Complex regional pain syndrome—significant progress in understanding

Frank Birklein*, Tanja Schlereth

Abstract
Research into complex regional pain syndrome (CRPS) has made significant progress. First, there was the implementation of the official IASP “Budapest” diagnostic criteria. It would be desirable to also define exclusion and outcome criteria that should be reported in studies. The next step was to recognize the complex pathophysiology. After trauma, some inflammation is physiological; in acute CRPS, this inflammation persists for months. There is an abundance of inflammatory and a lack of anti-inflammatory mediators. This proinflammatory network (cytokines and probably also other mediators) sensitizes the peripheral and spinal nociceptive system, it facilitates the release of neuropeptides from nociceptors inducing the visible signs of inflammation, and it stimulates bone cell or fibroblast proliferation, and endothelial dysfunction leading to vascular changes. Trauma may also expose nervous system structures to the immune system and triggers autoantibodies binding to adreno- and acetylcholine receptors. In an individual time frame, the pain in this inflammatory phase pushes the transition into “centralized” CRPS, which is dominated by neuronal plasticity and reorganization. Sensory-motor integration becomes disturbed, leading to a loss of motor function; the body representation is distorted leading to numbness and autonomic disturbances. In an attempt to avoid pain, patients neglect their limb and learn maladaptive nonuse. The final step will be to assess large cohorts and to analyze these data together with data from public resources using a bioinformatics approach. We could then develop diagnostic toolboxes for individual pathophysiology and select focused treatments or develop new ones.

Keywords: Complex regional pain syndrome, Posttraumatic inflammation, Neuroplasticity, Central reorganization, Pathophysiology, Bioanalysis

1. Introduction
To date, scientific articles about complex regional pain syndrome (CRPS), including our own, have very often begun with a sentence like: “CRPS is painful posttraumatic disorder that is incompletely understood and difficult to treat.” This sentence is the result of one major problem in pain research that is not only specific to CRPS but also applies to, eg, fibromyalgia syndrome, low back pain, or headache (as a whole): all of these pain syndromes are human without reliable animal models being available, and as a result, they are clinically defined and have no quantifiable biomarkers. Nobody would expect a unique pathophysiology or a universal treatment for “headaches,” but in contrast one for migraine or cluster headache. The same is true for low back pain. Even in fibromyalgia, there is a paradigm shift; at least 1/3 of fibromyalgia syndrome patients have small fiber pathology.104 Unfortunately, it is CRPS that is still usually regarded as a single disease entity and therefore should respond to a standardized treatment. Luckily, CRPS research has made huge steps in understanding the various pathophysiological aspects in recent years. This review includes the latest results but also milestones of previous CRPS research, which significantly contribute to the understanding. The article is focused on a hypothesis about a pathophysiologically oriented differentiation of CRPS subtypes; it is not a comprehensive review.

2. What is complex regional pain syndrome, what is not?
Complex regional pain syndrome can be diagnosed when clinical diagnostic criteria are fulfilled. In practice, however, this could be the first stumbling block. A recent publication demonstrated that the incidence of CRPS after limb trauma critically depends on the diagnostic criteria used.2 Of the 596 participants, 7% were diagnosed with CRPS according to the actual IASP criteria, 49% according to the former IASP criteria, and 21% according to the criteria often used by surgeons.115 The current IASP criteria are not perfect. Nevertheless, we should agree only to use these criteria11 to make a CRPS diagnosis (Table 1).

It is very important to consider 2 elements of these criteria that are often neglected: point 1, “Continuing pain, which is disproportionate to any inciting event”; and point 4, “No other diagnosis better explains the signs and symptoms.” Point 1 means that there should be an “inciting event” and a timely connection to it. Typically, CRPS develops as a pain disorder with a patient requesting treatment within 4 to 8 weeks after trauma to an extremity. The exact latency between the trauma and the earliest possible diagnosis of CRPS depends on the expected recovery period for the trauma.2,121 A premature diagnosis might confuse normal or delayed healing with CRPS.53

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115 Must be vigorously excluded. For exclusion, blood, magnetic resonance imaging (MRI), 3-phase bone scintigraphy, plain X-ray and antinuclear antibodies, or white blood cell count can demonstrate an increased bone metabolism, leading to an increase in the osteoblast activity marker osteoprotegerin in CRPS serum. Whether this finding has the potential to become a biomarker has to be systematically assessed in the future. Dynamic temperature differences (affected vs. unaffected side) of >1 °C support the diagnosis of CRPS.

