Complex regional pain syndrome: facts on causes, diagnosis and therapy

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Summary

Complex Regional Pain Syndrome (CRPS) is still a debated topic although the most recent advances in the knowledge of its pathophysiological mechanisms. This syndrome affects more than 200,000 people in the USA and more than 154,000 people in the European Union each year. Primum movens of CRPS pathophysiology is probably an inadequate response to a damage due to a severe post-traumatic inflammation. To date, the Budapest Criteria are the most used in diagnosis of this painful condition. Biochemical markers, including IgG serum autoantibodies against β2-adrenergic or M2-muscarinic and small non-coding RNAs, are promising instruments, still under investigation, that could be included in the diagnostic criteria. Bisphosphonates (BPs) are the most effective drugs in the early stage of CRPS, probably due to the interference with the inflammatory and nociceptive pathway and their pro-inflammatory mediators. In particular, the only BP approved for the treatment of CRPS type I is infusion of 100 mg neridronate given every third day four times over a period of 10 days, that demonstrated significant benefits in terms of pain relief and quality of life.

KEY WORDS: complex regional pain syndrome; CRPS; etiology; diagnosis; therapy; neridronate.

Introduction

In orthopedic and physiatric clinical practice, it is common to find patients, in particular women, suffering from a severe pain, disproportionate to the underlying cause and often associated to a reduced physical functioning that persists even after a long time from the traumatic event and/or from the surgery (i.e. Colles' fracture), even if properly managed. Sometimes, painful symptoms are accompanied by vasomotor and trophic disorders of the affected site. This painful and dysfunctional disorder is usually called Complex Regional Pain Syndrome (CRPS) type I.
Although it is not common in terms of absolute frequency, this condition has to be considered a serious complication because of its incidence and detrimental impact on both functioning and quality of life (QoL) of patients who have suffered a trauma particularly at distal upper and lower limbs.
The relevance of CRPS type I was recently emphasized in the Session "Complex Regional Pain Syndrome: Facts on Causes, Diagnosis and Therapy", held at the last World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases in Krakow.
During that symposium the CRPS was rightly defined as *"a skein to untangle and a challenge for clinicians to overcome among all conditions characterized by chronic pain"*.
This syndrome affects more than 200,000 people in the USA and more than 154,000 people in the European Union each year (1, 2). However, the use of different diagnostic criteria for CRPS has often given discrepancies in the epidemiologic findings of the disease; indeed, this syndrome has had a controversial history in its definitions (3).
During the symposium, speakers addressed the state of the art about the CRPS, including the current critical issues in diagnostics and therapeutic options.

Facts on causes of CRPS

To date there is a unanimous consensus that a multifactorial process, involving both central and peripheral mechanisms, might cause the CRPS-I. Each pathophysiological disorder could play a role in clinical manifestation but little is known about how they might interact to produce the symptoms and which are the precipitating causes (4).
Bruehl (4) described several factors involved as possible mechanisms causing CRPS-I, such as nerve injury, ischemic reperfusion injury or oxidative stress, central or peripheral sensitization, inflammatory and immune related factors, altered sympathetic nervous system (SNS) function or sympatho-afferent coupling, brain changes, genetic factors, psychological distress, and disuse.
The first step of CRPS pathophysiology is probably the post-traumatic inflammation that could cause main clinical signs, such as redness, swelling, hyperthermia, pain, and an impaired function (5). These symptoms are associated to the release of pro-inflammatory cytokines, such as transforming growth factor (TGF)-β1, interleukin (IL)-1β -2 -6 and vascular endothelial growth factor (VEGF), synthesized

by keratinocytes, endothelial or immune cells. These cytokines stimulate the metabolism of connective tissues (6), including bone cells; indeed, an enhanced osteoclastogenesis can explain the regional osteoporosis commonly found in CRPS-I (7). In addition, a role of adaptive immune system has been recently hypothesized, considering the increased number of pro-inflammatory monocytes (CD14+ CD16+) and mast cells in patients with CRPS compared with healthy controls (8). Mast cells degranulation, especially the release of tryptase, proteases, histamine, cytokines, and eicosanoids might contribute to pain sensitization (9) and higher skin temperature (10).

