Dystonia in complex regional pain syndrome : clinical, pathophysiological and therapeutic aspects

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1

Introduction

Complex Regional Pain Syndrome

The first description of what nowadays is known as Complex Regional Pain Syndrome (CRPS) originates from 1864 when Weir Mitchell, an American neurologist, reported a syndrome in casualties of the American Civil War that was accompanied by partial nerve lesions. He named the associated pain "causalgia"[1,2]. In 1900, Sudeck described a similar syndrome which he named "acute reflektorische knochenatrophie", characterized by bone changes that occurred after an injury without obvious nerve damage[3]. In the following decades, several comparable syndromes were described using terms including algodystrophy, post-traumatic dystrophy and Sudeck atrophy. The supposed pathophysiological mechanism for these syndromes was an exaggerated reflex to an injury caused by dysregulation of the sympathetic nervous system. Therefore, around 1940, the term Reflex Sympathetic Dystrophy (RSD) was introduced to specify all syndromes characterized by the combination of autonomic and trophic changes[4]. As it became increasingly clear that the clinical features of the syndrome were insufficiently explained by dysfunction of the autonomic nervous system, a consensus meeting was held in 1994 which resulted in a new set of diagnostic criteria and the introduction of the terms "complex regional pain syndrome (CRPS)" type I and type II. These terms were meant to substitute for RSD (type I) and causalgia (type II) (table 1)[5,6]. 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.

Table 1. Diagnostic criteria for CRPS type 1 of the International Association for the Study of Pain (IASP) [5].

1) the presence of an initiating noxious event or a cause of immobilization
2) continuing pain, allodynia or hyperalgesia with which the pain is disproportionate to any inciting event
3) evidence at some time of edema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain
4) absence of a condition that would otherwise account for the degree of pain and dysfunction Criteria 2-4 are necessary for a diagnosis of CRPS.

CRPS generally affects distal extremities and is preceded by a trauma in a majority of patients[7,8]. A spontaneous onset has been described in 3–11% of cases[8-13]. CRPS occurs more frequently in women and may occur at all ages although the highest incidence is found between 50 and 70 years. The reported incidence ranges from 5.5 to 26.2 per 100,000 person-years[7,14].

CRPS is characterized by pain with various combinations of sensory disturbances

such as allodynia and hyperalgesia, and autonomic features like changes in skin blood flow, transpiration and abnormal hair and nail growth[5,8]. Occasionally, symptoms may spread to other extremities and body parts[13,15]. Furthermore, patients with CRPS may suffer from movement disorders (MDs), like tremor, myoclonia and dystonia[16-19].

Pathophysiology of CRPS

CRPS is regarded a multifactorial disorder where both environmental and genetic factors contribute to the development of the disease. The role of environmental factors is evident as in ninety percent of the patients symptoms are preceded by a traumatic injury[8]. However, as some patients develop CRPS spontaneously, other factors must contribute[20]. The role of genetic factors is supported by the fact that CRPS may occur in a familial form and that these patients develop the disease at a younger age and have a more severe phenotype than sporadic cases[21] which suggests an increased susceptibility to develop the disease[22,23]. A genetic predisposition for CRPS is also apparent from genetic associations that were found with different human leukocyte antigen (HLA) factors[24-27]. However, so far the role of HLA factors in CRPS has remained illusive.

The pathophysiology of CRPS has been increasingly studied over the past decades. Hitherto several different pathophysiological mechanisms underpinning CRPS or parts of its clinical spectrum have been forwarded.

Autonomic dysfunction

For long, impairment of the sympathetic nervous system was held responsible for maintaining pain ("sympathetically maintained pain", SMP) and autonomic dysfunctions in CRPS. In SMP, spontaneous and evoked pain is elicited by sympathetic hyperactivity through sympathetic afferent coupling, in which adrenergic receptors are expressed on primary sensory afferent fibres[28,29]. However, there are several reasons that argue against the sympathetic nervous system as the key player in the generation and maintenance of CRPS: for example, sweating and trophic disturbances are not the most predominant features of CRPS[8,30] and can also be induced by the neuropeptides calcitonin-gene-related peptide (CGRP) and substance P (SP)[31]. Additionally, vasoconstriction does not always reflect sympathetic activity[32] and alternative mechanisms like endothelial dysfunction may account for the vasomotor impairments[33,34]. Finally, although sympatholytic strategies have been recommended for decades, in many patients they are not beneficial[35]. Compelling evidence therefore suggests that SMP and sympathetic dysregulation may play a role in CRPS, but the

pathophysiology of the syndrome cannot be reduced to a sole dysfunction of the sympathetic nervous system.

