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Sex, quality of life and brain function in complex regional pain syndrome

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Chapter 1

General introduction and aims

CLINICAL CHARACTERISTICS

Complex regional pain syndrome (CRPS) is a severely disabling pain syndrome characterized by autonomic, sensory, trophic and motor disturbances of the affected limb. In the initial stage, the affected limb of a patient is very painful, swollen, red and warm and shows changes in hair and nail growth. In the course of the syndrome these inflammatory and trophic signs can subside, but pain including allodynia, decreased temperature and motor disturbances of the affected limb can persist and even progress to adjacent or distant limbs¹.

Two CRPS subtypes are being recognised based on possible nerve damage; CRPS type 1 without obvious nerve damage (formerly known as reflex sympathetic dystrophy) and CRPS type 2 with definitive nerve damage (formerly known as causalgia). In this thesis we will focus on patients with CRPS type 1. To date, due to the lack of definitive biomarkers, the diagnosis is made on clinical signs and symptoms using the International Association for the Study of Pain (IASP) Budapest research or clinical criteria² (table 1).

Table 1

IASP Budapest criteria for CRPS	
1	Continuing pain, which is disproportionate to any inciting event
2	Symptoms: • Sensory: Reports of hyperesthesia and/or allodynia • Vasomotor: Reports of temperature asymmetry and/or skin colour changes/asymmetry • Sudomotor/edema: Reports of edema and/or sweating changes/asymmetry • Motor/Trophic: Reports of decreased range of motion and/or motor disfunction (weakness, tremor, dystonia) and/or trophic changes (hair/nail/skin)
3	Signs: • Sensory: Evidence of hyperalgesia and/or allodynia (to light touch/temperature sensation/deep somatic pressure/joint movement) • Vasomotor: Evidence of temperature asymmetry (>1°C) and/or skin colour changes/asymmetry • Sudomotor/Edema: Evidence of edema and/or sweating changes/asymmetry • Motor/Trophic: Evidence of decreased range of motion and/or motor disfunction (weakness, tremor, dystonia) and/or trophic changes (hair/nail/skin)
4	There is no other diagnosis that better explains the signs and symptoms.
Clinical criteria: three symptoms and two signs in different categories	
Research criteria: four symptoms and two signs in different categories	

EPIDEMIOLOGY

The incidence ranges from 5.5 to 26.2 per 100,000 person years, with the highest incidence rates occurring between 61 and 70 years. Arms are more often affected than legs (3:2) and females are affected 3–4 times more often than men^{3,4}. The prognosis is worrisome. In a recent prospective study, 25% percent of patients (n=59) still fulfilled the strict Budapest research criteria at one year follow up⁵. In line with these findings, Beerthuizen⁶ reported that none of the 205 CRPS patients (fulfilling the previous IASP criteria known as the Orlando criteria⁷) were symptom-free after 1 year and De Mos⁸ found that the majority of patients had persistent impairments after 2 years. In addition, 64% of the patients continued to meet the Orlando criteria after almost 6 years.

Quality of life

Not depicted in the epidemiological data but equally worrisome is the impact of the syndrome on health-related quality of life (HRQoL, in short QoL). HRQoL encompasses those aspects of overall quality of life that can be clearly shown to affect health, either physical or mental⁹. It includes different domains such as physical and mental health perceptions, functional status, social support and socioeconomic status⁹. Previous studies in CRPS reported poor QoL due to high levels of disability, chronic pain and motor disturbances, making patients unable to (fully) take part in the most basic parts of today's life: family relations, work and education¹⁰. However, these data are derived from studies with small sample sizes or selection bias, which renders the generalizability of the findings difficult^{11–15}.

Sex differences

To date, little is known about possible sex-differences in CRPS other than the disparity in incidence. Studies in the general population reported that women have more severe levels of pain, longer disease duration, more affected regions of the body¹⁶ and more often neuropathic pains¹⁷. Many hypotheses have been postulated for these apparent sex effects including; hormonal differences, less effective endogenous pain modulatory mechanisms such as decreased *diffuse noxious inhibitory controls* (pain induced in distant body parts elicit analgesia), increased susceptibility to allodynia and secondary hyperalgesia as well as psychological and social factors¹⁸. Across the studies, however, the results are inconclusive and often contradictory^{18,19}.

PATHOPHYSIOLOGY

Aberrant inflammation and endothelial dysfunction

The pathophysiology of CRPS is multifactorial: In the acute phase after tissue damage due to a traumatic event, a combination of classic and neurogenic inflammation is initiated. The

classic inflammation is thought to be mediated by T-lymphocytes and mast cells, resulting in the release of proinflammatory cytokines such as interleukine-1 β , -2, -6 and tumor necrosis factor α (TNF- α)²⁰⁻²³. The neurogenic inflammation is induced by affected nociceptive fibers, resulting in the release of neuropeptide mediators such as substance P, calcitonin gene-related peptide (CGRP) and bradykinin^{24,25}. Together these mediators induce vasodilation, increased vascular permeability and increased protein extravasation which clinically reflects the classic signs of calor (elevated temperature), tumor (swelling) and rubor (red colour) of the affected limb. However, later in the course of the disease when the initial inflammation subsides, the vasomotor signs can alter significantly: The affected limb often becomes cold and bluish due erroneous vasoconstriction. The vasoconstriction is likely mediated by a combination of endothelial dysfunction^{26,27} and peripheral adrenergic receptor upregulation²⁸. This in turn leads to local tissue hypoxia which is thought to account for the trophic signs of CRPS²⁹.

