Complex Regional Pain Syndrome or Limb Pain: A Plea for a Critical Approach

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Abstract: Most frequently, complex regional pain syndrome (CRPS) develops after a trauma and affects distal parts of the limbs. Early recognition and initiation of adequate treatment is crucial for a favorable outcome. On the other hand, misdiagnosing other disorders as CRPS is detrimental because more appropriate treatment may be withheld from the patients. Despite intensive research, a specific biomarker or paraclinical measure for CRPS diagnosis is still lacking. Instead, clinical criteria approved by the International Association for the Study of Pain (IASP) and latest adapted in 2019 are central for diagnosing CRPS. Thus, the CRPS diagnosis remains challenging with the risk of a “deliberate diagnosis” for unexplained pain, while at the same time a delayed CRPS diagnosis prevents early treatment and full recovery. CRPS is a diagnosis of exclusion. To clinically diagnose CRPS, a vigorous exclusion of “other diseases that would better explain the signs and symptoms” are needed before the patients should be referred to tertiary centers for specific pain treatment. We highlight red flags that suggest “non-CRPS” limb pain despite clinical similarity to CRPS. Clinical and neurological examination and paraclinical evaluation of a probably CRPS patient are summarized. Finally, we pinpoint common differential diagnoses for CRPS. This perspective might help CRPS researchers and caregivers to reach a correct diagnosis and choose the right treatment, regardless whether for CRPS mimics or CRPS itself.

Keywords: diagnostic criteria, differential diagnoses, paraclinical evaluation, misdiagnoses

Introduction

During the last decades, CRPS has attracted attention from clinicians and pain researchers and this enigmatic disease has become partially decoded. Experimental data support that exaggerated posttraumatic immune inflammatory responses,3,4 central nervous system reorganization5 and involvement of the autonomic nervous system6 might be responsible for the different symptoms of CRPS.7

In our 2018 position paper,8 we state that general practitioners may refer all kinds of “limb pain” patients early in the course to specialized pain centers for the treatment of CRPS in order to save time for effective treatment and rehabilitation. Possibly triggered by public awareness campaigns (eg, https://www.burningnightscrps.org/crps-rsd-support/donations/crps-awareness-month/) and compensation in insurance cases, we can confirm a steady increase of “suspected CRPS” referrals to our clinic over the past years although differential diagnoses have not been excluded before referral.

Risk of Misdiagnosis

Pain treatment centers either confirm or reject the CRPS diagnosis according to the International Association for the Study of Pain (IASP) diagnostic criteria (Table 1). After diagnosis, the CRPS severity score is relevant to grade the severity of CRPS and to monitor the progression or remission of the condition.9,10

Basically, CRPS is a clinical diagnosis based on reported symptoms and observed signs with no technical investigations to confirm or refute the clinical hypothesis of CRPS. These validated and internationally approved diagnostic criteria help to distinguish CRPS from other types of limb pain after stroke, single nerve lesions, polyneuropathy or...
Limb diseases with inflammatory-related and vegetative symptoms mimicking CRPS, however, were not addressed nor was the distribution of CRPS signs (eg, proximal or distal; limb or trunk; affected joint only or whole limb) part of the diagnostic criteria. In theory, these criteria are perfect because they require exclusion of other diagnosis, which might explain the individual symptoms (criterion 4). In practice, however, criterion 4 depends on the experience of the examiner and vigorous investigations to confirm the presence or absence of other diseases. This could lead to a false-positive diagnosis of CRPS as highlighted by the following two cases:

Case 1: Traumatic ulnar nerve lesion led to spontaneous pain (Table 1, criterion 1), evoked pain, bluish cold skin and muscular atrophy and paresis (Table 1, criteria 2 and 3), refined to the innervation area of the ulnar nerve. If one does not take into account that this is the typical constellation of a peripheral ulnar nerve lesion and overlooks criterion 4 (no other diagnosis better explains the signs and symptoms) CRPS type II may erroneously be misdiagnosed. The correct diagnosis is neuropathic pain with associated autonomic phenomena in the innervation area of the ulnar nerve, which eventually requires nerve repair (Figure 1).

An identical scenario could be outlined lesioning the median nerve, which contains numerous bundles with autonomic nerve fibers. The treatment of choice for carpal tunnel syndrome is surgery or immobilization, which is not recommended in CRPS. As clarified by the Valencia consensus-based adaptation of the IASP complex regional pain syndrome diagnostic criteria, CRPS type II is present in a patient with a nerve injury when symptoms and signs cross the dermatomal borders of the lesioned nerve.

