Complex regional pain syndrome related movement disorders: studies on pathophysiology and therapy.
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Summary and conclusions
This thesis described studies on the pathophysiology and therapy of complex regional pain syndrome (CRPS) related movement disorders.

Chapter 1. General introduction and aims
A short overview about the current knowledge on CRPS-related movement disorders is given in chapter 1. The syndrome is frequently associated with sensory and autonomic disturbances. It is often preceded by a limb trauma. The current theory is that the syndrome is caused by a combination of trauma related peripheral and central neuroimmunological changes. A key neurophysiological finding is a lack of central inhibition. CRPS is a severe and disabling condition, and treatment options are limited.

Chapter 2. How psychogenic is dystonia? Views from past to present
In the last few centuries there has been a constant sway between organic and psychogenic explanations for dystonia. In chapter 2 we investigate this history, assuming the perspective of a spectrum from organic to psychogenic, between which ideas were moving. We have focussed on (i) primary generalised dystonia; (ii) cervical dystonia; (iii) writer’s cramp; and (iv) fixed dystonia related to CRPS. We have studied medical texts published since the 19th century and their references. Jean-Martin Charcot advocated the concept of hysteria: disorders in which, besides predisposition, environmental factors were involved in its pathogenesis. Sigmund Freud introduced psychoanalysis as an explanatory therapy for psychic disorders. Previous theories, together with the lack of an organic substrate for dystonia, made a strong case for psychogenic explanations. Consequently, many dystonia patients were told that they suffered from psychological conflicts and were treated for them. However, after the description of new hereditary cases in the 1950s, the limited efficacy of psychotherapy in torsion dystonia, the effects of surgical treatments and the lesion studies in the 1960s, more physicians became convinced of the organic nature. The culminating point was the discovery of the DYT1 gene in 1997. In the meantime, experts had already convinced the neurological community that cervical dystonia and writer’s cramp were focal dystonias, i.e. minor forms of generalised dystonia, and therefore organic disorders. In contrast, the pathophysiology of fixed dystonia related to CRPS remained controversial. Knowledge of this history, which played on the border between neurology and psychiatry, is instructive and reflects the difficulty in discriminating between them. Today, new insights from functional imaging and neurophysiological studies again challenge the interpretation of these disorders, while the border between psychogenic and organic has become more
blurred. Abnormalities of sensorimotor integration and cortical excitability that are currently supposed to be the underlying cause of dystonia bring us back to Sherringtonian physiology. We suggest that this may lead to a common explanation of the four afflictions of which we have traced the history.

Chapter 3. Thermal hypesthesia in patients with complex regional pain syndrome related dystonia
The quantitative thermal test showed cold and warmth hypesthesia without increased heat pain sensitivity in the affected limbs of CRPS patients with tonic dystonia (n=44) in comparison with healthy controls with a similar age and gender distribution (n=35). The degrees of cold and warmth hypesthesia were strongly correlated. We conclude that dysfunction in small nerve fiber (i.e., C and Aδ) processing is present in patients with CRPS-related dystonia.

Chapter 4. Fixed dystonia in complex regional pain syndrome: a descriptive and computational modelling approach
Background: CRPS may occur after trauma, usually to one limb, and is characterized by pain and disturbed blood flow, temperature regulation and motor control. Approximately 25% of cases develop fixed dystonia. Involvement of dysfunctional GABA (gamma aminobutyric acid)-ergic interneurons has been suggested, however the mechanisms that underpin fixed dystonia are still unknown. We hypothesised that dystonia could be the result of aberrant proprioceptive reflex strengths of position, velocity or force feedback.
Methods: We systematically characterized the pattern of dystonia in 85 CRPS patients with dystonia according to the posture held at each joint of the affected limb. We compared the patterns with a neuromuscular computer model simulating aberrations of proprioceptive reflexes. The computer model consists of an antagonistic muscle pair with explicit contributions of the musculotendinous system and reflex pathways originating from muscle spindles and Golgi tendon organs, with time delays reflective of neural latencies. Three scenarios were simulated with the model: (i) increased reflex sensitivity (increased sensitivity of the agonistic and antagonistic reflex loops); (ii) imbalanced reflex sensitivity (increased sensitivity of the agonistic reflex loop); and (iii) imbalanced reflex offset (an offset to the reflex output of the agonistic proprioceptors). Results: For the arm, fixed postures were present in 123 arms of 77 patients. The dominant pattern involved flexion of the fingers (116/123), the wrists (41/123) and elbows (38/123). For the leg, fixed postures were present in 114 legs of 77 patients. The dominant pattern was plantar
flexion of the toes (55/114), plantar flexion and inversion of the ankle (73/114) and flexion of the knee (55/114). Only the computer simulations of imbalanced reflex sensitivity to muscle force from Golgi tendon organs caused patterns that closely resembled the observed patient characteristics. In parallel experiments using robot manipulators we have shown that patients with dystonia were less able to adapt their force feedback strength. Conclusions: Findings derived from a neuromuscular model suggest that aberrant force feedback regulation from Golgi tendon organs involving an inhibitory interneuron may underpin the typical fixed flexion postures in CRPS patients with dystonia.

