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What is This?
Complex regional pain syndrome: observations on diagnosis, treatment and definition of a new subgroup

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Abstract
Several definitions and sets of diagnostic criteria of complex regional pain syndrome have been proposed, but to date none has been accepted completely. This article presents a specific subtype of the disease, called ‘chronic, refractory complex regional pain syndrome’ which is extremely severe, disabling and resistant to treatment. It also emphasizes difficulties with diagnosing complex regional pain syndrome because of its variable clinical presentation and diagnostic criteria being insufficiently precise. The necessity to distinguish between criteria for clinical use and for scientific purposes is suggested with a proposal of practical guideline for diagnosing acute complex regional pain syndrome. A review of treatments for complex regional pain syndrome is presented, with opinion on their effectiveness: good in an early stage, less well in chronic and generally poor in the chronic, refractory subtype.

Keywords
Complex regional pain syndrome, diagnosis, classification

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Introduction
Complex regional pain syndrome (CRPS) is a complex of symptoms typically occurring following trauma of the extremity. It usually presents with severe pain at rest or with the slightest movement, swelling, vasomotor instability (changes of colour, temperature and sweating) and is accompanied by functional impairment of the affected limb (reduction of movements and strength). CRPS comprises a broad spectrum of clinical forms including acute CRPS, chronic CRPS, causalgia, shoulder–hand syndrome and sympathetically mediated pain. These forms differ with respect to their symptomatology, appropriate treatment and prognosis. Several definitions and sets of diagnostic criteria have been proposed, but to date none of them has been accepted completely. The International Association for the Study of Pain (IASP) criteria of diagnosis, both original (Merskey and Bogduk, 1994) and modified (Harden et al., 1999; Harden et al., 2007) have recently attracted increased popularity and are frequently used in scientific studies [Table 1]. There is no definitive single test for confirming or excluding CRPS and diagnosis relies on clinical assessment with the requirement for a sufficient number of symptoms and signs to be present (Harden et al., 2007; Harden, 2010).

Classically CRPS is classified into two forms: type I (formerly reflex sympathetic dystrophy) and type II (formerly causalgia). CRPS I implies no definite nerve injury [the majority of cases], whereas CRPS II diagnosis requires evidence of nerve damage as a causative event. The necessity of distinguishing these two forms has been recently questioned, since in most cases nerve involvement cannot be definitively excluded and the 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 in their symptoms, treatment requirements and prognosis (Bruehl et al., 1999).

Acute [early] CRPS is the most common type. It is characterized by a characteristic symptomatology
but with very variable severity. It is relatively easy to treat when diagnosed early and so has a good prognosis (Goris et al., 2010; Zyluk and Puchalski, 2008; Zyluk and Mosiejczuk, in Press) (Figure 1). It occurs most commonly after fractures of the distal radius, but also surgery for hand diseases and injuries. It affects mainly middle or older aged women. It can be recognized as early as two weeks after injury/operation although this may lead to overdiagnosis, because early CRPS and the post-traumatic period display many similarities (Birklein et al., 2001; Field, submitted; Field and Atkins, 1997).

If not spontaneously withdrawn, overlooked or misdiagnosed, the acute form passes into chronic CRPS. It is characterized by moderate pain in the hand, mild swelling, cold, pale skin, frequently hyperhydrosis, tenderness/hyperpathia but most symptomatic of all finger stiffness. Neurological signs may develop in a proportion of patients, such as hyperpathia, allodynia, tremor and muscle spasms and their appearance is characteristic for passing from acute to chronic CRPS (Birklein et al., 2000; Veldman et al., 1993). Unlike in acute CRPS, effective treatment is not available and even after stabilization of the disease and some resolution of most of the features, the residual symptoms may be marked and functional impairment severe. There is no precise timing of passing from the acute to the chronic form; it usually occurs within three to six months of the onset of the condition, but treatment may interrupt this transition.

