Recent advance

Type I complex regional pain syndrome

Le syndrome douloureux régional complexe de type I

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Abstract

First described by Ambroise Paré in the mid-17th century complex, regional pain syndrome (CRPS) can be defined as an articular and periarticular pain syndrome associated with vasomotor deregulation triggered by various stresses with no relationship between the intensity of the initial injury and severity of the continuing pain. Several names have been given to Type 1 complex regional pain syndrome (CRPS-I): causalgia, reflex sympathetic dystrophy, shoulder-hand syndrome and algodystrophy. The reported incidence of CRPS-I is about 25 per 100,000. Predisposing factors are tobacco consumption and being female (W/M ratio = 4). Although all the limbs can be affected, the upper limb is by far the most affected. CRPS-I is a classic complication of distal radius fractures (4–37%) and carpal tunnel surgery (2–4%). Early diagnosis and management are the most important elements of treatment because this syndrome has a long and disabling course. Some of the proposed treatments include NSAIDs, antidepressants and anticonvulsants. The latter, despite their good analgesic effects, do not cure CRPS-I. In select cases, a surgical procedure aiming at removing a nociceptive stimulus can lead to spectacular improvements.

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Keywords: Complex regional pain syndrome; Algodystrophy; Pathophysiology; Treatment

Résumé

Décrit pour la première fois par Ambroise Paré au milieu du XVI e siècle, le syndrome douloureux régional complexe (SDRC) peut être défini comme un syndrome douloureux articulaire et péri-articulaire lié à des perturbations vasomotrices déclenchées par des agressions diverses, sans relation entre la sévérité de la douleur persistante et l’intensité du traumatisme initial. La forme clinique sans atteinte nerveuse identifiable, ou syndrome douloureux régional complexe de type I (SDRC I) a été associée à de nombreux noms tels que causalgie, dystrophie sympathique réflexe, syndrome épaule-main, et le plus utilisé en France : algodystrophie, terme théoriquement obsolète depuis 1994. L’incidence reportée du SDRC I se situe autour de 25 pour 100 000. Les facteurs favorisants reconnus sont la consommation de tabac et le sexe féminin (F/H = 4). Si tous les membres peuvent être atteints, le membre supérieur est de loin le plus fréquemment touché. Le SDRC I est une complication classique et fréquente des fractures de l’extrémité distale du radius (4–37 % des cas), et de la chirurgie du canal carpien (2–4 % des cas). Un diagnostic et une prise en charge précoce sont les éléments les plus importants du traitement de cette pathologie à l’évolution longue et invalidante. De nombreux traitements médicamenteux ont été proposés, AINS, antidépresseurs et anticonvulsivants ; ces derniers, malgré leurs effets antalgiques intéressants, ne permettent pas de guérir le SDRC I. Dans certains cas précis, une intervention chirurgicale visant à retirer un stimulus nociceptif, neurogène ou mécanique peut améliorer le pronostic de façon spectaculaire.

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Mots clés : SDRCI ; Syndrome douloureux régional complexe ; Revue ; Algodystrophie

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1. Introduction

Complex regional pain syndrome (CRPS) is the current name for a syndrome first described by Ambroise Paré in the 17th century [1]. Various names have been used since then to describe it: causalgia, algodystrophy, reflex sympathetic dystrophy, shoulder-hand syndrome, and Sudeck syndrome [2]. Hand surgeons dread this all-too-common pathology, which is primarily characterized by chronic pain, autonomous nervous system involvement and motor and sensory problems [3]. Typically, only one limb is affected. The symptoms can appear in the absence of a known nerve injury, at which point the disease is called Type I complex regional pain syndrome [4], or following a peripheral nerve injury, which is then called Type II complex regional pain syndrome.

Chronic pain and stiffness are the main symptoms associated with this syndrome. The course is often drawn out and can result in permanent sequelae. The diagnosis of CRPS-I is solely based on clinical observations. Various paraclinical exams only help to guide the diagnosis when faced with an unusual presentation or to eliminate a potential differential diagnosis. In 2004, the International Association for the Study of Pain (IASP) published standardized diagnostic criteria for CRPS, which provide a nosological framework for a disease often misdiagnosed [1].

Although the pathophysiology is not fully understood, reviewing its history shows us how the medical community, by focusing solely on one theory, has made CRPS-I a disease mediated only by the sympathetic nervous system for the past half century [2]. Only since the mid-1990s, with the development of modern neurosciences and an animal model of CRPS-I, have the causes and mechanisms started to reveal themselves [1]. A better overall understanding of the pathology has led to the development of innovative therapies [1].

Early diagnosis and management are the most important components for treating this disabling pathology [5]. Some of the proposed treatments include NSAIDs, antidepressants and anticonvulsants. The latter, despite their good analgesic effects, do not cure CRPS-I. In selected cases, a surgical procedure aiming at removing a nociceptive stimulus can lead to spectacular improvements [6]. Overall, 80% of patients who are diagnosed and treated have had a positive outcome after one year. However, the prognosis of CRPS-I, when it complicates a distal radius fracture for example, is not as good. Stiffness of the metacarpophalangeal joints 12 weeks after the initial trauma is strongly correlated with development of chronic CRPS-I [1].

