Pomeranian J Life Sci 2025;71(2):23-31 doi: 10.21164/pomjlifesci.1154

Complex regional pain syndrome of the upper extremity: a narrative review

Andrzej Żyluk[1, A] ✉, Nadine Hollevoet[2, B]

[1] Pomeranian Medical University in Szczecin, Department of General and Hand Surgery, Unii Lubelskiej 1, 71-252 Szczecin, Poland
[2] Ghent University Hospital, Department of Orthopaedic Surgery and Traumatology, Corneel Heymanslaan 10, 9000 Gent, Belgium

[A] ORCID: 0000-0002-8299-4525; [B] ORCID: 0000-0002-6101-8170

✉ azyluk@hotmail.com

ABSTRACT
Complex regional pain syndrome (CRPS) is a condition for which diagnosis and treatment are not unequivocally attributed to a particular medical speciality. This article presents a set of updated information about this condition, including the specific subtypes of CRPS, which differ from each other with respect to symptomatology, susceptibility to treatment, and prognosis. A new subtype called "chronic, refractory complex regional pain syndrome", which is extremely severe, disabling, and resistant to standard treatments, is proposed. The article also emphasizes the difficulties in diagnosing the condition due to its variable clinical presentation and vague, imprecise diagnostic criteria. A review of treatments is presented, with commentary on their effectiveness: good in the early stage, less effective in the chronic stage, and generally poor in the chronic, refractory variant.
Keywords: complex regional pain syndrome; pathophysiology; classification; diagnostic criteria; treatment.

INTRODUCTION

Complex regional pain syndrome (CRPS) is a descriptive term for a complex of symptoms and signs, including pain at rest or with the slightest movement, swelling, vasomotor instability (changes in colour, temperature, and sweating), and severe functional impairment of the affected hand or entire extremity. It is usually caused by trauma or surgery and is characterised by the presence of symptoms and signs that are more severe than would normally be expected for the degree of trauma associated with the precipitating event (which can sometimes be very minor) and extend beyond the area affected by the initial trauma [1, 2]. The clinical presentations of CRPS vary between patients [3, 4]. Complex regional pain syndrome is not confined to the hand and upper extremity; involvement of the foot, knee, and hip has been described. In general, although very infrequently, it can occur anywhere in the body [1, 4]. Complex regional pain syndrome in the upper extremity most commonly occurs after trauma or surgery, but it can also develop after a stroke, heart disease, or spontaneously [1, 3].

Complex regional pain syndrome is a condition for which diagnosis and treatment are not unequivocally attributed to a particular medical specialty. In most European countries and in the United States, it is primarily managed by anaesthetists and therapists, less commonly by neurologists and rheumatologists. However, in most cases, the condition is a complication of injuries treated by orthopaedic and general surgeons. Unfortunately, the "authors" of this clinical problem often do not attempt to address it. The author of this paper is a hand surgeon who has for more than 30 years been involved in research, diagnosis, and management of CRPS. The objective of this article is to present updated information about this condition in the form of a narrative review.

PATHOPHYSIOLOGY

The aetiology of CRPS is likely multifactorial. It is thought to be pathological, not psychopathological, in origin. Several theories have been proposed, including involvement of the sympathetic nervous system, abnormal inflammatory reaction, neurogenic inflammation, central sensitisation, altered central processing, psychological disturbances, and as a result of inactivity. Some of these will be presented below.

The sympathetic theory

The sympathetic theory attracted wide popularity over several decades in the last century, followed by the coining of the former name of the syndrome – reflex sympathetic dystrophy (RSD). The clinical course of CRPS during its chronic phase is characterised by the affected area being cyanotic, wet, and cold due to vasoconstriction. This mechanism has been suggested to result from excessive sympathetic nervous system activity, which is considered an indicator of disease progression and a contributing factor to pain. Experimental studies have reported that expression of adrenergic receptors on nociceptive fibres after tissue damage and nerve trauma might provide a potential mechanism for sympathetically induced pain [5]. Several treatment modalities have been developed involving sympathicolysis, such as stellate ganglion block and regional intravenous block with guanethidine, some of them being very effective [6]. This theory has eventually been questioned because it did not adequately explain all the clinical aspects of the disease; however, involvement of the sympathetic nervous system in the chronic stage of CRPS seems to be justified.

Inflammatory mechanism

An exaggerated inflammatory response to trauma as an underlying mechanism for CRPS was postulated as early as 1942 by Paul Sudeck, and this theory was constructively developed by Goris et al. in the 1980s [7]. Clinical presentation of the acute phase of CRPS confirms that inflammatory mechanisms are involved in the pathophysiology of the condition [8]. Tissue injury is considered to trigger an exaggerated and persistent release of pro-inflammatory cytokines such as tumour necrosis factor α (TNF-α), interleukin (IL)-1β and IL-6, which activate the cascade of inflammation that results in a painful, red, and swollen extremity. It was found that IL-8 is significantly elevated in the serum during the acute phase of CRPS, while other pro-inflammatory mediators such as TNF-α, interferon γ, IL-2, monocyte chemoattractant protein 1 (MCP-1), and bradykinin are elevated during the chronic phase [9]. Increased concentrations of IL-6, MCP-1, and macrophage inflammatory protein 1β were also found in the affected limb [10]. Although the classic inflammation hypothesis fits more with the warm phase of CRPS, some studies have shown that even in the cold stage inflammation may still play a role. It has been shown that the concentrations of inflammatory cytokines IL-6 and TNF-α in the affected extremity are comparably disturbed in both cold and warm CRPS [11]. Several studies showed the effectiveness of treatment utilising free radical scavengers such as mannitol, corticosteroids, N-acetylcysteine, and dimethyl sulfoxide (DMSO), particularly in the acute stage of the condition [12, 13, 14]. Moreover, an inflammatory component does not preclude a role for the sympathetic nervous system as a factor involved in the whole spectrum of abnormalities in CRPS, particularly in the chronic stage.

