IFSSH Scientific Committee on Pain Syndromes

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Complex regional pain syndrome from hand surgeon perspective: a review

INTRODUCTION

Complex regional pain syndrome (CRPS, formerly reflex sympathetic dystrophy) is a descriptive term for a complex of symptoms and signs, including pain at rest or at the slightest movement, swelling, vasomotor instability (changes of colour, temperature and sweating) and is accompanied by severe functional impairment of the affected hand or whole extremity. It is usually caused by trauma or surgery and is characterized by presence of these symptoms and signs which are more severe than would normally be expected for the degree of trauma of the precipitating event (which can sometimes be very minor) and extend beyond the area involved by the initial trauma. CRPS is not confined to the hand and upper extremity. Involvement of the foot, knee and hip have been described and generally (although very infrequently) it can occur anywhere in the body. CRPS in upper extremity most commonly occurs after trauma or surgery, but it can occur after a stroke, heart disease or spontaneously (Zyluk, 2004).

PATHOPHYSIOLOGY

There is lack of conclusive evidence, demonstrating the pathophysiological mechanisms leading to development of CRPS. Several theories have been proposed, including involvement of the sympathetic nervous system, abnormal inflammatory reaction, sequelae of nerve injury, central sensitization, psychological disturbances and as a result of inactivity.

The sympathetic theory had attracted wide popularity over several decades in the last century, followed by coining the former name of the syndrome - reflex sympathetic dystrophy (RSD). Several treatment modalities have been developed involving sympathycolysis, such as stellate ganglion block and regional intravenous block with guanethidine, some of them being very effective (Hannington-Kiff, 1974; Livingstone and Atkins, 2002). This theory has been eventually questioned, because it did not explain adequately all clinical aspects of the disease, however, involvement of the sympathetic nervous system in the chronic stage of the CRPS seems to be justified.

An exaggerated inflammatory response to trauma as an underlying mechanism for CRPS was postulated as early as in 1942 by Paul Sudeck and this theory has been constructively developed by Goris and his group (Goris, 1987). The role of toxic free oxygen and hydroxyl radicals in the development and maintaining an excessive inflammatory response has been supposed and confirmed (Goris, 1987, Oyen et al., 1993). An inflammatory process excellently explains all objective clinical findings in the acute stage of CRPS, such as pain, swelling, redness, increased temperature and

impaired function of the extremity. Several studies showed effectiveness of treatment utilising free radical scavengers, such as mannitol, corticosteroids, N-acetylcysteine and dimethys sulfoxide (DMSO), particularly in the acute stage of the condition (Perez et al., 2001; Perez et al., 2003; Zyluk 2008). Moreover, an inflammatory component does not preclude a role of the sympathetic nervous system as a factor involved in the whole spectrum of abnormalities in CRPS, particularly in the chronic stage.

The pathophysiological role for 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 for the degree of trauma of the precipitating event, hyperpathia and allodynia. The model of neuropathic pain is proposed in which ongoing nociceptive afferent input form a peripheral focus dynamically maintains altered central processing that accounts for allodynia, severe pain and other sensory and motor abnormalities (Gracely et al., 1992). Brain imaging by functional MRI showed changes in brain function in patients with chronic CRPS, thus giving support for altered central processing theory.

CLINICAL SUB-TYPES

Classically CRPS is classified into two forms: Type 1 (formerly reflex sympathetic dystrophy) and type 2 (formerly causalgia). CRPS type 1 comprises a 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 two forms has been recently questioned, since in most cases nerve involvement cannot be definitively excluded and both forms are clinically identical (Harden, 2010; Oaklander et al., 2006). Likewise, the traditional, three-staged (acute, dystrophy, atrophy) evolution of CRPS has been questioned and now two 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 (Bruehl et al. 2002; Żyluk 1998b). There is no precise timing of passing from the acute to the chronic form, but it usually occurs within 3-6 months after onset of the condition, with the observation that any therapeutic intervention may disturb this evolution. 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 (Handen et al., 2007; Harden, 2010). In the International Association for Study of the Pain (IASP) set of diagnostic criteria, four categories of features are established, including sensory, vasomotor, sudomotor/oedema and motor trophic (Table 1).

