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

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Aan alles, aan alles, komt een begin
(Herman van Veen)

Voor Milcar en Barbara

Contents

1

Introduction

Complex Regional Pain Syndrome

The first description of what nowadays is known as Complex Regional Pain Syndrome (CRPS) originates from 1864 when Weir Mitchell, an American neurologist, reported a syndrome in casualties of the American Civil War that was accompanied by partial nerve lesions. He named the associated pain "causalgia"[1,2]. In 1900, Sudeck described a similar syndrome which he named "acute reflektorische knochenatrophie", characterized by bone changes that occurred after an injury without obvious nerve damage[3]. In the following decades, several comparable syndromes were described using terms including algodystrophy, post-traumatic dystrophy and Sudeck atrophy. The supposed pathophysiological mechanism for these syndromes was an exaggerated reflex to an injury caused by dysregulation of the sympathetic nervous system. Therefore, around 1940, the term Reflex Sympathetic Dystrophy (RSD) was introduced to specify all syndromes characterized by the combination of autonomic and trophic changes[4]. As it became increasingly clear that the clinical features of the syndrome were insufficiently explained by dysfunction of the autonomic nervous system, a consensus meeting was held in 1994 which resulted in a new set of diagnostic criteria and the introduction of the terms "complex regional pain syndrome (CRPS)" type I and type II. These terms were meant to substitute for RSD (type I) and causalgia (type II) (table 1)[5,6]. The difference between the two types of CRPS is based on the absence (CRPS-type I) or presence (CRPS-type II) of an overt nerve lesion.

Table 1. Diagnostic criteria for CRPS type 1 of the International Association for the Study of Pain (IASP) [5].

1) the presence of an initiating noxious event or a cause of immobilization
2) continuing pain, allodynia or hyperalgesia with which the pain is disproportionate to any inciting event
3) evidence at some time of edema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain
4) absence of a condition that would otherwise account for the degree of pain and dysfunction Criteria 2-4 are necessary for a diagnosis of CRPS.

CRPS generally affects distal extremities and is preceded by a trauma in a majority of patients[7,8]. A spontaneous onset has been described in 3–11% of cases[8-13]. CRPS occurs more frequently in women and may occur at all ages although the highest incidence is found between 50 and 70 years. The reported incidence ranges from 5.5 to 26.2 per 100,000 person-years[7,14].

CRPS is characterized by pain with various combinations of sensory disturbances

such as allodynia and hyperalgesia, and autonomic features like changes in skin blood flow, transpiration and abnormal hair and nail growth[5,8]. Occasionally, symptoms may spread to other extremities and body parts[13,15]. Furthermore, patients with CRPS may suffer from movement disorders (MDs), like tremor, myoclonia and dystonia[16-19].

Pathophysiology of CRPS

CRPS is regarded a multifactorial disorder where both environmental and genetic factors contribute to the development of the disease. The role of environmental factors is evident as in ninety percent of the patients symptoms are preceded by a traumatic injury[8]. However, as some patients develop CRPS spontaneously, other factors must contribute[20]. The role of genetic factors is supported by the fact that CRPS may occur in a familial form and that these patients develop the disease at a younger age and have a more severe phenotype than sporadic cases[21] which suggests an increased susceptibility to develop the disease[22,23]. A genetic predisposition for CRPS is also apparent from genetic associations that were found with different human leukocyte antigen (HLA) factors[24-27]. However, so far the role of HLA factors in CRPS has remained illusive.

The pathophysiology of CRPS has been increasingly studied over the past decades. Hitherto several different pathophysiological mechanisms underpinning CRPS or parts of its clinical spectrum have been forwarded.

Autonomic dysfunction

For long, impairment of the sympathetic nervous system was held responsible for maintaining pain ("sympathetically maintained pain", SMP) and autonomic dysfunctions in CRPS. In SMP, spontaneous and evoked pain is elicited by sympathetic hyperactivity through sympathetic afferent coupling, in which adrenergic receptors are expressed on primary sensory afferent fibres[28,29]. However, there are several reasons that argue against the sympathetic nervous system as the key player in the generation and maintenance of CRPS: for example, sweating and trophic disturbances are not the most predominant features of CRPS[8,30] and can also be induced by the neuropeptides calcitonin-gene-related peptide (CGRP) and substance P (SP)[31]. Additionally, vasoconstriction does not always reflect sympathetic activity[32] and alternative mechanisms like endothelial dysfunction may account for the vasomotor impairments[33,34]. Finally, although sympatholytic strategies have been recommended for decades, in many patients they are not beneficial[35]. Compelling evidence therefore suggests that SMP and sympathetic dysregulation may play a role in CRPS, but the

pathophysiology of the syndrome cannot be reduced to a sole dysfunction of the sympathetic nervous system.

Vasomotor dysfunction

Decreased skin temperature and skin discoloration both suggest that mechanisms underpinning vasomotor dysfunction are involved in CRPS. Skin capillary hemoglobin oxygenation (HbO2) is lower[36] and skin lactate is increased, reflecting enhanced anaerobic glycolysis[16,36,37] in muscles of limbs affected by CRPS. Muscle tissue obtained from amputated limbs of CRPS patients showed evidence of oxidative stress and ischemic conditions resulting from microangiopathy in muscle tissue[38]. Collectively, this information underscores that vasomotor dysfunction is an important component of CRPS. Both sympathetic dysfunction and endothelial dysfunction have emerged as mechanisms of disease that potentially may contribute to vasomotor dysfunction in CRPS[39].

Aberrant inflammation

Similarities between the classical symptoms of inflammation and the clinical features of CRPS have led several investigators to suggest that the disease is caused by an exaggerated inflammatory response. This view is supported by research in blister fluid of CRPS patients which showed high levels of pro-inflammatory cytokines[40,41]. Some researchers found evidence for an increased level of inflammatory mediators in cerebrospinal fluid[42], although others could not confirm this[43]. Additionally, an enhanced migration of injected radiolabelled autologous leukocytes or non-specific immunoglobulines towards the CRPS affected location has been described[44,45] and open label studies with immunomodulating drugs like infliximab[46,47] and thalidomide[48] report beneficial effects. Collectively, this led to the assumption that CRPS I is induced by an exaggerated inflammatory response to tissue injury, mediated by an excessive production of toxic oxygen radicals[49]. Support for the role of free radicals in CRPS I was found in randomized clinical trials in human CRPS with scavengers like dimethylsulfoxide, N-acetylcysteine and vitamin C in early treatment[50,51].

Finally, involvement of the immune system may be supported by reports on an increased prevalence of antecedent viral infections in CRPS patients and the presence of autoantibodies against a surface epitope of autonomic neurons[52].

Alterations in the somatic nervous system

Several studies have reported axonal degeneration in small distal nerve fibers of patients with CRPS[38,53,54], but there is debate among researchers whether this is a cause or a consequence of the syndrome. Increasing evidence hints towards a perturbed function

of both non-myelinated C and myelinated Aδ fibres of sensory nerves, resulting in the increased secretion of neuropeptides such as SP and CGRP, a process called neurogenic inflammation[55,56]. Animal studies in neuropathic pain syndromes have shown that these neuropeptides are also released spinally (by central nerve endings of primary afferents) which, in turn, may lead to central sensitization[57]. Central sensitization is induced in dorsal horn neurons and involves a reduction in pain threshold, amplification of pain responses and spread of pain sensitivity to adjacent, non-injured areas[58]. It is associated with neurochemical changes, functional alterations of excitatory and inhibitory connections, cell death of neurons and interneurons, and sprouting of new connections in the spinal cord[59].

In addition to spinal alterations, supraspinal sensorimotor neural networks are likely to contribute to the pathophysiology of CRPS. Which level of the CNS is the primary site where pathological alterations originate, remains unsolved. 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 CRPS[60]. For example, in CRPS patients watching the mirror-image of the unaffected limb elicits pain on the affected side[61] and referred sensations of a tactile or painful stimulus were experienced outside its expected somatic territory[62]. A fMRI study in CRPS focusing on mechanical hyperalgesia, reported alterations in nociceptive, cognitive and motor processing[63]. Schwenkreis et al.[64] studied patients with unilateral CRPS I involving the hand by means of transcranial magnetic stimulation using a paired-pulse paradigm. The authors found a significant bilateral reduction of intracortical inhibition in patients with CRPS compared with control subjects. Recently, regional grey matter atrophy and abnormal gray-white matter interactions, including decreased connectivity between the ventromedial cortex and basal ganglion have been observed[65].

Psychological factors

In the absence of a clear somatic cause, CRPS has often been considered as a psychogenic disorder[66]. Non-organic factors are often advanced as potential predisposing factors and some authors argue that the symptoms can be interpreted as a conversion reaction[67,68]or malingering[69]. However, much research on this topic is of poor methodologic quality and only a few prospective, well controlled studies have been performed. A recent population-based study by De Mos et al.[70] compared the medical history of patients who developed CRPS with age and sex matched patients who did not develop CRPS after a similar trauma and found that psychological factors were not associated with an increased probability to develop CRPS. Another prospective study comprising 596 patients with a single fracture found that there were no baseline differences in any of the psychological factors as measured by the SCL-90 between the 42 patients who

developed CRPS versus those who did not[71]. Three other prospective studies compared baseline data between patients who did and did not develop CRPS after surgery. None of these found a unique psychological profile in patients who developed CRPS[72-74].
There are no indications that childhood trauma plays a unique role in the onset of CRPS, as evidenced by a study from Ciccone [75] who found that child hood trauma and abuse were evenly distributed among patients with CRPS, local neuropathic pain and low back pain (LBP). Reports for the role of stressful life events are contradictory[76,77].
The majority of studies on psychological factors in CRPS involve cross-sectional studies, in which psychological and personality traits are compared between CRPS patients and patients with other pain syndromes. This approach does not permit conclusions regarding potential predisposing factors, since the present health status will inevitably reflect changes that occurred as a consequence of the condition. Three studies cross-sectionally compared patients with CRPS with patients with other pain conditions, using the Symptom Checklist (SCL-90) or its short version, the Brief Symptom Inventory. DeGood et al. found that, in comparison with patients with headache or low back pain (LBP), patients with CRPS had lower scores on 6 of the 10 scales despite experiencing the highest level of pain intensity; differences on the other scales were not significant[78]. No differences in psychological profile were found in a study comparing CRPS patients with patients waiting for hand surgery[76]. Bruehl et al. reported that CRPS patients exhibited some elevations on the somatisation and phobic anxiety subscales compared to patients with LBP or limb pain; differences on the other scales were not significant[79]. In contrast with Bruehl[79], van der Laan[80] found that CRPS patients with dystonia exhibited lower scores on the somatisation subscale than a control population of rehabilitation patients. Together the results of these prospective and cross-sectional studies do not support a unique psychological profile that characterizes patients with CRPS.

Movement disorders in CRPS

Motor abnormalities in war casualties with causalgia were first reported by Mitchell in the 19th century. This is illustrated by his description of case 28 from *Injuries of Nerves and their Consequences*: D.H., a girl of thirteen accidentally ran a small penknife blade into her right hand and developed burning pain, swelling, livid discoloration and a low temperature of the hand. A few months after the accident "the fingers became contracted, and the hand flexed, the palm continuing to suffer with burning pain. These conditions existed .....up to March 1869.....and the flexions became extreme"[2].
A more extensive description of the movement disorders (MDs) in CRPS followed in

the last two decades of the 20th century by Marsden and Schwartzman[18,81]. These MDs are not infrequent, as data from studies where selection bias towards MDs was unlikely indicate that 9-49% of the CRPS patients may develop MDs with dystonia being the most prevalent (14-25%)[8,18,82,83]. The increasing awareness that CRPS patients may suffer MDs has resulted in a proposal to add this clinical category to the new diagnostic criteria set[84].

Dystonia in CRPS is predominantly characterized by fixed flexion postures (figure 1), frequently has a delayed onset and may spread to other extremities[18,19]. Several small studies found that the interval between the onset of CRPS and that of MDs can be up to 3 years[81,85,86]. In Veldman's study, the prevalence of MDs increased with the duration of CRPS[8].

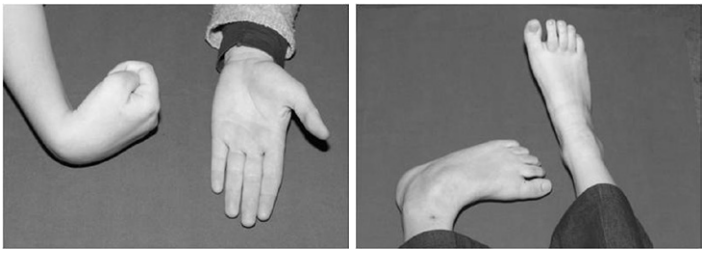

Figure 1. Flexion postures in dystonia of CRPS.

Dystonia is defined as abnormal involuntary muscle contractions that cause twisting or repetitive movements or sustained postures[87]. In primary dystonia, no other abnormality than dystonia is present and the cause is genetic or unknown. However, dystonia may also be brought on by a large and diverse group of disorders (secondary dystonia), such as an exogenous insult (exposure to certain drugs) or may be the result of heredodegenerative and metabolic disorders. One of the potential causes of secondary dystonia is trauma. Although there is general agreement that traumatic brain injury can cause dystonia, the question whether peripheral trauma can cause dystonia has since long been a subject of debate[88-90].

Traditionally, dystonia is associated with basal ganglia dysfunction, but recent developments have led to further maturing of the concept of dystonia. First, the influence of sensory tricks in reducing dystonia severity and evidence from neurophysiological studies highlighted the role of faulty sensory-motor processing in dystonia[91-93]. Second, recent studies have reported the occurrence of dystonia in cerebellar disease and thereby expanded the anatomical territory of dystonia to include the cerebellum[94-96]. Finally, two interventional studies on DYT1 dystonia and levodopa-responsive dystonia have shown that both disorders are associated with neurophysiological abnormalities

along the whole neuraxis that improved after deep brain stimulation or after levodopa challenge[97,98]. These findings have positioned dystonia as a manifestation of aberrant neural networks that are involved in sensory-motor processing required for the control and execution of voluntary movement[99]. In line with this new concept, several neurophysiological studies in CRPS-related dystonia have found evidence of impaired inhibition at the spinal cord and motor cortex[64,100,101].

The treatment of movement disorders of CRPS is a field still in its infancy. Randomized controlled studies of physical therapy, occupational therapy or pharmacotherapy are lacking. In Schwartzman and Kerrigan's report[18], some CRPS patients with dystonia benefited from oral baclofen and benzodiazepines. Splints and plaster casts have been used for the treatment of dystonic postures but are often ineffective or may even worsen the dystonia[85]. Although in some cases favorable responses have been reported following sympathetic blocks[102], no solid evidence is available to support this treatment mode for MDs in CRPS. Continuous intrathecal baclofen administration was evaluated in six CRPS patients with multifocal or generalized dystonia[103]. During prolonged therapy, three patients regained normal hand function, and two patients regained the ability to walk. In one woman the pain and violent jerks disappeared and the dystonic posturing of the arm decreased. In two women the spasms or restlessness of the legs decreased without any change in dystonia.

Prognosis of CRPS

Contradicting reports have been published regarding the outcome of CRPS. Sandroni et al performed a population-based study[7] and mentioned complete symptom resolution in 74% of the patients within one year after CRPS onset, on the basis of the medical chart review. In contrast, Veldman et al.[8] and Galer [104] et al. objectively assessed patients and found persistent disturbances in most of them after one or more years follow-up. In addition, Geertzen et al.[105] reported impairments and disability in 62% of patients 5.5 years after CRPS onset. In a population based retrospective comparative cohort study, de Mos et al[106] found that a majority of patients had persistent impairments at 2 or more years since the onset of CRPS. Sixty-four percent of the patients still fulfilled IASP criteria at an average of 5.8 years after the initial injury. The impact of the disease on the ability to work was high: 31% had become permanently incapable of work, whereas another 28% had to make working adjustments. Population based studies on the prognosis of CRPS patients with movement disorders are lacking but observational studies report a poor prognosis after several years of follow-up[107].

MDs occur frequently in patients with CRPS, have a poor prognosis and form a major challenge in the clinical management of patients with CRPS. 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.

Aim of this thesis

1. To study the clinical characteristics and disease course of patients with CRPS in multiple extremities and of CRPS patients with movement disorders, in particular dystonia.
2. To study the neurophysiologic and neuroradiological characteristics of dystonia in CRPS.
3. To evaluate the efficacy and safety of intrathecal baclofen treatment for dystonia of CRPS.

These three aims will be addressed in studies described in chapter 2 to 8 of this thesis. A general discussion of the results and suggestions for further research are provided in chapter 9.

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2

Spreading of Complex Regional Pain Syndrome: not a random process

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Submitted

Abstract

Background: Complex Regional Pain Syndrome (CRPS) generally remains restricted to one limb but occasionally may spread to other limbs. Knowledge of the spreading pattern of CRPS may lead to hypotheses about underlying mechanisms but to date little is known about this process.
Objective: To study patterns of spread of CRPS from a first to a second limb and the factors associated with this process.
Methods: One hundred-eighty-five CRPS patients were retrospectively evaluated. Cox's proportional hazards model was used to evaluate factors that influenced spread of CRPS symptoms.
Results: Eighty-nine patients exhibited CRPS in multiple limbs. In 72 patients spread from a first to a second limb occurred showing a contralateral pattern in 49%, ipsilateral pattern in 30% and diagonal pattern in 14%. A trauma preceded the onset in the second limb in 37, 44 and 91%, respectively. The hazard of spread of CRPS increased with the number of limbs affected. Compared to patients with CRPS in one limb, patients with CRPS in multiple limbs were on average 7 years younger and more often had movement disorders.
Conclusions: In patients with CRPS in multiple limbs, spontaneous spread of symptoms generally follows a contralateral or ipsilateral pattern whereas diagonal spread is rare and generally preceded by a new trauma. Spread is associated with a younger age at onset and a more severely affected phenotype. We argue that both spinal and supraspinal processes may play a role in the spontaneous spread in CRPS.

Introduction

Complex regional pain syndrome (CRPS) is characterized by various combinations of sensory, autonomic and motor disturbances, and is usually preceded by a minor to severe trauma affecting a limb.[1-3] CRPS usually remains restricted to one limb, but it can spread to other body parts.[4,5] Although several small studies have reported spread of specific sensory, autonomic or motor features of the syndrome, the overall picture remains unclear.[4-7] CRPS in one limb may extend to another limb either as result of a new trauma to a previously unaffected limb, or because the syndrome spreads spontaneously. Although different causes of spontaneous spread have been proposed, including genetic predisposition, aberrant regulation of neurogenic inflammation and maladaptive neuronal plasticity, the underlying mechanisms have not been elucidated.[4,5,8]

We were able to characterize a large sample of patients in whom CRPS in one limb spread to involve another limb. We were particularly interested in patients in whom spreading occurred spontaneously, because this may reflect true spread of the disorder, which might provide important information about the mechanisms behind this process. For example, if systemic factors underpin spontaneous spread, then one would expect an indiscriminate pattern of spread; if cortical mechanisms underpin spontaneous spread, then one would expect an ipsilateral pattern, and if spinal mechanisms underpin spontaneous spread, then one would expect a contralateral pattern.

The present study aims to evaluate patterns of spread of CRPS from one to a second limb and consider potential mechanisms that could explain this process. In addition, factors that are associated with the occurrence of spread are studied.