This clinical scenario is also conditioned by the neurogenic inflammation. In CRPS-I nerve injuries regards mainly small fibers, resulting in axonal degeneration and dysfunction producing vasomotor and trophic effects, especially the antidromic release of vasoactive neuropeptides, including calcitonin gene-related peptide (CGRP) and substance P (SP) (11, 12). The first induces vasodilation, with hyperthermia and erythema, whereas the second leads to plasma protein extravasation and edema (13). Neuropeptides released from small-fibers directly interact with inflammatory cells including lymphocytes, macrophages and mast cells amplifying the local inflammation (14). In absence of a nerve lesion, the activation or sensitization of peripheral nociceptors caused by cytokines might result in pain at rest or while moving a joint (15).

Considering the difficulties in explaining all forms of pain (including CRPS-I) through the two classic categories of nociceptive or neuropathic pain, the International Association for the Study of Pain (IASP) hypothesized a third category of pain called “nociplastic”, defined as “pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain” (16).

In association with peripheral nervous sensitization, the ongoing noxious input causes changes also in Central Nervous system (CNS) thanks to the neuronal plasticity; the continuous pain stimulation activates intracellular kinases, leading to an increased excitability and responsiveness to pain of nociceptive neurons (17).

Persistent pain in CRPS-I causes even several functioning and morphological brain changes. Some studies demonstrate an impaired activation of pain inhibitory pathways, in particular those from periaqueductal gray and cingulate cortex (18) and reduced opioid receptor availability in the amygdala, suggesting alterations in modulation of pain control (19). Moreover, in CRPS-I can be also noted brain morphological alterations, such as a significant reduction in cortical thickness of dorsolateral prefrontal cortex (20) involved in the top-down inhibition of the nociceptive transmission system (21).

Over the nervous system changes, an altered behavior of the SNS might play a key role in patients affected by CRPS-I. Autonomic system dysfunction could range from sympathetic deficit, with increased skin blood flow and warmth, to sympathetic hyperactivity, with decreased blood flow, coolness and sweating. The warmth and skin redness commonly found in the early stages of CRPS-I are caused by functional inhibition of central cutaneous vasoconstrictor activity, leading to cutaneous vasodilation (22). Furthermore, hyperactivation of peripheral adrenoreceptors determines the release of norepinephrine (23) that directly stimulates the SNS. This mechanism, called sympatho-afferent coupling, is an essential pathway for the “sympathetically maintained pain” (24) and the persistence of vasoconstriction and coolness that could explain sympathetic symptoms in the cold form.

Finally, it was hypothesized a role of genetic factors, such as HLA-DQ8 and HLA-B62, that might be involved in CRPS-I, but their clinical implications are not well understood (25).

The clinical manifestation of CRPS-I is not homogeneous and the two main clinical forms are the warm CRPS, with the dominance of inflammatory characteristics (Figure 1), and the cold CRPS, with the dominance of autonomic features.

Moreover, Bruehl et al. (26) proposed 3 subgroups of CRPS patients based on signs and symptoms, that could be considered as three different patterns and not on sequential staging:

- a relatively limited syndrome mostly with vasomotor signs (color and temperature asymmetry)
- a relatively limited syndrome with neuropathic pain/sensory abnormalities
- a florid syndrome with high levels of signs/symptoms in all categories.

