Complex regional pain syndrome: A comprehensive and critical review

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Abstract

Complex regional pain syndrome (CRPS) is a term used to describe a variety of disorders characterized by spontaneous or stimulus-induced pain that is disproportional to the inciting event and accompanied by a myriad of autonomic and motor disturbances in highly variable combinations. There are no standards which can be applied to the diagnosis and would fulfill definitions of evidence-based medicine. Indeed, there are almost as many diagnostic criteria as there are names to this disorder. The umbrella term CRPS has been subdivided into type I and type II. CRPS I is intended to encompass reflex sympathetic dystrophy and similar disorders without a nerve injury; while CRPS II occurs after damage to a peripheral nerve. There are numerous etiological pathophysiological events that have been incriminated in development of CRPS, including inflammation, autoimmune responses, abnormal cytokine production, sympathetic-sensory disorders, altered blood flow and central cortical reorganization. However, the number of studies that have included appropriate controls and have sufficient numbers of patients to allow statistical analysis with appropriate power calculations is vanishingly small. This has led to over-diagnosis and often excessive pharmacotherapy and even unnecessary surgical interventions. In this review we provide a detailed critical overview of not only the history of CRPS, but also the epidemiology, the clinical features, the pathophysiological studies, the proposed criteria, the therapy and, in particular, an emphasis that future research should apply more rigorous standards to allow a better understanding of CRPS, i.e. what it is, if it is, and when it is.

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1. Introduction

Complex regional pain syndrome (CRPS) is a term coined by the International Association for the Study of Pain (IASP) to describe disorders characterized by spontaneous or stimulus-induced pain that is disproportionate to the inciting event and accompanied by a wide variety of autonomic and motor disturbances in highly variable combinations. CRPS is a syndrome steeped in confusion and often inaccurate.

Although there had been earlier reports of such disorders, Mitchell, Morehouse, and Keen in 1864 [1] are generally credited for providing the first detailed account of the burning pain, swelling, skin color and temperature changes, the exquisite sensitivity to touch, and the tenderness and stiffness of the joints that sometimes result from peripheral nerve injury due to gunshot wounds. In a later publication, they coined the term causalgia, meaning burning pain, for this syndrome. A milestone came in 1900, when Sudeck [2,3] reported a painful, rapidly progressing, severe bone atrophy that developed after soft tissue injury and other forms of trauma and included many of the features of causalgia described by Mitchell et al. [1]. Importantly, Sudeck postulated an inflammatory origin for this condition. Some descriptions of the vasomotor and trophic changes that frequently accompany these syndromes already had been provided by Mitchell et al. and others in the late 19th century [1] as well as Sudeck [2,3]. In 1916, the French surgeon Leriche reported that causalgia could be successfully treated by surgical sympathectomy [4]. Subsequently, the possible role of the sympathetic nervous system became the focus of attention not only in causalgia but also in similar entities arising without obvious peripheral nerve injury. Approximately 80 different names for such disorders can be found in the English literature alone, more than 100 in other languages [5], reflecting the precipitating event, the predominant symptoms, the specialty and country of origin of the treating physician, or the presumed pathogenetic mechanism. The most common designations include Sudeck's atrophy (or dystrophy), algodystrophy, algoneurodystrophy, and reflex neurovascular dystrophy. However, the most widely accepted one was reflex sympathetic dystrophy (RSD) coined by Evans in 1946 in an attempt to unify causalgia and similar entities as both being due to a hyperactive sympathetic nervous system [6].

2. Diagnostic criteria

There are almost as many diagnostic criteria as there were names [7]. The resulting patient heterogeneity makes it impossible to compare the results of studies that attempted to elucidate pathophysiological mechanisms or to assess treatment outcomes. In addition, it was eventually recognized that there was little evidence of sympathetic hyperactivity and of the involvement of a reflex. In an attempt to address these problems, the IASP proposed a new taxonomy and consensus-based diagnostic criteria (see Table 1a) [8,9]. The new umbrella term CRPS is subdivided into types I and II. CRPS I is intended to encompass RSD and similar disorders arising without any nerve injury, while CRPS II is intended to be equivalent to causalgia, i.e. develops after damage to a peripheral nerve. There is no gold standard diagnostic test for CRPS, therefore, the diagnosis entirely rests on the assessment of clinical criteria and is a diagnosis of exclusion.

The IASP criteria have not been widely accepted [7] and were shown to lack specificity and internal validity [10–12]. Validation of diagnostic criteria in the absence of an objective diagnostic test involves circular reasoning, since criteria must be used both to define a patient sample and then to distinguish it from other diagnostic groups. According to factor analysis, patients originally diagnosed according to IASP criteria formed four clusters of covarying signs and symptoms, namely sensory, vasomotor, edema/sudomotor and motor/trophic clusters (see also Table 2) rather than the sensory and vasomotor/edema/sudomotor categories suggested by the IASP criteria. These four clusters then became the basis on which Bruehl and Harden proposed modified diagnostic criteria (see Table 1b) [11,12]. Whereas patient-reported symptoms alone are, at least theoretically, sufficient to fulfill the IASP

<table>
<thead>
<tr>
<th>CRPS Diagnostic Criteria for CRPS [19].</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The presence of an initiating noxious event, or a cause of immobilization.</td>
</tr>
<tr>
<td>2. Continuing pain, alldynia, or hyperalgesia in which the pain is disproportionate to any known inciting event.</td>
</tr>
<tr>
<td>3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain.</td>
</tr>
<tr>
<td>4. This diagnosis is excluded by the existence of other conditions that would otherwise account for the degree of pain and dysfunction.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CRPS II</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Type II is a syndrome that develops after nerve injury. Spontaneous pain or alldynia/hyperalgesia occurs and is not necessarily limited to the territory of the injured nerve.</td>
</tr>
<tr>
<td>2. There is or has been evidence of edema, skin blood flow abnormality, or abnormal sudomotor activity in the region of the pain since the inciting event.</td>
</tr>
<tr>
<td>3. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.</td>
</tr>
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</table>
Table 1b
The Harden/Bruehl Criteria, which became The Budapest Research* Criteria with minor modifications [20,439]:

1. Continuing pain which is disproportionate to any inciting event
2. Must report at least one symptom in each of the four following categories:
   - Sensory: report of hyperesthesia
   - 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
3. Must display at least one sign in two or more of the following categories:
   - Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch)
   - 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
4. There must be no other diagnosis that better explains the signs and symptoms.

The Budapest consensus panel proposed a third subtype of CRPS, namely CRPS-NOS (not otherwise specified) for patients who fulfill the Veldman criteria [17].

Note that the Budapest criteria have now been published in several slightly different versions [20,439,440]. For example, the original version clarified that the signs that a patient is required to display at the time of evaluation are “counted only if observed at time of diagnosis” [20]. This has not been repeated in subsequent versions [439,440].

In the third version, Harden et al. [440] for the first time specify that the temperature asymmetry should be >1 °C only to use a cutoff of 0.6 °C in a subsequent validation study [21].

* The clinical decision rule requires at least 2 signs and at least 4 symptom categories.

Table 1c
The Veldman criteria [17]:

1. The presence of 4 of 5 of the following:
   - Unexplained diffuse pain
   - Difference in skin color relative to other limb
   - Diffuse edema
   - Difference in skin temperature relative to other limb
   - Limited active range of motion
2. Occurrence or increase of above signs and symptoms after use.
3. The above signs and symptoms are present in an area larger than the area of primary injury or operation and include the area distal to the primary injury.

(see Table 1c) criteria [15,18]. Since there is a considerable proportion of patients meeting the Veldman [17], but not the IASP [19], criteria [15], it also should be determined whether different sign and symptom clusters would emerge in such a patient group.

These concerns were not included in an international consensus meeting held in Budapest, Hungary, during which the Harden/Bruehl criteria were adopted with minor modifications [20] (see Table 1b). One of these modifications is the formulation of different decision rules for clinical diagnosis and research purposes, respectively. In a subsequent validation study against non-CRPS neuropathic pain patients, the Budapest clinical and research criteria achieved a specificity of 0.68 and 0.79, respectively [21]. The Budapest consensus was to include a category “CRPS not otherwise specified” (CRPS-NOS) for patients who fulfill the IASP, but not the Budapest, criteria and whose manifestations cannot be explained by any other condition, except that it was never specified how many criteria they would have to meet. Although published in an IASP-sanctioned book, these criteria have not been officially endorsed by the IASP and they appear flawed as discussed above.

As long as the pathophysiological mechanisms underlying CRPS or subsets of CRPS remain unknown and, therefore, a standard diagnostic test is unavailable, valid diagnostic criteria will remain elusive. For the time being, the choice of a specific set of diagnostic criteria is arbitrary. It would greatly improve the comparability of results, however, if everybody agreed on the same criteria set by rigorous analysis. Otherwise many patients will arbitrarily be diagnosed with CRPS. All of the signs and symptoms of CRPS can feature in a variety of other conditions and diseases. Consequently, the differential diagnosis is extensive and includes a variety of focal or multifocal neuropathies, infectious, inflammatory, and vascular disorders (see Table 3). Importantly, if one looks at data on the number of autoimmune diseases, there is no evidence based on criteria of whether the disease is mediated by cell mediated immunity or autoantibodies to suggest that there is any relationship between breach of tolerance and the development of reflex sympathetic dystrophy [22–41].

3. Diagnostic procedures

The diagnosis of CRPS is clinical, but a variety of tests help in the exclusion of other diagnoses. Patients with suspected CRPS should have a thorough neurological examination. Nerve conduction velocity studies and electromyography should be performed to exclude nerve lesions. For the detection of small fiber dysfunction, bedside sensory testing or even quantitative sensory testing (QST) may be helpful. These techniques should be supplemented with somatosensory evoked potential studies and transcranial magnetic stimulation of motor pathways in order to evaluate central pathways. Since electromyography procedures can be extremely painful, some guidelines consider them cruel and present them as actually unnecessary because their results supposedly do not affect therapy [42]. They fail to mention that placebo-controlled diagnostic local anesthetic peripheral nerve blocks offer another possibility for determining the presence of neurologic disease. The disappearance of symptoms during such a block can help identify the nerve(s) that constitute(s) the source of pain input and direct further exploration or suggest the appropriate form of management [43,44].

There are no specific laboratory diagnostic procedures for CRPS, but a variety of tests are in use to evaluate sympathetic function. These include laser Doppler flowmetry for assessing blood flow and peripheral vasoconstrictor reflexes, thermography, and various tests for measuring sudomotor function. However, lack of standardization limits their usefulness. A variety of imaging techniques, including MRI, PET, and SPECT, are helpful mainly for excluding other diagnoses. Although three-phase bone scintigraphy was long considered an objective diagnostic procedure it is not specific enough to be used for this purpose [45]. Nonetheless, a pattern of increased uptake in all three phases, and particularly diffuse periarticular uptake in and around the joints of the affected extremity during the delayed phase, is considered to be typical.
of CRPS especially during the first 6 months of CRPS. Yet several guidelines do not recommend the use of three-phase bone scans [46,47]. Bone scans may be important for identifying patients that might benefit from bisphosphonate treatment. In contrast to adults, children and adolescents with RSD more often show diffusely decreased tracer uptake in all three phases, but bone scans with increased uptake have also been reported [48–50].

Interobserver agreement on clinical signs of CRPS appears to be only fair, with agreement on a diagnosis being equally low [51]. Concordance between physician’s judgment and the actual measurement of the absence or presence of symptoms is also only poor to moderate [52]. This highlights the need to standardize the methods for assessing CRPS signs and to establish reference ranges. Such efforts need to take into account that even widely accepted methods can yield divergent results because the outcome measure may be differentially affected by disease duration [53] or greatly influenced by seemingly minor differences in the experimental set-up [54–56]. Of note, the German Research Network on Neuropathic Pain (DFNS) has developed a standardized QST protocol [57] and established gender- and age-specific reference values for three body sites [57,58]. This test battery was shown to have high test–retest and interobserver reliability if performed by trained examiners [59]. It has already been used in several investigations of patients with CRPS [60–62]. Regrettably, the data are not presented in the same way, making comparisons difficult. Since CRPS patients may display combinations of sensory gain and loss [60], it would be desirable to report the proportion of patients exhibiting a particular sensory sign rather than (or in addition to) the customary group means. This essentially holds for any outcome measure in CRPS.