2. Historical perspective

Often in the art of medicine, knowing a disease’s history helps us better understand and grasp more recent developments, which are generally quite distant from what we learned during our medical academic training. This is especially true for CRPS-I. This historical review aims to show how ideas about the pathophysiologic mechanisms of a disease, which are still largely a mystery for those researching and treating it, have evolved over time. If the reader wants an expanded historical perspective going back to the end of the 20th century, the review by François Moutet is the most complete to date [7].

2.1. A new syndrome

The presence of chronic pain following peripheral nerve injury was first observed in wounded soldiers by Ambroise Paré in the 17th century. John Hunter (1766) and Weir Mitchell (1864) later described burning-type sensations and dystrophy secondary to trauma and ballistic nerve injuries and named this condition “causalgia” [7,8]. In the late 19th century, Hunter was the first to describe potential remote effects, away from the site of initial trauma, without any known nerve injury. In 1900, Sudeck described a post-traumatic pain syndrome resembling causalgia, but not involving a nerve injury, which he called “acute inflammatory bone atrophy” In the 1930s, the pathology was called “painful post-traumatic osteoporosis” by Leriche [9], and then “reflex dystrophy of the extremities” by De Takats [2].

2.2. Sympathetic theory

In 1946–1947, James Evans described patients presenting with intense pain combined with specific symptoms of what he called “stimulation of the sympathetic nervous system, associating redness, paleness or both, along with sweating and trophic changes”. In a series of four publications, he described these symptoms in combination with fractures, sprains, vascular problems, amputations, etc. The pain was described as deep, troubling and diffuse; it increased when the limb was used or manipulated, or trigger points were stimulated. Evans attributed the pain to a sympathetic nervous system abnormality and was the first to use the term “reflex sympathetic dystrophy” At that point, Evans suggested that excess effenter activity combined with a triggering injury event, activated the central nervous system that, when propagating towards a group of spinal interneurons, stimulated the sympathetic nervous system. This generated sympathetic activity was assumed to induce the arterial spasm and ischemia responsible for the increased capillary filtration pressure causing the observed edema.

One year after the term “reflex sympathetic dystrophy” was first used by Evans, Philip Foisie, a Boston surgeon, found that a sustained weak arterial spasm occurring, following soft tissue injury, could lead to a syndrome comprising significant pain, allodynia (pain due to a stimulus that does not normally provoke pain), edema, muscle atrophy, osteoporosis and joint stiffness. This grouping of symptoms that Evans had called “reflex sympathetic dystrophy” was labelled “traumatic arterial vasospasm” by Foisie. According to Foisie, a subacute, infra-clinical vasospasm brings about a reduction in blood flow and is responsible for degenerative problems primarily affecting the musculoskeletal system. Foisie specified that vasospastic events occurred in the arterioles, not in the large vessels. He found the syndrome to be more common in patients suffering from crush-type injuries, because of the increased tissue pressure. He also noticed that edema was often
present early in the disease course, especially after cast immobilization. He concluded that edema may have been at the origin of the ischemia by creating microvascular lesions responsible for increasing permeability of the capillary wall and plasma extravasation.

Evans and Foisie identified arterial vasospasm and capillary permeability as key elements of the pathology, but they had completely opposite views on the role of the sympathetic nervous system. Evans felt that sympathetic hyperactivity was crucial in triggering vasconstriction. Foisie felt that the injury itself initiated the vasospasm and that sympathetic blocks were the simplest way of counteracting it. Evans’ conclusions were adopted by the great majority of the medical community, while Foisie’s ideas went nearly unnoticed. The term “reflex sympathetic dystrophy” became the common medical name for this syndrome and the sympathetic nervous system became the main therapeutic target, serving as a focal point for research over the next 60 years [2].

2.3. Recent history (2000 decade)

When the central nervous system was found to play a role in the pathogenesis, a seismic shift occurred in our understanding of CRPS-I. In 2002, Janig and Baron hypothesized that CRPS-I could also be a central nervous system disease when they showed that central representation of the sympathetic, motor and sensory systems was altered [10]. The central alterations were evidenced by changes in somatic sensations (including pain sensations), the motor system (tremor, muscle weakness) and peripheral tissues regulated by the sympathetic nervous system (blood vessels, inflammatory cells, sweat glands, etc.). Their work showed that complex regional pain syndrome, especially Type I, may be a systemic disease of these neuronal networks [1]. They proposed a multifactorial model to explain how CRPS-I could develop after a seemingly trivial injury, an injury affecting an area far from the affected limb, or even after taking a drug.

Another piece of evidence that led to wavering in the sympathetic “dogma” of CRPS-I was the description of an animal model of ischemia-reperfusion syndrome in 2004. Codere showed that placing a tourniquet on the leg of an anesthetized rat for several hours led to the appearance of CRPS symptoms in more than 70% of cases. A moderate increase in intra-compartmental pressure for 72 hours, insufficient to trigger compartment syndrome, increases vascular permeability, induces edema and reduces functional capillary density [11].

Thus in early 2010, CRPS-I was now considered as having a multifactorial etiology [12], implicating not only the sympathetic nervous system, but the peripheral and central somatosensory system.