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**Table 1 Clinical Diagnostic Criteria for CRPS**

1) Continuing pain, which is disproportionate to any inciting event
2) Must report at least one symptom in three of the four following categories:
   - **Sensory**: Reports of hyperalgesia and/or allodynia
   - **Vasomotor**: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   - **Sudomotor/Edema**: Reports of edema and/or sweating changes and/or sweating asymmetry
   - **Motor/Trophic**: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin)
3) Must display at least one sign at time of evaluation in two or more of the following categories:
   - **Sensory**: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)
   - **Vasomotor**: Evidence of temperature asymmetry and/or skin color changes and/or asymmetry
   - **Sudomotor/Edema**: Evidence of edema and/or sweating changes and/or sweating asymmetry
   - **Motor/Trophic**: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin)
4) There is no other diagnosis that better explains the signs and symptoms

The valid International Association for the Study of Pain (IASP) diagnostic criteria for clinical purposes, which are the most important for clinical routine. CRPS patients must qualify for all four criteria.

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Figure 1 Thermography depicting the cold skin after forearm injury refined to the ulnar nerve innervation territory (5th and ulnar half of the 4th finger). The patient suffered from typical neuropathic pain which could be treated successfully with anticonvulsants. The correct diagnosis is posttraumatic neuralgia of the ulnar nerve.
Case 2: If a patient reports pain, temperature and color difference localized to one interdigital joint and the physician finds pain while pressing the affected joint and a reduction of the active range of motion regardless of the origin (eg, pain-related movement restriction), the patient fulfills criteria 2 and 3 in Table 1. Although there was no inciting event (Table 1, criterion 1) there is a risk of misdiagnosing the patient as having “spontaneous” CRPS. However, more probably, reasons for the localized joint symptoms are osteoarthritis, rheumatic or Lyme arthritis (Table 1, criterion 4).

These examples highlight the importance of being critical with diagnosing “CRPS”, in particular if CRPS develops spontaneously or after a minimal trauma, and if the complaints are locally restricted and if the pain history is short.

Red Flags in Favor of Differential Diagnoses

Diagnosis of CRPS is straightforward after a distal radial fracture if posttraumatic carpal tunnel syndrome is excluded either clinically or by electroneuronography. There is no need for further extensive evaluation. In contrast, complicated pain conditions with red flags in history or at the clinical examination (Table 2) should lead to a far more extensive evaluation to find possible differential diagnoses (Table 3). On the other hand, pain in CRPS is disproportionate and usually not responding to classical analgesics. Thus, pain only during weight bearing and movement, or pain responding well to analgesics (Table 2) might suggest a non-CRPS origin of the complaints. The evaluation needs to be individualized based on the patient’s history. Other conditions like diabetic neuropathy can co-occur with CRPS and it is not necessarily always one or the other.

“Spontaneous” CRPS as a Red Flag

Spontaneous CRPS might be diagnosed in up to 10% percent. However, CRPS-like symptoms with spontaneous occurrence can be the first sign of a significant underlying disease. Examples are spinal cord pathologies, deep vein thrombosis, infection, immune-mediated neuropathies, paraneoplastic syndromes or brachial plexus affections, eg, by

| Table 2 Red Flags Suggesting Non-CRPS Limb Pain |
|-------------------------------------------------|
| • Spontaneous development                        |
| • Fever, biochemistry suggesting infection or possible entrance for an infection |
| • History of inflammatory disease (eg, rheumatoid arthritis) |
| • Abnormal neurological investigation with signs of central or peripheral nerve lesion |
| • Former malignancy or B symptoms                |
| • Simultaneous multiple limb affection           |
| • Spreading of pain                              |
| • Pain only during weight bearing                |
| • Pain responds extraordinary to simple analgesics|
| • History of psychological disorders             |
| • Compensation claims                            |