Methods

Patients

All patients who visited the outpatient movement disorders clinic of the department of Neurology of the Leiden University Medical Center in the period from January 1998 to April 2004 were considered for inclusion in the study. Patients were eligible if they met the CRPS criteria of the International Association for the Study of Pain (IASP), either at the time of disease onset or at the time of presentation at the clinic. The IASP criteria include the combination of: 1) the presence of an initiating noxious event or a cause of immobilization, 2) continuing pain, allodynia or hyperalgesia with which the pain is disproportionate to any inciting event, 3) evidence at some time of edema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain

and 4) absence of a condition that would otherwise account for the degree of pain and dysfunction. Although only criteria 2-4 have to be satisfied[3], we only included patients who identified an initiating noxious event in the first affected limb. Patients consent was obtained according to the Declaration of Helsinki and the study was approved by the Ethical Committee of the Leiden University Medical Center

Data Collection

Dates of onset of CRPS signs or symptoms for every involved limb were obtained from the patient's history. Medical records were reviewed to verify data wherever possible. Recorded sensory features included pain, hypoalgesia, hyperalgesia and allodynia. Recorded autonomic features involved oedema, temperature changes, colour changes, hyper- or hypohidrosis, and changes in nail and hair growth. Recorded movement disorders included dystonia, tremor and myoclonus. For all affected limbs we evaluated if the symptoms and signs fulfilled the IASP criteria for CRPS. Age at onset in the first limb and length of interval to onset of symptoms in subsequent limbs were calculated. The presence and type of traumas (soft tissue injury, fracture, surgery) preceding CRPS was registered. We categorized patients according to three criteria. First, if CRPS was present in one limb, patients were categorized as 'Single-CRPS'. If CRPS was present in more than one limb, they were categorized as 'Multiple-CRPS'. Second, Multiple-CRPS cases were categorized according to whether or not spread was associated with a separate trauma to the limb. If not, patients were categorized as 'Spontaneous spread'. If so, they were categorized as 'Separate trauma'. Third, Multiple-CRPS cases were categorized according to which limb was subsequently affected: 'Contralateral' (e.g. left hand to right hand), 'Ipsilateral' (e.g. left hand to left leg) or 'Diagonal' (e.g. left hand to right leg).

Statistical analysis

The independent-samples t-test was used to assess differences between groups in normally distributed continuous data, while non-parametric tests were used to assess differences in non-normally distributed continuous or categorical data. Baseline differences in disease duration were taken into account and analyzed with analysis of covariance. The time from onset of initial symptoms to extension to other limbs was calculated for each limb, where time to spread was censored at the time of last assessment. In patients who showed spontaneous spread of symptoms to subsequent limbs, a multivariate analysis of factors associated with spread of symptoms was carried out with Cox's proportional hazards model. At any point in time, an individual has an instantaneous risk ("hazard") to reach the endpoint (here: "spread to a second limb"). The Hazard ratio presents the increased or decreased risk on reaching the endpoint at any point in time (compared

to a reference value), adjusted for other potentially confounding variables in the model. Patients with simultaneous onset of symptoms in more than one limb or with simultaneous spread from one affected limb to more than one subsequent limb were excluded from this analysis. The hazard of spread was estimated while several variables were accounted for, including trauma characteristics, location of initial symptoms, presence of movement disorders and patient characteristics. The probabilities of spread to other limbs were calculated as cumulative incidences (competing risks).[9] For the analysis of rate of spread comparing the presence of one, two or three affected limbs, the variance of the estimated coefficients was adjusted by using a sandwich estimator, accounting for possible correlations of event times within patients.[10] P values £0.05 were considered significant. All statistical analyses were performed with SPSS (version 14.0), except for the survival analyses, which were performed with 'R' (version 2.0.1).

Results

One-hundred-eighty-five patients were included in the study (table 1, figure 1). At assessment, 96 patients (52%) had a single affected limb, whereas 89 (48%) had multiple affected limbs. Signs and symptoms are presented in Table 2. In the Multiple-CRPS group, the syndrome started in one limb in 78 patients (i.e. 88%), a simultaneous start in two limbs occurred in 10 patients (11%) and a simultaneous start in four limbs occurred in one patient (1%).

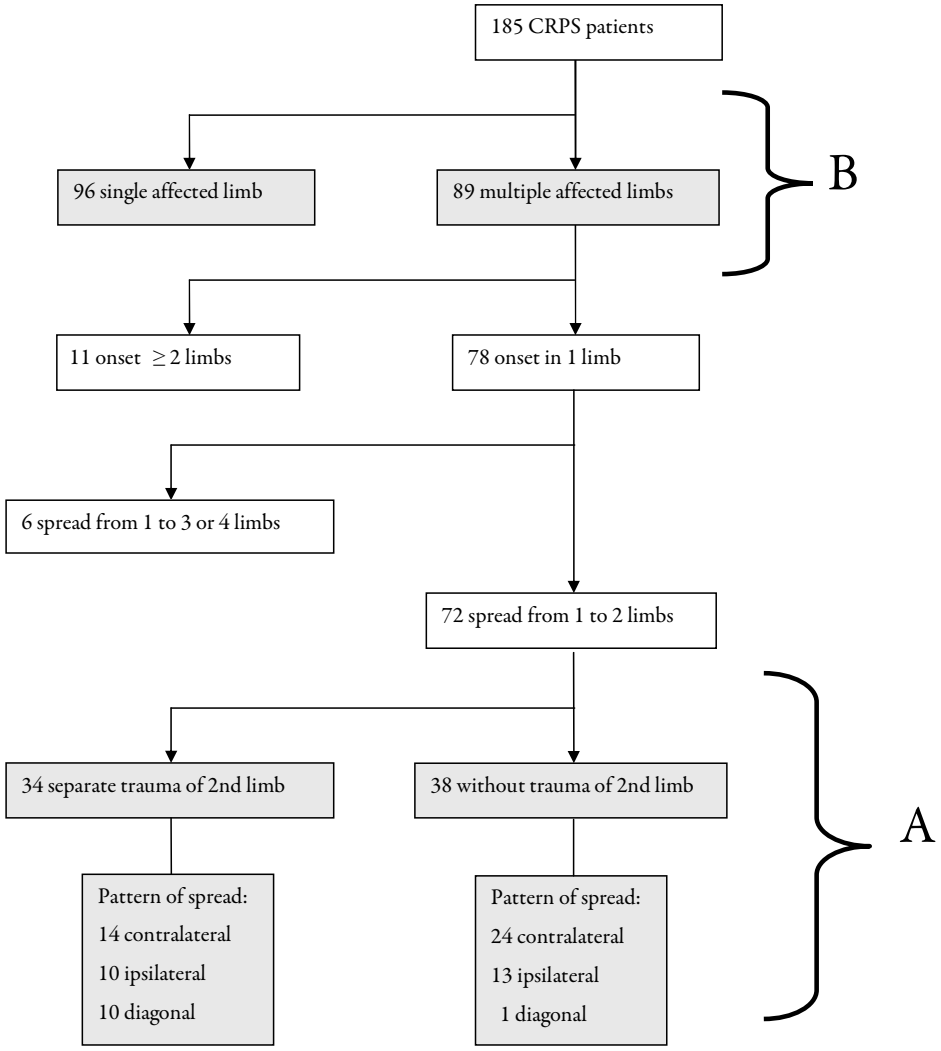
Spread of CRPS from one to two limbs

CRPS had spread to another limb in 78 patients. Spread occurred simultaneously from one to three limbs in 5 patients and from one to four limbs in one (figure 1). CRPS spread from one to two limbs in 72 patients according to the following patterns (table 3): contralateral pattern in 38 patients (53%; 22 arm to arm, 16 leg to leg); ipsilateral pattern in 23 patients (32%; 12 arm to leg, 11 leg to arm) and diagonal pattern in 11 patients (15%). New trauma preceded the onset of CRPS in the second limb in 37 % of the patients with contralateral spread, in 44% of the patients with ipsilateral spread and in 91 % of the patients with diagonal spread, which indicates that diagonal spreading is almost always associated with a new trauma. Patient characteristics did not differ between the three types of spread.

Table 1. Demographics of 185 patients with CRPS.

Characteristic	Value
females - no (%)	160 (86.5)
disease duration, mean (SD) - years	6.0 (6.0)
age at assessment, mean (SD) - years	43.5 (15.4)
age at onset of CRPS, mean (SD) - years	37.5 (15.4)
preceding trauma - no (%)	
soft tissue injury	92 (49.7)
fracture	48 (25.9)
surgery	45 (24.3)
CRPS involvement - no (%)	
- single limb	96 (51.9)
- multiple limbs	89 (48.1)
affected limbs at initial CRPS onset - no (%)	
1	78 (87.6)
2	10 (11.2)
3	0
4	1 (1.1)
affected limbs at assessment - no (%)	
2	45 (50.6)
3	18 (20.2)
4	26 (29.2)

Figure 1. Flow diagram of patients included in the study.



Section A shows the included patients in which CRPS symptoms spread from one to two limbs and who were evaluated for different patterns of spread. Section B shows the included patients with multiple and single affected limbs that were compared for differences in clinical characteristics.

Table 2. Signs and symptoms of CRPS in affected limbs

Variable	Affected limb 1st (n = 185)	2nd (n = 89)	3rd (n = 44)	4th (n = 26)
Pain				
Present/absent/unknown, no.	185/0/0	89/0/0	44/0/0	26/0/0
Hyperalgesia/allodynia				
Present/absent/unknown, no.	101/78/6	40/48/1	19/24/1	10/16/0
Hypoalgesia				
Present/absent/unknown, no.	152/30/3	72/17/0	39/5/0	23/3/0
Edema				
Present/absent/unknown, no.	168/9/8	67/20/2	27/13/4	17/8/1
Temperature changes				
Present/absent/unknown, no.	165/9/11	73/9/7	41/2/1	21/4/1
Color changes				
Present/absent/unknown, no.	176/3/6	82/5/2	33/7/4	24/2/0
Hyper/hypohidrosis				
Present/absent/unknown, no.	122/44/19	59/27/3	26/15/3	13/12/1
Hair and nail growth changes				
Present/absent/unknown, no.	134/42/9/	52/32/5	27/13/4	18/7/1
Movement disorders*				
Present/absent/unknown, no.	115/70/0	67/22/0	36/8/0	25/1/0

Variables were deemed to be present if a symptom, a sign or both were reported or observed.
* Recorded movement disorders were dystonia, tremor and myoclonus.

Table 3. Patterns of spread in 72 patients who spread from one to two limbs spontaneously or after a separate trauma of the second extremity

Pattern of spread*	Total N=72	Spontaneous spread N=38	Separate trauma N=34
Contralateral - no.(%)	38 (53)	24 (63)	14 (41)
Ipsilateral - no.(%)	23 (32)	13 (34)	10 (29)
Diagonal - no.(%)	11 (15)	1 (3)	10 (29)

* Patterns of spread were significantly different between patients with spontaneous spread and spread after a separate trauma; $\chi^2(2) = 10.2$; p=0.006.

Spontaneous spread versus spread after separate trauma

In thirty-eight patients who showed spontaneous spread of CRPS from a first to a second limb, contralateral spread occurred in 24 (63%, 11 arm to arm and 13 leg to leg) (table 3). Ipsilateral spread occurred in 13 patients (34%, 8 arm to leg and 5 leg to arm) and diagonal spread in 1 (3%). In 34 patients who showed spread after a separate trauma of the second limb, contralateral spread occurred in 14 (41%, 11 arm to arm and 3 leg to leg). Ipsilateral spread occurred in 10 patients (29%, 4 arm to leg and 6 leg to arm) and diagonal spread also occurred in 10 (29%, 4 arm to leg and 6 leg to arm). Patterns of spread differed significantly between patients with spontaneous spread and spread after a separate trauma ($\chi^2(2) = 10.2$; p=0.006). Patient characteristics did not differ significantly between patients who spread spontaneously and those who spread after a separate trauma. Patients in whom spreading occurred spontaneously showed a non-random pattern of spread, so further analysis were performed on data from this subgroup.

Characteristics of spontaneous spread

The median interval between occurrence in the first and second limb was 21 months (n=24, range 2-95) for contralateral spread, 19 months (n=13, range 3-58) for ipsilateral spread and 10 months (n=1) for diagonal spread. The difference in intervals between contralateral and ipsilateral pattern was not significant (Mann-Whitney U test; p =0.16).

Next, the hazard of the different types of spontaneous spread was calculated (table 4). Compared to patients with contralateral pattern (reference value of 1.00) the hazard of ipsilateral spread was 0.44 (95% CI: 0.22-0.89), whereas the hazard of diagonal spread was 0.04 (CI 0.005-0.30) (figure 2). Age at onset, sex, onset of symptoms in arm or leg, or in left or right sided limbs, did not affect the hazard. Compared to presence of CRPS in one limb, the presence in two limbs increased the hazard of spread of CRPS to a third limb with 2.19 (95% CI: 1.35-3.57). CRPS in three limbs increased the hazard of spread to a fourth limb to 3.75 (95% CI: 1.92-7.32). The hazard of spread in patients with onset of CRPS on the left side was 1.46 (95% CI: 1.00-2.11, P=0.047) compared to patients with right-sided onset, indicating a somewhat higher risk of spread in patients with left sided onset.

Table 4. Hazard on spread of CRPS - Multivariate Cox regression model

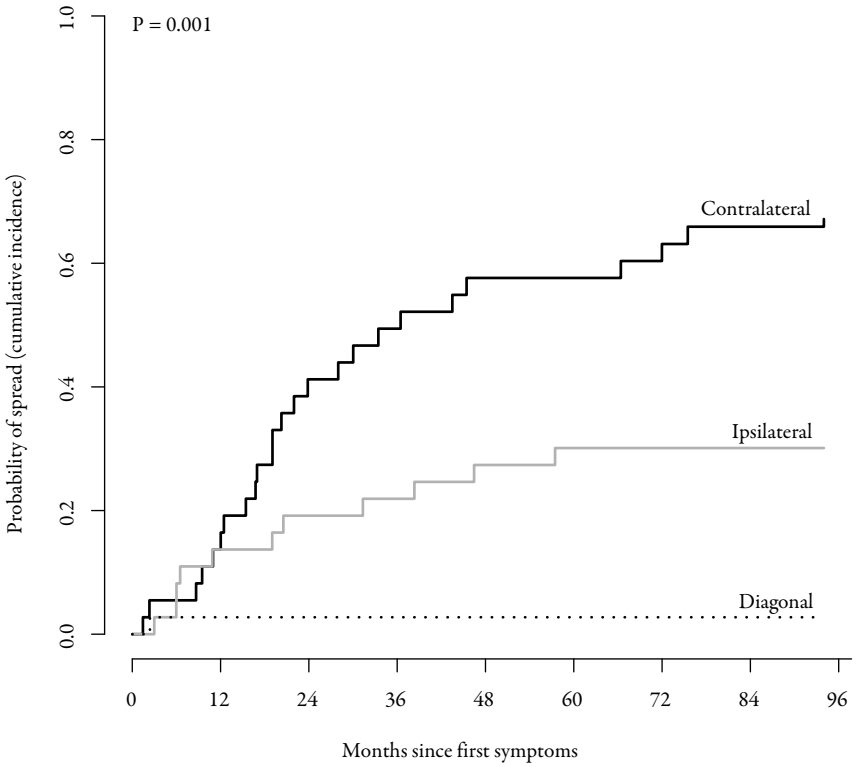
Variable	Hazard ratio	95%-CI
Pattern of spread to second affected limb		
Mirror-image	1	
Ipsilateral	0.44	0.22-0.89
Diagonal	0.04	0.005-0.30
Onset in limb		
Right sided	1	
Left sided	1.46	1.00- 2.11
Number of limbs already affected by CRPS		
1	1	
2	2.19	1.35- 3,57
3	3.75	1.92- 7.32

* Regression coefficient with 95%-CI

Comparison of Single and Multiple CRPS patients

Ninety-six patients with Single-CRPS were compared with 89 patients with Multiple-CRPS (figure 1, section B). Patients with Multiple-CRPS had longer disease duration, and were significantly younger at onset, than patients with Single-CRPS (table 5). Additional analyses with adjustment for differences in disease duration showed that patients with Multiple-CRPS were 6.7 years younger (95% CI: 6.3-7.1). There was no significant difference in type of trauma ($\chi^2(2) = 5.67$; p=0.06) between groups. Movement disorder was more common in those with Multiple-CRPS than it was in those with Single-CRPS (78% versus 54%, mean (95% CI) difference = 23% (10-37)). No difference between groups was found in the type of sensory symptoms ($\chi^2(2) = 0.73$; p=0.69). Patients with spontaneous spread had a shorter disease duration than those with secondary trauma-related spread (6.4 versus 9.6 years, mean difference 3.2 years, 95% CI: 0.4-5.8) but there were no other differences between these two groups.

Figure 2. The probability of spread of CRPS.



The probability on the occurrence of different types of spread in CRPS patients since the onset of symptoms in the first limb. In this multivariate model differences in patient characteristics were accounted for.

Table 5. Comparison of characteristics of CRPS patients with single and multiple affected limbs

Parameter	Total N=185	single N= 96	multiple N=89	Difference in % (95% CI)
Female - no. (%)	160 (86.5)	84 (87.5)	76 (85.4)	2.1 (-10.6;14.8)
First aff. limb arm - no. (%) n=174	91 (52.3)	50 (52.1)	41 (52.6)	0.5 (-14.4;15.4)
Disease duration - mean (SD) yr	6.0 (6.0)	4.1(4.7)	8.1 (6.6)	4.0 (2.3;5.7)
Age at onset CRPS - mean (SD) yr	37.5 (15.4)	40.7 (14.7)	34.0 (14.7)	6.7 (6.3;7.1)
Kind of trauma - no. (%)				
soft tissue injury	92 (49.7)	43 (44.8)	49 (55.1)	χ^2 (df=2) = 5.67
fracture limb/other	48 (25.9)	32 (33.3)	16 (18.0)	P= 0.06
operation limb/other	45 (24.3)	21 (21.9)	24 (27.0)	
Movement disorders - no. (%)	121 (65.4)	52 (54.2)	69 (77.5)	23.3 (10.1;36.5) [a]
Type sensory symptoms - no. (%) n=165				
hypaesthesia/hypalgesia	81 (49.1)	43 (52.4)	38 (45.8)	χ^2 (df=2) = 0.73
hyperaesthesia/hyperalgesia/ allodynia	41 (24.8)	19 (23.2)	22 (26.5)	P= 0.69
both	43 (26.1)	20 (24.4)	23 (27.7)	

[a] Adjusted for disease duration

Discussion

We set out to determine patterns of spread of CRPS and the factors that are associated with spread. Our results show that CRPS usually affects one limb but in some cases it spreads to another limb, most often in a contralateral (53%) or ipsilateral (32%) pattern and usually without secondary trauma. A diagonal pattern of spread was nearly always triggered by a new trauma. Spontaneous spread and spread after a separate trauma followed different patterns.

The mechanism underlying spontaneous spread of CRPS to other limbs is unclear. Common patterns of spontaneous spread of CRPS may hint at the origin of the pattern. Spread after a separate trauma followed no particular pattern, which strongly suggests that CRPS in one limb does not specifically predispose a particular other limb to CRPS and supports the idea that these patients have multiple CRPS rather than CRPS of multiple limbs. In contrast, spontaneous spread to the contralateral limb was 2.3 times more likely than spread to the ipsilateral limb and 25 times more likely than

diagonal spread. This result casts light on previous reports of similar rates of ipsilateral and diagonal spread[5] because that work did not differentiate between spontaneous and second trauma-related spread.