What is not stated in the current IASP criteria is that symptoms affect the extremities and occur distally, irrespective of nerve innervation territory. In the case of isolated proximal pain in specific joints (shoulder, hip) or symptoms in the head or torso, a diagnosis of CRPS should not be given. The existence of knee CRPS remains a topic of discussion.

3. Are there different forms of complex regional pain syndrome?

Widely accepted is the trauma-related differentiation of CRPS by the absence (CRPS I) and presence (CRPS II) of evident nerve lesions, although it is not excluded that this differentiation could be artificial because of depending on standard electrophysiology. All nerve lesions that cannot be assessed by electrophysiology (eg, partial nerve lesions, small fiber lesions, deep somatic nerves) could lead to wrong classification. CRPS II should not be mixed up with posttraumatic neuralgia in which the symptoms (sensory loss, paresis [in mixed nerves], pain, hyperalgesia, and autonomic symptoms such as temperature or color changes [not after nerve root lesion]) are confined to the nerve–nerve root innervation territory. A second possible differentiation is to define more and less severe CRPS cases that require different resources. The CRPS Severity Score is the first scale providing such a differentiation and CRPS grading. Future studies have to show whether there are CRPS Severity Score cutoff values that predict outcome and allow treatment allocation.

Probably, most comprehensive would be a pathophysiology-oriented classification. Such a classification would also predict primary treatment. A first attempt was to classify CRPS into primarily warm and cold cases by skin temperature directly after the trauma at the onset of symptoms. This differentiation, however, suffers from its retrospective nature. More promising seems to be the analysis of the presented clinical symptoms and to draw conclusions for a pathophysiology-based classification.

### Table 1

**IASP-approved CRPS diagnostic criteria.**

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
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<tbody>
<tr>
<td>(1) Continuing pain, which is disproportionate to any inciting event</td>
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<tr>
<td>(2) Must report at least 1 symptom in 3 of the 4 following categories:</td>
<td></td>
</tr>
<tr>
<td>Sensory: reports of hyperesthesia and/or allodynia</td>
<td></td>
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<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 motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)</td>
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</table>

(3) Must display at least 1 sign at the time of evaluation in 2 (clinical) or 3 or more (scientific) 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 skin color 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, nail, skin)

(4) There is no other diagnosis that better explains the signs and symptoms.

The so-called "Budapest" criteria for CRPS. The diagnosis of complex regional pain syndrome (CRPS) requires compliance with all 4 points. There are 2 versions: the criteria for clinical use are fulfilled if under point 3 more than 2 sign categories are qualified; the criterion for inclusion in scientific studies was if 3 or more sign categories are qualified.

It may be helpful to recognize in the first week after the trauma that particular patients who are in severe pain (>5/10 rating scale) are at risk. Complex regional pain syndrome diagnoses that are made months or even years after the initial trauma simply due to persistent pain and limb nonuse without typical CRPS symptoms documented in their case history should be questioned.

Point 1 also addresses so-called "spontaneous" CRPS cases. In the literature, there are reports of spontaneous CRPS cases; however, point 4 of the diagnostic criteria warrants, in particular in these cases, a comprehensive differential diagnostic workup. Normal posttraumatic healing, rheumatic disease, or other inflammatory diseases and also psychological disorders must be vigorously excluded. For exclusion, blood, magnetic resonance imaging (MRI), 3-phase bone scintigraphy, plain X-ray examinations, or a psychological workup may be helpful.

Diagnostic tests to support a positive CRPS diagnosis are, however, more difficult. There are no MRI indications for CRPS, plain X-rays are insensitive, and there are no serum markers. Only 3-phase bone scintigraphy can demonstrate an increased bone metabolism in the mineralization phase with moderate specificity. Recently, we have been able to demonstrate that this increased bone metabolism leads to an increase in the osteoblast activity marker osteoprotegerin in CRPS serum. Whether this finding has the potential to become a biomarker has to be systematically assessed in the future. Dynamic temperature differences (affected vs. unaffected side) of >1 °C support the diagnosis of CRPS.

