Complex Regional Pain Syndrome – What's in a Name?

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Introduction

In 1994 the term Complex Regional Pain Syndrome (CRPS) was introduced along with its criteria, which focused on sensory and autonomic features of this disorder [1]. These criteria were to replace the term "reflex sympathetic dystrophy" (RSD) with CRPS type I and causalgia with CRPS type II, respectively [1]. The difference between the two types of CRPS is based on the absence (CRPS type I) or presence (CRPS type II) of an overt nerve lesion. CRPS frequently follows tissue injury, which can be minimal or severe (sprain/strain, fracture, contusion/crush injury) [2]. But in 5–16% of the patients, no inciting event can be identified. As with prior RSD criteria sets, the CRPS criteria of the IASP focus on the different aspects of sensory and autonomic features [3, 4]. However, there is a growing recognition that the clinical spectrum of CRPS is broader including also movement disorders. Additionally, the CRPS criteria set has a low specificity [5]. Recent reviews on the utilisation of diagnostic criteria in studies/trials on CRPS highlight a lack of consensus on the content and application of criteria sets [4–6]. Together, these short-comings have led to new criteria that were published in 2005 (see below) [7].

Modified IASP research diagnostic criteria for CRPS-1 – Budapest criteria [2] (submitted to Committee for Classification of Chronic Pain of the IASP for the 3rd taxonomy, not yet accepted):

1. Continuing pain, which is disproportionate to any inciting event.
2. Must report at least one symptom in each of the four following categories:
   - Sensory: reports of hyperesthesia and/or allodynia.
   - Vasomotor: reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry.
   - Sudomotor/edema: reports of edema and/or sweating changes and/or sweating asymmetry.
   - Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin).
3. Must display at least one sign* in two or more of the following categories:
   - Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)
   - Vasomotor: e.vidence of temperature asymmetry and/or skin color changes and/or asymmetry.
   - Sudomotor/edema: evidence of edema and/or sweating changes and/or sweating asymmetry.

* A sign is counted only if observed at the time of diagnosis.

- Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin).

4. There is no other diagnosis that better explains the signs and symptoms.

The Clinical Spectrum of CRPS: How Complex?

Defining the typical spectrum of CRPS is a challenging task (because symptoms and signs can be difficult to identify), may occur in different combinations, and vary over time. Key features in the acute phase of CRPS are characterized by various combinations of sensory and autonomic symptoms and signs [3]. Although, the CRPS criteria require the presence of pain, this has been a controversial issue. In the series of Veldman, 4–7% of the cases had prominent autonomic symptoms and signs but no pain [3]. Additionally, while there has always been a focus on the sensory and autonomic features, there is increasing evidence that movement disorders are part of the spectrum of CRPS. Movement disorders may precede the occurrence of non-motor features of CRPS [3, 8, 9]. Some studies have even highlighted the sole occurrence of dystonia or tremor following trauma [10–13]. These movement disorders are concordant with those encountered in CRPS patients that suffer from sensory and autonomic features as well. The movement disorders occurring in CRPS patients may include weakness, dystonia, tremor and myoclonus, but frequently different combinations of these movement disorders may coincide within one patient [3, 8, 14, 15]. There is no reliable information on the incidence and prevalence of the different movement disorders in CRPS because epidemiological studies on CRPS suffer from methodological shortcomings, including selection bias (data are obtained from university-based tertiary chronic pain clinics or trauma units), design, and anecdotal reports. Nevertheless, the increasing awareness that CRPS patients may suffer from movement disorders has resulted in adding this clinical category to the new criteria set (see above) [7]. Many studies have documented the presence of weakness or a limited range of motion. However, both are not necessarily motor features as they may result from pain, edema or arthrogenic changes. A frequent finding in CRPS patients with weakness and/or dystonia is the so-called loss of voluntary control; patients will describe this phenomena as "My mind tells my hand to move, but it won't work" [8, 16, 17]. The loss of voluntarily control has also been reported in primary dystonia [18]. In our experience, bradykinesia is a typical abnormal movement characteristic in CRPS, even in patients that solely suffer from pain. Dystonia, a prominent motor feature of CRPS, is characterized by involuntary abnormal, predominant flexor postures (fixed dystonia) of the fingers, wrist and feet [8, 15]. In more severely affected patients the dystonia may progress to more proximal sites with again predominant flexor involvement [15]. Clinically, fixed dystonia may show a variable degree of flexion of the digits. In less affected patients, the hands may appear seemingly normal at inspection. In these patients, dystonia may only appear following the performance of repetitive tasks. In many patients there is a relative sparing of the first two digits that has been explained by a larger proportion of direct cortico-motoneuronal connections relative to interneuronal-motoneuronal connections of flexors of digits I and II [15]. Hence, the preferential involvement of flexors III–V has been interpreted as evidence pointing towards a role of abnormal function of interneuronal circuits [15]. Passive stretching of the affected digits results in a contraction of the stretched muscle suggesting a stretch reflex hyperexcitability [15, 17]. Dystonia may worsen by activity of the involved extremity, under circumstances of cold temperatures and humidity and in the more severely affected patients by tactile and auditory stimuli [15]. Myoclonus and tremor (3–7 Hz) are frequently reported by CRPS patients with dystonia, but in rare cases this may occur as the sole or predominant movement disorder [8, 15, 18, 20].

