Post-traumatic complex regional pain syndrome: clinical features and epidemiology

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Summary

Complex Regional Pain Syndrome (CRPS) is a chronic pain condition that occurs after a tissue injury (fractures, sprain, surgery) of the upper or lower extremities. A clear pathophysiological mechanism has not been established yet and different patterns are considered to play a role in the genesis of the disease. The diagnosis is made by different diagnosis criteria and a gold standard has not been established yet. Incidence of CRPS is unclear and large prospective studies on the incidence and prevalence of CRPS are scarce. The aim of this review is to give an overview on the prevalent data regarding this chronic syndrome.

KEY WORDS: complex regional pain syndrome; chronic pain condition; chronic noncancer pain; CRPS epidemiology; CRPS incidence.

Introduction

Complex Regional Pain Syndrome (CRPS) is one of the most challenging pain condition in medicine; it is classified as a rare disorder by the United States Food and Drug Administration and is associated with a little agreement regarding aetiology, symptoms, clinical presentation, diagnosis and treatment (1).

CRPS is characterized by a chronic neurological disorder involving upper or lower limbs after any type of injury or after surgery; in some cases it occurs spontaneously. Sensory and autonomic disturbances are the main features of this syndrome (allodynia or hyperalgesia, edema, changes in skin blood flow or abnormal sudomotor activity) and are disproportionate to the starting event.

Intensity and duration are variable, and the course of the disease seems to be unpredictable between various patients (1).

The underlying mechanism for the development of CRPS is still unknown, and little is known about the predictors of CRPS incidence. Multiple mechanisms are considered to play a role in the generation and maintenance of CRPS: biofeedback from autonomic nervous system, alterations of central nervous system, neurogenic inflammation and immunological mechanisms (2, 3). It is generally considered that the inflammation process may be the major mechanism because the initial signs of CRPS represent the typical signs of inflammation (4, 5).

Nevertheless the real pathophysiology pathway is not completely understood yet. There is no specific diagnostic test for CRPS. History, clinical examination, symptoms and signs of the patient are the main aspects to be considered for a correct diagnosis.

Definition and diagnosis criteria

CRPS is the current consensus-derived name, but historically it was called in different ways [Sudeck atrophy, causalgia, Reflex Sympathetic Dystrophy (RSD), algodystrophy, post-traumatic dystrophy, shoulder-hand syndrome] and with different names in different countries as well (79 names in Anglo-Saxon literature, 51 in German and 33 in French), proving the complexity and multifaceted aspects of this syndrome (6).

During the first American civil war S. Weir Mitchell provided a first name for this chronic and burning pain condition, ‘causalgia’, Sudeck in 1900 ‘Sudeck dystrophy’, Homans in 1941 ‘minor causalgia’ and RSD by Evans in the late 40s (7). In 1994 the International Association for the Study of Pain (IASP) described for the first time CRPS as a ‘Syndrome characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of pain after trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor edema, and/or trophic findings. The syndrome shows variable progression over time (8).

The first pattern of diagnostic criteria was proposed by the IASP in 1994 (9) (Table 1). Developed as a starting point, these criteria were extremely sensitive (0.99) but poorly specific (0.41) with a clear risk of over diagnosis. Galer et al. empirically demonstrated the potential risk of false positive over diagnosis: a new revision of this pattern was needed (10).

Recognized the problem, a closed workshop of experts was held in Hungary in 1999 and a new pattern of diagnostic criteria, the ‘Bruehl and Harden 1999 criteria’, was published (11) (Table 2). The sensitivity of the previous system was retained but the specificity was increased (0.68) and in addition was added a new subtype of CRPS, CRPS-NOS (8).

The same Authors made a revision of the ‘Bruehl and Harden Criteria’ in 2007 in Budapest (8) (Table 3).
The new diagnostic system called ‘Budapest Criteria’ showed a better specificity; modifying the decision rules, two of four sign categories and four of four symptom categories, sensitivity improved to 0.70 and specificity to 0.94 (8). The reduction of false positive diagnosis is due to the simultaneous presence of clinical signs and symptoms in each of four categories (sensory, vasomotor, sudomotor and trophic/motor); this produced a better discrimination in CRPS associated with neuropathic pain, a better diagnostic accuracy and more cost-effective approaches to treat and cure this disease (8).