### Methods and materials

Our institutional CRPS register has been built over a period of 20 years and comprises 220 patients with the condition involving mostly the upper limb; 170 (77%) with acute and 38 (17%) with chronic CRPS. Dealing with CRPS over many years, we noticed some features that are mentioned rarely in the literature. We have analysed our data and present our experience of diagnosing and treating of CRPS, with particular attention paid to a specific subtype called 'chronic, refractory CRPS' which we have found to be extremely severe and difficult to treat.

### Discussion

We outline our findings based upon analysis of our database considering a new form of CRPS and the diagnosis and treatment of CRPS in general.

**Chronic, refractory CRPS: a new subgroup**

This is the rarest and most severe form 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 a trivial injury (contusions, sprains, superficial wounds, skin infections, small operations), but not after fractures of the distal radius or hand surgery. This form involves exclusively young women aged from 18 to 40 years. All these patients

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

<table>
<thead>
<tr>
<th>Presence of continuing pain, disproportionate to any inciting event</th>
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<tbody>
<tr>
<td>Must report at least one symptom in each of the four categories (*)</td>
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<table>
<thead>
<tr>
<th>Sensory</th>
<th>Hyperalgesia and/or allodynia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor</td>
<td>Temperature asymmetry and/or skin colour changes and/or skin colour asymmetry</td>
</tr>
<tr>
<td>Sudomotor/oedema</td>
<td>Oedema and/or sweating changes and/or sweating asymmetry</td>
</tr>
<tr>
<td>Motor/trophic</td>
<td>Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia and/or trophic changes [skin, hair, nails])</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Sensory</th>
<th>Hyperalgesia (to pinprick) and/or allodynia (to light touch, temperature sensation, deep somatic pressure and/or joint movement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor</td>
<td>Temperature asymmetry (&gt;1 °C) and/or skin colour changes and/or skin colour asymmetry</td>
</tr>
<tr>
<td>Sudomotor/oedema</td>
<td>Oedema and/or sweating changes and/or sweating asymmetry</td>
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</tr>
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There is no other diagnosis that better explains the symptoms and signs

(*) In each of the 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.
presented to our unit with the disease in a chronic stage (Figures 2 and 3). In our register we have 12 patients (6%) with this form of the disease: nine with hand, two hand and foot, and one involving only her foot (Figure 4). This form is characterised by severe pain (reaching 9–10 VAS) and other painful phenomena (hyperpathia, allodynia) requiring regular analgesia (including opioids) and very severe functional impairment of the affected hand (extremity) with near total disability in most cases. By contrast to the acute and ‘normal’ chronic forms, this subtype always involves neurological disturbances: hyperpathia, allodynia (mechanical or thermal), tremor, muscle cramps, or dystonia (Figure 5). Contrary to opinions in the literature on the non-responsiveness to opioids in CRPS, we noted very good response to opioids in these patients, but – for obvious reason – we recommend that it is not be used over a long time. We usually attempted various treatments in these patients and any response, even partial or temporary, is considered a success, particularly if we gain some pain control. Pain is the most important problem for these patients and hand (foot) disability remains a second- or third-line problem. All our patients with hand involvement eventually received at least one implantation (a mean of 3, range 1–6) of a catheter into their brachial plexus for continuous analgesia with bupivacaine (Figure 6). These surgically inserted catheters stayed on site for a mean of four months (range 2–9) allowing patients effective pain control (Żyluk, 2006). However, after removing the catheter, pain recurred in all of them. Patients with lower extremity involvement receive continuous epidural anaesthesia with bupivacaine for one week, which resulted in partial pain relief lasting two to three months. Patients suffering from this CRPS
form quickly consider the affected hand or foot ‘lost’ and discontinue regular physiotherapy, which is usually ineffective and painful. Traditional rehabilitation fails in these patients, but specific treatments, directed on the disease, such as ‘mirror therapy’ may be useful (Cacchio et al., 2009; Field, submitted).

