General discussion

IX

For years there have been two schools concerning the pathophysiology of CRPS 1. One school considered CRPS, to be a dysregulation of the sympathetic nervous system, the other considered CRPS, to be a chronic inflammation.

One of the problems in studying CRPS is the lack of a gold standard. For clinical use it is important to work with a standardized set of criteria. The criteria used nowadays, such as the Veldman criteria [1], the IASP criteria [2] and the Bruehl criteria [3] are not always easy to apply. Studies on CRPS should focus on developing 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.

Temperature is one of the diagnostic tools used in CRPS. Temperature at the surface of an extremity is mainly the result of skin blood flow and this is the result of a complex combination of central and local regulation systems. The tympano thermometer is nowadays the most popular device to monitor temperature in research on CRPS.[4] It is cheap, easy to use, non invasive and reliable. We have however demonstrated the limitations of the use of this device in CRPS. Other investigators have studied the usefulness of videothermography as a diagnostic tool for CRPS.[5] With videothermography we are able to see differences in local temperature, but this is a qualitative and mainly subjective interpretation. A videothermographic image is build up of thousands of pixels. Calculation of the mean of the measured values of these pixels results in a loss of important information by regression to the mean. Therefore we proposed a new calculation method which quantifies the difference in what we call an asymmetry factor.[6] Compared to the use of the tympano thermometer for diagnosis of CRPS, there is a clear increase in sensitivity and specificity. Further research is needed to evaluate the validity of this method. It would be interesting, to see whether a temperature stress test with videothermograpy, as performed by Wasner et al. with a tympanothermometer, [7] can further improve the sensitivity and specificity.

In the clinical picture of CRPS rubor, calor, dolor and functio laesa are an indication that at least in part an inflammatory process is playing a role in the pathophysiology of CRPS.

Paul Sudeck, a German surgeon, was the first to hypothyse on the pivoting role of an inflammatory process.[8] Jan Goris, a Dutch trauma surgeon, supported this notion by reporting many studies focussing on a prolonged inflammation.[9] Veldman and colleagues described the signs and symptoms of 829 patients with a relatively short-lasting CRPS. This group described the clinical picture of regional inflammation, which increases after muscle exercise.[1] Heerschap et al. investigated the lower leg skeletal muscles of 11 patients with CRPS at rest with ^{31}P nuclear resonance spectroscopy. An impairment of the high-energy phosphate metabolism was found. It was suggested that this may be caused by cellular hypoxia or diminished oxygen utilisation. This could be the result of a reduced oxygen extraction in CRPS extremities, a phenomenon which is classically detectable in areas of inflammation.[10] A scintigraphic study of van Oyen et al. demonstrated that there is

a vascular leakage of macromolecules in the acute phase of CRPS 1, which also suggests an inflammatory process.[11]
Birklein et al. showed that neuropeptides are increased in plasma of patients with CRPS.[12]
Leis et al. showed that administration of neuropeptides in CRPS extremities results in an exacerbation of the disease.[13]
In contrast, in several other studies no indication of an inflammatory immune response was found.
Ribbers et al. could not find any differences between lymphocytes and activated T cells in blood from patients with CRPS 1 and healthy controls.[14]
Van de Beek et al. analysed blood plasma levels of the cytokines interleukin-1β, interleukin-6, interleukin-8, interleukin-10 and TNFα and found no differences between patients with CRPS and healthy controls.[15]

If an inflammatory immuno-respons plays a pivoting role, the substances, (e.g. neuropeptides, cytokines and eicosanoids) which attribute to the process should be detected in increased amounts in the involved extremity. Secondly, there has to be a worsening of the signs and symptoms of CRPS after administration of these substances to patients with CRPS. Finally, the therapeutic activity of specific antagonists or synthesis inhibitors for these substances has to be proven.[16]

