

# **CHAPTER 1**

## **General Introduction**

## **Complex Regional Pain Syndrome**

Complex Regional Pain Syndrome (CRPS) is a pain disorder of the extremities which is characterized by, autonomic, trophic and motor disturbances (1). Pain is the most prominent and disabling symptom of CRPS (2) and is reported to be of neuropathic nature (3). The pain experienced by CRPS patients is usually spontaneous, continuous and of burning and stinging character. Sensory thresholds of the affected extremity appear to be lowered, causing an exacerbated pain response and augmented (and sometimes painful) perception of non-painful mechanical stimuli such as light touch, heat and cold (4). Besides this augmented sensibility, patients may also experience a decreased perception of (painful) stimuli (hypoesthesia and hypoalgesia) (5). Other signs and symptoms include changes in skin temperature, skin color, edema and sweating, atrophy of skin and bone, changes in hair and nail growth, muscle weakness, tremor and dystonia.

CRPS usually occurs after a trauma, however CRPS may also develop without a known preceding event. Above mentioned signs and symptoms are usually disproportionate in nature, and are often spread outside the area of the initiating tissue injury. CRPS is classified into 2 types, whereby CRPS type 1 occurs without identifiable nerve trauma and type 2 occurs as a consequence of an established nerve lesion (6). About 4300 patients are estimated to develop CRPS in the Netherlands each year (7). Furthermore, CRPS occurs 3 times more often in females than in males and the highest incidence is found in the age range of 61 to 70 years (7).

### **Diagnosing CRPS 1**

As there is no complete understanding of the pathophysiological mechanism of CRPS 1, a gold standard for diagnosis of this complaint is lacking, therefore diagnosis of CRPS 1 is based on medical history and observation of clinical manifestations in patients. As a consequence, different diagnostic criteria sets and methods have been proposed in literature, which vary in assessment method, signs and symptoms patients should meet and diagnostic accuracy.

The most applied diagnostic criteria are the Veldman et al.'s, IASP and Bruehl et al.'s criteria. The Veldman et al.'s criteria (1) are based on reportage of patients and physical examination, and were derived from a cross-sectional cohort study of 829 patients. The criteria include the observation of a limited number of signs of inflammation, in combination with two criteria describing the disproportionate character of the complaint. The consensus derived IASP criteria (8) are solely based on the reportage of symptoms by patients. The IASP criteria further include sensory

and sudomotor signs/symptoms, and provide specific reference to the absence of other conditions that could account for the degree of pain and dysfunction. Bruehl et al.'s criteria (9;10) are a further specification of the IASP criteria, in which an explicit distinction is made between features of sensory, vasomotor, sudomotor-edema and motor-trophic nature reported by the patient (symptoms), and those observed by the physician (signs). The latter criteria were derived from the evaluation of 117 IASP–CRPS patients and 43 patients with neuropathic pain of other origin. Recently, new adaptations have been formulated to the IASP criteria. These Budapest criteria (11;12) are similar to the Bruehl et al.'s criteria but are extended with reportage of allodynia and the observation of allodynia to deep somatic pressure and joint muscle movement. Also, additional diagnostic decision rules specific for the clinical setting or research purposes were incorporated into the Budapest criteria.

The use of these criteria is not uniform, possibly leading to differences between study populations between different studies. Furthermore, none of the diagnostic sets measure the whole scale of complaints associated with CRPS 1 (13). To guarantee comparability of different CRPS 1 trials and to prevent the misdiagnosis of CRPS 1 patients, use of uniform and valid criteria, comprising a wide range of CRPS 1 complaints is required. The additional use of objective measurement instruments may also help to improve the diagnosis of CRPS 1.

### **Pathophysiological mechanisms of CRPS 1**

CRPS 1 is a complex and multifactorial condition. Different underlying disease mechanisms have been proposed, although none of these explain the full complexity of features exhibited by CRPS 1 patients. Current opinion points in the direction of neurogenic and immune mediated inflammation, oxidative stress and vascular dysfunction, increased central neuronal excitation and cortical reorganization to play a role in CRPS 1.

#### Neurogenic inflammation

After injury of nerve fibers and/or soft tissue, neuropeptides such as Substance P (SP) and Calcitonine Gene Related peptide (CGRP) are released from primary afferent fibers in the periphery (14). These peptides induce vasodilatation, provoke vascular permeability resulting in plasma extravasation and attract immune mediators which further enhance the pathological changes in the affected extremity (14). In addition, central and peripheral release of SP and CGRP contribute to the generation of (neuropathic) pain (15). It has been suggested that altered release

of neuropeptides in CRPS 1 might be responsible for the clinical features of CRPS 1. Indeed, CGRP levels were shown to be increased in serum of CRPS patients (16). In addition, experimentally induced neurogenic inflammation via transcutaneous electrical stimulation (17) and the direct application of SP (18) has been shown to provoke protein extravasation in CRPS patients, but not in healthy subjects.

