PAIN®

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 criteria[31] 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.[83]

Table 1

IASP-approved CRPS diagnostic criteria.

(1) Continuing pain, which is disproportionate to any inciting event

(2) Must report at least 1 symptom in 3 of the 4 following categories

Sensory: reports of hyperesthesia 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, nail, skin)

(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 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.[34] 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.[73] 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[12]; 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[94] 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 (**Table 2**).

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.[119] 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.[47] 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.[49]

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.[106]

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,[31] 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[116] (**Fig. 1**).

A second possible differentiation is to define more and less severe CRPS cases that require different resources. The CRPS Severity Score[32] 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.[115] 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 2

Technical investigations helpful to exclude differential diagnosis.

Investigation/parameter	Exclusion/suspicion of
White blood cell count	Infection (eg, postsurgery)
C-related peptide, blood sedimentation rate, antinuclear antibodies	Rheumatic disease
Plain X-ray	Fracture, nonfusion, osteoarthritis, rheumatic arthritis, osteomyelitis
Tc99m bone scintigraphy	Rheumatic arthritis, polyarthritis, oligoarthritis, osteomyelitis
Magnetic resonance imaging	Fatigue fracture, nonfusion, tendovaginitis, osteomyelitis

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, eg, posttraumatic stress disorder, factitious disorder, somatization, or nonuse. Psychological assessment must be done by an experienced psychologist.

dorsal view   palmar view
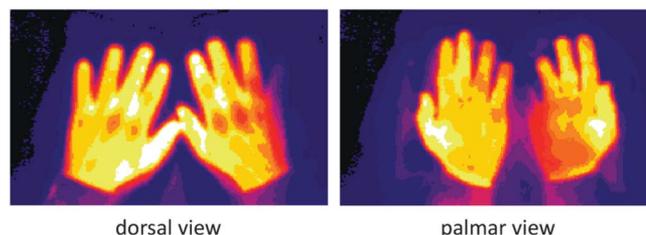
Figure 1. Thermographic picture (left dorsal view, right palmar view) of a 53-year-old male patient after elbow fracture referred to our complex regional pain syndrome (CRPS) outpatient department. He presented with pain and allodynia limited to the fourth and fifth finger, which were bluish and significantly 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.[78] It could turn out in future research that, eg, 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.[115] 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.[88] 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.[64] 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.[24] Although pinprick hyperalgesia is generally regarded as a central phenomenon,[101] it is often driven by peripheral input in acute cases.[33]

Visible and measurable signs of inflammation are edema, skin discoloration, and increased skin temperature in CRPS.[5] 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.[4] Edema is exacerbated through strain.[115] Less well known is that hyperhidrosis and hypohidrosis could be the results of peripheral inflammatory mediators (neuropeptides),[92,93] as are trophic changes such as increased hair or nail growth induced by cytokines.[28] 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.[113] 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[84]; skin blood vessels show endothelial dysfunction[89] probably by downregulation of nitric oxide and upregulation of endothelin-1 (ET-1) leading to cold skin.[27] Endothelial dysfunction is mediated directly[58] or indirectly[97] by proinflammatory cytokines.

4.2. Systemic findings indicating ongoing or past inflammation

A recent review summarizes publications that indicate an inflammatory process in CRPS.[81] In serum samples, the mRNA and the protein profile of proinflammatory and anti-inflammatory cytokines were shifted to an inflammatory phenotype.[103] The most striking difference was the reduction of the anti-inflammatory cytokines such as interleukin-10. The latter is normally produced by CD14$^+$16$^+$ mononuclear cells, which are reduced in CRPS, in particular if cold allodynia is present.[87] Increased levels of the soluble tumor necrosis factor-α (TNF-α) receptors are present in patients with pinprick hyperalgesia.[61] 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.[47] 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.[38] 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.[48] In CRPS, several microRNAs, which control inflammatory processes, are downregulated.[79] 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.[67]

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,[7] calcitonin gene-related peptide (CGRP),[6] and substance P (SP)[91] 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.[41] Endothelin-1 was also increased in CRPS sera.[18]

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.[44] 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-adrenoceptors on a variety of cells, including neurons, and inflammatory and soma cells, induce the release of inflammatory cytokines in preclinical models.[34] Very recently, activating autoantibodies directed against alpha1-adrenoceptors were additionally described.[15] 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 there 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).
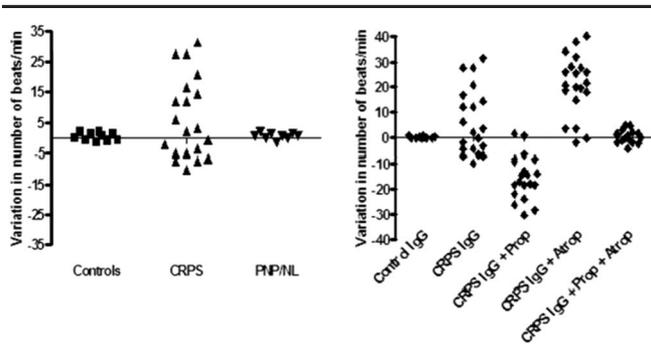
Figure 2. Functional effect of affinity-purified IgG from healthy controls (HC; n = 10), complex regional pain syndrome (CRPS; n = 20), or neuropathy and peripheral nerve lesion (PNP/NL; n = 9) patients on spontaneously beating cardiomyocytes. Left panel: CRPS antibodies induced changes in the beating frequency, whereas control subjects and PNP/NL did not ($P < 0.005$). Right panel: Addition of propranolol or atropine to CRPS IgG shifted 90% of the samples to the negative or positive range. Reprinted with permission.[44]

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 over-production 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 reduced[78] 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 unaltered[102] (**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 learning[85]; interesting research is going on in this field.[68] 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.[48]