Based on our clinical experience, the following clinical sub-types 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 twenty-years clinical experience of diagnosing and treating more than 200 CRPS patients.

a. Acute (early) CRPS after fractures of the distal radius. This is a very specific and the most common form, characterized by mild to moderate clinical severity, typical symptomatology, relatively easy to treat when diagnosed early and having a good prognosis (Atkins et al., 1990; Goris et al., 2010; Żyluk, 1998a; Żyluk and Puchalski, 2008). It is believed that it can be recognized as early as 2 weeks after fracture, however this may lead to overdiagnosing, because early CRPS and the post-traumatic period display many similarities and may be interpreted in a different manner (Birklein et al., 2001; Field and Atkins, 1997). CRPS after distal radius fractures has a natural tendency to spontaneous resolution within the mid-term perspective (Żyluk, 1998a; Bickerstaff and Kanis, 1994). There is also a spectrum of patients presenting with mild, transient CRPS forms which - although meeting the criteria for diagnosis (i.e. IASP) at 1-2 months after fracture - are only moderately disturbing for patients and may be left untreated or by physiotherapy alone (Dijkstra et al., 2003; Goris et al., 2010; Żyluk, 1998b). After withdrawal of most CRPS symptoms and signs, patients can experience some "residual" complaints as long as one year, or more, after onset of the disease (Field and Atkins, 1997; Zyluk, 2001). CRPS after fractures of the distal radius involves mainly (90%) mid- or older age women, and relatively infrequently (less than 10%) progresses into the chronic stage.

b. Acute (early) CRPS after surgery for hand diseases and injuries (carpal tunnel syndrome, Dupuytren's contracture, trigger digits, hand fractures, tendon and nerve injuries) occurs much less frequently than after fractures of the distal radius (1-2%) and is characterised by similar, typical for early condition symptoms and signs, appearing usually within one month after trauma or surgery. This form is relatively easy to diagnose, because the patients are still under post-operative control. It is necessary to differentiate this form with occult infection spreading through the synovial sheaths of the palm proximally or distally, particularly after mini-invasive surgery. We were faced with such situations and sometimes the differential diagnosis may be difficult. Women are more frequently affected, but the difference is not as big as after fractures of the distal radius. As this form is usually diagnosed early, treatment is effective, the prognosis good and recovery may be expected within a reasonable time. Very infrequently this form progresses into chronic CRPS, unless overlooked or neglected. There is no information about the natural course of this subtype, but it is probably self-limiting, likewise after distal radius fractures.

c. Chronic CRPS. As mentioned earlier, it occurs relatively infrequently. If not spontaneously withdrawn, overlooked or misdiagnosed, the acute form passes within 3-4 months into chronic CRPS, presenting with moderate pain in the hand, mild swelling, colder and pale skin, frequently hyperhydrosis, tenderness/hyperpathia but with prevailing finger stiffness, which gives the patients the greatest difficulties, impairs hand function and results in disability. Many of the CRPS symptoms and signs typical for the early stage may disappear, and these changes in the clinical picture may mean that the patient no longer meets the diagnostic criteria of CRPS. Obviously, it does not mean recovery, but evolution of the disease into the chronic stage. Diagnosis of the chronic form is relatively easy, but treatment is more difficult, sometimes challenging and the prognosis towards regaining normal hand function is doubtful. Unlike in acute

CRPS, effective treatment is not available and even after stabilization of the disease and partial withdrawal of most of the features the residual symptoms may be nasty and functional impairment severe (reduced finger movements and grip strength). Neurological signs may develop in a proportion of patients, such as hyperpathia, allodynia, tremor and muscle spasms (Birklein et al., 2000; Verdugo and Ochoa, 2000).

d. Chronic, refractory CRPS. This is the rarest, most severe and peculiar subtype with the poorest prognosis. It is not distinguished in the literature as a separate form, but - for practical purposes – it should be (Zyluk, 2006). Typically it develops as a consequence of trivial injuries (contusions, sprains, superficial wounds, skin infections, small operations) but rather not after fractures of the distal radius or regular hand surgery. This form involves exclusively (100%) young women. Recognized treatment modalities and rehabilitation typically fail in these patients, but specific treatments, directed on the disease such as "mirror therapy" may be useful. Patients suffering from this form of CRPS display mild to moderate psychological disturbances and are susceptible to depression, but it is difficult to distinguish whether it is a cause or a consequence of this disabling, painful disease (Puchalski and Żyluk, 2005).