3. Definition(s) and diagnosis

3.1. Definition(s)

CRPS-I can be defined as an articular and periarticular pain syndrome associated with vasomotor deregulation triggered by various stresses with no relationship between the intensity of the initial injury and severity of the continuing pain. CRPS-I is a clinical condition without any specific markers. Diagnostic criteria set out by the IASP are shown in Table 1.

CRPS-I corresponds to the standard definition of algodystrophy and is defined by the presence of CRPS with no identifiable nerve injury, contrary to Type II CRPS, which corresponds to the old definition of causalgia and is associated with a nerve injury [1].

The diagnosis of CRPS-I requires detailed history-taking and a clinical examination. The examination should aim at eliminating various differential diagnoses of neurological, vascular, inflammatory, musculoskeletal or psychological origin (Table 2).

The typical progression of CRPS-I consists of an acute “inflammatory” stage (Fig. 1) during the first three months; the next stage, between the third and sixth month, is characterized by trophic changes (Fig. 2); it then progresses towards atrophy (Fig. 3) around the sixth month. The duration of these phases is extremely variable and the stages and symptoms do not necessarily happen in sequence. Many textbooks state that CRPS-I resolves without sequelae in a year or two. This opinion is obviously not consistent with the experience of hand and upper limb surgeons [13–16].

3.2. Suggestive signs

The following signs are suggestive of CRPS-I in or near an injured limb:

- edema that is fairly firm, persisting beyond the healing of the initial injury;
- pain occurring after a symptom-free period of a few days or weeks upon restarting to use the joint or at rest, sometimes at night;
- functional disability, sometimes significant;
- vasomotor problems with local changes in skin color and temperature;

Table 1

<table>
<thead>
<tr>
<th>IASP diagnostic criteria for Type I CRPS in their original form (A) and as modified by Harden (B).</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) IASP diagnostic criteria (Merskey, 1994)</td>
</tr>
<tr>
<td>Presence of an initiating noxious event, or a cause of immobilization</td>
</tr>
<tr>
<td>Continuing pain, allodynia or hyperalgesia in which the pain is disproportionate to any known inciting event</td>
</tr>
<tr>
<td>Evidence at some time of edema, changes in skin blood flow or abnormal sudomotor activity in the region of pain (can be sign or symptom)</td>
</tr>
<tr>
<td>This diagnosis is excluded by the existence of other conditions that would otherwise account for the degree of pain and dysfunction</td>
</tr>
<tr>
<td>(B) Modified diagnostic criteria (Harden, 2007)</td>
</tr>
<tr>
<td>Continuing pain, which is disproportionate to any inciting event</td>
</tr>
<tr>
<td>The patient must present at least one symptom in each of the following categories and one sign in two or more categories</td>
</tr>
<tr>
<td>Sensory (alldynia, hyperalgia, hypoesthesia)</td>
</tr>
<tr>
<td>Vasomotor (temperature or skin color asymmetry)</td>
</tr>
<tr>
<td>Sudomotor (edema, hyper- or hyposudation)</td>
</tr>
<tr>
<td>Motor/trophic (muscle weakness, tremor, changes in hair, skin, nails)</td>
</tr>
</tbody>
</table>
Table 2
Main differential diagnoses for Type I complex regional pain syndrome.

<table>
<thead>
<tr>
<th>Differential diagnoses for Type I CRPS</th>
<th>Neurogenic pain</th>
<th>Inflammatory pain</th>
<th>Vasogenic pain</th>
<th>Musculogelous pathological pains</th>
<th>Psychological problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathy</td>
<td>Erysipelas</td>
<td>Thrombosis</td>
<td>Overuse/missuse</td>
<td>Somatization disorder</td>
<td></td>
</tr>
<tr>
<td>Nerve compression</td>
<td>Bursitis</td>
<td>Acrocyanosis</td>
<td>Epicondylitis</td>
<td>Munchausen syndrome</td>
<td></td>
</tr>
<tr>
<td>Radiculalgia</td>
<td>Seronegative arthritis</td>
<td>Atherosclerosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-herpetic neuralgia</td>
<td>Inflammatory arthritis</td>
<td>Raynaud’s disease</td>
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<td></td>
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<tr>
<td>Deafferentation pain</td>
<td></td>
<td>Erythromelalgia</td>
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</tbody>
</table>

- hyperhidrosis;
- joint stiffness during active and passive movements.

The clinical signs may appear with some time lag and be constantly changing [7].

3.2.1. Pain associated with CRPS-I

Pain is the over-riding symptom of CRPS-I. Its magnitude is disproportionate relative to the initial injury and can extend to areas adjacent to the area injured initially. Patients suffering from CRPS-I often describe their pain as a burning, crushing or stinging feeling. The pain in CRPS-I can be qualified as hyperalgesia (exaggerated sensation of pain in response to a painful stimulus), allodynia (sensation of pain during application of a normally painless stimulus) or hyperpathy [1]. It is also important to differentiate spontaneous pain from pain that may have a mechanical cause, either from an external (e.g. overly tight cast) or internal (e.g. improperly reduced fracture) source. The pain in CRPS-I is often exacerbated by cold, heat or physical contact (alldonyia).

