been described (7). The diagnosis of CRPS is based on clinical criteria. Currently, the “Budapest criteria” are the most widely used and validated diagnostic tool for CRPS. Those are based on 4 distinct components (8):

1. continuing pain, which is disproportionate to any inciting event;
2. presence of at least one symptom in 3 of the 4 following categories: sensory, vasomotor, sudomotor/edema and motor/trophic;
3. at least one sign at time of evaluation in ≥2 of the categories mentioned above;
4. no other diagnosis that better explains the signs and symptoms.

The scientific community agrees on the existence of 3 subgroups of CRPS, including CRPS I (previously reflex sympathetic dystrophy), a post traumatic syndrome with spontaneous pain not limited to the distribution of a single nerve and not proportionate to the causative event, in the absence of nerve injury, CRPS II (previously causalgia) defined in the presence of nerve injury, and CRPS-NOS (Not Otherwise Specified) (9).
Epidemiology and physiopathology of CRPS in major orthopaedic surgery

Epidemiological data suggest that CRPS is a rare disease. Sandroni et al. (2) reported that this condition has a female:male ratio of 4:1, with an incidence of 8.57/100,000 for women and 2.16/100,000 for men. Recently, Sumitani et al. (10) analyzing a population of 185,378 Japanese patients with fracture of upper limbs, lower limbs or multiple fractures in different regions of upper or lower limbs treated osteosynthesis, reported only 39 cases (0.021%) of CRPS, 29 (0.058%) after a fracture of the upper limbs and 8 (0.006%) after a fracture of lower limbs, and 2 (0.074%) with multiple trauma of the upper and lower limbs. Patients over 60 years old are the most affected. The higher incidence in the elderly suggests that aging might play a major role in the pathogenesis of CRPS.

Several mechanisms are involved in the genesis of CRPS. The traumatic event that causes the fracture can be considered as the "primum movens" to trigger the cascade of pathogenic mechanisms involved in the onset of CRPS. Fracture healing occurs commonly after traumatic bony disruption. This is a complex process that involves the coordinated participation of hematopoietic and immune cells through 4 phases that progressively produce high quality bone tissue regeneration. In the early phase of fracture healing, the hematoma includes pro-inflammatory cytokines and cells that have multilineage mesenchymal differentiation potential. Macrophages, granulocytes, lymphocytes and monocytes reach the fracture site, where growth factors and pro-inflammatory cytokines (IL-6, IL-1, TNF-α) are released and Mesenchimal Stem Cells (MSC) are recruited (11). In this complex framework, the musculoskeletal unit undergoes a general subacute inflammatory status that can become chronic if the inflammatory cascade is not stopped by repairing mechanisms. It has been demonstrated a local pro-inflammatory unbalance between the increased IL-6 (12, 13), and the decreased IL-10 (14) levels during CRPS. IL-6 is a pro-inflammatory cytokine also involved in the development of neuropathic pain syndromes (15). On the other side, IL-10 is an anti-inflammatory cytokine inhibiting pro-inflammatory factors, such as IFN-γ (16), IL-2 (17), and TNF-α (18). Another major factor in the pathogenesis of CRPS that develops following a fracture is linked to surgical treatment. Usually, the use of external materials like fixation system or prosthesis during orthopaedic surgery, can enhance the local inflammatory reaction contributing to the onset of algodystrophy. It is also to be considered that already the only insertion of the prosthetic components during the knee or hip arthroplasty, causes compressive trauma of the trabecular bone and a prompt formation of an haematoma rich of proinflammatory factors (19). The traumatic surgical trigger can expose nervous system structures to immune-modulated reactions that leads to sensory, motor and autonomic disturbances (20). Endothelial damage both caused by the fracture that surgical incision could result in an increase of Reactive Oxygen Species (ROS), pro-inflammatory mediators (IL-6, TNF-α), ET-1, and decreased production of NO leading to vasocostriction (5).

All patients affected by CRPS reported a change in skin color, temperature and edema between the affected and unaffected side, linked to these vasomotor disturbances. Moreover, also trophic changes affecting the soft tissues (capsula articularis, ligaments, and fascia) can occur in chronic CRPS. In addition, histological findings showed signs of oxidative stress and microangiopathy in muscle biopsies collected from amputation after CRPS; in particular, lipofuscin deposits and collapsed capillaries were shown in muscle tissue during algodystrophy (21).

The timing of fracture healing has a key role in the pathogenesis of vascular disturbances (22). The early hematoma leads to a condition of transient hypoxia, with increased production of Hypoxia Inducible Factors (HIF) that can probably activate genes upregulating neo-angiogenesis and callus mineralization. Vascular disturbances might induce an inflammatory substrate and oxidative stress in muscle tissue. Other factors can have a meaningful influence on the onset of CRPS after major orthopedic surgery, including prolonged time of surgery, use of tourniquet, and type of anesthesia. A long surgical time and a prolonged application of a tourniquet could increase the risk of significant vascular disturbances, endothelial damage, and CRPS. However, Sumitani et al. (10) suggested that a longer duration of anesthesia, but not type of anesthesia, was significantly associated with a higher incidence of CRPS. In addition, surgical treatment _per sé_ is another risk factor for the development of this condition. However, only few data and retrospective studies documenting the presence of CRPS after major surgery are available in literature (Table 1). Algodystrophy syndromes, including typical CRPS, may represent complications after knee, most frequently, or hip joint replacement.