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.[5] 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.[16] 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.
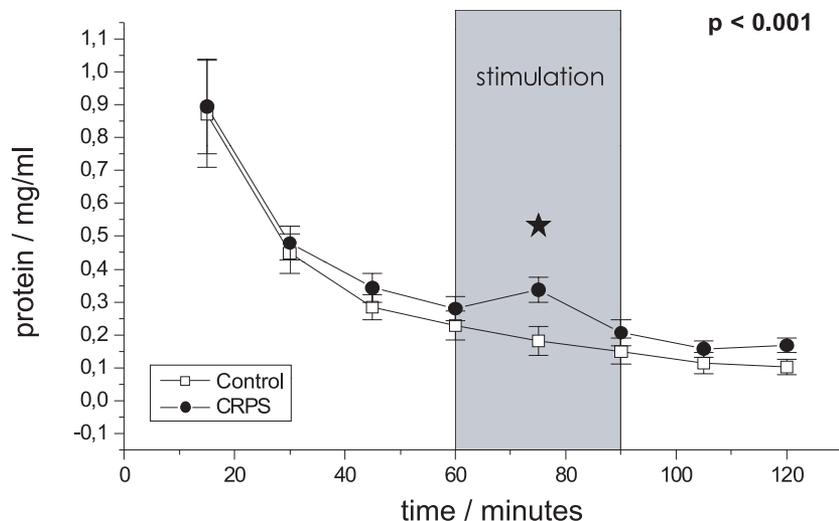
Figure 3. Plasma protein extravasation (PPE) in complex regional pain syndrome (CRPS) patients and healthy controls measured with dermal microdialysis. Electrical stimulation (gray area) induced a significant PPE in patients with CRPS (circles) after 15 minutes when compared with controls ($P < 0.001$). 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.

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,[20] which should not be confused with neglect in neurological disorders. However, some indications for parietal dysfunction exist in subsets of patients with CRPS.[10,45] The perception of body symmetry is distorted in the dark,[86] the ability of hand laterality recognition is impaired,[69] and the affected extremity is often regarded as too large.[82] Reduction of hand size by diminutive lenses reduces pain and edema, whereas enlargement increases pain.[74] 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 also of the healthy extremity if it is held near the usual position of the affected one (crossing of extremities).[72] The underlying patho-physiological changes for these sensory phenomena are not identified in detail but magnet encephalography studies revealed that the representation of the affected extremity in the primary somatosensory cortex is rearranged comparably with a phantom limb pain, and that efficacious pain treatment reverses this reorganization[62] and probably also the perception disturbances.

Many "autonomic" signs of the affected limb are consequences of the peripheral inflammation and its mediators. However, 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 must be a cortical phenomenon.[75] A similar phenomenon is the change in skin temperature differences if the hands are crossed, ie, the affected hand is brought into the peripersonal space of the healthy hand.[71]

5.4. Findings supporting the central origin of the complex regional pain syndrome motor disorder

Much of the movement disorder literature supports tremor, myoclonus, and focal dystonic posturing, mainly of flexor muscles of the fingers or feet/toes, being CNS motor symptoms in CRPS.[76] In addition to pain, motor symptoms may become the leading symptoms in chronic CRPS.[65] In particular, dystonic posturing must not be confused with contractures, which occur as the consequence of inflammation and are peripherally mediated.

There has been ongoing discussion about the presence of a psychogenic component to the movement disorder,[35,109] with good arguments and observations supporting both opinions. However, a peripheral trauma (in particular with a peripheral nerve lesion) together with chronic pain seems sufficient to induce a posttraumatic movement disorder.[112] It is intriguing that the pattern of dystonic posturing is very similar in many cases and patients with dystonia more often share the human leukocyte antigen HLA-DR 13.[110] It is in particular the motor disorder in CRPS that can spread to contralateral or even distant extremities.[111]

The tremor is described as an enhanced physiological tremor[13]; the myoclonic jerks are irregular. Some patients show entrainment of myoclonus, which is, however, regarded as a sign of a psychogenic movement disorder.[53] The most frequently evaluated motor symptoms are fixed dystonia and abnormal posturing. Physiological investigations and pharmacological interventions favor a spinal mechanism.[108] 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,[1] which derives from Golgi tendon organ dysfunction impacting on spinal motor inhibitory interneurons.[76] Supraspinal motor control was investigated by transcranial magnetic stimulation and fMRI. Transcranial magnetic stimulation revealed decreased inhibitory mechanisms and increased excitability in the contralateral[17] but also the ipsilateral primary motor cortex in CRPS.[96] Patients with CRPS have to recruit much more activity of the motor circuits than controls despite bradykinesia and reduced finger-tapping velocity[59] (**Table 3**).

Table 3

Symptoms possibly supporting either peripheral or central CRPS pathophysiology.

History/symptom/finding	Peripheral	Central
Significant trauma, eg, fracture, surgery, heavy sprain	×	
Minor injury, eg, hitting or vaccination		×
Clearly visible significant edema	××	
Warm/red skin	××	
Hyperhidrosis/hypohidrosis	×	
Trophic changes (nails, hairs)	××	
Pain only while moving the joint	×	
Hyperalgesia to heat	××	
Allodynia		××
Glove/stocking-like sensory deficits		××
Contractures	××	
Motor disorder (tremor, myoclonus, fixed dystonia)		××
Neglect-like symptoms		××
Disproportionate feeling of swelling		×
Improvement of function by crossing the limbs/ watching the mirror image of healthy limb		××
Positive 3-phase bone scan/X-ray	××	
Significant treatment response to bisphosphonates, steroids, IvIGs	×	

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.
IvIG, intravenous polyvalent immunoglobulins; ××, means strong indication; ×, weak indication.