CRPS: How Regional?

CRPS is commonly known as a disorder affecting one extremity. However, several studies have highlighted that in 4–7% of the cases, the disease may spread to other extremities [15, 20, 21]. The spread of CRPS may result in rather unusual patterns characterized by multifocal or generalized distribution [15, 20, 21]. These more severely affected patients tend to be younger than those patients where CRPS remains restricted to one extremity [20, 21].

In more severely affected CRPS patients where the disease has spread to other extremities, it is not unusual to encounter bladder (urgency, retention) and bowel (obstipation, diarrhoea, or a combination of both) disorders as manifestations of CRPS [22, 23].

CRPS: Multiple Underlying Pathophysiological Mechanisms?

Although several hypotheses have been suggested, including sympathetic hyperactivity, changes in adrenergic sensitivity and psychological predisposition, the pathophysiological basis of CRPS is still unclear. Similarities between the classical symptoms of inflammation and the clinical features of CRPS have led several investigators to suggest an inflammatory origin of the disease [24, 25]. Indeed, the evidence pointing towards a possible involvement of the peripheral nervous system in the generation of inflammatory response in CRPS is compelling. CRPS has not been reported in patients with complete nerve lesions, suggesting that at least some continuity of a nerve is a pre-requisite to develop this disorder [26]. Both sensory and autonomic symptoms of CRPS occur in a similar glove- or stocking-like distribution pattern pointing towards a common underlying mechanism of both features [15]. Increasingly, research is documenting a perturbed function of C- and Aδ-fibres of sensory nerves as a potentially important candidate mechanism in the acute phase of CRPS [27–30]. Besides warning us of imminent or actual tissue damage of the skin, C and Aδ-fibres of sensory nerves respond to this damage as a first line of defence through the release of the neuropeptides substance P and Calcitonin gene-related peptide (CGRP) from the afferent nerve endings, a process known as neurogenic inflammation [31, 32]. This in turn results in local vasodilatation and increased capillary permeability causing edema and an increase of skin blood flow. Although peripheral nerve involvement is likely to play an important role in the acute phase of CRPS, numerous abnormalities on the neuroimmune level may play a role as well.