### 4. Presentation/clinical course

#### 4.1. Precipitating events and symptom onset

The events that precipitate CRPS most commonly are fractures, sprains, and surgery, but also include injections, local infections, burns, frostbites, even pregnancy, as well as stroke or myocardial infarction [14,17,21,63–67]. The exact nature and combination of symptoms and their severity are not related to the severity of trauma, and more than 10% of patients may not recall any precipitating event [17,64,66–69]. While it is widely held that CRPS I frequently follows trivial injuries, Table 2

<table>
<thead>
<tr>
<th>Factor 1</th>
<th>Factor 2</th>
<th>Factor 3</th>
<th>Factor 4</th>
<th>Factor 5</th>
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</thead>
<tbody>
<tr>
<td>Hyperalgesia signs (0.75)</td>
<td>Temperature asymmetry symptoms (0.68)</td>
<td>Edema signs (0.69)</td>
<td>Swelling asymmetry (0.62)</td>
<td>Edema symptoms (0.56)</td>
</tr>
<tr>
<td>Hyperesthesia signs (0.78)</td>
<td>Temperature change symptoms (0.67)</td>
<td>Color change symptoms (0.61)</td>
<td>Swelling change (0.59)</td>
<td>Skin color change (0.60)</td>
</tr>
<tr>
<td>Allodynia signs (0.44)</td>
<td>Motor dysfunction signs (0.67)</td>
<td>Edema symptoms (0.55)</td>
<td>Trophic signs (0.67)</td>
<td>Motor dysfunction symptoms (0.67)</td>
</tr>
</tbody>
</table>

For ease of comparison, the factors identified in Japanese patients are listed under the corresponding factors identified in US patients rather than in numerical sequence. Note that temperature-asymmetry and color changes were also assessed in the Japanese study.

**Table 3**

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
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</thead>
<tbody>
<tr>
<td>Bone or soft tissue injury</td>
</tr>
<tr>
<td>Stress fractures</td>
</tr>
<tr>
<td>Ligament damage</td>
</tr>
<tr>
<td>Neuropathies</td>
</tr>
<tr>
<td>Due to peripheral nerve damage, entrapment or compression</td>
</tr>
<tr>
<td>Due to CNS or spinal lesions</td>
</tr>
<tr>
<td>Diabetic</td>
</tr>
<tr>
<td>Infectious, e.g., Lyme disease, Post-herpetic</td>
</tr>
<tr>
<td>Guillain Barre syndrome (chronic inflammatory demyelinating polyneuropathy)</td>
</tr>
<tr>
<td>Erythromelalgia</td>
</tr>
<tr>
<td>Thoracic outlet syndrome</td>
</tr>
<tr>
<td>Vascular disorders</td>
</tr>
<tr>
<td>Raynaud's disease</td>
</tr>
<tr>
<td>Arterial insufficiency due to atherosclerosis, trauma, or Burger's disease</td>
</tr>
<tr>
<td>Phlebothrombosis</td>
</tr>
<tr>
<td>Compartment syndrome</td>
</tr>
<tr>
<td>Inflammatory/autoimmune disorders</td>
</tr>
<tr>
<td>Arthritis, including reactive arthritis, rheumatoid arthritis, multiple sclerosis</td>
</tr>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Viral, fungal or bacterial infections (including Lyme) of bone, joint, soft tissue, skin</td>
</tr>
<tr>
<td>Rare disorders</td>
</tr>
<tr>
<td>Gardner–Diamond syndrome</td>
</tr>
<tr>
<td>Toxic exposure</td>
</tr>
<tr>
<td>Vinca alkaloids (antitumor agents), heavy metals</td>
</tr>
<tr>
<td>Psychological</td>
</tr>
<tr>
<td>Somatoform disorders, including conversion disorder</td>
</tr>
<tr>
<td>Malingering, factitious disorder</td>
</tr>
</tbody>
</table>

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Long-term outcome

The long-term outcome of CRPS is variable. Some patients recover gradually, while others may experience persistent symptoms or even develop chronic pain. The factors influencing the outcome are complex and include the duration of the disease, the severity of the initial injury, the effectiveness of initial treatment, and the patient’s psychological resilience. Long-term pain management often involves a combination of medications, physical therapy, and psychological support.
the surgery and other medical procedures used in the treatment of the original injury may make more important contributions than is generally realized [70]. CRPS I may be only an artifact. In pediatric CRPS, overall ~28% (range 4–60%) of patients are unable to identify an inciting injury or trauma, [48–50,71–82]. Most of the precipitating injuries are minor and fractures or surgery are rarely involved [50,81,82]. While high-velocity missiles are by far the most frequent cause of causalgia (in ≥70% of reported cases) [83,84], it can also develop after nerve injury during surgical procedures and improperly placed injections [85]. In more than 90% of cases, the nerve is only partially transected. The median nerve and the sciotic trunk are involved in ~60% of upper and lower extremity causalgia, respectively. Onset of symptoms most commonly occurs within a few days to a month in causalgia [83] and causalgia [84], but a considerable portion of patients with causalgia report immediate onset. Signs and symptoms of CRPS develop in many patients after fractures, but are more frequent and severe as early as one week after fracture in those who are eventually diagnosed with the disorder [54,86]. The time at which the highest number of patients fulfilled diagnostic criteria occurred 3 months after the fracture [18]. The pain, sensory, autonomic, trophic and motor symptoms of CRPS usually start in a single limb but can begin simultaneously in 2 extremities, very rarely in 3 or more limbs [17,87]. They generally develop distally to the site of the original injury, but can spread proximally or even to an ipsilateral or contralateral extremity, to the neck and head, and occasionally the whole body [88]. Spreading to one or more other extremities may eventually occur either spontaneously or after a separate trauma in 23–48% of patients [66–68,87,88]. In addition, subclinical involvement of the contralateral extremity and systemic features are not uncommon [61,78,89–94].

4.2. Sensory disturbances

The major characteristic of CRPS is pain that is out of proportion in both intensity and duration to the original injury or trauma and not limited to a single nerve territory. It can be spontaneous and continuous, episodic or undulating or arise in response to physical and often also emotional stimuli. Patients with causalgia almost invariably describe their pain as burning [83,95], and this is claimed to be true in patients with CRPS I as well [12,96]. Yet it is increasingly common to find CRPS I pain described in terms that suggest a deep tissue localization such as dull, aching or tearing [65,97–99]. Many adult and pediatric patients suffer from alodynia and/or hyperalgesia, but some also from hypoalgesia, to mechanical and thermal stimuli [49,50,60,65,75,82,100–104]. The majority of adult patients with supposed CRPS I and CRPS II exhibit combinations of sensory loss and gain [60]. The most frequent pattern consists of increased sensitivity to painful stimuli and decreased perception of nonpainful stimuli. Only 34.6% of patients with CRPS I and 15.4% of CRPS II patients display exclusively sensory gain (alodynia/hyperalgesia), this difference being statistically significant. Patients with CRPS may also display referred sensations, i.e., the referral of somatosensory feelings to areas that are adjacent in the cortical map, or mislocalization of tactile stimuli [105–107] and a variety of other sensory abnormalities as listed in Table 4. Sensory disturbances often are confined to the palms or soles or have a glove- or stocking-like distribution limited to the affected extremity [17,65,95]. However, in approximately one third of patients, particularly those with longer disease duration, sensory disturbances extend to the whole upper quadrant or even much of the body half ipsilateral to the affected limb [101,108,109].

4.3. Autonomic disturbances

Patients with CRPS quite commonly present with a warm, red, swollen extremity. However, the affected limb is colder at the onset of symptoms (which is called primarily cold CRPS) in at least 10% of patients if the temperature is actually measured [17,65]. Considerably higher proportions of patients report their limb to feel cold [17]. Edema is seen in almost all patients at the onset of symptoms regardless of skin color and temperature [17,65]. It decreases in frequency with increasing disease duration, but nonetheless persists in at least 40% of patients with chronic disease [17,65,66]. With longer disease duration, the number of adult CRPS patients with a colder limb increases [17,21,53,61,65,110], but whether and when patients develop a colder extremity is highly variable [89,111,112]. Even in individual patients, skin color and particularly skin temperature are not static manifestations, but fluctuate considerably over time [113,114]. Side-to-side differences further depend on ambient temperature [56,110]. Whether one-time measurements reveal a temperature asymmetry between the involved and uninvolved limb depends on what cut-off, if any, is used for defining asymmetry. The available data on thermal asymmetry in healthy subjects are limited, but suggest a cut-off value of ≥1 °C [115,116]. Using such a cut-off, less than half of adult CRPS II patients exhibit significant temperature asymmetry after acclimatization [60,89,117], while 60% of pediatric patients do [104]. In pediatric RSD/CRPS, the involved extremity is far more often cold and blue at the onset compared to adult patients [71,80–82,104,118]. Swelling or edema has been reported to be less frequent in children compared to adults [48,81], but affects at least 60% of patients in most other studies [74,75,78,80,82,104].

CRPS patients also can experience sudomotor disturbances (hyperhidrosis or hypohidrosis) [17,60,65,66,104]. Trophic changes include thin and shiny skin, increased or decreased hair and nail growth, with the nails often becoming brittle, ridged, curved or dull. Note that there also may be atrophy of muscles and bones, the latter showing as patchy osteoporosis or osteopenia on plain radiographs.

4.4. Motor disturbances

A vast majority of patients with RSD/CRPS I and causalgia/CRPS II have some sort of motor disturbance, most commonly weakness or limited active range of motion (ROM) [16,17,65,66,68,95,119,120]. Tendon reflexes are frequently exaggerated [65,95,119], but can be diminished in a few patients [119]. In addition, CRPS patients are often slower in initiating movement and/or slower and more inaccurate in executing targeted movement with the affected hand, [65,92,121–123]. Similar impairment has also been noted in the unaffected hand in some studies [92,93], but this is not a consistent finding possibly due to the different methods used for assessing motor function [122]. Severe movement disorders such as muscle spams, myoclonus, and dystonia are rare in some cohorts [16,124,125], but much more frequent in others [65,66,95]. Interestingly, abnormal movement (dystonic spasms, irregular jerks and/or postural tremors) are claimed to occur in 58 of the 379 patients with CRPS I, but in none of the 307 patients with CRPS II [125]. In marked contrast, others found the combined frequency of myoclonic jerks and dystonic muscle contractions to be significantly higher in patients with type II compared to type I CRPS, namely 48% versus 27% [65]. In another group of 39 CRPS II patients, 20 (51%) experienced myoclonic jerks, but there is no mention of dystonia [95]. There are few
descriptions of movement disorders in pediatric CRPS, but a recent publication suggests that they actually may be at least as common in this patient group as in adults [126].

It has long been held that RSD/CRPS evolves through three distinct phases, an acute stage where pain, sensory abnormalities, edema and sudomotor function predominate and signs of motor function can also be present; a dystrophic stage when pain and sensory dysfunction become more marked, vasomotor abnormalities persist and significant motor and trophic changes develop; and an atrophic stage where pain and sensory abnormalities decrease, vasomotor disturbances persist, but motor and trophic changes progress [14]. The results of cluster analysis did not confirm the existence of such stages, but instead suggested that there were distinct subtypes of CRPS [14]. Note, however, that similar analyses in other cohorts yielded quite different and only partially overlapping subtype profiles [15,16]. Yet, they confirmed that the prevalence of CRPS signs and symptoms did not correlate with disease duration [15]. Due to the small sample sizes in at least two of these studies [14,16], these results should be interpreted with considerable caution.