Neurogenic inflammation

Neurogenic inflammation mechanisms are also involved in the development of CRPS. Stimulation of peripheral endings of the nociceptive C-fibres subsequently conducts the stimulus not only afferently to the dorsal ganglia, but also efferently through branches extending back into the involved tissue (backward firing). This stimulation causes the release of several pro-inflammatory neuropeptides such as: substance P, calcitonin gene-related peptide (CGRP), neurokinin A, adrenomedullin, neurokinin B, vasoactive intestinal peptide, neuropeptide Y, and gastrin-releasing peptide (GRCP). The GRCP activates the CGRP receptor in smooth muscle and endothelial cells, inducing vasodilation of arterioles. Moreover, substance P and neurokinin A promote vascular permeability by activating neurokinin A1 receptors in endothelial cells [15]. These changes result in hyperaemia, tissue oedema, and exudation of leukocytes. The GRCP and substance P activate resident cells such as mast and dendritic cells. These, in turn, release inflammatory mediators including histamine, serotonin, and TNF-α, which stimulate inflammatory cells and further increase inflammation, but also act upon local nociceptive Aδ-fibres, inducing peripheral nerve sensitisation. Over and above, CGRP promotes sweat gland function and hair growth [16, 17].

Altered central processing

The pathophysiological role of altered central processing has recently attracted increasing popularity and received support from animal and human investigations. This theory explains well the peculiar pain phenomena associated with CRPS, such as pain being disproportionate to the degree of trauma of the precipitating event, hyperpathia, and allodynia. Brain imaging by functional magnetic resonance imaging (MRI) has shown changes in brain function in patients with chronic CRPS, thus providing support for the altered central processing theory [18]. There are reports that the affected limbs of CRPS patients make up a smaller representation in the somatosensory cortex than unaffected limbs. This may lead to increasing central nervous system symptomatology as the disease progresses, such as motor dysfunction, neglect, and impaired recognition. There is also decreased range of motion and dystonia with flexion of fingers and wrists in some patients [19]. A model of neuropathic pain is proposed in which ongoing nociceptive afferent input from a peripheral focus dynamically maintains altered central processing that accounts for allodynia, severe pain, and other sensory and motor abnormalities [19, 20].

Psychological stress

It has been hypothesised that CRPS may be a condition of psychogenic origin, may be psychologically mediated, and that psychological or psychiatric disturbances can be facilitating factors [3, 4]. Some findings from the literature support this view [3, 4, 21]:

- the fact that symptom severity and duration are out of proportion to the relatively innocuous inciting injury;
- a significant number of psychiatric disorders (e.g., depression) and personality abnormalities (neuroticism, anxiety, emotional imbalance) have been frequently diagnosed in patients with CRPS;
- the beneficial effect of psychological support in the treatment of CRPS is regarded as indirect evidence of the psychogenic origin of the condition;
- a high incidence of positive placebo responders is reported in controlled studies on the effectiveness of the treatment of CRPS.

Geertzen et al. found that traumatic social life events or other psychological problems were present in 60% of CRPS patients at the time of the causative trauma. A disparity was reported between the high level of perceived disability and the minimal objective impairments measured in long-term follow-up of CRPS patients who eventually recovered [22].

CLINICAL SUB-TYPES

Classically, CRPS is classified into 2 forms – type 1 (formerly RSD) and type 2 (formerly causalgia). Complex regional pain syndrome type 1 comprises the majority of post-traumatic cases, whereas CRPS type 2 diagnosis requires evidence of nerve damage as a causative event (some authors suggest the need for objective, electrophysiological confirmation of nerve involvement). The necessity of distinguishing these 2 forms has recently been questioned, since in most cases nerve

involvement cannot be definitively excluded and both forms are clinically identical [23, 24]. Likewise, the traditional 3-staged (acute, dystrophy, atrophy) evolution of CRPS has been questioned. Now, 2 forms are distinguished in the course of the condition: acute/early and chronic/late, which differ significantly with regard to symptomatology, treatment requirements, and prognosis [25, 26]. There is no precise timing for the transition from the acute to the chronic form, but it usually occurs within 3–6 months after onset of the condition, with the caveat that any therapeutic intervention may alter this progression.

There is no definitive single test for confirming or excluding CRPS, and diagnosis relies on clinical examination with the requirement for a sufficient number of symptoms and signs to be present. According to the Budapest diagnostic criteria, 4 categories of features are established: sensory, vasomotor, sudomotor/oedema, and motor/trophic – Table 1 [2, 23]. Based on our clinical experience, the following clinical subtypes of the condition may be distinguished, differing significantly with respect to symptomatology, treatment susceptibility, functional impairment, and prognosis. This classification is not necessarily consistent with that officially existing in the literature, but it is based on our clinical experience with the diagnosis and treatment of 220 CRPS patients over a period of 32 years (1990–2022).

TABLE 1. Modified International Association for the Study of Pain criteria (the Budapest criteria) for diagnosis of complex regional pain syndrome

Presence of continuing pain, disproportionate to any inciting event	
Must report at least 1 symptom in each of the 4 categories*	
Sensory	hyperalgesia and/or allodynia
Vasomotor	temperature asymmetry and/or skin colour changes and/or skin colour asymmetry
Sweating/ oedema	oedema and/or sweating changes and/or sweating asymmetry
Motor/trophic	decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (skin, hair, nails)
Must display at least 1 sign at the time of evaluation in 2 or more of the following categories	
Sensory	hyperalgesia (to pinprick) and/or allodynia (to light touch, temperature sensation, deep somatic pressure and/or joint movement)
Vasomotor	temperature asymmetry (>1°C) and/or skin colour changes and/or skin colour asymmetry
Sweating/ oedema	oedema and/or sweating changes and/or sweating asymmetry
Motor/trophic	decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (skin, hair, nails)
There is no other diagnosis that better explains the symptoms and signs	

* In each of the 4 categories, all conditions must be met for research purposes. For clinical purposes, a report of at least 1 symptom in 3 of the 4 categories is sufficient to meet this criterion.