In other inflammatory processes, e.g. rheumatoid arthritis, rhinitis and psoriasis, the substances which play a role in inflammation are locally detectable only. Therefore we focussed on a method whereby we could sample material from the involved area. Especially in dermato-immunologic research, the induction of artificial suction blisters is a well known and reliable method to harvest samples of interstitial fluid.[17]
In a group of 9 patients with a relatively short duration of CRPS we sampled venous blood and fluid from artificial suction blisters in the involved and uninvolved extremity in order to measure the cytokines IL-6, IL-1β and TNFα, the neuropeptides NPY and CGRP, and prostaglandin E_2. In plasma no differences in these mediators of inflammation were observed. In the blister fluid of the involved extremity, however, we found a significantly higher level of IL-6 and TNFα.[18] This was the first time that the involvement of mediators in CRPS 1 has been demonstrated directly. Later we confirmed this observation in two additional studies in larger groups of patients.[19,20]
Cytokines are produced by many different types of cells such as T-lymphocytes, monocytes, macrophages and skin resident cells (like mast cells). Mast cell activity can be monitored relatively easy with tryptase measurement.[21] In 20 CRPS patients we induced artificial blisters and detected significantly higher levels of tryptase in the blister fluid of the involved extremity. This is direct evidence for involvement of mast cells in CRPS 1. A limitation of this study is that we did not include a control group with neuropathic pain only. Consequently,

doubt remains as to whether the higher tryptase levels are uniquely characteristic for CRPS 1, or just for a neuropathic injury. Further investigations in patients with neuropathic pain only have to be conducted before definite conclusions can be drawn. In this study there was a significant correlation between IL-6 and TNFα levels found in blister fluid of the involved extremity, but no significant correlation between tryptase and IL-6 and tryptase and TNFα. This confirms our hypothesis that also other cells than mast cells must be involved. More studies are needed to detect the involvement of other cells. A significant correlation between the Visual Analogue Scale and tryptase levels in the involved extremity was found. 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 anti-histaminic and mast cell stabilizing drugs.[19]

If TNFα plays an important role in CRPS, anti-TNF could have a positive effect on the inflammatory aspects of CRPS 1. We have started an open label study which includes 8 patients. The findings in two patients are very promising.[22] Patient 1, who has had the disease for 5 years, has now been treated during 3 time periods. As expected and comparable with anti-TNF treatment in other diseases (e.g. rheumatoid arthritis and Crohn's disease) there is a need to repeat the treatment. Anti-TNF has a long half-life time, but in chronic diseases, treatment has to be repeated about 4 times a year. Little is known about the long-term treatment with anti-TNF. The second patient, who had a relatively short duration of CRPS, did not need repeated treatments and recovered almost completely. The question remains whether this result can be attributed to the anti-TNF treatment or whether it is just a fortunate natural course. Completion of the open label study followed by a double-blind randomised controlled trial is necessary to draw more definite conclusions.

We also need to know how the cytokines behave during the course of the disease. Do cytokines always play a role in long-standing CRPS 1, or do they only play a role in a subgroup, as described by Bruehl et al, which shows the full blown picture of CRPS 1.[23] Further research is necessary to gain more insight. Without doubt not only proinflammatory substances but also anti-inflammatory substances (like IL-10) are involved. Due to the lack of a sufficient amount of blister fluid, the blister fluid samples have a volume of about 300 ul or less, we were not able to answer these questions in the performed studies. Moreover, it takes many hours to produce an artificial blister and although it is not harmfull it does leave small scars. It would be unethical to induce more blisters in one patient, therefore new patients are required to address this question.

Remarkable is the fact that Birklein et al. found higher levels of neuropeptides in plasma, but could not find a difference between the involved and the uninvolved extremity. They suggested an impaired metabolism of neuropeptides as a reason for the higher levels.[12]

We doubt this explanation. The question arises whether the venous blood circulation compartment which they were looking at is able to show differences in plasma neuropeptide levels between the involved and uninvolved extremity. It is possible that differences are mixed before detection. In blister fluid, however, we also found no significant differences in neuropeptide levels between the involved and uninvolved extremity. After treatment with capsaicin we showed an improvement in the clinical picture, but we could not demonstrate any significant changes in the local levels of CGRP in blister fluid.[20] Thus the question arises how important neuropeptides are in the pathophysiology of CRPS. We think this indicates that neuropeptides are only secondarily involved in CRPS 1. Supplementary to this idea is the observation of Birklein et al. that the levels of neuropeptides are higher in patients with CRPS 2 in comparison to the levels in patients with CRPS 1.[12] Further investigation is necessary to elucidate the role of neuropeptides in CRPS. Interesting for future research is the role of NK-1 receptor antagonists in CRPS. Animal studies have shown that in the chronic constriction injury model an NK-1 receptor antagonist is effective.[24] There are, however, two problems: first, the fact that this model is probably more representative for CRPS 2 and how comparable a relatively short lasting model can be for a chronic disease. Secondly, there is a difference in activity of NK-1 receptor antagonists between species.[25] Until now the effects of NK-1 receptor antagonists in humans are rather disappointing. Nevertheless it would be interesting to study the effect of an available NK-1 receptor antagonist in patients with CRPS.