5. The epidemiology of CRPS

In Olmsted County, MN, the annual incidence of CRPS I according to retrospectively applied ISAP criteria was 5.46/105 for the period 1989–1999 [63]. The prevalence in 1999 was 20.57/105. Only 43% of these patients fulfilled the diagnostic criteria proposed by Harden/Bruehl et al. [12]. In contrast, analysis of >217,000 patient records from 52 general practitioners in the Netherlands yielded an incidence of CRPS according to expert diagnosis of 26.2/105 [127], which was revised to ~20/105 after patient interviews [64]. The discrepancy between the Dutch and the US rates cannot be due to the inclusion of CRPS II cases in the Dutch study since these constituted only 3% of all cases. In contrast, patients with CRPS II represented ~13% of the total cases identified in Olmsted County, with the annual incidence of CRPS II being 0.82/105 [63]. Note, however, that a substantial number of patients with CRPS II may be misclassified as CRPS I because the differential diagnosis is not fully and thoroughly explored [43,44].

The incidence of CRPS I (algodystrophy, RSD, Sudeck's atrophy) in prospective studies after distal radial fracture has ranged between 0 and 37% and is quite variable regardless of which diagnostic criteria are used [18,54,86,128–137]. The incidence rates reported after fracture of the tibial shaft [138], foot or ankle [18], total knee arthroplasty [139], or carpal tunnel release also cover a similar range [140]. In a recent study, patients with ankle fractures were found to be at significantly higher risk of developing CRPS I compared to fractures of the hand, wrist, or foot [18]. Intraarticular fractures and dislocated fractures were also associated with a significantly higher incidence of CRPS I [18], but these are not entirely consistent findings [128,129]. By far the most important determinant of the incidence of CRPS I, however, was the specific criteria set (ISAP, Bruehl, Veldman) used for the diagnosis of this entity [18], although the Atkin [141] and the Bruehl criteria yielded very similar incidence rates [135]. Here again, any discussion of CRPS I should be interpreted with caution.

CRPS can occur at any age, but is relatively rare in childhood and adolescence [63,127], with pediatric patients constituting ~10% of CRPS patients seen at tertiary centers [81,142]. Mean or median age at onset varies from ~37–52 years in population-based and cohort studies [17,63,65–68,127,142]. The age group with the highest incidence is even more variable, ranging from the 4th to the 7th decade of life [63,68,127]. Familial cases of CRPS I are characterized by a significantly younger age of onset [143,144], and this has also been observed for patients with spontaneous onset of CRPS I, i.e., without a known precipitating trauma or tissue injury [69]. Onset of pediatric CRPS occurs most frequently in early adolescence, with the lower end of the range usually being 7 to 9 years [50,71,81]. Only isolated cases of CRPS have been described in younger children [73,82], the youngest ones being 2.5 and 3 years of age, respectively [145,146]. Note, however, that onset can even occur at birth or at the age of only a few months in children with inherited mitochondrial disease [147].

In populations of mainly European descent, women have a 3.4–4-fold higher incidence rate of CRPS in population-based studies [63,127] and constitute between 66 and 80% of CRPS patients seen at tertiary clinics specializing in the treatment of CRPS patients [17,65–68,81]. Interestingly, the sex distribution in two different Korean patient groups showed a slight male preponderance [148,149], while women constituted ~2/3 of patients in a Japanese cohort [13]. More than 80% of pediatric CRPS patients described to date are female [48–50,71,75–81]. It has been suggested that CRPS is rare in people of non-European ancestry both in adults [150] and children [151], but actual data on this issue are lacking.

In adult CRPS, an upper extremity generally is affected slightly more frequently than a lower limb, whereas the right and left side of the body are involved in approximately equal numbers of cases [13,17,63,65,66,68,81,127]. A notable exception are two Korean cohorts, in whom a lower limb was affected more often than an upper extremity [148,149]. In pediatric RSD/CRPS, the incidence of lower extremity involvement is even higher, ranging from ~60% to 100% in various studies and being >80% overall [48,50,71,75–81,152]. The side of involvement is reported much less frequently in pediatric compared to adult cohorts, but most of the available data suggest a fairly even distribution [50,79,81,153].

6. Pathophysiology

6.1. Psychological factors

Since the severity and duration of signs and symptoms of CRPS is disproportionate to the inciting event, or such an event is even absent, it is often thought that CRPS is of hysterical or psychogenic origin or that psychological factors contribute to its development. Whether the dystonia or myoclonus associated with CRPS is psychogenic continues to be a matter of intense debate [125,154–159]. As long as the same data can be interpreted as showing an organic or a psychogenic origin of CRPS-associated movement disorders [157,158,160,161], this issue is unlikely to be resolved. Nonetheless, reports of disease resolution with psychiatric counseling and reassurance [125] or significant improvement with multidisciplinary inpatient treatment consisting of cognitive behavioral therapy, occupational therapy and psychotherapy demonstrate that dystonia and myoclonus are psychiatric disorder in some CRPS patients [154]. Similarly, certain CRPS patients without movement disorders exhibit a variety of behaviors that only allow the conclusion that their symptoms are psychogenic [162,163]. Cases of somatoform disorders, some with overlap of conversion and factitious disorders, have been reported [164–168]. These may not always be easy to distinguish from malingering or may co-exist with it [169], and malingerers with the diagnosis of CRPS I have also been described [125,162,170,171]. In addition, CRPS patients with dystonia had similar scores for somatoform dissociation as patients with conversion disorder and significantly higher scores compared to patients with affective disorder [156]. Similarly, others found remarkable similarities in the psychological profiles, as obtained with the Minnesota Multiphasic Personality Inventory (MMPI), of patients with CRPS I and patients with conversion disorder, including a similar frequency of Axis I disorders [172].

In a systematic review by Beethruizen et al. [173], the majority of prospective studies did not reveal a relationship between the development of CRPS I and psychological factors, in particular depression or anxiety but a more recent prospective study confirmed the lack of association with depression [174]. Yet, an anxious personality, though not the level of anxiety around the time of cast application, was significantly associated with the development of CRPS I. According to the systemic review, only a few prospective studies
## Table 5

<table>
<thead>
<tr>
<th>Animal models of CRPS I</th>
<th>Species</th>
<th>Procedure comparison group</th>
<th>Procedure or model</th>
<th>Time of appraisal</th>
<th>Duration</th>
<th>Extravasation</th>
<th>Warmth</th>
<th>Duration</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Tibia fracture + cast</td>
<td>Sprague-Dawley (male)</td>
<td>Total tibial fracture plus cast</td>
<td>Constant pain</td>
<td>4-26 weeks post-fracture</td>
<td>1-26 weeks</td>
<td>No</td>
<td>No</td>
<td>n.a.</td>
<td>[185]</td>
</tr>
<tr>
<td>Ischemia</td>
<td>Long Evans rats (male)</td>
<td>3-h ischemia with tight-fitting O-rings with subsequent reperfusion</td>
<td>Constant pain</td>
<td>1-65 days</td>
<td>1-6 weeks</td>
<td>No</td>
<td>No</td>
<td>n.a.</td>
<td>[289]</td>
</tr>
<tr>
<td>Ischemia-reperfusion</td>
<td>Sprague-Dawley (male)</td>
<td>3-h ischemia with right hind-limb ischemia-reperfusion</td>
<td>Constant pain</td>
<td>2-4 h-reperfusion</td>
<td>1-24 h</td>
<td>No</td>
<td>Yes</td>
<td>n.a.</td>
<td>van der Laan</td>
</tr>
<tr>
<td>Infusion of a free radical donor</td>
<td>Wistar (male)</td>
<td>Infusion of tert-butyl-radical donor</td>
<td>No</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
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</table>

n.a. = not assessed; CPIP = chronic post-ischemic pain.

The mechanisms underlying the development of warmth, edema, and stimulus-induced pain, edema, temperature asymmetries, skin color changes, limited AROM, stiffness, weakness and, more rarely, sudomotor abnormalities, [66,89,98,129]. This suggests that, as in rats, these symptoms are part of a spectrum of physiological responses. The addressed neuroticism or hostility/anger, and these did not show significant differences between CRPS I patients and controls [173]. Retrospective or cross-sectional studies yielded more conflicting results regarding these and other psychological factors. This is particularly obvious for somatization, with 5 studies showing that patients with RSD/CRPS have similar or even significantly lower somatization scores compared to various pain control groups, whereas the opposite was observed in 3 other investigations. Similarly discrepant results have been reported for hysteria/hypochondria. In contrast, there is general agreement that patients with CRPS I exhibit similar or even lower levels of obsessive–compulsive behavior compared to controls (usually with chronic pain). Note that some of the discrepant results may be due to the use of a large variety of standardized and non-standardized assessment tools and different patient characteristics due to their identification via numerous different diagnostic criteria. In addition, many of these studies were of poor to modest methodological quality.

More recently, Beerthuizen et al. [175] conducted a large (n = 596) prospective multicenter study to determine potential demographic, medical, and psychological predictors of the development of CRPS after fractures. One of the significant predictors that emerged from logistic regression analysis was the score on the somatization subscale of the symptom checklist-90 (SCL-90). However, this subscale contains items that represent symptoms used to diagnose CRPS. After discarding these confounded items, somatization scores lost significance. This study also did not replicate the results of several previous analyses that found the development of CRPS I to be associated with the occurrence of major life events in close temporal association with the precipitating trauma [173].

Children and adolescents with RSD/CRPS were not included in Beerthuizen’s systematic review [173]. Numerous cohort descriptions contain reports of high incidences of anxiety, depression, evidence of somatization, and history of psychological diagnosis as well as family dysfunction, enmeshment with parents, parental pressure to perform, and a high rate of participation in organized sports and school activities in this population [71,72,80,152,153,176–178]. However, these data were not obtained prospectively and adequate controls were generally missing, making it impossible to determine whether psychological factors contribute to, or result from, RSD/CRPS. Results from the only prospective study failed to show major differences in individual and family functioning, but remain published in abstract form only [179].

### 6.2. Immobilization

Immobilization is a common treatment of limb injuries, particularly fractures. Both adult and pediatric patients with CRPS I frequently have a history of immobilization even without a preceding fracture [65,67,68,71,79,82] and this is associated with worsening of symptoms [71]. As recognized by the IASP diagnostic criteria [19] (see also Table 1a), immobilization alone can transiently produce many of the signs and symptoms of CRPS I, including skin temperature asymmetry, pain upon movement, and cold and mechanical hyperalgesia not restricted to the territory of a single nerve, though not spontaneous pain [180–182].

Similarly, approximately 2/3 of Sprague–Dawley rats develop many of the signs and symptoms of human CRPS I after hind limb casting for 4 weeks [183] (see Table 5). These changes greatly resemble those observed after distal tibial fracture followed by hind limb casting except that many of them resolve faster after casting alone (see also Table 5). The mechanisms underlying the development of warmth, edema, and sensory abnormalities were shown to be the same in both groups. Of note, one or more of the signs and symptoms of CRPS also develop in almost all patients with fractures or after surgery, including spontaneous and stimulus-induced pain, edema, temperature asymmetries, skin color changes, limited AROM, stiffness, weakness and, more rarely, sudomotor abnormalities, [66,89,98,129].
difficulty, then, is to determine at which point of the spectrum the changes become pathological and is indeed CRPS and not another diagnosis.