#### Immune mediated inflammation

Features of CRPS 1 in the early phase resemble those exhibited in classical inflammatory process. Increased levels of the pro-inflammatory cytokines IL-6 and TNF $\alpha$  (19), and tryptase (a protein released by activation of mast cells) (20) have been found in blister fluid of the affected extremities of CRPS 1 compared to the non-affected extremities, pointing towards involvement of the immune system in generation of inflammatory features of CRPS 1. Cytokine levels of IL-1 $\beta$  and IL-6 were higher in the cerebrospinal fluid of CRPS 1 patients compared to controls, also suggesting central inflammatory responses to occur (21).

#### Oxidative stress and Reactive Oxygen Species

Increased oxidative stress and the production of Reactive Oxygen Species (ROS), following inflammation and/or tissue injury, have also been suggested to play a role in the pathogenesis of CRPS 1 (22). Excessive production of ROS, in turn, would subsequently cause local tissue damage, further maintaining the inflammatory state in CRPS 1 (23). Support for the role of ROS in the pathogenesis of CRPS 1 comes from the finding of significantly elevated levels of malondialdehyde and lactic hydrogenase (markers for oxidative stress) and uric acid, peroxidase and superoxide dismutase (antioxidant markers) in the serum and saliva of CRPS 1 patients (24). Moreover, treatment of CRPS 1 with the free radical scavengers Dimethylsulfoxide and N-acetylcysteine (25) was shown to be beneficial in reducing CRPS complaints. In addition, administration of the antioxidant vitamin C to patients with wrist fractures was shown to have a preventive effect on the occurrence of CRPS 1 (26).

#### Vasomotor dysfunction

##### *1. Sympathetic nervous system*

For many years, hyperactivity of sympathetic system has been thought to be the primary pathophysiological mechanism of CRPS 1 (hence the name Reflex Sympathetic Dystrophy) (27). Increasing evidence however, points towards decreased sympathetic vasoconstrictor activity in both acute and chronic CRPS (28). Augmented pain and altered vasoconstrictive response resulting in a cold and

bluish limb often observed in chronic CRPS 1, may be explained by increased alpha-adrenergic hypersensitivity (29).

## *2. Endothelial dysfunction*

A more recent explanation for vasomotor disturbances in CRPS 1 patients has been linked to impaired endothelial functioning. Abnormal functioning of the endothelium (layer of cells that cover the internal surface of blood vessels) has been found in CRPS 1 patients, resulting in impaired local blood flow, hypoxia, and acidosis in chronic CRPS patients (30;31).

## Central sensitization and the N-Methyl-D-Aspartate (NMDA) receptor

Central sensitization is believed to be the key mechanism underlying chronification of CRPS 1 (32). Central sensitization is a process whereby central and peripheral structures involved in sensory processing are sensitized and/or up-regulated, resulting in an increased reaction to peripheral stimuli (33-35). Features such as allodynia to movement and light touch, secondary hyperalgesia (hyperalgesia outside the site of tissue injury) and wind-up (progressive increase in the response of dorsal horn nociceptive neurons to repeated stimuli), are exhibited by CRPS 1 patients and have been linked to the process of central sensitization (36-38). Central sensitization may additionally influence spinal motor circuits in CRPS 1 resulting in movement disorders (39).

The NMDA receptor plays an essential role in the development of nerve injury induced central sensitization (40). Following (peripheral) trauma and inflammation, local structures (C and A $\delta$ -fibers) are sensitized, and elicit the release of SP, CGRP and glutamate (41). Continued release of glutamate activates AMPA receptors resulting in calcium influx in the post synaptic cleft. Calcium influx in turn depolarizes and releases the voltage dependent magnesium block and awakens the dormant NMDA receptors. NMDA activation results in an increased calcium influx into the cell, increasing synaptic efficiency, and induces several intracellular messengers (42) and kinases (43;44), which further potentiate NMDA receptor response via phosphorylation, increasing synaptic efficiency and further lowering pain thresholds. Glutamate levels have been increased in serum (45) and cerebrospinal fluid (46) of CRPS 1 patients, pointing towards involvement of the NMDA receptor in CRPS 1. Central sensitization further contributes to the production of pro-inflammatory cytokines (47) and oxidative stress (48) in a SP mediated fashion (49). Both (neurogenic) inflammation and central sensitization influence each other in a reciprocal fashion. NMDA receptors are distributed throughout the nervous

system (50;51) and may contribute to sensitization of central as well as peripheral structures. Activation of peripheral NMDA receptors may further decrease nociceptor thresholds and augment central sensitization.