Patients with a spontaneous onset or who have a familial form of CRPS develop the syndrome at a younger age and are more likely to have a more severe phenotype.[11] Additionally, CRPS patients younger than 50 have an increased risk of having siblings with CRPS.[12] In line with these studies, patients with Multiple-CRPS more often exhibited movement disorders and also had a significantly younger age at onset of CRPS than patients with Single-CRPS. Collectively, these findings indicate that in patients with a younger onset of CRPS, genetic factors may play a role in the onset or chronicity of the syndrome. A genetic predisposition is also suggested by associations that were found with different human leukocyte antigen (HLA) class I and II factors.[13-16] Interestingly, HLA class I molecules have been implicated in non-immune roles including neuroplasticity.[17,18]

The dominant patterns of spontaneous spread observed here strongly suggest that CRPS does not spread according to some systemic vulnerability, but is more likely to spread via spinal or cortically mediated mechanisms.

Pain that spreads contralaterally has been reported in CRPS and other chronic pain conditions, such as atypical facial pain[19], phantom limb pain[20] and repetitive strain injury.[21] Several animal models of neuropathic pain and CRPS have reported contralateral spread of symptoms after nerve lesions or inflammation.[22-24] In a recent rat model of CRPS, 57% of the animals exhibited contralateral hindpaw mechanical hypersensitivity after unilateral needle stick distal nerve injury.[25] Following an intradermal injection of capsaicin, human subjects developed contralateral hyperalgesia and allodynia.[26] The etiology behind the contralateral spread of pain is largely unknown; however, increasing evidence from experimental studies on neuropathic pain suggests that contralateral changes arise via altered spinal processing of incoming sensory information.[22,27] This may be mediated by growth factors via commissural interneurons in the spinal cord and brainstem. In addition, spinal glia cells and pro-inflammatory cytokines have been documented as important factors behind the contralateral spread of symptoms.[28,29]

In contrast to the number of studies on contralateral spread, data on mechanisms underlying spread of symptoms to the ipsilateral limb are scarce. Axial spread of disease along the spinal cord is well documented for degenerative diseases such as amyotrophic lateral sclerosis and infectious agents such as the poliovirus.[30] It is conceivable that glial mediated changes at one segment of the spinal cord can reach remote segments by axonal transport via descending or ascending fibre tracts. This is also suggested by a recent autopsy paper on a patient with longstanding CRPS that started in the left leg,

but eventually spread to all limbs.[31] The researchers demonstrated a significant loss of posterior horn cells and activation of both microglia and astrocytes not only at the site of the initial injury, but extending throughout the entire length of the spinal cord. These diffuse alterations may support the hypothesis that segmental changes in the spinal cord induced by CRPS in one limb, may not only spread to the contralateral side but can extend more rostrally and caudally from the initially affected segment. Interestingly, this latter study[31] also reported that the greatest degree of microglial cell activation in the spinal cord was seen in the left lumbar segments and the least in the right cervical cord, which suggests that ispilateral changes are induced more easily than diagonal changes.

Another explanation for spread of symptoms may be found at the supraspinal level. Rommel et al[32] showed hemisensory impairment in CRPS patients with only one affected limb, and that this was more commonly found in those with left-sided CRPS. They proposed that the results may reflect functional alterations in the thalamus. Relevant to this is the recent discovery of space-based, but not arm-based shift in tactile processing in people with CRPS of one arm.[33] Of further relevance here is the observation that left-sided CRPS is associated with a higher hazard of spontaneous spread – space-based tactile neglect after stroke commonly involves the left side of the body, consequent to right sided brain damage.[34]

Contralateral spread probably involves different supraspinal mechanisms. Noxious stimuli activate bilateral regions of the brain associated with descending control pathways including the thalamus and rostral ventral medulla, which suggests one putative mechanism for mediating altered spinal gating contralaterally.[35,36] Additionally, the growing body of data implicating cortical changes in CRPS (see[37] for review), offers potential mechanisms. For example, watching the mirror-image of the unaffected limb being touched elicits pain on the affected side[38] and referred sensations of a tactile or painful stimulus were also experienced outside its expected somatic territory.[39] Forss et al.[40] describe a patient with chronic CRPS type-1 in whom pain and motor symptoms spread to the contralateral arm, and whole-head-magnetoencephalography demonstrated abnormal bilateral activation in the primary somatosensory cortices to unilateral tactile stimuli, which suggests that interhemispheric spread of cortical activation may contribute to contralateral spread. Furthermore, supraspinal glia and glial-derived proinflammatory cytokines may play a role in spread of symptoms as well as their major influence on pain modulation.[27] Whether these supraspinal changes can initiate spread of CRPS symptoms or if they are secondary to peripheral or spinal processes remains to be elucidated.

Our study demonstrates that if CRPS develops spontaneously in more than one limb, there is a greater risk of spread to subsequent limbs without the requirement of a new

trauma. This accelerated occurrence has been documented for clinical manifestations of other diseases and probably reflect changes in the central nervous system, perhaps in an attempt to adapt to the altered condition by remodelling of neuronal contacts and circuits, a process also known as neuronal plasticity.[41-44]

Interpretation of our results should consider some methodological issues. A retrospective design is less accurate than prospective designs and may result in incomplete data, although such issues would seem unlikely to bias the results in one direction over another. Furthermore, follow-up data were not available and Single-CRPS patients had shorter disease duration than patients with Multiple-CRPS, which raises the possibility that some Single-CRPS patients would have ultimately developed Multiple-CRPS if we left it longer to find out. We addressed this issue by controlling for disease duration in the analysis.

In conclusion, this study shows that spread of CRPS symptoms often occurs spontaneously and contralateral spread is twice as likely as ipsilateral spread, but diagonal spread is rare. We contend that these patterns of spread implicate spinal cord and/or supraspinal mechanisms rather than systemic mechanisms, although further work is required to elucidate them in detail.

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Onset and progression of dystonia in Complex Regional Pain Syndrome

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Abstract

Complex Regional Pain Syndrome (CRPS) may lead to movement disorders (MDs) in some patients. Reliable information on the nature, chronology and clinical determinants of MDs in CRPS patients is lacking but could provide better insight in the underlying pathophysiological mechanism. We retrospectively 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. 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.

Introduction

Complex Regional Pain Syndrome (CRPS) is commonly known as a disorder that follows a minor to severe trauma to an extremity and occurs more frequently in women.[1,2] In the acute phase, CRPS is characterized by pain, changes in skin blood flow, sweating and swelling.[3,4] Occasionally, CRPS may spread to other extremities and body parts.[5,6] Patients with CRPS may also suffer from movement disorders (MDs), like tremor, myoclonia and dystonia.[7-10] These MDs are not infrequent, as data from studies where selection bias towards MDs was unlikely indicate that 9-49% of the CRPS patients may develop MDs, 14-25% of which involve dystonia.[11-14] The increasing awareness that CRPS patients may suffer MDs has resulted in a proposal to add this clinical category to the new criteria set.[15]

Little is known about the interval between the onset of CRPS and MDs in the same extremity and the determinants of spread of MDs to other extremities. Available information shows that the interval may vary considerably between patients.[16,17] Obviously, the longer the interval between CRPS and the onset of MDs, the less certain one is about the causal relation. Some investigators consider a cause-effect relation between trauma and MD for peripherally induced MDs unlikely if the interval is more than one year[18], but others have accepted intervals as long as several years.[19] Reliable information on the distribution of the interval duration between CRPS and the onset of MDs is important, because the presence of an interval may indicate that different mechanisms underlie the initial (sensory and autonomic) and late (motor) features of CRPS. Similarly, accurate data on the temporal characteristics of spread to other extremities may provide insight in the nature of mechanisms that play a role in MDs in CRPS.

Our clinic's special interest in MDs and CRPS provided a unique opportunity to collect and study a large sample of patients over the years. Since the phenomenology of the MDs in CRPS has been described in detail elsewhere[8,20-22], the objective of the current study was to describe the temporal characteristics of MDs in CRPS, and to evaluate factors associated with their onset and progression.

Methods

Patients

All patients who visited the Movement Disorders Clinic of the department of Neurology, Leiden University Medical Center with a diagnosis of CRPS between January 1998 and April 2004 were considered for inclusion in the study. Patient with a possible or definitive diagnosis of CRPS were referred by general practitioners, anesthesiologists,

rehabilitation physicians and other neurologists throughout the Netherlands. Patients were eligible if the first affected extremity met the CRPS criteria of the International Association for the Study of Pain (IASP), either at the time of disease onset or at the time of presentation at the clinic. The IASP criteria include the combination of 1) the presence of an initiating noxious event or a cause of immobilization, 2) continuing pain, allodynia or hyperalgesia with which the pain is disproportionate to any inciting event, 3) evidence at some time of edema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain and 4) absence of a condition that would otherwise account for the degree of pain and dysfunction.[3] To increase the homogeneity of the population, we only included patients in whom a noxious event triggered the onset of CRPS in the first affected extremity. For similar reasons, we also excluded patients in whom a MD developed before the onset of other symptoms and signs of CRPS. Blood tests, and nerve conduction and imaging studies (computed tomography, magnetic resonance imaging) of the spinal cord and brain were used to rule out other causes of MDs. Patient consent was obtained according to the Declaration of Helsinki and the study was approved by the ethical committee of the Leiden University Medical Center.

Data collection

Data from physical examination and patient's history were collected in a standardized way during the first visit with respect to the current diagnosis, after which historic information was verified by reviewing medical records. Dates of onset of CRPS and MDs were recorded for every affected extremity. Age at onset and the time interval between onset of CRPS and MDs in the same extremity were subsequently determined. The type (soft tissue injury, fracture, surgery) of the trauma preceding CRPS and MDs was registered. The evaluated MDs included dystonia, tremor and myoclonus, and were considered present if observed at assessment. We did not consider muscle weakness a MD as this could result from pain or oedema. Sensitivity to light touch (hypaesthesia, hyperaesthesia and allodynia) and pinprick (hyperalgesia, hypalgesia) were assessed.

Statistical analysis

We compared the characteristics of CRPS patients with MDs in any extremity with those of CRPS patients without MDs. Continuous variables were compared with a t-test for independent samples or Mann-Whitney-U test as appropriate. Chi-square tests were used to compare categorical data. A multivariate analysis of factors associated with the onset of MDs was carried out with Cox's proportional hazards model. The hazard of developing MDs was estimated for several variables, including the number of extremities with initial sensory and autonomic symptoms but without MDs, the number of extremities previously affected by MD (both as time-dependent covariates)

and patient characteristics. We used time from onset of initial symptoms to development of MDs for each extremity, where time to MD of an extremity was censored at the time of assessment. Robust standard errors of the estimated coefficients were used to account for correlation of event times of extremities within patients. P values ≤ 0.05 were considered significant. All statistical analyses were performed with SPSS (version 10.0), except for the Cox analysis, which was performed with the statistical program R (version 2.0.1, R Development Core Team).

Results

One-hundred-eighty-five patients fulfilled IASP criteria 1-4 for CRPS-1 in the first affected extremity and were included in the study (table 1). Included patients were mainly female (86.5%). At assessment, 96 (51.9%) patients had more than one affected extremity. We noted a simultaneous onset of CRPS in multiple extremities in 13 patients (7.0%). In general, treatments with benzodiazepines, oral baclofen, amitriptyline, antiepileptics, analgetics including morfine, and mannitol infusions proved unrewarding with respect to the MDs or were stopped because of side-effects. One-hundred-twenty-one patients (65.4%) suffered from at least one type of MD (table 1). Dystonia was present in 110 (90.9%) patients with MDs, whether or not combined with other types of MDs.

Dystonia was predominantly characterized by tonic flexion postures. In the majority of patients dystonia was limited to the distal extremity and mostly involved flexion of digits and wrists in the arms, and inversion and flexion postures in the feet. In a minority of patients, dystonia extended proximally to either elbows or shoulders, and knees or hips. In patients with bilateral arm or leg involvement, characteristics of dystonia were generally very similar. We encountered combinations of (intermittent) dystonia, myoclonus or tremor in 24.8% of the patients with MDs. Fifty-six patients (30.3%) had a MD in one extremity, whereas 32 patients (17.3%) had two, 13 patients (7.0%) had three and 21 patients (11.4%) had four affected extremities. In patients with multiple subsequently extremities affected by MDs, 81.2% of the extremities with MDs fulfilled both IASP criterion 2 (continuing pain, or allodynia, or hyperalgesie; present in 91.4% of the patients) and criterion 3 (evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain; present in 89.1% of the patients).

Table 1. Characteristics of patients and movement disorders (MDs)

Number of patients	185
Number (%) of females	160 (86.5)
Mean (SD) disease duration - yrs	6.0 (6.0)
Mean (SD) age at assessment - yrs	43.5 (15.4)
Mean (SD) age at onset of CRPS - yrs	37.5 (15.4)
Preceding trauma – n (%)	
soft tissue injury	92 (49.7)
fracture	48 (25.9)
surgery	45 (24.3)
Extremities affected by CRPS at assessment - n (%)	
one	89 (48.1)
more than one	96 (51.9)
Extremities affected by CRPS at initial onset of symptoms - n (%)	
one	172 (93.0)
arm	91 (49.2)
leg	81 (43.8)
more than one	13 (7.0)
Number of patients with MDs (%)	121 (65.4)
Extremities affected by MDs- n (% of total number of patients)	
1	56 (30.3)
2	32 (17.3)
3	13 (7.0)
4	21 (11.4)
Type of MD - n (% of patients with MDs)	
tonic dystonia	75 (62.0)
intermittent dystonia	9 (7.4)
myoclonus	6 (5.0)
tremor	1 (0.8)
combination of (intermittent) dystonia and myoclonus	13 (10.7)
combination of (intermittent) dystonia and tremor	2 (1.7)
combination of tremor and myclonus	4 (3.3)
combination of (intermittent) dystonia, myoclonus and tremor	11 (9.1)

As dystonia was by far the most common MD, we focussed our further analyses on comparing CRPS patients with and without dystonia.
Compared to patients without dystonia, patients with dystonia had longer disease duration (7.4 versus 4.0 years respectively) and more frequently displayed CRPS in multiple extremities (table 2). Differences in disease duration were therefore taken into account in subsequent analyses. The presence of the various sensory signs was approximately equally distributed in both groups and not associated with disease duration. Patients with dystonia were on average 10.6 years (95% confidence interval (CI):7.6-13.6) younger at disease onset than patients without dystonia (33.4 versus 44.0 years, respectively). Patients with CRPS in multiple extremities had a 6.5 (95% CI: 3.4-9.6) younger age at onset than those with CRPS in one extremity.

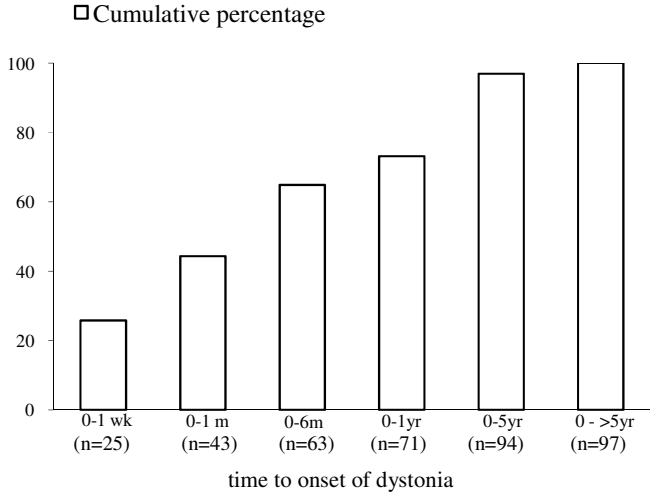
We calculated the latency to onset of dystonia in patients in whom CRPS started in one extremity and dystonia developed in that same extremity simultaneously with or after CRPS onset (n=97). This latency showed a skewed distribution with a median of 61 days (figure 1). Dystonia developed simultaneously (i.e., within one week) with non-motor CRPS symptoms in 25.8% of the patients. Dystonias that did not develop simultaneously with non-motor symptoms of CRPS were preceded by a new trauma in only six patients (6.2%). Three patients (3.1%) developed dystonia more than five years after CRPS onset, but the dystonia characteristics of these patients were similar to those of patients with an earlier onset of dystonia. The duration of the interval between onset of CRPS and dystonia was not related to age at onset, gender, type of trauma, onset in upper or lower extremity, disease duration or the number of affected extremities at assessment.
The presence of dystonia in the first affected extremity increased the hazard of developing dystonia in a second extremity with 2.29 (CI: 1.67-3.14). Dystonia in two extremities increased the hazard of developing dystonia in a third extremity to 2.15 (CI: 1.33-3.48). If dystonia was present in three extremities, the hazard of dystonia in the fourth affected extremity increased to 7.4 (CI: 3.74-14.65) (figure 2). In contrast, as the number of extremities with only non-motor CRPS symptoms (i.e. pain, sensory and autonomic symptoms) increased, the hazard of developing dystonia decreased (2 affected extremities 0.91 (CI: 0.62-1.32); 3 affected extremities 0.67 (CI: 0.35-1.27); 4 affected extremities 0.27 (CI 0.06-0.94)). Upper extremity involvement (HR 1.35 (CI 1.06-1.72)) was associated with a higher risk of dystonia, whereas age at onset, gender and trauma were not.

