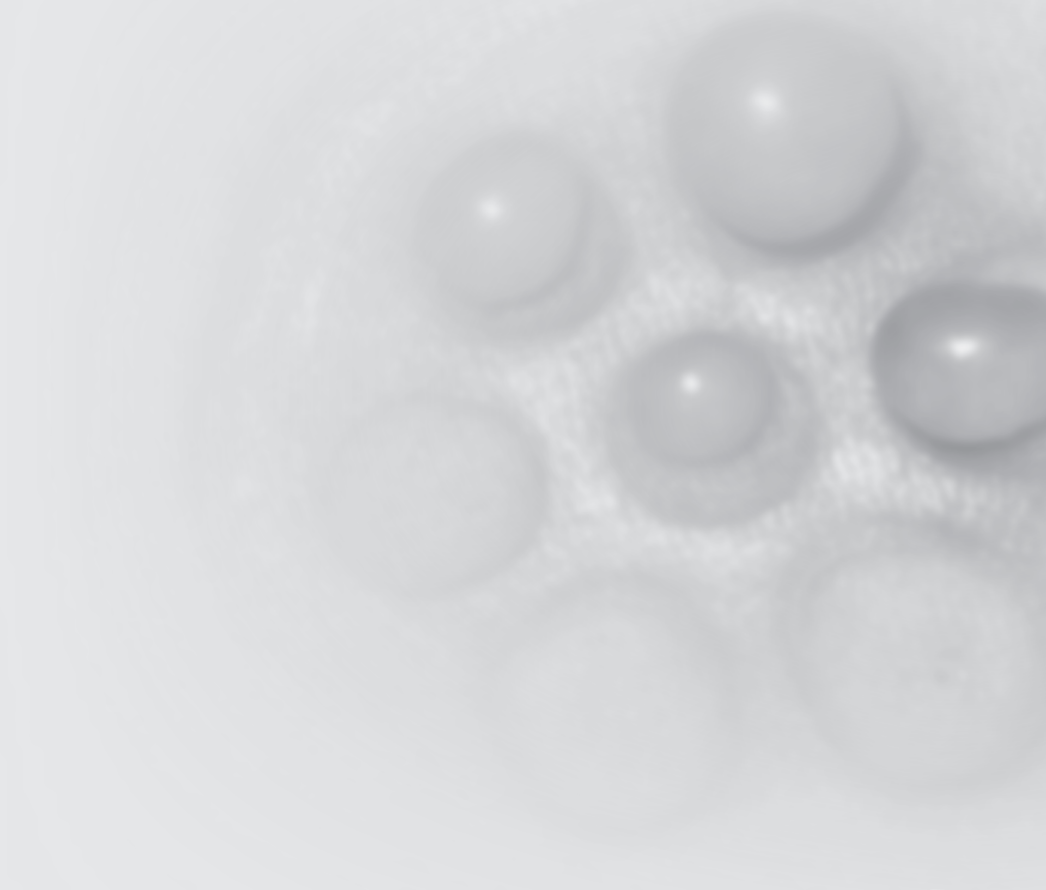
Introduction



Complex regional pain syndrome type 1 (CRPS 1) is generally induced by surgery or trauma. Spontaneous development is described but the question remains whether there was an unrecognised trauma in those patients.

CRPS 1 is a disease which is characterized by continuing pain, and sensory, 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 combination of a sterile inflammatory process and disuse. Characteristic for CRPS is that this normal reaction does not stop; the normal sterile inflammatory process seems to continue out of control. This clinical picture is often combined with disturbances of the central nervous system, such as sympathetic dysregulation.

The actual incidence of CRPS remains unclear. An incidence of 1-2% is reported after various fractures, 2-5% after peripheral nerve injury, and 7-35% in prospective studies of Colles fracture. In 10-26% of the cases no precipitating factor is found.[1] There is a preference for women in a ratio of 2:1. In the Netherlands there are about 8000 new cases each year and it is estimated that about 20000 patients in the Netherlands have a chronic form of CRPS.

Also the pathofysiology of CRPS remains unclear. However, the last decade has brought more insight into the pathofysiology of CRPS. In 1864 Mitchell reported on gunshot wounds and other injuries of the peripheral nerve which resulted in a CRPS like disease. He was probably the first person to describe the disease in detail.[2] Paul Sudeck, a German surgeon, was the first to propose an excessive inflammatory response.[3]
In 2000 the International Association of the Study of Pain (IASP) organized a meeting in Cardiff (UK) focussing CRPS. Afferent, efferent and central mechanisms were discussed.[4]

The lack of comprehension about the pathophysiology has caused much confusion. The disease has been given many different names, depending on the precipitating factor, the country concerned, or the treating specialist. Sudeck's atrophy, reflex sympathetic dystrophy, and shoulder-hand syndrome are the names most frequently used.[1]

Another problem is the lack of an objective method to confirm the diagnosis. The literature describes several criteria to assist in the diagnosis; for example the Veldman criteria, the IASP criteria and the Bruehl criteria.[1,5,6] However, there is no uniform use of these criteria.