Figure 2. Chronic, refractory CRPS in 20-year-old lady. Severely disabled hand, with trophic skin changes and allodynia.

Figure 3. Chronic, refractory CRPS in 32-year-old lady. (a) and (b) Totally disabled, swollen left hand. (c) Associated inability to move (pseudoparalysis) of the involved extremity.
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. These disorders are usually mild and infrequently require psychological or psychiatric support (Zyluk, 2006). It is suspected that some particular psychological trait (defect) may be involved in the development of the disease in these patients, but there is a lack of evidence to confirm it. All 12 patients with chronic, refractory CRPS were identified with a florid disease initially, therefore we have no idea how it might be possible to recognize early the individuals with susceptibility to this very severe form of the CRPS.

An interesting observation is that these young women, coping with constant, debilitating pain and having a ‘totally’ disabled extremity (or two) become unexpectedly well-adapted to their disease. Two patients in our group graduated after university studies (one in medicine) and started to work, three continue in their original jobs and the remaining seven – although receiving a disability pension – run their households. In none of the 12 patients was any treatment option found to be effective, allowing a middle-time perspective free of pain.

An example of one patient with refractory CRPS was a 21-year-old lady with chronic CRPS of the right (dominant) hand resistant to any treatment. She subsequently sustained a left ankle sprain when under supervision in our clinic for her hand problem. In spite of immediate presentation within two days and adequate treatment of the foot injury including preventive administration of mannitol with dexamethasone, then continuous epidural anaesthesia, she developed acute CRPS of her left foot. We observed a rapid (two month) evolution from the acute to the chronic stage of the disease and the ineffectiveness of all our therapeutic interventions.
Diagnosing CRPS is associated with substantial doubts and confusion, which is the result of a lack of commonly accepted diagnostic criteria. A wide variety of these criteria sets were applied in research studies and practice. Historically, the condition was diagnosed when causing total disability of the hand (Böhler, 1956), the presence of pain in the hand and shoulder, swelling and limited motion of fingers (Frykman, 1967) or pain in the hand, tenderness, swelling, vasomotor instability and finger stiffness (Atkins et al., 1990; Bickerstaff and Kanis, 1994). The incidence of CRPS after fractures of the distal radius reported by these authors varied from 0.02% to 37% (Böhler, 1956; Atkins et al., 1990). Veldman et al. (1993) proposed criteria that included the presence of diffuse pain, swelling, vasomotor instability and reduction of movement.

These symptoms and signs should increase after load on the hand and involve a much larger part of the extremity than the site of precipitating injury. The modified IASP diagnosis criteria are now recommended for scientific studies on CRPS (Table 1). They assess CRPS within each of four statistically derived domains: sensory, vasomotor, sudomotor/oedema and motor/trophic. They include both objective signs noted on examination and patient-reported symptoms (Harden et al., 1999; Harden et al., 2007). These criteria have been validated, but, nevertheless, their utilization causes problems of overdiagnosis owing to poor specificity (Harden, 2010).

From a practical point of view, based on our personal/institutional experience, the following three conditions are necessary to consider CRPS as the most likely diagnosis.

**Diagnosing CRPS**

Figure 6. (a) Catheter implanted into brachial plexus for continuous anaesthesia with bupivacaine. (b) Access for self-administration of bupivacaine. (c) Catheter implanted percutaneously into brachial plexus. This type of catheter works maximum 2–3 weeks.
1. Presence of diffuse pain in the hand/extremity, spontaneously or with the slightest movement.
2. Functional impairment of the hand or extremity.
3. Absence of any disease that might explain the problem.