### Table 2

**Technical investigations helpful to exclude differential diagnosis.**

<table>
<thead>
<tr>
<th>Investigation/parameter</th>
<th>Exclusion/suspicion of</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count</td>
<td>Infection (e.g., postsurgery)</td>
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<tr>
<td>C-related peptide, blood sedimentation rate, antinuclear antibodies</td>
<td>Rheumatic disease</td>
</tr>
<tr>
<td>Plain X-ray</td>
<td>Fracture, nonfusion, osteoarthritis, rheumatic arthritis, osteomyelitis</td>
</tr>
<tr>
<td>Tc99m bone scintigraphy</td>
<td>Rheumatic arthritis, polyarthritis, oligoarthritis, osteomyelitis</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>Fatigue fracture, nonfusion, tendovaginitis, osteomyelitis</td>
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</table>

These investigations are helpful to exclude differential diagnosis mimicking complex regional pain syndrome (CRPS) if there is a doubt with the diagnosis. Positive findings should lead to in-depth investigations. There are no psychological scales that safely differentiate, e.g., posttraumatic stress disorder, factitious disorder, somatization, or nonuse. Psychological assessment must be done by an experienced psychologist.

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Figure 1. Thermographic picture (left dorsal view, right palmar view) of a 53-year-old male patient after elbow fracture referred to our complex regional pain syndrome (CRPS) outpatient department. He presented with pain and allodynia limited to the fourth and fifth finger, which were bluish and significantly colder. The nails grew more slowly, and weakness of finger flexion was present. Thermography revealed that only the innervation territory of the ulnar nerve was colder; neurography confirmed traumatic ulnar paresis. Diagnosis was changed to posttraumatic neuralgia, and the pain was successfully treated with drugs for neuropathic pain. The nerve regenerated over the following year and the symptoms resolved.
These conclusions are supported by recent CRPS research. We want to emphasize that this classification should be regarded as a suggestion. It is simplified, does not cover all CRPS cases, but could be the basis for an in-depth discussion and for confirming or refuting studies in the future. Concentrating on inflammatory or central CRPS phenotypes in this article also does not mean that other mechanisms such as neuropathic or sympathetic pain components do not exist. It could turn out in future research that, e.g., taking a skin biopsy is more important for classifying CRPS as the classification proposed in this review.

4. “Peripheral inflammatory phenotype” of complex regional pain syndrome

4.1. Clinical signs indicating ongoing or past inflammation

In particular (but not exclusive), within the first months of disease in 75% of CRPS cases, clinical signs resemble peripheral inflammation. Some posttraumatic inflammation is physiological and includes activation of the innate and adaptive immune system initiated, eg, by activation of Toll-like receptors after cell damage or blood extravasation. In CRPS, this inflammation is exaggerated for yet unclear reasons. The most important inflammation-related symptom is pain while moving a joint which is exaggerated with load or strain. This pain arises from sensitization of deep somatic primary afferents (eg, in joints, tendons, muscles) by inflammatory mediators. This type of pain becomes significantly better at rest and is felt deep in the limb. Accordingly, the majority of patients have hyperalgesia to blunt pressure on muscles or bones. Preclinical studies have repeatedly shown that hyperalgesia to heat is a hallmark of inflammation; heat hyperalgesia is present on CRPS skin in approximately 40% of patients. Although pinprick hyperalgesia is generally regarded as a central phenomenon, it is often driven by peripheral input in acute cases.

Visible and measurable signs of inflammation are edema, skin discoloration, and increased skin temperature in CRPS. Skin color is reddish or blue-livid; skin temperature differences are variable, not fixed, and according to the inflammatory pathophysiology, skin temperature is often increased in acute stages of CRPS. Edema is exacerbated through strain. Less well known is that hyperhidrosis and hypohidrosis could be the results of peripheral inflammatory mediators (neuropeptides), as are trophic changes such as increased hair or nail growth induced by cytokines. Motor function is also impaired by peripheral inflammation. Edema limits the range of motion and motor performance decreases with an increase in muscle hyperalgesia as a surrogate of the sensitized primary afferents. Even in more chronic CRPS cases when inflammation seems to fade away, some signs are still definitely related to inflammation. Articular contractions occur because of overstimulation of fibroblast growth during acute inflammation; skin blood vessels show endothelial dysfunction probably by downregulation of nitric oxide and upregulation of endothelin-1 (ET-1) leading to cold skin. Endothelial dysfunction is mediated directly or indirectly by proinflammatory cytokines.