Changes in its diagnostic criteria have simplified the identification of CRPS, but the ‘real diagnosis’ must be made by exclusion because no definitive test exists for CRPS; however disorders that mimic the syndrome (infection, vascular disease or neuropathy and trauma) must be ruled out.

The complexity of this disorder is strictly connected with its unknown pathophysiology. In literature it is now generally agreed that a multifactorial process (peripheral and central mechanisms) is involved and a psychogenic origin is also been hypothesized, but the severity of the symptoms hardly support this view. Therefore, as showed by Perez et al. in 2007, since a clear pathophysiological pathway will not be established the diagnosis of CRPS remains arbitrary in spite of the general agreement on Budapest criteria (12). This aspect taking with the variability in diagnostic criteria, taxonomy and treatment regimens make very hard to clearly define the epidemiology and natural history of CRPS.

Epidemiology

Although CRPS was described decades ago, its epidemiology has not been well studied and convincing epidemiological data regarding this disorder are still lacking and incidence data are meagre and mostly hospital based.

Table 1 - IASP CRPS Diagnostic Criteria (9).

<table>
<thead>
<tr>
<th>CRPS I</th>
<th>CRPS II</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4 of the following with 2, 3, and 4 being mandatory:</td>
<td>All of the following:</td>
</tr>
<tr>
<td>1. The presence of an initiating noxious event, or a cause of immobilization.</td>
<td>1. The presence of continuing pain, allodynia, or hyperalgesia after a nerve injury, not necessarily limited to the distribution of the injured nerve.</td>
</tr>
<tr>
<td>2. Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event.</td>
<td>2. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain.</td>
</tr>
<tr>
<td>3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain.</td>
<td>3. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.</td>
</tr>
<tr>
<td>4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.</td>
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Table 2 - Harden/Bruehl CRPS Diagnostic Criteria (11).

<table>
<thead>
<tr>
<th>CRPS I</th>
<th>CRPS II</th>
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<tbody>
<tr>
<td>1. Continuing pain, which is disproportionate to any inciting event</td>
<td>All of the following:</td>
</tr>
<tr>
<td>2. Must report ≤ 1 symptom in 3 of the following 4 categories:</td>
<td>1. The presence of continuing pain, allodynia, or hyperalgesia after a nerve injury, not necessarily limited to the distribution of the injured nerve.</td>
</tr>
<tr>
<td>Sensory: Reports of hyperesthesia and/or allodynia</td>
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</tr>
<tr>
<td>Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry</td>
<td></td>
</tr>
<tr>
<td>Sudomotor/Edema: Reports of edema and/or sweating changes and/or sweating asymmetry</td>
<td></td>
</tr>
<tr>
<td>Motor/Trophic: Reports of decreased range of motion and/or dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin)</td>
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<tr>
<td>3. Must display ≤ 1 sign at time of evaluation in ≥ 2 of the following categories:</td>
<td></td>
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<tr>
<td>Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)</td>
<td></td>
</tr>
<tr>
<td>Vasomotor: Evidence of temperature asymmetry (&gt;1 grado) and/or skin color changes and/or asymmetry</td>
<td></td>
</tr>
<tr>
<td>Sudomotor/Edema: Evidence of edema and/or sweating changes and/or sweating asymmetry</td>
<td></td>
</tr>
<tr>
<td>Motor/Trophic: Evidence of decreased range of motion and/or dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin)</td>
<td></td>
</tr>
<tr>
<td>4. There is no other diagnosis that better explains the signs and symptoms</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>CRPS II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same as CRPS I but with the evidence of a peripheral or central nerve injury</td>
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<table>
<thead>
<tr>
<th>CRPS NOS</th>
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<tr>
<td>Patients who do not fully meet the clinical criteria, but whose signs and symptoms cannot be better explained by another diagnosis</td>
</tr>
</tbody>
</table>
Simultaneously in Europe, specifically in Netherlands, a big the population in exam can changes results.

The retrospective study of Sandroni shows various common involvement in CPRS II was more frequent compared to type I (17).

CRPS (80% positive results) (17). Only 11 cases of CRPS II were identified using IASP criteria, and subsequently Harden Criteria were used to confirm the diagnosis (17).

De Mos et al. tried to explain this important difference by the ethnical composition and socio economic situation of the population (American and Dutch). The biggest limitation appears to be the lacking of a gold standard for the diagnosis of CRPS (18).