DIAGNOSIS

Diagnosing CRPS may be difficult for several reasons: (a) there is great variability in the presence and severity of specific symptoms and signs; (b) 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; and (c) the acute and chronic forms are very different. Acute CRPS is characterised by pain at rest, swelling, redness, increased temperature of the hand and reduction of movement because of the pain. Chronic CRPS is characterised by pain, tenderness, hyperpathia/allodynia, pallor, reduced temperature, hyperhydrosis 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. The presence of pain is considered obligatory to the diagnosis. No specific test is known to confirm or exclude CRPS diagnosis and imaging such as radiography, bone scintigraphy, CT and NMR have limited influence on decision making (Marshall and Crisp, 2000; Żyluk, 1999). To date no formal, standardised diagnostic criteria for CRPS have been widely accepted. The International Association for the Study of Pain (IASP) criteria of diagnosis, both the original (Merskey and Bogduk, 1994) and the modified forms (Table 1) (Harden et al., 2007; Harden, 2010) have recently attracted increased popularity and are frequently used in scientific studies

Early diagnosis of CRPS and initiation of treatment appears beneficial, because early CRPS is relatively easy to treat, its prognosis is good and full recovery can be expected within a reasonable time. In contrast chronic CRPS is - in most cases - a disabling condition with a poor prognosis and limited treatment options. As early diagnosis of CRPS is extremely important, a practical protocol has been introduced in author's

institution. The following three conditions are necessary to consider CRPS as the most likely diagnosis:

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

Presence of all other symptoms and signs, their number and severity are of secondary importance, because their occurrence is variable, dependent on many circumstances, such as predisposing event, stage of the disease, received 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 all other possible conditions, such as, e.g. infection, acute arthritis, tendovaginitis, acute carpal tunnel syndrome or neglect-like syndrome. The presence, absence and intensity of secondary features, including swelling, vasomotor disturbances, sweating and trophic changes as well as neurological symptoms are of minor importance, if there is no other explanation for pain and impairment. No other examinations, such as biochemical tests, imaging or electrodiagnostics are necessary for establishing the diagnosis which is purely clinical.

TREATMENT

CRPS is a syndrome of an uncertain prognosis, hence it was reported that a majority of early forms tend to spontaneous resolution within one year or earlier (Bickerstaff and Kanis, 1994; Zyluk, 1998a). Progression to the chronic stage is uncommon, but if it occurs, significantly worsens the prognosis, although does not preclude success of the treatment (Perez et al., 2003). Treatment of CRPS, when commenced early, results in recovery in 80-90% of the cases, including relief of the pain and restitution of the function of the hand. Treatment of chronic forms is much more difficult and usually at this stage a control of the pain is considered a success, but function of the affected hand remains poor. The rate of recovery in chronic CRPS is about 20% (Zyluk and Puchalski, 2008).

Various treatment methods have been used for CRPS, including those showed in Table 2. The most commonly treatment modalities reported in the literature include sympathetic interruptions, calcitonin and various form of physiotherapy (Bickerstaff and Kanis, 1991; Livingstone and Atkins, 2002). The effectiveness of these treatments is not definitively proven and they are used in different stages of the syndrome. Early forms of CRPS are commonly treated with physiotherapy, calcitonin and free radical scavengers (Bickerstaff and Kanis, 1991; Goris, 1985; Zyluk and Puchalski, 2008). At this stage, one may expect a significant reduction of pain within 1 month and improvement of finger movement after 1-2 months of outpatient treatment. The rate of recovery is reported up to 90%, although, complete restoration of hand function is rarely achieved earlier than after 1 year from the onset of the disease. In the chronic form of the CRPS the treatment is much more difficult and recovery rate does not exceed 20% (Zyluk and Puchalski, 2008).

Treatment of CRPS by free radical scavengers has been introduced by Goris (1985). This therapy is based on the assumption that CRPS is caused by an exaggerated inflammatory response to trauma, mediated by an overproduction of toxic oxygen and hydroxyl free radicals (Goris et al., 1987; Oyen et al., 1993). Several substances were used including topical dimethyl sulfoxide (DMSO), mannitol and N-acetylcysteine, all of them having propriety to neutralize toxic free radicals. A combination of mannitol and steroid, dexamethasone in an original method intended for early CRPS, which has been introduced in author's institution (Zyluk and Puchalski, 2008).