Chapter 5. Analysis of cerebrospinal fluid inflammatory mediators in chronic complex regional pain syndrome related dystonia

There is compelling evidence of central nervous system involvement in neuropathic pain and movement disorders in patients with CRPS. Previously, elevated cerebrospinal fluid (CSF) levels of interleukin-1β and interleukin-6 were found in CRPS patients with and without movement disorders. The aim of the study in chapter 5 was to replicate these findings and to search for additional CSF biomarkers in chronic CRPS patients with dystonia. CSF samples of 20 patients and 29 subjects that underwent spinal anaesthesia for surgical interventions were used. We measured interleukin-1β, interleukin-6, interferon-γ inducible protein-10, RANTES (regulated upon activation, normal T-cell expressed and secreted), complement C3, mannose-binding lectin, complement C1q, soluble intercellular adhesion molecule-1, endothelin-1, nitric oxide, human lactoferrin and hypocretin-1 levels in these samples. No differences in the CSF levels of these effector mediators between patients and controls were found. Our CSF findings do not support a role of a variety of inflammatory mediators or hypocretin-1 in chronic CRPS patients with dystonia.

Chapter 6. Clinical and neurophysiological characterisation of myoclonus in complex regional pain syndrome

The origin of myoclonus in patients with CRPS is unknown. Eight patients with CRPS-related myoclonus were clinically evaluated and studied with intermuscular and corticomuscular coherence analysis. Jerks were present at rest, aggravated during action and were frequently associated with tremulousness or dystonia. Electromyography demonstrated a burst duration ranging from 25-240 ms with burst frequencies varying
from <1 jerk/s during rest-20 Hz during action. Coherence studies showed increased intermuscular coherence in four patients in the 6-12 Hz band, as reported in patients with enhanced physiological tremor. In two patients side-to-side coherence was observed, pointing to a central oscillatory drive. Significant coherence entrainment was detected in 5 patients. We conclude that the characteristics of myoclonus in CRPS are different from other forms of myoclonus.

Chapter 7. Intrathecal baclofen for dystonia of complex regional pain syndrome
Dystonia in CRPS responds poorly to treatment. Intrathecal baclofen (ITB) may improve this type of dystonia, but information on its efficacy and safety is limited. 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 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.

Chapter 8. Intrathecal glycine for pain and dystonia in complex regional pain syndrome
Since glycinergic neurotransmission plays an important inhibitory role in the processing of sensory and motor information, intrathecal glycine (ITG) administration may be a potential therapy for both pain and movement disorders in patients with CRPS. Aims of the study described in chapter 8, which is the first report on ITG in humans, were to evaluate its safety and efficacy. ITG treatment during 4 weeks was studied in CRPS patients with
dystonia in the period before they received ITB treatment. Twenty patients were assessed and after exclusion of one patient, the remaining 19 patients were randomised in a double-blind placebo-controlled crossover study. Safety was assessed by clinical evaluation, blood examinations and electrocardiograms. Efficacy measures involved pain (numeric rating scale, McGill pain questionnaire), movement disorders (Burke-Fahn-Marsden dystonia rating scale, unified myoclonus rating scale, tremor research group rating scale), activity (Radboud skills questionnaire, walking ability questionnaire), and a clinical global impression (CGI) and patient’s global impression score (PGI). Treatment-emergent adverse events were generally mild to moderate and not different from placebo treatment. During ITG treatment growth hormone levels were slightly increased. Although there was a trend to worsening on the CGI and PGI during ITG treatment, there were no significant differences between ITG and placebo treatment in any of the outcomes. ITG given over 4 weeks was ineffective for pain or dystonia in CRPS. Although no serious adverse events occurred, further studies are required to rule out potential neurotoxicity of ITG.

Chapter 9. Efficacy and safety of a single intrathecal methylprednisolone bolus in chronic complex regional pain syndrome

Activated immune cells in the spinal cord may play an important role in the development and maintenance of neuropathic pain, such as occurs in response to peripheral inflammation or tissue injury. Immune activation may therefore serve as a therapeutic target for immune modulating drugs like corticosteroids. This double-blind randomised placebo-controlled parallel-group trial aimed to investigate the efficacy and safety of a single intrathecal administration of 60 mg methylprednisolone (ITM) in chronic patients with CRPS. The primary outcome measure was change in pain (pain intensity numeric rating scale; range 0-10) after 6 weeks. With 21 subjects per group the study had a 90% power to detect a clinically relevant difference (≥2 points). After 21 patients (10 on ITM) were included, the trial was stopped prematurely after the interim analysis had shown that ITM had no effect on pain (difference in mean pain intensity numeric rating scale at 6 weeks 0.3, 95% CI -0.7 to 1.3) or any other outcome measure. We did not find any difference in treatment-emergent adverse events between the ITM and placebo group. We conclude that a single bolus administration of ITM is not efficacious in chronic CRPS patients, which may indicate that spinal immune activation does not play an important role in this phase of the syndrome.
Chapter 10. Post-dural puncture headache in complex regional pain syndrome: a retrospective observational study