Vasomotor dysfunction

Decreased skin temperature and skin discoloration both suggest that mechanisms underpinning vasomotor dysfunction are involved in CRPS. Skin capillary hemoglobin oxygenation (HbO2) is lower[36] and skin lactate is increased, reflecting enhanced anaerobic glycolysis[16,36,37] in muscles of limbs affected by CRPS. Muscle tissue obtained from amputated limbs of CRPS patients showed evidence of oxidative stress and ischemic conditions resulting from microangiopathy in muscle tissue[38]. Collectively, this information underscores that vasomotor dysfunction is an important component of CRPS. Both sympathetic dysfunction and endothelial dysfunction have emerged as mechanisms of disease that potentially may contribute to vasomotor dysfunction in CRPS[39].

Aberrant inflammation

Similarities between the classical symptoms of inflammation and the clinical features of CRPS have led several investigators to suggest that the disease is caused by an exaggerated inflammatory response. This view is supported by research in blister fluid of CRPS patients which showed high levels of pro-inflammatory cytokines[40,41]. Some researchers found evidence for an increased level of inflammatory mediators in cerebrospinal fluid[42], although others could not confirm this[43]. Additionally, an enhanced migration of injected radiolabelled autologous leukocytes or non-specific immunoglobulines towards the CRPS affected location has been described[44,45] and open label studies with immunomodulating drugs like infliximab[46,47] and thalidomide[48] report beneficial effects. Collectively, this led to the assumption that CRPS I is induced by an exaggerated inflammatory response to tissue injury, mediated by an excessive production of toxic oxygen radicals[49]. Support for the role of free radicals in CRPS I was found in randomized clinical trials in human CRPS with scavengers like dimethylsulfoxide, N-acetylcysteine and vitamin C in early treatment[50,51].

Finally, involvement of the immune system may be supported by reports on an increased prevalence of antecedent viral infections in CRPS patients and the presence of autoantibodies against a surface epitope of autonomic neurons[52].

Alterations in the somatic nervous system

Several studies have reported axonal degeneration in small distal nerve fibers of patients with CRPS[38,53,54], but there is debate among researchers whether this is a cause or a consequence of the syndrome. Increasing evidence hints towards a perturbed function

of both non-myelinated C and myelinated Aδ fibres of sensory nerves, resulting in the increased secretion of neuropeptides such as SP and CGRP, a process called neurogenic inflammation[55,56]. Animal studies in neuropathic pain syndromes have shown that these neuropeptides are also released spinally (by central nerve endings of primary afferents) which, in turn, may lead to central sensitization[57]. Central sensitization is induced in dorsal horn neurons and involves a reduction in pain threshold, amplification of pain responses and spread of pain sensitivity to adjacent, non-injured areas[58]. It is associated with neurochemical changes, functional alterations of excitatory and inhibitory connections, cell death of neurons and interneurons, and sprouting of new connections in the spinal cord[59].

In addition to spinal alterations, supraspinal sensorimotor neural networks are likely to contribute to the pathophysiology of CRPS. Which level of the CNS is the primary site where pathological alterations originate, remains unsolved. Referred sensations, changes in the size and organization of the somatosensory map, and changes in motor cortex representation are strongly suggestive of cortical involvement in CRPS[60]. For example, in CRPS patients watching the mirror-image of the unaffected limb elicits pain on the affected side[61] and referred sensations of a tactile or painful stimulus were experienced outside its expected somatic territory[62]. A fMRI study in CRPS focusing on mechanical hyperalgesia, reported alterations in nociceptive, cognitive and motor processing[63]. Schwenkreis et al.[64] studied patients with unilateral CRPS I involving the hand by means of transcranial magnetic stimulation using a paired-pulse paradigm. The authors found a significant bilateral reduction of intracortical inhibition in patients with CRPS compared with control subjects. Recently, regional grey matter atrophy and abnormal gray-white matter interactions, including decreased connectivity between the ventromedial cortex and basal ganglion have been observed[65].