6.3. The sympathetic nervous system

6.3.1. The sympathetic nervous system and vasomotor disturbances

The characteristic clinical signs and symptoms of autonomic dysfunction, such as edema, changes in skin temperature and color, and hyperhidrosis indicate a role of the sympathetic nervous system in the pathophysiology of CRPS. It was long held that RSD was due to an overactive sympathetic nervous system. However, in the early phase of RSD/CRPS, the affected extremity is warm, red, and swollen in the majority of patients, and cutaneous and subcutaneous blood flow in the affected extremity is often increased [111,112,184–186]. Very early in the course of CRPS, vasoconstrictor reflexes after sympathetic provocation maneuvers are impaired, and this distinguishes CRPS from acute or recently resolved limb trauma [54,89,98,187,188]. These disturbances normalize with clinical improvement [187,188]. All of these findings suggest that basal sympathetic function is decreased, rather than increased, in early CRPS. The results of skin blood flow and temperature measurements throughout an entire thermoregulatory cycle indicate that cutaneous vasodilation due to unilaterally decreased sympathetic vasoconstrictor activity constitutes one reason for the increased skin temperature of the involved limb in acute CRPS I [110]. In addition, there is evidence that this is due to central rather than peripheral inhibition [189]. Yet, there are patients who do not show increased blood flow in the early phases of CRPS I, their vasoconstrictor responses are impaired bilaterally, and there is no correlation between increased blood flow and skin temperature [54,89,188]. This suggests that other mechanisms contribute to the warmth of the affected extremity.

Some patients have a cold, bluish or pale extremity from the onset of symptoms [17], others develop these manifestations later [17,21,53,61,65,110–112]. In such patients skin blood flow is more often decreased [111,112,185,190]. However, blood flow, skin temperature and skin color fluctuate with environmental conditions. This is most clearly illustrated in a study of 12 CRPS patients 10 of whom reported that their skin became bluish pale and much colder in cold environments and under emotional stress [56]. When the patients were assessed after they had just come in from a cold environment, skin blood flow was low on the affected side, indicating marked vasoconstriction. Further vasoconstrictor reflexes could not be elicited in the affected limb at this time. After acclimatization to a warm environment, blood flow no longer showed any side-to-side differences, and vasoconstrictor reflexes were identical in both upper limbs and nearly identical to those of healthy controls. While there have been other reports of normal [186] or even enhanced vasoconstrictor reflexes in patients with chronic RSD after acclimatization to a warm environment [184], others report impaired vasoconstrictor reflexes to a variety of sympathetic provocation maneuvers impaired in chronic RSD/CRPS [110,190], and this can occur regardless of thermoregulatory blood flow [112,185], and can affect both the ipsilateral and the contralateral extremity [191,192].

In some RSD/CRPS patients, concentrations of norepinephrine (NE), its major intracellular metabolite, or neuropeptide Y are decreased on the affected compared to the unaffected side [110,193–196]. This has even been observed in a few patients with chronic “cold” RSD/CRPS [110,193]. In addition, sympathetic postganglionic neuron (SPGN) secretion of NE was decreased in chronic CRPS [197]. Furthermore, microneurography of skin nerve fascicles in a patient with chronic RSD showed normal sympathetic activity at rest and after various stimuli despite signs of pronounced vasoconstriction [198]. There are also evidence that sympathetic innervation is not reduced [197,199]. Together, these results suggest functional rather than organic sympathetic denervation. Such functional sympathetic denervation can lead to upregulation of α-adrenoceptors, as has been demonstrated in the hyperalgesic skin of RSD patients [200]. The cell type with enhanced α-adrenoceptor expression was not determined in that study [200], but RSD patients were shown to exhibit vascular adrenergic supersensitivity [201]. Altogether, these data suggest that enhanced vasoconstriction in patients with “cold” CRPS may actually be due to vascular hypersensitivity to catecholamines rather than a hyperactive sympathetic nervous system.

Plasma NE levels in the unaffected extremity of CRPS patients were significantly increased compared to healthy controls [202,203], and similar trends become apparent in other data [193]. At first glance this seems to argue against adrenergic supersensitivity due to decreased catecholamine concentrations. However, it actually accords with data showing that sympathetic hypofunction is confined to the distal portion of the affected extremity, whereas there is an increase of sympathetic outflow proximal to the site of the trauma that precipitated RSD, as evidenced by decreased relative brachial artery distention at baseline [112].

It is frequently argued that the increased sweat production observed in patients with CRPS must be centrally mediated because sweat glands do not develop denervation supersensitivity. However, even though sweat gland innervation is cholinergic, the sweat response to iontophoresis of phenylephrine, an α1-adrenergic agonist, was increased in patients with acute CRPS I compared to healthy controls and patients with resolved CRPS, suggesting α1-adrenoceptor supersensitivity of the sudomotor fibers themselves [204]. This is consistent with the co-expression of cholinergic and adrenergic markers in adult human sweat gland innervation [205]. In addition to vasoconstriction due to dysregulated sympathetic function or adrenergic supersensitivity, there are indications that endothelial dysfunction contributes to decreased blood flow not only in chronic “cold” CRPS [206], but may already be present in the early stages of the disease process [117]. Furthermore, as will be discussed in the following section, neuropeptides may play an important role. Sadly, most studies, however, are poorly controlled.

6.3.2. The sympathetic nervous system and pain

Much of the argument for a role of the sympathetic nervous system in the development or maintenance of pain in CRPS rests on the observation that individual patients report pain relief after sympathetic blockade [83,207,208]. Such patients are said to have sympathetically maintained pain (SMP). Data from primarily uncontrolled studies further suggest that some patients with RSD/CRPS I can be successfully treated with agents targeting α-adrenoceptors [209]. In addition, intradermal application of NE or the specific α1-adrenoceptor agonist phenylephrine can evoke pain in the affected limb of some CRPS patients with SMP, but not in healthy controls [210,211], and rekindle pain and hyperalgesia in a subset of patients while they are free of pain after sympathetic blockade [212]. A subset of RSD patients report an increase in spontaneous pain and the area of dynamic and punctate mechanical hyperalgesia during increased sympathetic vasoconstrictor activity [102,213] and pain relief during low cutaneous sympathetic outflow [214]. There are data suggesting that sympathetically induced exacerbation of pain involves a central pathway in some patients [215]. Of particular note, none of 20 patients with very acute CRPS (disease duration of 2–15 weeks) reported pain after iontophoresis of NE, indicating that the sympathetic nervous system does not contribute to pain in the early stages of CRPS [216].

Normally, there is no interaction between the sympathetic nervous system and peripheral nociceptors. However, sympathetic-afferent coupling can occur under pathological conditions. In animal models of peripheral or spinal nerve injury or compression, i.e., causalgia/CRPS II, there is clear evidence of interactions between sympathetic efferent and primary afferent nociceptors at the site of axonal injury, the neuroma, the cutaneous nociceptor terminal, or the dorsal root ganglion (DRG) [208]. Particular attention has been focused on the sympathetic sprouting that results in the formation of basket-like structures around
nociceptor activation after sympathetic provocation maneuvers such as 24 patients with CRPS I and II (IASP criteria) found no evidence of sympathetic activity. Most importantly, however, microneurography in sympathetically maintained component of pain than does the cutaneous including muscle, bone, tendons, and joints, contributes more to the [214]. This suggests that sympathetic innervation of deep somatic tissue, whereas determining the effectiveness of sympathetic blockade [227]. In addition, there is no correlation between pain relief and the typical duration, or degree. However, clinical signs do not allow to conclusively show the activation of mechano-insensitive C-fibers after a sympathetic arousal stimulus or injection of NE [229], it does not argue for a major role of cutaneous sympathetic-fibers coupling in the pain perception of patients with CRPS.

6.4. Neurogenic inflammation

6.4.1. Neurogenic inflammation and vasomotor disturbances

Patients with CRPS supposedly exhibit all the signs of inflammation, i.e., redness, heat, pain, and swelling. Yet, there is little histological evidence of a classical inflammatory infiltrate in skin, joint, or muscle biopsies [230,231] although in select studies numerous Langerhans cells have been detected in skin biopsies [232], and slight cellular infiltration consisting chiefly of lymphocytes has been observed in synovial biopsy specimens [233]. This suggests that the inflammation is neurogenic. Action potentials resulting from stimulation of nociceptive C-fibers not only travel centrally but, via axonal reflex or dorsal root reflex, also invade peripheral nerve terminals, where they result in the release of neuropeptides. In rodents, key players among these neuropeptides are calcitonin gene-related peptide (CGRP) and substance P (SP), which are mainly responsible for vasodilatation and protein extravasation, respectively. These along with edema are the cardinal manifestations of neurogenic inflammation.

Plasma/serum concentrations of CGRP are highly variable in patients with CRPS I, but are elevated in at least a subset of patients during the acute phase of CRPS compared to healthy controls [234,235]. In these patients, serum CGRP levels were found to correlate with the presence of hyperalgesia [234], which agrees with the finding that CGRP enhances acetylcholine-induced sweating [236]. Serum CGRP did not correlate with the severity of spontaneous pain or the presence of hyperalgesia or allodynia [234], which argues against a major role of this neuropeptide in pain or central sensitization. In the later stages of CRPS I, CGRP levels have been reported to be decreased [237], unaltered [196] or increased [238]. No significant side-to-side differences were found in plasma or artificially raised blister fluid [196]. As to SP, the available data suggest that its systemic concentrations are elevated in a subset of patients but the differences in group means do not always reach statistical significance due to large interindividual variability [235,237,238].

Experimentally induced neurogenic inflammation results in stronger reflex vasodilatation not only on the affected extremity [239], but also on the contralateral side of CRPS patients compared to healthy controls [91]. Unlike in rodents, human C-fibers normally do not contain sufficient SP to trigger plasma protein extravasation (PPE) [240]. However, PPE occurred under these experimental conditions in the affected limb of CRPS patients, but not on the uninvolved side or in healthy controls [91,239]. Upon intradermal application of SP via microneedle, some CRPS patients exhibited PPE in response to 100-fold lower concentrations of SP than are required in healthy subjects [90]. Such responses were even observed on the unaffected side of patients whose CRPS symptoms had almost completely resolved. This suggests that heightened responsiveness to SP may constitute a predisposing factor to the development of CRPS.

The role of CGRP and particularly SP in neurogenic inflammation has been investigated most extensively in the rat tibial fracture and casting model, which is characterized by edema, hind paw warmth, allodynia, and decreased weight bearing on the healed hind paw at the time of cast removal [183]. At this time, upregulation of SP, CGRP and other neuropeptides is evident in skin and sciatic nerve, and expression of their mRNA is enhanced in DRG [241]. Further data from this model show that SP plays an important role in the development of hind paw warmth and edema, the latter being attributable to SP-induced protein extravasation [183,242], and similar findings have been reported in the nerve transaction model of CRPS II [243]. After tibia fracture, this enhanced extravasation appears to be due primarily to upregulation of the primary receptor for SP, the neurokinin-1 (NK1) receptor, on endothelial cells and keratinocytes, whereas decreased enzymatic degradation of SP does not appear to make a major contribution [241]. SP was also shown to be largely responsible for the enhanced keratinocyte proliferation and epidermal thickening in this model [241,244]. In a skin biopsy sample from a single patient with CRPS I, a similar epidermal thickening and upregulation of NK1 receptor expression on keratinocytes was noted [245]. Together, these results suggest that neuropeptide release in response to ongoing C-nociceptor activation may contribute to the enhanced vasodilatation, increased skin temperature, red skin color and possibly edema in some patients with acute “warm” CRPS. It seems unlikely, however, that antidromic vasodilatation is solely

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responsible for these signs and symptoms since it can be overridden by intact sympathetic vasoconstrictor reflexes [187].

There are data suggesting that the cold and bluish or pale skin in more chronic cases of CRPS may also be attributable to neuropeptide signaling, more specifically the powerful vasoconstrictor endothelin-1 (ET-1) and its inverse association with the vasodilator nitric oxide (NO) [246,247]. However, the original findings could not be replicated, and a topical NO donor did not affect skin temperature asymmetry or pain [248]. Others did not find increased ET-1 concentrations in plasma or cerebrospinal fluid of CRPS I patients [249,250], and plasma levels did not correlate with the skin temperature of the affected limb, even though on average the painful extremity was colder than the contralateral side [249].