Table 2. Comparison of CRPS patients with and without dystonia

Variable	Total n=174	Without dystonia n= 64	With dystonia n=110	Difference (95% CI)
Female - no. (%)	149 (85.6)	52 (81.3)	97 (88.2)	6.9 (-4.4;18.2)
Age at onset CRPS - mean (SD) yrs	37.3 (15.4)	44.0 (14.1)	33.4 (14.1)	-10.6 (-13.6; -7.6)*
Disease duration - mean (SD) yrs	6.1 (6.2)	4.0 (3.8)	7.4 (6.9)	3.4 (1.6;5.3)
Multiple extremities affected by CRPS – n (%)	89 (51.1)	21 (32.8)	68 (61.8)	29.0 (14.3;43.7)
Sensory signs - n (%) (n = 171)	155 (90.6)	52 (83.9)	103 (94.5)	10.6 (0.5;20.7)
Type sensory signs - n (%) (n =155)				
hypaesthesia and/or hypalgesia	74 (47.7)	29 (55.8)	45 (43.7)	-12.1 (-28.7;4.5)
hyperaesthesia, hyperalgesia and/or allodynia	40 (25.8)	11 (21.2)	29 (28.2)	7.0 (-7.1;21.1)
combination of hyper and hyposensitivity	41 (26.1)	12 (23.1)	29 (28.2)	5.1 (-13.8;24.0)

* : adjusted for disease duration

Figure 1. Latency between non-motor symptoms and dystonia in the first affected extremity



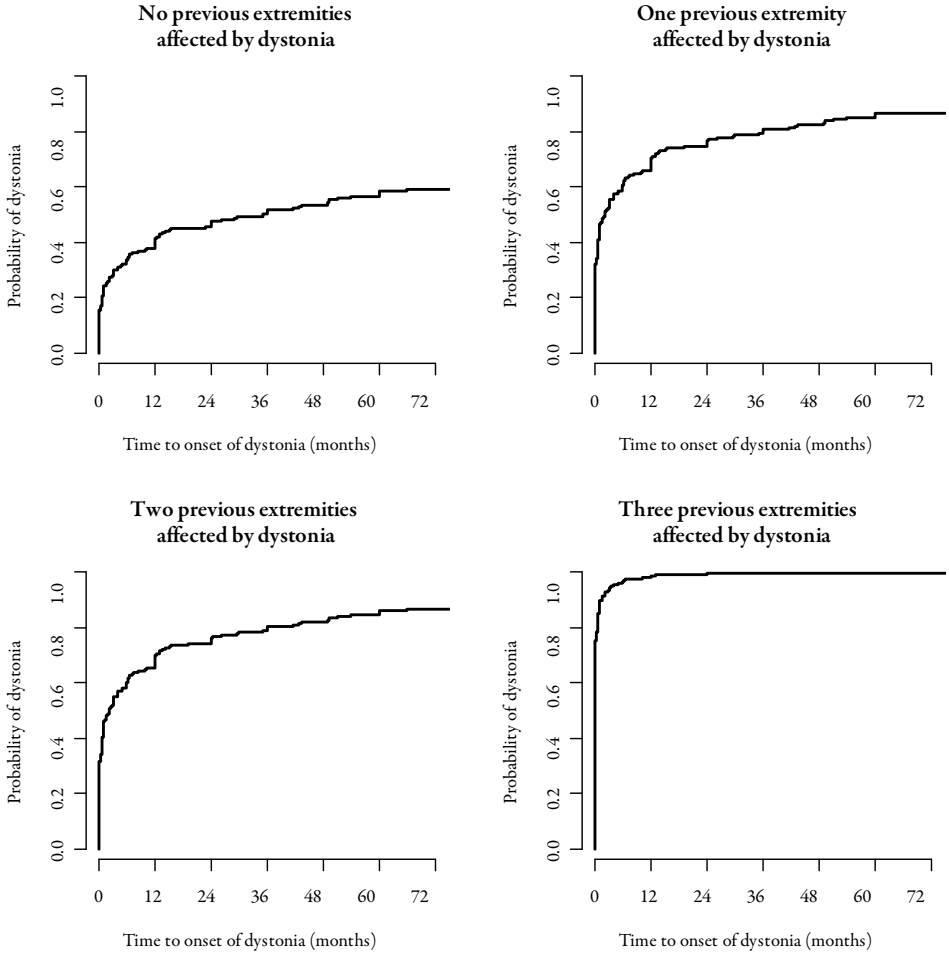
Latency to onset of dystonia assessed in the 97 patients who initially developed non-motor symptoms in one extremity

Table 3. Hazard of of dystonia - Multivariate Cox regression model

Variable	Hazard ratio	95%-CI
Extremity		
Lower	1	
Upper	1.35	1.06; 1.72
Age at onset	-0.009 *	-0.021;0.002 *
Number of extremities already affected by dystonia		
0	1	
1	2.29	1.67; 3.14
2	2.15	1.33; 3.48
3	7.40	3.74; 14.65
Number of extremities with CRPS but without dystonia		
1	1	
2	0.91	0.62; 1.32
3	0.67	0.35; 1.27
4	0.27	0.06; 0.94

* Regression coefficient with 95%-CI

Figure 2. Probability of developing dystonia



The probability of developing dystonia expressed as a function of the number of extremities that are already affected by dystonia. For example, for patients with CRPS symptoms in one extremity, the probability of immediately developing dystonia is 20% and this increases to approximately 40% after one year. In this multivariate model differences in patient characteristics were accounted for (see data in table 3).

Discussion

This study shows how CRPS may evolve into a disabling disorder with prominent motor involvement of multiple extremities. Sixty-five percent of the patients in our sample suffered some form of MD, with dystonia being the most prevalent. Compared to other studies the proportion of patients with MDs in our sample is high, which likely reflects referral bias, since especially CRPS patients with neurological symptoms will be referred to a neurology clinic. Nevertheless, the large number of CRPS patients with MDs seen at our department over a period of six years, as well as the data from studies where selection bias towards MDs was unlikely, underscores that this development is far from rare.[23-26]

Previous studies, which were based on small numbers, showed that the interval between the onset of CRPS and onset of dystonia may vary.[27-29] 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 rare.[30]

Till recently, dystonia was considered to reflect basal ganglia dysfunction.[31] Mounting evidence, however, suggests that, opposed to a disorder of a single brain structure, dystonia is a disorder of neural circuits with abnormalities at multiple levels of the central nervous system (CNS).[32] Accordingly, in CRPS, disinhibition has been demonstrated on both a spinal and cortical level but the sequence of involvement remains unclear.[8,33] However, the initial (non-motor) symptoms of CRPS have been attributed to a perturbed function of C and Aδ-sensory nerve fibres. These fibres are capable of inducing inflammation by releasing the neuropeptides substance P (SP) and Calcitonin-Gene-Related-Peptide (CGRP), a process called neurogenic inflammation.[34,35] In case of tissue or nerve injury, SP may also activate SP receptors on lamina I neurons in the dorsal horn of the spinal cord, thus enhancing synaptic transmission efficiency , i.e. long-term potentiation (LTP), a form of neuronal plasticity.[36] As a result, pain may become chronic and positive sensory signs, including allodynia and hyperalgesia, may develop, a process known as central sensitization.[37,38] It seems unlikely that LTP only involves pathways that deal with perception of pain and not those that mediate the response to pain. C and Aδ sensory fibres, however, are also connected with spinal circuits that

mediate nociceptive withdrawal reflexes (NWRs), which serve to minimize or avoid potential tissue damage[39] and exhibit LTP after intense nociceptive stimulation.[40] Animal models of neurogenic inflammation have shown that SP released at the dorsal horn of the spinal cord, enhances NWRs.[41] Flexor muscles play a prominent role in NWRs and, interestingly, there also is a conspicuous involvement of flexor postures in CRPS-related dystonia.[42,43] Neurophysiologic studies have shown a decreased presynaptic GABA-ergic inhibition in CRPS patients with dystonia.[44] 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.[45,46] 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.

We found that once dystonia was present, the hazard of dystonia in subsequent extremities increased with the number of extremities already affected by dystonia. Interestingly, both the delayed onset and an accellerated disease course are characteristics of maladaptive neuronal plasticity and have been documented for clinical manifestations of other diseases.[47-50] In those patients where the number of extremities with only non-motor CRPS symptoms increased, the hazard of dystonia decreased. Apparently, CRPS may evolve into two different chronic phenotypes, again suggesting a distinct underlying mechanism for dystonia, which, once set into motion, has the capacity to facilitate the occurrence of dystonia in other body parts. Additionally, a more severe phenotype with dystonia or multiple affected extremities was associated with a considerable younger age at onset of CRPS.

Our findings suggest the existence of a subgroup that develops MDs, likely reflecting the involvement of a distinct biological pathway, which may be induced by the mechanisms underlying CRPS. This raises the question whether the criteria should be broadened to encompass the complete phenotype, or if mechanism-related criteria should be devised. An argument in favor of the latter is that homogenous CRPS subgroups may benefit research aiming to unravel the clinical, pathophysiological and genetic coherence.

This study was not designed to address the question as to what extent psychogenic factors contribute to the onset of trauma-related MDs, as suggested by others.[51] Although a role of psychogenic factors cannot be ruled out in the absence of an established pathophysiological explanation, we consider a major role for psychological factors unlikely for several reasons. First, the phenotype has distinct characteristics, which are similar across populations of different cultural background.[52] Second, neurophysiologic and pharmacotherapeutic data on CRPS-related dystonia show reduced central inhibition and are thus in line with the current concept of dystonia as a central circuit disorder of impaired processing of afferent information.[8,53]

As a consequence of the retrospective design, this study has some limitations. First, information on the exact dates of onset is less accurate than those that would have been obtained in a prospective design. However, the error associated with such inaccuracy is unlikely to bias the results in one direction. Second, follow-up data were not available and patients without dystonia had shorter disease duration than patients with dystonia. Therefore, the possibility that some patients ultimately would have developed dystonia cannot be ruled out. To minimize the effect of this confounder, we controlled for disease duration in the analyses. It is also possible that in some cases dystonia may have resolved. However, most patients had CRPS for several years and both our experience as well as evidence from the literature underscore a poor prognosis for dystonia in CRPS.[54,55]

This study is the largest series of CRPS patients with dystonia and our findings suggest that in a proportion of the patients, CRPS may trigger a new mechanism, which underlies the development of dystonia. The temporal characteristics of dystonia in our patients hint that maladaptive neuroplasticity which is associated with disinhibition of spinal mediated withdrawal reflexes may underlie this MD in CRPS.

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4

Psychological Features of Patients with Complex Regional Pain Syndrome Related Dystonia

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Abstract

The objective of this study was to evaluate psychological features in severely affected patients with Complex Regional Pain Syndrome (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 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. 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.

Introduction

Complex Regional Pain Syndrome (CRPS), formerly known as reflex sympathetic dystrophy (RSD) or Sudeck syndrome,[1] is commonly preceded by a minor to severe trauma to an extremity and occurs more frequently in women.[2] CRPS is characterized by various combinations of sensory, autonomic and trophic features, in absence of any evident nerve lesions.[1,2] Compelling evidence indicates that patients with CRPS may develop movement disorders (MDs), which may occur early in the disease course but generally tend to occur with a variable delay.[2-5] Fixed dystonia is among the most common MDs in CRPS and may spread to other extremities.[6]

Although compelling evidence suggests a role for disinhibition of spinal and supraspinal neuronal circuits in dystonia of CRPS,[5,7,8] the nature of CRPS and its associated MDs has since long been subject of debate. While some consider CRPS a somatic disorder,[9,10] others have suggested that the MDs and other features of the disorder are psychogenic.[11,12] From the latter perspective the symptoms of CRPS could be interpreted as a conversion reaction[13] or malingering.[14] Affective and anxiety disorders are often noted among CRPS patients,[15,16] and similarities between CRPS and conversion disorder (CD) have also been documented.[17] Many clinicians who treat CRPS patients feel there is a psychological aspect to the syndrome, either primary, as predisposing personality traits and premorbid psychiatric disorders, or secondary, as a result of the pain and disabilities.[13] A specific CRPS-personality has been suggested in the literature,[12] but has not been confirmed.[1,13] Studies of personality profiles and pre- and co-morbid psychiatric disorders in CRPS have primarily focused on patients with acute CRPS, and have yielded conflicting results.[13,15,16]

To obtain more insight in the psychological features of patients with CRPS related dystonia, we assessed a chronic group of severely affected patients and compared them to two historical psychiatric control groups. Personality traits, psychiatric co-morbidity, dissociative experiences, and the number of traumatic experiences were studied. In addition, the experienced quality of life was assessed.

Methods

Patients

The department of Neurology of the Leiden University Medical Center (LUMC) is a national referral center for patients with CRPS related movement disorders. CRPS patients that suffer dystonia in at least one extremity are offered to participate in a trial which aims to evaluate the efficacy and safety of intrathecal administration of baclofen,

which is a specific γ-amino butyric acid (GABA) receptor agonist. Baclofen inhibits sensory input to the spinal cord,[18] reducing muscle tone and stiffness. A total of 46 patients who participated in a screening for responsiveness to intrathecal baclofen between July 2003 and September 2005 were included in this study. All patients met the International Association for the Study of Pain (IASP) criteria of CRPS[19] for their first affected extremity. Blood tests, nerve conduction and imaging studies of the spinal cord and brain were used to rule out other causes of dystonia. Dystonia generally affected the distal limb and was characterized by flexion postures. Medication used at the time of the screening falls into three categories: antidepressants (Selective Serotonin Re-uptake Inhibitors (used by 9% of the patients) and Tricyclic antidepressants (TCA) (15%), though the TCA's were mainly used as pain medication), muscle relaxing agents (baclofen (35%) and benzodiazepines (41%)), and pain medication (anticonvulsant drugs (15%), acetaminophen or NSAIDs (24%) and opiods (30%)). This study was approved by the medical ethical committee of the LUMC, and the patients gave their informed consent. Psychological features of the CRPS patients were assessed by means of self-report instruments before they entered the baclofen trial.
Two historical control groups were used which included 54 patients with CD and 50 patients with at least one affective disorder (AD). Both control groups were part of a previous study on the involvement of emotional traumas and dissociative features of CD.[20] Data collection of this study took place from 1997 until 2000 and all patients were seen by a psychiatrist to determine whether the diagnosis of CD or AD as stated in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)[21] was applicable. The physical examination in the CD patients was performed by a neurologist. All patients gave their informed consent (for more detail, see the study of Roelofs et al.[20]).

Instruments
The *Personality Diagnostic Questionnaire-Revised* (PDQ-R)[22] can be used for screening for DSM-III-R[23] personality disorders. The PDQ-R consists of 133 true/false items. A high total score indicates severe personality pathology.
The *Traumatic Experiences Checklist* (TEC)[24] is a 25-item questionnaire that evaluates the presence or absence of emotional life events. Among these are emotional neglect, physical abuse, sexual harassment, sexual abuse, parentification and life threatening experiences.
The Dutch *Recent Life Event Questionnaire* ("Vragenlijst Recent Meegemaakte Gebeurtenissen", VRMG)[25] measures the perception of recent life events. The original instrument consists of 115 items, but in the current study a shortened version of the VRMG was used.[26] The addressed categories include health, pregnancy/birth, work,

relationships, and "other". For each event, patients had to indicate whether it had occurred in the twelve months preceding the symptom onset.

The *Dissociative Experiences Scale* (DES)[27] is a 28-item self-report questionnaire which assesses the frequency of various psychological or psychoform dissociative symptoms. The mean of all item scores ranges from 0 to 100 and is called the DES score. High DES scores indicate severe psychoform dissociative problems. The DES addresses disturbances in memory, awareness, identity and cognition, and feelings of depersonalization and derealisation.[27]

To measure somatoform dissociation, the *Somatoform Dissociation Questionnaire-20* (SDQ-20) was used. The SDQ-20 consists of 20 items rated on a five-point scale with a total score range of 20-100. The items address medically unexplained analgesia, anesthesia, motor disturbances, alternating preferences for tastes and smells, pain, and loss of consciousness. A high total score is an indicator for many somatoform dissociative experiences.[28]

To screen for the general level of psychopathology we used the *Symptom Checklist-90-Revised* (SCL-90-R),[29] consisting of 90 items rated on a five-point scale with a total score range of 90-450. High total scores indicate high levels of psychopathology.

The *Research and Development-36* (RAND-36)[30] was administered to measure quality of life. The questionnaire consists of 36 items and assesses physical, psychological and social well-being on eight subscales. The maximum total score per subscale is 100. People with high scores view their health in a positive manner and report few psychical and emotional problems. The RAND-36 was not used in both control groups, yet was added to the current study to assess the quality of life of the CRPS patients.

Dutch versions of all instruments were used. All questionnaires were completed by the patients themselves, with the exception of patients in whom the severity of the dystonia would not allow this. In those cases the questionnaires were orally administered by a trained research nurse.

Statistics

SPSS for Windows, version 11.0, was used for data-analysis. As most of the data were not normally distributed, non-parametric test methods were used. The Mann Whitney U test was used when comparing two groups, whereas the Kruskall Wallis test was used for comparison of three groups. To compare the results with normative data available in the literature, mean scores and standard deviations were also calculated. To compare means of the CRPS group on the RAND-36 to norm data, an unpaired t-test was used. A 5% significance level was used.

Results

Characteristics of all patient groups are presented in table 1. There were no significant differences with respect to sex (χ^2=4.64, df=2, p=0.10), marital status (χ^2=7.68, df=6, p=0.26) and age (χ^2=1.53, df=2, p=0.46). Table 2 reflects the characteristics and symptoms of the CRPS patients. In table 3 the results for PDQ-R, TEC, VRMG, DES, SDQ-20 and SCL-90-R for the three groups are presented.

Personality

No normative data for the PDQ-R were available in the literature. The total PDQ-R score of the CRPS patients is significantly lower than that of the CD patients (z=-3.97, p<0.001) and the AD patients (z=-5.26, p<0.001). Among the CRPS patients, most personality traits were observed in the schizoid, obsessive-compulsive, borderline, paranoid and schizotypical personality clusters.

Life events

No significant differences in the total number of traumatic experiences on the TEC were found between the CRPS patients and the CD patients (z=-1.34, p=0.18) or AD patients (z=-1.07, p=0.29). A total of 87% of the CRPS patients experienced at least one of the listed traumatic experiences. In specific they reported intense pain (67%); witnessing traumatic experiences of others (46%); emotional neglect (35%); emotional abuse (39%); physical abuse (28%); sexual traumas (35%); and incestuous acts (22%). A total of 52% of the CRPS patients reported at least one form of physical, emotional or sexual abuse.

The results on the VRMG showed that the CRPS patients experienced less life events in the year before the onset of their symptoms than both control groups (z=-4.72, p<0.001 compared to the CD patients; z=-5.02, p<0.001 compared to AD patients).

Dissociative experiences

The mean DES-score of the CRPS patients fell in the normal range (3.7-7.8), in contrast to both control groups. Fifteen CRPS patients (33%) obtained a score above 7.8. All three groups had lower scores than the mean scores of psychiatric patients (14.6-17.0), patients with dissociative identity disorder (49.5) and patients with other dissociative disorders (>25).[27,31] The score of the CRPS group was significantly lower than the CD group score (z=-2.95, p=0.003), but did not differ significantly from the AD group score (z=-1.82, p=0.07).

For the SDQ-20 no normative data are available in the literature. Compared to the CD patients, no significant differences were found (z=-0.30, p=0.76), indicating that both

groups had similar levels of somatoform dissociation. In comparison to AD patients, CRPS patients had significantly higher scores (z=-4.96, p<0.001).
Table 4 shows correlations between the total number of traumatic life events (TEC) on the one hand, and the DES and SDQ-20 scores on the other hand. The CD and AD groups showed moderate significant positive correlations between the number of traumatic life events and psychoform dissociative experiences. Only the CRPS patients demonstrated a moderate significant positive correlation between the number of traumatic life events and somatoform dissociative experiences[1*].

General psychopathology

Compared to normative data for the general population,[29] the CRPS patients obtained a high total score on the SCL-90-R, indicating an increased general level of psychopathology. However, the CRPS group had a significantly lower score compared to both control groups (CD group: z=-4.51, p<0.001; AD group: z=-4.90, p<0.001). For the CPRS-I patients, scores on the somatic and depression subscales were elevated. However, compared to the normative data[29] of chronic pain patients, no differences were found.

Quality of life

In comparison to normative data consisting of randomly chosen individuals from the general population,[32] the quality of life of the CRPS patients was severely impaired, as measured by the RAND-36 (table 5). The patients reported severe limitations in physical activities, and indicated that this had a negative impact on work-related or other daily activities. Also, pain, fatigue and limitations in social functioning were reported more often by the CRPS patients.

[1*] Previous investigations in the CD group using a structured trauma interview did show a significant correlation with SDQ-20 scores.[20] Here we only found a trend. This discrepancy is presumably due to the use of a different trauma measure.

