

# **CHAPTER 9**

**General discussion**

The research presented in this thesis has been focused on the assessment (diagnosis and measurement of complaints and symptoms) and involvement of NMDA receptors in CRPS 1. Furthermore, we investigated whether NMDA receptor antagonists, in particular magnesium, can be considered as new treatment candidates to target aspects of central sensitization in CRPS 1. In this final chapter, the main findings of the previous chapters and suggestions for future research are discussed.

### **Assessment of CRPS 1**

Proper diagnosis is important to identify and distinguish a disorder from other conditions. Diagnosing CRPS 1, however, remains a difficult process as there is no objective measurement instrument or laboratory assessment available for diagnosing this illness. Consequently, researchers and clinicians must rely on clinical criteria for the diagnosis of CRPS 1. Despite the development of officially recognized criteria for formal diagnosis of CRPS 1 by the IASP in 1994 (1), different diagnostic sets have been simultaneously used to diagnose CRPS 1. In chapter 2 we compared the most applied diagnostic criteria at the moment, the IASP, Bruehl et al. and Veldman et al., in 372 CRPS 1 patients and demonstrated that the use of different diagnostic sets could lead to dissimilar numbers of patients receiving the diagnosis of CRPS 1. Furthermore, differences in clinical profiles between patients meeting the different criteria sets were found. Significant differences between the criteria sets were found with regard to the number of patients reporting continuing disproportionate pain, a larger area affected than the initial trauma, increase of symptoms due to exercise, edema, temperature asymmetry, hyperesthesia, allodynia and hyperalgesia. Significant differences between the diagnostic sets were also found for physicians' observation of allodynia and hyperalgesia. The latter indicates that the different diagnostic sets could represent different types or subgroups (e.g., more inflammatory or sensory subtype) of CRPS 1 patients. Consequently, results of individual studies using different diagnostic criteria for inclusion of CRPS 1 cannot be compared without restriction, and cannot be generalized to other CRPS 1 samples. A first step to improve the comparability of different studies, is that studies clearly describe the used diagnostic criteria. Van de Beek et al. (2), however, showed in their assessment of the diagnostic criteria in CRPS studies that many studies fail to adequately report the diagnostic criteria used. Van de Beek et al. (2) also found that studies in which the diagnostic criteria were described were not homogenous in the use of the diagnostic criteria. Therefore, a second step to improve comparability of studies is the need for international consensus about the use of one set of diagnostic

criteria. The research presented in this thesis were performed for Trauma Related Neuronal Dysfunction (TREND) consortium, a knowledge consortium that integrates research on CRPS 1. Within TREND was agreed to use the (for that moment) internationally accepted IASP criteria for the diagnosis of CRPS 1. There has been some debate about the use of the IASP criteria. Validation studies demonstrated high sensitivity but inadequate specificity of the IASP criteria (3;4), therefore, the use of the IASP criteria could lead to overdiagnosis and the unnecessary treatment of patients. The criteria of Bruehl et al. (4) were subsequently developed to improve the IASP criteria. Specificity was shown to be increased, however sensitivity was lowered compared to the IASP criteria, therefore the Bruehl et al. criteria should only be used for research purposes. The recently formed Budapest criteria showed excellent sensitivity comparable with the IASP criteria and considerably increased specificity (5). These findings suggest that the Budapest criteria may be adopted as uniform standard diagnostic set for CRPS 1. When we started our research the Budapest criteria were not developed yet, therefore the IASP criteria were used. Furthermore, to ensure a broad view on the heterogeneous CRPS population, standardized diagnostic lists were developed for TREND in which patient information about the observed and reported features of CRPS 1 patients were recorded. Based on this collected comprehensive information, classification of CRPS 1 could also be made according to the IASP criteria but also according to Bruehl et al., Veldman et al. and later by the newly formed Budapest criteria. Consequently, post hoc analyses of the data can be performed according to the Budapest criteria.

The heterogeneity of the CRPS 1 population is even more highlighted by means of our Trend Symptom Inventory as described in chapter 3. Based on the hypothesis of Marinus and van Hilten (6), which stated that CRPS 1 patients exhibit other local and systemic complaints outside the scope of the diagnostic criteria (e.g., bowel, bladder and sicca complaints), reliable and valid measurement instruments that assess a broad range of both local and systemic complaints associated with CRPS 1 are needed. In chapter 3 we presented data regarding the development, reliability and practical use of the Trend Symptom Inventory (TSI) in CRPS 1 and fibromyalgia patients. The TSI was developed to make uniform systematic assessment and evaluation of clinical manifestations and demographic characteristics of patients with CRPS 1 and potentially related syndromes possible. Complaints associated with fibromyalgia could possibly also occur in CRPS 1, therefore, comparison of the disorders could contribute to better understanding of CRPS 1 complaints. We demonstrated that the TSI was reliable and valid when measured in CRPS 1 and fibromyalgia patients. Furthermore, complaints outside the scope of the diagnostic

criteria (e.g., diarrhea, incontinence, dry eyes) were found for CRPS 1.