6.4.2. Neuropeptides and pain

SP and CGRP do not directly induce pain in humans [245,251] or rats [252]. Nonetheless, there is evidence that SP and CGRP play a role in spontaneous pain behavior and nociceptors sensitization (allodynia) in the tibia fracture model of CRPS I [183,242,244,252,253] and the sciatic nerve transaction model of CRPS II [243]. After tibia fracture, these effects were shown to be indirect and to require the induction of a network of mediators that have the ability to sensitize nociceptors and heighten pain responses [242,253–259]. This network includes tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and IL-18, with nerve growth factor (NGF) possibly acting as the proximate effector. These agents, in turn, can further upregulate the production of neuropeptides [259,260], resulting in additional inflammation and nociceptive sensitization. One major source of these cytokines in the tibia fracture model is keratinocytes [244,254–256]. In addition, SP was found to be responsible for the increase in the total number of skin mast cells and their enhanced NK1 receptor expression after tibial fracture [261]. Skin mast cells produce a variety of mediators, such as tryptase and other proteases, histamine, prostaglandins, cytokines, and neuropeptides. Many of these substances can sensitize nociceptors and could, therefore, contribute to the mechanical alldynia and spontaneous pain behavior in this rat model [262–264]. Indeed, chronic administration of a mast cell degranulator or mast cell depletion partially reversed hind paw hyperalgesia and unweighting, suggesting that mast cells contribute to the stimulus-induced and spontaneous pain behavior in this model.

SP, CGRP and other neuropeptides are not only released peripherally, but also from the central nocicepter terminals. There, they play an important role in the induction and maintenance of central sensitization [265], i.e., the heightened excitability of dorsal horn neurons. Although central sensitization usually depends on C-fibers, it can also arise from non-nociceptive A-fibers that have undergone a change in phenotype [266]. After peripheral nerve injury, both damaged and nearby uninjured nerve fibers exhibit pathological ectopic and ongoing discharges that will ultimately lead to central sensitization. Pro-inflammatory cytokines such as IL-1β and TNFα are not only able to sensitize but also to directly activate peripheral nociceptors [260,264]. While peripheral inflammation can also produce pathological ectopic activity, it is a much weaker inducer of the complex processes that induce and maintain central sensitization than peripheral nerve injury [266]. Central sensitization, in turn, is thought to contribute to the chronification of pain in a variety of disorders and diseases, including CRPS [267]. Note that microneurography revealed abnormal spontaneous discharges of nociceptive C-fibers in 6 of 11 patients with CRPS II, but in none of the 13 patients with CRPS I [228].

6.4.3. Cytokines in CRPS

There are some indications that skin is an important source of pro-inflammatory cytokines not only in experimental animal models of CRPS, but also in CRPS patients. Of note, repeated non-painful mechanical stimuli are sufficient to increase TNFα release in human skin, whereas painful electrical stimuli are not [268]. Artificially induced skin blister fluid from the affected side of CRPS patients was found to contain significantly higher concentrations of TNFα and IL-6, but not IL-1β, compared to the unaffected side or healthy controls [196,246,269,270]. Note that the side-to-side differences were minimal in some patients, and some actually had lower concentrations on the involved compared to the uninvolved side [271]. Hence since none of these studies included a control group to establish normal side-to-side variation, it cannot to be determined how many CRPS patients actually show truly abnormal differences. In longitudinal studies, changes in symptom severity were clearly dissociated from the evolution of these cytokine asymmetries [269–272], suggesting a minimal influence of skin TNFα and IL-6 levels on signs and symptoms of CRPS I. Recently, skin punch biopsies from patients with CRPS I were found to contain significantly higher concentrations of TNFα compared to biopsy specimens from patients with acute limb fracture and patients with osteoarthritis, whereas serum concentrations of this cytokine did not differ significantly between CRPS and osteoarthritis, but were higher in both conditions compared to the fracture group [273]. The cellular source of these cytokines was not determined. Data from the tibial fracture model suggest that keratinocytes and mast cells are major candidates [244,254,256,261]. Indeed, tryptase, a product of mast cells, was found to be upregulated in suction blister fluid from the affected limb compared to the healthy side of patients with CRPS I [274]. However, tryptase levels did not correlate with IL-6 or TNFα concentrations in the blister fluid, but were associated with the level of pain. This does not suggest that skin mast cells are a major source of these cytokines in CRPS patients. In humans, the concentrations of SP required to induce mast cell degranulation are even higher than those needed for protein extravasation [251]. It remains to be established whether the heightened SP responsiveness demonstrated by a subset of patients in the PPE experiments [90] extends to skin mast cells and whether endogenous SP concentrations are sufficient for mast cell degranulation.

Systemic concentrations of proinflammatory cytokines are not generally elevated in CRPS patients compared to controls [62,196,237,275,276]. However, a subset of patients in the acute and chronic stages of CRPS displays markedly increased plasma levels of TNFα and IL-1β along with a variety of other cytokines and chemokines [277,278] and soluble cytokine receptors [235,277,278]. The results of a recent analysis of numerous cytokines (including IFNγ, IL-1β, -2, -4, -5, -6, -7, -8, and -10, and TNFα), chemokines and their soluble receptors in a large cohort of CRPS patients (n = 148) confirm the existence of two distinct patient subtypes [277]. In 36% of the patients plasma levels of almost all mediators were markedly increased, whereas the remainder of the patients exhibited values very similar to those of healthy controls for all analytes except sIL-1R1. Separate analysis in these two clusters showed moderate, but statistically significant, positive correlations of TNFα and IFNγ with disease duration; of sTNFRI, sTNFRII, and IL-1Rα with overall pain levels; and of sIL-1R1 with heat hyperalgesia. Further cluster analysis revealed that increased plasma concentrations of TNFα or IL-1β correlated with disease duration or severity only in those subjects without a simultaneous increase in soluble receptors or receptor antagonists for these cytokines. This may implicate these cytokines in the pathophysiology of the disorder in this patient subgroup or alternatively suggest that there is an alternate diagnosis [277]. Further evidence for the involvement of TNFα comes from the finding that a polymorphism in the promoter region of the TNFA gene is associated with certain subtypes of CRPS [279]. In addition, there are isolated reports of patients who benefited from treatments that antagonize this cytokine [280–282], but this was not observed in a recent RCT [283].

After tissue injury or trauma, the inflammatory reaction is eventually downregulated via the action of anti-inflammatory substances, including IL-4 and IL-10 [284]. The results for these cytokines in CRPS patients are conflicting [62,237,275–277], but suggest that a subset of patients may exhibit decreased systemic IL-10 levels [62,275], possibly due to an increase in the proportion of CD14+CD16+ monocytes, which have a
decreased ability to secrete IL-10 [275]. Discrepant results have also been obtained regarding cytokine concentrations in cerebrospinal fluid (CSF), even though the available data all come from the same group of investigators [250,285]. This again suggests either the existence of subgroups of CRPS patients or incorrect diagnosis. Activated glial cells are major sources of a variety of pro-inflammatory mediators that were shown to be upregulated in CSF of some CRPS patients, including cytokines, glutamate and NO [285,286]. At autopsy, there was evidence of increased glial activation in the spinal cord from a patient with severe CRPS after an exercise-induce muscle injury sustained seven years previously [287]. This was accompanied by neuronal loss throughout the entire posterior horn of the spinal cord, the changes being most evident at the level of the original injury. Although this patient underwent numerous treatments that may have contributed to the glial activation and neuronal loss, the distribution of the changes argues for her illness being the major cause.

6.5. The deep-tissue microvascular pathology hypothesis

Ischemia–reperfusion (I–R) of the Long Evans rat hind paw results in a model of CRPS I that starts with transient hyperemia and edema, followed by mechanical hyperalgesia and allodynia and cold allodynia that last for at least 1 month [288] (see also Table 5). In Wistar rats these findings could not be replicated, but this may have been due to major methodological differences [289] (see Table 5). The observations in their chronic post-ischemic pain (CPP) model prompted Codere and Bennett [290] to develop the hypothesis that spontaneous and stimulus-induced pain in at least a subset of CRPS patients is due to deep-tissue microvascular pathology. According to this hypothesis, deep tissue injury (the most frequent precipitating event in CRPS I) induces an inflammatory response with edema, which then results in a compartment-like syndrome leading to ischemia–reperfusion injury of the microvasculature and eventually deep tissue ischemia and chronic inflammation. This could in turn lead to ectopic discharges from sensory afferents or sensitization of muscle or bone nociceptors and ultimately central sensitization.

6.6. The small-fiber neuropathy hypothesis

In specimens obtained from amputated limbs of patients with severe chronic CRPS, a loss of C-fibers in the sural nerve, but not tibial or peroneal nerve, was observed in 4 of 8 patients [225]. There was a marked reduction in C and Aδ fibers in skin samples from amputated limbs, and the innervation of sweat glands was not only reduced but differed markedly from controls in its expression of neuropeptides and other markers [291]. Muscle specimens from amputated limbs showed evidence of denervation followed by reinnervation in 4/14 samples, and of denervation after reinnervation in 2/14 samples [292]. In punch biopsy samples taken from the area of maximum pain in 18 patients with CRPS I, the group median intraepidermal nerve fiber density (IENFD, i.e. density of C-fibers and thinly myelinated Aδ fibers) was significantly decreased compared to an ipsilateral control (a nearby area free of symptoms) and a contralateral control sample [70]. Such a difference in IENFD was not observed between the painful and control sides of 7 patients with osteoarthitis pain. Unfortunately, data on the proportion of patients with significant differences were not provided. Based on the above observations, similarities between the clinical features of CRPS I and small-fiber–predominant polyneuropathies, and findings in rodent models, Oaklander et al. [293] hypothesized that the mechanism underlying CRPS I is the post-traumatic degeneration of small diameter axons and that, therefore, CRPS I constitutes a small-fiber neuropathy.

Using a commercially available standard biopsy method for assessment of IENFD, others did not detect a significant difference in the group mean IENFD or sweat gland nerve fiber density in CRPS I patients with a median disease duration of 5.4 years (range 0.2–22.8 years) compared to normative laboratory data [294]. A sample from a proximal site was chosen as a control for edema, no contralateral sample was taken. Abnormal IENFD (below the 5th percentile of controls) was found in 21% of samples taken from a distal site of the affected limb and in 7% of the biopsy samples from a proximal site. Like the results obtained in amputated limbs of CRPS I [225,292], these findings indicate that small fiber degeneration is confined to a subset of patients.

Furthermore, data on small-fiber axonal degeneration come either from patients with long-standing disease severe enough to necessitate amputation [225,291,292], or almost exclusively from patients with chronic disease of >2 year duration [70,294]. Therefore, it cannot be determined whether these neuropathological changes are causally involved in the development of CRPS I or arise as a consequence of other disease-associated processes, such as tissue hypoxia or inflammation.

As proof of a causal connection between neurite loss and the development of CRPS, Oaklander et al. [293] cited their own animal study showing a similar decrease in neurite density after needlestick nerve-injury [295]. It should be noted, however, that this model involves piercing the surgically exposed tibial nerve with a needle that may be as large as the nerve itself, which would seem to be a model of CRPS II rather than CRPS I. In addition, a subsequent detailed analysis of data from these animals revealed that the severity of endoneurial vascular pathology and inflammation were much more strongly associated with hyperalgesia than neurite density [296], suggesting that axonal loss is not the primary determinant of pain behavior in this model. Of note, similar endoneurial vascular changes have been detected in tissue specimens from amputated limbs of CRPS patients [225]. After hind paw ischemia–reperfusion injury, a model of CRPS I, neurite count was decreased, but also did not correlate with the extent of mechanical allodynia [297]. Conversely, the tibia fracture model reproduced many of the features of CRPS I in the absence of any significant changes in skin neurite density [241].