4.2. Systemic findings indicating ongoing or past inflammation

A recent review summarizes publications that indicate an inflammatory process in CRPS. In serum samples, the mRNA and the protein profile of proinflammatory and anti-inflammatory cytokines were shifted to an inflammatory phenotype. The most striking difference was the reduction of the anti-inflammatory cytokines such as interleukin-10. The latter is normally produced by CD14+CD16+ mononuclear cells, which are reduced in CRPS, in particular if cold allodynia is present. Increased levels of the soluble tumor necrosis factor-α (TNF-α) receptors are present in patients with pinprick hyperalgesia. Very recently, our own group has been able to demonstrate increased levels of osteoprotegerin, a member of the TNF receptor superfamily, which becomes activated by trauma-related inflammation and regulates bone repair. Any inflammation induces processes that terminate inflammation, such as anti-inflammatory cytokines or proteinases and peptidases. In an unbiased whole genome screen, the mRNA of the matrix metalloproteinase 9, which cleaves cytokines and neuropeptides, was upregulated 4-fold in CRPS. MicroRNAs are small interfering noncoding RNAs that regulate transcription of RNA into protein. MicroRNAs have the ability to control several physiological processes and are therefore “master switches,” in particular between the immune system and neurons. In CRPS, several microRNAs, which control inflammatory processes, are downregulated. Physiologically, these microRNAs travel with exosomes released from inflammatory cells in the blood and systemically control inflammation in target cells. Downregulation of microRNAs might contribute to nonresolution of posttraumatic inflammation in CRPS.

Neuropeptides are responsible for the visible symptoms of inflammation such as vasodilation or edema and are abundantly released as a result of stimulation of sensitized peptidergic nociceptors (neurogenic inflammation) in the skin and deep tissue. In the serum of patients with CRPS, bradykinin, calcitonin gene-related peptide (CGRP), and substance P (SP) were found to be increased. Endothelin-1 is not a neuropeptide, it is a peptide produced mainly in the endothelium. Endothelin-1 is a very potent vasoconstrictor and contributes to posttraumatic pain and hyperalgesia. Endothelin-1 was also increased in CRPS sera.

A recent finding that opens a new avenue in CRPS pathophysiology is autoantibodies and autoimmunity. We contributed to a study discovering agonistic autoantibodies on surface structures at β2-adrenergic receptors and m2-cholinergic acetylcholine receptors in patients with CRPS. These autoantibodies belong to the immunoglobulin G class and are directed against peptide sequences from the second extracellular loop of both receptors. The antibodies might be of particular importance because they provide a link to the sympathetic nervous system, which has been regarded central in CRPS pathophysiology for a long time. Activation of β-adrenergic receptors on a variety of cells, including neurons, and inflammatory and soma cells, induce the release of inflammatory cytokines in preclinical models. Very recently, activating autoantibodies directed against alpha1-adrenoceptors were additionally described. The role of all these autoantibodies has to be determined because the detection of molecular mechanisms explaining CRPS symptoms is still missing. However, the fact that immune therapy relieves pain even in some long-standing patients with CRPS supports a significant contribution. Unfortunately, only some of these findings could be related to CRPS symptoms. This might come from non-comprehensive data recording or analyzing, and thereby missing of network changes (Fig. 2).

4.3. Findings in the affected tissue indicating local inflammation

Complex regional pain syndrome usually causes regional pain and symptoms; only rarely are complaints about generalized symptoms by the patients. Moreover, patients very often use their unaffected limb more than usual to protect the painful one (eg, hobbling or learning to use the nondominant hand for writing).
Therefore, the most specific results can be expected from the direct analysis of the affected tissue. Investigations of skin biopsies, suction blisters, or dermal microdialysis are available.

4.3.1. Analysis of skin biopsies

In acute CRPS, our own group could demonstrate an overproduction of cytokines by immune histochemistry (qualitative) in keratinocytes from the affected limb, a proliferation of keratinocytes and an increased number of mast cells in the skin (quantitative). In chronic CRPS, the findings were just the opposite, thinner skin and less cytokines and macrophages indicating a reduction in local inflammation.3 We could confirm by quantitative enzyme-linked immune assays that in skin biopsies from patients with CRPS, there are higher levels of TNF-α protein than in non-CRPS fracture controls.46 Not directly related to inflammation, epidermal nerve fibers were found to be either reduced78 or unchanged,40 or a change in membrane receptors was described.14

Peptides are more difficult to identify. Microdialysis measurements give an indication of a facilitated neurogenic inflammation. Vasodilation as a surrogate for the release of CGRP was increased and plasma extravasation as a surrogate for SP release occurred on the affected side.117 In skin samples from 2 CRPS amputees, there was a significant increase in CGRP immune staining in keratinocytes.37 The release of noradrenalin, which is often discussed as an alternative explanation for cold skin, was unaltered117 (Fig. 3).