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).[9] 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.[52] Reactive oxygen species scavengers reduced symptoms[50] and infusion of free radical donors induced them.[105] Sympathetic blocks, α1 antagonists and α2 agonists, inhibited mechanical allodynia in the CPIP model.[120] 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.[57] Substance P, CGRP, and SP-receptors (NK1-R) are upregulated in the skin, neurons, and endothelial cells.[118] In the spinal cord, the chemokine CCL2 contributes to central sensitization.[21] Blocking inflammation with prednisolone reduced edema and warmth,[30] anti-NGF or anti-interleukin-1 prevented mechanical hyperalgesia behavior,[57] and NK1-receptor antagonists reduced

visible inflammation and mechanical hyperalgesia behavior.[29] In this rodent model, SP induces mast cell proliferation and degranulation.[56] 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.[100] Blocking of the sympathetic nervous system reduced all symptoms, and the beta-2-antagonist butoxamine reduced nociceptive sensitization through reduction of Il-6 production.[55] 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.[98] 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.[43] Further models suggested for CRPS II are the combination of spinal nerve ligation and knee joint immobilization,[80] and the chronic constriction injury model and tissue trauma.[26] 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**).
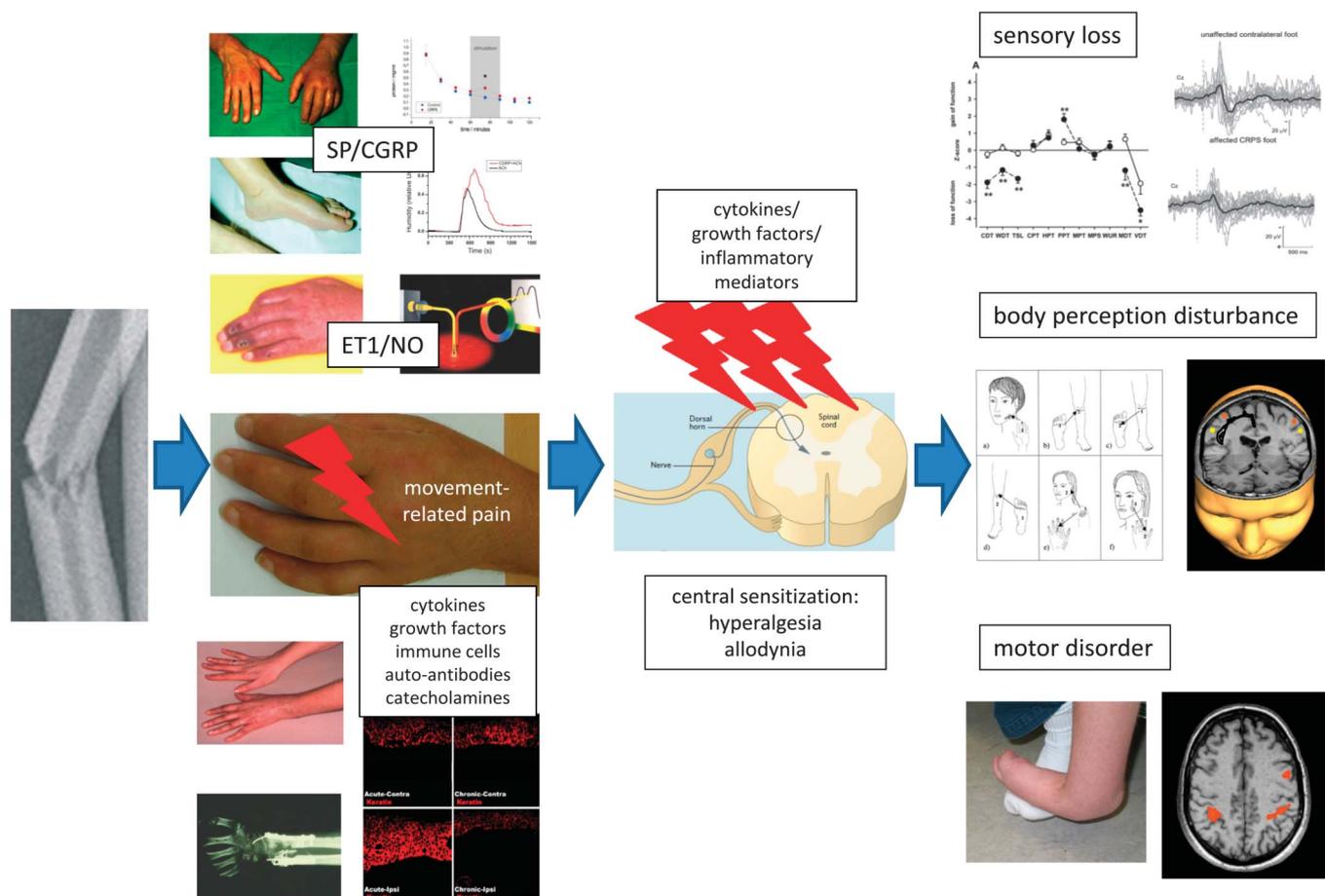
7. Could complex regional pain syndrome phenotypes translate into individual treatment?

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."[77] 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.[77]

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

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.

glucocorticoids that nonselectively reduce inflammation; high doses and longer or repetitive treatment might be necessary.[19] 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.[25] Topical dimethyl sulfoxide (DMSO 50% cream) scavenges free oxygen radicals that occur during inflammation and could best be used as an add-on.[19] 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.[66] 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.[70] Rather new developments in the treatment of "centralized" CRPS are pain-exposure physical therapy (PEPT)[107] and the concept of graded exposures (GEXP).[11] 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.[95] Successful ketamine pain treatment might have a small effect on function as well.[90] 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 particularly when treating CRPS of the lower limbs.[39] 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.[108] The application of spinal cord stimulator and

the implantation of an intrathecal pump for baclofen must be restricted to specialized centers. Otherwise complications are frequent, and we believe that the risk of overlooking a relevant psychosomatic comorbidity in these "treatment-resistant" patients is high by a selection process, like it is in epilepsy, headache, vertigo, or tertiary care movement disorders centers.[94]

Only for completeness, we want to mention that there are no positive trials in CRPS for drugs such as antidepressants, anticonvulsants, pain killers, or opioids, which are otherwise frequently used for treating chronic pain. The same is true for vasodilating agents or sympathectomy.[99]

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 (eg, 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 (eg, predomination of inflammation, central neuroplasticity, autoimmune, psychological) and the selection of appropriate treatments for individual patients.