Another question whch remains is why do some people with the same trauma or same kind of surgery develop CRPS and others not? Is there a genetic predisposition for susceptibility for CRPS 1. Earlier studies reported differences in the HLA system between CRPS patients and healthy controls.[25,26,27] This is an indication of the involvement of changes in the immune system. Recently, Vaneker et al. reported the involvement of the TNF2 allele in CRPS 1.[29] Humans with this allele synthesize more TNFα in inflammatory situations. This phenomenon could be an explanation for the higher levels of TNFα we detected in CRPS 1 patients.
Another interesting finding was made by van der Vusse et al.[30] They reported an increase in antibody levels against the Parvo B19 virus. Perhaps this results in an acquired immune alteration. This could change the susceptibility and could also explain why some patients are more vulnerable to CRPS than others.

This thesis does not focus on the other important aspect of CRPS, namely sensitisation. Sensitisation is the process in which temporary or definite changes in the nervous system occur resulting in stronger or weaker transport of impulses through pain pathways or changes in, for example, the function of the sympathetic nervous system. Sensitisation is often a result of a combination of chronic nervous system stimulation, release of peptides

and an inflammatory process. It is responsible for especially the chronic signs and symptoms of the disease, such as allodynia and dystonia, and in part responsible for the sympathetic dysfunction. Of course much research is also needed on this aspect of the disease. CRPS is a model *in vivo* as to how our nervous system can act in chronic pain states.

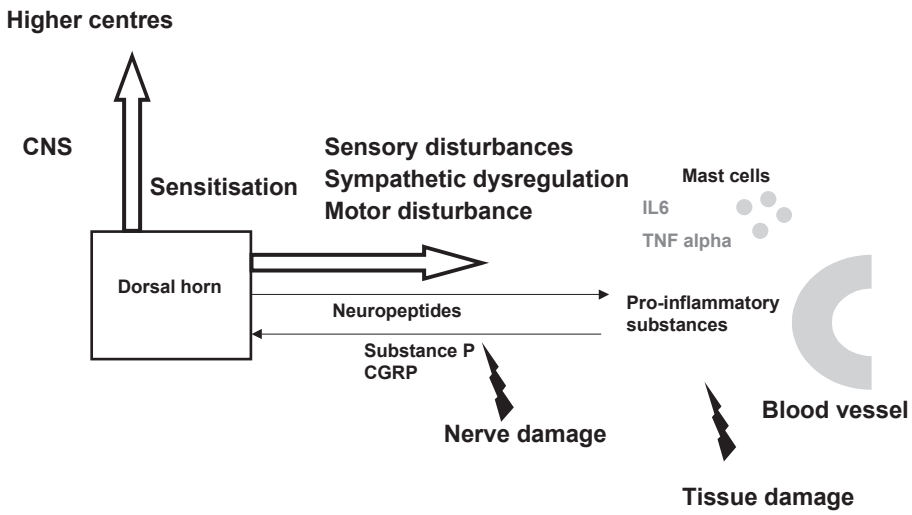
Nowadays, the two schools of thought regarding the pathophysiology on CRPS are communicating with each other more and more. Almost everyone is convinced that a dysregulation of the sympathetic system and an inflammatory process are both part of CRPS. Consequently, solutions should be sought in combinations of therapies focussed on causal mechanisms.

For researchers, CRPS 1 is a very challenging disease. For patients, physicians and other health care workers, however, it can be a very frustrating disease. Due to developments in research, slowly but surely we are understanding more about CRPS 1. However, we still have a long way to go.

Figure 1

Hypothesis pathophysiology CRPS 1 and CRPS 2

Higher levels of IL-6, TNFα and tryptase (Mast cells) in the involved extremity



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