Complex regional pain syndrome (CRPS) presents with clinical symptoms that can no longer be explained by the initial trauma, including pain, sensory, motor, and trophic symptoms, and impairment of autonomic control of the limb. These symptoms spread distally and go beyond single nerve innervation territories. Typically, the symptoms change through the course of CRPS as a result of the varying pathophysiology. Diagnosis is made clinically after the rigorous elimination of other possible causes, and 3-phase bone scintigraphy can be a useful tool for confirming CRPS.

In acute stages, inflammatory symptoms prevail and should be treated with anti-inflammatory agents (steroids), bisphosphonates, or topical application of dimethyl sulfoxide. In chronic stages, many symptoms are related to so-called central neuroplasticity; these include hyperalgesia, sensory loss, motor symptoms, body perception disturbance, autonomic symptoms, and learned incorrect behavior such as nonuse. At this stage, the only medical treatment that is effective against pain without improving the function is ketamine infusions, but this has side effects. Physical therapy, graded motor imagery, and pain exposure/graded exposure in vivo therapy can help to overcome central reorganization. If a relevant mental comorbidity is present, the patient should be referred for psychotherapeutic treatment. Invasive treatment should be restricted to special cases and only offered after psychosomatic assessment. If these recommendations are followed, CRPS prognosis is not as poor as commonly assumed. Whether the patients can return to their previous life depends on particular individual factors.
spontaneous CRPS; however, that is rare and requires a comprehensive differential diagnostic workup, particularly for rheumatic, inflammatory, or neuropathic diseases.

CRPS can be differentiated by the absence (CRPS I) and presence (CRPS II) of evident nerve lesions, or by skin temperature at onset (often only retrospectively); 70% present with warm CRPS and 30% with cold CRPS, the latter having a worse prognosis. The diagnostic criteria for CRPS. The criteria do not reflect that symptoms occur distally, affect the extremities, and do not correspond to a 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.

The following noninvasive examinations can improve the reliability of the diagnosis. Skin temperature should be measured at several different times and different ambient temperatures. Dynamic temperature differences (affected vs unaffected side) of >1°C are significant. The dynamics of the temperature difference arise from the pathology on the affected side but also from the normal thermoregulatory regulation of the healthy side. We also quantify the edema using a water bath and record sweating differences.

MRI is helpful for eliminating differential diagnoses but not for diagnosing CRPS. Plain X-rays show patchy osteoporosis, but this is insensitive (<30%). X-ray is only useful if both hands are on one radiogram. Probably the most helpful diagnostic tool is the quantitative region of interest analysis of 3-phase bone scans. A typical finding is increased (ipsilateral >1.32 contralateral) radiotracer uptake in the mineralization phase in joints that are not affected by the initial trauma. Such a finding strongly supports the diagnosis; an equivocal indication does not exclude CRPS. In cases where an expert appraisal is expected to be requested, we recommend performing a scintigram. Quantitative sensory testing is not suitable for making a diagnosis, but pressure pain over the bones and joints supports CRPS.

Although its validation has not been published, the CRPS Severity Score can assist in monitoring the disease course and communication between...
medical practitioners. The score correlates well with clinical symptoms, with small values indicating that the diagnosis should possibly be reappraised (table).

### CLINICAL SYMPTOMS OF CRPS
Clinical symptoms include pain, sensitivity loss, motor symptoms, autonomic symptoms, and trophic changes of the affected extremities.

**Pain and sensitivity.** CRPS pain is most often deep in the limb. Frequently, it is exacerbated through movement, temperature changes, contact, or stress. Additionally, allodynia (painful touch) or mechanical hyperalgesia are often present. There are also sensory deficits in a glove- or stocking-type pattern (objectified by laser-evoked potentials) or disturbances in body perception like a feeling of foreignness or oversize of the affected extremity.

**Motor disorders.** All patients have pain-related functional reduction in their muscle strength. In acute stages, movement is limited by edema and pain, and in the chronic stage by fibrotic contractures or central motor symptoms. Central motor symptoms include tremors, irregular myoclonus, and fixed dystonia-like postures. Some of these motor disorders can be traced to central reorganization processes (see below) and can spread to contralateral or distant extremities.