Conflict of interest statement

Acknowledgements

References

[1] Bank PJ, van Rooijen DE, Marinus J, Reilmann R, van Hilten JJ. Force modulation deficits in complex regional pain syndrome: A potential role for impaired sense of force production. Eur J Pain 2014;18:1013–23.

[2] Beerthuizen A, Stronks DL, Van't Spijker A, Yaksh A, Hanraets BM, Klein J, Huygen FJ. Demographic and medical parameters in the development of complex regional pain syndrome type 1 (CRPS1): prospective study on 596 patients with a fracture. PAIN 2012;153:1187–92.

[3] Birklein F, Drummond PD, Li W, Schlereth T, Albrecht N, Finch PM, Dawson LF, Clark JD, Kingery WS. Activation of cutaneous immune responses in complex regional pain syndrome. J Pain 2014;15:485–95.

[4] Birklein F, Riedl B, Claus D, Neundörfer B. Pattern of autonomic dysfunction in time course of complex regional pain syndrome. Clin Auton Res 1998;8:79–85.

[5] Birklein F, Riedl B, Sieweke N, Weber M, Neundorfer B. Neurological findings in complex regional pain syndromes—analysis of 145 cases. Acta Neurol Scand 2000;101:262–9.

[6] Birklein F, Schmelz M, Schifter S, Weber M. The important role of neuropeptides in complex regional pain syndrome. Neurology 2001;57:2179–84.

[7] Blair SJ, Chinthagada M, Hoppenstehdt D, Kijowski R, Fareed J. Role of neuropeptides in pathogenesis of reflex sympathetic dystrophy. Acta Orthop Belg 1998;64:448–51.

[8] Caty G, Hu L, Legrain V, Plaghki L, Mouraux A. Psychophysical and electrophysiological evidence for nociceptive dysfunction in complex regional pain syndrome. PAIN 2013;154:2521–8.

[9] Coderre TJ, Xanthos DN, Francis L, Bennett GJ. Chronic post-ischemia pain (CPIP): a novel animal model of complex regional pain syndrome-Type I (CRPS-I; reflex sympathetic dystrophy) produced by prolonged hindpaw ischemia and reperfusion in the rat. PAIN 2004;112:94–105.

[10] Cohen H, McCabe C, Harris N, Hall J, Lewis J, Blake DR. Clinical evidence of parietal cortex dysfunction and correlation with extent of allodynia in CRPS type 1. Eur J Pain 2013;17:527–38.

[11] de Jong JR, Vlaeyen JW, Onghena P, Cuypers C, den Hollander M, Ruijgrok J. Reduction of pain-related fear in complex regional pain syndrome type I: the application of graded exposure in vivo. PAIN 2005;116:264–75.

[12] de Rooij AM, Perez RS, Huygen FJ, Eijs FV, Kleef MV, Bauer MC, van Hilten JJ, Marinus J. Spontaneous onset of complex regional pain syndrome. Eur J Pain 2009;14:510–13.

[13] Deuschl G, Blumberg H, Lücking CH. Tremor in reflex sympathetic dystrophy. Arch Neurol 1991;48:1247–53.

[14] Drummond ES, Dawson LF, Finch PM, Bennett GJ, Drummond PD. Increased expression of cutaneous alpha1-adrenoceptors after chronic constriction injury in rats. J Pain 2014;15:188–96.

[15] Dubuis E, Thompson V, Leite MI, Blaes F, Maihofner C, Greensmith D, Vincent A, Shenker N, Kuttikat A, Leuwer M, Goebel A. Longstanding complex regional pain syndrome is associated with activating autoantibodies against alpha-1a adrenoceptors. PAIN 2014;155:2408–17.

[16] Egloff N, Sabbioni ME, Salathe C, Wiest R, Juengling FD. Nondermatomal somatosensory deficits in patients with chronic pain disorder: clinical findings and hypometabolic pattern in FDG-PET. PAIN 2009;145:252–8.

[17] Eisenberg E, Chistyakov AV, Yudashkin M, Kaplan B, Hafner H, Feinsod M. Evidence for cortical hyperexcitability of the affected limb representation area in CRPS: a psychophysical and transcranial magnetic stimulation study. PAIN 2005;113:99–105.

[18] Eisenberg E, Erlich T, Zinder O, Lichinsky S, Diamond E, Pud D, Davar G. Plasma endothelin-1 levels in patients with complex regional pain syndrome. Eur J Pain 2004;8:533–8.

[19] Fischer SG, Zuurmond WW, Birklein F, Loer SA, Perez RS. Anti-inflammatory treatment of Complex Regional Pain Syndrome. PAIN 2010;151:251–6.

[20] Frettloh J, Huppe M, Maier C. Severity and specificity of neglect-like symptoms in patients with complex regional pain syndrome (CRPS) compared to chronic limb pain of other origins. PAIN 2006;124:184–9.

[21] Gallagher JJ, Tajerian M, Guo T, Shi X, Li W, Zheng M, Peltz G, Kingery W, Clark JD. Acute and chronic phases of complex regional pain syndrome in mice are accompanied by distinct transcriptional changes in the spinal cord. Mol Pain 2013;9:40.

[22] Geber C, Magerl W, Fondel R, Fechir M, Rolke R, Vogt T, Treede RD, Birklein F. Numbness in clinical and experimental pain—a cross-sectional study exploring the mechanisms of reduced tactile function. PAIN 2008;139:73–81.

[23] Geha PY, Baliki MN, Harden RN, Bauer WR, Parrish TB, Apkarian AV. The brain in chronic CRPS pain: abnormal gray-white matter interactions in emotional and autonomic regions. Neuron 2008;60:570–81.