One of the first attempts to overcome these problems was a meeting held in Orlando organised by the IASP in 1993. The members of this meeting decided to use the name Complex Regional Pain Syndrome. Criteria for the diagnosis complex regional pain syndrome are: pain and/or allodynia/hyperalgesia, not limited to a single nerve and not

related to the original trauma or surgery. There are or have been signs of oedema, skin blood flow disturbances and/or abnormal sudomotor activity. The diagnosis is excluded in the presence of other reasons for the pain or dysfunction. A distinction between type 1 without nerve damage, and type 2 with nerve damage was made. The new criteria were described in an article by Stanton-Hicks and published in 1995.[5]

In 1997 the group of Bruehl started a discussion about the sensitivity and specificity of the IASP criteria.[6] They concluded that the criteria had a high sensitivity (0.98) which makes them valuable for clinical use, but they had a lack of specificity (0.36) which limits the use of the IASP criteria for research purposes. In clinical practice there is a change of overdiagnosis when the IASP criteria for the diagnosis of CRPS are used. Bruehl proposed extra criteria in which the patient tells his/her own story about the complaints and the observer confirms a number of these complaints by physical examination. The extra criteria result in a gain in specificity (0.94) but a loss in sensitivity (0.70). This makes the Bruehl criteria more useful for research, since it is very important to get an as uniform as possible study group which is not polluted by other (unknown) diseases.

We started our research at the end of 2000 by examining the literature and published a review covering the existing theories on the pathophysiology of CRPS.[7] Based on associations with a neuroimmune activation, that review discussed possible neuroimmune changes.

Secondly a hypothesis was developed in which we made a distinction between CRPS 1 and CRPS 2.

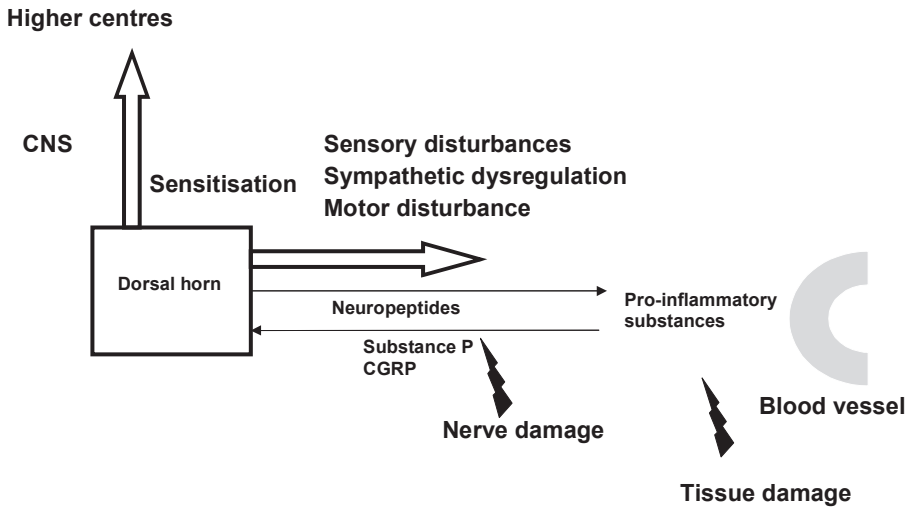
In our hypothesis CRPS 1 starts with tissue damage. This leads to an inflammatory response in which lymphocytes, monocytes, macrophages and mast cells play a role. Cytokines and possibly other inflammatory products may also be involved. This inflammatory process is responsible for the clinical picture with the classical signs of rubor, calor, dolor and functio laesa. The inflammatory process triggers the nerve ends to release neuropeptides. In the proximal part of the nerves, in the dorsal horn and higher centres in the central nervous system, the neuropeptides create sensitisation. This results in a clinical picture of sensory abnormalities like allodynia and dystonia. The sympathetic disturbance seems to be an intricate composition of central and peripheral mechanisms (Figure 1).

Hypothetically, CRPS 2 starts with damage to nerve(s), leading to a leakage of neuropeptides. These neuropeptides migrate through the nerve to the distal and proximal ends. Distally they create an inflammatory response in which lymphocytes, monocytes, macrophages and mast cells play a role, as well as cytokines and other inflammatory products. These mechanisms are responsible for the clinical picture of an inflammatory process with the classical signs of rubor, calor, dolor and functio laesa.

In the proximal part of the nerve the neuropeptides create sensitisation in the dorsal horn and higher centres in the central nervous system. This results in a clinical picture as described above (Figure 1).

This thesis is based on clinical studies which focussed on different aspects of the hypothesis.

Figure 1 Hypothesis pathophysiology CRPS 1 and CRPS 2



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