Table 1. Characteristics of CRPS patients and control groups

	CRPS (N=46)	Conversion disorder (N=54)	Affective disorder (N=50)
Men/women (% female)	2/44 (96)	9/45 (83)	9/41 (82)
Median age in years (IQR)	41 (28-50)	36 (28-47)	36 (28-46)
Mean age in years (SD)	40 (12)	38 (12)	36 (11)
Marital status			
- Married (%)	23 (50)	28 (52)	26 (52)
- Divorced (%)	3 (7)	7 (13)	0 (0)
- Cohabiting (%)	7 (15)	7 (13)	8 (16)
- Not married (%)	13 (28)	12 (22)	16 (32)
Mean disease duration in years (SD)	10.1 (6.5)	5.1 (7.1)	not available
No. of affected extremities with dystonia (%)		not applicable	not applicable
- Two	8 (17)		
- Three	12 (26)		
- Four	26 (57)		

IQR: interquartile range; SD: standard deviation

Table 2. Characteristics of the symptoms in CRPS patients

ID	Sex	Age	No. affected extremities	Preceding Trauma[1]	Pain	Hyperalgesia/ hyperesthesia/ allodynia	Hypoalgesia/ hypesthesia	Autonomic Symptoms[2]	TCA	SSRI	Anti-psychotics
1	F	24	3	fracture	+	+	+	+	+	-	-
2	M	26	3	soft tissue injury	+	+	+	+	+	-	-
3	F	34	4	soft tissue injury	+	+	+	+	-	-	-
4	F	39	3	soft tissue injury	+	-	+	+	-	-	-
5	F	26	4	fracture	+	+	+	+	-	-	-
6	F	48	4	none	+	+	+	+	-	-	-
7	F	50	4	soft tissue injury	+	+	+	+	-	-	-
8	F	51	4	fracture	+	+	+	+	-	-	-
9	F	50	4	facture	+	+	+	+	-	-	-
10	F	21	4	soft tissue injury	+	+	-	+	-	-	-
11	F	38	4	soft tissue injury	+	+	+	+	-	+	-
12	F	44	2	soft tissue injury	+	+	+	+	-	-	-
13	F	23	2	soft tissue injury	+	+	+	+	-	+	-
14	F	18	3	soft tissue injury	+	-	+	+	-	-	-
15	F	53	4	soft tissue injury	+	-	+	+	-	-	-
16	F	33	4	soft tissue injury	+	+	+	+	-	-	-
17	F	42	4	soft tissue injury	+	+	+	+	-	-	-
18	F	32	4	none	+	+	+	+	-	-	-
19	F	38	4	none	+	+	+	+	-	-	-
20	F	38	4	soft tissue injury	+	+	+	+	-	-	-
21	F	21	2	none	+	+	+	+	-	-	-
22	F	55	2	soft tissue injury	+	+	+	+	-	-	-
23	F	28	4	none	+	-	+	+	+	-	-
24	F	47	4	soft tissue injury	+	-	+	+	+	-	-
25	F	45	4	soft tissue injury	+	-	+	+	-	-	-

Table 2. continued

ID	Sex	Age	No. affected extremities	Preceding Trauma[1]	Pain	Hyperalgesia/ hyperesthesia/ allodynia	Hypoalgesia/ hypesthesia	Autonomic Symptoms[2]	TCA	SSRI	Anti-psychotics
26	F	37	2	none	+	+	+	+	+	-	-
27	F	55	4	none	+	+	+	+	-	-	-
28	F	33	4	facture	+	-	-	+	-	-	-
29	F	65	2	none	+	-	-	+	-	-	-
30	F	47	3	soft tissue injury	+	+	+	+	-	-	-
31	F	54	3	fracture	+	-	+	+	+	-	-
32	F	18	4	soft tissue injury	+	+	+	+	-	-	-
33	F	41	3	soft tissue injury	+	+	+	+	-	-	-
34	F	26	2	soft tissue injury	+	+	+	+	+	-	-
35	F	57	4	none	+	+	+	+	-	-	-
36	F	43	3	soft tissue injury	+	+	+	+	-	-	-
37	F	56	3	fracture	+	-	+	+	-	-	-
38	F	46	3	none	+	-	+	+	-	-	-
39	M	46	3	soft tissue injury	+	+	-	+	-	-	-
40	F	40	4	soft tissue injury	+	+	+	+	-	-	-
41	F	59	4	soft tissue injury	+	+	+	+	-	-	-
42	F	24	4	fracture	+	+	+	+	-	-	-
43	F	43	4	none	+	-	+	+	-	+	-
44	F	28	2	fracture	+	+	+	+	-	-	-
45	F	40	4	soft tissue injury	+	+	+	+	-	+	-
46	F	24	3	soft tissue injury	+	+	+	+	-	-	-

[1] Preceding trauma of the first affected extremity

[2] Autonomic symptoms include edema, changes in skin blood flow (temperature or colour changes) or abnormal sudomotor activity .

TCA = tricyclic antidepressants, always used as analgesics

SSRI = selective serotonine reuptake inhibitors, always used as antidepressants

Table 3. Mean total scores and medians

	CRPS (N=46)	Conversion disorder (CD) (N=54)	Affective disorder (AD) (N=50)
PDQ-R			
- Mean (SD)	19.3 (13), (N=45)#	29.2 (13.5)	35.2 (13.8)
- Median (IQR)	14 (10.5-24)*CD, AD	26.5 (19-38.3)	37 (24.8-45)
TEC			
- Mean (SD)	4.5 (3.9)	5.4 (3.8)	3.7 (3.6)
- Median (IQR)	4 (1.8-6.3)	5 (2-8)	2 (1-6)
VRMG			
- Mean (SD)	1.2 (1.6) (N=45)#	4.2 (3.8; N=53)#	3.8 (3.1)
- Median (IQR)	0 (0-2)*CD, AD	4 (1-6.5)	3.5 (1-5)
VRMG impact rating			
- Mean (SD)	-1.9 (7.6)	-9.2 (15.8)	-8.2 (10.8)
- Median (IQR)	0 (-5-0)*CD, AD	-6 (-15-0)	-6 (-15.3-0)
DES			
- Mean (SD)	6.6 (5.8)	12 (10.9)	8.7 (7.1)
- Median (IQR)	4.3 (2.1-9.8)*CD	8.5 (4.3-16.9)	7.9 (3.6-11.4)
SDQ-20			
- Mean (SD)	30.86 (9.7)	30.7 (8.2)	23.6 (4.5)
- Median (IQR)	28.5 (25-34.3)*AD	29.5 (24-36)	22 (20-26)
SCL-90-R			
- Mean (SD)	145.6 (39.8) (N=40)#	201.2 (66.5)	204.4 (59.9)
- Median (IQR)	134 (119.3-166.5)*CD, AD	192.5 (147.8-241.5)	200 (157.5-233.5)

#: smaller sample size due to missing data

*: significantly different scores ($p<0.05$); only presented for medians, since non parametric tests were used to assess differences between groups

SD=standard deviation; IQR=interquartile range; PDQ-R=Personality Diagnostic Questionnaire-Revised; TEC=Traumatic Experiences Scale; VRMG=Recent Life Event Questionnaire ("Vragenlijst Recent Meegemaakte Gebeurtenissen"); DES=Dissociative Experiences Scale; SDQ-20=Somatoform Dissociation Questionnaire-20; SCL-90-R=Symptom Checklist-90-Revised.

The CRPS patients had significantly lower total scores on the PDQ-R, VRMG and SCL-90-R, compared to the conversion patients and patients with affective disorders. On the TEC, no significant differences were found. On the DES, the CRPS patients had a significantly lower score than the conversion patients only, and on the SDQ-20, both the CRPS and conversion patients had a significantly higher score than the patients with affective disorders.

Table 4. Correlation values between life events (TEC) and psychoform dissociation (DES) on the one hand and somatoform dissociation (SDQ-20) on the other hand

	Spearman's rho DES	Spearman's rho SDQ-20
CRPS	0.22 (p=0.15)	0.30 (p=0.04)
Conversion disorder	0.28 (p=0.04)	0.25 (p=0.07)
Affective disorder	0.30 (p=0.03)	0.22 (p=0.13)

TEC=Traumatic Experiences Scale; DES=Dissociative Experiences Scale; SDQ-20=Somatoform Dissociation Questionnaire-20

Table 5. Mean (SD) RAND-36 scores

	CRPS (N=40)	General population (N=1063)	significance
PF	15.6 (16.9)	81.9 (23.2)	p<0.005
SF	55.3 (23.2)	86.9 (20.5)	p<0.005
PR	20.0 (30.6)	79.4 (35.5)	p<0.005
ER	69.2 (41.6)	81.1 (32.3)	p<0.005
MH	72.9 (18.1)	76.8 (18.4)	p=0.19
V	49.3 (17.5)	67.4 (19.9)	p<0.005
BP	35.1 (17.7)	79.5 (25.6)	p<0.005
GHP	46.6 (19.9)	72.7 (22.7)	p<0.005
PHC	24.3 (26.0)	52.4 (19.4)	p<0.005

RAND-36= Research and Development-36; SD=standard deviation; PF=physical functioning, SF=social functioning, PR=role limitations due to physical health problems, ER=role limitations due to emotional problems, MH=mental health, V=vitality, BP=bodily pain, GHP=general health perceptions, PHC=perceived health change
An unpaired t-test was used to compare means of the CRPS group to the norm group.

Discussion

In accordance with other studies in CRPS patients[15,16,33] and chronic CRPS patients with dystonia[34] our study does not support the presence of a unique disturbed psychological profile. Compared to the general Dutch population, the general level of psychopathology was elevated in the CRPS patients in an extent similar to chronic pain patients[29] but this level was significantly lower than both psychiatric control groups. The total level of psychopathology is slightly higher as compared to earlier studies.[34,35] However, these studies had smaller sample sizes and included patients with a shorter disease duration, and moreover these patients were less severely affected by CRPS. The relatively low scores with regard to affective, dissociative and anxiety features among patients with CRPS related dystonia contrast with the study of Schrag et al.,[36] who found affective disorders in 85%, dissociative symptoms in 42% and anxiety disorders in 58% of a group of 26 patients with fixed dystonia. However, one should be cautious comparing these results as the focus of the study of Schrag et al.[36] were patients with fixed dystonia of which a minority met the IASP-criteria of CRPS, while also different instruments were used.

CRPS patients reported only few relevant life events in the year preceding the symptom onset, but more than three quarters of the patients reported at least one traumatic experience in their early history. In more than half of the patients at least one form of physical, emotional or sexual abuse, or neglect had occurred. No official normative data of the TEC are available, but it has been administered in 73 Dutch students and in the general population (N=147).[37] The total TEC scores of the CRPS, CD and AD groups we studied are much higher than those of the students and the general population. An interesting observation is that the total score of the CRPS patients is higher than the total score of the AD group and than the score of a group of various female psychiatric patients (eating disorders, substance abuse disorders and ADs, among others) in an earlier study.[38] Possibly, this is caused by the fact that one of the included traumas is the experience of intense pain, which is inherent to CRPS. However, when the data are corrected for this type of trauma, the total mean score for the CRPS patients is 3.89, which is still higher than the score of the AD patients of the current study. One may therefore conclude that in patients with CRPS related dystonia early traumatic experiences are more prevalent.

An association between somatoform dissociation and lifetime traumatic experiences has been suggested earlier, both in clinical[20,24,39] and non-clinical populations.[37] In our study, we also found a significant, though moderate (r=0.30) association between the number of traumatic life events and levels of somatoform dissociation in CRPS patients. The elevated SDQ-20 scores that we found among the CRPS patients are

in the range of patients with somatoform disorders.[40] These results suggest similarity to the conversion disorder patients and may indicate that in chronic CRPS patients dissociative phenomena may be present. Though the association between traumatic experiences and somatoform dissociation in this study is only moderate, these results generate interesting hypotheses for further research. Also, a 0.3 correlation is considered meaningful in the social sciences.[41] A relationship between psychological trauma and physical complaints, such as lung diseases,[42,43,44] peptic ulcer,[43] diabetes,[43,44] cardiac disease[43,44] and headache[44] has been found, yet also a relation between trauma and the severity of 'medically unexplained symptoms', as chronic pelvic pain,[45,46] irritable bowel syndrome,[47,48,49,50] pseudo-epileptic seizures,[48] chronic fatigue[51] and somatization disorder,[52] has been found in previous studies. However, it should be noted that the SDQ-20 scores of CRPS patients are possibly inflated because some items of the SDQ-20, such as voiding symptoms and feelings of numbness, are features known to be associated with CRPS.[4,53]

The current study clearly shows that the CRPS patients experience less personality pathology than both psychiatric control groups. Personality traits of the schizoid, obsessive-compulsive, borderline, paranoid and schizotypical personality disorders were most prevalent among the CRPS patients, which partly corresponds to results found by Monti et al.[54]

In contrast to our study, Shiri et al.,[17] found no significant differences in the psychological profiles of CRPS patients and CD patients. Possible explanations for these conflicting results include the use of different instruments and the smaller sample size (17 CRPS patients and 20 CD patients). The predominance of male CRPS patients (94%) in the study of Shiri and colleagues[17] is conspicuous, but the difference in gender distributions between these studies is an unlikely explanation for the differences in results in view of the fact that in general both CRPS-1 and CD are more frequent among women.

The CRPS patients in our study reported poorer general health and quality of life as compared to the general population. The general health score of the CRPS patients in the current study, however, is similar to those reported for patients with other causes of chronic pain.[55]

One of the strengths of this study is the applied extensive set of psychological instruments. Additionally, we were able to compare our patients with two psychiatric control groups. Some limitations of the present study should also be noted. Data was collected retrospectively and therefore no data on premorbid psychological symptoms and disorders are available. In this study self report instruments were used. Reported life events and other psychological symptoms were not confirmed by a clinical examination, and were not verified with third parties or authorities. Also, the mean disease duration of the CRPS patients was 10.1 years, much longer than in the conversion disorder

group, and it cannot be ruled out that some patients may have developed secondary psychological disorders during this period. Here recall bias could also have played a role since patients were asked about life events which occurred in the year preceding the first signs and symptoms. Also, the results of this study cannot be generalized to acute or milder forms of CRPS, as the CRPS group consisted of severely affected patients with a long mean disease duration. Next, due to the severity of their dystonia, some patients were not able to complete the questionnaires themselves. In these cases they were orally administered by a trained research nurse, which may have led to social desirable answers. Lastly, a normal control group was not used.

In summary, CRPS is a multifactorial condition where, aside biological factors, psychological and social factors may play a role in the onset or development of chronicity of the condition. Although in this study patients with CRPS related dystonia showed elevated scores on some of the scales we used, there does not seem to be a unique psychological profile on a group level, and only few similarities between the profiles of patients with CRPS and CD were found. Early traumatic lifetime experiences were frequently reported and may be a possible, though not necessary, predisposing factor for CRPS-related dystonia.

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5

Hyperacusis in patients with Complex Regional Pain Syndrome related dystonia

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Abstract

Introduction: In Complex Regional Pain Syndrome (CRPS), patients may have manifestations of central involvement, including allodynia, hyperalgesia or dystonia. We noted that more severely affected patients may experience hyperacusis, which may also reflect central involvement. Aim of this study is to evaluate the occurrence and characteristics of hyperacusis in patients with CRPS related dystonia.
Methods: Presence of hyperacusis, speech reception thresholds (SRT), pure-tone thresholds (PTT) and uncomfortable loudness (UCL) were evaluated in 40 patients with CRPS-related dystonia.
Results: PTT and SRT were normal for all patients. Fifteen patients (38%) reported hyperacusis and this was associated with allodynia/hyperalgesia and with more affected extremities. UCLs of patients with hyperacusis were significantly lower than UCLs of patients without hyperacusis.
Conclusion: Hyperacusis is common among severely affected patients with CRPS related dystonia and may indicate that the disease spreads beyond those circuits related to sensory-motor processing of extremities.

Introduction

Complex Regional Pain Syndrome (CRPS) is frequently preceded by a trauma (70-90%). In the acute phase, the clinical presentation is dominated by various combinations of sensory and autonomic symptoms and signs.[1,2] Some patients with chronic CRPS may also develop movement disorders (MDs) like tremor, myoclonia and dystonia.[3]
Because of our clinic's special interest in MDs and CRPS, we had the opportunity to evaluate the more severely affected patients in whom CRPS evolved into a disabling disorder with prominent dystonia of multiple extremities. In the course of these evaluations, we noted that some patients reported hyperacusis,[4] that is, an intolerance of ordinary sound levels. Hyperacusis is primarily associated with painful sensations to sound, which eventually may result in avoidance-like behavior, whereas phonophobia is an anxious sensitivity towards specific sound, largely independent of its volume.[5] Contrary to phonophobia, hyperacusis is not directly related to fear to sound.[6] Hyperacusis can arise from damage to the inner ear and 8th nerve, but has also been associated with central nervous system involvement as may occur in migraine.[7,8]
In CRPS, patients may experience an increased response to a painful stimulus (hyperalgesia) or even pain when the skin is gently touched (allodynia). Both sensory features have been associated with abnormal excitability of nociceptive neurons within the central nervous system, a process known as central sensitization.[9] Pathophysiological studies in CRPS have provided evidence of functional changes at different levels of the central nervous system changes.[10,11]
Taken together, the increased sensitivity to ordinary sound levels in patients with CRPS may suggest that this is yet another manifestation of central involvement in this disorder. Against this background we evaluated the occurrence and characteristics of hyperacusis in patients with CRPS related dystonia.

Methods

Patients

Patients with a diagnosis of CRPS and dystonia in one or more extremities who were referred to our department for treatment of dystonia between January 2000 and May 2006, were included in this study. Patients were generally referred from pain clinics and from departments of anaesthesiology, rehabilitation medicine and surgery. Patients had to meet the CRPS diagnostic criteria of the International Association for the Study of Pain (IASP).[12] According to these criteria patients must have (1) continuing pain, allodynia or hyperalgesia, in which the pain is disproportionate to any inciting event, (2)

evidence at some time of oedema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain, and (3) no condition that would otherwise account for the degree of pain and dysfunction. Exclusion criteria were other disorders that could cause auditory impairment. The study protocol was approved by the hospital ethics committee and all patients gave informed consent.

Audiogram

Pure-tone audiogram thresholds (PTT), uncomfortable loudness (UCL) and speech reception thresholds (SRT) were assessed with an ENT audiometer by a certified audiologist using a standard method.[13,14] Briefly, for the determination of PTT, patients wearing a headphone had to press a button when they heard a tone in the frequency range of 250-8000 Hz that was presented at 5 dB increments (within the range of 0 dB to 120 dB). To establish the patient's UCL, tones were presented in similar manner as for determination of the PTT and patients had to indicate when they considered the sound level as uncomfortably loud. The speech reception threshold was determined with the standard CVC (Consonant-Vowel-Consonant) word list on CD (prerecorded female speaker) of the Dutch Society of Audiology.[15] All words were balanced on a rms level, sub-lists were homogeneous with regard to speech reception scores and normative values were available. Each list consisted of equivalent sub-list of 11 Dutch three-phoneme monosyllables. Based on the individual pure tone threshold, tests were done at a fixed presentation level around the pure tone threshold. The first list of words is always presented at a level of +20 dB above the threshold. For most subjects this will result in a 100% phoneme score. Afterwards, lists are presented at levels in steps of 10 dB down until the subject can hardly understand the tokens and reaches a score below 50%. The threshold is then determined by simple linear interpolation of the percentages found for the levels just above and below 50%.

For the PTTs and UCLs a low Fletcher Index (FI-low: mean over the frequency range 500 Hz-2000 Hz) and a high Fletcher Index (FI-high: mean over frequency range 1000 Hz-4000 Hz) were calculated. In general, normal values for the SRT and PTT do not exceed 20dB.[16] An UCL threshold of 100 dB is considered normal and values below 100 dB indicate the presence of hyperacusis.[17]

Clinical characteristics

Demographic and clinical information was collected and included pain intensity, number of affected extremities, type of motor impairments, presence of allodynia or hyperalgesia, and presence of hyperacusis. Additionally, the Pain Coping and Cognition List (PCCL) was administered.[18] The PCCL includes a subscale on pain catastrophizing (12 items), which was used as an approximate to assess the potential relation between a more focused attention to external stimuli and hyperacusis.