Objective: To describe the unusual course of post-dural puncture headache after pump implantation for ITB administration in patients with CRPS-related dystonia. Design: Case series based on data collected from 1996-2005. Setting: Movement disorders clinic, university hospital. Patients: A total of 54 patients with CRPS-related dystonia who were treated with ITB. Results: A high incidence (76%) and prolonged course (median 18 days, range 2 days-36 months) of post-dural puncture headache was found. Radionuclide studies performed in 2 patients with long-lasting symptoms (12-16 months) did not reveal CSF leakage. In patients without signs of CSF leakage (n=38), epidural blood patches administered in 24 patients were effective in 54%, while ketamine infusions administered in 6 patients were effective in 67%. Conclusions: Our observations may suggest that other mechanisms besides intracranial hypotension play a role in the initiation and maintenance of post-dural puncture headache in CRPS and stimulate new directions of research on this topic.

Conclusions

Prior to the start of the studies included in this thesis, the mechanisms underlying the development of movement disorders in CRPS were poorly understood. Moreover, randomised controlled trials were lacking.

Studies on pathophysiology

Although thermal hypesthesia was earlier shown in CRPS patients without dystonia, its presence in those with dystonia was unknown. We found thermal hypesthesia in CRPS patients with dystonia. Apparently, dysfunction in small nerve fiber (i.e. C and Aδ) processing is present in these patients. Since similar findings have been documented in CRPS without dystonia, it remains unclear whether this sensory abnormality is involved in the causal pathway to dystonia.

By systematically evaluating the extremities of 85 patients with CRPS-related dystonia, we identified a dominant pattern of fixed dystonia. Fixed flexion of the fingers was observed in 95% of affected arms and a multisegmental pattern of finger flexion, wrist and/or elbow flexion and shoulder internal rotation/adduction, was observed in 66% of affected arms. A similar pattern was observed in affected legs: plantar flexion/inversion of the ankle was observed in 88% of affected legs, and a multi-segmental pattern of ankle plantar
flexion/inversion, toe and knee flexion, internal rotation of the hip, was observed in 66% of affected legs. Our modelling study showed that aberrant force feedback from Golgi tendon organs may be related to these postures.

Our CSF findings did not support a role of a variety of inflammatory mediators in chronic CRPS patients with dystonia. A search for CSF biomarkers involved in molecular pathways that play a role in neuroplasticity may be more fruitful.

We evaluated eight patients with CRPS-related myoclonus. Both clinically and electrophysiologically, myoclonus was diverse. The significant coherence entrainment that was detected in five patients may point to central nervous system disinhibition. However, coherence entrainment has also been suggested as clue for psychogenic movement disorders. Further studies towards the value of entrainment are warranted.

Studies on intrathecal therapy
A single intrathecal administration of 60 mg methylprednisolone was not efficacious in chronic CRPS. Furthermore, continuous ITG in doses up to 32 mg/24 h was not efficacious in CRPS-related dystonia. In contrast, ITB reduced severity of CRPS-related dystonia, improved quality of life and remained efficacious over a period of one year (median dose of 615 µg/day). Unfortunately, ITB was associated with a high complication rate and therefore methods to improve patient selection and catheter-pump integrity are warranted to enhance its therapeutic potential. Collectively, the findings from these studies lend support to the role of GABA-ergic mechanisms in this cause of dystonia.

Future studies
Hitherto, studies on the pathogenesis of dystonia in CRPS have focused on the role of single biochemical CSF components and distinct neurophysiological characteristics. Instead, modern 'omics' approaches are able to measure the overall metabolic or proteomic content of biological samples. The output of these experiments may be interpreted as a signature, or 'endophenotype', of the disease. Extrapolation on other 'omics' data potentially uncovers mechanisms of disease. Currently, such studies using different body fluids from CRPS patients with dystonia are ongoing.

The central nervous system controls the behaviour of the musculoskeletal system through many feedback loops. Their dynamic behaviour can be quite unpredictable from the individual components. The results from our modelling study suggest that it may be
worthwhile to study dystonia with closed loop system identification techniques. Currently, such studies are employed in the evaluation of CRPS-related dystonia.

Through intrathecal delivery of drugs, we have focused on modulation of predominantly spinal mechanisms in CRPS-related dystonia. Results of these studies confirmed the findings of neurophysiological studies which showed that disinhibition plays an important role. Enhancing central GABA, but not glycine, mediated inhibition seemed to decrease the severity of dystonia. However, in view of the large number of complications related to the delivery technique required to administer baclofen, new GABA-ergic drugs with a better blood-brain barrier passage, are desirable.

Pain and dystonia presumably are disorders of neural circuits as opposed to disorders of a single nervous system structure. Hence, neuromodulation techniques that target supraspinal regions of interest, like repetitive transcranial stimulation or epidural cortical stimulation, may also provide new therapeutic possibilities for CRPS-related movement disorders.