Summary

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Chapter I Introduction

Complex Regional Pain Syndrome (CRPS) is a disease which occurs as a complication after surgery or trauma, although spontaneous development is described.
CRPS is characterized by continuing pain, sensory and vasomotor, sudomotor, motor and trophic disturbances. Many of these symptoms are normal during a period of recovery after surgery or trauma and are part of a sterile inflammatory process and disuse. This is the process which normally leads to restoration. Characteristic for CRPS is that this reaction does not seem to stop, the normal sterile inflammatory process seems to continue. This clinical picture is often combined with disturbances of the central nervous system including allodynia, sympathetic dysregulation and dystonia. A difference is made between CRPS type 1 (CRPS 1), without nerve damage and CRPS type 2 (CRPS 2), with nerve damage.

Chapter II Neuroimmune alterations in the Complex Regional Pain Syndrome

In a literature review we focused on some clinical aspects of CRPS, such as oedema, local temperature changes and chronic pain, as a result of supposed neurogenic inflammation. Involvement of the immune system could imply the subsequent release of neuropeptides, pro-inflammatory cytokines and eicosanoids which, in turn, leads to a complex interaction of primary and secondary generated mediators of inflammation. The development and application of drugs that act via selective receptor antagonism or enzymatic synthesis inhibition to prevent further stimulation of this cascade, that could lead to chronicity of CRPS are extensively discussed.

Chapter III Computer-assisted skin videothermography is a highly sensitive tool in the diagnosis and monitoring of Complex Regional Pain Syndrome type 1

The use of thermography in the diagnosis and evaluation of CRPS 1 is based on the presence of temperature asymmetry between the involved and uninvolved extremity. Interpretation of thermographic images is however, subjective and not validated for routine use. The aim of this study was to develop a sensitive, specific and reproducible mathematical model based on the infrared masurements of computer-assisted skin videothermography in patients with early stage CRPS 1 in one hand. A total of 18 patients with CRPS 1, fulfilling the Bruehl criteria, in one hand and 13 healthy volunteers were included in the study. The severity of the disease was determined by means of a visual analogue scale (VAS) and a McGill Pain Questionnaire (MPQ), measurements of mobility with “active range of motion” (AROM) and

oedema volume. Temperature asymmetry in resting condition between two extremities was calculated using three different methods: i.e. the temperature asymmetry factor, the ratio, and the average temperature difference. The discriminating power of the three methods was determined by the receiver operating curve (ROC). The regression between the determined temperature distributions of both extremities was plotted. Subsequently, the correlation between the data was calculated. In healthy individuals the asymmetry factor was 0.91± 0.01 (SD) compared with 0.45 ± 0.07 (SD) in the CRPS patients. The performance of the mathematical model based on the ROC curve was excellent. The area under the curve was 0.97, the p-value was <0.001, the sensitivity 92% and specificity 94%. Furthermore, the temperature asymmetry factor was correlated with the duration of the disease and VAS pain. In conclusion, in resting condition, videothermography is a reliable additional diagnostic tool in the early stage of CRPS 1. It was proposed that this objective tool could be used for monitoring purposes during experimental therapeutic interventions.

Chapter IV Evidence for local inflammation in Complex Regional Pain Syndrome type 1

The purpose of this study was to examine the involvement of neuropetides, cytokines and eicosanoids as locally formed mediators of inflammation in the CRPS 1.

Nine patients with proven CRPS 1, fulfilling the Bruehl criteria, were studied. Disease activity and impairment was determined by means of a VAS, the MPQ, difference in volume and temperature between involved and uninvolved extremity, and the reduction in AROM of the involved extremity.

Venous blood was sampled from and suction blisters made on the involved and uninvolved extremity for measurement of cytokines Interleukine-6 (IL-6), Interleukine-1β and Tumour Necrosis Factor alpha (TNFα), the neuropetides Calcitonine Gene Related Peptide (CGRP) Neuropeptide-Y, and Prostaglandin E_2.

The patients included in this study had a moderate to severe disease activity and impairment. In plasma no changes in the mediators of inflammation were observed. In blister fluid, however, significantly higher levels (median ± interquartile range, Wilcoxon signed-ranks test $p<0.05$) of IL-6 and TNFα in the involved extremity in comparison to the uninvolved extremity were observed. IL-6: 18 (11-37) pg/ml in the involved extremity versus 7 (4.7-8.2) pg/ml in the uninvolved extremity and TNFα: 54 (19-68) pg/ml in the involved extremity versus 17 (4.9-20) pg/ml in the uninvolved extremity.

This is the first study in which the involvement of mediators of inflammation in CRPS 1 has been so clearly and directly demonstrated. This observation opens new approaches for the successful use and development of immunosuppressives in CRPS 1.

Chapter V Successful treatment of CRPS 1 with anti-TNF

Anti-TNF has been successfully used in Crohn's disease, rheumatoid arthritis and a few other inflammatory disorders in which TNFα contributes to the clinical symptoms of the disease.

Based on: a) our own observation that IL-6 and TNFα are involved in the pathophysiology of CRPS 1, b) a proposed possible genetic predisposition and specifically a role for the TNF2 allele in CRPS 1 in a study by Vaneker, c) the observation in the chronic constriction ligature model that IL-6 and TNFα play a key role in the development of clinical signs and d) that the signs in this model can be antagonated by anti-TNF, we felt there were sufficient indications to presume a role for anti-TNF in the treatment of CRPS 1. Two patients with CRPS 1, full filling the criteria of Bruehl, were succesfully treated with anti-TNF. Improvement was evidenced by changes in clinical and biochemical parameters.