Acute (early) complex regional pain syndrome after distal radial fractures

Acute (early) CRPS after distal radial fractures is shown in Figures 1 and 2. This form represents approx. 80% of cases in our register. It is a very specific and the most numerous form, characterised by mild to moderate clinical severity, typical symptomatology, relatively easy treatment when diagnosed early, and a good prognosis [27, 28]. It is believed that it can be recognised as early as 2 weeks after the fracture; however, this may lead to overdiagnosis, because early CRPS and the post-traumatic period share many similarities and may be interpreted differently [28, 29]. Complex regional pain syndrome after distal radius fractures has a natural tendency toward spontaneous resolution in the mid-term perspective [30, 31]. There is also a spectrum of patients presenting with mild, transient forms of CRPS which – although meeting the Budapest criteria for diagnosis at 1–2 months after the fracture – are only moderately disturbing for patients and may be left untreated or managed with physiotherapy alone [2, 29]. After the withdrawal of most CRPS symptoms and signs, patients can experience some "residual" complaints for as long as 1 year or more after disease onset [32, 33]. Complex regional pain syndrome after fracture of the distal radius occurs mainly (90%) in middle-aged or older women and progresses into the chronic stage relatively infrequently (less than 10%).

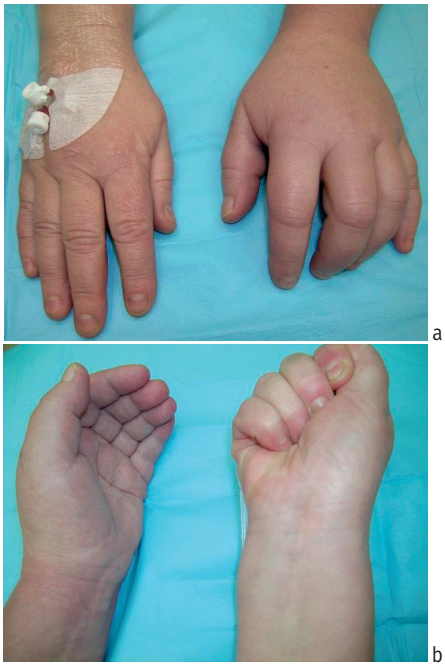

FIGURE 1. Acute complex regional pain syndrome after distal radius fracture: (a) note severe swelling of the left hand; (b) note reduction of fingers movement

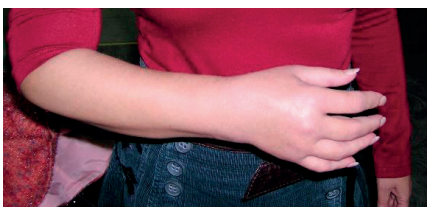

FIGURE 2. Acute complex regional pain syndrome after fracture of the distal radius – typical appearance and position of the hand

Acute (early) complex regional pain syndrome after surgery for hand diseases and injuries

Acute (early) CRPS after surgery for hand diseases and injuries (carpal tunnel syndrome, Dupuytren's disease, trigger digits, hand fractures, tendon and nerve injuries) occurs much less frequently than after fractures of the distal radius, representing approx. 2% of cases in our register. It is characterised by similar symptoms and signs typical of the early condition, usually appearing within 1 month after trauma or surgery. This form is relatively easy to diagnose because patients are still under postoperative care. It is necessary to differentiate this form from occult infection spreading through the synovial sheaths of the palm proximally or distally, particularly after minimally invasive surgery. The author has encountered such situations, and in some cases making the correct diagnosis was difficult. Women are more frequently affected, although the difference is not as pronounced as after distal radial fractures. As this form is usually diagnosed early, treatment is effective, the prognosis is good, and recovery may be expected within a reasonable timeframe. Very infrequently, this form progresses into chronic CRPS, unless it is overlooked or neglected. There is no information about the natural course of this subtype, but it is probably self-limiting, similar to cases following distal radial fractures [1].

Chronic (long-lasting) complex regional pain syndrome

As mentioned earlier, chronic CRPS occurs relatively infrequently (approx. 17% of patients in our register). If not spontaneously resolved, overlooked, or misdiagnosed, the acute form progresses within 3–4 months into chronic CRPS, presenting with moderate hand pain, mild swelling, colder and pale skin, frequent hyperhidrosis, tenderness or hyperpathia, and prevailing finger stiffness, which causes the greatest difficulties, impairs hand function, and results in disability. Many CRPS symptoms and signs typical of the early stage may disappear, and these changes in the clinical picture may mean that the patient no longer meets the diagnostic criteria for CRPS. This, however, does not indicate recovery but rather the evolution of the disease into its chronic stage. Diagnosis of the chronic form is relatively straightforward, but treatment is more difficult, and sometimes challenging, and the prognosis for regaining normal hand function is uncertain. Unlike in acute CRPS, effective treatment is not available, and even after stabilisation of the disease and partial withdrawal of most features, residual symptoms may be troublesome and functional impairment severe (reduced finger movement and grip strength) [32, 34]. Neurological signs may develop in a proportion of patients, such as: hyperpathia, allodynia, tremor, and muscle spasms [3, 4, 32, 34].

Chronic, refractory complex regional pain syndrome (long-lasting, therapy-resistant complex regional pain syndrome)

This is the rarest, most severe, and most peculiar subtype, with the poorest prognosis (Fig. 3, 4, 5, 6). A total of 24 patients (1%) were identified in our register as suffering from this form of CRPS. It typically develops as a consequence of trivial injuries (contusions, sprains, superficial wounds, skin infections, small operations), but not usually after distal radial fractures or standard hand surgery. This form affects almost exclusively young women and is characterised by severe pain (reaching 9–10 on the visual analogue scale – VAS) and other painful phenomena (hyperpathia, allodynia), a need for regular analgesic consumption (including opioids), severe functional impairment of the affected extremity, and poor or no response to treatment [35]. No effective standard treatment is known that provides medium-term pain relief in these patients. It is recognised in the literature, and in extreme cases, patients may be offered amputation of the affected limb [35, 36, 37]. Recognised treatment modalities and rehabilitation typically fail in these patients, but specific treatments directed toward the disease, such as mirror therapy, ketamine infusions, or continuous brachial plexus analgesia, may be useful [38, 39]. Patients suffering from this form of CRPS often display psychological disturbances and are susceptible to depression, but it is difficult to determine whether these are causes or consequences of the primary disease.