The results of IENFD measurements and QST often show only weak correlations and the nature and direction of these associations vary between studies [294,298,299], and IENFD may be somewhat more sensitive in small-fiber neuropathy [300]. Nonetheless, QST is an accepted tool for the diagnosis of small-fiber neuropathy [300]. The results of QST performed in 298 patients with CRPS I according to a standardized and validated protocol revealed isolated small fiber dysfunction in only 14% of patients, and combined small and large fiber dysfunction in 25% of patients, suggesting that isolated small fiber neuropathy does not constitute a major pathogenetic mechanism in CRPS I [60]. Large myelinated Aβ fiber function was assessed by mechanical and vibration detection thresholds, small-fiber (Aδ or C-fiber) function was evaluated by thermal testing. In another investigation using the same standardized QST protocol, thermal and mechanical detection thresholds were significantly increased at the group level in chronic CRPS I patients compared to healthy controls [100]. Unfortunately, no information on the proportion of patients with significant sensory loss was provided. The same group of investigators found both warm and cold hypoesthesia to be significantly worse in patients with chronic (>12 months) CRPS compared to those in the more acute stages of the disorder (≤12 months) [100]. This suggests that small fiber dysfunction or loss results from, rather than being the cause of, the disease process.

6.7. Central processes

6.7.1. Cortical reorganization

Brain mapping studies show that the representation of the CRPS-affected hand in the contralateral primary somatosensory cortex (SI) is significantly smaller compared to the unaffected hand or that of healthy controls [94,301–303] and shifted towards the cortical representation of the lip [302]. This was associated with increased SI
activation in response to tactile stimulation of the affected compared to the healthy hand, possibly due to blurring of the cortical representations of individual fingers [94,302]. These cortical changes were found to be reversible upon clinical improvement [304,305]. The amount of cortical reorganization correlated with the extent of pinprick hyperalgesia [302], suggesting that central sensitization and cortical reorganization are closely related. It also was associated with the overall pain intensity, but not the acute pain level at the time of the investigation [302,303], implicating pain in the induction of cortical reorganization. Reorganization also occurs in the motor cortex, as indicated by a significantly reduced representation of the long extensor muscles of the fingers in the motor cortex contralateral to the affected side compared to the unaffected hand both in size and motor evoked potential amplitude [306]. There was no significant asymmetry among healthy subjects. Of note, the sizes of the cortical representation of both the involved and the uninvolved hand were significantly greater in patients compared to controls.

Functional MRI (fMRI) during electrical stimulation revealed reduced index strength within SI and SII representations of the stimulated index finger of the affected hand compared to the healthy hand, and the extent of these signal changes correlated with the degree of impairment in tactile discrimination [307]. In contrast, fMRI during finger tapping with the CRPS-affected hand showed significantly larger activations in bilateral M1, pre-supplementary motor area (pre-SMA) and SMA proper, and intraparietal sulci, and in contrast to healthy subjects these activations were bilateral [122]. Abnormal activations in classical motor areas and in regions of the posterior parietal cortex (PPC) correlated with the extent of motor impairment. This increased neural activity in M1 may be due to defective inhibitory GABA-ergic circuits [301,308,309]. However, not all inhibitory neuronal circuits are affected in patients with CRPS I [310]. Disinhibition has also been observed in the somatosensory cortex of patients with CRPS I, whereas it was not present in patients with non-neuropathic pain [311]. Increased excitability in the somatosensory cortex as well as the motor cortex was seen not only in the hemisphere contralateral to the affected hand, but also contralateral to the unaffected side [301,311,312]. This suggests that disinhibition is not merely a response to pain, but could be a factor predisposing towards the development of CRPS I. However, in the other study of motor pathway excitability, disinhibition was confined to the affected limb [309].

Reorganization of SI may underlie various manifestations of CRPS, including the glove- or stocking-like distribution of sensory signs over a whole quadrant or even one whole side of the body [108], referral or mislocalization of tactile sensations [105], and the referred sensations [105] are very similar to those observed in patients with CRPS I [94,301,302], the disturbed body schema [315,318], the altered perception of the affected limb [119,313,329], the difficulties CRPS patients experience with initiating and executing movements [92,121–123], and the referred sensations [105] are very similar to what is seen in amputees and suggest that sensory-motor incongruence may also play a role in CRPS patients. They also suggest that not only the cortical reorganizations in SI, S2 and M1, but also functional disturbances in PPC may contribute to the chronification of pain. Indeed, preliminary data suggest a correlation between the extent of body perception disturbances and pain [311].

6.7.2. Central changes in pain processing

Functional neuroimaging studies have revealed a network or brain regions that are most commonly activated during the experience of acute pain. These include S1, S2, insular, anterior cingulate and prefrontal cortices and, less consistently, the thalamus [332,333]. These regions are often referred to as the “pain matrix” or pain neuromatrix, but it should be understood that activation of this network is not specific for painful stimuli and that a variety of other regions are activated and contribute to the pain experience in a context-dependent manner [332].

Functional MRI in adult and pediatric patients with CRPS I during brush-evoked mechanical allodynia showed stronger activation of the pain matrix compared to brushing of the unaffected extremity [334,335]. Allodynia additionally induced signals in regions involved in cognitive processing (frontal regions) that were not observed during stimulation of the uninvolved side. Only adults with upper extremity CRPS also showed activations of the contralateral M1 [334]. A similar pattern of activation was seen during mechanical hyperalgesia in adults [336]. In children and adolescents with CRPS brush-evoked allodynia also resulted in strong signals in the thalamus [335], (the investigations in adults focused exclusively on cortical areas [334]). Regions in thalamus and brain stem were found to specifically relate to central sensitization in experimental capsaicin-induced hyperalgesia [337].

Since CRPS I resolves much more frequently in pediatric compared to adult patients, this population provides a unique opportunity for comparisons between the symptomatic and symptom-free state. Two of the most notable findings of such comparisons were that 1) in the acute state, the brushing of the unaffected limb resulted in a large number of activation foci, whereas brushing of the same area after symptomatic resolution of CRPS produced far fewer activations; and 2) after symptomatic recovery, some of the changes in response to brushing (or cooling) of the affected limb persisted, even though these stimuli evoked only moderate pain at this time [335]. The same group of pediatric patients also exhibited a variety of connectivity changes after cold stimulation [338]. Some of these changes disappeared after symptomatic recovery, although cold sensitivity was still increased in
these patients. Other connectivity changes, particularly those involving the postcentral gyrus and posterior cingulate cortex, and the basal ganglia and amygdala, persisted after symptomatic recovery. This persistence of altered response and connectivity patterns suggests a possible predisposition for the relapses that frequently occur in pediatric CRPS I patients [49,50,75,77,79–81].

Connectivity in the resting state and brain morphometry have also been analyzed in adult patients with CRPS I and showed gray matter atrophy in areas involved in pain processing, in particular the ventromedial prefrontal cortex, anterior portion of the insula, and nucleus accumbens, while white matter connectivity was increased between the prefrontal cortex and the insula, but decreased to the basal ganglia [339]. Of note, anterior parts of the insula are specifically activated during allodynia [334,335] and hyperalgesia [336]. Similar morphological changes in gray matter morphology were observed in another investigation, which also showed that different chronic pain conditions have distinct brain morphological signatures [340]. This raises the hope of using such analyses in identifying neuroplastic changes that make relevant contributions to the chronification of pain. Clearly any such analysis must take into account the specific patient diagnosis; otherwise there are too many confounding issues and perhaps unrelated diagnoses that make interpretation impossible.

While studies of stimuli that are painful to patients and innocuous to controls compare two fundamentally different modes of perception, there have also been investigations of changes in processing of stimuli that induce the same intensity of pain in patients and controls [94,341]. These revealed stronger activation in the ipsilateral posterior cingulate cortex, but weaker activation of the contralateral and ipsilateral posterior operculum and ipsilateral anterior operculum in CRPS patients compared to healthy controls in response to painful electrical stimuli [341] and implicated defective PPC activation in the increased heat pain perception of patients with CRPS I [94].

During pain suppression tasks, CRPS I patients showed decreased activation of the periaqueductal gray (PAG) and the anterior cingulate cortex when either the painful or the unaffected hand was stimulated compared to healthy controls, even though both groups were similarly effective in suppressing pain [342]. Since the PAG has been implicated in descending pain modulation [332], this is consistent with data suggesting that endogenous pain modulation is disturbed in patients with CRPS in such a way as to facilitate nociceptive input [343]. The parameters used to assess endogenous pain modulation were not correlated with disease duration, acute or ongoing spontaneous pain, stimulus-induced pain, or other disease characteristics. Therefore, these results suggest that a shift towards net facilitation of nociceptive input may predispose for the development of CRPS I rather than result from it.

Altogether, these data suggest that pain and possibly central sensitization contribute to cortical reorganization [302,303], while maladaptive cortical reorganization in turn contributes to the maintenance or chronicification of pain. Both processes may be further enhanced by disturbances in endogenous pain processing pathways [94,341–343]. While there are some findings suggesting that certain of these alterations in central processing may predispose to the development of CRPS [308,311,343], there are as yet no conclusive data on whether cortical reorganization and altered brain processing are the cause or the result of CRPS.

### 6.8. Genetic predisposition

Several observations suggest that genetic determinants play a role in the predisposition to develop CRPS: 1) familial cases of CRPS (RSD, algodystrophy) have been reported [17,143,144,344–350]; 2) these patients often experience severe disease marked by early disease onset, disease recurrences, spreading of the disease to multiple sites, and/or dystonia [143,144,344,349,350]; and 3) in some instances, affected siblings show identical HLA profiles [344,350]. However, a clear pattern of inheritance cannot be determined [143,144].

HLA-DQ1 was significantly more frequent in 52 Dutch RSD patients compared to 295 regional controls [351] (for a discussion of the appropriateness of this control group see [352,353]), indirectly confirming data from a pilot study suggesting that the closely linked DR2 [15] might be associated with RSD [150]. In a study comparing 26 Dutch CRPS patients with multifocal or generalized tonic dystonia to healthy blood donors, no association with DQ1 was seen, but HLA-DR13 was significantly over-represented among patients [352]. This was supported by a significant association of CRPS with dystonia with microsatellite markers of a locus that is in linkage disequilibrium with HLA-DR-13 in the same group of patients [354]. In contrast, there was no association with HLA-DR13 in a larger cohort of CRPS patients with dystonia, who instead exhibited increased frequencies of HLA-B62 and DQ8 [355]. No significant associations with any HLA DR-DQ genotypes were detected in the overall group of another 161 Dutch patients with CRPS I [279]. However, HLA-DR6 and HLA-DQ1 were overrepresented in the subgroup of patients with primarily cold CRPS I as reported by the patient. The TNF2 allele of the polymorphism in the TNFα promoter region was associated with primarily warm CRPS I, and homozygosity for this allele increased the risk of having more than one extremity involved. There is no mention of whether any of these patients had dystonia.

The distribution of polymorphisms in various cytokine, neurotransmitter, and adrenergic receptor genes was examined in a prospective study of northern German patients who did or did not develop CRPS I after surgery because of distal radial fracture [136]. Despite the small number of CRPS I patients (n = 15), a significant association with a polymorphism in the α1a-adrenoceptor gene was detected. The relevance of this finding is unclear since the variants do not differ pharmacologically [356]. Angiotensin-converting enzyme (ACE) is one of the enzymes involved in the degradation of neuropeptides, in particular SP and bradykinin. Treatment with ACE inhibitors has been associated with an increased risk of developing CRPS I [357]. In a small Japanese study, the DD (deletion/deletion) genotype of the ACE gene was overrepresented in CRPS I patients [358]. These results were not replicated in two German studies, but one suffered from a small sample size [136], the other from inappropriate controls [345]. A GT-repeat polymorphism in the promoter region of the NEP gene, encoding another endopeptidase involved in the degradation of neuropeptides, also did not show any association with CRPS I in a southern German cohort and further analyses indicated that common variants of NEP were not likely to constitute a significant risk factor for the development of CRPS I [359].