**Autonomic symptoms.** The edema is regarded as an autonomic symptom although it results from inflammation (see below). It is exacerbated through strain. In 50% of cases and relatively specific to CRPS, hyperhidrosis is obvious. All patients report a change in skin color (reddish or bluish) and the skin temperature is laterally different.

**Trophic changes.** Trophic changes affect the connective tissue. Hair growth increases, and growth of nails can increase or decrease. At very early stages, contraction and fibrosis of joints and fascia occur, and in chronic CRPS, atrophy of the skin is apparent.

### PATHOPHYSIOLOGY OF CRPS
The pathophysiology of CRPS is as diverse as in many other clinically defined pain-related illnesses (e.g., lower back pain), and it may change during the course. Processes influence each other and contribute to varied clinical symptoms.

#### Is there a (genetic) predisposition to CRPS?
This question cannot be answered conclusively. One difficulty lies in the fact that to demonstrate a hereditary factor, family members must have had an injury causing CRPS, CRPS must then be correctly diagnosed, and this diagnosis must be known. Because there is remission of CRPS in many patients, this is often not straightforward. However, there are some clues suggesting hereditary components. We treat “CRPS families,” as do other groups, and there are reports of CRPS occurring in identical twins (Dr. Stanton-Hicks, personal communication, 2002). In patients with fixed dystonia, links to the human leukocyte antigen (HLA)–DR 13 have been found, and in CRPS cases without motor symptoms, to HLA-DR 15 and DQ1, possibly predisposing them to autoimmune diseases. There is also a marked association between migraine and CRPS.

#### Posttraumatic inflammation in acute CRPS
The beginning of CRPS represents “excessive posttraumatic inflammation.” Visible signs are reddening, edema, and temperature increase, accompanied by pain of movement and hyperalgesia, which is caused by nociceptor sensitization. Further CRPS symptoms that could be explained by inflammation are the proliferation of connective tissue, which leads to contractures (e.g., of the palmar aponeurosis and of the joints), high-turnover osteoporosis with activation of osteoblasts and osteoclasts, increased hair growth, and hyperhidrosis.

### Table: Complex regional pain syndrome severity score

<table>
<thead>
<tr>
<th>Symptoms (reported)</th>
<th>Signs observed</th>
<th>Score (maximum 17 points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allodynia, hyperpathia</td>
<td>Hyperpathia to pinprick</td>
<td></td>
</tr>
<tr>
<td>Temperature asymmetry</td>
<td>Allodynia</td>
<td></td>
</tr>
<tr>
<td>Skin color asymmetry</td>
<td>Temperature asymmetry by palpation</td>
<td></td>
</tr>
<tr>
<td>Sweating asymmetry</td>
<td>Skin color asymmetry</td>
<td></td>
</tr>
<tr>
<td>Asymmetric edema</td>
<td>Sweating asymmetry</td>
<td></td>
</tr>
<tr>
<td>Trophic changes</td>
<td>Asymmetric edema</td>
<td></td>
</tr>
<tr>
<td>Motor changes</td>
<td>Trophic changes</td>
<td></td>
</tr>
<tr>
<td>Decreased active range of motion</td>
<td>Motor changes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased active range of motion</td>
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</table>

The score is validated as a measure for complex regional pain syndrome (CRPS) severity. If there are questions of the symptom category being related to, e.g., those last week, the CRPS severity score might also be useful for documenting the course of CRPS. A study is currently ongoing to address this.
In patients’ serum and CSF samples, increased levels of proinflammatory cytokines (tumor necrosis factor [TNF]-α receptors; interleukin [IL]–6, IL-12) and decreased levels of anti-inflammatory cytokine RNA were found. These changes do not affect all CRPS patients, rather a subset of them. Cytokines cause pain and hyperalgesia through the sensitization of nociceptors. Neuropeptides are responsible for the visible symptoms of inflammation, and are abundantly released as a result of the facilitated stimulation of these sensitized nociceptors. In the serum of CRPS patients, bradykinin, calcitonin gene-related peptide (CGRP), and substance P (SP) were found to be increased.