The work of Allen et al. was a starting point to understand the diversity of CRPS’s clinical presentation (15).

The specialist-diagnosed population was subsequently reduced to 95 cases for the discriminating criteria of anamnesis, signs and symptoms recorded at the time of the visit.

According to the different diagnosis Criteria (IASP, Bruehl and Harden and Veldman) were respectively identified a percentage of 93, 47 and 53% of CRPS cases in the specialist diagnosed population.

The results of the statistical analysis showed features in common with the American study of Sandroni: gender (female), mean age (52.7 years), cause (fractures 44%), interested limb (upper extremities 59.2%). But despite that, incidence appears to be more than fourfold higher 26.2 per 100,000 person-years, with a peak incidence at 61-70 years of age.

Gender-specific incidence rates was 40.4 (95% CI: 34.8-46.8) for females and 11.9 (95% CI: 9.0-15.4) for males per 100,000 person years (RR: 3.4, 95% CI: 2.9-3.9) with an increased risk in postmenopausal women (18).

Taken together these retrospective studies show how medical and demographic variables play a role in the evolution and development of CRPS. Many works agree on CRPS high prevalence in upper limb and female sex but limited data are available on the influence of fracture type (17-19).

**Epidemiology of CRPS in fractures**

Beerthuizen et al. investigated the incidence of CRPS I in different fracture types and the prevalence of the disease after trauma (20).

A large cohort of 596 patients, recruited from the emergency room with a single fracture of the ankle or scaphoid or wrist or metatarsal V was enrolled and followed for 1 year.

<table>
<thead>
<tr>
<th>No.</th>
<th>Category</th>
<th>Signs/Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sensory</td>
<td>Allodynia (pain to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement and/o hyperalgesia to pinprick)</td>
</tr>
<tr>
<td>2</td>
<td>Vasomotor</td>
<td>Temperature asymmetry and/or skin color changes and/or skin color asymmetry</td>
</tr>
<tr>
<td>3</td>
<td>Sudomotor/edema</td>
<td>Edema and/or sweating changes and/or sweating asymmetry</td>
</tr>
<tr>
<td>4</td>
<td>Motor/trophic</td>
<td>Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair/nail/skin)</td>
</tr>
</tbody>
</table>

Little published data are available before 2000 (13, 14), and the work of Allen et al. was a starting point to understand the diversity of CRPS’s clinical presentation (15).

Until then the epidemiological aspects of CRPS were carried out from small prospective chart reviews with limitations not only in the study design itself but, also in the selection criteria of the population study (13, 16).

Sandroni et al. published the first population based study of CRPS focused on subtype I in 2003 (17). Potential cases of CRPS were identified using a computerized system from all health care providers for the local population of Olmsted County (Mayo Clinic and its affiliated hospitals, Olmsted Medical Group, Olmsted Community Hospital, local nursing homes, and a few private practitioners) from 1989 to 1999.

Recorded diagnosis for RSD, CRPS and synonyms were used to identify these cases. IASP criteria, and subsequently Harden Criteria were used to confirm the diagnosis (17).

Seventy-four cases of CRPS I were identified using IASP criteria and 32 (43%) with Harden criteria, resulting in an incidence rate of 5.46 per 100,000 person years at risk, and a period prevalence of 20.57 per 100,000 (17). Female sex appears to be the gender more associated with CRPS I (ratio 4:1), with a higher prevalence in the fourth, fifth and sixth decades (median age 46 yo) (17). Gender specific rates in incidence and prevalence appear to be significant different between male and female (2.16 vs 8.57 per 100,000 person years at risk) (5.06 vs 35.33 per 100,000 person years) (17).

Upper limb was affected twice compared to lower limb and the most common clinical manifestations were vasomotor (swelling, colour, and temperature asymmetry) with an excellent concordance between signs and symptoms (18). Laboratory indices were analysed, and the three-phase bone scan appeared to be the most useful to assess diagnosis of CRPS (80% positive results) (17).

Only 11 cases of CRPS II were identified with an incidence of 0.82 per 100,000 person years at risk and prevalence of 4.2 per 100,000. Gender had not a statistical significance although upper extremities involvement in CPRS II was more frequent compared to type I (17).