Psychological factors

In the absence of a clear somatic cause, CRPS has often been considered as a psychogenic disorder[66]. Non-organic factors are often advanced as potential predisposing factors and some authors argue that the symptoms can be interpreted as a conversion reaction[67,68]or malingering[69]. However, much research on this topic is of poor methodologic quality and only a few prospective, well controlled studies have been performed. A recent population-based study by De Mos et al.[70] compared the medical history of patients who developed CRPS with age and sex matched patients who did not develop CRPS after a similar trauma and found that psychological factors were not associated with an increased probability to develop CRPS. Another prospective study comprising 596 patients with a single fracture found that there were no baseline differences in any of the psychological factors as measured by the SCL-90 between the 42 patients who

developed CRPS versus those who did not[71]. Three other prospective studies compared baseline data between patients who did and did not develop CRPS after surgery. None of these found a unique psychological profile in patients who developed CRPS[72-74].
There are no indications that childhood trauma plays a unique role in the onset of CRPS, as evidenced by a study from Ciccone [75] who found that child hood trauma and abuse were evenly distributed among patients with CRPS, local neuropathic pain and low back pain (LBP). Reports for the role of stressful life events are contradictory[76,77].
The majority of studies on psychological factors in CRPS involve cross-sectional studies, in which psychological and personality traits are compared between CRPS patients and patients with other pain syndromes. This approach does not permit conclusions regarding potential predisposing factors, since the present health status will inevitably reflect changes that occurred as a consequence of the condition. Three studies cross-sectionally compared patients with CRPS with patients with other pain conditions, using the Symptom Checklist (SCL-90) or its short version, the Brief Symptom Inventory. DeGood et al. found that, in comparison with patients with headache or low back pain (LBP), patients with CRPS had lower scores on 6 of the 10 scales despite experiencing the highest level of pain intensity; differences on the other scales were not significant[78]. No differences in psychological profile were found in a study comparing CRPS patients with patients waiting for hand surgery[76]. Bruehl et al. reported that CRPS patients exhibited some elevations on the somatisation and phobic anxiety subscales compared to patients with LBP or limb pain; differences on the other scales were not significant[79]. In contrast with Bruehl[79], van der Laan[80] found that CRPS patients with dystonia exhibited lower scores on the somatisation subscale than a control population of rehabilitation patients. Together the results of these prospective and cross-sectional studies do not support a unique psychological profile that characterizes patients with CRPS.

Movement disorders in CRPS

Motor abnormalities in war casualties with causalgia were first reported by Mitchell in the 19th century. This is illustrated by his description of case 28 from *Injuries of Nerves and their Consequences*: D.H., a girl of thirteen accidentally ran a small penknife blade into her right hand and developed burning pain, swelling, livid discoloration and a low temperature of the hand. A few months after the accident "the fingers became contracted, and the hand flexed, the palm continuing to suffer with burning pain. These conditions existed .....up to March 1869.....and the flexions became extreme"[2].
A more extensive description of the movement disorders (MDs) in CRPS followed in

the last two decades of the 20th century by Marsden and Schwartzman[18,81]. These MDs are not infrequent, as data from studies where selection bias towards MDs was unlikely indicate that 9-49% of the CRPS patients may develop MDs with dystonia being the most prevalent (14-25%)[8,18,82,83]. The increasing awareness that CRPS patients may suffer MDs has resulted in a proposal to add this clinical category to the new diagnostic criteria set[84].

Dystonia in CRPS is predominantly characterized by fixed flexion postures (figure 1), frequently has a delayed onset and may spread to other extremities[18,19]. Several small studies found that the interval between the onset of CRPS and that of MDs can be up to 3 years[81,85,86]. In Veldman's study, the prevalence of MDs increased with the duration of CRPS[8].

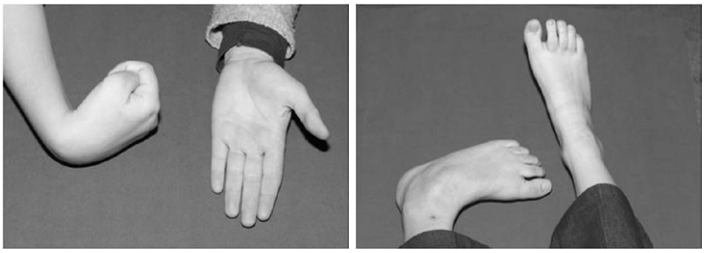

Figure 1. Flexion postures in dystonia of CRPS.