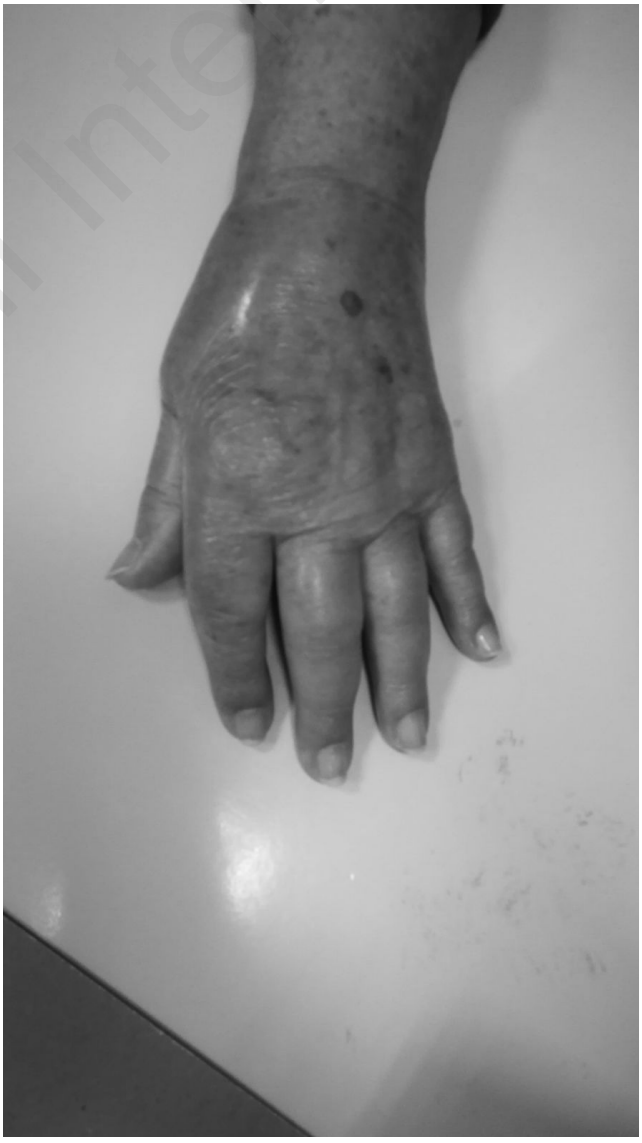

Figure 1 - A case of warm CRPS.

Facts on diagnosis of CRPS

In the recent past several Authors and consensus conferences proposed diagnostic criteria for CRPS. In particular, the IASP established the following diagnostic criteria for CRPS type I (27):

1) a noxious event or immobilization able to start the process
2) allodynia, hyperalgesia or anyway pain out of proportion compared to the precipitating event
3) edema, changes in skin blood flow or abnormal sudomotor activity of the affected region in any stage of the disease process
4) the diagnosis can be excluded if the presence of this kind of pain and dysfunction could be related to other diseases.

Nevertheless, these Orlando Conference Criteria showed sensitivity close to 90%, but a low specificity, less than 50%; therefore they included even patients affected by other clinical conditions with features similar to CRPS. Some years later, Harden et al. proposed a substantial revision of these criteria taking into account other relevant clinical signs, in combination with patients reported symptoms (28).

However, in a crucial consensus conference held in Budapest in 2003, the IASP task force presented the new diagnostic criteria for CRPS type I (Table 1) (29).

Although the "Budapest criteria" are commonly used in clinical practice, around 15% of subjects affected by CRPS do not meet the criteria; therefore, the IASP included these forms in a new subtype, defined "CRPS - not otherwise specified" (CRPS-NOS) (26-30).

However, even if more commonly used, the "Budapest criteria" are not the only ones proposed for the diagnosis of CRPS-I. Previously, Atkins et al. considered the loss of mobility as an important feature in the disease assessment, proposing that his diagnostic criteria for CRPS to be applied specifically in the orthopedic field (Table 2) (31).

On the other side, Veldman et al. considered CRPS as an altered inflammatory response to a local noxious stimulus and identified both a cold and a warm form of the disease; therefore, Authors proposed other criteria to diagnose CRPS, emphasizing the worsening of symptoms after physical activity (Table 3) (32).

All the criteria previously mentioned include all the typical signs and symptoms of the disease, without considering biochemical parameters; indeed, there are no specific biomarkers predictive of CRPS-I or treatment response.