It takes several hours to induce a suction blister. The blister fluid can then be quantitatively analyzed. A subset of patients with CRPS had notably increased concentrations of inflammatory cytokines, peptides, and tryptases on the affected side.36 A recent investigation found increased inflammatory and decreased anti-inflammatory cytokines in blister fluids on both sides, which normalized after treatment when symptoms improved.54 The bilaterality should not be regarded as “generalized” inflammation in CRPS; it might be related to the long suction period that allows systemic substances to enter the fluid, as shown repetitively in pharmacokinetic studies.51 In patients with CRPS characterized by cold extremities, higher levels of the ET-1 and decreased NO indicating endothelial dysfunction were found in the blisters.27

In summary, clinical and biochemical investigations of the affected tissue suggest an exaggerated posttraumatic inflammation as an important part of CRPS pathophysiology. They also suggest a switch in pathophysiology during the course of CRPS.

5. “Central neuroplasticity phenotype” of complex regional pain syndrome

In a significant subset of patients, CRPS gradually “centralizes.” The time frame until “centralization” occurs differs by individual. It could take months or be right from the beginning. Complex regional pain syndrome symptoms that are generated in the central nervous system (CNS) include mechanical allodynia, nondermatomal sensory deficits, body perception disturbances and the CRPS movement disorder, and some sympathetic phenomena.

Symptoms that are also generated in the CNS but will not be extensively reviewed here are psychological issues. It is widely accepted for most chronic pain disorders that psychological factors contribute to suffering and adaptation in particular when treatment was not successful. This should not be different in CRPS. What is special for CRPS is the interrelation of movement-related pain, pain and movement avoidance, and maladaptive learning185, interesting research is going on in this field.56 If pain is regularly caused or exacerbated, the use of a hand will be performed less and less, reinforced through the reward of pain avoidance and guarding. The result of this behavior on the background of ongoing inflammation (eg, limitations in movement, contractures) is deleterious. Especially, in the case of children, pain avoidance and guarding is very prominent. It remains speculative, but these psychological symptoms might be controlled by noncoding RNAs that are regulated after trauma in predisposed subjects.46

5.1. Findings supporting central pain components

The most important central pain symptom is mechanical hyperalgesia/allodynia. Although pressure pain on the affected side could be generated by local inflammation, generalized hyperalgesia in CRPS is not.101,114 In a cross-sectional investigation of our group, approximately 25% of patients with CRPS have brush-evoked pain at the affected side.3 Patients with allodynia show activation of pain-related brain areas (formerly called “pain matrix”) in functional MRI during brushing of the skin in contrast to brushing of the unaffected side.60 In chronic CRPS cases, a reduction in gray matter is observed in the right insular cortex, the nucleus (ncl) accumbens and the ventromedial prefrontal cortex. This reduction of gray matter density was partly related to pain duration and pain intensity.23 Ligand positron emission tomographic studies of central opioid receptor availability demonstrated a reduced opioid binding capacity to neurons in the contralateral amygdala.42 Although these studies give strong arguments for a central pain component, admittedly they cannot prove causality.

5.2. Findings supporting central sensory loss

It is intriguing that more patients with CRPS consistently report hypesthesia and hypalgesia during sensory testing than hyperalgesia on the affected side.24 Sensory disturbances follow a glove-type or stocking-type pattern as so-called pain-related nondermatomal somatosensory deficits.63 In a subset of patients with nondermatomal somatosensory deficits, a reduced neuronal activity in primary and secondary sensory cortex areas could be found.19 Very recently, reduced pain-evoked potentials on the affected side categorized ipsilateral hypalgesia in patients with CRPS.8 The fact that this sensory loss is dynamic and disappears if pain is gone supports a functional central rather than a structural peripheral problem of sensory processing.22 What is less clear is the specificity to CRPS.

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which should not be confused with neglect in CRPS. It is in particular the motor disorder in CRPS that can spread to contralateral or even distant extremities.

Patients with CRPS have to compete with their unaffected extremity, which is often regarded as too large. This can lead to a change in hand size, which is measured by comparing the affected hand to the peripersonal space of the healthy hand. 

van de Heijning et al. 

Reduction of hand size by diminutive lenses reduces pain and edema, whereas enlargement increases pain. In tasks testing the simultaneousness of vibrotactile nonpainful stimuli, perception of the affected side is delayed, when on stimulation of the affected extremity but rather of the healthy extremity if it is held near the usual position of the affected one (crossing of extremities). 

When testing the change in skin temperature differences if the hands are crossed, it must be a cortical phenomenon. The fact that a patient simply thinks about movement (that could be painful) led to an activation of the sympathetic nervous system (as opposed to pain controls) and to an increase in the edema. 

van de Heijning et al. 