[24] Gierthmuhlen J, Maier C, Baron R, Tolle T, Treede RD, Birbaumer N, Huge V, Koroschetz J, Krumova EK, Lauchart M, Maihofner C, Richter H, Westermann A. Sensory signs in complex regional pain syndrome and peripheral nerve injury. PAIN 2012;153:765–74.

[25] Goebel A, Baranowski A, Maurer K, Ghiai A, McCabe C, Ambler G. Intravenous immunoglobulin treatment of the complex regional pain syndrome: a randomized trial. Ann Intern Med 2010;152:152–8.

[26] Gradl G, Gaida S, Finke B, Gierer P, Mittlmeier T, Vollmar B. Exaggeration of tissue trauma induces signs and symptoms of acute CRPS I, however displays distinct differences to experimental CRPS II. Neurosci Lett 2006;402:267–72.

[27] Groeneweg JG, Huygen FJ, Heijmans-Antonissen C, Niehof S, Zijlstra FJ. Increased endothelin-1 and diminished nitric oxide levels in blister fluids of patients with intermediate cold type complex regional pain syndrome type 1. BMC Musculoskelet Disord 2006;7:91.

[28] Grossman RM, Krueger J, Yourish D, Granelli-Piperno A, Murphy DP, May LT, Kupper TS, Sehgal PB, Gottlieb AB. Interleukin 6 is expressed in high levels in psoriatic skin and stimulates proliferation of cultured human keratinocytes. Proc Natl Acad Sci U S A 1989;86:6367–71.

[29] Guo TZ, Offley SC, Boyd EA, Jacobs CR, Kingery WS. Substance P signaling contributes to the vascular and nociceptive abnormalities observed in a tibial fracture rat model of complex regional pain syndrome type I. PAIN 2004;108:95–107.

[30] Guo TZ, Wei T, Kingery WS. Glucocorticoid inhibition of vascular abnormalities in a tibia fracture rat model of complex regional pain syndrome type I. PAIN 2006;121:158–67.

[31] Harden RN, Bruehl S, Perez RS, Birklein F, Marinus J, Maihofner C, Lubenow T, Buvanendran A, Mackey S, Graciosa J, Mogilevski M, Ramsden C, Chont M, Vatine JJ. Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome. PAIN 2010;150:268–74.

[32] Harden RN, Bruehl S, Perez RS, Birklein F, Marinus J, Maihofner C, Lubenow T, Buvanendran A, Mackey S, Graciosa J, Mogilevski M, Ramsden C, Schlereth T, Chont M, Vatine JJ. Development of a severity score for CRPS. PAIN 2010;151:870–6.

[33] Haroutounian S, Nikolajsen L, Bendtsen TF, Finnerup NB, Kristensen AD, Hasselstrom JB, Jensen TS. Primary afferent input critical for maintaining spontaneous pain in peripheral neuropathy. PAIN 2014;155:1272–9.

[34] Hartung JE, Ciszek BP, Nackley AG. β2- and β3-adrenergic receptors drive COMT-dependent pain by increasing production of nitric oxide and cytokines. PAIN 2014;155:1346–55.

[35] Hawley JS, Weiner WJ. Psychogenic dystonia and peripheral trauma. Neurology 2011;77:496–502.

[36] Heijmans-Antonissen C, Wesseldijk F, Munnikes RJ, Huygen FJ, van der MP, Hop WC, Hooijkaas H, Zijlstra FJ. Multiplex bead array assay for detection of 25 soluble cytokines in blister fluid of patients with complex regional pain syndrome type 1. Mediators Inflamm 2006;2006:28398.

[37] Hou Q, Barr T, Gee L, Vickers J, Wymer J, Borsani E, Rodella L, Getsios S, Burdo T, Eisenberg E, Guha U, Lavker R, Kessler J, Chittur S, Fiorino D, Rice F, Albrecht P. Keratinocyte expression of calcitonin gene-related peptide β: implications for neuropathic and inflammatory pain mechanisms. PAIN 2011;152:2036–51.

[38] Jin EH, Zhang E, Ko Y, Sim WS, Moon DE, Yoon KJ, Hong JH, Lee WH. Genome-wide expression profiling of complex regional pain syndrome. PLoS ONE 2013;8:e79435.

[39] Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FA, van Kleef M. Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: five-year final follow-up of patients in a randomized controlled trial. J Neurosurg 2008;108:292–8.

[40] Kharkar S, Venkatesh YS, Grothusen JR, Rojas L, Schwartzman RJ. Skin biopsy in complex regional pain syndrome: case series and literature review. Pain Physician 2012;15:255–66.

[41] Khodorova A, Montmayeur JP, Strichartz G. Endothelin receptors and pain. J Pain 2009;10:4–28.

[42] Klega A, Eberle T, Buchholz HG, Maus S, Maihofner C, Schreckenberger M, Birklein F. Central opioidergic neurotransmission in complex regional pain syndrome. Neurology 2010;75:129–36.

[43] Klein MM, Lee JW, Siegel SM, Downs HM, Oaklander AL. Endoneurial pathology of the needlestick-nerve-injury model of Complex Regional Pain Syndrome, including rats with and without pain behaviors. Eur J Pain 2012;16:28–37.

[44] Kohr D, Singh P, Tschernatsch M, Kaps M, Pouokam E, Diener M, Kummer W, Birklein F, Vincent A, Goebel A, Wallukat G, Blaes F. Autoimmunity against the β2 adrenergic receptor and muscarinic-2 receptor in complex regional pain syndrome. PAIN 2011;152:2690–700.

[45] Kolb L, Lang C, Seifert F, Maihofner C. Cognitive correlates of "neglect-like syndrome" in patients with complex regional pain syndrome. PAIN 2012;153:1063–73.

[46] Kramer HH, Eberle T, Uceyler N, Wagner I, Klonschinsky T, Muller LP, Sommer C, Birklein F. TNF-α in CRPS and 'normal' trauma—significant differences between tissue and serum. PAIN 2011;152:285–90.