In a recent systematic review, Van Bussel et al. (23) reported knee algodystrophy in 53% of cases in patients who undergone knee surgical treatment, of which more than 20% met the Budapest diagnostic criteria for CRPS. The Authors suggested that arthroscopic knee surgery is a significant inciting factor for the development of CRPS. Therefore, in patients with knee pain, it is advisable to avoid knee arthroscopy to rule out causes other than CRPS, since this surgical technique may increase the risk for developing that condition. However, in a previous study, Burns et al. (24) analyzed 1,500 patients received total knee arthroplasty and found an incidence of 0.7% (8 cases) of CRPS. Interestingly, Authors reported that this complication is associated with a

<table>
<thead>
<tr>
<th>Study</th>
<th>Site</th>
<th>Patients (n)</th>
<th>Patients with CRPS (n)</th>
<th>Type of CRPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Bussel CM 2013 (23)</td>
<td>Knee</td>
<td>-</td>
<td>368</td>
<td>CRPS I</td>
</tr>
<tr>
<td>Burns AW 2006 (24)</td>
<td>Knee</td>
<td>1,280</td>
<td>8 (07%)</td>
<td>CRPS I (Reduction of ROM -17°)</td>
</tr>
<tr>
<td>Wolter T 2012 (27)</td>
<td>Spine</td>
<td>-</td>
<td>6 patients</td>
<td>CRPS II</td>
</tr>
<tr>
<td>Rewhorn MJ 2014 (25)</td>
<td>Leg, ankle, foot</td>
<td>390</td>
<td>17 patients (4,36%), (14 females, 3 males)</td>
<td>82.35% CRPS I, 17.65% CRPS II</td>
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reduction of 17° in the knee range of motion. The incidence of CRPS is higher after surgery of the upper and lower limbs. Rewhorn et al. (25) in a retrospective study of 390 patients who underwent elective foot and/or ankle surgery, reported a diagnosis of CRPS in 4.36% of cases, of which 82% were women.

Recently, Roh et al. (26), in a prospective observational study of 477 patients, reported CRPS I, according to Budapest criteria, in 42 (8.8%) of them within 6 months of surgery. Patients who developed this condition were more frequently older women and were more likely to sustain a high energy injury or have a comminuted fracture. It was hypothesized that also spine surgery can induce CRPS in the extremities. Wolter et al. (27), in a cohort of 35 patients, reported only 6 cases of CRPS (lumbar spine surgery, n = 5; cervical spine surgery, n = 1) within 2 weeks after spinal surgery. In this population, only 2 patients suffered from CRPS I.

The pathogenesis of CRPS is complex and it includes different factors that act during the fracture healing process, from the trauma to the postoperative period (Figure 1). This condition is limited to the affected limb with a progressive loss of biomechanical and functional properties. It is well known that in an attempt to avoid pain, patients start a maladaptive nonuse. Furthermore, a long period of immobilization, by reducing the mechanical stimulus that skeletal muscle exerts on bone, lead to bone and muscular loss with a progressive deterioration of the muscle-bone unit (28, 29).

In this scenario, aging might represent an important risk factor for CRPS. It is not surprisingly that two common age-related musculoskeletal diseases, such as sarcopenia and osteoporosis, could impair bone healing after a fracture occurs (30). We demonstrated that the skeletal muscle of sarcopenic individuals showed substantial biological changes, including increased oxidative stress, cellular vacuolization, and mitochondrial alterations, which compromise the oxidant-scavenging systems (29). In sarcopenic muscles, the denervation of single muscle fibers leads to a significant reduction of type II (fast) fibers, which are gradually replaced by type I (slow) fibers and adipose tissue (31). Moreover, in patients with osteoporosis and sarcopenia, impaired muscle protein synthesis strongly affects bone strength and functional mobility. In particular, Bone Morphogenetic Proteins (BMPs), members of the Transforming Growth Factor Beta (TGF-β) superfamily of cytokines, are upregulated following a fracture and can be detected during the bone regeneration process, but this mechanism seems to be strongly reduced in osteoporotic patients. This leads to a reduced regenerative potential for damaged bone and probably increases the risk of CRPS (32).

It was hypothesized that vitamin D might exert a pivotal role in muscle-bone crosstalk since the early embryonic age (33). It is possible that hypovitaminosis D, causing a disregulation of muscle-bone interactions, can contribute to generate and maintain CRPS.

**Conclusion**

CRPS is a pathological condition severely affecting the quality of life of patients and their functional outcome. Commonly it follows a trauma, especially after surgical treatment. Even if less frequently, CRPS develops after major surgery, such as arthroplasties. Generally, the severity of the pain and disease progression do not correlate with the severity of the trauma or surgical injury. Pain, sensorimotor impairments and local osteoporosis characterizing CRPS can get confused with other conditions in patients undergoing major orthopaedic surgery, such as osteoarthritis, severe osteoporosis or rheumatic diseases. The inflammatory pattern and the vascular disturbances are common in all those musculoskeletal degenerative diseases, and this means that patients and physicians do not ascribe symptoms to CRPS. Since the bone and muscle cross-talk plays an important role in all bone and muscle diseases, it is likely that this interaction is involved in the pathogenesis of CRPS.
References