5.3. Findings indicating disturbances of body representation in the central nervous system

These findings are probably the most stunning published in CRPS research in recent years. The fact that patients with CRPS, usually after many years of pain,-taking multiple pain killers and a multitude of frustrating treatments, were compared with healthy controls might have led to some overinterpretation with respect to the specificity of the results. It is, therefore, of utmost importance to include comparable limb pain control groups. This has been performed increasingly in the last years. 

Many patients with CRPS must concentrate on the affected extremity to use it. This is named a “neglect-like symptom” in the CRPS literature, which should not be confused with neglect in neurological disorders. However, some indications for parietal dysfunction exist in subsets of patients with CRPS. The perception of body symmetry is distorted in the dark, the ability of hand laterality recognition is impaired, and the affected extremity is often regarded as too large. Reduction of hand size by diminutive lenses reduces pain and edema, whereas enlargement increases pain. 

van de Heijning et al. 

In tasks testing the simultaneousness of vibrotactile nonpainful stimuli, perception of the affected side is delayed, when on stimulation of the affected extremity but rather of the healthy extremity if it is held near the usual position of the affected one (crossing of extremities). 

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The tremor is described as an enhanced physiological tremor, the myoclonic jerks are irregular. Some patients show entrainment of myoclonus, which is, however, regarded as a sign of a psychogenic movement disorder. The most frequently evaluated motor symptoms are fixed dystonia and abnormal posturing. Physiological investigations and pharmacological interventions favor a spinal mechanism. Sensitization of sensory-motor circuits by ongoing inflammation was suggested together with an impairment of voluntary force control and an impaired sense of force production, which derives from Golgi tendon organ dysfunction impacting on spinal motor inhibitory interneurons. Supraspinal motor control was investigated by transcranial magnetic stimulation and fMRI. Transcranial magnetic stimulation revealed decreased inhibitory mechanisms and increased excitability in the contralateral but also the ipsilateral primary motor cortex in CRPS. Patients with CRPS have to recruit much more activity of the motor circuits than controls despite bradykinesia and reduced finger-tapping velocity. (Table 3).

Table 3

<table>
<thead>
<tr>
<th>Symptom</th>
<th>CRPS</th>
<th>Healthy</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
<td>10</td>
<td>5</td>
<td>0.001</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>13</td>
<td>7</td>
<td>0.001</td>
</tr>
<tr>
<td>Dystonia</td>
<td>20</td>
<td>10</td>
<td>0.001</td>
</tr>
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Figure 3. Plasma protein extravasation (PPE) in complex regional pain syndrome (CRPS) patients and healthy controls measured with dermal microdialysis. Electrical stimulation (gray area) induced a significant PPE in patients with CRPS (circles) after 15 minutes when compared with controls (p < 0.001). Substance P, which is released from peptidergic C-fibers, binds to neurokinin-1 receptors (NK1-R) on postcapillary venules and induces short-lived PPE. After activation, NK1-R was rapidly internalized and refractory to ongoing stimuli. Electrical stimulation is not sufficient to induce PPE in healthy skin.
6. What do rodent models tell us?

It is crucial to prove hypotheses in animal models. Many central neuroplasticity symptoms in CRPS require higher brain functions, which cannot be expected in rodents. Available CRPS models therefore concentrate on peripheral pathophysiology and simple behavioral consequences. Only a few attempts have been made to assess complex behavioral changes in the fracture model.

A tight fitting O-ring is applied to the hind limb for 3 hours in the post-ischemia pain model (CPIP). After reperfusion, the animals develop hyperemia and edema for only a few hours, but behavior was indicative of spontaneous pain, mechanical, and cold hyperalgesia for at least 4 weeks. The symptoms might even spread to the uninjured contralateral hind paw. The CPIP model leads to the massive appearance of free oxygen radicals and proinflammatory cytokines, which induce microvascular spasms and capillary dysfunction, reducing nutritive blood flow and oxygenation and increasing acidosis. Reactive oxygen species scavengers reduced symptoms and infusion of free radical donors induced them. Sympathetic blocks, α1 antagonists and α2 agonists, inhibited mechanical allodynia in the CPIP model. The biggest disadvantage of the CPIP model is its artificial lesion.

The most popular and realistic CRPS model is the fracture model. After tibia fracture and immobilization, the animals develop edema, increase of skin temperature, periarticular osteoporosis, increased protein extravasation, spontaneous pain behavior, and mechanical hyperalgesia. Keratinocytes upregulate proinflammatory cytokines and nerve growth factor. Substance P, CGRP, and SP-receptors (NK1-R) are upregulated in the skin, neurons, and endothelial cells. In the spinal cord, the chemokine CCL2 contributes to central sensitization.