[47] Kramer HH, Hofbauer LC, Szalay G, Breimhorst M, Eberle T, Zieschang K, Rauner M, Schlereth T, Schreckenberger M, Birklein F. Osteoprotegerin: a new biomarker for impaired bone metabolism in complex regional pain syndrome? PAIN 2014;155:889–95.

[48] Kress M, Huttenhofer A, Landry M, Kuner R, Favereaux A, Greenberg D, Bednarik J, Heppenstall P, Kronenberg F, Malcangio M, Rittner H, Uceyler N, Trajanoski Z, Mouritzen P, Birklein F, Sommer C, Soreq H. microRNAs in nociceptive circuits as predictors of future clinical applications. Front Mol Neurosci 2013;6:33.

[49] Krumova EK, Frettloh J, Klauenberg S, Richter H, Wasner G, Maier C. Long-term skin temperature measurements—a practical diagnostic tool in complex regional pain syndrome. PAIN 2008;140:8–22.

[50] Kwak KH, Han CG, Lee SH, Jeon Y, Park SS, Kim SO, Baek WY, Hong JG, Lim DG. Reactive oxygen species in rats with chronic post-ischemia pain. Acta Anaesthesiol Scand 2009;53:648–56.

[51] Laethem T, De Lepeleire I, McCrea J, Zhang J, Majumdar A, Musson D, Rogers D, Li S, Guillaume M, Parneix-Spake A, Deutsch P. Tissue penetration by ertapenem, a parenteral carbapenem administered once daily, in suction-induced skin blister fluid in healthy young volunteers. Antimicrob Agents Chemother 2003;47:1439–42.

[52] Laferriere A, Abaji R, Tsai CY, Ragavendran JV, Coderre TJ. Topical combinations to treat microvascular dysfunction of chronic postischemia pain. Anesth Analg 2014;118:830–40.

[53] Lang AE, Angel M, Bhatia K, Chen R, Fahn S, Hallett M, Schrag A, Thompson P. Myoclonus in complex regional pain syndrome. Mov Disord 2008;24:314–6.

[54] Lenz M, Uceyler N, Frettloh J, Hoffken O, Krumova EK, Lissek S, Reinersmann A, Sommer C, Stude P, Waaga-Gasser AM, Tegenthoff M, Maier C. Local cytokine changes in complex regional pain syndrome type I (CRPS I) resolve after 6 months. PAIN 2013;154:2142–9.

[55] Li W, Shi X, Wang L, Guo T, Wei T, Cheng K, Rice KC, Kingery WS, Clark JD. Epidermal adrenergic signaling contributes to inflammation and pain sensitization in a rat model of complex regional pain syndrome. PAIN 2013;154:1224–36.

[56] Li WW, Guo T-Z, Liang DY, Sun Y, Kingery WS, Clark DJ. Substance P signaling controls mast cell activation, degranulation, and nociceptive sensitization in a rat fracture model of complex regional pain syndrome. Anesthesiology 2012;116:882–95.

[57] Li WW, Sabsovich I, Guo TZ, Zhao R, Kingery WS, Clark JD. The role of enhanced cutaneous IL-1beta signaling in a rat tibia fracture model of complex regional pain syndrome. PAIN 2009;144:303–13.

[58] Lorenz M, Wilck N, Meiners S, Ludwig A, Baumann G, Stangl K, Stangl V. Proteasome inhibition prevents experimentally-induced endothelial dysfunction. Life Sci 2009;84:929–34.

[59] Maihofner C, Baron R, Decol R, Binder A, Birklein F, Deuschl G, Handwerker HO, Schattschneider J. The motor system shows adaptive changes in complex regional pain syndrome. Brain 2007;130:2671–87.

[60] Maihofner C, Forster C, Birklein F, Neundorfer B, Handwerker HO. Brain processing during mechanical hyperalgesia in complex regional pain syndrome: a functional MRI study. PAIN 2005;114:93–103.

[61] Maihofner C, Handwerker HO, Neundorfer B, Birklein F. Mechanical hyperalgesia in complex-regional pain syndrome: A role for tnf-alpha? Neurology 2005;65:311–3.

[62] Maihöfner C, Handwerker HO, Neundorfer B, Birklein F. Cortical reorganization during recovery from complex regional pain syndrome. Neurology 2004;63:693–701.

[63] Mailis-Gagnon A, Giannoylis I, Downar J, Kwan CL, Mikulis DJ, Crawley AP, Nicholson K, Davis KD. Altered central somatosensory processing in chronic pain patients with "hysterical" anesthesia. Neurology 2003;60:1501–7.

[64] Mainka T, Bischoff FS, Baron R, Krumova EK, Nicolas V, Pennekamp W, Treede RD, Vollert J, Westermann A, Maier C. Comparison of muscle and joint pressure-pain thresholds in patients with complex regional pain syndrome and upper limb pain of other origin. PAIN 2014;155:591–7.

[65] Marinus J, Moseley GL, Birklein F, Baron R, Maihofner C, Kingery WS, van Hilten JJ. Clinical features and pathophysiology of complex regional pain syndrome. Lancet Neurol 2011;10:637–48.

[66] McCabe CS, Haigh RC, Ring EF, Halligan PW, Wall PD, Blake DR. A controlled pilot study of the utility of mirror visual feedback in the treatment of complex regional pain syndrome (type 1). Rheumatology (Oxford) 2003;42:97–101.

[67] McDonald MK, Tian Y, Qureshi RA, Gormley M, Ertel A, Gao R, Aradillas Lopez E, Alexander GM, Sacan A, Fortina P, Ajit SK. Functional significance of macrophage-derived exosomes in inflammation and pain. PAIN 2014;155:1527–39.

[68] Meulders A, Harvie DS, Bowering JK, Caragianis S, Vlaeyen JW, Moseley GL. Contingency learning deficits and generalization in chronic unilateral hand pain patients. J Pain 2014;15:1046–56.