Data analysis and statistics

Data were analyzed with SPSS 12.01 (SPSS Inc., 2003), using parametric tests for normally distributed continuous data and non-parametric tests for other data. Pearson's correlation coefficient was used to compare SRT, PTT, and UCL between both ears of each patient. The significance threshold was set at $p<0.05$.

Results

Demographic information and CRPS characteristics of the forty included patients are presented in table 1, whereas table 2 enlists the differences in CRPS characteristics between patients with and without hyperacusis.

Since the correlations of SRTs, PTTs, and UCLs (both for FI-low and FI-high) between the right and left ear of each patient were high (all > 0.7; $p< 0.001$), we used the mean thresholds of both ears in the subsequent analyses. The SRT and the PTT (FI-low and FI-high) for all patients were within the normal range (Table 3). The mean UCL for both FI-low and FI-high were significantly lower ($p <0.001$ for both thresholds) in our patient group compared to the normal population value of 100 dB.

Patients with hyperacusis had significantly lower UCLs at all the indicated frequencies compared to patients without hyperacusis (Figure 1). Disease duration did not differ significantly between patients with hyperacusis (13.1 years) compared to patients without hyperacusis (10.4 years; $p = 0.365$). Seven of the 15 patients with hyperacusis reported tinnitus.

Thirty-one patients had 3 or 4 affected extremities of which 15 reported hyperacusis. Interestingly, none of the nine patients with 1 or 2 affected extremities reported hyperacusis (Fisher's exact test, $p =0.015$). However, patients with 1 or 2 affected extremities did not differ significantly in UCL thresholds (FI-high nor FI-low) from patients with 3 or 4 affected extremities.

Patients without hyperalgesia and/or allodynia less frequently reported hyperacusis compared to patients with these sensory symptoms (Chi-square; $p =0.026$). The odds ratio on hyperacusis in patients with hyperalgesia / allodynia was 7.0 (95% CI: 1.7-12.4). The UCLs did not differ significantly for both FI-low and Fl-high between patients with hyperalgesia/allodynia and patients without these symptoms.

Patients with hyperacusis had lower scores on the pain catastrophizing subscale of the PCCL (2.5 vs 3.2; $p < 0.05$).

Table 1. Demographic data and CRPS characteristics of patients.

Number of patients	40
Female/Male	38/2
Mean (SD) age in years	41.9 (10.2)
Mean (SD) duration of complaints (years)	11.4 (7.5)
Type of onset	
unknown	11
contusion	10
fracture	10
operation or IV	9
Location of onset	
Upper extremity (L/R)	6/9
Lower extremities (L/R)	9/16
Number of affected extemities	
1	2
2	7
3	12
4	19
Spreading pattern	
none	2
ipsilateral	22
heterolateral	12
diagonal	4
Mean (SD) VAS pain (0-100 mm)	71.4 (16.3)
Movement Disorders	
dystonia	21
dystonia + tremor	6
dystonia + myoclonia	11
dystonia + tremor + myoclonia	2
Allodynia and/or hyperalgesia	
Yes	25
No	15
Hyperacusis	
Yes	15
No	25

VAS, Visual Analogue Scale

Table 2. Differences between patients with and without hyperacusis

	No Hyperacusis	Hyperacusis	P-value
Number of patients	25	15	
Female / Male*	25 / 0	13 / 2	0.061
Mean (SD) age in years**	42.7 (9.6)	40.6 (11.3)	0.538
Mean (SD) disease duration in years**	10.4 (4.9)	13.1 (10.5)	0.365
Type of onset			
unknown	8	3	
contusion	7	3	
fracture	4	6	
operation or IV	6	3	
Location of onset			
Upper extremity (L/R)	3/5	3/4	
Lower extremities (L/R)	4/13	0/8	
Number of affected extemities			
1	2	0	
2	7	0	
3	6	6	
4	10	9	
Spreading pattern			
none	2	0	
ipsilateral	12	10	
heterolateral	9	3	
diagonal	2	2	
Mean (SD) VAS pain (0-100 mm)**	68.7 (16.1)	75.4 (16.4)	0.278
Movement Disorders			
dystonia	15	6	
dystonia + tremor	5	1	
dystonia + myoclonia	4	7	
dystonia + tremor + myoclonia	1	1	
Allodynia and/or hyperalgesia*			
Yes	13	13	0.026
No	12	2	

* Chi-square ** T-test for independent samples

Table 3. Values of thresholds

Measurement	Mean value (dB)	95% CI
PTT FI-Low	12.1	8.9;15.4
PTT FI-High	15.5	11.4;19.5
SRT	10.3	7.7;12.9
UCL FI-Low	79.9	71.4;88.3
UCL FI-High	78.9	70.4;87.5

The means and 95% confidence interval (CI) of the thresholds for all 40 patients. PTT: pure one threshold; SRT: speech reception threshold; UCL: uncomfortable loudness; FI-low/high: low/high fletcher index.

Figure 1. UCL levels of patients with and without hyperacusis

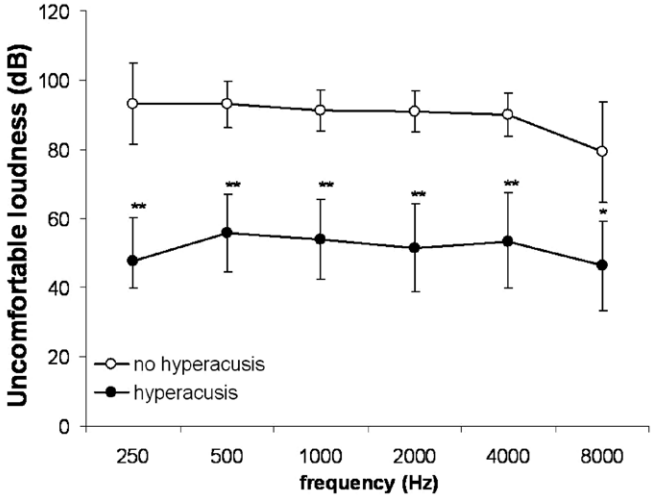

Figure 1: Uncomfortable loudness levels with 95% confidence interval in CPRS patients with (N=15) and without hyperacusis (N=25); ** $p < 0.001$, * $p < 0.05$, compared to patients without hyperacusis. High and low fletcher index for patients with hyperacusis (52.6 dB and 53.8 dB, respectively) were significantly lower ($p<0.001$) compared to the high and low fletcher Index of patients without hyperacusis (91.0 dB and 91.7 dB, respectively).

Discussion

Although our findings are limited to an extreme phenotype, to the best of our knowledge this is the first study to evaluate hyperacusis in CRPS. Thirty-eight percent of the patients with CRPS related dystonia in our study reported hyperacusis, whereas the prevalence of hyperacusis in the general population is less than 2%.[19] Auditory function, evaluated by means of the PTT and SRT, showed no differences between the patients and general population data. UCLs of CRPS patients not experiencing hyperacusis were normal. In contrast, UCLs of patients with hyperacusis were significantly lower than UCLs of patients without hyperacusis. It is unlikely that the presence of hyperacusis is explained through a more focussed attention to external stimuli, since then also higher scores on pain catastrophizing would have been expected in patients with hyperacusis compared to patients without hyperacusis, but, surprisingly, the opposite was found.

Interestingly, patients with hyperacusis more often experienced allodynia and/or hyperalgesia, which are manifestations of central sensitization. This phenomenon concerns the increased sensitivity of spinal neurons, despite a lack of change of afferent input.[20] Patients with hyperacusis also had more extremities with dystonia, which is associated with central disinhibition.[21,22] The degree of spread of dystonia, therefore likely reflects a marker of severity of central involvement. Although the difference was not significant, patients with hyperacusis had a mean duration of disease of 2.7 years longer than those without hyperacusis, which may hint at the possibility that with further progression of the disease, some of the patients without hyperacusis in this study ultimately would develop hyperacusis. Together, the sensory and motor features of this phenotype provide circumstantial evidence that hyperacusis in these patients initiates centrally. The high correlations of SRTs, PTTs, and UCLs between both ears in each patient make an unilateral peripheral cause unlikely and further support the central involvement in hyperacusis. However, the question remains how the pathophysiology of hyperacusis and the central features of CRPS intersect.

Key to central sensitization is the disturbed inhibitory-excitatory balance, which is associated with multiple biological changes in the central nervous system. These biological changes may include increased activity in excitatory pathways where substance P, excitatory neurotransmitters and adenosine triphosphate act via voltage-gated calcium channels and/or diminished activity in inhibitory pathways via gamma-aminobutyric acid (GABA) and glycine.[23] Interestingly, these neurotransmitters and neuropeptides not only play a role in synaptic transmission of the auditory system, but also act as tropic agents that modulate auditory signal processing as a results of sensory experience.[24,25] By altering auditory type I neural excitability to glutamate, these neuropeptides, for example, could induce hyperacusis and contribute to the induction, maintenance, or

exacerbation of tinnitus in the auditory periphery.[26]
In CRPS, central sensitization may spread in an ipsilateral somatotopic distribution up the neuraxis to involve nociceptive processing at the level of the thalamus or higher cortical centers.[27] Because different sensory inputs converge at the level of the thalamus, central sensitization may affect auditory circuitry. On the other hand, hyperacusis in our patients was related to the perception of discomfort, and not to the sound perception threshold. Hence, the "annoyance factor" of hyperacusis may hint at a role of the limbic activation as has been implicated for other features of CRPS and tinnitus.[28-31]
A potential limitation of this study is that the included patients reflect an extreme phenotype of CRPS, limiting any conclusion regarding the prevalence of hyperacusis in CRPS patients in general. The association between hyperacusis and dystonia could be more thoroughly evaluated if data regarding the occurrence of hyperacusis in severely affected patients without dystonia would have been available. It is also important to realize that the assessment technique of evaluating UCL thresholds relies on patient-provided information, rendering the findings sensitive to subjective influences. Our findings may stimulate the development of objective assessment techniques that aim to evaluate manifestations of central sensitisation in the auditory system.
In conclusion, we found that hyperacusis is common among severely affected patients with CRPS related dystonia. Hyperacusis in these patients may reflect the spreading of central sensitization to auditory circuitry.

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6

Spatiotemporal integration of sensory stimuli in Complex Regional Pain Syndrome and dystonia

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Abstract

Objective: The aetiology of dystonia in Complex Regional Pain Syndrome (CRPS) is incompletely understood. In primary dystonia, somatosensory evoked potentials (SSEP) after spatially or temporally separated stimulation revealed impaired central sensory integration. Information on somatosensory processing in dystonia in CRPS patients may provide better insight in the underlying pathophysiological mechanism.
Methods: We studied 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.
Results: 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.
Conclusions: Central sensory integration of proprioceptive afferent input is normal in patients with CPRS-related dystonia. Other mechanisms may underlie the development of dystonia in this disorder.

Introduction

Complex Regional Pain Syndrome (CRPS) is commonly known as a disorder that is preceded by a minor to severe trauma to an extremity in the absence of an obvious nerve lesion and occurs more frequently in women.[1-3]

There is compelling evidence indicating that aberrant inflammation plays an important role in the acute phase of CRPS.[4,5] In some patients, the acute phase of CRPS may lead to a new phase called central sensitisation which is associated with neurochemical changes, functional alterations of excitatory and inhibitory connections, cell death of neurons and interneurons, and sprouting of new connections in the spinal cord.[6] Such changes may have important influences on sensory processing and movement control. Indeed, central sensitization is typically associated with chronic pain, allodynia, hyperalgesia and about 20% of the CRPS patients develop dystonia which may spread to multiple extremities.[6-8] Traditionally, dystonia is associated with basal ganglia dysfunction, but recent studies have broadened the concept of dystonia by defining it as a disorder of neural circuits that mediate sensory-motor integration as opposed to a disorder of a single brain structure.[9-11] In line with this new concept, several neurophysiological studies in CRPS-related dystonia have found evidence of impaired inhibition at the spinal cord and motor cortex.[12-14]

The recording of somatosensory evoked potentials (SSEP) in a spatially or temporally separated stimuli design is another method to evaluate cortical disinhibition. In primary segmental or generalized dystonia, this approach has revealed evidence of impaired cortical inhibition.[15,16] In one study, SSEPs were recorded after stimulating the median and ulnar nerves both separately and simultaneously.[15] In normal subjects, adding SSEPs obtained separately for the two nerves resulted in amplitudes that were higher than when the two nerves were stimulated simultaneously, showing that there is a cortical 'competition'. In dystonia patients this effect was less pronounced, which was explained as a defect of surrounding inhibition. In another study, SSEPs were recorded after single shocks and after pairs of shocks.[16] The response to the second of the two shocks is normally lower in amplitude than that to the first one, but this effect was less pronounced in patients with dystonia, supporting the concept of cortical disinhibition. It is not known whether such changes also occur in secondary forms of dystonia such as dystonia associated with CPRS. The current study therefore applied SSEP's with temporal and spatial separated stimuli and their interactions in CRPS-related dystonia to evaluate the integrity of cortical proprioceptive afferent processing.

Patients and methods

Patients and controls

We studied SSEPs in 33 consecutive CRPS patients (table 1, 32 women, one men, age range 18-60, mean age 39.7 years) in whom dystonia progressed to a multifocal or generalized distribution and 19 healthy controls (19 women, age range 23-55, mean age 40.2 years). All patients fulfilled the criteria for CPRS of the International Association for the Study of Pain (IASP).[17] All patients had tonic dystonia of at least two extremities including one upper extremity. In the majority of patients dystonia was limited to the distal extremity and mostly involved flexion of digits and wrists in the arms, and inversion and flexion postures in the feet. In a minority of patients, dystonia extended proximally to either elbows or shoulders, and knees or hips.

None of the patients had a history of birth trauma or abnormal development. Other causes of dystonia had been excluded using appropriate blood and imaging studies (computed tomography, magnetic resonance imaging) of the spinal cord and brain. Patients were allowed to continue current medication. Informed consent was obtained according to the Declaration of Helsinki and the study was approved by the ethical committee of the Leiden University Medical Center.

SSEP acquisition

SSEPs were recorded using a Nicolet Viking III P (Nicolet Biomedical, Madison, USA). Patients were instructed to lie supine on an examination couch. Electrical stimuli of 0.2 ms duration were given to the median and ulnar nerves at the wrist of the affected arm in the patient group and the right arm in the control group. The sampling rate was 10.000 per second. Stimulus intensity was adjusted to result in a small twitch of the hand muscles innervated by the nerve in question. Stimulation frequency was 4.7 Hz. Each SSEP consisted of a four-channel recording (30-1000 Hz bandpass filter): Erb's point; a cervical lead aimed at the N14 peak, and the other two recorded ipsilateral and contralateral cortical activity. For all leads a 100 ms period was recorded.

SSEPs were acquired with two sessions of 350 stimuli which allowed reproducibility to be judged visually before the automated analysis (see below). We used three 'temporal' settings, consisting of single shocks, paired shocks with an interstimulus interval (ISI) of 20 ms and paired shocks with an ISI of 40 ms. The single shocks will further be labeled as having an ISI of 0 ms. We used three spatial settings: stimulation of the median nerve, of the ulnar nerve, and of both nerves together. All combinations were studied with nonrandom intervals, resulting in 9 SSEPs.

Table 1. Demographics of 33 patients with CRPS and dystonia.

Characteristic	Value
Females - no (%)	32 (97)
Disease duration, mean (SD) - years	9.0 (6.4)
Age at assessment, mean (SD) - years	39.7 (10.9)
Age at onset of CRPS, mean (SD) - years	30.7 (10.0)
Affected extremities with CRPS- no	
2	10
3	7
4	16
Affected extremities with dystonia- no	
2	16
3	6
4	11
Concomitant oral medication – no.(%)	
Antidepressants	10 (30)
Baclofen	11 (33)
Benzodiazepines	12 (36)
Anticonvulsant drug	4 (12)
Acetaminophen or NSAIDs	14 (42)
Opiods	14 (42)

SSEP analysis

Responses to single stimuli were subtracted from those obtained following temporal paired stimuli (Figure 1). This procedure resulted in SSEPs that started at the onset of the second stimulus, and that represent neural activity resulting only from the second of the paired stimuli. Afterwards, SSEPs following median and ulnar nerve stimulation were summed separately per ISI (Figure 2). This resulted in four groups of SSEPs representing: 1. median nerve stimulation, 2. ulnar nerve stimulation, 3. simultaneous stimulation of median and ulnar nerves (labelled as 'simultaneous'), and 4. the mathematical sums of the SSEPs obtained separately for median and ulnar nerves (labelled 'nonsimultaneous'). Grand averages were constructed to aid visualization of

responses. The result of these procedures was 12 SSEP's per subject: for each of the three temporal conditions ISIs (0, 20 and 40 ms) there were four spatial variants (median, ulnar, simultaneous and nonsimultaneous).
Peaks were analysed objectively using a computer programme (written in Matlab, The Mathworks, Natick, version 6.1.0.450, release 12.1). For example, Erb's peak was identified as the point of maximum electrical potential in an 8-12.5 ms window in the appropriate channel. Beginnings and end of these windows were based on inspection of grand averages. A local miminum just following the identified maximum was located in a 10-17.5 ms window in the same channel, and Erb's peak amplitude was defined as the difference in voltage between the two points. The N14 peak was identified using a local maximum in a 10-17.5 ms window, compared to a local minimum in a 12.5-22.5 ms window, similarly as for Erb's peak. For the N20 peak, a 15-22.5 ms peak was used, and its amplitude was compared to the N25 local minimum, found with a 20-27.5 ms window. Additional later potentials in the cortical leads were identified using a 22.5- 42.5 ms lead (N35) and a 32.5-50 ms window to help measure N35 amplitude. This was done for ipsilateral as well as for contralateral cortical leads. Peaks were considered absent if there was no local maximum or minimum, i.e., if the point of maximum potential coincided with an edge of the search window. Interpeak latencies were calculated for the Erb-N14 latency and the N14-N20 latency.

Statistical analysis
As amplitudes and latencies showed a skewed distribution a logarithmic transformation was performed. Subsequently, the analysis was carried out in the following order:
1. Latencies and amplitudes obtained after stimulation with single shocks of the median and ulnar nerves separately were first descriptively evaluated. Differences between SSEPs of the median and ulnar nerves were investigated with the paired samples t-test. Differences between patients and controls were evaluated using the t-test for independent samples.
2. To evaluate temporal and spatial effects of stimulation, a linear mixed model analysis of variance was used. Amplitude of the N20 and N35 peaks were entered as the dependent variable. Spatial stimulation (simultaneous or nonsimultaneous), temporal stimulation (ISI of 0, 20 or 40 ms) and group (patient or control) were entered as fixed factors. The amplitude of the N9 peak was added as covariate to adjust for its possible effects on N14, N20 and N35 amplitudes.
Interactions were taken into account with all three factors (group x spatial x temporal), and when the factor group revealed a nonsignificant effect, the analysis was rerun without the three-way interaction of group, temporal stimulation and spatial stimulation. P-values of <0.05 were considered significant. All statistical analyses were performed with SPSS (version 12.0).