Dystonia is defined as abnormal involuntary muscle contractions that cause twisting or repetitive movements or sustained postures[87]. In primary dystonia, no other abnormality than dystonia is present and the cause is genetic or unknown. However, dystonia may also be brought on by a large and diverse group of disorders (secondary dystonia), such as an exogenous insult (exposure to certain drugs) or may be the result of heredodegenerative and metabolic disorders. One of the potential causes of secondary dystonia is trauma. Although there is general agreement that traumatic brain injury can cause dystonia, the question whether peripheral trauma can cause dystonia has since long been a subject of debate[88-90].

Traditionally, dystonia is associated with basal ganglia dysfunction, but recent developments have led to further maturing of the concept of dystonia. First, the influence of sensory tricks in reducing dystonia severity and evidence from neurophysiological studies highlighted the role of faulty sensory-motor processing in dystonia[91-93]. Second, recent studies have reported the occurrence of dystonia in cerebellar disease and thereby expanded the anatomical territory of dystonia to include the cerebellum[94-96]. Finally, two interventional studies on DYT1 dystonia and levodopa-responsive dystonia have shown that both disorders are associated with neurophysiological abnormalities

along the whole neuraxis that improved after deep brain stimulation or after levodopa challenge[97,98]. These findings have positioned dystonia as a manifestation of aberrant neural networks that are involved in sensory-motor processing required for the control and execution of voluntary movement[99]. In line with this new concept, several neurophysiological studies in CRPS-related dystonia have found evidence of impaired inhibition at the spinal cord and motor cortex[64,100,101].

The treatment of movement disorders of CRPS is a field still in its infancy. Randomized controlled studies of physical therapy, occupational therapy or pharmacotherapy are lacking. In Schwartzman and Kerrigan's report[18], some CRPS patients with dystonia benefited from oral baclofen and benzodiazepines. Splints and plaster casts have been used for the treatment of dystonic postures but are often ineffective or may even worsen the dystonia[85]. Although in some cases favorable responses have been reported following sympathetic blocks[102], no solid evidence is available to support this treatment mode for MDs in CRPS. Continuous intrathecal baclofen administration was evaluated in six CRPS patients with multifocal or generalized dystonia[103]. During prolonged therapy, three patients regained normal hand function, and two patients regained the ability to walk. In one woman the pain and violent jerks disappeared and the dystonic posturing of the arm decreased. In two women the spasms or restlessness of the legs decreased without any change in dystonia.

Prognosis of CRPS

Contradicting reports have been published regarding the outcome of CRPS. Sandroni et al performed a population-based study[7] and mentioned complete symptom resolution in 74% of the patients within one year after CRPS onset, on the basis of the medical chart review. In contrast, Veldman et al.[8] and Galer [104] et al. objectively assessed patients and found persistent disturbances in most of them after one or more years follow-up. In addition, Geertzen et al.[105] reported impairments and disability in 62% of patients 5.5 years after CRPS onset. In a population based retrospective comparative cohort study, de Mos et al[106] found that a majority of patients had persistent impairments at 2 or more years since the onset of CRPS. Sixty-four percent of the patients still fulfilled IASP criteria at an average of 5.8 years after the initial injury. The impact of the disease on the ability to work was high: 31% had become permanently incapable of work, whereas another 28% had to make working adjustments. Population based studies on the prognosis of CRPS patients with movement disorders are lacking but observational studies report a poor prognosis after several years of follow-up[107].

MDs occur frequently in patients with CRPS, have a poor prognosis and form a major challenge in the clinical management of patients with CRPS. A better delineation of clinical, pathophysiological and therapeutic aspects of MDs in CRPS may potentially contribute to better management strategies for this disabling component of the syndrome.

Aim of this thesis

1. To study the clinical characteristics and disease course of patients with CRPS in multiple extremities and of CRPS patients with movement disorders, in particular dystonia.
2. To study the neurophysiologic and neuroradiological characteristics of dystonia in CRPS.
3. To evaluate the efficacy and safety of intrathecal baclofen treatment for dystonia of CRPS.

These three aims will be addressed in studies described in chapter 2 to 8 of this thesis. A general discussion of the results and suggestions for further research are provided in chapter 9.

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