Other symptoms associated with CRPS-I are difficulty falling asleep because of “burning sensations” or excessive skin tension, particularly due to edema in the limb. Use of the visual analogue scale to quantify pain levels provides an objective assessment and allows the patient’s pain to be monitored during the disease course [17].

3.2.2. Vasomotor problems in the affected area

In the early stages of the disease, the limb is edematous, the skin can be red or cyanotic and in some cases, moderate joint
effusion can be observed. The edema gradually disappears, but trophic changes become evident in the tissues:

- skin that is cold, dry, cyanotic (especially when inclined) or pale, and atrophic, resembling scleroderma;
- sweating problems;
- abnormal skin appendages: nails that are atrophic and brittle, hyper- or hypopigmentation;
- tendon, ligament or capsule contractures.

3.2.3. Motor problems

Motor signs observed in CRPS-I are variable and non-specific. Various degrees of tremor, weakness and muscle contractures occur.

Together, these symptoms often lead to functional exclusion of the limb, and in certain extreme cases, a genuine “neglect-like” syndrome [1].

4. Epidemiology

The incidence of CRPS-I is extremely difficult to evaluate because of the wide range of medical specialties involved. The few studies that have been performed estimate the incident to be between 5 and 25 per 100,000 people/year, with the frequency being higher with age (peak at 40–60 years) and in females (sex-ratio of about 4:1). Although any limb can be affected, upper limb is involved more often than the lower limb [18].

CRPS-I secondary to trauma is by far the most common. CRPS-I is a common and standard complication of distal radius fractures (4–37% of cases), carpal tunnel surgery (2–4% of cases) or surgery for Dupuytren’s contracture. However, it can occur after any type of injury, even benign ones such as a fall or sprain [17].

5. Clinical examination

History-taking often reveals a triggering injury or surgical procedure, which may actually have been a fairly minor event. It is important to have the patient describe the nature of the triggering injury and the treatments already performed, to help with diagnosis and also future disease management [1].

A full physical examination must be performed, looking not only for physical signs of CRPS-I, but also symptoms consistent with nerve injury, such as area of hypoesthesia, or motor problems. The first step is the look for changes in the skin texture and color. The range of motion in both limbs must be measured and compared [19].

The skin’s examination looks for mechanical allodynia, hyperalgesia, hypoalgesia and hypoesthesia. Side-to-side difference in skin temperature, skin color, edema or dyshidrosis (eczema in the palms of the hands) must also be noted [3].

The examination also looks for trophic changes that would help confirm the CRPS-I diagnosis (Table 1) and define the disease stage: joint stiffness, edema, osteopenia, atrophy of skin appendages (nails, hair). Non-reducible joint stiffness with arthrofibrosis is common in chronic CRPS-I. The affected limb can be either warm or cold relative to the healthy side, depending on the disease stage [17].

The neurological examination looks for defective use of the affected limb, which is present in 70% of patients with CRPS-I, or even a sensation of not belonging that may translate into pseudonegligence of the limb in the most severe cases [1]. Motor signs such as muscle weakness, trembling or dystonia can also be encountered [1].

The final step is to look for an enhancing factor responsible for chronic pain, because the only hope for a cure at the present time is to manage this enhancing factor.

6. Paraclinical evaluation

6.1. Standard X-rays

Standard X-ray assessment is used to look for osteopenia (reduced bone density), which is often present in patients with CRPS-I, but would only be seen on standard X-rays in advanced stages of the disease. The bone must have lost 30% of its mineral content for its effects to be visible on X-rays. Typical signs of subchondral atrophy are diffused involvement of the subcortical and subchondral areas of the affected limb [1].

6.2. Bone scan

Bone scans are often used to reinforce the CRPS-I diagnosis since they are more sensitive than standard X-rays. Periarticular uptake in every joint in the affected limb is often observed during the three scan phases in classic forms of CRPS-I. But the sensitivity and specificity of bone scans reported in published studies is extremely variable. In general, a triphasic bone scan is helpful in the early stage of the disease when faced with atypical disease presentation, but becomes less sensitive as the disease progresses [20]. A positive bone scan is currently not required for the diagnosis of CRPS-I [1].

7. Pathophysiologic mechanisms

As we touched on during the historical overview, the pathophysiologic mechanisms of CRPS-I are not fully understood, we have now moved beyond the concept of isolated deregulation of the sympathetic nervous system, which dominated the second half of the 20th century [2]. Greater research efforts focused on understanding CRPS-I during the last decade have led to important discoveries about pathophysiologic mechanisms, especially the likely multifactorial etiology of CRPS-I and central nervous system contribution [10]. Evidence for this contribution (discussed later on) was mostly based on observed alterations in the pain, temperature and touch modalities of the somatosensory system in affected patients [21], bilateral changes in the sympathetic nervous system observed in patients with unilateral CRPS-I [1], and motor dysfunction in select cases [21]. The various pathophysiologic mechanisms likely involved in the appearance of CRPS-I are summarized in Fig. 4.
7.1. Post-traumatic changes in skin innervation

A peripheral nerve injury may be an important factor in triggering the cascade of events leading to development of the disease, even in CRPS-I. This suggestion is based on skin biopsies from patient with CRPS-I, who by definition should not have any signs of nerve involvement. But Oaklander et al. found a significant reduction (30%) in the density of epidermal sensory endings in the limb affected by CRPS-I relative to the healthy contralateral limb; these changes mostly affected the primary nociceptive afferent fibres (C and Aδ). This degree of asymmetry was not found in patients presenting with other causes of chronic joint and bone pain. These results suggest that CRPS-I, even without an initial macroscopic nerve injury, can nevertheless be associated with significantly fewer nociceptive nerve endings in the affected limb. But there are currently no human studies conclusively demonstrating a causal link between the initial injury and neuronal loss.