[69] Moseley GL. Why do people with complex regional pain syndrome take longer to recognize their affected hand? Neurology 2004;62:2182–6.

[70] Moseley GL. Graded motor imagery for pathologic pain: a randomized controlled trial. Neurology 2006;67:2129–34.

[71] Moseley GL, Gallace A, Iannetti GD. Spatially defined modulation of skin temperature and hand ownership of both hands in patients with unilateral complex regional pain syndrome. Brain 2012;135:3676–86.

[72] Moseley GL, Gallace A, Spence C. Space-based, but not arm-based, shift in tactile processing in complex regional pain syndrome and its relationship to cooling of the affected limb. Brain 2009;132:3142–51.

[73] Moseley GL, Herbert RD, Parsons T, Lucas S, Van Hilten JJ, Marinus J. Intense pain soon after wrist fracture strongly predicts who will develop

complex regional pain syndrome: prospective cohort study. J Pain 2014;15:16–23.

[74] Moseley GL, Parsons TJ, Spence C. Visual distortion of a limb modulates the pain and swelling evoked by movement. Curr Biol 2008;18:R1047–8.

[75] Moseley GL, Zalucki N, Birklein F, Marinus J, van Hilten JJ, Luomajoki H. Thinking about movement hurts: the effect of motor imagery on pain and swelling in people with chronic arm pain. Arthritis Rheum 2008;59:623–31.

[76] Munts AG, Mugge W, Meurs TS, Schouten AC, Marinus J, Moseley GL, van der Helm FC, van Hilten JJ. Fixed dystonia in complex regional pain syndrome: a descriptive and computational modeling approach. BMC Neurol 2011;11:53.

[77] O'Connell NE, Wand BM, McAuley J, Marston L, Moseley GL. Interventions for treating pain and disability in adults with complex regional pain syndrome. Cochrane Database Syst Rev 2013;4:CD009416.

[78] Oaklander AL, Rissmiller JG, Gelman LB, Zheng L, Chang Y, Gott R. Evidence of focal small-fiber axonal degeneration in complex regional pain syndrome-I (reflex sympathetic dystrophy). PAIN 2006;120:235–43.

[79] Orlova IA, Alexander GM, Qureshi RA, Sacan A, Graziano A, Barrett JE, Schwartzman RJ, Ajit SK. MicroRNA modulation in complex regional pain syndrome. J Transl Med 2011;9:195.

[80] Ota H, Arai T, Iwatsuki K, Urano H, Kurahashi T, Kato S, Yamamoto M, Hirata H. Pathological mechanism of musculoskeletal manifestations associated with CRPS type II: an animal study. PAIN 2014;155:1976–85.

[81] Parkitny L, McAuley JH, Di Pietro F, Stanton TR, O'Connell NE, Marinus J, van Hilten JJ, Moseley GL. Inflammation in complex regional pain syndrome: a systematic review and meta-analysis. Neurology 2013;80:106–17.

[82] Peltz E, Seifert F, Lanz S, Muller R, Maihofner C. Impaired hand size estimation in CRPS. J Pain 2011;12:1095–101.

[83] Pepper A, Li W, Kingery WS, Angst MS, Curtin CM, Clark JD. Changes resembling complex regional pain syndrome following surgery and immobilization. J Pain 2013;14:516–24.

[84] Postlethwaite AE, Lachman LB, Kang AH. Induction of fibroblast proliferation by interleukin-1 derived from human monocytic leukemia cells. Arthritis Rheum 1984;27:995–1001.

[85] Punt TD, Cooper L, Hey M, Johnson MI. Neglect-like symptoms in complex regional pain syndrome: Learned nonuse by another name? PAIN 2013;154:200–3.

[86] Reinersmann A, Landwehrt J, Krumova EK, Ocklenburg S, Gunturkun O, Maier C. Impaired spatial body representation in complex regional pain syndrome type 1 (CRPS I). PAIN 2012;153:2174–81.

[87] Ritz BW, Alexander GM, Nogusa S, Perreault MJ, Peterlin BL, Grothusen JR, Schwartzman RJ. Elevated blood levels of inflammatory monocytes (CD14+ CD16+) in patients with complex regional pain syndrome. Clin Exp Immunol 2011;164:108–17.

[88] Schaible HG, Ebersberger A, von Banchet GS. Mechanisms of pain in arthritis. Ann N Y Acad Sci 2002;966:343–54.

[89] Schattschneider J, Hartung K, Stengel M, Ludwig J, Binder A, Wasner G, Baron R. Endothelial dysfunction in cold type complex regional pain syndrome. Neurology 2006;67:673–5.

[90] Schilder JC, Sigtermans MJ, Schouten AC, Putter H, Dahan A, Noldus LP, Marinus J, van Hilten JJ. Pain relief is associated with improvement in motor function in complex regional pain syndrome type 1: secondary analysis of a placebo-controlled study on the effects of ketamine. J Pain 2013;14:1514–21.

[91] Schinkel C, Scherens A, Koller M, Roellecke G, Muhr G, Maier C. Systemic inflammatory mediators in post-traumatic complex regional pain syndrome (CRPS I)—longitudinal investigations and differences to control groups. Eur J Med Res 2009;14:130–5.

[92] Schlereth T, Breimhorst M, Werner N, Pottschmidt K, Drummond PD, Birklein F. Inhibition of neuropeptide degradation suppresses sweating but increases the area of the axon reflex flare. Exp Dermatol 2013;22:299–301.

[93] Schlereth T, Dittmar JO, Seewald B, Birklein F. Peripheral amplification of sweating—a role for calcitonin gene-related peptide. J Physiol 2006;576:823–32.

[94] Schrag A, Trimble M, Quinn N, Bhatia K. The syndrome of fixed dystonia: an evaluation of 103 patients. Brain 2004;127:2360–72.

[95] Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: A double-blind placebo controlled study. PAIN 2009;147:107–15.