The higher levels of IgG serum autoantibodies against β2-adrenergic or M2-muscarinic receptor seem to be specific, although further studies need to be done (33). Recently, small non-coding RNAs (microRNAs) are proposed as diagnostic and prognostic biomarkers. MicroRNAs could be involved in chronic pain conditions, including CRPS-I, by regulating intracellular pathways and reducing pain thresholds (34). Circulating serum levels of 18 microRNA were significantly different between patients affected by CRPS-I and control subjects; therefore, they could be a useful parameter for clinical stratification of patients affected (35). Moreover, serum microRNAs levels changes in relation to the treatment, such as ketamine, and might used as biomarkers to predict treatment response (36).

Until now, imaging is not required to make the diagnosis, but in some cases, could be used to support clinical findings and

Table 1 - Budapest Criteria for CRPS.

1. Continuing pain, which is disproportionate to any inciting event
2. At least one symptom in three (clinical diagnostic criteria) or four (research diagnostic criteria) of the following categories:
   a) sensory: hyperesthesia or allodynia
   b) vasomotor: temperature asymmetry, skin color changes, or skin color asymmetry
   c) sudomotor/oedema: edema, sweating changes, or sweating asymmetry
   d) motor or trophic: decreased range of motion, motor dysfunction (weakness, tremor, ordystonia), or trophic changes (hair, nails, or skin)
3. At least one sign at time of diagnosis in two or more of the following categories:
   a) sensory: hyperalgesia (to pinprick) or allodynia (to light touch, deep somatic pressure, or joint movement)
   b) vasomotor: temperature asymmetry, skin color changes or asymmetry
   c) sudomotor/oedema: oedema, sweating changes, or sweating asymmetry
   d) motor/trophic: decreased range of motion, or motor dysfunction (weakness, tremor, or dystonia), or trophic changes (hair, nails, or skin)
4. No other diagnosis better explains the signs and symptoms

Table 2 - Atkins criteria for CRPS.

1. Neuropathic pain: nondermatomal distribution, without cause, burning, with associated allodynia and hyperpathia
2. Vasomotor instability and abnormalities of sweating: warm red and dry, cool blue, clammy or an increase in temperature sensitivity
   Associated with an abnormal temperature difference between the limbs
3. Swelling
4. Loss of joint mobility with associated joint and soft tissue contracture, including skin thinning and hair and nail dystrophy

Table 3 - Veldman criteria for CRPS.

1. Four or five of these conditions:
   - unexplained diffuse pain
   - difference in skin color relative to other limb
   - diffuse edema
   - difference in skin temperature relative to other limb
   - limited active range of motion
2. Occurrence or increase of above signs and symptoms after use
3. Above signs and symptoms present in an area larger than the area of primary injury or operation and including the area distal to the primary injury

to exclude other pathological conditions, such as infections, arthritis, osteoarthritis, compartment syndrome. In this perspective, X-ray imaging, Magnetic Resonance Imaging (MRI), and three-phase bone scintigraphy (TPBS) are the most useful diagnostic tools. X-ray is able to identify regional osteoporosis, juxta-articular and subchondral bone erosions and other bone diseases (37). MRI is commonly performed in patients with persistent pain after trauma. In the early stages of CRPS-I it could relieve abnormal signal intensity of the bone marrow, edema of soft tissue (38) or synovial effusion (39). These radiological findings are prevalent in patients affected by CRPS-I, but they are not pathognomonic for the disease. Moreover, MRI could be useful for differential diagnosis with radiculopathy or rheumatological diseases.

Finally, three-phase bone scintigraphy seems to be the most promising diagnostic approach in combination with clinical criteria. This multi-step imaging procedure uses the radiotracer technetium 99m-labeled methyldiphosphonate, which could detect information about perfusion status, soft tissue edema and inflammation, and degree of osteoblastic activity or bone turnover. It includes three phases: the first one is a radionuclide angiogram; second phase is the blood pool or tissue phase; the third phase consists of delayed images obtained 3 to 4 hours after radionuclide injection. Mackinnon et al. (40) demonstrated that a delayed increase of tracer uptake in the third phase is diagnostic for CRPS, with high sensitivity and specificity (96 and 98%, respectively) (41).

On the other hand, it was found only a poor correlation between TPBS findings and the Budapest research criteria (41). In our opinion, even if the role of TPBS in the CRPS workup is still controversial, a careful evaluation of the early perfusion phases of TPBS might predict treatment response with infusion therapies (42, 43).