Genetic disorders of mitochondrial DNA can also be associated with manifestations of CRPS [147]. Among ~500 children seen at a Genetics Clinic because of symptoms of dysautonomia or chronic idiopathic pain, 8 children from 7 families not only had a clinical diagnosis of mitochondrial disease, but also experienced at least one episode of CRPS that fulfilled the IASP diagnostic criteria, with 6 of these also meeting the Bruehl criteria [11]. In addition, all of the children had several less severe episodes that did not always satisfy these diagnostic criteria [147]. All of the children also had other dysautonomic manifestations, including frequent bowel dysmotility, chronic fatigue, cyclic vomiting, gastroesophageal reflux, migraine headaches and temperature instability. In addition, they responded well to multidisciplinary treatment approaches commonly employed in patients with mitochondrial dysfunction and autonomic disturbances. Importantly, several children with periodic relapses of RSD, CRPS or similar disorders have been described [76,126,349,360,361] and occasionally multiple recurrences have also been reported in adults [362]. In one series, gastrointestinal problems affected a considerably higher proportion of pediatric patients compared to healthy controls [78], others described several children with inexplicable severe or recurrent abdominal pain [79,126], and migraine has been found to
affect between 15 and 24% of pediatric CRPS patients [72,153]. Migraine headaches also have been identified as a risk factor for the development of CRPS in at least two separate adult cohorts [64,363], and an association of migraine with familial CRPS has been suggested [144]. Heightened awareness of the possible association between CRPS I and mitochondrial genetic disorders will be important for identifying cases that may respond to treatment for mitochondrial dysfunction.

6.9. Autoimmunity

Sera of patients with CRPS I and II have been reported to harbor autoantibodies that recognize a differentiation-dependent surface antigen on autonomic neurons [364,365]. However, these data are poorly controlled and have not been independently recapitulated. In a subset of these patients, these antibodies are functionally active in that they exert agonistic effects on the β2-adrenergic receptor or the muscarinic-2 receptor, with 5/11 sera binding to both receptors [366]. In addition, passive transfer of serum IgG from CRPS patients caused behavioral changes and motor impairment in mice [367]. Furthermore, some patients with CRPS experienced pain relief after intravenous immunoglobulin treatment [367]. The relevance of these findings still remains unclear, particularly since they await independent confirmation. Nonetheless, an autoimmune model for CRPS has been developed, in which injury facilitates the binding of pre-existing autoantibodies to autoantigens [364,365]. However, these data are poorly controlled and have not been independently recapitulated. In a subset of these patients, these antibodies are functionally active in that they exert agonistic effects on the β2-adrenergic receptor or the muscarinic-2 receptor, with 5/11 sera binding to both receptors [366]. In addition, passive transfer of serum IgG from CRPS patients caused behavioral changes and motor impairment in mice [367]. Furthermore, some patients with CRPS experienced pain relief after intravenous immunoglobulin treatment [367]. The relevance of these findings still remains unclear, particularly since they await independent confirmation. Nonetheless, an autoimmune model for CRPS has been developed, in which injury facilitates the binding of pre-existing autoantibodies to target structures, thereby enhancing central sensitization [367]. On the other hand, these autoantibodies appear to be considerably more frequent in patients with CRPS II compared to those with CRPS I [364,365], suggesting that they could be mere epiphenomena.

7. Treatment

7.1. Outcome measures

Impairments in particular changes in pain intensity, are the most common outcome measures in RCTs and other interventional or observational studies [368]. It is only quite recently that the importance of assessing disabilities in performing activities of daily living (ADL), and handicaps, i.e., limitations in social functioning and role fulfillment, is increasingly recognized [100,368–373]. Of note, an instrument for objectively measuring limitations in limb usage during everyday life has been developed [374,375]. There is no general consensus on what constitutes resolution or recovery in CRPS, i.e., to what extent residual pain and functional limitations may still be present. It should also be noted that residual functional impairment or disability may not be attributable to CRPS but to the original injury that precipitated it or to comorbid conditions [63,370].

7.2. Rehabilitation

Since the pathophysiological mechanisms of CRPS are essentially unknown and the mechanisms are likely to differ between individual patients, treatment of these disorders is based on trial and error. The mainstay of treatment is physiotherapy (PT) and occupational therapy in order to improve ROM and to avoid atrophy and contractures. There is no conclusive evidence in favor of any particular approach [376]. It is usually recommended to adjust the intensity and form of PT so as not to aggravate pain and swelling. However, intensive aerobic and weight-bearing exercise therapy that was clearly not pain-contingent was very effective in pediatric patients [49,71]. It has even been speculated that the higher resolution rate of CRPS in children might be due to a greater willingness in children to fully participate in the recommended PT rather than to true differences in the characteristics of adult and pediatric CRPS [151]. Some support for this hypothesis comes from recent interventional studies in adults showing that “pain exposure” PT, is safe and quite effective in reducing pain and increasing functionality even in long-standing therapy-resistant CRPS [372,377]. A RCT comparing “pain exposure” physical therapy to conventional treatment, including pain-contingent physical therapy, is being planned [378].

Another rehabilitation approach, graded motor imagery (GMI), is aimed at eliminating the mismatch between motor intention and sensory feedback that is thought to contribute to pain perception in chronic CRPS. It starts with hand laterality recognition, followed by imagined hand movements, and finally mirror therapy [379]. The exact sequence of interventions was found to be important [380]. While GMI significantly reduced pain and swelling in patients with CRPS I in several RCTs [379–381], it may not translate easily into the normal clinical setting [382].

7.3. Pharmacological agents

Pharmacological treatments are intended to provide pain relief and, thereby, to facilitate physical rehabilitation. It is customary to start patients on analgesics and NSAIDs with some guidelines recommending the use of the WHO ladder except for strong opioids [47,383]. These medications are often ineffective in sufficiently reducing pain and are then followed by pharmaceuticals used in the treatment of neuropathic pain [46,47,383]. For patients with dystonia, oral baclofen is the first-line treatment of choice, while intrathecal baclofen should be used only as a last resort [46,47,383]. According to a recent summary of systematic reviews of therapeutic interventions for pain relief and functional improvement in RSD/CRPS, the existing evidence is too weak to draw any conclusions for any of these pharmaceutical interventions [376].

Since CRPS has been suggested as due to an exaggerated inflammatory response, which generates excessive amounts of free radicals, topical antioxidants/free radical scavengers have been tested in a few RCTs. Although the overall evidence in favor of topical free radical scavengers is weak at best [376], Dutch treatment guidelines recommend their use for inflammatory symptoms [47,383]. They also recommend considering prescription of 500 mg of vitamin C for 50 days in order to reduce the risk of CRPS after wrist fracture [131,384]. However, once again we emphasize the absence of evidence-based research. It is important that patients not be turned into a polypharmacy. Steroids have no role in CRPS.

7.3.1. Bisphosphonates

With the recent publications of the results from an RCT with neridronate [370] there now is fairly convincing evidence that various bisphosphonates have an acceptable safety profile and can significantly relieve spontaneous and stimulus-evoked pain and improve functional status in patients with early disease (<6 months duration) and abnormal uptake in 3-phase bone scintigraphy [370,385–388]. Follow-up was short in most studies, but in the most recent and largest study, improvement seen after neridronate treatment was sustained or even further enhanced over follow-up of at least one year [370]. There are indications that the doses necessary to achieve long-term remission are quite high, namely 100 mg neridronate or 90 mg pamidronate, each given i.v. four times over a period of 10 days [370]. Recruitment in all but one of these studies [388] was restricted to patients in whom generation and maintenance of pain was most likely associated with osteoclastic overactivity [389]. Bisphosphonates have analgesic properties that go beyond their effect on bone metabolism, and preclinical data suggest that they have antinociceptive effects in animal models of neuropathic pain [389]. Therefore, their efficacy may not be limited to CRPS patients with bone-related pain, but relevant clinical data are not yet available.

7.4. Sympathetic nerve blocks and sympathectomy

According to a recent Cochrane review of reviews, there is moderate evidence that sympathetic nerve blocks with local
anesthetics and i.v. regional blockade with guanethidine are not effective [376]. No RCTs have been performed to compare sympathectomy to a sham procedure or placebo in patients with CRPS, but it has long been perceived as effective in the treatment of causalgia [83,390] and continues to be used at various treatment centers around the world [95,391,392]. Follow-up was generally quite short, but extended up to 6 years in some patients, none of whom had a recurrence [83]. It should be kept in mind that up to 40% of patients experience temporary post-sympathetic neuralgia [393,394]. Compensatory hyperhidrosis and pathological gustatory sweating occur in <10% of patients in most series [207,393–395]. Sympathectomy is now most commonly performed via endoscopy or percutaneous radiofrequency, but it is not certain whether these procedures reduce the rate of severe complications.

7.5. Surgery

There is great reluctance to perform surgery in patients with CRPS because of the fear of aggravating or rekindling the signs and symptoms [396]. However, there is considerable evidence that nerve compression and entrapment are under-recognized causes of the complaints in patients diagnosed with “CRPS” [43,44,397–402]. Compression of the median, ulnar, or radial nerve is a known complication of distal radial fracture [130,137], which in turn frequently precipitates CRPS [18,86,128,129]. A correlation has been observed between above-average pressure in the carpal tunnel immediately before and during reduction of dislocated fractures of the distal radius and the subsequent development of Sudeck’s dystrophy [403]. Importantly, there are several reports that surgical decompression, neurolysis, resection of neuroma, and joint denervation singly or in combination can result in significant or even complete relief of pain and other symptoms and functional restoration in a substantial number of patients originally diagnosed as RSD or CRPS I, even if a minority of patients do not benefit [43,44,130,397–402]. The potential magnitude of the issue becomes obvious when considering that retrospective chart review of 100 consecutive patients with CRSP I according to IASP criteria identified a total of 70 patients (40 upper and 30 lower extremity) in whom surgery was indicated because of one or more injured or compressed peripheral nerve(s), as identified by nerve blocks of joint and/or cutaneous afferents [44,397]. According to predefined criteria that included measures of pain, opiate use, ability to perform ADL and return to work, the outcome of surgery was excellent in 40% of upper extremity involvement and 47% of lower extremity involvement, the corresponding figures for good outcome were 40 and 33%, respectively. In other words, failure was only seen in 20% of patients possibly due to the failure to perform placebo controls for the somatic nerve blocks. This indicates that diligent and thorough exploration of the differential diagnosis – rather than being satisfied with the label “CRPS” – may reveal peripheral nerve lesions that can be corrected surgically.

In a considerable number of patients with causalgia, the pain and other signs and symptoms may also be attributable to the persistence of some active noxious input, including retained foreign bodies, fibrosis resulting in nerve entrapment or compression, or false aneurysms or arteriovenous fistula leading to nerve distortions [84,404]. Instead of aggravating causalgia, surgical interventions frequently result in good pain relief in conjunction with partial improvement in nerve function [84,404–408].

7.6. Amputation

Amputation should be reserved for patients with severe, recurrent infections and severe limb dysfunction [46,47]. Since the incidence of recurrence and of phantom pain are high, it should not be considered for pain relief alone [409].

7.7. Psychological interventions

The preponderance of the evidence suggests that psychological factors do not play a major role in the development of CRPS in the majority of patients [173]. Nonetheless, there certainly are cases with a strong psychogenic component [164–168]. In many cases the diagnosis of CRPS follows a traumatic injury and many of the complaints may be due to issues of secondary gain. It is therefore particularly important that objective physical examinations and neurologic exams be performed. In addition, the rates of depression, anxiety and other signs of psychological distress are elevated in CRPS patients most likely as a result of the chronic pain and other disabling consequences [410–412]. Therefore, a comprehensive approach to treating CRPS must include addressing the psychosocial components of the disorders by providing cognitive-behavioral therapy, including counseling, operant treatment, and instructions in pain coping strategies and relaxation techniques [46,47].

Unfortunately, the proportion of patients who achieve a predetermined (e.g., 30% or 50%) reduction in pain intensity or improve in other outcome measures in RCTs often remains unreported [413–417]. When such figures are provided, they almost invariably indicate that there are complete responders, partial responders, non-responders, and occasionally even patients whose symptoms worsen [418–420]. This is confirmed in observational studies in both adults [421,422] and children [76,82]. In addition, there are data suggesting that patients with primarily warm and cold CRPS I may respond differently to certain interventions [369].