Some medications may induce visceral complaints, however, the medications used by our CRPS 1 and fibromyalgia patients were not included in our analyses. Consequently we do not know whether the reported visceral complaints were attributed to the used medications. The intestinal permeability was found to be increased in CRPS patients (7). The altered intestinal permeability may interact with additional factors (abnormalities in the mucosal immune system) (7), resulting in abdominal symptoms such as diarrhea. Therefore, we think that for a part of our patients the reported abdominal complaints could be related to CRPS 1. Visceral complaints were not reported by all CRPS 1 patients and indicate the presence of subgroups within the CRPS 1 population. Therefore, the occurrence of subtypes of CRPS 1 patients needs to be further assessed.

Bruehl et al. (8) used a statistical pattern recognition methodology (K-means cluster analysis) in 113 CRPS patients meeting the IASP criteria to derive homogenous subgroups of CRPS patients based on similarities in signs and symptoms. They were able to identify 3 statistically CRPS patient subgroups: 1; a relatively limited form with vasomotor signs prevailing 2; a relatively limited form with neuropathic/sensory signs prevailing 3; a florid form with high occurrences of all signs/symptoms. However, the cluster analysis performed by Bruehl et al. was only based on a limited set of criteria. Based on the findings of the TSI, pattern recognition techniques should be performed to investigate whether the subgroups as identified by Bruehl et al. will be maintained or whether other subgroups will emerge.

Many parallels and some dissimilarities were found in complaints between CRPS 1 and fibromyalgia patients. To further evaluate differences and similarities between CRPS 1 and other trauma related disorders, the reliability of the TSI should also be evaluated in other potentially related disorders such as repetitive strain injury. Whether these result hold true for larger samples, than in the present study, needs further investigations. Subgroup analyses based on clinical features should be accompanied with physical biomarkers or parameters (e.g., specific proteins in blood, urine or artificially blister fluid obtained from CRPS 1 patients) which may provide indication for underlying pathophysiological mechanisms.

The evaluation of the Semmes Weinstein Monofilaments was described in chapter 4. We demonstrated that the SWM can be used reliably to measure sensory abnormalities of the plantar side of the feet when assessed by one researcher. However, limited interrater-reliability of the SWM was found, therefore caution is warranted when interpreting studies in which different researchers performed the SWM measurements. To obtain good SWM measurements it is important that

measurements are performed by one researcher. Secondly, longitudinal variations in sensory thresholds have to be taken in account. Factors influencing sensory thresholds (e.g., differences in concentration levels of subjects and researchers and different outside temperatures) concern both feet. These factors could be filtered out by examining differences in sensory scores between the right and left foot. Furthermore, the standard error of measurement ( $SEM = \sigma\sqrt{1-ICC}$ ) could be used to calculate the minimal detectable change in sensory scores, whereby sensory changes between two measurements exceeding the interval:  $1.96 * \sqrt{2} * SEM$  are considered as real changes. Using these calculations, improvements in sensory thresholds within subjects can be described better. Finally, other test locations besides the plantar side of the feet should be evaluated for the SWM.

### **Involvement of the NMDA receptor and treatment with NMDA receptor antagonists**

An increase in spinal NMDA receptors, resulting in central sensitization, has been related to the sensory disturbances exhibited in CRPS 1 patients. In chapter 5, peripheral NMDA receptor expression was evaluated to assess the contribution of peripheral sensitization in CRPS 1 patients. We found that the expression of NMDA1 and pNMDA1 receptors in sweat glands of CRPS 1 hand tissue was increased compared to non-CRPS 1 hand tissue. The increase in peripheral NMDA receptors may contribute to peripheral sensitization and therefore the sensory signs and symptoms expressed by CRPS 1 patients. These findings may provide support for effects found for locally administered therapies, and provide a basis for development of topical NMDA antagonists. Indeed, it has recently been shown that treatment with topical ketamine resulted in the reduction of sensory complaints (allodynia) in CRPS 1 (9;10). To evaluate whether the observed increased expression of NMDA receptors are local or systemic, tissue samples of both the affected and non-affected extremity should be compared. A few studies have performed skin punch biopsies in CRPS 1 patients to investigate skin pathologies in CRPS 1 (11;12). No adverse events were reported, therefore with the use of skin punch biopsies, peripheral NMDA receptors in CRPS 1 could be further evaluated.

Since NMDA receptor activity appear to be involved in CRPS 1, we set out to evaluate whether NMDA receptor antagonists may be effective in CRPS 1. To that matter, a systematic literature review was conducted (chapter 6) in which the effects of different NMDA receptor antagonists on different neuropathic pain disorders (including CRPS 1) were evaluated. Although many large individual effect trials were

found, we were only able to summarize the effect of a small number of trials due to heterogeneity of studies in the used interventions, route of administration and type of pain condition evaluated. A large number of trials examined ketamine for the treatment of neuropathic pain, including three studies in which the effects of ketamine were evaluated in CRPS (9;13;14). Two of these studies used an intravenous route of administration for ketamine and could be pooled. No significant pooled effect was found for ketamine in CRPS, possibly due to large statistical heterogeneity between the two studies. The majority of studies focused on ketamine for the treatment of neuropathic pain, however, the therapeutic use of ketamine is limited by the occurrence of psychomimetic adverse effects (15). Therefore, in addition to ketamine, other NMDA receptor antagonists should be evaluated in CRPS and other neuropathic pain conditions. In summary, based on the results of this analysis no definite conclusions about the efficacy of individual NMDA receptor antagonists on neuropathic pain can be drawn, and the overall value of medicinal interventions targeting the NMDA system remain to be determined.

