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2014

document version

Publisher's PDF, also known as Version of record

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citation for published version (APA)

Fischer, S. G. L. (2014). *A burning matter: Investigations into inflammation and central sensitization in CRPS*. [PhD-Thesis - Research and graduation internal, Vrije Universiteit Amsterdam].

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Summary

A burning matter

Investigations into inflammation and central sensitization in CRPS

This thesis comprises studies on underlying pathological mechanisms, treatment and assessment tools in Complex Regional Pain Syndrome (CRPS). We hereby focused on the role of inflammation, oxidative stress and subsequent sensitization in patients with CRPS.

In **Chapter 1** the aim of the thesis was outlined and the performed studies are introduced.

In **Chapter 2** a general introduction is presented about the current state of research performed on CRPS-1. The development of clinical diagnostic criteria resulting in the internationally accepted IASP Budapest criteria is presented, which may help to uniform diagnosis and maximize comparability between studies on CRPS. Several pathological mechanisms for CRPS have been suggested in recent years, such as inflammation, oxidative stress, but also autonomic disturbances, vascular pathology, central sensitization, cortical deregulation and psychological factors. In line with these proposed mechanisms a wide range of therapies are described, related to pain management, and mechanism related approaches (e.g. anti-inflammatory therapy, vasodilatory medication). Invasive therapy, such as spinal cord stimulation, is still in an experimental stage. Furthermore, physical and psychological modalities have been developed to improve clinical conditions of patients with CRPS.

Recently, several epidemiological, genetic and clinical studies have been performed in an attempt to identify factors which may be involved in developing CRPS. This information may help in understanding disease mechanisms and identify patient profiles to prevent development of CRPS.

Chapter 3 presents a study on co-morbidities occurring with CRPS. Questionnaires on demographic characteristics, symptoms, general health status, medication use and history of surgery were collected in a sample containing 669 CRPS-1 patients and 180 non-CRPS pain patients from four University Medical Centers. The main findings were a high prevalence of gastro-intestinal disorders and muscle, bone and skin disorders. This may be related to disturbed inflammatory balance, but can also relate to autonomic disorders as proposed for CRPS patients. However, muscle, bone and skin disorders were also described in other chronic pain syndromes which is suggestive for mechanisms occurring in pain conditions in general. Future case-control studies where both patient and medical assessed co-morbidities

are systematically evaluated should be conducted to confirm our findings and help to recognize patient profiles with higher chances to develop CRPS.

In **Chapter 4** we present a systematic review on effects of anti-inflammatory therapy for CRPS-1. Twenty-two independent studies were analysed in this review investigating effects of corticosteroid treatment, free radical scavengers and the combination of both substances. Pain reduction, improvement of range of motion and improvement of clinical outcome were found after treatment with free radical scavengers and with corticosteroids. In addition, the free radical scavenger vitamin C showed substantial preventive effects. More research on anti-inflammatory therapy in patients with CRPS-1 is indicated, since most included studies exhibited methodological deficiencies. Research targeted at well-defined subgroups of CRPS-1 patients with a clear inflammatory profile may add to a more mechanism based approach.

In **Chapter 5** a study was presented investigating levels of markers for oxidative stress in patients with CRPS-1. In nine female patients with a short duration of CRPS and nine age matched healthy female volunteers samples of blood and urine were analyzed. In this study, levels of markers of lipid peroxidation (MDA and F2 isoprostanes) and DNA damage (8OHdG) were not found to be elevated in CRPS patients. This was in contrast with previous studies whereby elevated levels of MDA were found in serum and saliva. This result may be related to the systemic measurements performed in bodily fluids while CRPS is, especially in early stages, thought to be a regional disease..

In **Chapters 6 and 7** clinical trials were presented evaluating therapeutic targets for patients with CRPS. **Chapter 6** describes a proof of concept study evaluating the effects of increasing acetylcholine availability. Autonomic endogenous subsystems such as the cholinergic anti-inflammatory pathway have been proposed to play a key role in regulation of inflammation. Whereas autonomic disturbances as well as inflammatory deregulation are proposed pathologic mechanisms in CRPS, influencing the cholinergic anti-inflammatory pathway in CRPS patients may provide a new therapeutic pathway for CRPS. In this study ten patients with CRPS-1 were treated with the cholinesterase inhibitor pyridostigmine in a cross-over design comprising two four week treatment phases and two three weeks control phases. Patients were screened for autonomic disturbances and the inflammatory profile was registered. All but one patient showed improvement at one or more outcome measurements, however these improvements were limited. In a small subgroup analysis patients with either autonomic disturbances or an inflammatory profile tended to have a better outcome after treatment. Although these findings may lend some support for a role for activating the

cholinergic anti-inflammatory pathway in CRPS, the effects are too limited to for current clinical application.

In **Chapter 7** a randomized controlled trial on the effects of intravenous administration of magnesium sulphate was presented. Inflammation following trauma can lead to increased peripheral and central sensitization by activating dormant NMDA receptors and local increase in density of NMDA receptors. In CRPS patients this can present as spontaneous pain and increased reaction to stimuli (e.g. allodynia). To counter the process of peripheral and central sensitization and to reduce sensory disturbances, NMDA receptor antagonists (e.g. magnesium, ketamine) have been proposed. In this study 56 patients were included and randomized to receive magnesium sulphate IV (MgSO_4) or placebo IV (NaCl 0.9%), during 5 consecutive days. Intravenous administration of magnesium as used in our study showed no improvement on pain or disability in patients with chronic CRPS-1 compared to placebo. .

Comprehensive assessment tools for the severity of CRPS which are in line with current views on diagnosis for CRPS have been lacking. Recently the CRPS severity score (CSS) has been proposed, in which clinical as well as anamnestic features of CRPS are incorporated. In **Chapter 8** we present a validation study of the assessment tool. In this study correlations between the CSS, the ISS and subjective change were assessed in 34 CRPS patients during a clinical trial. The results of this study show fair to excellent correlations between the CSS and ISS and the CSS and subjective change. These findings are in line with previous research showing positive correlations between the CSS and the indices measuring quality of life (Rand-36), temperature abnormalities and limitations in range of motion. Therefore, we may conclude that the CSS can be regarded as a valid assessment tool for disease severity in CRPS-1. Changes of the CSS and the Impairment level Sum Score over the course of a trial correlated well, suggesting that the CSS can be used as a follow up tool on disease severity. To improve the CSS, a more even distribution of signs and symptoms in the total score is proposed, as well application of weighting of individual signs and symptoms according to their severity.

Chapter 9 includes a general discussion about the research presented in this thesis.