CRPS typically occurs on one side. Therefore, a direct examination of the affected tissue is mandatory. In skin biopsies from patients with CRPS for <6 months, we found high levels of TNF-α. Using suction blisters, a significant proportion of CRPS patients had increased concentrations of inflammatory cytokines, peptides, and tryptase—either isolated to the affected side, or on both sides, the latter possibly due to a long suction period. Recently, we could demonstrate an overproduction of cytokines in keratinocytes, a proliferation of these keratinocytes, and an increased number of mast cells in the affected skin in acute CRPS. In chronic CRPS, the findings were the opposite. Cytokines normalize over the course, indicating a change in the pathophysiology.

The (neuro)peptides are more difficult to quantify. Indirect measurements (flare as a surrogate for CGRP and plasma extravasation for SP release) show that C-fibers abundantly release peptides on the affected side. The released peptides have increased biological activity, which might be caused by ineffective inactivation. In patients characterized by cold extremities, higher levels of the vasoconstricting endothelin-1 are found.

**Neuronal plasticity of the CNS in chronic CRPS.** If CRPS is not successfully treated during the first 3–6 months and persists or worsens, symptoms occur that can no longer be explained by a peripheral pathophysiology. The time interval until this happens is variable, in extreme cases right from the beginning. In part, these symptoms can be traced back to a learning process. For example, if pain is regularly exacerbated by movement, it will be performed less and less, reinforced through the reward of pain avoidance. The results are disastrous (e.g., contractures). Especially in children, pain avoidance is very prevalent. Other symptoms are reflexive. Pain as the unavoidable result of movement inhibits motor function, impairs proprioception, and restricts physiologic movement; everyone with a joint injury will have observed the same. The result is a pathologic movement pattern that reinforces musculoskeletal pain through improper weight-bearing. However, as a function of time in pain, many symptoms result from a reorganization of the brain. Patients must concentrate on the affected extremity in order to use it, so that perception of body symmetry shifts to the affected side. The visual perception of the affected extremity is of being too large and somatosensory perception of the affected arm is delayed. This is also valid if the healthy arm is held in the usual position of the affected one (crossing of extremities).

Through magnetoencephalography and MRI, it has been demonstrated that the representation of the affected extremity in the primary somatosensory cortex is altered and that pain reduction reverses it. Patients with allodynia have stronger activation of the gyrus cinguli, and those with motor deficits, of the parietal lobe. In chronic cases, a reduction in gray matter is observed in the right insular cortex, the nucleus accumbens, and the ventromedial prefrontal cortex—regions important for stress processing.

**What is the role of the sympathetic nervous system?** Autonomic symptoms in CRPS are undisputed, but there are doubts concerning the construct of sympathetically maintained pain. These doubts arise from the lack of convincing evidence that blocking the sympathetic nervous system (SNS) is effective. Presumably hyperactivity in the SNS such as sweating and skin color/temperature asymmetry in the acute phase can now be explained by (neuro-)peptides. Case reports even describe inhibited sympathetic activity, which further questions the rationale to therapeutically block an inhibited SNS. The role of the SNS in chronic CRPS is more interesting. If an inhibition of the SNS is present, adrenoceptors, e.g., on blood vessels, could become supersensitive, which might then contribute to cold extremities. There is also enough evidence pointing to a central disturbance of the SNS. If a patient even thinks of a movement that could be painful, the SNS will be activated. The same happens if the hands are crossed, i.e., the affected hand is brought into the space of the healthy hand. One finding that links inflammation and the SNS is the discovery of agonistic autoantibodies on β2-adrenergic receptors and m2-acetylcholine receptors. These autoimmune findings are of particular interest because of the HLA association of CRPS. However, the relevance of these autoantibodies remains to be assessed.