7.2. Peripheral sensitization

In addition to central sensitization, the initial injury also induces local and regional peripheral sensitization. After a tissue injury, the primary afferent fibres in the injured area release numerous neuropeptides locally, especially prostanoids, which sensitize nociceptive nerve endings to the action of other substances such as bradykinin and histamine. These sensitization phenomena likely contribute to hyperalgesia and allodynia, which are major components of CRPS-I [22]. Local hyperalgesia is seemingly the result of both central and peripheral sensitization. And given that peripheral sensitization is triggered by the initial injury, this likely happens very early in the disease process, even if its role in the onset of CRPS-I has never been directly evaluated [1].

7.3. Altered sympathetic functions

Historically, it had been assumed the autonomic signs of CRPS-I, such as skin redness and temperature disorders, were symptoms of excess sympathetic tonus, and that pain could be fuelled by excess sympathetic system activity [23].

There may be a relationship between CRPS pain and sympathetic activity. Animal studies have shown that after a nerve crush injury, nociceptive fibres express adrenergic receptors, which provides a potential avenue for direct triggering of nociceptive nerve impulses by the activity of the sympathetic nervous system. Given that in CRPS-I a nerve injury can be involved in triggering the disease, the expression of adrenergic receptors by nociceptive fibers could then contribute to sympathetic-afferent coupling. This phenomenon has been clearly demonstrated in numerous studies in man. For example, intradermal injection of norepinephrine increases pain in patients with CRPS-I, suggesting a role for the sympathetic nervous system in CRPS-associated pain [1]. This
presumed role of sympathetic hyperactivity is the basis for treatment with sympathetic blocks. Available physiological data on sympathetic-afferent coupling suggest that pain and certain other CRPS-I symptoms can be related to sympathetic nervous system activity, but there is no proof that hyperactivity of the sympathetic nervous system is responsible. Nevertheless, some arguments suggest that even if the sympathetic nervous system is not the main etiological player in the disease, it still has a role in the early stages. Schürmann et al. looked at the sympathetic activity of patients presenting with unilateral fractures during the immediate post-injury period [24]. They found that in cases where CRPS-I developed 12 weeks after the initial injury, it was correlated to early sympathetic dysfunction. These sympathetic nervous system disorders were evident in both the involved and healthy side well before CRPS-I was present, which suggests that systemic changes in the sympathetic nervous system occurred not long after the injury. These results are supported by the work of Ackerman et al. [1] who evaluated the incidence of CRPS-I after carpal tunnel syndrome on a patient population having a history of resolved CRPS-I. In patients presenting with vasomotor disorders before the surgery, the incidence of postoperative CRPS-I was 73%; it was only 13% in patients with a normal vasomotor response. This evidence suggests that sympathetic dysfunction could be a contributing factor in the appearance of CRPS-I.

7.4. Role of circulating catecholamines

The alterations observed in CRPS-I symptomatology when going from the acute to chronic phase of the disease could be, at least in part, be due to changes occurring in the catecholaminergic system. Although patients with CRPS-I have lower circulating levels of catecholamines in the affected limb than the healthy one, there is often exaggerated vasoconstriction in response to cold. This observation may indicate that this response could, paradoxically, be due to an increase in the expression of adrenergic receptors peripherally. This over-expression would also be responsible for the affected limb being overly sensitive to circulating catecholamines released in response to physiological stress, leading to excessive sweating, vasoconstriction and cold, blue skin, all typical features of chronic CRPS-I [25].

But no matter if CRPS-related vasoconstriction is due to over-expression of catecholaminergic receptors, endothelial dysfunction or a reduction in local anti-oxidant substances, these could all contribute to development of trophic changes observed in the “cold” phase, via the resulting chronic hypoxia.

7.5. Inflammatory mediators

Some clinical trials have shown the intake of corticosteroids during the acute phase of CRPS-I to significantly improve symptoms in certain patients, suggesting that certain inflammatory mechanisms may contribute to CRPS-I, at least during the “hot” phase [26]. Recent studies support this hypothesis and suggest two distinct sources for the inflammation. The first is activation of classical inflammatory mechanisms, via the action of lymphocytes and mastocytes that secrete pro-inflammatory cytokines such as IL-1β, IL-2, IL-6 and TNFα upon tissue injury, leading to local edema via increased plasma extravasation. The second is the possibility of neurogenic inflammation. The latter is mediated by pro-inflammatory cytokines and neuropeptides directly released by nociceptors in response to various triggering factors, including injury to the nerve endings themselves. The neuropeptides substance P, CGRP (calcitonin gene-related peptide) and bradykinin have been implicated in neurogenic inflammation. These neuropeptides are responsible both for plasma extravasation and the vasodilation that can come into play in the classic triad (redness, edema, heat) characterizing the “hot” phase of CRPS-I. Substance P and TNFα activate osteoblasts and could contribute to the typical speckled or mottled appearance of osteoporosis. CGRP can increase the growth of the skin appendages and induce sweating. Pro-inflammatory cytokines and neuropeptides are also responsible for peripheral sensitization leading to increased nociceptor responses [22].