Facts on therapy of CRPS

The therapeutic approach to CRPS-I includes pharmacological and non-pharmacological interventions that should be started as early as possible from the time of diagnosis (44).

Timely initiation is mandatory to prevent troubling complications, such as painful contractures, muscle retractions and anxious-depressive psychological repercussions (45).

Unfortunately, there is no standardized and univocal approach to treat patients affected by CRPS-I, due to both the intrinsic variability of the disease course and its severity, and the several pathogenic hypotheses that partly justify the use of a drug compared to another one (46-48).

Bisphosphonates (BPs), antiresorptive drugs, have been suggested as a potential treatment in the early stage of CRPS, probably because of the interference with the inflammatory and nociceptive pathway and their pro-inflammatory mediators, such as TNF-α and IL6 (47). Moreover, BPs could play a role on bone microenvironment reducing local acidosis, with a consequent analgesic effect (49).

In Italy, neridronate represented the only BP approved for the treatment of CRPS-I. It is administered intravenously at a dose of 100 mg every third day four times over a period of 10 days. Indeed, in a well-designed randomized controlled trial (RCT) versus placebo, Varenna et al. showed the clinical and persistent benefits of neridronate in early CRPS-I; in particular they demonstrated a reduction of pain, assessed by a Visual Analogue Scale (VAS), an improvement in health related quality of life (HRQoL), assessed by the 36-Item Short Form Health Survey (SF-36), along with no serious drug-related adverse effects (50). This study showed two evidences of efficacy, one in the reduction of the mean VAS in the intervention group, the other one in the increase of the percentage of responders (VAS reduction ≥50% from baseline). Indeed, within the first 20 days of treatment, VAS decreased in both groups, but mostly in the group treated with neridronate (p=0.043). Subsequently, further pain reduction was observed only in patients previously treated with neridronate. Moreover, 73.2% of patients included in the intervention group achieved a clinically significant response (VAS reduction ≥50% from baseline). After 50 days from treatment initiation, similar benefits of neridronate were reported in patients previously treated with placebo who switched to active treatment in the open extension phase (Figure 2).

In the past, were performed other studies investigating the effects of different BPs for the treatment of CRPS-I, such as alendronate, pamidronate, and clodronate (51, 52), in particular in the countries where neridronate is not available (47).

A recent Italian retrospective analysis performed on patients with CRPS-I showed that an early disease, a fracture as a predisposing event, and the "warm" disease subtype are all predictors of responsiveness to BP therapy (53).

Other treatments for CRPS-I that can be considered in case of BP failure include:

- Anti-inflammatory drugs, such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), cyclo-oxygenase (COX)-2 inhibitors, corticosteroids, and free-radical scavengers. In particular, NSAIDs and COX-2 inhibitors do not seem to be effective to treat the inflammation process in CRPS-I (54). Pulsed doses of steroids might be effective in early stages of CRPS even if there is a lack of long-term follow-up data. Free-radical scavengers (i.e. topic dimethyl sulfoxide, oral N-acetylcysteine, and vitamin C) may have a role in the reduction of reactive oxygen species linked to inflammation in CRPS-I (55), and high doses of vitamin C seem to prevent the incidence of disease after wrist fracture (47).
- Cation channel blockers (i.e. gabapentin, carbamazepine) have demonstrated a mild pain reduction in some studies with poor evidence (56).
- Opioids use, similarly to what is reported in other conditions characterized by neuropathic pain, is controversial in the treatment of CRPS-I (56).
- N-Methyl-D-Aspartate (NMDA) receptor antagonists were studied for neuropathic pain and CRPS-I (57). It was shown that intravenous (IV) administration of ketamine over five days in patients affected by CRPS-I could be beneficial, even if serious side effects may occur (58, 59).
- Anti-hypertensives and α-adrenergic antagonists were studied in two case series, one demonstrating that nifedipine might be useful in early CRPS-I, as well as phenoxybenzamine (60, 61), while transdermal clonidine, an α2-adrenergic agonist, could lead to some local relief (62).