In chapter 7 the results of a pilot study were presented, evaluating the efficacy and tolerability of the uncompetitive NMDA receptor antagonist magnesium in a small sample of CRPS 1 patients. Ten acute CRPS 1 patients diagnosed according to the IASP criteria were included, in a blinded randomized study, of which eight received 70 mg/kg magnesium infusions in four hours for five days. Several measurements on pain, impairment, disability and quality of life level were performed to study the effects of the intravenous magnesium treatment in a comprehensive fashion. SWM measurements were included to evaluate sensitivity of the skin, performed by one researcher as recommended in chapter 4. Furthermore, to filter out longitudinal variations in SWM sensory thresholds, differences in sensory scores between the affected and unaffected extremity were examined. The tolerability of intravenous magnesium in CRPS 1 patients was evaluated by performing continuous ECG monitoring during the infusions and registration of side effects. Pain recorded by patients was significantly reduced at all follow up points compared to baseline. Impairment and quality of life also improved significantly, however, this improvement was only found after 12 weeks. The latter suggest a more direct effect of the intervention on pain and to a lesser extent on impairment and quality of life, possibly modulated indirectly due to pain decrease. Furthermore, mild side effects were reported (e.g., infusion site pain, flushing, dizziness) and the infusions were well tolerated. Although these results are promising, only acute CRPS 1 patients with a CRPS 1 duration shorter than 6 months were included in this pilot study. Consequently, the positive results found in this study could be related to the natural

course of disease. Besides conducting placebo controlled randomized trial to assess the true effect of magnesium infusion for CRPS 1, it is important to also examine the effects of magnesium in chronic CRPS 1 patients. At present, a randomized controlled trial evaluating the effects of intravenous magnesium in 66 acute and chronic CRPS 1 patients compared to placebo is ongoing.

As described previously, the CRPS 1 population is heterogeneous. Differences in prevailing disease mechanisms between individual patients could well lead to differences in response to treatment. The latter may be the case with regard to the findings in our pilot study: although in general positive effects were found, individual responses to the intervention differed, whereby both responders and non responders were found. In chapter 8 we investigated whether response to intravenous magnesium treatment might be related to differences between CRPS 1 patients in magnesium status. Magnesium status of 25 CRPS 1 patients, who had participated in a RCT in which the effect of intravenous magnesium were evaluated, was measured by means of the magnesium retention test. Our sample of CRPS 1 patients were imbalanced in magnesium body uptake compared to population based samples of healthy subjects, whereby half of the CRPS 1 patients in this sample could be considered magnesium deficient. Furthermore, for the group of patients considered magnesium deficient, pain was significantly reduced during the infusions and three weeks after the infusions, whereas for the patients with normal magnesium status pain was only significantly decreased during the infusions. Although these findings result from a small and highly selected sample of patients and should be considered purely observational, these findings warrant further study as this might point to a relationship between magnesium status and treatment response for a subgroup of CRPS 1 patients. To evaluate whether subjects with lowered magnesium availability may be more susceptible to develop and maintain CRPS 1, prospective studies should be performed wherein the course of CRPS 1 complaints after trauma are followed in magnesium deficient and non magnesium deficient patients.

### **Future perspectives**

Besides suggestions for further research described in the previous section, we also provide recommendations for additional investigations outside the scope of this thesis. CRPS 1 is a very complex and heterogeneous disorder, comprising subtypes of patients exhibiting predominantly sensory, inflammatory, vasomotor or motor complaints. Consequently, besides targeting central sensitization in

CRPS 1, therapy should also be focused on the treatment of other clinical profiles in CRPS 1 patients. To improve treatment options aimed at specific subtypes of CRPS 1 patients, the different clinical profiles and the associated underlying pathophysiological mechanisms should be investigated further. In recent years, a better understanding has been obtained about the incidence (16), genetics (17) and the role of psychological factors (18) in CRPS 1. Research with regard to long term disease outcome of CRPS 1, however, is still limited. The recently developed CRPS severity score (CSS) (19), a continuous score used to index the severity of CRPS, may be used in future studies to follow the degree and course of CRPS 1 complaints, and identify ill defined concepts of remission, relapse and healing of this disease. The impact of CRPS 1 on patients' daily life and work has been pointed out by a few studies (20-22). Therefore, attention should also be given to the societal and personal burden of CRPS 1, preferably measured in a prospective manner with repeated measurements during the course of the complaint.

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