Several other studies have looked into the potential relationships between CRPS-I and cytokines. Many of them have shown that in patients with CRPS-I, pro-inflammatory cytokine levels are increased not only in the affected limb, but also in plasma and cerebrospinal fluid; concurrently, levels of circulating anti-inflammatory cytokines such as IL-10 are decreased [1]. It also appears that administering TNF-α antibodies can improve symptoms in some patients with CRPS-I [5].

7.6. Cerebral plasticity and CRPS-I

It is now commonly accepted that in several chronic pain conditions, cortical representation of the painful limb is distorted [27]. One obvious symptom of this distortion is referred sensations, which are somatosensory feelings in an area of the body other than the one being stimulated [1]. This phenomenon is often reported in amputated or deafferented patients, who experience sensations in the missing limb when certain body parts are stimulated [1]. Functional brain imaging studies have demonstrated that mapping changes occur in the somatosensory cortex after a limb is lost. Regions of the cortex no longer receiving afferent inputs are invaded by adjacent cortical areas [28].

Janig and Baron [10] were the first to suggest a role for the central nervous system in the pathophysiology of CRPS-I. McCabe et al. demonstrated the presence of referred sensations in patients with CRPS-I [29]. Interestingly, they found that different types of skin stimulation induced referred sensations in patients with CRPS-I when their eyes were closed, but not when their eyes were open. Although the disappearance of these referred sensations when the visual pathway was present was not discussed, in our opinion, they indicate “functional proprioceptive deafferentation” of the cutaneous and muscular pathways; we will elaborate on this idea later in this review.
Various studies have also shown reorganization of the cortical somatotopic maps in patients with CRPS-I. In particular, representation of the affected limb in the somatosensory cortex is reduced relative to the representation of the healthy limb. These observations suggest that cerebral plasticity plays a role in the development of CRPS-I, instead of revealing a condition that existed before the disease [1].

Functional magnetic resonance imaging (fMRI) was used to look at the brain activity in patients with CRPS-I presenting with hyperalgesia and to compare it with the healthy side [30]. The activity was increased in the primary and secondary sensory regions, insular cortex, associative parietal cortex, cingulate gyrus and frontal cortex. Regions where the activity seemed altered in patients with CRPS-I were ones involved in processing of proprioceptive information and also in formulating motor commands and executing movement [1].

The origin of the observed somatotopic reorganization is not known, but work related to other chronic pain conditions such as phantom limb pain, have shown that similar reorganizations are observed when proprioceptive inputs from a limb are reduced or removed. But we still lack information about when these cortical reorganizations occur during the development of CRPS-I. These changes have measurable clinical consequences. The amount of somatotopic reorganization seems correlated to the intensity of pain and degree of hyperalgesia [1].

7.7. CRPS-I and psychological problems

Contrary to popular belief, CRPS-I does not seem associated with a pre-existing psychological disorder. However certain diseases, such as conversion hysteria, can sometimes mimic the symptoms of CRPS-I.

Historically, because of the stress demonstrated by certain patients, unusual nature of presenting symptoms and misunderstood pathophysiology, several authors have described CRPS-I as a psychosomatic condition. This opinion continues to be propagated within a small circle. Although it is theoretically plausible for certain psychological factors to contribute to the development of CRPS-I, a psychosomatic-only disease model is not supported by the facts.

In reality, from the viewpoint of other pathophysiologic factors described in this review, any psychological factor (i.e. anxiety, stress, anger, etc.) able to interact with catecholamine release, for example, could theoretically interfere with the pathophysiologic factors implicated in the onset of CRPS-I. Nevertheless, no study up to now has been able to test the hypothesized involvement of psychological factors in the development of CRPS-I [1].

8. Treatments

Management of CRPS-I continues to be a therapeutic challenge. Several treatment protocols using various opioid analgesics, antipsychotics, antidepressants and anti-inflammatory agents have been carried out with the goal of treating CRPS-I [31–33]. However, most of these molecules were used because of their efficacy in treating non-CRPS neuropathic pain. Attempts at demonstrating efficacy in CRPS have been relatively disappointing. Some agents specifically targeting the hypothetical sympathetic/adrenergic component of CRPS, such as phenoxybenzamine (Dibenzyline®) or transdermal clonidine (Catapressan®), were effective in a few non-placebo-controlled trials, however appropriately controlled trials are needed to more conclusively demonstrate their efficacy.

The most effective first-line treatments are summarized below, along with an inventory of recent research on CRPS. Calcitonin, which has long been used throughout the medical community, has never been shown more effective than placebo and must not be prescribed as treatment for CRPS-I. The French health authority suspended its approval for this indication in 1994 [1].