### Changes in the brain

Brain imaging studies in CRPS 1 patients revealed cortical reorganizations in the primary and secondary somatosensory cortices (52;53) and the primary motor cortex (54). Together with alterations in cerebral pain and motor processing (54-57), these observations provide an explanation for the sensory (allodynia, hyperalgesia, hypoesthesia) and motor (dystonia, tremor) disturbances associated with CRPS 1. These changes in the brain could be a consequence of the pathology of CRPS 1 (58), or may be a generalized maladaptation resulting in a susceptibility to develop CRPS 1 (55).

### **Treatment of CRPS 1**

Although various treatment methods have been proposed for CRPS 1 (59), establishing a long-lasting therapeutic effect in CRPS 1 patients remains difficult. As described above, the NMDA receptor is assumed to play an important role in inflammation and nerve injury induced central sensitization (40), thereby prolonging the disease state of CRPS 1. To determine whether the NMDA receptor is an interesting target in the management of CRPS 1, the role of the NMDA receptor in the development of central sensitization in CRPS 1 needs to be evaluated further. Since changes in subunit expression and activity of spinal NMDA receptors have been suggested to be involved in central sensitization (33;34), the examination of NMDA receptors in tissues of CRPS 1 patients could provide support for the involvement of NMDA receptor in CRPS 1. Although the evaluation of central NMDA receptors in CRPS 1 is limited by the absence of brain and spinal CRPS 1 tissues for scientific appraisal, peripheral CRPS 1 tissue of CRPS 1 amputee patients has been used for histopathological research in CRPS 1 (60-62), and provides a more accessible target for research. Observed changes in NMDA receptors in peripheral tissues of CRPS 1 patients may provide indications for changes occurring in centrally located NMDA receptors.

Another way to demonstrate the involvement of the NMDA receptor on aspects of central sensitization in CRPS 1 is to perform “proof of concept” studies in which the effects of NMDA receptor antagonist on sensory disturbances in CRPS 1 are evaluated. Indeed, positive effects of the NMDA receptor antagonist ketamine on

CRPS 1 were found (63;64), suggesting a beneficial role for targeting the NMDA mechanism in CRPS 1. The therapeutic use of ketamine, however, is limited by the development of psychometric adverse effects (65). Magnesium, a physiological antagonist of the NMDA receptor, was shown to reduce pain in neuropathic pain patients (66). Furthermore, no serious adverse effects were found in studies evaluating administration of high doses of magnesium IV in pregnant women with pre-eclampsia (67;68). The effect of magnesium IV on pain in CRPS 1 has not been examined yet. Evaluating the effects of magnesium in CRPS 1 may therewith add to present insights about the role of central sensitization in the development of CRPS 1 complaints. Additionally, analysis of differences between CRPS 1 patients in their response to the magnesium treatment may provide more insight into the underlying pathophysiological mechanism(s) of CRPS 1.

### **Aim and outline of the thesis**

The aim of this thesis is to contribute to the assessment of CRPS 1. Furthermore, we will explore the role of the NMDA receptor in CRPS 1, and we will investigate whether NMDA receptor antagonists, in particular magnesium, can be a possible new treatment candidate to target central sensitization in CRPS 1.

In chapter 2, 3, and 4, measurement techniques are proposed to optimize the assessment of CRPS 1. In *chapter 2* relationships between most applied criteria (Veldman et al. (1), IASP (6) and Bruehl et al. criteria (9)) used for diagnosing CRPS are evaluated and the consequences of using different criteria for the clinical patient profile are discussed.

The development and the reliability of the TREND Symptom Inventory, a broad range CRPS 1 symptoms questionnaire will be evaluated in *chapter 3*. Comparisons between CRPS 1 and fibromyalgia patients will additionally be described in this chapter.

The reliability for use in lower extremity CRPS 1 of the Semmes Weinstein Monofilaments, an instrument used to determine coetaneous sensibility, will be addressed in *chapter 4*.

Chapter 5, 6, 7 and 8 concern the involvement of NMDA receptors and the value of NMDA receptor antagonists, in particular magnesium, for the treatment of pain in CRPS 1 patients.

Evaluation of possible changes in the expression of the NMDA receptor in the skin of CRPS 1 patients is described in *chapter 5*.

In *chapter 6*, a systematic review is presented in which the efficacy of different NMDA receptor antagonists for the treatment of pain in different neuropathic pain conditions (including CRPS 1) will be evaluated.

The NMDA receptor antagonist magnesium was shown to reduce pain in neuropathic pain patients (66). In *chapter 7*, a study pilot study is described exploring the feasibility of intravenous magnesium administration as a potential candidate intervention for a large size trial in CRPS 1.

The CRPS 1 population represents a heterogeneous group of patients, possibly leading to differences in response to treatment. In *chapter 8* will be investigated whether response to intravenous magnesium treatment is related to differences between CRPS 1 patients in magnesium status, expressed in the percentage of retained magnesium IV.

Finally, in *chapter 9*, the results of this thesis and suggestions for further research are presented.

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