The retrospective study of Sandroni shows various common epidemiological aspects with the small analysis of Allen (gender, race, age) but demonstrates how the selection of the population in exam can changes results.

Simultaneously in Europe, specifically in Netherlands, a big retrospective cohort study was held. With the help of Integrated Primary Care Information Project (IPCI) a number of 190,902 persons was analyzed (18).

Using an extensive string search (synonyms and abbreviations of CRPS) and prescriptions of Dimethyl Sulfoxide (DMSO), in the Dutch general practice research database 238 incident cases were identified (61 diagnosed by general practitioner and 177 by a specialist).
Diagnosis was set with different patterns of criteria: Veldman (21.3% of diagnosis), IASP (48.5% of diagnosis) and Harden and Bruhl (7% of diagnosis). Highest peak of incidence was reported after 3 months from trauma (20). In contrast with the general opinion of literature about CRPS incidence (0.9-51%) (17, 18, 21, 22), the lower percentage in the present study demonstrates again how the lacking of a gold standard in diagnosis and different rate of specificity criteria influence the correct selection of CRPS cases. No difference between upper and lower extremities was identified but intra-articular fracture, ankle fracture and dislocation appeared to be risk factors for the development of this disease. Furthermore, musculoskeletal comorbidities and rheumatoid arthritis appeared to be risk factors as well to developing CRPS (20). In agreement with the others big retrospective studies (17, 18, 23) the majority of CRPS patients were females, in accordance with the possible explanation that the incidence of upper limb fractures is higher in women.

Fractures of distal radius

Analysing the studies about incidence in patients with Fracture of Distal Radius (FDR) a variety from 0 to 37% can be found (24-27). This difference can be explained by the different criteria used in the CRPS classification and by the different populations taken in exam.

CRPS occurring after FDR is more common in elderly patients with psychological or psychiatric conditions (28) but not all Authors agree regarding physiological factors as predictors of CRPS incidence (27) in this kind of trauma. Additionally, in a case control study, it was found a higher possibility to develop CRPS I after fracture in patients with social life adverse events compared to the control group (29).

In a study considering plaster cast treatment for a FDR, the incidence of CRPS was higher in female with a medium and low energy trauma, associated with alteration of physical QoL and pain functional discomfort. However, psychological or psychiatric conditions did not appear to be related to the onset of the disease. The average time debut is 21.7±23.7 days after cast removal (24).

On the other side surgical treatment of distal radius fracture is associated with a high risk of CRPS development in old female patients with a high-energy trauma or comminute fractures (25). These data were obtained from a large observational prospective study. A number of 477 patients were analysed with a medium follow-up of 6 months and the 8.8% satisfied Budapest Criteria for CRPS diagnosis (25). Taken together these results can be useful for the identification of potential risk factors of CRPS after conservative or operative treatment of FDR.

Lower limbs fractures

Very little is known about CRPS and post-traumatic injuries in lower limbs. No large systematic studies exist in the literature, and Sarangi et al. postulated a probable 30% of incidence after tibial fractures in 1993 (30). This consideration emerges from a prospective study of 60 patients treated with a conservative or operative treatment. The development of CRPS is independent by the type of treatment used (30). Similar considerations can be found in Smith et al. work as well. 25% of patients develops CRPS after external fixation of tibial fractures. In addition, acute localised osteoporosis appears to be associated to CRPS (31).

CRPS and surgery

CRPS can be triggered by surgery. Hand, foot and ankle surgery seems to be the main cause of CRPS development after an operative treatment (25, 30). The exact incidence of CRPS after orthopaedic surgery is unknown and this reflects the poorness of information regarding the real incidence and prevalence of this syndrome. Carpal tunnel surgery, surgery for Dupuytren contracture and surgical treatment of distal radius fractures are associated with a variable incidence of CRPS: 2 to 5%, 4.5 to 40% and 22 to 39% respectively (32). This condition can complicate the postoperative management of the patient, and a rapid diagnosis and treatment of CRPS can help in the prevention of different clinical consequences (swelling, atrophy, osteoporosis, pseudarthrosis, joint stiffness and tendon adhesions) (33).

Elective foot and ankle surgery can be another cause of CRPS. In the retrospective work of Rewhorn et al. the incidence of CRPS after foot and ankle surgery was 4.36% (17 patients on 390 total). IASP criteria were used to diagnose potential cases of CRPS and 52.94% of cases were in fore-foot surgery group, 17.65% in the hindfoot, 17.65% in ankle and 11.76% in midfoot (34).