Figure 1. Scheme of SSEP analysis

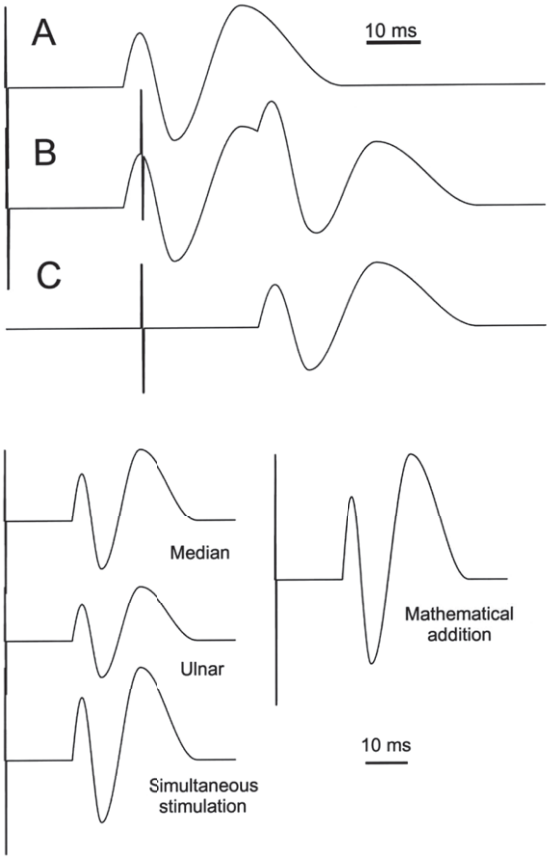
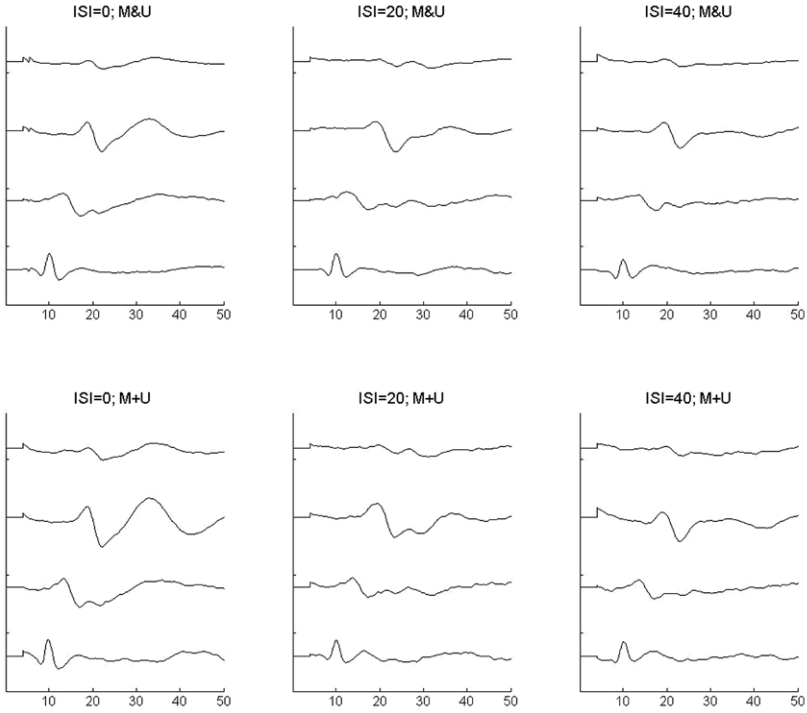


Figure 1a shows temporal effects. Simulated cortical leads are shown to explain the subtraction procedure. Panel A shows a SSEP obtained after a stimulus at the beginning of the trace. Panel B shows the result after paired stimulation with an interstimulus interval of 20 ms (recognizable through the stimulus artifact): the recording contains the added response to both stimuli. Panel C shows the remainder after trace A is subtracted from trace B: the response to the first stimulus is negated, leaving an isolated response to the second stimulus. For further analysis the first 20 ms were cut from the trace (not shown).

Figure 1b shows spatial effects. The left-hand side of the figure shows simulated cortical SSEPs obtained for stimulation of the median nerve (top), the ulnar nerve (middle) as well of stimulation of both nerves stimulated simultaneously (bottom). The right-hand side shows the mathematical addition of the two separate and non simultaneously acquired median and ulnar nerve SSEPs.

Figure 2. Grand averages of patients' SSEPs



The six panels show grand averages for SSEPS obtained with temporal manipulation (ISI 0, 20 and 40 ms) and spatial manipulation ('M&U': simultaneous stimulation of the median and ulnar nerves; 'M+U': mathematical sum of the SSEPs obtained with separate stimulation of the median and ulnar nerves). Horizontal scales denote ms. The four channels shown in each panel concern, from top to bottom, the ipsilateral cortical lead, the contralateral one, the N14 lead, and the lead showing Erb's peak.
Distances between ticks on the vertical axes denote 5 microVolt. The first 4 ms are set to zero to suppress the stimulus artefact.

Results

Descriptive analysis

In both patients and controls, the amplitudes of the N9, N14 and N20 peaks evoked after stimulation of the median nerve were significantly higher than those evoked after stimulation of the ulnar nerve ($p < 0.001$, table 2). The N35 amplitude did not differ significantly between median and ulnar nerve stimulation.

Latencies of the N14 peak were shorter after median nerve stimulation than after ulnar nerve stimulation in patients and controls (both groups; $p \leq 0.001$). This was also found for the N20 latency in controls ($p < 0.001$). Compared to controls, patients had a significantly shorter N9 latency after median nerve stimulation ($p=0.02$) and a significantly shorter N20 latency after ulnar nerve stimulation ($p=0.02$).

Spatiotemporal interaction

The temporal factor resulted in highly significant differences for all SSEP amplitudes after adjusting for the influence of the N9 amplitude ($P<0.001$ for N9, N14, N20 and N35 amplitudes). Table 3 shows that this was due to lower amplitudes following the second of the two stimuli. The spatial factor also resulted in highly significant differences for all SSEP amplitudes ($P<0.001$ for N9, N14, N20 and N35 amplitudes). Simultaneous stimulation of median and ulnar nerve evoked amplitudes that were smaller than the arithmetic sum of separately obtained SSEPs of the median and ulnar nerves.

The factor group did not show a significant interaction with either the spatial or temporal factor, meaning that patients and controls responded similarly to spatial and temporal effects. The three-way interaction did not result in significant differences for any peak, so the analysis was rerun without interactions with group. The interaction between the spatial and temporal factors did not show significant differences for SSEP amplitudes ($p= 0.92, 0.27, 0.18$ and 0.30 for N9, N14, N20 and N35 amplitudes respectively). The interaction between the factor group and the factor spatiotemporal stimulation was not significant either. Within patients, there was no significant interaction between the use of benzodiazepines or baclofen and the factor spatiotemporal stimulation.

Table 2. Median values and interquartile range of amplitudes (μV) and latencies (ms) of median and ulnar nerve SEP components in controls and patients

		Control subjects			Patients			Patients vs Controls	
		Median	Ulnar	Median vs Ulnar p-value	Median	Ulnar	Median vs Ulnar p-value	Median p-value	Ulnar p-value
N9	amplitude	3.42 (2.40)	1.70 (1.15)	<0.001	2.42 (2.76)	1.19 (1.02)	<0.001	0.07	0.38
	latency	104 (5.50)	108 (10.0)	0.12	101 (8.8)	102 (9.0)	0.23	0.04	0.14
N14	amplitude	2.57 (0.90)	1.57 (0.65)	<0.001	2.37 (1.70)	1.25 (0.93)	0.02	0.62	0.07
	latency	137 (7.5)	145 (4.0)	<0.001	134 (10.8)	143 (19.0)	0.001	0.09	0.55
N20	amplitude	2.59 (2.55)	2.42 (1.29)	<0.001	2.92 (2.53)	2.28 (1.87)	<0.001	0.76	0.50
	latency	191 (9.0)	197 (5.0)	<0.001	189 (8.8)	192 (14.0)	0.50	0.39	0.02
N35	amplitude	2.28 (1.12)	2.46 (1.32)	0.64	2.35 (2.62)	1.80 (1.98)	0.06	0.53	0.08
	latency	323 (35.0)	336 (31.8)	0.09	338 (36.0)	334 (24.0)	0.94	0.46	0.89

Table 3. Median values and interquartile range of N20 and N35 SSEP amplitudes (μV) after spatiotemporal stimulation in controls and patients.

			Temporal stimulation		
			Interstimulus interval		
	SSEP Amplitude		0ms	20ms	40ms
Simultaneous stimulation of median and ulnar nerve (spatial stimulation)	N20	controls	3.46 (3.38)	3.55 (4.20)	2.88 (3.20)
		patients	3.03 (2.81)	3.17 (2.62)	2.70 (2.35)
	N35	controls	2.92 (1.78)	2.71 (1.96)	1.79 (1.49)
		patients	2.54 (1.67)	1.47 (2.17)	1.83 (1.54)
Mathemetical sum of individual stimulation of median and ulnar nerve	N20	controls	4.49 (3.76)	4.58 (2.89)	4.00 (1.23)
		patients	4.33 (4.05)	3.51 (2.92)	2.82 (1.66)
	N35	controls	4.37 (2.44)	3.07 (2.85)	2.39 (2.29)
		patients	3.82 (3.63)	2.71 (2.20)	2.44 (2.90)

The temporal factor resulted in highly significant differences for the N20 and N35 amplitudes after adjusting for the influence of the N9 amplitude ($P<0.001$). The spatial factor also resulted in highly significant differences for the N20 and N35 amplitudes ($P<0.001$).

Discussion

In patients with primary dystonia SSEPs after spatial or temporal separated stimuli have yielded evidence of impaired cortical inhibition.[15,16] Against this background we evaluated the presence of disinhibition in the sensory cortex by studying SSEPs obtained after spatiotemporal stimuli.

Contrary to the reported findings in patients with primary dystonia, spatial and temporal SSEP stimulation did not reveal a difference between CRPS patients with dystonia and controls. The temporal factor proved highly significant, in that the second of two stimuli given with a short interval evoked a potential of lesser amplitude than the first one. As such, clear evidence of differential processing was obtained, involving habituation or inhibition of successive stimuli. Stimuli given simultaneously to two different nerves resulted in amplitudes that were smaller than the sum of two SSEP's obtained separately, indicating 'competition' for cortical processing. However, both approaches did not differ between groups. As the amount of sensory input with

spatiotemporal stimulation to the somatosensory system is larger than with temporal or spatial stimulation alone, one would expect additional suppression of SSEP's. However, interactions of spatial and temporal effects did not reveal an additional suppression of amplitudes, in patients nor controls. Possibly, this is due to saturation or habituation of the gating capacity of the somatosensory system.

The current results thus indicate that sensory processing of proprioceptive input is normal in patients with CPRS and dystonia. One other study on CRPS patients measured EMG responses to TMS preceded by paired median nerve stimulation and found suppression similar to healthy controls suggesting a normal sensorimotor interaction.[18] Since spatial and temporal stimulation in both our groups suppressed SSEP amplitudes, methodological issues are an unlikely explanation of our findings. It is also unlikely that medication was of influence, as we found no significant effects of the use of benzodiazepines or baclofen. We don't think that that our results were influenced by ongoing dystonic contraction of the muscles in the affected arm. Gantchev et al. studied this issue in healthy subjects and found no difference between the "hold" condition (isometric contraction) and rest.[19]

The failure to demonstrate abnormalities in our patients may be interpreted as evidence in favour of the notion that psychogenic factors contribute to the dystonia in many of these patients.[20] However, seventy-three percent of the patients in our study also participated in a case-control study, in which their psychological characteristics were compared with those of patients with affective and conversion disorders.[21] In line with another case-control study[22], this study found no evidence to support a distinct psychological profile in patients with CRPS-related dystonia.

To the best of our knowledge, SSEPs after spatial or temporal separated stimuli have not been applied to other secondary causes of dystonia and it may well be that disinhibition of the sensory cortex is an exclusive finding of primary dystonia. In line with the concept of dystonia as a disorder of neural circuits that mediate sensory-motor integration, several studies have documented physiologic abnormalities at multiple levels of the central nervous system in dystonia of varying etiology.[9,11,23] This raises an interesting issue about the commonality of neural circuits involved in dystonia of different aetiology. The generally disappointing responses of secondary dystonia to deep brain stimulation[24], may indicate that different causes of dystonia are associated with differential circuit involvement. In CRPS,

C and Aδ-sensory nerve 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.[25] Both SP sensitized NWRs in

animal models and dystonia in CRPS patients respond to the $GABA_B$ agonist baclofen, which enhances spinal GABA-ergic inhibition.[26,27] Hence, loss of spinal GABAergic inhibition likely is an important mechanism in this type of dystonia. As SSEPs primarily depend on conduction of proprioceptive input, we can not exclude a role of abnormal processing of small fibre input in CPRS-related dystonia. Possibly, preferential stimulation of small fibres by means of laser evoked potentials[28] or by stimulation with intra- epidermal needle electrodes[29] provides a better mode to establish abnormal cortical sensory processing.

Median nerve SSEP amplitudes appeared to be larger than ulnar nerve SSEP amplitudes, a finding that was reported by others[30] and may be explained by that fact that the ulnar nerve, innervating fewer fingers than the median nerve, simply contains fewer sensory fibres. An alternative explanation resides in stimulus intensity: this was set on the basis of a motor response, and thresholds for sensory and motor responses might differ between the two nerves, perhaps because of different localisation of sensory and motor fibres in the nerves.

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-I with secondary changes at supraspinal sites of the circuit.

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7

Cerebral Activation during Motor Imagery in Complex Regional Pain Syndrome with Dystonia

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Abstract

Background: The pathogenesis of dystonia in Complex Regional Pain Syndrome (CRPS) is unclear. In primary dystonia, functional magnetic resonance imaging (fMRI) has revealed changes in cerebral networks during execution of movement.
Objectives: To determine cerebral network function in CRPS patients with dystonic postures.
Design: Assessment of cerebral processing related to both execution and imagining of hand movements with fMRI in patients and controls.
Subjects: 8 CRPS patients with dystonic postures of the right upper extremity and 17 age matched healthy controls.
Results: 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.
Conclusions: The altered cerebral activation pattern in patients with CRPS linked dystonia most likely reflects an interface between pain-associated circuitry and higher order motor control, which points at a specific mechanistic pathophysiology of this type of dystonia.

Introduction

Complex Regional Pain Syndrome type 1 (CRPS), also called Reflex Sympathetic Dystrophy (RSD), is a syndrome predominantly characterised by a variety of sensory, autonomic and trophic features[1,2]. Symptoms include pain, oedema, hyperhydrosis and impaired function. Growing evidence indicates that CRPS may also include some form of movement disorder, like tremor and dystonia[3-5].

Dystonia is characterised by involuntary sustained muscle contractions, causing twisting and repetitive movements or abnormal postures[3,6]. Functional brain imaging with PET and fMRI has provided valuable new insights in the role of altered activation of basal ganglia-cortical networks during execution of movement in focal and generalized dystonia. Underactivation of the primary motor cortex and overactivation of the somatosensory cortex, prefrontal -, premotor - and parietal cortical regions have been reported. Other studies showed an overactivation of the primary motor cortex and underactivation of the premotor cortex[7-9]. These inconsistencies may result from a combination of differences in scanning procedures, tasks and a varying degree of dystonia during motor execution. However, a distinct pathophysiology underlying different forms of dystonia may equally be an option[8].

The pathophysiology of CRPS itself remains a controversial issue[10]. Some features of CRPS favour a spinal aetiology[5], other indicate a cerebral reorganization in both the sensory and motor domain[11,12]. A recent fMRI study in CRPS, focussing on mechanical hyperalgesia, reported alterations in nociceptive, cognitive and motor processing[13]. Hitherto, no functional imaging study in dystonia of CRPS during movement execution has been performed.

In overt dystonic movement, altered sensory feedback (in particular noxious input) during painful movements is a potential confounder in functional brain imaging, which can be reduced by motor imagery, i.e. mental rehearsal of a motor act without overt movement. Previous work suggests that the volume of brain activation differs between execution and motor imagery, but the distribution of cerebral activity tends to be partly similar[14,15]. Motor imagery is used in sport to improve performance. A positive effect of motor imagery in the rehabilitation of CRPS patients has been established[16,17].

In this study we aimed to explore the distribution of cerebral activations in CRPS patients with tonic dystonia during both motor execution and imagining of movement, of affected as well as unaffected limbs. Based on the clinical resemblance with other forms of dystonia, we hypothesised to find a functional alteration in regions supporting a primary motor function, and in circuitry associated with higher-order motor control, particularly in the parietal cortex.

Subjects and methods

Subjects

Eight patients (seven female, mean age 46.4, SD 6.0 years) with CRPS related dystonia from the Leiden University Medical Center and seventeen healthy volunteers (15 female, age 42.9, SD 9.2 years), matched for age, were studied. All patients fulfilled the officially accepted diagnostic criteria for CRPS of the IASP[18]. Revisions of these diagnostic criteria are under consideration[19]. Furthermore, the presence of tonic dystonia in at least the right upper extremity was obligatory. The presence of dystonia in the CRPS-affected limb was based on the presence of prolonged muscle contractions resulting in abnormal postures or movements of the limb. In upper limb dystonia such involuntary muscle contractions resulted in typical flexion postures of the hand and fingers. In all patients a tonic stretch reflex was present. Passive stretching of the affected digits induced increased flexor activity. The dystonic limb was also always the CRPS affected limb. In five patients the right leg was also affected, in one the left leg and in one both legs (Table 1). Patients in which the left arm was affected by CRPS were excluded. Right handedness was obligatory and was assessed according to the Dutch Handedness Questionnaire[20]. The ability to perform mental imagery was assessed by the Vividness of Movement Imagery Questionnaire (VMIQ)[21]. Further assessments included a neurological examination. The T1 weighted MRI scan did not show pathology. Informed written consent was obtained and the study was approved by the Medical Ethical Committees of the Groningen and Leiden University Medical Centers.

Tasks

Subjects performed four tasks: execution and imagination of flexion/extension movements of the separate right and left wrist. The movements were performed in a vertical plane and paced at 0.5 Hz by a visual stimulus: in response to each stimulus one self-paced extension-flexion cycle was made. The forearms were positioned in pronation on pillows. All tasks were preceded by a rest condition. All conditions had a duration of 30 seconds. Three runs were performed lasting 12 minutes each. In each run, 12 response blocks were scheduled. For each subject, tasks were presented in a random, but balanced order. Subjects were monitored and videotaped during scanning. Special attention was paid to voluntary and involuntary movements of wrists. Prior to the experiment, subjects practised the tasks outside the MRI scanner. They were instructed to imagine moving their wrist freely. Their limbs were not within their field of view. After data acquisition all patients reported pain during the movement execution task. None of the patients reported pain during the imagined movements. Pain was not formally quantified by standardized questionnaires.

Functional imaging

Subjects were scanned using a 3 Tesla Philips MRI scanner (Best, the Netherlands). The following pulse sequence parameters were used: single shot EPI; 46 slices; 3.5 mm slice thickness; no gap; 224 x 224 mm field of view; 64 x 64 scan matrix; transverse slice orientation; repetition time 3000 ms; echo time 35 ms; flip angle 90°. Three runs of 240 brain volumes each were acquired, i.e. 10 volumes per 30 seconds condition block. In addition, a T1-weighted whole brain anatomical image was acquired (resolution 1x1x1 mm).