| Table 3 Common Differential Diagnoses |
|---------------------------------------|
| Local limb pathology                  |
| • Acute: Fracture, inflammation (arthritis, osteomyelitis, cellulitis), compartment syndrome, immobilization-induced symptoms |
| • Chronic: Persistent defects after limb injury, osteoarthritis developing after joint fractures, myofascial pain due to changed (protective) movement patterns, bone nonunion |
| Affection of arteries, veins or lymphatic vessels |
| • Acute: Traumatic vasospasm, vasculitis, peripheral artery disease, venous thrombosis |
| • Chronic: Lymphedema, Raynaud’s syndrome |
| Autoimmune diseases, paraneoplastic disorders in malignancies |
| • Central nervous system lesions: Spinal cord tumor, stroke, syringomyelia |
| Peripheral nervous system lesions: Nerve compression, thoracic outlet syndrome, traumatic nerve plexus lesions, polyneuropathy, mononeuritis (eg, posttraumatic vasculitic neuritis; infectious), malignancy/occult malignancy (eg, plexus infiltration) |
| Psychological disorders: Factitious disorder, malingering during compensatory claims |

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tumor infiltration or by a Parsonage-Turner syndrome. Inferior brachial plexus lesions are painful, have multisegmental sensorimotor symptoms at the distal arm/hand and the nerves contain many sympathetic fibers. They might mimic CRPS. However, plexus lesions usually do not show trophic changes in acute or intermediate stages, reflexes are lost and muscle atrophy occurs exclusively in muscles that are innervated by the respective nerve trunks.

A published case of spontaneous symptoms mimicking CRPS in a 75-year-old woman with ovarian cancer was a paraneoplastic condition called palmar fasciitis polyarthritus syndrome (PAPS; probably immune-mediated) which developed before the cancer was recognized\(^{15}\) (Figure 2). This case exactly mirrors a case, which was referred to us under the suspicion of spontaneous bilateral CRPS.

Clinical signs of central or peripheral nervous system lesions (eg, hyporeflexia or hyperreflexia with pyramidal tract signs) are red flags suggesting neuropathic central or peripheral pain with associated autonomic symptoms. When a limb spontaneously or after an everyday skin trauma becomes red, swollen, warm and painful, infection is one possibility that needs to be excluded by, eg, visible entrance for an infection, fever or blood investigations. Spontaneous CRPS-like symptoms after a period of extensive physical training should raise the suspicion of spontaneous fatigue fracture.\(^{16}\)

Finally, a history of previous cancer should raise suspicion of cancer relapse.\(^{17}\)

### Multiple Limb Affection as a Red Flag

CRPS normally starts in one extremity. However, if pain and skin reddening start bilaterally in the feet, possible reasons are peripheral neuropathies like erythromelalgia,\(^{18}\) small fiber polyneuropathy\(^{19,20}\) or spinal cord affection. Pain starting in both arms might indicate cervical spinal cord pathology like syringomyelia.\(^{21}\) Rarely, CRPS spreads, eg, to the mirror image limb. For evaluating possible spreading of CRPS, the full diagnostic criteria must be applied to each limb.\(^{2}\) The spread of CRPS follows a continuous hemibody or mirror image pattern, whereas spread to unrelated extremities is rare and usually preceded by a new trauma.\(^{22}\) Diagnosis of spreading CRPS first needs exclusion of a systemic (eg, autoimmune disease) or spinal cord pathology. CRPS patients often have diffuse complaints and pain in multiple regions distant from the CRPS limb without the typical CRPS signs like discoloration, temperature difference, sweating, and passive limb movement restriction. This is not spread of CRPS but maybe related to overuse of unaffected limbs. Alternatively, the spread of pain (without signs of CRPS) may be due to not CRPS – specific central sensitization mechanisms or disruptions in pain-control\(^{23–25}\) resulting in hypersensitivity to both noxious and non-noxious stimuli, which is denominated “central sensitization syndrome” and often described in fibromyalgia. The central sensitization inventory may be helpful to get an idea for such a differential diagnosis.\(^{26}\)

Protection or guidance of the CRPS extremity can lead to inappropriate overuse of contralateral joints, overuse-induced nerve entrapment (eg, contralateral carpal tunnel syndrome)\(^{27}\) or myofascial pain because of non-physiological movement patterns.\(^{28}\) Moreover, the chronic use of crutches in leg CRPS may lead to ulnar nerve compression and neuropathic pain related to but finally independent from CRPS. A list of some of the possible differential diagnoses to CRPS is provided in Table 3.

