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Dystonia in complex regional pain syndrome : clinical, pathophysiological and therapeutic aspects

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Summary, conclusions and future plans

This thesis describes the results of studies on movement disorders in patients with Complex Regional Pain Syndrome (CRPS). First we explored the clinical characteristics and disease course of CRPS and movement disorders (MDs), in particular dystonia, in patients with multiple affected extremities. Next we evaluated the pathophysiological mechanism underlying dystonia of CRPS by neurophysiologic investigations and functional brain imaging. Finally we assessed the safety and efficacy of intrathecal baclofen treatment for dystonia of CRPS.

Chapter 1 is the introduction to this thesis. It shortly describes the naming of the syndrome and its clinical characteristics which are defined by pain and various combinations of sensory disturbances, autonomic features, and sudomotor and trophic changes. Furthermore, patients with CRPS may suffer from movement disorders, of which dystonia is the most prevalent. Dystonia of CRPS can affect multiple extremities, is often resistant to treatment and seems to have a poor prognosis. Reliable information on the nature, chronology and clinical determinants of dystonia in CRPS patients is lacking but could provide better insight in the underlying pathophysiological mechanism. Currently, CRPS is regarded as a multifactorial disease involving complex interactions between the immune system and (peripheral and central) nervous system. Several current disease concepts underpinning CRPS are discussed. As for CRPS-related dystonia, few studies report on possible underlying mechanisms and some neurophysiological studies have found evidence of impaired inhibition in the spinal cord and motor cortex, which is supported by the result of a small study that showed a beneficial effect of intrathecal baclofen administration.

In **Chapter 2** we studied patterns of spread in CRPS and the patient characteristics associated with this phenomenon in patients with CRPS in multiple extremities. One hundred-eighty-five CRPS patients were retrospectively evaluated. Eighty-nine patients exhibited CRPS in multiple extremities. The pattern of spread was studied in the 72 patients in whom CRPS started in one extremity and extended to the next, showing contralateral spread in 49%, ipsilateral spread in 30% and diagonal spread in 14%. A trauma preceded the onset in the second extremity in 37, 44 and 91%, respectively. Patterns of spread differed significantly between patients with spontaneous spread and patients who showed spread after a separate trauma. Compared to patients with CRPS in one extremity, patients with CRPS in multiple extremities were on average 7 years younger and more often had movement disorders. The hazard of spread of CRPS increased with the number of extremities affected. It can be concluded that, in patients with CRPS in multiple extremities, spread of symptoms generally follows a contralateral or ipsilateral pattern that commonly occurs spontaneously, whereas diagonal spread is

rare and generally preceded by trauma. Spread is associated with a younger age at onset and the presence of movement disorders. We argue that processes in the spinal cord as well as supraspinal changes are responsible for spontaneous spread in CRPS.

Chapter 3 describes findings of a retrospective study in which we evaluated the clinical and temporal characteristics of MDs in patients with CRPS. Cox's proportional hazards model was used to evaluate factors influencing the onset of MDs. One-hundred-and-eighty-five patients suffered CRPS in one or more extremities. MDs occurred in 121 patients, with dystonia (91%) being the most prevalent. Sixty-two percent of these patients displayed dystonia in multiple extremities. Patients with dystonia were on average eleven years younger and more often had CRPS in multiple extremities. The interval between the onset of CRPS and dystonia in the first affected extremity varied from less than one week in 26% of the patients to more than one year in 27%. The hazard of developing dystonia in subsequent extremities increased with the number of extremities affected by dystonia. From these results we conclude that dystonia in CRPS shows highly variable onset latency and is associated with younger age at onset and increased risk of developing dystonia in other extremities. The delayed onset and progression of dystonia in CRPS may indicate the involvement of a different underlying mechanism, possibly associated with maladaptive neuroplasticity.