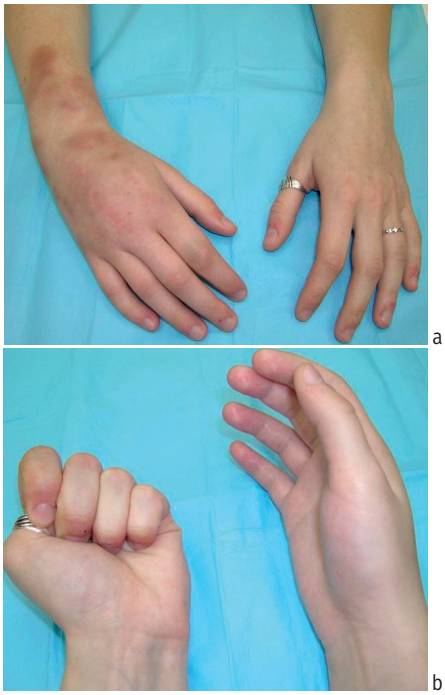

FIGURE 3. Chronic, refractory complex regional pain syndrome in a 20-year-old woman: (a) severely disabled right hand with trophic skin changes; (b) note stiffness of the fingers in the right hand

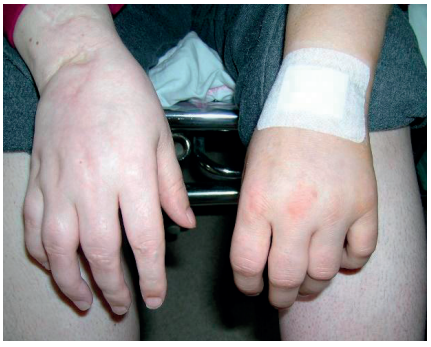

FIGURE 4. Chronic, refractory complex regional pain syndrome in a 41-year-old woman. Note pale, swollen skin with trophic changes (right hand)

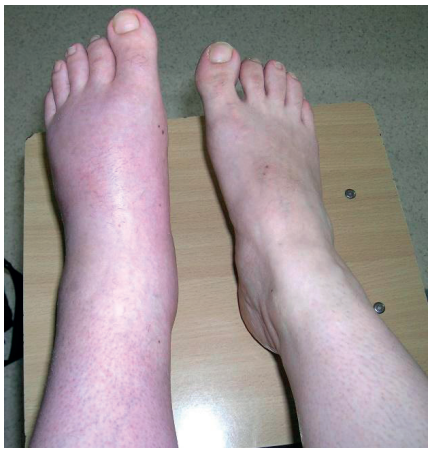

FIGURE 5. Involvement of the left foot in the patient from Figure 4

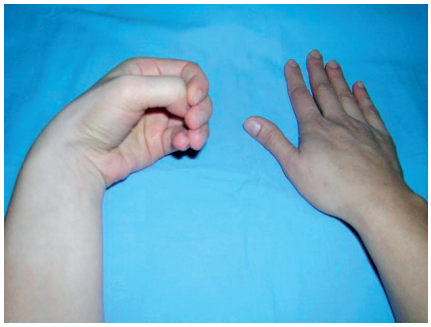

FIGURE 6. Dystonia in the left hand in a patient with chronic, refractory complex regional pain syndrome

DIAGNOSIS

Diagnosing CRPS may be difficult for several reasons:

- there is great variability in the presence and severity of specific symptoms and signs;
- the syndrome comprises a broad spectrum of clinical forms, i.e. acute, chronic, causalgia, shoulder-hand syndrome, and sympathetically mediated pain. These forms differ with respect to the symptomatology, treatment modalities and prognosis;
- acute and chronic forms are very different. Acute CRPS is characterized by: pain at rest, swelling, redness, increased temperature of the hand and reduction of movement due to pain. Chronic CRPS is characterized by: pain, tenderness, hyperpathia/allodynia, pallor, reduced temperature, hyperhidrosis and digital stiffness.

The diagnosis of CRPS is based on clinical grounds, and the presence of a specified constellation of symptoms and signs is required to make the decision [2, 23, 24]. The presence of pain is considered obligatory for the diagnosis. No specific test is known to confirm or exclude CRPS, and imaging such as radiography, bone scintigraphy, computed tomography (CT), and nuclear magnetic resonance (NMR) have limited influence on decision-making [2, 3, 4, 40]. The Budapest criteria of diagnosis (Tab. 1) are now considered the standard in CRPS diagnosis and are used in scientific studies [23, 24]. In 2019, the European Pain Federation task force developed updated standards for the diagnosis and management of CRPS, which replaced older criteria [2].

Early diagnosis of CRPS and initiation of treatment appear beneficial, because early CRPS is relatively easy to treat, has a good prognosis, and full recovery can be expected within a reasonable time. By contrast, chronic CRPS is – in most cases – a disabling condition with an uncertain prognosis and limited treatment options. As early diagnosis of CRPS is extremely important, a practical protocol has been developed in the author's institution. The following 3 conditions are necessary to consider CRPS as the most likely diagnosis:

- presence of diffuse pain in the hand/extremity, spontaneous or at the slightest movement;
- functional impairment of the hand/extremity; and
- non-existence of any disease that might explain the problem.

The presence of other symptoms and signs, such as swelling, vasomotor disturbances, sweating, and trophic changes – their number and severity – are of secondary importance because their occurrence is variable and dependent on many circumstances, such as the predisposing event, stage of the disease, and previous treatment or physiotherapy. Therefore, when a patient presents with a painful and functionally impaired hand following trauma or surgery, CRPS should be considered seriously after exclusion of other possible conditions such as: infection, acute arthritis, tendovaginitis, acute carpal tunnel syndrome, or neglect-like syndrome. No other examinations, such as biochemical tests, imaging, or electrodiagnostic tests, are necessary for establishing the diagnosis, which is purely clinical.

TREATMENT OPTIONS

Complex regional pain syndrome is a syndrome of uncertain prognosis; however, it has been reported that a majority of early forms tend to resolve spontaneously within 1 year or earlier [30, 31]. Progression to the chronic stage is uncommon, but if it occurs, the prognosis worsens significantly, although this does not preclude treatment success. When commenced early, treatment of CRPS results in recovery in 80–90% of cases, including relief of pain and restoration of hand function. Treatment of chronic forms is much more difficult, and at this stage, pain control is often the primary goal, while functional recovery remains limited.