Other pharmacological treatments, such as IV or topical administration of lidocaine seem to be clinically effective for pain relief (63), whereas low-dose IV immunoglobulin (IVIG) may reduce pain in patients with refractory CRPS-I (64).

Rehabilitative approach has a key role in the CRPS-I treatment (65) and should start from an adequate patient educa-

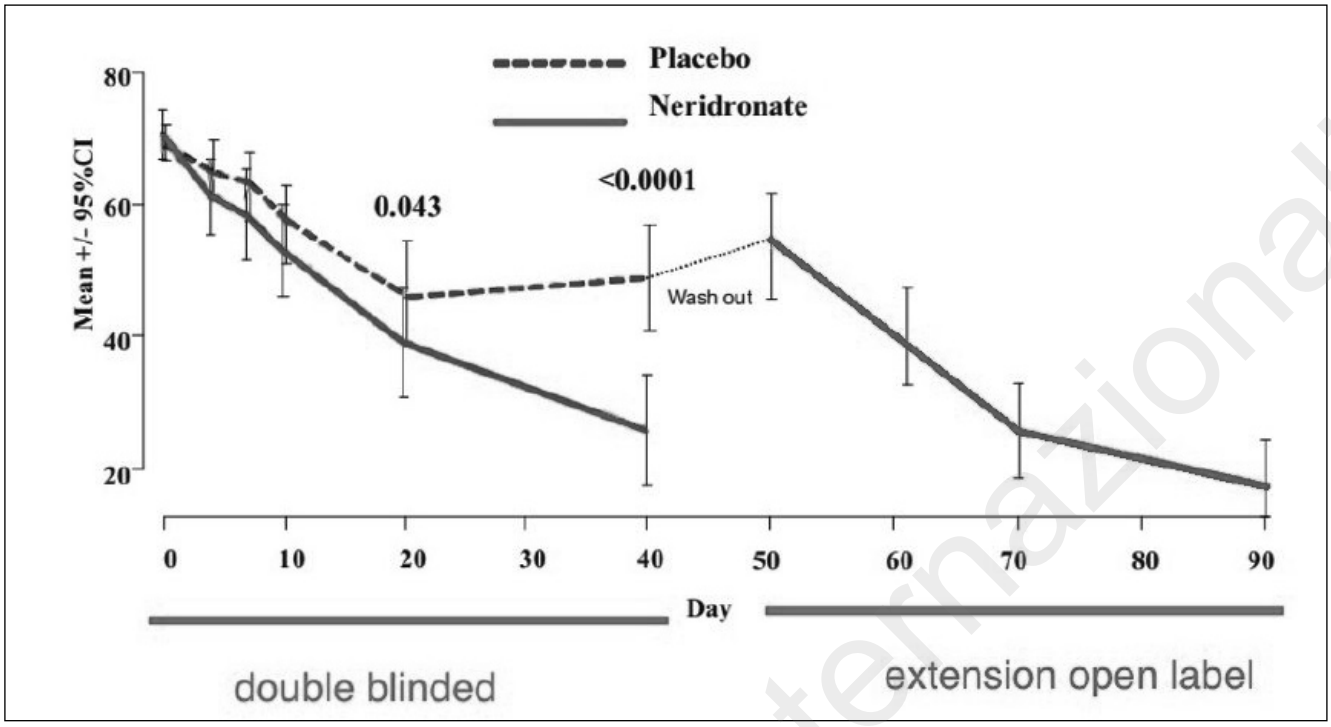

Figure 2 - Efficacy of neridronate on pain relief in patients with CRPS type I. Adapted from Gatti et al. (48).

tion, in particular to avoid the pain-related fear, encouraging patients to maintain the mobility of the affected limb, mainly during the activities of daily life (55).

Conclusions

CRPS is a critical disease that has to be adequately defined, investigated, diagnosed, and treated in order to reduce its negative impact in terms of pain, functioning, and HRQoL. To date the IV administration of neridronate is related to clinically relevant and persistent benefits and represents the treatment of choice for CRPS-I.

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