The objective of the study in **Chapter 4** was to evaluate psychological features in severely affected patients with CRPS related dystonia. Personality traits, psychopathology, dissociative experiences, the number of traumatic experiences, and quality of life were studied in 46 patients. Findings were compared to two historical psychiatric control groups (54 patients with conversion disorder (CD) and 50 patients with affective disorders (AD)) and to normative population data. The CRPS patients showed elevated scores on the measures for somatoform dissociation, traumatic experiences, general psychopathology and lower scores on quality of life compared to general population data, but had significantly lower total scores on the measures for personality traits, recent life events and general psychopathology compared to the CD and AD patients. The general level of psychopathology was elevated in the CRPS patients in an extent similar to chronic pain patients but this level was significantly lower than both psychiatric control groups. Rates of early traumatic experiences were comparable to the CD and AD patients, and the level of somatoform dissociation was comparable to the CD patients but was elevated in comparison to the AD patients. Early traumatic experiences were reported in 87% of the CRPS patients and were found to be moderately related to somatoform dissociative experiences, indicating that early traumatic experiences might be a predisposing, though not necessary factor for

the development of CRPS related dystonia. Although the psychological profile of the patients with CRPS related dystonia shows some elevations, there does not seem to be a unique disturbed psychological profile on a group level.

In **Chapter 5** we evaluated the occurrence and characteristics of hyperacusis in patients with CRPS related dystonia. More severely affected patients may experience hyperacusis, which may reflect central involvement. The presence of hyperacusis, speech reception thresholds (SRT), pure-tone thresholds (PTT) and uncomfortable loudness (UCL) were evaluated in 40 patients with CRPS-related dystonia. PTT and SRT were normal for all patients. Fifteen patients (38%) reported hyperacusis and this was associated with allodynia/hyperalgesia and with the presence of more affected extremities. UCLs of patients with hyperacusis were significantly lower than UCLs of patients without hyperacusis. These results show that hyperacusis is common among severely affected patients with CRPS related dystonia and may reflect the spreading of central sensitization to auditory circuitry.

Chapter 6 involves a study on somatosensory processing in dystonia in CRPS patients. We studied somatosensory evoked potentials (SSEPs) in 33 patients with CRPS and dystonia and 19 healthy controls. N9, N14, N20 and N35 amplitudes were recorded after paired stimulation of median and ulnar nerves ('spatial') and after stimulation of both nerves with single stimuli and with interstimulus intervals of 20 and 40 ms ('temporal' stimulation). Finally, both methods were integrated resulting in spatiotemporal stimulation. Statistical testing was performed using linear mixed model analysis of variance. SSEP amplitudes were significantly suppressed after spatial and temporal stimulation. No difference was observed between patients and healthy controls. Spatiotemporal stimulation did not show an additional suppressive effect in any group. In conclusion our and previous findings may suggest that proprioceptive sensory processing in CRPS is unimpaired and that inhibition at a cortical level is restricted to the motor cortex. In view of the concept of dystonia as a circuit disorder, the finding of motor cortex disinhibition raises an interesting chicken and egg issue, which at this stage cannot be solved. However, in view of the peripheral initiation of the disorder, we favour a spinal origin of dystonia in CRPS with secondary changes at supraspinal sites of the circuit.

Chapter 7 describes the findings of functional magnetic resonance imaging (fMRI) study. The aim of this study was to determine cerebral network function in CRPS patients with dystonic postures. Cerebral processing related to both execution and imagining of hand movements in patients and controls was assessed with fMRI. Eight

CRPS patients with dystonic postures of the right upper extremity and 17 age-matched healthy controls were studied. Compared with controls, imaginary movement of the affected hand in patients showed reduced activation ipsilaterally in the premotor and adjacent prefrontal cortex, and in a cluster comprising frontal operculum, the anterior part of the insular cortex and the superior temporal gyrus. Contralaterally, reduced activation was seen in the inferior parietal and adjacent primary sensory cortex. There were no differences between patients and controls when they executed movements, nor when they imagined moving their unaffected hand. In conclusion, patients with CRPS and dystonia displayed areas with decreased activation during imagining tasks that are involved in planning of movement, multimodal sensorimotor integration, autonomic function and pain. Pain may profoundly alter the cerebral organization of movement by functional interaction between these regions.