Involvement of the central nervous system

The proinflammatory neuropeptides that are released during neurogenic inflammation reduce the thermal and mechanical thresholds of peripheral nociceptive fibers and increase their firing rate^{30,31}. This is called peripheral sensitisation and accounts for another characteristic sign of CRPS, namely hyperalgesia. Hyperalgesia is the term for increased pain perception of a painful stimulus. Furthermore, the peripheral neurogenic inflammation also induces activation of spinal cord based glial cells³²⁻³⁴. The latter is associated with upregulation of N-methyl-D-aspartic-acid (NMDA) receptors of spinal nociceptive neurons and a loss of function of intraneuronal circuits mediating inhibition^{35,36}. Lastly, some data suggest an additional reduced supraspinal modulation of nociceptive input based on differential activation of subcomponents of the endogenous pain modulatory system³⁷. Collectively, this culminates in increased excitability of the spinal cord which is called central sensitization. Central sensitization is clinically identifiable as allodynia: a non-painful stimulus is perceived as painful^{24,25}.

Next, central sensitization is seen as the driving force of aberrant neuroplasticity in the spinal cord and brain. In the brain this neuroplasticity is depicted by cortical sensorimotor reorganization of the affected limb³⁸⁻⁴⁰, changes in local grey matter volume⁴¹⁻⁴⁴, altered cortical activity patterns in rest⁴⁵ and alterations in cortical excitability and inhibition^{46,47}. Many of these changes are assumed to underlie the clinical observations of altered central processing of sensory stimuli⁴⁸⁻⁵¹ and motor control⁵²⁻⁵⁴. Unfortunately, many of the reported findings are inconsistent in terms of spatial or quantitative measures and correlations with clinical features. In addition, the nature of movement disorders in CRPS has been a source of debate. Although evidence has been published suggesting a mismatch between aberrant afferent signals and the internal sensory representation of a limb as the source of motor disturbances⁵⁵⁻⁵⁷ many clinicians consider CRPS movement disorders as functional movement

disorders⁵⁸ due to their clinical similarities; functional movement disorders are movement disorders that lack an organic substrate and are associated with psychological stressors^{59,60}, peripheral trauma, pain and fixed postures⁵⁹⁻⁶².

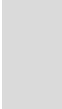
To further substantiate this rationale, studies should investigate neurophysiological characteristics between patients with CRPS and functional movement disorders. Conventional neurophysiological tests are unable to reliably differentiate between ‘organic’ and ‘functional’ movement disorders⁶³. However, studies on specific cortical excitability measures during motor tasks show promising results in differentiating both groups. In functional paresis a dissociation in motor cortical excitability was seen between explicit, voluntary tasks and implicit automatic motor tasks⁶⁴⁻⁶⁶. This dissociation was regarded as the result of interference from other, possibly limbic, brain areas in line with the established rationale of psychological stressors as the source of functional movement disorders. The question therefore is, if this approach may shed new light on the nature of CRPS associated movement disorders.

Aims and outline of this thesis

This thesis is divided in two parts. In the first part (chapter 2 and 3) we evaluate health-related quality of life (QoL) and possible sex differences in CRPS using data of The Netherlands’ database of CRPS patients. More specifically, in chapter 2 we investigate the influence of sex, pain, pain duration, and type of affected limb on quality of life. These data are important since many patients struggle with pain and disabilities years after the first diagnosis and a cure is not yet in sight. Insights into factors that may play a role in QoL of patients with CRPS may contribute to more tailored treatment approaches.

In chapter 3 we study possible differences in the way CRPS expresses between the sexes: Are there differences in terms of pain, disability and psychological factors between both sexes? Potential differences may be rooted in basic biological differences, as well as in cultural and socioeconomic factors. If so, these sex differences potentially may require differential treatment approaches.

In part two (chapter 4, 5 and 6) the aim is to evaluate if CRPS is associated with changes in the brain. More specifically, in chapter 4 we search for CRPS-specific and relevant changes in brain function in rest using multiple modalities of magnetic resonance imaging (MRI) of the brain. In addition, we compare our results with those published in literature and evaluate the current evidence for specific, clinically relevant changes in brain structure and function in rest in CRPS. This is relevant since some therapies are based on the presumptive changes in brain structure and function.



In chapter 5 we focus on brain activation in response to a painful stimulus administered to the affected arm of CRPS patients and the right hand of healthy controls to better understand the networks involved in somatosensory, motor and behavioural processing.

Lastly, in chapter 6, we focus on the (dis)similarities of CRPS movement disorders with functional movement disorders by using Transcranial Magnetic Stimulation (TMS) during motor imagery. Motor imagery is the neuronal correlate of motor activity without the actual execution of the movement itself. Using this method, we aim to evaluate if cortical brain activations in CRPS are similar to those previously reported in functional movement disorders.

Chapters 7 (With Dutch translation) provides a summary of the main conclusions, a general discussion of the results and suggestions for further research.