**Psychosocial factors in CRPS.** It has been confirmed in multiple studies that common psychological factors such as anxiety, depression, and personality are not predictors for the development of CRPS. The many objective findings also preclude that CRPS is a
psychosomatic illness. It is nevertheless naïve to assume that CRPS, in contrast to all other chronic pain conditions, is not influenced by psychosocial factors, especially the treatment response and the persistence of symptoms.\(^4\) Our own results (submitted but not yet published) suggest that, analogously to fibromyalgia,\(^44\) traumatic life events (abuse and violence) and depersonalization phenomena are more frequent in CRPS patients compared to limb pain controls. In the case of fixed dystonia, especially when the CRPS diagnosis is unclear, a somatoform cause is expected in 35% of cases.\(^45\)

Searching PubMed for the keywords “CRPS” and “compensation claim” or “litigation” yields no prospective studies. The only hit is one retrospective chart review reporting 17% of CRPS patients involved in lawsuits and 54% in workers compensation claims.\(^46\) In our clinic, it is striking that many patients who display few objective signs but still report intense pain are involved in injury benefit claims. This is not specific to CRPS and is also valid for other pain disorders, but the expected compensation can make a treatment that requires active participation intolerable. However, these observations are likely biased. A controlled study is needed.

**The special case of multilimb CRPS.** In rare, longstanding, and treatment-resistant cases, CRPS could spread to distant, e.g., mirror, limbs.\(^47\) This spread seems to be more frequent in CRPS patients with predominant dystonic symptoms. The pathophysiology is unclear. Cerebral disinhibition,\(^48\) spinal nociceptive sensitization, e.g., by glutamate, reduced GABAergic inhibition (in case of dystonia), or spinal microglial activation is suggested. Histologic changes have been objectified postmortem in the spinal cord of one patient.\(^49\) Beyond “organic” reasons, psychogenic or even artifact disorders were also discussed in these CRPS cases.\(^50\) For all these assumptions, there are supporting but also refuting arguments; a scientific assessment is needed.

**RATIONAL THERAPIES** Fundamental considerations.

Major multicenter randomized controlled trials are lacking and the primary outcome parameters (pain, clinical symptoms, or function) are diverse. A further problem is the variable pathophysiology, which makes a “one fits all” approach impossible. This complicates meta-analyses or guidelines. There is consensus that early therapeutic intervention is desirable, such that the transition to chronic CRPS is prevented. We personally follow the principle “better treat one too many than one too few.” This does not refer to the frequency of diagnosis: we have strived to improve surgeons’ awareness of CRPS in our region, but as a “side effect,” about 50% of the patients with limb pain referred to us do not fulfill the diagnostic criteria. Nevertheless, these patients also benefit from mild pharmacologic and physiotherapeutic interventions.

**Nonmedical treatment options.** Physical and occupational therapy is essential.\(^51\) Patients should be expressly encouraged to use the affected extremities, even if this is associated with a transient increase in pain and exacerbation of visible symptoms, which does not indicate deterioration.\(^52\) The widely held opinion that CRPS patients should avoid pain in order to prevent deterioration is deleterious. However, painful external interventions by therapists, “insensitive” doctors, or unjustified invasive treatment going against the will of the patient should be avoided. Such trauma will reinforce anxiety and passive coping, and can lead to further functional impairment.

The following physiotherapeutic treatments with behavioral therapy components are suitable:

**Mirror therapy.** The therapeutic process is based on the mirror image of the healthy extremity being seen in place of the affected extremity and as a result the functional impairment will be ameliorated. This is most effective in patients with acute CRPS.\(^53\)

**Graded motor imagery.** This therapeutic approach involves first recognizing the right and left extremities. In a second step, imagined movement is introduced, and finally mirror therapy is conducted. In controlled monocentric studies, this approach has been very effective; in a multicenter study, effectiveness was not reproduced.\(^54\)

**Pain-exposure physical therapy/graded exposure in vivo.** Pain-exposure physical therapy (PEPT) is a progressive-loading physical exercise program and management of pain-avoidance behavior.\(^55\) Graded exposure in vivo (GEXP) first reduces irrational disease-related fears (e.g., worsening by movement) and identifies the most “dangerous” or “threatening” practice tasks, which then have to be faced step by step by the patients until fear and anxiety is reduced.\(^56\) It is important to unburden the doctor–patient interaction from the topic of “pain,” which usually dominates conversation. Emphasis is placed on positive developments. In chronic CRPS, the worry of causing damage through movement is a predictor for functional derogation, more so than pain itself. After 3 months of observation, an improvement in function and in pain was found in the majority of patients. However, both are active therapies in which patients have to inflict pain (movement) on themselves. Only if patients understand the reasoning and long-term goals will they be motivated; otherwise they will give up. We conduct PEPT/GEXP in an outpatient setting and monitor progress by defining goals to be...
reached by the next appointment. Confirmatory multicenter studies are lacking.