Blocking inflammation with prednisolone reduced edema and warmth, anti-NGF or anti-interleukin-1 prevented mechanical hyperalgesia behavior, and NK1-receptor antagonists reduced visible inflammation and mechanical hyperalgesia behavior. In this rodent model, SP induces mast cell proliferation and degranulation. This model also impairs working memory and social engagement accompanied by structurally changed dendritic architecture in the amygdala and perirhinal cortex and decreased levels of neurotrophic factors. Blocking of the sympathetic nervous system reduced all symptoms, and the beta-2-antagonist butoxamine reduced nociceptive sensitization through reduction of IL-6 production. The disadvantage of the fracture/immobilization model is that most of the symptoms spontaneously remitted within a few weeks as in normal human fracture healing. Nevertheless, it is the most naturalistic CRPS model so far.

Recently, the needlestick injury model was introduced for CRPS II. The sciatic nerve is surgically exposed, and the nerve is pricked with a needle. The rats developed mechanical hyperalgesia after 14 days on the treated and also on the contralateral side. Visible CRPS signs are rare. Histological examination revealed endoneurial edema, axonal degeneration, and an increase of mast cells. Further models suggested for CRPS II are the combination of spinal nerve ligation and knee joint immobilization, and the chronic constriction injury model and tissue trauma. The disadvantages of these models are the minimal inflammatory signs and that it has not been reported whether the symptoms go beyond the respective nerve innervation territory.

Despite their imperfection, all these models impressively demonstrate the peripheral pathophysiology of CRPS and significantly contributed to our understanding of posttraumatic mechanisms leading to CRPS (Fig. 4).

7. Could complex regional pain syndrome phenotypes translate into individual treatment?

It is the nature of a hypothesis that confirmation has to be done in the future. On an evidence-based level, the answer to the above question is therefore: "not yet, it is speculative." Even if CRPS is treated without pathophysiological differentiation, reliable and large controlled and randomized studies conducted in multiple centers are lacking. Very heterogeneous target parameters (pain, changes of the clinical symptoms, recovery of function) and short observation periods impair the comparison of study results. One reason for this finding might be the rarity of CRPS, which qualifies as an orphan disease (http://rarediseases.info.nih.gov/gard/4647/complex-regional-pain-syndrome/resources/1). It is, therefore, not surprising that meta-analyses regularly lead to the frustrating assumption that there is "a lack of good evidence for or against (a particular) treatment." However, there is the common sense in CRPS research that these conclusions should not lead to therapeutic nihilism. This common sense also says that treatment should start early and should be multimodal. Physical, behavioral, pharmaceutical, and interventional treatments (as last options in specialized centers) should be offered. For up-to-date best evidence-based suggestions, we must refer to the existing guidelines or comprehensive meta-analyses.

Only treatments for which positive recommendations in guidelines exist are reported, and which fit into our proposal of different symptom-specified CRPS phenotypes independent from CRPS duration. This does not mean that treatments not mentioned cannot be effective.

8. Treatment of “peripheral inflammatory symptoms”

High doses of bisphosphonates inhibit osteoclasts. Osteoclasts are mainly driven by inflammatory mediators. The same applies to

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<th>Table 3</th>
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<tbody>
<tr>
<td>Symptoms possibly supporting either peripheral or central CRPS pathophysiology.</td>
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<tr>
<td><strong>History/symptom/finding</strong></td>
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<tr>
<td>Significant trauma, eg, fracture, surgery, heavy sprain</td>
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<tr>
<td>Minor injury, eg, hitting or vaccination</td>
</tr>
<tr>
<td>Clearly visible significant edema</td>
</tr>
<tr>
<td>Warm/red skin</td>
</tr>
<tr>
<td>Hyperhidrosis/hypohidrosis</td>
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<tr>
<td>Trophic changes (nails, hairs)</td>
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<tr>
<td>Pain only while moving the joint</td>
</tr>
<tr>
<td>Hyperalgesia to heat</td>
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<tr>
<td>Allodynia</td>
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<tr>
<td>Glove/stocking-like sensory deficits</td>
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<tr>
<td>Contractures</td>
</tr>
<tr>
<td>Motor disorder (tremor, myoclonus, fixed dystonia)</td>
</tr>
<tr>
<td>Neglect-like symptoms</td>
</tr>
<tr>
<td>Disproportionate feeling of swelling</td>
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<tr>
<td>Improvement of function by crossing the limbs</td>
</tr>
<tr>
<td>Watching the mirror image of healthy limb</td>
</tr>
<tr>
<td>Positive 3-phase bone scan/X-ray</td>
</tr>
<tr>
<td>Significant treatment response to bisphosphonates, steroids, IvIGs</td>
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</table>

These symptoms might contribute to classify complex regional pain syndrome (CRPS) as a peripheral (eg, inflammatory) or central pathophysiology. Frequent CRPS symptoms, which are not mentioned here (eg, mechanical hyperalgesia; cold bluish skin), cannot be attributed to any pathophysiology.