Chapter 8 describes a study on the efficacy and safety of intrathecal baclofen (ITB) in CRPS related dystonia. A single-blind, placebo-run-in, dose-escalation study was carried out in 42 CRPS-patients to evaluate whether dystonia responds to ITB. Thirty-six of the 38 patients who met the responder criteria received a pump for continuous ITB administration and were followed for 12 months to assess long-term efficacy and safety (open-label study). Primary outcome measures were global dystonia severity (both studies) and dystonia-related functional limitations (open-label study). The dose-escalation study showed a dose-effect of baclofen on dystonia severity in 31 patients in doses up to 450 µg/day. One patient did not respond to treatment in the dose-escalation study and three patients dropped out. Thirty-six patients entered the open-label study. Intention-to-treat analysis revealed a substantial improvement in patient and assessor-rated dystonia scores, pain, disability and quality of life (QoL) at 12 months. The response in the dose-escalation study did not predict the response to ITB in the open-label study. Eighty-nine adverse events occurred in 26 patients and were related to baclofen (n=19), pump/catheter system defects (n=52), or could not be specified (n=18). The pump was explanted in 6 patients during the follow-up phase. Dystonia, pain, disability and QoL all improved on ITB and the treatment remained efficacious over a period of one year. However, ITB is associated with a high complication rate in this patient group and methods to improve patient selection and catheter-pump integrity are warranted.

Concluding remarks

In the last two decades knowledge on movement disorders of CRPS is slowly increasing. The awareness that CRPS patients may suffer MDs has resulted in a proposal of an expert consensus panel to add this clinical category to the new criteria set¹. A better delineation of clinical, pathophysiological and therapeutic aspects of MDs in CRPS may potentially contribute to better management strategies for this disabling component of the syndrome and these three topics will be discussed in the following sections.

Clinical characteristics

The first aim of this study was to improve our knowledge on clinical characteristics and the disease course of multiple CRPS and MDs of CRPS. We studied a group of patients with a severe phenotype with disabling features. We realize that this subgroup of patients does not represent the “average” CRPS patient, but the large number of these patients seen at our department over the last years, underscores that this development is not rare. Patients with a more severe CRPS phenotype with dystonia and/or multiple affected extremities were significantly younger at the onset of CRPS symptoms compared to patients with a milder phenotype. This finding may suggest a genetic susceptibility, as has been shown for other diseases². CRPS may occur in a familial form and these patients develop the disease at younger age and have a more severe phenotype than sporadic cases³, which also suggests an increased susceptibility to develop the disease^{4,5}. Another hint for a genetic component came from a study that found an increased for siblings of CRPS patients with an age at onset younger than 50⁶. Finally, a genetic predisposition is apparent from genetic associations that were found with different human leukocyte antigen (HLA) factors⁷⁻¹⁰.

Fifty-six percent of the patients in our study developed dystonia more than one month after onset of CRPS, 27% beyond a year and three patients developed dystonia even more than 5 years following CRPS. The clinical characteristics of patients with onset of dystonia before or after one year were similar, likely suggesting a common mechanism of dystonia in these patients. The delayed onset of dystonia encountered in many CRPS patients may suggest that mechanisms underlying the acute phase of CRPS and dystonia differ. In line with another study, we found that if dystonia developed in a later stage than the non-motor symptoms of CRPS, the occurrence of a new trauma before the onset of dystonia was rare¹¹. Whether dystonia that is related to peripheral trauma is caused by organic or psychogenic factors is an ongoing controversy. However, in accordance with other studies in CRPS patients¹²⁻¹⁴ and in chronic CRPS patients with dystonia,¹⁵ our study does not support the presence of a unique disturbed psychological profile. Compared with the general Dutch population, the general level of psychopathology

was elevated in the CRPS patients in an extent similar to chronic pain patients,¹⁶ but this level was significantly lower than in psychiatric control groups of patients with affective disorders and conversion disorders. Early traumatic experiences are more prevalent in patients with CRPS-I-related dystonia as compared to students and the general population and may be a possible, although not necessary predisposing factor for CRPS-I-related dystonia. As expected, the study group reported poorer general health and quality of life as compared to the general population.

It should be stressed that, in analogy to the care of other chronic pain patients, effective management of CRPS requires that psychosocial and behavioral aspects are addressed as part of an integrated multidisciplinary treatment approach¹⁷. Comorbid psychiatric disorders or major ongoing life stressors should be identified and treated to improve successful treatment.