**Psychotherapy.** Not every CRPS patient needs an extensive psychological assessment. However, when there are existing psychological factors or insufficient improvement under somatic-oriented therapy, psychotherapeutic approaches should be initiated early. The technique should be selected depending on the individual situation. There are virtually no studies about the use of psychotherapy in CRPS, but insight can be gained from other chronic pain disorders.

**Medical therapy options.** **Glucocorticoids.** Glucocorticoids reduce posttraumatic inflammation. The effectiveness of glucocorticoids has been demonstrated in 2 controlled and open studies. The optimal dose is undetermined. We have had success with a high initial dose of 100 mg prednisolone per day with a 25% reduction every 4 days. Steroids are a sensible treatment option particularly in the first 6–9 months of the disease. The value of IV immunoglobulins needs to be confirmed.37

**Bisphosphonates.** Bisphosphonates inhibit the activity of osteoclasts, and 4 controlled studies have shown uniformly positive effects. Whether bisphosphonates are preferable in acute or chronic CRPS remains unclear; pathophysiologically, their action makes more sense in acute CRPS.

**Topical dimethyl sulfoxide (DMSO 50% in a grease-based cream).** Topical dimethyl sulfoxide seems to have a positive effect on pain and the symptoms in patients with “primarily warm” CRPS.38

**Pain medication.** The effectiveness of conventional medications for chronic pain has not been demonstrated formally. Gabapentin might have a marginal but clinically unimportant effectiveness. A tricyclic antidepressant is advisable, especially if sleep disturbances are present. Pain therapy via the continuous IV infusion of ketamine can lead to a 12-week sustained reduction in pain.59 However, serious side effects may occur, especially if treatment is repeated.

**Treating the movement disorder.** Botulinum toxin has very limited effects. Case series indicate that a baclofen pump (intrathecal) led to decline in pain and dystonia.60 This treatment should only be conducted in an experienced center, as complications are frequent and the risk of incorrectly treating a psychosomatic disease is high.

**Invasive pain treatment.** **Blocking the SNS.** In a current Cochrane Analysis, the effectiveness of blocking the SNS could not be shown due to the lack of good quality studies.39 Because the absence of evidence is not the same as the evidence of absence, after 1 or 2 successful probationary blocks, a limited series over 5 weeks (twice weekly) can be performed if the patient explicitly agrees. However, blocking the SNS is no longer considered a first-line therapy.

**Spinal cord stimulation.** If noninvasive therapies fail, spinal cord stimulation represents an alternative and well-documented therapeutic option, particularly when treating CRPS of the lower limbs. The use of spinal cord stimulation must be restricted to specialized centers.

**OUTLOOK** CRPS is a fascinating, complex, and “visible” pain disorder. The understanding of CRPS has made significant advances, which will lead to demystification and improved therapies. If the treating physician bears in mind that patients should understand the reasoning underlying the prescribed therapy, actively motivates the patient to use the painful limb, and avoids unjustified interventions, then the chance of successful treatment is reasonable. Whether a patient can return to his or her previous working life is another question, and is dependent on many external factors.

CRPS research has a considerable way to go. One avenue for progress will be to abandon categorizations that lump together too many pathophysiologies and introduce too much variation into scientific studies; CRPS research must be more specific. Headache research and headache classification (in which homogeneous patient groups are defined) might provide a model for this.

**AUTHOR CONTRIBUTIONS**

Dr. Birklein: study concept and design, analysis and interpretation, study supervision. Dr. O’Neill: analysis and interpretation, critical revision of the manuscript. Dr. Schlereth: study concept and design, analysis and interpretation.

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