'SZCZECIN' TREATMENT PROTOCOL FOR EARLY CRPS

Our institutional treatment protocol for acute CRPS includes administration of 10% mannitol, 250 ml twice a day by intravenous infusion, combined with dexamethasone 8 mg a day, injected intravenously in a bolus. In the course of the treatment, no particular physiotherapy is applied, except encouraging the patients to elevate the hand and to move the fingers in the painless range of motion, both passively and actively. Patients are motivated to profit by analgesic and anti-oedema effect of the drugs to achieve full finger flexion at 1 week. One can call it a psychological feedback done by the medical staff, although it was not conducted according to clearly designed protocol. An important element of this therapy is an in-patient regime. The majority of CRPS patients, even with short lasting disease, were frightened and tired because of experienced progression of complaints and disability after trauma, in spite of improvement. Usually this anxiety was exacerbated by unawareness of the nature of these complaints and ineffective outpatient treatment. An admission to the hospital, explaining why and how the syndrome develops and assurance of the possibility of recovery are important, positive psychological stimuli augmenting the effectiveness of the drug therapy, and motivating the patient to better compliance in reaching the assumed aim of the therapy. Another important element of our protocol is making the diagnosis as early as possible, to prevent progression to the florid, fully-symptomatic form (see above institutional diagnostic criteria for early CRPS). Even the diagnosis of the "incipient" CRPS Type 1 is made in patients who complain of pain, swelling and reduction of finger movement as early as 1-2 weeks after trauma or surgery. These patients are immediately given treatment with our protocol what allowed us to prevent effectively the progression of the disease in many cases. Until now, almost 100 patients suffering from acute CRPS have been treated according to this protocol, with permanent improvement obtained in 95% of them (Zyluk and Puchalski, 2008).

In contrast, we have failed to work out a reliable, effective treatment for chronic CRPS. Attempts have been made with use of regional intravenous steroid blocks, with moderate outcomes, but no permanent functional recovery achieved. Patients having signs of sympathetic hyperactivity and responding positively to intravenous phentolamine (relief of pain, warming of the affected hand) received regional, intravenous sympathetic blocks with good results for several weeks, but not permanently. For chronic CRPS patients we

also regularly use an anticonvulsant - gabapentin and an antidepressant - amitrypyline as a supportive therapy, which alleviate pain and is well tolerated by the patients. Some of them had implanted spinal cord stimulators (in neurosurgical department), but its effectiveness is rather modest. Fortunately, patients with chronic condition suffer less from pain, but more from stiffness and partial disability of the hand. They usually adapt well to reduced dexterity of the hand and their functioning in daily living is typically "acceptable".

As it 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 function of the hand and/or be the source of considerable discomfort to the patients. Therefore, the term "recovery from CRPS", particularly in chronic disease not always means return to normality (Żyluk, 2001) .

PREVENTION

There are no specific measures which are known to prevent CRPS after trauma of surgery. It was suggested that careful operative technique, knowledge of anatomy, avoidance of nerve traction and proper postoperative care can reduce of CRPS after operations. It is also a common belief that early mobilization and prompt physiotherapy prevent the development of CRPS after fractures. 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. Reduction of CRPS incidence has been shown in patients after fracture of the distal radius by a two-months administration of oral vitamin C, but this beneficial effect has not been confirmed by other studies (Zollinger et al., 1998). In patients with a history of CRPS, a new injury or operation to that (or contralateral) extremity is known to increase the risk of a recurrence. Therefore, specific measures are recommended such as avoiding a tourniquet at the operation, pharmacological prevention by mannitol, calcitonin, steroids or vitamin C. However, the necessity of use of these measures has been questioned in some studies, showing that risk of a new episode of the condition in patients who recovered from CRPS is minimal (Zyluk, 2004).

In this paper we present some impressions and thoughts about CRPS which we have found useful in our proceedings with CRPS patients. Most hand surgeons, 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.

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Table 1. Modified IASP criteria of diagnosis for CRPS
(Harden et al. 2007; Harden, 2010)

Presence of continuing pain, disproportionate to any inciting event	
Must report at least one symptom in each of the four categories (*)	
Sensory	Hyperalgesia and/or allodynia
Vasomotor	Temperature asymmetry and/or skin colour changes and/or skin colour asymmetry
Sudomotor/ 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 one sign at time of evaluation in two 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^{o}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 four categories is a condition for research purposes. For clinical purposes a report of at least one symptom in three of the four categories is enough to meet this criterion.

Table 2. Methods used in the treatment of CRPS Type 1

Method
Free radical scavengers (mannitol, dimethyl sulfoxide, N-acetylcysteine)
Regional intravenous steroid blocks
Systemic steroids
Regional intravenous sympathetic blocks (with guanethidine, bretylium, ketanserin)
Sympathetic ganglia blocks (i.e. stellate ganglion block)
Sympathectomy (cervical or thoracic)
Systemic sympathycolysis (fentolamin, fenoksybenzamine, buflomedil)
Salmon calcitonin
Epidural administration of analgesics and other drugs (i.e. clonidine, baclofen)
Continuous epidural anaesthesia with bupivacaine
Continuous brachial plexus blocks with bupivacaine
Transdermal, electric nerve stimulation (TENS)
Direct stimulation of medulla spinalis
Antidepressants (i.e. amitryptyline)
Anticonvulsants (phenytoin, gabapentin)
Thalidomide