In contrast to the sensory and autonomic features, movement disorders in CRPS tend to become more prevalent as the disease duration lengthens [3]. Consequently, this suggests that a different mechanism may underlie the occurrence of movement disorders in CRPS. Most likely, this mechanism reflects the development of altered sensory motor integration on the spinal cord level as has been noted for peripheral nerve lesions [33–35]. The ability to experience pain serves a purpose as noxious stimuli elicit protective withdrawal reflexes, which generally involve flexor muscles to minimize or avoid potential tissue damage. The conspicuous involvement of flexor muscles in CRPS patients who have dystonia therefore hints towards the involvement of spinal motor programs that are involved in protective responses against pain [36]. Neurophysiological studies have revealed impairment of interneuronal circuits that mediate presynaptic inhibition of motoreurons of distal musculature and postsynaptic inhibition of motoneurons of proximal musculature [17, 37]. Successful pharmacological treatment of dystonia of CRPS by means of intrathecal administration of baclofen, a GABA B agonist, has highlighted the involvement of spinal GABAergic inhibitory interneurons [38]. These interneurons inhibit the amount of excitatory synaptic transmitter released by the sensory input on motoneurons in the spinal cord by means of presynaptic inhibition [39]. Spinal GABAergic interneurons receive both inputs from sensory nerves and descending fibres from the brainstem and motor cortex (supraspinal), and therefore have a strategic position in the regulation of muscle tone [39, 40]. Through impairment of these interneurons, motoneurons are exposed to an uninhibited sensory and supraspinal input explaining the worsening of dystonia by tactile stimuli, low temperatures, activity of the involved extremity, and emotional stress. Taken together, the above findings on fixed dystonia of CRPS are in line with the general pathophysiological concept of abnormal central sensorimotor processing in primary and secondary dystonia [38, 39].

Central sensitization is an important mechanism in pain and reflects the increased sensitivity of spinal neurons, despite unchanged afferent input. As a result, pain becomes chronic, and non-noxious stimuli become painful [44]. On a molecular level, central sensitization is associated with changes in the release of neuropeptides, neurotransmitters, prostaglandine E2, and the expression of N-methyl aspartate (NMDA) receptors [44, 45]. In view of the mechanisms by which they evolve and the time frame in which they appear, the movement disorders of CRPS most likely evolve within the context of central sensitization [36]. Although, the mechanism underlying the impairment of GABAergic inhibitory interneurons in CRPS is unknown; there are indications that substance P may mediate these changes [46, 47].

CRPS: A Multifactorial Disease?

CRPS has many characteristics that are typical of multifactorial disease. On the one hand, in CRPS a wide range of precipitating trauma has been identified [3]. In response to trauma, the body responds with a series of specific reactions aiming to repair the damage, promote wound healing and recruit host

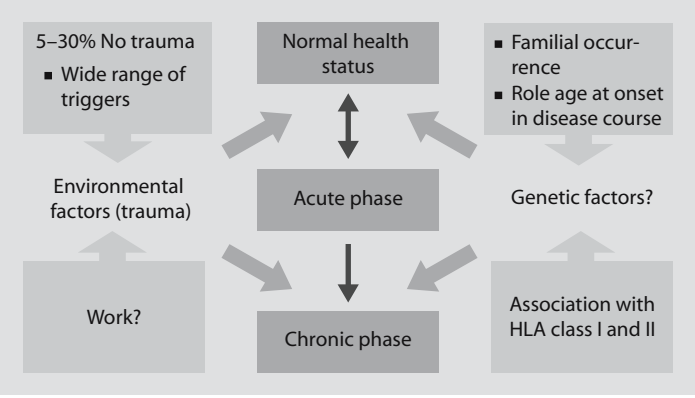

Fig. 2.1. Mechanisms to trauma

defence mechanisms that involve bi-directionally acting components of the nervous system and the immune system [48]. In CRPS, this biological defence mechanism to noxious or non-noxious stimuli apparently has the capacity of becoming detrimental when it cannot be controlled appropriately. On the other hand, as indicated by a younger age at onset in cases with a progressive disease course and the association with HLA factors, there is evidence suggesting a role for genetic factors conferring susceptibility to develop or sustain CRPS [23, 49]. Taken together, CRPS likely stands as an intriguing human model of aberrant response mechanisms to trauma (Fig. 2.1).

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