The presence of all other symptoms and signs (swelling, vasomotor disturbances, sweating and trophic changes) are of secondary importance, because their occurrence is variable, dependent on many circumstances, such as the predisposing event, the stage of the disease and treatment received. 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 infection, acute arthritis, tenovaginitis, acute carpal tunnel syndrome or neglect-like syndrome. The presence of neurological features (hyperpathia, allodynia, tremor, dystonia) in the chronic stage of the condition makes the diagnosis more likely, but their absence does not exclude it (Zyluk and Mosiejczuk, 2013). As was mentioned earlier, there is no single test for definitive confirmation or exclusion of CRPS. Imaging such as radiography, bone scintigraphy, CT and NMR have limited (if any) influence on decision making (Harden, 2010).

Although for scientific purposes the proposed diagnostic criteria may be insufficiently accurate and reliable, they are nonetheless very useful in our clinical practice. Obviously in scientific studies we employ well-recognized sets of diagnostic criteria, but in the clinic we follow the general rule that diagnosing CRPS as early as possible (even ‘incipient’ disease) is optimal, even at the risk of some overdiagnosis.

Treatment of CRPS

Various treatments have been used for CRPS, but their effectiveness is not definitively proven and they are used variably in different stages of the development of the syndrome. Acute CRPS is usually treated effectively with physiotherapy, steroids, calcitonin and free radical scavengers, such as mannitol, dimethyl sulfoxide [DMSO] and N-acetylcysteine. Progression to the chronic stage significantly worsens the prognosis, although this does not entirely preclude successful treatment.

In chronic CRPS, treatment includes specific physiotherapy [mirror therapy, stress loading], psychotherapy, drug therapy [steroids, anticonvulsants – gabapentin, antidepressants, calcium channel blockers], transcutaneous electrical nerve stimulation, spinal cord stimulation, sympathetic interruptions, autonomic blocks and surgery [nerve decompression, sympathectomy] (Patterson et al., 2011; Zyluk and Puchalski, 2008; Field, submitted).

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. This treatment is conducted for a week, during which patients receive no formal physiotherapy, but are encouraged to elevate the hand, move the fingers [both passively and actively] disregarding the pain it causes. Patients are motivated to achieve full finger flexion [make a fist] at one week, awaiting themselves of the analgesic and anti-oedema effect of various drugs. The treatment is supervised by medical staff and its progress is controlled every day, since the patients are admitted to the hospital for a week. An important element of this therapy is an in-patient regime. The majority of CRPS patients, even with short-lasting disease, are tired, in pain and frightened because they have experienced/are experiencing worsening of their symptoms and increasing disability. Usually, this anxiety is exacerbated by ignorance of the nature of the disease and possible previous, ineffective [out-patient] therapy. Admission to the hospital and assurance of the possibility of recovery are important, positive stimuli augmenting the basic therapy and motivating patients to optimize compliance. 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 (Zyluk, 1998). 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. Fortunately, patients with a 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’.

Conclusion

Refractory CRPS should be recognized as a specific subtype of the disease, because of its extremely severe, disabling course and resistance to treatment. We hope that other authors will confirm our findings of a separate refractory subgroup and help categorize
the features of this subgroup to advance their early diagnosis and hopefully treatment.

Diagnosing CRPS is difficult because its clinical presentation is variable and present criteria are neither precise/specific nor universal. Our clinical practice indicates the necessity to distinguish between criteria for clinical and scientific purposes. From a practical point of view, we believe diagnosing CRPS as early as possible (even ‘incipient’ disease) as optimal, even at the risk of some overdiagnosis. Much more work is needed to work out criteria/tests to diagnose accurately CRPS in all its forms.

There is not one, commonly accepted treatment for CRPS; various treatments have been used, but their effectiveness was not definitively proven and they are used variably in different stages of the development of the syndrome. Treatment of CRPS is relatively easy and effective in an early stage, but less well in chronic, with generally poor outcomes in chronic, refractory subtype. We recommend use of a combination of the mannitol with steroid for acute CRPS, which has been found effective and has attracted increased popularity in our country.

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Conflict of interests
None declared.

References