Pathophysiology

The results of our studies on clinical and neurophysiologic aspects of patients with multiple CRPS and MDs in CRPS provided data that suggest disturbances at multiple levels of the CNS.

Convincing evidence points to the initiating role of the immune system and peripheral nervous system in CRPS, both contributing to aberrant inflammation^{18,19}. However, the occurrence of spread of symptoms and the occurrence of MDs cannot exclusively be explained by peripheral disturbances. The results of the research presented in this thesis provide arguments for changes at both spinal and supraspinal level.

Arguments for alterations on spinal level:

- Spontaneous spread of CRPS symptoms occurs most frequently according to a contralateral pattern which can be explained by spinal processing of incoming sensory information^{20,21} and may occur through commissural spinal interneurons and likely also involves spinal glia cells and pro-inflammatory cytokines^{22,23}.
- In many CRPS patients, we encountered a delayed onset of dystonia. Once dystonia is present, the hazard of dystonia in subsequent extremities increased with the number of extremities already affected by dystonia. Likewise, the presence of CRPS in multiple extremities increases the hazard of spread of symptoms to subsequent extremities without the requirement of a new trauma. Both the delayed onset and an accelerated disease course are characteristics of maladaptive neuronal plasticity and have been documented for clinical manifestations of other diseases²⁴⁻²⁷. In this respect, maladaptive plasticity at a spinal level may manifest as disinhibition of spinally nociceptive withdrawal reflexes (NWRs, see hereafter).

However, the findings may also be explained by supraspinal alterations.

- Our placebo-controlled dose-escalation study showed that ITB reduces dystonia in CRPS and lends further support to the role of spinal GABAergic mechanisms; C and A δ sensory fibres play a role in neurogenic inflammation and are connected with spinal circuits that mediate nociceptive withdrawal reflexes (NWRs). One of the primary mediators of neurogenic inflammation, Substance P (SP), may also activate SP receptors on lamina I neurons in the dorsal horn of the spinal cord, and induce long-term potentiation (LTP), a form of neuronal plasticity. Animal models of neurogenic inflammation have shown that SP enhances NWRs.²⁸ Flexor muscles play a prominent role in NWRs and, interestingly, there also is a conspicuous involvement of flexor postures in CRPS-related dystonia.^{29,30} Neurophysiologic studies have shown a decreased presynaptic GABA-ergic inhibition in CRPS patients with dystonia.³¹ Both SP sensitized NWRs in animal models and dystonia in CRPS patients respond to the intrathecal administration of GABA_B agonist baclofen, which enhances spinal GABA-ergic inhibition.³² In view of the sequence of events in CRPS, these findings may suggest disinhibition of spinal mediated NWRs as a primary causal mechanism of dystonia in CRPS, reflecting maladaptive plasticity.

Arguments for alterations on supraspinal level:

- Hyperacusis is common among severely affected patients with CRPS related dystonia and may reflect the spreading of central sensitization to auditory circuitry in the thalamus.
- Functional brain imaging with fMRI of patients with CRPS and dystonia displayed cortical areas with decreased activation during imagining tasks that are involved in planning of movement, multimodal sensorimotor integration, autonomic function and pain.
- Some researchers provided arguments for disinhibition at the level of the motor cortex in CRPS patients^{33,34}. The findings of the SSEP study indicate that cortical sensory processing of proprioceptive input is normal in patients with CRPS and dystonia. If cortical inhibition plays a role it is probably restricted to the motor cortex.

Taken together, the results of our studies on movement disorders and spread in CRPS provide evidence for changes in the CNS at both the spinal and supraspinal level. Maladaptive neural plasticity likely is an important mechanism underpinning the MDs that may occur in CRPS. Neural plasticity is a property of the CNS that is characterized by remodelling of neuronal contacts and circuits in the CNS in an attempt to adapt to