Various treatment methods have been used for CRPS. The most commonly reported treatment modalities include sympathetic interruption, calcitonin, bisphosphonates, steroids, and various forms of physiotherapy [41]. The effectiveness of these treatments is not definitively proven, and they are used at different stages of the syndrome. In acute CRPS, one may expect significant pain resolution within 1 month and improvement of finger movement after 1–2 months of outpatient treatment [12, 14, 16]. The rate of recovery is reported

to be up to 90%, although complete restoration of hand function is rarely achieved earlier than 1 year from disease onset. In chronic CRPS, treatment is much more difficult, and the recovery rate does not exceed 20%.

The treatment protocol for acute CRPS used in the author's institution includes intravenous administration of 10% mannitol, 250 mL twice a day, combined with intravenous dexamethasone 8 mg daily. To date, almost 100 patients suffering from acute CRPS have been treated according to this protocol, with permanent improvement obtained in 95% of them [12]. By contrast, no reliable or effective treatment has been developed for chronic CRPS. Regional intravenous steroid blocks have been attempted, with moderate outcomes but no permanent functional recovery. Patients showing signs of sympathetic hyperactivity and responding positively to intravenous phentolamine (with relief of pain and warming of the affected hand) received regional intravenous sympathetic blocks with good short-term results. For chronic CRPS patients, the anticonvulsant gabapentin and the antidepressant amitriptyline are regularly used as supportive therapy to alleviate pain and are well tolerated. Some patients have had spinal cord stimulators implanted (in neurosurgical departments), but their effectiveness is rather modest. Fortunately, chronic patients suffer less from pain and more from stiffness and partial disability of the hand. They usually adapt well to reduced dexterity, and their functioning in daily life is typically "acceptable".

A large number of treatments have been investigated, but major multicentre randomised controlled trials are lacking. There is consensus regarding the fundamental role of early therapeutic intervention, as it may prevent the disease from transitioning from acute to chronic form, although it remains to be proven how this alters the course of CRPS [12, 41]. Below is a brief narrative review of recognised treatment methods for CRPS.

Calcitonin

Calcitonin has been used in CRPS due to its analgesic properties – via β-endorphin release in the central nervous system – and its inhibition of bone resorption. The efficacy of calcitonin is limited to early CRPS (less than 6 months duration) [42]. One disadvantage is that approx. 30% of patients experience unpleasant side effects. Scientific evidence for its use in CRPS is weak, and due to recent safety concerns, it is no longer recommended [3, 4, 41].

Biphosphonates

These drugs have been used for their potential to inhibit bone resorption and their anti-inflammatory activity. There is no strong evidence supporting their efficacy, although positive findings have been reported for intravenous pamidronate and oral alendronate. A randomised study comparing pamidronate to oral prednisolone in post-stroke CRPS showed both to be equally effective in pain control [43]. Despite the weak evidence, bisphosphonates are relatively frequently used in clinical practice [44].

Free radical scavengers

These have been used in CRPS because of their anti-inflammatory potential. The substances include topical DMSO, mannitol, steroids, and N-acetylcysteine, all capable of neutralising toxic free radicals [13, 14]. A combination of mannitol and dexamethasone is an original method developed for early CRPS and introduced in the author's institution [12]. There is moderate evidence for the effectiveness of 50% topical DMSO cream and intravenous mannitol combined with steroids in reducing early CRPS symptoms. Similarly, there is moderate evidence for oral N-acetylcysteine in chronic CRPS [41]. This therapy is used widely in clinical practice, particularly in the Netherlands and Poland.

Intravenous regional sympathectomy

Based on the assumption that CRPS involves sympathetic dysfunction, this therapy uses intravenous regional blocks (Bier blocks) with a local anaesthetic and anti-sympathetic drug. Guanethidine-based blocks were popular in the 1990s, but randomised trials later showed no superiority over placebo [6]. Evidence for this treatment is weak, and it is currently used only in chronic CRPS patients who respond to a positive phentolamine test [41].

Sympathetic ganglia blocks

The stellate and lumbar sympathetic ganglia are responsible for the sympathetic innervation of the upper and lower limbs, respectively. Blocking of these ganglia results in inhibition of sympathetic efferent action in the affected limb. Likewise, with intravenous regional sympathectomy, there is relatively weak evidence supporting the effectiveness of sympathetic ganglion blocks in CRPS. Despite the low quality of evidence, they are relatively commonly performed in patients who respond to this treatment, mostly with chronic lower limb CRPS [4, 41].

Steroids

Steroids have been used in CRPS because of their anti-inflammatory action. The underlying rationale was the same as in the use of free radical scavengers. In spite of relatively weak evidence for the effectiveness of steroids for treatment of CRPS, they are frequently used in clinical practice, especially in patients with early CRPS with a prominent inflammatory component [4, 41, 45]. Steroids appear to be useful also in chronic CRPS for patients after stroke [46].

Anticonvulsants

The use of anticonvulsants is based on the assumption that pain in CRPS may be (at least in part) neuropathic. Anticonvulsants (gabapentin, pregabalin), with proven analgesic effects in other neuropathic pain syndromes, might be beneficial in pain control. There is weak evidence for the effectiveness of these drugs in reducing some of the pain symptoms (including hyperaesthesia and allodynia) in CRPS. Although frequently used, anticonvulsants appear not to be particularly effective in clinical practice [41, 47, 48].

Physiotherapy (various types)

Various methods of physiotherapy are recommended as part of the multimodal treatment of CRPS. It seems obvious that exercises are beneficial in the restoration of ranges of motion, and strength, and in improving the function of the affected hand. However, the underlying mechanisms of physical therapy in pain control remain obscure. There are several theories explaining this, including the release of endorphins in the central nervous system, stimulation of sensory nerve endings of peripheral afferent nerves, spinal cord-mediated analgesia, and anti-inflammatory effects [49]. Graded motor imagery (GMI) and mirror therapy may reduce pain and increase mobility by ameliorating maladaptive somatosensory and motor cortex reorganisation [50, 51]. In general, physiotherapy is aimed at better adaptation to pain, and improving posture, movement, activities of daily living, and psychosocial functioning [52]. There is moderate evidence of the effectiveness of GMI and mirror therapy in CRPS. Physiotherapy in general is likely to have a positive effect on the impairment level in patients with chronic CRPS but less effect on pain reduction. It is commonly accepted as an important component of the standard treatment of CRPS.