8.1. Preventative treatment

Perioperative administration of ascorbic acid (Vitamin C) is currently the only preventative treatment with sufficient level of proof that can be advocated. The concept of vitamin C prevention for CRPS was given light in a randomized, double-blind study by Zollinger et al. [34]. Administration of vitamin C during the perioperative period reduces the incidence of CRPS-I by more than 50% in wrist fracture patients. More recent studies published by other groups have confirmed these results [35–37]. The current recommended dose is 50 mg per day for 50 days [38].

8.2. Traditional treatments

8.2.1. Drug treatments

There are currently no curative drug treatments for CRPS-I. Nevertheless, the various treatments used aim at reducing the symptoms (especially pain) or curing the problem (based on pathophysiologic mechanisms). Several published reviews have looked at drug treatments for CRPS-I [1].

8.2.1.1. Corticosteroids. As mentioned previously, inflammatory mechanisms seem to play an important role in CRPS-I, especially during the acute stage. These mechanisms cause the most common clinical form, combining redness, heat and edema. A few randomized, placebo-controlled trials have shown that one course of corticosteroids can significantly improve the symptoms of CRPS-I during the acute stage [39].

8.2.1.2. Antipsychotics. Use of antipsychotic agents have been proposed because neuropathic pain is among the main symptoms in CRPS-I. The most commonly used molecule is gabapentin (Neurontin®), which has been shown to provide significant pain relief in several meta-analyses in patients with neuropathic pain, but not CRPS-I. The only clinical study evaluating gabapentin to specifically treat CRPS-I showed only moderate effects [39].

8.2.1.3. Antidepressants. Although the analgesia produced by the intake of antidepressants has never truly been studied in patients with CRPS-I, meta-analyses have shown that
antidepressants are effective against neuropathic pain outside of CRPS-I. One study showed that about one-third of patients taking antidepressants for neuropathic pain had roughly a 50% reduction in pain. Tricyclic and heterocyclic antidepressants seem to have better efficacy than selective serotonin reuptake inhibitors [5].

8.2.1.4. Opioids. The reported efficacy of opioids in CRPS-I only stems from parallels drawn with controlled studies in patients with neuropathic pain, but without CRPS-I. The only randomized, placebo-controlled study on opioids and CRPS-I showed that extended-release morphine did not significantly reduce pain beyond eight days, although the findings may have been affected by the maximum titrated dose of morphine allowed. Results of a placebo-controlled study in neuropathic pain when morphine was used with gabapentin suggested an additive effect, although no treatment has clearly been shown effective for CRPS-I [5].

8.3. Non-drug treatments (physical and occupational therapy)

In 2000, a panel of clinicians and scientists concluded that the ultimate goal of CRPS-I treatment should be functional restoration via physical therapy (PT) and occupational therapy (OT) [40]. Patients receive massage, desensitization, isometric muscle work, muscular release, orthoses, and active mobilization within the non-painful range of motion. The exercises must be performed below the pain threshold, to avoid prolonged increase in pain. A large randomized trial has shown that functional therapies are effective in improving CRPS conditions [41]. Patients are even more invested in functional therapies when the disease management plan also has pharmacological, interventional and psychological components. But the goal of having pain disappear without functional gains or improvements in activities of daily living is not realistic and must be put aside.

8.4. Interventional treatments

8.4.1. Sympathetic blocks

Interventional techniques intended to block somatic or sympathetic nerve conduction (i.e. cervicothoracic (stellate) ganglion blocks) are often used during treatment of CRPS-I and are beneficial in some cases [42]. Nevertheless, their use is somewhat disproportional relative to their demonstrated efficacy. Benefits are obtained only for a short period of time; patients who noticed an improvement also noted these effects wear off. A single placebo-controlled trial in seven CRPS-I patients evaluated the efficacy of selectively blocking sympathetic ganglia [39]. The initial decrease in pain was comparable to the one achieved with placebo (saline), but this reduction lasted significantly longer (about four days) than the one obtained with placebo (less than one day).

Intravenous regional anesthesia (IVRA) also has only limited proof of efficacy. One meta-analysis of all placebo-controlled studies with guanethidine IVRA found no significant short-term or long-term efficacy overall in CRPS-I patients. Two randomized, placebo-controlled studies using ketanserine and bretylium IVRA have shown some efficacy.

Few studies on sympathetic blocks has been done and published; the ones performed often are not placebo-controlled. Sympathetic blocks must not be viewed as curative in themselves, but as adjuvant therapies facilitating the adherence to functional therapies in patients where pain would reduce their compliance and in which sympathetic pain mechanisms are activated [5].