These studies show similar epidemiological aspects (gender and age) with the big retrospective studies of Sandroni and De Mos (38, 39).

CRPS and genetic

Recent evidences suggest a possible implication of genetic factors in the development of CRPS. Genetic factors associated with complex regional pain syndrome I were leukocyte antigen polymorphism (17, 35, 36) and tumor necrosis factor-α polymorphism (37).

To date is known that a genetic predisposition to CRPS is associated with a severe phenotype and a younger age of debut (compared in patients with a stabilization or remission of the disease) (38, 39). Nevertheless the hypothesis that CRPS has a genetic basis and a familial risk (40) is only recently supported by some retrospective studies (41, 42).

Shirani et al. and de Rooij et al. conclude that CRPS may occur in familial form but a pure inheritance pattern is not cleared yet. More studies are necessary to discover how the genetic factors are really implicated in CRPS predisposition and evolution (41, 42).

Clinical features and subtypes

CRPS still not have a pathognomonic sign. The key symptom is prolonged pain that may be constant and disproportionate to the initial injury and the 10% of the patients don’t remember the starting event (13).

The characteristics of the pain are various: undulating, continuous, spontaneous or episodic. Patients with CRPS frequently described this symptom as burning (43, 44) and this aspect can demonstrate the possible proinflammatory and immunological response elicited by the starting event, as already shown in different animal models (45, 46).

The distal part of the limb is the most common interested area and the typical clinical manifestations are red skin, pain, calor and swelling. Symptoms may change over time and vary from patient to patient. Over time the injured limb can became pale, cold and in addition muscle spasm and tightening can appear: this condition is often irreversible (47, 48).
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The current subtypes classification of CRPS is represented by type I (previously known as RSD, Sudeck’s atrophy and reflex neurovascular dystrophy), type II (previously known as causalgia) and NOS (Not Otherwise Specified) (8) (Table 2). These are divided on the basis of presence/absence of nerve lesion: type 1 occurs after an illness or injury that did not directly damage a nerve in the affected area, type 2 follows a distinct nerve injury. CRPS I is the most common form (90%) and in literature the majority of the works refers to this type of syndrome. On the other side CRPS II appears to be the most difficult form to treat (18).

CRPS can be divided into three stages of progression based on the duration of symptoms. This staging was provided by Bonica and may be helpful to an easier diagnosis and treatment (49).

Stage I (acute) is associated with burning pain and may last up to 3 months, stage II (dystrophic) can last from 3 to 12 months and is associated with more swelling and no skin wrinkles, stage III (atrophic) occurs after 1 year with important modifications of soft tissue characteristics (pale, dry, tightly stretched, and shiny skin, muscle atrophy, tendon retraction) (49).

Now, it is clear that CRPS does not progress through these stages sequentially: some patients develop severe symptoms right away and others stay in the first stage for all the disease duration (50). The ‘warm’ and ‘cold’ forms represent another classification of CRPS based on the main clinical features. This is not a formal classification and was primarily described by Steinbrocker at the end of the 50s (51). The clinical presentation of the distal limb permits to distinguish the two forms (red, and edematous extremity in the warm form and dusky, sweaty extremity in the cold one). It is generally accepted that CRPS usually starts with a warm phase that can get into a cold phase during its chronicization (47).

To date a clear discrimination between these two phases is not completely clear, but a retrospective study of Vaneker demonstrated a better outcome in the warm phase compared to the cold one (52).

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Conclusions

CRPS remains one of the most unknown chronic pain conditions. Epidemiological studies have given some instruments to understand better this disease, but too many aspects remain uncertain: pathophysiology, incidence, prevalence, treatment and therefore diagnosis should be made cautiously. This lack of knowledge may lead to the absence of a general agreement on the correct diagnosis of this syndrome and correctly recognize early stage of CRPS is a real challenge. Furthermore the latest diagnostic criteria aren’t widely used yet in literature. Epidemiological data from different studies are not univocal and the little knowledge hold is not representative of the general population.

To better understand the epidemiology of CRPS, the rule of genetics, hormonal balance, races and social and economic conditions in the development of the disease should be further studied.

References