Chapter VI Mast cells are involved in inflammatory reactions during Complex Regional Pain Syndrome type 1

The pathogenesis of the CRPS 1 remains debatable. Afferent, efferent and central nervous system mechanisms are proposed. Earlier we showed the involvement of the pro-inflammatory cytokines IL-6 and TNFα in the pathogenenis of CRPS 1. This is a direct evidence for an inflammatory process. Many types of cells, such as activated T-lymphocytes, monocytes, macrophages and skin resident cells like mast cells, could contribute to the production of cytokines. Involvement of mast cells is relatively easy to detect by measurement of tryptase.

This study examined 20 patients fulfilling the Bruehl criteria with CRPS 1 in one extremity. Impairment was assessed by registration of a VAS and measurement of differences in temperature, volume and mobility between the involved and uninvolved extremity. Blisters were raised with a suction method in order to determine levels of IL-6, TNFα and mast cell derived tryptase in the involved and uninvolved extremity.

In the blister fluid a significant difference (median ± interquartile range, Wilcoxon signed-ranks test $p<0.05$) was found between the involved and uninvolved extremity in the levels of IL-6, TNFα and tryptase. IL-6: 53.5 (17.3-225) pg/ml in the involved extremity versus 6.2 (2-20.3) pg/ml in the uninvolved extremity, TNFα: 31 (15.5-131.5) pg/ml in the involved extremity versus 8 (4-39) pg/ml in the uninvolved extremity and tryptase 37 (20.5-62.3) ng/ml in the involved extremity versus 12.5 (6.7-23.5) ng/ml in the uninvolved extremity. There was a significant correlation (0.455) between the intensity of pain and tryptase levels in the involved extremity (Spearman's test, $p<0.05$).

Based on these findings we concluded that mast cells are involved in inflammatory reactions during the CRPS 1 and suggest that mast cells could play a role in the production of cytokines such as TNFα.

Chapter VII Use of topical capsaicin in Complex Regional Pain Syndrome type 2: a case report

This case report describes the successful treatment of a patient with a complex regional pain syndrome type 2 (CRPS 2) with topical capsaicin. In literature some cases have been described for the successful treatment of CRPS 1 with capsaicin. After 6 weeks treatment a clinical improvement was observed as evidenced by a reduction in pain, edema and skin temperature, and an improvement in mobility. The levels of CGRP and TNFα measured in the fluid of artificially raised blisters in the involved extremity decreased during treatment with capsaicin.

Chapter VIII Use of topical capsaicin in the treatment of Complex Regional Pain Syndrome type 1: an open label study in 14 patients

This study examined the clinical and biochemical effects of the topical application of capsaicin in the treatment of 14 patients with a CRPS 1, full filling the Bruehl criteria, in one extremity.

At the start and end of 6 weeks treatment we measured signs and symptoms of impairment and made artificial blisters, in the involved and uninvolved extremity in which we measured levels of IL-6, TNFα and CGRP.

Clinically, there was a significant improvement after treatment with capsaicin. This was shown by a significant improvement in the VAS, blood flow distribution and AROM. Biochemically, the improvement was detectable in blister fluid in the involved extremity as a significant decrease in the levels of TNFα; start 24.0 (13.8-77.3) pg/ml versus end 17.0 (7.3-42) pg/ml. There was a nonsignificant decrease in the levels of CGRP. There was a nonsignificant increase in the levels of IL-6, possibly as a result of a neurotoxic effect of capsaicin. Clinically, this does not seem to result in a limitation for treatment with capsaicin.

Chapter IX General discussion

Our observation of involvement of IL-6 and TNFα in CRPS 1 is a direct evidence for inflammation. The question remains how the cytokines behave during the course of the disease. Do cytokines always play a role in long standing CRPS 1, or do cytokines only play a role in the subgroup, as described by Bruehl et al., showing the full blown picture of CRPS 1. Without doubt not only pro-inflammatory but also anti-inflammatory substances like IL-10 are involved. Further study is needed to examine their involvement.

We have demonstrated successfull treatment of two patients with CRPS 1 with anti-TNF. Completion of our open label study with anti-TNF followed by a double-blind randomised controlled trial is necessary to draw more definite conclusions.

We have also shown the involvement of mast cells in CRPS 1. Our findings suggest a role for mast cells in the delivery of cytokines. Further investigation is needed to detect the involvement of other cells.

Based on these findings there is a possible place for pharmacological intervention studies in patients with CRPS 1 with mast cell specific anti-allergic drugs, such as histaminic and mast cell stabilisers.

More study is needed on the role of neuropeptides in CRPS. Interesting for future research on CRPS is the role of neurokinine-1 receptor antagonists.

One problem in research in CRPS 1 is the lack of a gold standard. Therefore, research on this disease should focus on getting markers to make the diagnosis in a more sensitive and specific way and to follow the development of the disease or the effect of interventions. Computerised videothermography seems to be a very promising tool, but more studies are needed to validate this tool.

The question remains why are some people with the same trauma or same kind of surgery develop CRPS, and others not? Is there a genetic predisposition or an acquired immunologic alteration for susceptibility for CRPS 1?

This thesis does not focus on the other important aspect of CRPS, namely sensitisation.

Nowadays, the two schools of thought regarding to pathophysiology of CRPS, namely those who believe in an inflammatory process and those who believe in a more central nervous system deterioration are paying more attention to each other. Almost everyone is convinced of the fact that an inflammatory process and a dysregulation of the central nervous system are both part of CRPS. Consequently, it is plausible that more than one therapeutic option is feasible. Solutions should be sought in combinations of therapies focussed on causal mechanisms.