### A Clinical Examination is Mandatory for CRPS

In particular, with red flags, a comprehensive clinical examination must be performed. The first steps are inspection and palpation. For instance, a skin lesion as an entrance for an infection could be found by inspection. If the “refractory” CRPS patient presents with an overprotected arm fixed to the body but without muscle wasting or contractures and with rough palms indicating physical work, there might be a mismatch between reported symptoms and objective findings. Objective typical CRPS findings are skin color changes, temperature difference, sweating, edema and reduced range of motion. However, those signs alone cannot differentiate between CRPS and localized inflammation like infection or arthritis. It is the distal limb generalization, which characterizes CRPS (see Figure 3 for illustration of non-CRPS where fingers are not affected).

Sweating might be of particular interest. A local trauma does not induce hyperhidrosis,\(^{29}\) a peripheral nerve lesion causes sweat loss within the innervation territory, while sympathetic chain lesion causes sweat loss in the respective quadrants of the body. This means that hyperhidrosis might be relatively specific for CRPS while hypohidrosis is unspecific. Affected distal and proximal joints and trigger points in muscles of the affected limb (possibly involved in...
Figure 2 Example of spontaneous “CRPS” which in fact was a paraneoplastic condition called palmar fasciitis polyarthritis syndrome (PAPS; probably immune-mediated), which developed before the cancer was recognized in a 75-year-old woman with ovarian cancer. Marie I, Cailleux N, Roca F, Benhamou Y, Scotte M, Levesque H. Palmar fasciitis and polyarthritis syndrome. QJM. 2010;103(9):703–704. by permission of Oxford University Press.15
guarding mechanisms) should be manually investigated. A generalized joint affection in connective tissue disease should be recorded. The peripheral arterial pulses should be palpated and the capillary responses have to be noticed in some cases. Signs of deep venous thrombosis with pain in the lower leg should be looked for particularly after immobilization or after travelling a long distance.

Thereafter, patients should be exposed to a full neurological examination looking for upper and lower motor neuron signs and sensory symptoms including the spatial distribution of sensory loss or gain.

**Technical Investigations Confirming CRPS or the Presence of Other Pathologies**

Technical investigations should be performed based on the findings of clinical examination. Table 4, Table 5 gives an overview of the rationale behind different technical investigations for CRPS.

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**Table 4 Clinical Examination**

| Inspection (side-to-side comparison) |
|------------------------------------|
| Skin color                          |
| Edema                              |
| Sweating                           |
| Contractures                       |
| Muscle atrophy                     |
| Muscle spasms, tremor, dystonic posture |
| Trophic changes (nails, hairs, skin) |
| Skin lesions                       |
| Posturing of the painful limb      |

| Palpation (side to side) |
|--------------------------|
| Warm/cold, wet/dry skin, pulses and capillary responses |

| Neurological examination |
|--------------------------|
| Muscle tendon reflexes (absent/present) |
| Motor strength (MRC grading; differentiate from pain-related weakness) |
| Test for touch-evoked pain, pinprick hyperalgesia (side to side), deep pressure pain (eg, at finger joints, side to side) |

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**Figure 3** Example of a toxic-induced skin ulcer. This painful extremity is red, swollen and has extensive hair growth, and the proximal skin was dry. The CRPS criteria 1–3 would be fulfilled but notice that the distal fingers have normal color and are without edema. The lack of a distal generalization of the symptoms speaks against CRPS. The obvious etiology in this case is a skin ulcer which developed after erroneous subcutaneous infusion of mitoxantrone and was finally cured with skin transplantation. In less obvious cases, when the phenomenon of distal generalization is ignored, such a constellation of symptoms could lead to a false CRPS diagnosis.
Table 5: Technical Investigations

| Suspecting local pathology: C-reactive protein and white blood cells, plain X-ray comparing both limbs, magnetic resonance imaging (MRI), computed tomography (CT) or three-phase bone scintigraphy |
|---|
| Suspecting perfusion deficits: blood pressure index, ultrasound, capillary microscopy, D-dimer test |
| Suspecting paraneoplastic or systemic disease: Laboratory testing for connective tissue disease, gammopathies, in selected cases cerebrospinal fluid analysis, in very selected cases paraneoplastic antibodies, CT-thorax- abdomen-pelvis and positron emission tomography |
| Suspecting central or peripheral nerve lesion: MRI findings, evoked potentials, nerve conduction studies and electromyography |