8.4.2. Medullary stimulation

Medullary stimulation (MS) is an invasive technique that is generally proposed only after other treatments have failed. The primary goal is pain reduction. This technique consists of permanently implanting electrodes in the epidural space to stimulate dorsal funiculi at the level of the area affected by CRPS. The efficacy and long-term efficacy of MS in CRPS-I has only been evaluated in one randomized controlled study [1]. Despite initially promising results, the five-year follow-up analysis found that patients who received MS in combination with physical therapy were statistically identical to those having received physical therapy only, in terms of pain and quality of life. When the analysis was limited to patients having truly received a permanently implanted medullary stimulation device, those treated with MS plus physical therapy had a significantly greater improvement overall and slightly greater reduction in pain than those treated with physical therapy only. The results of this study indicate that, although MS initially provides pain relief in two-thirds of the patients with CRPS, the analgesic effects diminish over time, such that the effects are barely superior to those obtained with physical therapy alone, five years later.

In addition, medullary stimulation is a costly, invasive procedure with a high complication rate, making it an unrealistic treatment option in most patients suffering from CRPS-I. Thus this technique should only be used with caution in carefully selected patients [1].

8.4.3. Psychological pain management

Meta-analyses of randomized, controlled studies indicate that psychological pain management (especially using behaviour modification therapy) can significantly reduce chronic pain. Although there are not enough controlled studies in patients presenting with CRPS-I, experts believe this is the most important treatment modality for patients with CRPS-I [5].

Figs. 5 and 6 summarize the standard treatment approaches used in CRPS-I patients, based on the various meta-analyses performed in recent years. Note that none of the current techniques, except for sympathectomy, aim to treat central nervous system disorders.

8.5. Emerging treatments aimed at the etiology

The two main objectives of CRPS-I treatment are reduced pain and improved range of motion. Recent advances in understanding the pathophysiologic mechanisms of CRPS-I,
especially in the role of the central nervous system in the onset and/or maintenance of the observed symptoms, which greatly resembles the deafferentation pain observed in patients with phantom limb syndrome, have led to the development of treatments aimed at the etiology of CRPS-I, which is distinct from traditional treatments that aimed only at treating the symptoms. Two innovative treatments have appeared recently: one drug-based (ketamine) and the other non-drug-based (mirror therapy).

8.5.1. Ketamine
Recent use of ketamine [1], a powerful N-methyl-D-aspartate (NMDA) receptor agonist, in the management of CRPS-I aims at the central sensitization phenomenon. This central sensitization is mostly expressed at the first integration relay for nociceptive information, where the synapses formed by the central endings of the Aδ and C fibre nociceptors with the nociceptive neurons of the dorsal horn of the spinal cord are greatly activated. Several factors intervene during the gradual establishment of this central sensitization. Multiple published studies have highlighted the role of a glutamate receptor (NMDA) in this process [1]. Various ketamine dosage schemes have been tested, from transcutaneous application to a ketamine-induced coma. Although the lowest doses seems to provide the best results, the lack of regulatory approval in this indication and various side effects limit the use of ketamine in current practice.

8.5.2. Mirror therapy and proprioceptive vibration rehabilitation
In CRPS-I, use of the affected limb is drastically reduced because of intense pain and hyperalgesia. Such motor exclusion necessarily induces a “functional deafferentation” of the limb, and in particular, considerable reduction in proprioceptive feedback from muscles and skin. This deafferentation could explain the high number of similarities observed between patients suffering from CRPS-I and amputees presenting with deafferentation pain (phantom limb pain).

As previously mentioned, it seems the discrepancy between the motor intentions and proprioceptive feedback from the affected limb can play a role in the initiation or maintenance of CRPS-I [29]. Mirror therapy has recently been used successfully for managing CRPS-I, both in terms of joint range of motion and pain [43]. This rehabilitation method consists of stimulating the visual proprioceptive pathway by asking the subject to look at the movement performed by the healthy limb in a mirror; this gives a visual illusion of the movement being performed with the affected limb.

A recent controlled clinical trial showed that performing a two-point discrimination test while looking at a reflection of the healthy limb in the mirror (instead of looking at the affected limb) significantly improved both pain and tactile discrimination in the affected limb. It was hypothesized that this treatment could normalize the cortical changes seen in sensory, motor and premotor areas [44]. Overall, mirror therapy (and the illusion of movement in the affected limb) seems to be a promising, non-invasive approach for improving the main symptoms of CRPS-I, without any side effects.

A preliminary study on stimulation of the muscular and cutaneous proprioceptive pathways using mechanical vibration showed that the induced proprioceptive reafference combats against both pain and movement problems in patients with CRPS-I. This novel rehabilitation method called “proprioceptive vibration therapy” is easy to implement, painless and free of side effects. When combined with conventional rehabilitation, it seems to accelerate the functional recovery of patients with CRPS-I in the upper limb.

9. Conclusion
Although the exact causes of CRPS-I have not yet been discovered, progress made over the past ten years in understanding the pathophysiologic mechanisms involved in both the initiation and maintenance of CRPS-I allows us to foresee new treatment options directed at the etiology. The increasing number of studies points to renewed interest in a disease that from now on might actually be curable. Preliminary results are promising since the control over pain has improved.
10. Key takeaways

CRPS-I is a clinical diagnosis that can be made with high sensitivity using the IASP criteria. CRPS-I is a seemingly multifactorial pathology where the central nervous system is involved in the onset and/or maintenance of the symptoms. Multidisciplinary management of the disease must be initiated early on to have a chance of quickly resolving the condition. Calcinonin must not be used anymore to treat CRPS-I.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