MG, intravenous polyvalent immunoglobulin; ××, means strong indication; ×, weak indication.
glucocorticoids that nonselectively reduce inflammation; high doses and longer or repetitive treatment might be necessary. Intravenous polyvalent immunoglobulins target the immune system with a rapid but not exclusive action on autoantibodies. Relatively low doses might be enough. Intravenous polyvalent immunoglobulins are safe but very expensive. Topical dimethyl sulfoxide (DMSO 50% cream) scavenges free oxygen radicals that occur during inflammation and could best be used as an add-on. Regular physical and sensory-integrative occupational therapy reduces the risk of developing contractures by proliferating connective tissue cells. Patients should also be encouraged to (voluntarily) use the affected extremities. The widely held opinion that patients with CRPS should avoid movement that triggers pain is no longer valid.

9. Treatment of “central neuroplasticity symptoms”

Restoring physiological brain circuits is primarily the task of physiotherapy with cognitive elements, or of behavioral treatment. The most popular technique is mirror therapy. A more elaborate treatment program including restoring body perception by recognizing right and left hands, imagination of movements, and mirror therapy is the graded motor imagery. Rather new developments in the treatment of “centralized” CRPS are pain-exposure physical therapy (PEPT) and the concept of graded exposures (GEXP). These approaches use progressive loading exercises (PEPT) and cognitive behavioral exposure to the most fearful activities (GEXP). Conventional physiotherapy uses elements of both PEPT and GEXP. Unfortunately, there has been no controlled study on the efficacy of psychotherapy for CRPS.

The only pain killer that has proven efficacy in CRPS is intravenously administered ketamine, which targets N-methyl-D-aspartate glutamate receptors mainly at the level of the spinal cord and the brain. Successful ketamine pain treatment might have a small effect on function as well. It is unclear how often ketamine can be used. Independent of pain, comorbid affective disorders such as anxiety and depression have to be treated, eg, by antidepressants.

If pain and hyperalgesia remain uncontrolled, spinal cord stimulation represents an alternative and well-documented therapeutic option, in particular when treating CRPS of the lower limbs. In case series, it was found that long-term intrathecal administration of baclofen through a pump led to a decline in dystonia and pain in >50% of patients. The application of spinal cord stimulator and

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Figure 4. Complex regional pain syndrome (CRPS) pathophysiology defined by signs and confirmed by experiments. The initial event is trauma. Posttraumatic inflammation is not properly controlled leading to edema, vasodilation, dyshidrosis (by substance P or CGRP), or cold skin (by endothelin-1 and lack of NO). Simultaneously, inflammatory mediators, growth factors, catecholamines, and autoimmune phenomena contribute to trophic changes and sensitize peripheral nociceptors in deep tissues inducing movement-related pain (left part of the figure). These mediators also sensitize second-order neurons in the spinal cord, which are responsible for mechanical hyperalgesia/allodynia (central part). Permanent barrage of nociceptive activity to the brain leads to central reorganization in susceptible patients. Symptoms are nondermatomal sensory deficits, disturbances of the body perception, and motor symptoms (right part). There is no time frame in which these changes happen, and there is no rule regarding which symptom category (peripheral or central) predominates. It might be different in individual patients.
10. Expected progress in the next years

Complex regional pain syndrome is a “fascinating,” complex, and visible pain disorder. The understanding of CRPS has made significant advances in recent years, which will in the medium term lead to improved therapies that can be tailored to the individual needs of the patient. This review is a call to leave behind CRPS categorizations that lump together too many pathophysiologies. Complex regional pain syndrome research must become more specific (e.g., like headache research and headache classification). We should combine our efforts to collect large numbers of patients with CRPS to be assessed in a standardized way and bring together clinical phenotypes with biochemical and psychophysical/neurophysiological/imaging findings and information from public resources. It will then be the responsibility of a state-of-the-art bioinformatics analysis to generate an evidence-based CRPS diagnostic toolbox with easy-to-use core data that allows patients to be categorized into major pathophysiological groups (e.g., predominance of inflammation, central neuroplasticity, autoimmune, psychological) and the selection of appropriate treatments for individual patients.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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