If local pathology is suspected (e.g., fracture, pseudoarthrosis, arterial occlusive disease, venous thrombosis or infection), X-ray, computed tomography, magnetic resonance imaging (MRI), C-reactive protein, white blood cells, bone scintigraphy, blood pressure index, ultrasound, capillary microscopy or D-dimer test might be helpful. Plain X-rays should be done with both limbs on one plate to recognize CRPS typical osteoporosis if present. Three-phase bone scintigraphy must be performed in the first 6 months and shows a generalized involvement of the distal joints. Tracer accumulation restricted to the affected joint might indicate a hidden fracture, pseudoarthrosis or osteoarthritis after trauma, generalized tracer accumulation also on the contralateral side might indicate inflammatory arthritis, and reduced tracer uptake could be a consequence of immobilization.

Suspected central or peripheral nerve lesions from the clinical examination should be evaluated with MRI, evoked potentials, or by nerve conduction and electromyography. When the examination suggests a peripheral nerve lesion, a careful examination should evaluate if the autonomic changes are restricted to the innervation area of the lesioned nerve, which renders CRPS unlikely. Thermographic pictures might be helpful in this respect. Spontaneous and evoked neuropathic pain and discoloration of the legs mimicking CRPS was reported in a patient in whom spinal MRI disclosed a contrast enhancing mass that at comprehensive investigation revealed neurosarcoidosis.

If clinical investigations suggest small fiber pathology, quantitative sensory testing (QST) might be helpful. Typical QST patterns in CRPS include loss of non-painful temperature sensation and pressure hyperalgesia. Other findings include pinprick hyperalgesia, cold and brush-evoked allodynia. In small fiber polyneuropathy, the intraepidermal nerve fiber density and sweat responses are reduced at the distal leg and loss of sensation for temperature and pain stimuli predominates, sometimes in combination with pain relief by cold and pain exacerbation by heat.

Psychological Disorders

Experts agree that CRPS is not a psychological disease. However, as in many other pain disorders, CRPS course might be influenced by psychological factors like anxiety or pain catastrophizing. History of abuse and violence might uphold CRPS symptoms by preventing adequate physical therapy. In case of compensation claims, the pain – but not the visible objective symptoms – might be reported as exaggeratedly strong. We do not want to review psychological issues in CRPS, but instead present specific situations that are rare but in which psychological issues trigger CRPS-like symptoms.

One major controversy is about CRPS motor symptoms, such as fixed dystonia or irregular myoclonic jerks. Among patients with fixed dystonia and a diagnosis of CRPS a significant proportion of patients has a probable or documented psychogenic movement disorder, although it is always problematic to prove the “psychogenic” origin of such a disease (e.g., old beliefs about torticollis or blepharospasm). Moreover, the difference between painless “functional” movement disorders and CRPS pain-induced and implicitly learned movement disorders might be fluid. However, psychogenic dystonia cases have doubtlessly been documented during hidden video surveillance. Future research might better distinguish between reduced motor control by CRPS-specific body perception disturbances or cortical reorganization and psychogenic movement disorders.

Another important point is self-mutilation and self-inflicted symptoms. It is important to differentiate self-mutilation from autonomic symptoms, which come from immobilization (non-use) of the affected limb in order to prevent pain. Simply letting a limb hang down without any movement, or not using a limb after a cold challenge (e.g., outside temperature), could lead to temperature differences between the rested and the used limb after 1 hour of up to 4°C in

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| Suspecting central or peripheral nerve lesion: MRI findings, evoked potentials, nerve conduction studies and electromyography |
healthy subjects. There are also well-documented reports about self-induced disorders (ligation of the limb, migrating skin ulcerations) referred to a tertiary care center under the suspicion of CRPS.\textsuperscript{44} It is of the utmost importance to recognize such phenomena. On the other hand, misdiagnosis of CRPS as a functional condition can have devastating functional consequences since appropriate treatment might be prevented.

**Conclusion**

Early and correct recognition of CRPS and initiation of the adequate treatment are crucial for a favorable outcome. Conversely, misdiagnosis of other disorders as CRPS is detrimental because appropriate treatment is withheld from patients. This means that treating physicians have to find the right balance between an early and a premature diagnosis of CRPS. This can be achieved by continuous medical education, having always a critical mind and, in case of uncertainty, by in-time referral to a treatment center with extensive experience in CRPS willing to check differential diagnoses.

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