the altered condition³⁵. Neural plasticity can be beneficial and is necessary for normal development of the CNS and learning. On the other hand abnormal plasticity may cause disorders like neuropathic pain, tinnitus, and levodopa induced dyskinesias^{25,27,35}. In neuropathic pain, maladaptive plasticity may manifest as ectopic generation of action potentials, facilitation and disinhibition of synaptic transmission, loss of synaptic connectivity, formation of new synaptic circuits, and altered neuroimmune interactions. Genetic polymorphisms, gender, and age all influence the risk of developing chronic pain³⁶. For both chronic pain and dystonia in CRPS, it can be postulated that peripheral neurogenic inflammation may induce maladaptive neural plasticity in the spinal cord (e.g. central sensitisation) which subsequently may spread to more rostral (that is supraspinal) structures. Referred sensations, changes in the size and organization of the somatosensory map, and changes in motor cortex representation are strongly suggestive of cortical involvement in CRPS³⁷. A recent fMRI study on pediatric CRPS patients reports on Blood-Oxygen-Level-Dependent (BOLD) responses during fulminating CRPS and again following their clinical recovery³⁸. The authors found significant changes in CNS circuitry that persisted despite resolution of pain. Hence, which level of the CNS is the primary site where pathological alterations originate, remains unsolved.

The presence of disturbances at multiple levels of the central nervous system in dystonia of CRPS parallels recent hypotheses on the underlying mechanisms suggested for other types of dystonia³⁹⁻⁴². For focal dystonia several researchers have provided evidence for abnormal cortical plasticity in susceptible individuals⁴³.

Therapy

Our study on intrathecal baclofen administration in patients with CRPS and dystonia showed marked improvement of dystonia and pain scores after one year. Improvements in the impairment and disability levels paralleled those of quality-of-life. The worsening of dystonia after catheter or pump dysfunction highlights that ITB acts on a symptomatic level. Complications of ITB can be severe and include infections, drain dysfunctions and psychiatric symptoms that can result in explantation of the pump-catheter system. Therefore, the therapy should be limited to patients who are resistant to conventional therapies and should be conducted by physicians with considerable experience in implantation and care of intrathecal devices. However, patient selection remains difficult as we were unable to identify variables that predicted a poor response or high chance on complications.

Future plans

Prospective longitudinal epidemiological studies are needed to describe the natural course of CRPS and identify risk factors that can predict which patients will display spread to other extremities or develop MDs. Genetic studies will possibly further unravel which individuals are predisposed to CRPS and MDs in particular. One of the other challenges for future research is to solve the chicken and egg issue on the sequence of pathophysiological mechanisms at different levels of the nervous system; the order and dynamics of the alterations at the peripheral, spinal and supraspinal level requires further elucidation. In this respect, longitudinal neurophysiologic and CSF biomarker studies may contribute to the development of tailored diagnostic and treatment strategies, which may prevent the spread of symptoms to other extremities and the occurrence of MDs. In the meantime, intrathecal baclofen administration is a promising treatment for MDs in CRPS, although it should be applied very selectively in view of the requirement of surgery and high complication rate. Additionally, the efficacy of ITB may be improved, for example by studying the effect of different infusion rates, the refinement of catheters and pump devices and a better identification of patients that will likely show a good response to therapy. Because of the nature of CRPS, however, non-invasive treatment strategies aiming to modulate aberrant neural plasticity are preferred. Both for focal forms of dystonia and CRPS, sensorimotor training programmes that target maladaptive cortical changes, for example mirror therapy and transcranial magnetic stimulation, have reported beneficial effects^{44,45}.

Peripheral trauma induced movement disorders (PTMDs) may present another focus of future research. Of all reported cases of PTMDs in literature fifty percent have CRPS (own data, submitted). PTMDs have been a controversial topic in the field of movement disorders for a long time. A relation between peripheral trauma and MDs has gained acceptance over time and a set diagnostic criteria were proposed by Cardoso and Jankovic in 1995. However, so far the apparent lack of consensus on the pathogenesis of PTMDs has remained unresolved. Some authors suggest that PTMDs are the result of maladaptive plasticity of the central nervous system^{46,47} but this is not supported by everyone⁴⁸. Studies on the role of peripheral trauma in CRPS induced MDs may contribute to a better understanding of involved mechanisms of disease.

Collectively, future studies on the mechanisms underpinning neural plasticity and studies on modulation of aberrant neural plasticity may lead to better management strategies of dystonia in CRPS and thus contribute to a better quality of life and prognosis of these patients.

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