[96] Schwenkreis P, Janssen F, Rommel O, Pleger B, Volker B, Hosbach I, Dertwinkel R, Maier C, Tegenthoff M. Bilateral motor cortex disinhibition in complex regional pain syndrome (CRPS) type I of the hand. Neurology 2003;61:515–9.

[97] Sen A, Most P, Peppel K. Induction of microRNA-138 by pro-inflammatory cytokines causes endothelial cell dysfunction. FEBS Lett 2014;588:906–14.

[98] Siegel SM, Lee JW, Oaklander AL. Needlestick distal nerve injury in rats models symptoms of complex regional pain syndrome. Anesth Analg 2007;105:1820–9.

[99] Stanton TR, Wand BM, Carr DB, Birklein F, Wasner GL, O'Connell NE. Local anaesthetic sympathetic blockade for complex regional pain syndrome. Cochrane Database Syst Rev 2013;8:CD004598.

[100] Tajerian M, Leu D, Zou Y, Sahbaie P, Li W, Khan H, Hsu V, Kingery W, Huang TT, Becerra L, Clark JD. Brain neuroplastic changes accompany anxiety and memory deficits in a model of complex regional pain syndrome. Anesthesiology 2014;121:852–65.

[101] Terkelsen AJ, Gierthmuhlen J, Finnerup NB, Hojlund AP, Jensen TS. Bilateral hypersensitivity to capsaicin, thermal, and mechanical stimuli in unilateral complex regional pain syndrome. Anesthesiology 2014;120:1225–36.

[102] Terkelsen AJ, Gierthmuhlen J, Petersen LJ, Knudsen L, Christensen NJ, Kehr J, Yoshitake T, Madsen CS, Wasner G, Baron R, Jensen TS. Cutaneous noradrenaline measured by microdialysis in complex regional pain syndrome during whole-body cooling and heating. Exp Neurol 2013;247:456–65.

[103] Uceyler N, Eberle T, Rolke R, Birklein F, Sommer C. Differential expression patterns of cytokines in complex regional pain syndrome. PAIN 2007;132:195–205.

[104] Uceyler N, Zeller D, Kahn AK, Kewenig S, Kittel-Schneider S, Schmid A, Casanova-Molla J, Reiners K, Sommer C. Small fibre pathology in patients with fibromyalgia syndrome. Brain 2013;136:1857–67.

[105] van der Laan L, Kapitein P, Verhofstad A, Hendriks T, Goris RJ. Clinical signs and symptoms of acute reflex sympathetic dystrophy in one hindlimb of the rat, induced by infusion of a free-radical donor. Acta Orthop Belg 1998;64:210–7.

[106] van Bussel CM, Stronks DL, Huygen FJ. Complex regional pain syndrome type I of the knee: a systematic literature review. Eur J Pain 2014;18:766–73.

[107] van de Meent H, Oerlemans M, Bruggeman A, Klomp F, van Dongen R, Oostendorp R, Frolke JP. Safety of "pain exposure" physical therapy in patients with complex regional pain syndrome type 1. PAIN 2011;152:1431–8.

[108] van Hilten BJ, van de Beek WJ, Hoff JI, Voormolen JH, Delhaas EM. Intrathecal baclofen for the treatment of dystonia in patients with reflex sympathetic dystrophy. N Engl J Med 2000;343:625–30.

[109] van Hilten JJ. Movement disorders in complex regional pain syndrome. Pain Med 2010;11:1274–7.

[110] van Hilten JJ, van de Beek WJ, Roep BO. Multifocal or generalized tonic dystonia of complex regional pain syndrome: a distinct clinical entity associated with HLA-DR13. Ann Neurol 2000;48:113–6.

[111] van Rijn MA, Marinus J, Putter H, Bosselaar SR, Moseley GL, van Hilten JJ. Spreading of complex regional pain syndrome: not a random process. J Neural Transm 2011;118:1301–9.

[112] van Rooijen DE, Geraedts EJ, Marinus J, Jankovic J, van Hilten JJ. Peripheral trauma and movement disorders: a systematic review of reported cases. J Neurol Neurosurg Psychiatry 2011;82:892–8.

[113] van Rooijen DE, Marinus J, Schouten AC, Noldus LP, van Hilten JJ. Muscle hyperalgesia correlates with motor function in complex regional pain syndrome type 1. J Pain 2013;14:446–54.

[114] van Rooijen DE, Marinus J, van Hilten JJ. Muscle hyperalgesia is widespread in patients with complex regional pain syndrome. PAIN 2013;154:2745–9.

[115] Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. Lancet 1993;342:1012–6.

[116] Verdugo RJ, Bell LA, Campero M, Salvat F, Tripplett B, Sonnad J, Ochoa JL. Spectrum of cutaneous hyperalgesias/allodynias in neuropathic pain patients. Acta Neurol Scand 2004;110:368–76.

[117] Weber M, Birklein F, Neundorfer B, Schmelz M. Facilitated neurogenic inflammation in complex regional pain syndrome. PAIN 2001;91:251–7.

[118] Wei T, Li WW, Guo TZ, Zhao R, Wang L, Clark DJ, Oaklander AL, Schmelz M, Kingery WS. Post-junctional facilitation of Substance P signaling in a tibia fracture rat model of complex regional pain syndrome type I. PAIN 2009;144:278–86.

[119] Wuppenhorst N, Maier C, Frettloh J, Pennekamp W, Nicolas V. Sensitivity and specificity of 3-phase bone scintigraphy in the diagnosis of complex regional pain syndrome of the upper extremity. Clin J Pain 2010;26:182–9.

[120] Xanthos DN, Bennett GJ, Coderre TJ. Norepinephrine-induced nociception and vasoconstrictor hypersensitivity in rats with chronic post-ischemia pain. PAIN 2008;137:640–51.

[121] Zollinger PE, Tuinebreijer WE, Kreis RW, Breederveld RS. Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomised trial. Lancet 1999;354:2025–8.