8. Outcome

There is very little reliable information on the overall outcome of RSD/CRPS. This is due to several factors. Firstly, almost all patient cohorts described to date consist of patients seen at tertiary pain clinics or similar institutions specialized in the treatment of CRPS and, therefore, are likely to represent the most severe and most chronic end of the spectrum. In fact, there may well be bias by those tertiary pain centers which only contributes to the general confusion of the literature. Secondly, there is possible selection bias in studies that rely on mailed questionnaires to assess current symptoms and have response rates of 56%–70% [142,346,423]. Finally, the use of numerous different sets of diagnostic criteria, a myriad of different treatment approaches as well as different – sometimes poorly defined and unstandardized – outcome measures make data interpretation difficult.

8.1. Symptom resolution

The results of prospective studies of patients with algodystrophy/ RSD/CRPS after fractures suggest that many of the symptoms resolve over the course of ~12 months [18,129,138,424]. Nonetheless, few if any patients are free of complaints one year or more after the initial trauma [18,425], and approximately 20–25% of cases become chronic [138] or still fulfill the IASP diagnostic criteria [18]. Even patients whose outcome after an acute episode of RSD or CRPS was considered good by their treating physician frequently reported pain, particularly use- and/or weather-dependent pain, finger stiffness and numbness, impaired grip strength, and sensory abnormalities upon reassessment after a mean of 11 and 18 months, respectively [373,425].

There are only two population-based studies of outcome in CRPS [16,63]. In Olmsted County, MN, the physicians’ notes indicated that 74% of patients experienced disease resolution, with symptoms lasting a median of 7 months [63]. In the Netherlands, only 30% of CRPS patients considered themselves recovered, 16% still suffered from severe progressive disease, and the remainder was stable an average of 5.8 years after onset [16]. This is similar to the results of cohort
studies showing that some combination of spontaneous or induced pain, stiffness and other symptoms affect at least 60% of respondents several years after symptom onset [142,423]. Spontaneous pain is the most important predictor of physical impairments and limitations in ADL [423,426], which in turn relate to restrictions in social function and role limitations due to physical problems [373,423].

8.2. Employment/work status

Data on the consequences of CRPS/RSD on the employment status have been accumulating but, unfortunately, are often presented in such a disorganized manner as to make it virtually impossible to extract any kind of concrete information regarding the number of patients capable of resuming the work (gainful employment or housework) they did before their diagnosis. The majority of patients who are employed at the time of CRPS onset stop working for at least 3 months, and often 12 or more months [427–429]. At the time of presentation to a tertiary pain center, fewer patients with RSD were employed (31%) compared to patients with chronic headaches (63.4%), or with chronic lower back pain (42%), and a higher proportion of patients with RSD (49%) were receiving compensation compared to both other patient groups (41% for back pain, 36% for chronic headaches) [412]. In the Dutch population-based study, 69% of patients were able to resume employment [16]; in other cohort, this figure ranges from ~20% to ≥75% [142,148,428–431]. Many patients are unable to return to the same occupation or require adjustment of the workplace [16,427,428,431]. Approximately 10–35% become officially disabled [16,63,142,427–429]. Of note, most studies do not break this figure down into disability due to CRPS itself and other causes. In the population-based study from Olmsted County, only two of the 55 patients who were not retired or not employed for other reasons had complete disability due to CRPS, four had partial disability [63]. However, another 11 were disabled from other causes, including the trauma that had triggered CRPS.

As a result of reduced full-time employment, mean household income decreases when an adult family member is affected by CRPS [430]. In addition, there is a significant shift in time allocation not only for the patients themselves, but also for their spouses, with both spending more time on household chores and less time on leisure activities.

8.3. Predictors of outcome in adults

In the two population-based studies, CRPS following fracture was found to be associated with a higher resolution rate [63] and better outcome [16], while involvement of an upper extremity, and cold CRPS were associated with worse outcome in the Netherlands [16]. Unfortunately, it is unclear whether patients were asked to report the temperature of the involved limb at onset or at the time of assessment. A colder skin temperature of the affected limb at the onset of symptoms was associated with the recurrence of RSD in, or spreading of RSD to, a second limb [432] and the development of dystonia [124,433], other severe complications [124], and possibly the requirement for amputation [434]. Unlike overall outcome [16], severe complications were also associated with involvement of a lower extremity in addition to younger age and female gender [124].

8.4. Outcome in pediatric CRPS

CRPS in children and adolescents is still underrecognized, often resulting in considerable diagnostic delay [50,79,81]. Disease severity in pediatric patients with CRPS or similar disorders is highly variable, as is the time to resolution or resumption of age-appropriate activities [50,72,75,79]. Nonetheless, one is left with the impression that the outcome in this age group is generally more favorable compared to adults, even though treatment is frequently conservative, relying mainly on PT and cognitive–behavioral interventions. In the largest pediatric series reported to date, 92% of children and adolescents were free of symptoms after an intensive PT program [49]. Recovery rates of ≥70% have been reported in other smaller series as well [50,72,75,80], but resolution or recovery is not always clearly defined.

Nonetheless, between 28% and 48% of patients with pediatric CRPS experience a relapse [49,50,75,77,79–81]. These recurrent episodes are often less severe and respond to treatment more quickly [49,75,77]. In addition, there are also data suggesting that the prognosis of pediatric CRPS can be far from favorable and that a substantial portion of patients continue to experience pain and functional impairment [73,80,82,176]. Most notably, in response to a mailed questionnaire (75% response rate), at least half of young adults who had experienced CRPS I during childhood or adolescence (a median of 12 years previously) still reported spontaneous pain (52%), pain after exercise (57%), and a variety of sensory, motor, and autonomic symptoms, even though the prevalence of most of these symptoms had decreased compared to the first visit [435]. In addition, the SF-36 scores indicated that these subjects experienced poorer health-related quality of life compared to normal Dutch controls, in particular scores for physical functioning were lower.

9. Discussion

One of the most peculiar features of the IASP and the Harden/Bruehl or Budapest diagnostic criteria is the specific mention that the diagnosis of CRPS is excluded “by the existence of other conditions that would otherwise account for the degree of pain and dysfunction” [19,20]. This clearly raises the question of whether CRPS is a disease or syndrome in its own right. In that case it should be defined by its diagnostic criteria rather than being made out as a default category. As it stands, this “criterion” quite accurately reflects the uncertainty as to whether this collection of sensory, autonomic, and motor disturbances in highly variable combinations that is now called CRPS is a valid concept. The heterogeneity in the constellations of signs and symptoms in individual patients classified as CRPS I and the great variability in the response to specific treatments at the very least suggest the existence of distinct subgroups with different underlying pathophysiological mechanisms.

The first question that comes to mind is whether CRPS I and II are really similar enough to include them under the same designation. There are few direct comparisons with a large enough sample size to yield meaningful results, and even fewer of these provided details on the type and extent of neurological testing that was performed in order to rule out a peripheral nerve injury in patients with CRPS I. The signs and symptoms appear to be quite similar in both conditions [60]. Even the somatosensory profiles for patients with CRPS I and II are almost identical. Nonetheless, some significant differences were also detected. These included that mechanical detection threshold values were significantly more often abnormal in CRPS II compared to CRPS I (54% vs. 30.9%) and the proportion of patients displaying exclusively sensory gain was significantly higher among patients with CRPS I compared to CRPS II (34.6 vs. 15.4%), respectively. The existing data also indicate that the incidence of movement disorders differs significantly between CRPS I and CRPS II patients. Unfortunately, however, the specific results are highly contradictory, with one group of investigators seeing them exclusively in patients with CRPS I [125], while other data suggest that the frequency of these disorder is significantly higher in patients with CRPS II compared to those with CRPS I [65]. Microneurography showed normal C-fiber activity in all 13 patients with CRPS I, whereas abnormal discharges of nociceptive C-fibers were observed in 6 of 11 patients with CRPS II [228]. This suggests that continued peripheral nociceptive input maintains pain in at least some patients with CRPS II, but that other processes must account for the spontaneous pain in CRPS I patients. These limited and variable results do not allow any firm conclusions regarding the
similarity of CRPS I and II, but they suggest the existence of subgroups within CRPS II.

It is possible that pediatric CRPS I constitutes another subgroup. In children and adolescents, the disorder most frequently affects the lower limb, which is more often blue and colder than the healthy side and frequently shows hypoperfusion in three-phase bone scintigraphy. While primarily cold CRPS is a poor prognosticator in adults, the majority of pediatric patients achieve improvement or symptom resolution mainly with PT and cognitive-behavioral interventions, even if relapses are common. In contrast, adults more often have involvement of an upper extremity, which initially is red and warmer than the healthy side, and only later may become cold and bluish and which shows hyperperfusion. In addition, RSD/CRPS appears to become chronic and resistant to any therapy more often in adults. This raises the question of whether pediatric CRPS is a subgroup of the same disorder as in adults or a different entity entirely.

Patients with a cold extremity at the onset of their symptoms may constitute another subgroup, as suggested by the association of primarily cold RSD/CRPS with worse overall outcome [16] recurrence or spreading of RSD to another limb [43] and the diagnosis of patients as primarily cold generally relied on patient recall of the skin temperature at symptom onset. And even though the potential prognostic significance of this subtype has been appreciated for some time, current studies may report the incidence of color and temperature asymmetries, but fail to specify the direction and nature of these changes [60,66].

Arguably the clearest demonstration of the existence of distinct subgroups comes from a recent investigations of a large patient cohort diagnosed according to the IASP criteria [277]. Approximately 1/3 of the patients exhibited markedly elevated levels of essentially all of the more than 20 cytokines, chemokines and their soluble receptors that were investigated; the other patients had normal values for nearly all of them. Of particular note is the finding that increased plasma concentrations of TNFα or IL-1β correlated with disease duration or severity only in those subjects without a simultaneous increase in soluble receptors or receptor antagonists for these cytokines. This implicates these cytokines in the pathophysiology of the disorder in this patient subgroup [277]. Together with the normal levels in ~2/3 of the patient cohort, this suggests that distinct mechanisms contributed to the development and maintenance of symptoms in the two patient subgroups.

What is even more peculiar than the explicit exclusion of a diagnosis of CRPS by the existence of other conditions that would otherwise account for the degree of pain and dysfunction, is the invention of a CRPS-NOS (not otherwise specified) category by the Budapest consensus panel [20]. This category is intended for patients who partially (partially is not ever defined!) fulfill the diagnostic criteria, but whose symptoms are “not better explained by any other condition.” What could better illustrate that CRPS is a default label rather than a diagnosis. Accordingly, it has been shown that “CRPS I” can be mononeuropathy [43,436], nerve compression or entrapment [44,397–402]; dysfunctions postural [437]; somatoform disorder, self-inflicted or factitious disorder, or malingerings [72,75,124,154,162–165,170,171]. Of course, these are almost all part of the differential diagnosis, but obviously are not always recognized by many treating physicians. This clearly indicates that “CRPS” is simply a catch-all label and, therefore, should not be considered a valid diagnostic endpoint, as Thimineur and Saberski [43] urged shortly after the IASP criteria had been proposed and as has been echoed by others in the context of CRPS II [84]. Therefore, both CRPS I and II should be considered to indicate the urgent need for extensive exploration of the differential diagnosis [43,436,438].

Take-home messages

- Complex regional pain syndrome is a poorly defined term used to describe a variety of disorders characterized by pain disproportional to the inciting event.
- There are almost as many diagnostic criteria for complex regional pain syndrome as there are names to this disorder.
- Numerous etiological pathophysiological events have been incriminated, including inflammation, autoimmunity, neurologic disorders, altered blood flow and central cortical reorganization. However, the number of studies involved most often have insufficient patients and lack controls.
- Future research should allow more rigorous standards to allow a better understanding of complex regional pain syndrome, including what it is, if it is and when it is.

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