Spinal cord stimulation

This therapy is based on the assumption that electrical stimulation of the spinal cord engenders spinal cord-mediated analgesia and anti-inflammatory effects. There is moderate evidence for the effectiveness of spinal cord stimulation in giving some reduction in pain symptoms in CRPS patients. Spinal cord stimulation has no effect on function, it is an invasive procedure, and its effect is unpredictable and appears only to be temporary [41, 47, 53]. Regardless, it enjoys increasing popularity, particularly for patients with chronic CRPS.

Ketamine

The use of ketamine for the treatment of CRPS is based on the role of the glutaminergic N-methyl-D-aspartate (NMDA) receptor in the process of "sensitisation" in the central nervous system. There is some evidence that ketamine has strong NMDA-receptor blocking (antagonist) properties, resulting in inhibition of the central sensitisation mechanism. The level of evidence suggests only a weak recommendation and moderate-quality evidence for the use of ketamine in the treatment of CRPS [54]. Regardless of this conclusion, i.v. ketamine treatment enjoys increasing popularity, particularly for patients with chronic CRPS resistant to any other therapy. It offers at least temporary relief from severe, debilitating pain; however, it does not improve the function of the affected limb [38].

Amputation

Amputation of the limb is a definitive treatment that may be considered in the so-called "end-stage" of CRPS. Fortunately, this is seen rarely. In this long-standing, therapy-resistant disease, apart from intractable, debilitating pain, several new problems may be encountered such as a totally dysfunctional limb, severe recurrent infections, and chronic trophic ulcers. The available evidence does not clearly delineate the beneficial and adverse effects of amputation for long-standing, therapy-resistant CRPS [36, 37]. Whether to amputate or not remains an unanswered question.

As was mentioned earlier, the results of treatment of early CRPS are satisfactory; however, resolution of the acute problem does not always restore normal function. Pain related to the weather, reduction of finger flexion and extension, weakness of the hand, cold intolerance, and numbness of the fingers can persist over the years and can impair the function of the hand and/or be the source of considerable discomfort to patients. Therefore, the term "recovery from CRPS", particularly in chronic disease, does not always mean a return to normality [32, 33].

PREVENTION

There are no specific measures known to prevent CRPS after trauma or surgery. It was suggested that careful operative technique, knowledge of anatomy, avoidance of nerve traction, and proper postoperative care can reduce the incidence of CRPS after operations. It is also a common belief that early mobilisation and prompt physiotherapy prevent the development of CRPS after fractures [1, 55]. Therefore, operative treatment of fractures would result in reduction of the risk of CRPS. However, although these factors are (in general) important determinants of the effectiveness of the treatment, their relationship to CRPS has not been scientifically confirmed. There is also very preliminary evidence about the value of steroids to prevent a prolonged course of CRPS after very early CRPS has been diagnosed. In patients with a history of CRPS, a new injury or operation to that (or contralateral) extremity is known to increase the risk of recurrence. Therefore, specific measures are recommended, such as avoiding the use of a tourniquet in the operation, or pharmacological prevention by mannitol, calcitonin, steroids, or vitamin C. However, the necessity of using these measures has been questioned in some studies, showing that the risk of a new episode of the condition in patients who have recovered from CRPS is minimal [1].

Vitamin C for prevention complex regional pain syndrome

Vitamin C has been suggested as a low-risk intervention that might limit excessive soft tissue injury and prevent CRPS. The mechanism of action of vitamin C is thought to be by inhibiting local inflammatory cascades via antioxidant mechanisms. Several studies have investigated the effect of vitamin C vs. placebo for preventing the development of CRPS [56, 57, 58]. All trials included predominantly older women and a mix of intra- and extra-articular fractures of the distal radius. In 2 trials, patients were treated with operative and nonoperative techniques, whereas the 2 other trials included only nonoperative management. The patients were randomised to 500 mg of vitamin C daily for 50 days vs. placebo (1 : 1); in 1 study a dose of 1000 mg of vitamin C was used in the same manner, whereas another randomised patients to 200, 500, or 1500 mg of vitamin C daily for 50 days vs. placebo (3 : 1). All studies showed a statistically significant reduction in CRPS incidence in groups

receiving vitamin C vs. placebo at a follow-up of 1 year. Therefore, a general conclusion from these studies is that it is likely that oral administration of 500–1000 mg of vitamin C per day for 50 days from the date of the injury reduces the incidence of CRPS in patients following distal radial fractures. Following this conclusion, it is frequently used in clinical practice and is also recommended by the American Association of Orthopaedic Surgery for patients following distal radial fractures [59].

However, all of the studies have numerous limitations, including:

- use of non-Budapest criteria of diagnosis of CRPS, using instead the older criteria, i.e. of Atkins et al. and Veldman et al. [27, 34];
- all studies reported a surprisingly high incidence of CRPS in the control groups of 10–12%, at a mean follow-up of 1 year, suggesting the use of invalid diagnostic criteria;
- there was a proportion of patients who were lost to follow-up across the trials. The scenario in which all the missing patients were assumed to have CRPS is improbable, but it is equally improbable that none of these patients developed CRPS, as was assumed in these studies.

Bearing in mind the above limitations, the systematic review by Evaniew et al. suggests that the literature is conflicting and fails to demonstrate a statistically significant effect of vitamin C in preventing CRPS in patients with distal radius fractures [60]. However, because of the low risk of intervention and some positive results in certain studies, the use of vitamin C for patients with distal radial fractures or after foot or ankle sprains could be safely utilised and recommended [59].

CONCLUSIONS

In this paper, we present some updated information about CRPS which we found useful in our proceedings with CRPS patients. Both classification and diagnosis have translation into research and clinical practice. Obviously, CRPS is not a basic area of interest for hand surgeons, but most have been, or (sooner or later) will be, faced with this problem. We believe that the information presented may support hand surgeons in resolving their diagnostic dilemmas associated with CRPS.

REFERENCES

1. Żyluk A. Complex regional pain syndrome type I. Risk factors, prevention and risk of recurrence. J Hand Surg Br 2004;29(4):334-7.
2. Goebel A, Barker C, Birklein F, Brunner F, Casale R, Eccleston C, et al. Standards for the diagnosis and management of complex regional pain syndrome: Results of a European Pain Federation task force. Eur J Pain 2019;23(4):641-51.
3. Misidou C, Papagoras C. Complex regional pain syndrome: an update. Mediterr J Rheumatol 2019;30(1):16-26.
4. Shim H, Rose J, Halle S, Shekane P. Complex regional pain syndrome: a narrative review for the practising clinician. Br J Anaesth 2019;123(2):e424-33.
5. Baron R, Schattschneider J, Binder A, Siebrecht D, Wasner G. Relation between sympathetic vasoconstrictor activity and pain and hyperalgesia in complex regional pain syndromes: a case-control study. Lancet 2002;359(9318):1655-60.
6. Livingstone JA, Atkins RM. Intravenous regional guanethidine blockade in the treatment of post-traumatic complex regional pain syndrome type 1 (algodystrophy) of the hand. J Bone Joint Surg Br 2002;84(3):380-6.
7. Goris RJ, van Dongen LM, Winters HA. Are toxic oxygen radicals involved in the pathogenesis of reflex sympathetic dystrophy? Free Radic Res Commun 1987;3(1-5):13-8.
8. Oyen WJG, Arnts IE, Claessens RAMJ, Van der Meer JWM, Corstens FHM, Goris JAR. Reflex sympathetic dystrophy of the hand: an excessive inflammatory response? Pain 1993;55(2):151-7.
9. Kortekaas MC, Niehof SP, Stolker RJ, Huygen FJPM. Pathophysiological mechanisms involved in vasomotor disturbances in complex regional pain syndrome and implications for therapy: A review. Pain Pract 2016;16(7):905-14.
10. Parkitny L, McAuley JH, Di Pietro F, Stanton TR, O'Connell NE, Marinus J, et al. Inflammation in complex regional pain syndrome: A systematic review and meta-analysis. Neurology 2013;80(1):106-17.
11. Dirckx M, Stronks DL, van Bodegraven-Hof EAM, Wesseldijk F, Groeneweg JG, Huygen FJPM. Inflammation in cold complex regional pain syndrome. Acta Anaesthesiol Scand 2015;59(6):733-9.
12. Żyluk A, Puchalski P. Treatment of early complex regional pain syndrome type 1 by a combination of mannitol and dexamethasone. J Hand Surg Eur Vol 2008;33(2):130-6.
13. Perez RS, Kwakkel G, Zuurmond WW, de Lange JJ. Treatment of reflex sympathetic dystrophy (CRPS type 1): a research synthesis of 21 randomized clinical trials. J Pain Symptom Manage 2001;21(6):511-26.
14. Perez MRSG, Zuurmond AWW, Bezemer DP, Kuik JD, van Loenen CA, de Lange JJ, et al. The treatment of complex regional pain syndrome type I with free radical scavengers: a randomized controlled study. Pain 2003;102(3):297-307.
15. Littlejohn G. Neurogenic neuroinflammation in fibromyalgia and complex regional pain syndrome. Nat Rev Rheumatol 2015;11(11):639-48.
16. Bussa M, Mascaro A, Cuffaro L, Rinaldi S. Adult complex regional pain syndrome type I: a narrative review. PM R 2017;9(7):707-19.
17. Birklein F, Schmelz M. Neuropeptides, neurogenic inflammation and complex regional pain syndrome (CRPS). Neurosci Lett 2008;437(3):199-202.
18. Gracely RH, Lynch SA, Bennett GJ. Painful neuropathy: altered central processing maintained dynamically by peripheral input. Pain 1992;51(2):175-94.
19. Di Pietro F, McAuley JH, Parkitny L, Lotze M, Wand BM, Moseley GL, et al. Primary somatosensory cortex function in complex regional pain syndrome: a systematic review and meta-analysis. J Pain 2013;14(10):1001-18.
20. Eldufani J, Elahmer N, Blaise G. A medical mystery of complex regional pain syndrome. Heliyon 2020;6(2):e03329.
21. Puchalski P, Żyluk A. Complex regional pain syndrome type 1 after fractures of the distal radius: a prospective study of the role of psychological factors. J Hand Surg Br 2005;30(6):574-80.
22. Geertzen JH, de Bruijn-Kofman AT, de Bruijn HP, van de Wiel HB, Dijkstra PU. Stressful life events and psychological dysfunction in complex regional pain syndrome type I. Clin J Pain 1998;14(2):143-7.
23. Harden RN. Objectification of the diagnostic criteria for CRPS. Pain Med 2010;11(8):1212-5.
24. Harden NR, Bruehl S, Perez RSGM, Birklein F, Marinus J, Maihofner C, et al. Validation of proposed diagnostic criteria (the "Budapest criteria") for complex regional pain syndrome. Pain 2010;150(2):268-74.
25. Bruehl S, Harden RN, Galer BS, Saltz S, Backonja M, Stanton-Hicks M. Complex regional pain syndrome: are three distinct subtypes and sequential stages of the syndrome? Pain 2002;95(1-2):119-24.
26. Żyluk A. The three-staged evolution of post-traumatic algodystrophy. Chir Narzadow Ruchu Orthop Pol 1998;63(5):479-86.
27. Atkins RM, Duckworth T, Kanis JA. Features of algodystrophy after Colles' fracture. J Bone Joint Surg Br 1990;72(1):105-10.
28. Field J, Atkins RM. Algodystrophy is an early complication of Colles' fracture. What are the implications? J Hand Surg Br 1997;22(2):178-82.
29. Birklein F, Kunzel W, Siewke N. Despite clinical similarities there are significant differences between acute limb trauma and complex regional pain syndrome I (CRPS I). Pain 2001;93(2):165-71.
30. Żyluk A. The natural history of post-traumatic reflex sympathetic dystrophy. J Hand Surg Br 1998;23(1):20-3.
31. Bickerstaff DR, Kanis JA. Algodystrophy: an under-recognized complication of minor trauma. Br J Rheumatol 1994;33(3):240-8.

32. Żyluk A. The sequelae of reflex sympathetic dystrophy. J Hand Surg Br 2001;26(2):151-4.
33. Lewellyn A, McCabe CS, Hibberd Y, White P, Davies L, Marinus M, et al. Are you better? A multi-centre study of patient-defined recovery from complex regional pain syndrome. Eur J Pain 2018;22(3):551-64.
34. Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. Lancet 1993;342(8878):1012-6.
35. Żyluk A. Chronic, refractory CRPS involving 3 limbs: a case report. Handchir Mikrochir Plast Chir 2013;45(3):186-9.
36. Krans-Schreuder HK, Bodde MI, Schrier E, Dijkstra PU, van den Dungen, den Dunnen WF, et al. Amputation for long-standing, therapy-resistant type-I complex regional pain syndrome. J Bone Joint Surg Am 2012;94(24):2263-8.
37. Schrier E, Dijkstra PU, Zeebregts CJ, Wolff AP, Geertzen JHB. Decision making process for amputation in case of therapy resistant complex regional pain syndrome type-I in a Dutch specialist centre. Med Hypotheses 2018;121:15-20.
38. Puchalski P, Żyluk A. Results of the treatment of chronic, refractory CRPS with ketamine infusions: a preliminary report. Handchir Mikrochir Plast Chir 2016;48(3):143-7.
39. Żyluk A, Puchalski P. Pain control in chronic, refractory CRPS by continuous brachial plexus analgesia. Handchir Mikrochir Plast Chir 2018;50(3):190-5.
40. Żyluk A. The usefulness of quantitative evaluation of three-phase bone scintigraphy in the diagnosis of post-traumatic reflex sympathetic dystrophy. J Hand Surg Br 1999;24(1):16-21.
41. Żyluk A, Puchalski P. Effectiveness of complex regional pain syndrome treatment: A systematic review. Neurol Neurochir Pol 2018;52(3):326-33.
42. Gobelet C, Waldburger M, Meier J. The effect of adding calcitonin to physical treatment on reflex sympathetic dystrophy. Pain 1992;48(2):171-5.
43. Eun Young H, Hyeyun K, Sang Hee I. Pamidronate effect compared with a steroid on complex regional pain syndrome type I: Pilot randomized trial. Neth J Med 2016;74(1):30-5.
44. Varenna M, Adami S, Rossini M, Gatti D, Idolazzi L, Zucchi F, et al. Treatment of complex regional pain syndrome type I with neridronate: a randomized, double-blind, placebo-controlled study. Rheumatology (Oxford) 2013;52(3):534-42.
45. Barbalinardo S, Loer SA, Goebel A, Perez RS. The treatment of long-standing complex regional pain syndrome with oral steroids. Pain Med 2016;17(2):337-43.
46. Kalita J, Misra U, Kumar A, Bhoi SK. Long-term prednisolone in post-stroke complex regional pain syndrome. Pain Physician 2016;19(8):565-74.
47. Tran QH, Duong S, Bertini P, Finlayson RJ. Treatment of complex regional pain syndrome: a review of the evidence. Can J Anesth 2010;57(2):149-66.
48. van de Vusse AC, Stomp-van den Berg SG, Kessels AH, Weber WE. Randomized controlled trial of gabapentin in complex regional pain syndrome type 1. BMC Neurol 2004;4:13.
49. Smart KM, Wand BM, O'Connell NE. Physiotherapy for pain and disability in adults with complex regional pain syndrome (CRPS) types I and II. Cochrane Database Syst Rev 2016;2(2):CD010853. doi: 10.1002/14651858.CD010853.pub2.
50. Moseley GL. Graded motor imagery is effective for long-standing complex regional pain syndrome: a randomized controlled trial. Pain 2004;108(1-2):192-8.
51. Moseley GL. Graded motor imagery for pathologic pain: a randomized controlled trial. Neurology 2006;67(12):2129-34.
52. Oerlemans HM, Oostendorp RA, de Boo T, Goris RJ. Pain and reduced mobility in complex regional pain syndrome I: outcome of a prospective randomized controlled trial of adjuvant physical therapy versus occupational therapy. Pain 1999;83(1):77-83.
53. Taylor RS, Van Buyten JP, Buchser E. Spinal cord stimulation for complex regional pain syndrome: a systematic review of the clinical and cost-effectiveness literature and assessment of prognostic factors. Eur J Pain 2006;10(2):91-101.
54. Azari P, Lindsay DR, Briones D, Clarke C, Buchheit T, Pyati S. Efficacy and safety of ketamine in patients with complex regional pain syndrome: a systematic reiew. CNS Drugs 2012;26(3):215-28.
55. Gillespie S, Cowell F, Cheung GC, Brown DJ. Can we reduce the incidence of complex regional pain syndrome type I in distal radius fractures? The Liverpool experience. Hand Ther 2016;21(4):123-30.
56. Zollinger PE, Tuinebreijer WE, Kreis RW, Breederveld RS. Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomised trial. Lancet 1999;354(9195):2025-8.
57. Zollinger PE, Tuinebreijer WE, Breederveld RS, Kreis RW. Can vitamin C prevent complex regional pain syndrome in patients with wrist fractures? A randomized, controlled, multicenter dose-response study. J Bone Joint Surg Am 2007;89(7):1424-31.
58. Malay S, Chung KC. Testing the validity of preventing chronic regional pain syndrome with vitamin C after distal radius fracture. J Hand Surg Am 2014;39(11):2251-7.
59. Lichtman DM, Bindra RR, Boyer MI, Putnam MD, Ring D, Slutsky DJ, et al. American Academy of Orthopaedic Surgeons clinical practice guideline on: the treatment of distal radius fractures. J Bone Joint Surg Am 2011;93(8):775-8.
60. Evaniew N, McCarthy C, Kleinlugtenbelt YV, Ghert M, Bhandari M. Vitamin C to prevent complex regional pain syndrome in patients with distal radius fractures: a meta-analysis of randomized controlled trials. J Orthop Trauma 2015;29(8):e235-41.