Statistical analysis

Spatial pre-processing and statistical analysis (random effects) was carried out using Statistical Parametric Mapping (version SPM2)[22]. The functional images were realigned, normalised and subsequently smoothed with an isotropic Gaussian filter using an 8 mm Full Width-Half Maximum Gaussian kernal. Head movements were more frequently seen in the patient group. This reflects the difficulties the patients had in performing the tasks. Optionally, the estimated head-motion parameters were used as covariates as described by Friston et al.[23]. Only minor differences were encountered in this comparison, indicating the presence of task-related head movements. However, areas affected by motion did not show overlap with areas activated during the tasks, demonstrating that the group result was not caused by head motion. Note, for the reported results motion correction has been applied. In the first analysis, the movement and imagining conditions of each hand were compared with rest for each single subject (first level analysis). For within-group analysis, for the patient and control group respectively, these contrasts were tested using a one sample T-test (second level analysis). For the larger control group (17 subjects), a high threshold at voxel level was used ($P < 0.05$ Family-wise Error (FWE); extent threshold ≥ 5 voxels). This avoided overlap of activations which would have blurred regional identification when thresholded at $P < 0.001$ (uncorrected). For patients (8 subjects) a threshold at $P < 0.001$ (uncorrected) was used. This was done as to look for the spatial distribution of a circuitry with general resemblance to that observed in controls. For a between-group analysis (i.e. patients compared to controls) a two-sample T-test was used ($P < 0.001$ (uncorrected)). Resulting clusters for both tests were considered significant at $P < 0.05$ (cluster-level corrected for whole brain volume).

Results

Findings on the VMIQ questionnaire (patients 110 ± 52, control subjects 83 ± 34; two-sample T-test, 2-tailed *P*=0.133) revealed no significant differences.
In both controls and patients, activated areas during imagining showed a symmetrical distribution and activation of the sensorimotor cortex was not observed. Activation in the patient group appeared to be less robust than in the controls for the four different tasks (Figure 1, Table 2). By visual inspection, it already was apparent that the patients' activation networks were most affected during imagining of motor performance with the affected hand. But direct comparison of the figures only allows observation of a trend, partly because of differences in population size (17 controls versus 8 patients). The statistical significance of differences between the two groups can only be established by formal between-group analysis. Such statistically significant differences between patients and controls were only obtained during imagining right hand movements. No statistically significant between-group differences were obtained for the three other tasks.
During imagining of right hand movements three regions were significantly less activated in patients compared with controls. No increases were seen in the patients during this task. These foci of reduced activation were distributed ipsilateral over both the middle frontal gyrus, comprising the prefrontal cortex and premotor cortex (P corrected-cluster-level 0.030, cluster size 186 voxels), and the anterior part of the insular cortex adjoining the superior temporal gyrus and the inferior frontal gyrus (*P* corrected-cluster-level 0.010, cluster size 242 voxels). In the hemisphere contralateral to the imaginary moving hand, the postcentral gyrus and inferior parietal cortex were less activated in the patient group (*P* corrected-cluster-level 0.030, cluster size 186 voxels), (Figure 2, Table 3).

Table 1. CRPS Patient characteristics

Patient	Age at scan	Sex	Preceding trauma	Disease duration in years	Affected body part	Dystonic posture	Sensory modalities	VMIQ	Movement during tasks[a]
1	44	f	local trauma*, local mannitol infusion and immobilisation°	7*, 6°	right hand°, left foot*	fist right hand, inversion/ flexion left foot	decreased touch and vibration in affected body parts, hyperpathia right arm; stereognosis intact	122	low frequency and amplitude during movement execution right
2	48	f	local trauma	8	right hand	flexion fingers, flexion hand right hand	decreased pain sense, hyperpathia and allodynia right arm; stereognosis intact	48	low frequency during movement execution right
3	42	f	head trauma	10	right arm, right foot	flexion dig 2-5, flexion right hand; inversion right foot	intact	102	low frequency and amplitude during movement execution right
4	42	f	local trauma*, years before ulnar fracture°	15*, 12°	right hand°, right leg*	flexion dig 2-5 right hand, inversion right foot	hemihypaesthesia right; stereognosis intact	81	low frequency and amplitude during movement execution right
5	55	f	1990 thrombosis right arm*, no trauma°	11*, 10°	right hand*, right leg°	extension dig 1; flexion PIP and DIP dig 2,5; extension MCP, flexion PIP and DIP dig 3,4; flexion elbow right arm; flexion toe	hyperpathia, allodynia right hand and leg; stereognosis intact	63	low frequency and amplitude during movement execution right

Table 1. continued

Patient	Age at scan	Sex	Preceding trauma	Disease duration in years	Affected body part	Dystonic posture	Sensory modalities	VMIQ	Movement during tasks[a]
6	41	m	local trauma*°	15*, 5°	right hand°, right foot*	fist and flexion right hand, inversion right foot	decreased touch, pain and position sense right hand	216	low frequency during movement execution right
7	43	f	no	9	right hand, right leg	flexion dig 4,5 right hand; inversion/flexion right foot	decreased touch and hyperpathia right side body; stereognosis intact	121	low frequency during movement execution right
8	56	f	operation*, local fracture°	11*, 9*, 7°	right arm°, both legs*	flexion dig 2-5 right hand; inversion/flexion both foot	allodynia both feet; stereognosis intact	132	low frequency and amplitude during movement execution right

[a] low frequency = 1/3 – 1/5 Hz

Table 2. Areas activated during motor execution and imagining in controls and patients, compared with rest

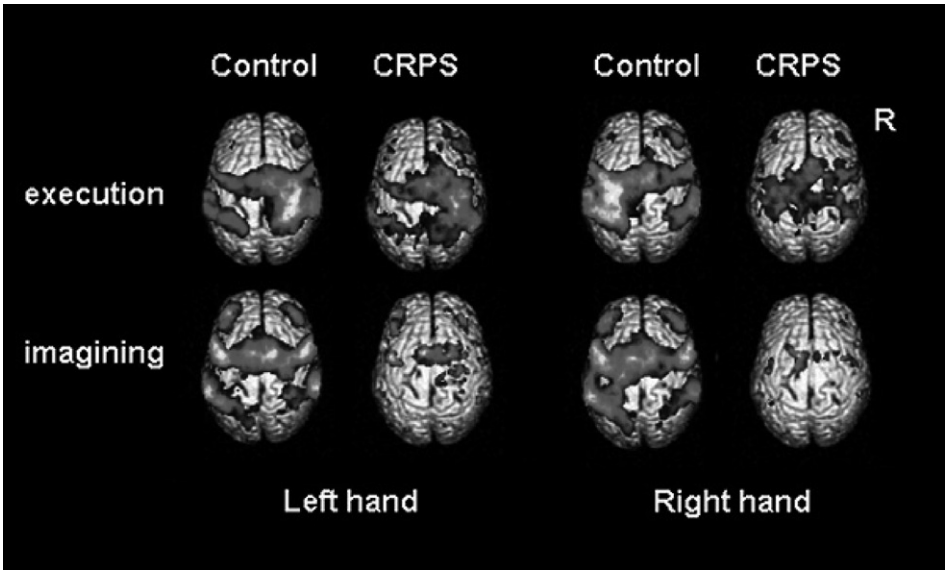
Localisation	Controls[a]								Patients[b]							
	Motor execution				Imagining				Motor execution				Imagining			
	Right		Left		Right		Left		Right		Left		Right		Left	
	Contra	Ipsi	Contra	Ipsi	Contra	Ipsi	Contra	Ipsi	Contra	Ipsi	Contra	Ipsi	Contra	Ipsi	Contra	Ipsi
Inferior frontal gyrus					+	+					+		+			+
Middle frontal gyrus					+	+	+	+			+		+		+	
preSMA					+					+	+					
SMA	+	+	+		+	+	+	+	+	+	+	+				
Premotor cortex	+		+		+	+	+	+	+	+	+					+
Cingulate gyrus	+		+						+		+	+				
Primary sensorimotor cortex	+		+						+	+	+					
Superior parietal cortex	+		+						+		+					
Inferior parietal cortex	+		+		+				+	+	+	+				
Insular cortex	+		+	+	+	+	+	+								
Superior temporal gyrus	+	+	+		+	+	+	+	+	+		+				
Temporal pole						+	+					+				
Caudatus												+				
Thalamus	+		+				+				+	+				
Putamen			+				+		+	+	+	+			+	
Globus pallidus		+							+		+	+			+	
Cerebellum		+	+	+		+	+	+	+	+	+	+				

Activations at *P* corrected on cluster-level of < 0.05 were considered significant, which is indicated by the + sign.
"Contra" denotes activation in the hemisphere contralateral to the performing limb, "ipsi" denotes activation in the hemisphere ipsilateral to the performing limb.

[a] Initial response height thresholded at voxel-level FWE < 0.05, extent threshold ≥ 5 voxels.

[b] Initial response height thresholded at voxel-level *P* uncorrected < 0.001, extent threshold ≥ 5 voxels.

Figure 1. Areas of activation in controls (n=17) and patients (n=8)



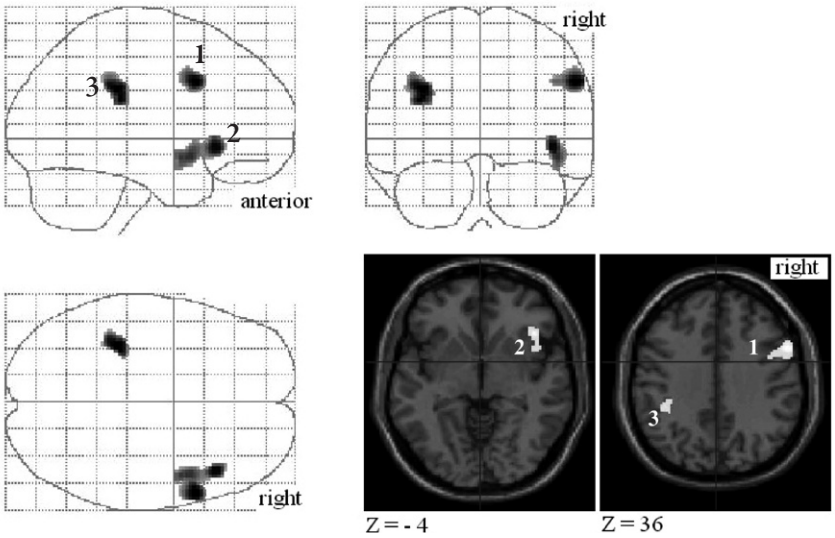
Four different tasks compared with rest condition, projected on a template rendered brain image.
P uncorrected < 0.01, extent threshold ≥ 5 voxels.

Table 3. Areas significantly less activated in patients than in controls during imagining of right hand movements

	Stereotactic coordinates							
	Ipsilateral (right)				Contralateral (left)			
Brain region (Brodmann Area)	*x*	*y*	*z*	*Z*-score	*x*	*y*	*z*	*Z*-score
Premotor cluster								
Middle frontal gyrus (BA 8,9)	56	14	36	4.15				
Premotor cortex (BA 6)	44	6	36	3.40				
Anterior peri-sylvian cluster								
Inferior frontal gyrus (BA 47)	44	24	-4	4.01				
Insular cortex (BA 13)	46	10	-12	3.69				
Superior temporal gyrus (BA 22)	46	4	-12	3.64				
Anterior parietal cortex								
Postcentral gyrus (BA 2)					-36	-32	24	4.96
Inferior parietal cortex (BA 40)					-34	-34	30	4.09

Anatomical regions, Brodmann areas and coordinates (according to the Montreal Neurological Institute) of activated clusters. Initial response height thresholded at voxel-level *P* uncorrected < 0.001, extent threshold ≥ 5 voxels. Activations at P corrected on cluster-level of < 0.05 were considered significant. Positive *x, y, z* coordinates indicate locations respectively right, anterior and superior of the middle anterior commissure.

Figure 2. Areas with reduced activation in patients compared with controls during imagining of movement of the right hand.



Areas projected on glass brain and transversal slices of a mean template image. $P < 0.05$ (volume corrected, cluster-level). (1) Ipsilateral middle frontal gyrus and premotor cortex, (2) ipsilateral anterior part of insular cortex, superior temporal gyrus and inferior frontal gyrus, (3) contralateral inferior parietal cortex and postcentral gyrus.

Discussion

Both execution and imagining of the motor task in our healthy volunteers results in activation of previously described cerebral circuitry[14,15,24]. In CRPS patients, however, the motor imagining paradigm revealed a conspicuously reduced activation of cortical networks that subserve imagining of movement of the affected limb, in comparison with controls. Only two other imaging studies have reported an imagining paradigm in dystonia patients. In a preliminary PET study idiopathic torsion dystonia patients showed a similar activation pattern as controls[25]. In a recent fMRI study on post-stroke dystonia, mental representations of movement of the affected hand resulted in overactivity of the ipsilateral inferior parietal cortex, insula, bilateral prefrontal cortex and other cortical areas[26]. Part of these regions are also involved in our CRPS patients, although we found underactivity. This difference may be due to differences in the underlying pathophysiology or the application of different scanning paradigms.

Imagining of Movement

All patients recalled the ability to perform the imagining task with their affected limb. Moreover, the ability of patients for imagining movement in general did not significantly differ from the controls, as we inferred from the VMQI questionnaire. This demonstrated the ability of the patients to perform a movement imagery task, although we have no behavioural characteristics to answer the question to what extent imagining movement of the affected hand was correct. In CRPS (without dystonia), prolonged time for imagining moving the affected body part, when compared to the not-affected body part, has previously been explained by a distorted cortical correlate of the body scheme[27,28]. Such a distorted body image has also been inferred from referred sensations[29], mislocalization of tactile stimulation [30] and the experience of an increased size of the affected limb[31].

The aforementioned behavioural findings are consistent with the idea that cortical reorganization plays an important role in CRPS [11,12]. We think it likely that changes in body scheme, associated with changes in cortical representation, play an important role in our results. By using sensory stimuli, cerebral reorganization in CRPS has also been demonstrated to occur in the nociceptive (or sensory) domain as well as in cognitive and motor domains[13,33,32]. A recently published case-report even mentioned a temporally increase in pain and swelling of the affected hand in a CRPS-patient after imagined movements[34]. Although this was not mentioned by our patients and the report was limited to one patient, it implies that symptoms of CRPS may be mediated by cortical mechanisms associated with (imagined) movement of the affected body part.

In order to comprehend the specific distribution of the regional decreases in our movement execution and movement imagining study, it is important to consider how the functions of these regions may provide a logical combination in the context of pain and disturbed motor control. The premotor cortex is related to planning and organization of movement[35]. Both impaired activation and enhanced activation in the premotor cortex during a motor task in different forms of dystonia has been reported (for an overview see[8]). The inferior parietal cortex is an association area, which receives information of different sensory modalities and thus holds a strategic position in processing space perception, body scheme and so in linking sensation to motor control[36]. The posterior part of the sensory cortex which constituted the anterior border of the parietal activation in our group is particularly involved in the proprioceptic sensation related to limb movement[37,38].

The posterior insula is known as a secondary motor area. For the anterior part of the insula, however, a relation with motor control is less obvious[39]. The latter has a dominant role in autonomic regulation. The paralimbic cortex in the anterior superior temporal sulcus, along with anterior insula and orbitofrontal cortex, have been proposed to pro-

vide an interface between limbic cortex in the medial temporal lobes and frontoparietal association cortices[36]. The anterior part of the insula and superior temporal sulcus are situated between the posterior cortex and frontal cortices, thus linking multimodal perception of stimuli and executive processes[40]. The anterior insula is involved in pathways that are critical for mental processing of pain related experiences in patients with an amputated hand during imagining of painful finger movements[41] and in a pin-prick hyperalgesia study in CRPS patients[13].
In view of the long disease duration (mean 11 years) of our patients, long-lasting pain may have induced changes on efficient motor control, reflected by a decreased activation in circuitry providing limbic access to higher-order motor control.

Execution of Movement
Motor execution of the affected side in patients showed only non significant differences between patients and controls. At first sight, this may look strange. On the other hand, the between–group comparison may not have reached statistical significance as a consequence of higher intersubject variability in the activated areas during execution. Such variability may be caused by differences in effort to move. Our most plausible explanation is the altered sensory feedback in the patients, as they experience pain when performing the movement task. This sensory feedback may result in activation of cortical areas, scaling down the areas activated in relation with the execution of movement. However, the fact that we did not find a consistently increased activation in pain-associated circuitry makes us reluctant to provide a definitive explanation in this matter.
Findings on motor execution in our patients with dystonia of CRPS, are different from those found in other causes of dystonia, although studies on dystonia, in general, have reported contradictory findings. This can often be attributed to methodological differences, but a different pathophysiology for different forms of dystonia may also be an option. In the case of CRPS, a different pathophysiology of dystonia is likely.
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.

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8

Intrathecal baclofen for dystonia of Complex Regional Pain Syndrome

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Abstract

Dystonia in Complex Regional Pain Syndrome (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.

Introduction

Complex Regional Pain Syndrome (CRPS) is a poorly understood disorder that predominantly affects women and usually is preceded by an injury or surgery[1,2]. Early clinical features of CRPS include persistent pain, swelling, increased sweating, and changes in skin color and temperature and may reflect an aberrant inflammatory response to trauma[2,3]. Various studies have reported the involvement of perturbed functions of both C and A delta fibers of sensory nerves (neurogenic inflammation) and also a perturbed function of the local immune system in the skin[4-7]. Several other studies have reported axonal degeneration in small distal nerve fibers of patients with CRPS[8-10]. Aberrant processing of spinal and supraspinal sensorimotor neural networks are held responsible for the development of chronic pain, allodynia, hyperalgesia, and movement disorders[11,12]. Approximately 20% of patients with CRPS develop dystonia[2,13,14], which is defined as abnormal involuntary muscle contractions that cause twisting or repetitive movements or sustained postures[15]. Dystonia in CRPS is predominantly characterized by fixed flexion postures, frequently has a delayed onset and may spread to other extremities[14,16,17]. Dystonia in CRPS is generally refractory to treatment[18] and therefore adds considerably to the disease burden, leaving some patients severely disabled.

Knowledge of the mechanism that underlies dystonia in CRPS is a prerequisite for the development of a treatment. In 2000, we reported on the beneficial effects of continuous administration of intrathecal baclofen (ITB) in six CRPS patients with multifocal or generalized dystonia[19]. Baclofen stimulates the presynaptic gamma-aminobutyric-acid B ($GABA_b$) receptor, which inhibits sensory input to spinal neurons[20], but may also act post-synaptically[21]. The aim of the current study was 1) to further elucidate the efficacy of ITB in a dose-escalation study of a large group of patients with CRPS-related dystonia and 2) to evaluate whether ITB is effective and safe in this population over a 12-month period.

Methods

Patients

All patients who visited our clinic with a diagnosis of CRPS and dystonia in at least one extremity and who fulfilled the CRPS criteria of the International Association for the Study of Pain (IASP)[3] were considered for inclusion in the study. The IASP criteria include a combination of 1) the presence of an initiating noxious event or a cause of immobilization, 2) continuing pain, allodynia or hyperalgesia with which

the pain is disproportionate to any inciting event, 3) evidence at some time of edema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain and 4) absence of a condition that would otherwise account for the degree of pain and dysfunction. Criteria 2-4 are necessary for a diagnosis of CRPS[3]. We increased the homogeneity of the population by only including CRPS patients in whom a noxious event triggered the onset of the syndrome in the first affected extremity. Patients were only eligible if they experienced no benefit of oral baclofen up to a minimum daily dose of 60 mg or if this treatment caused dose-limiting side effects. Exclusion criteria were other causes of dystonia (birth injury, head trauma, neuroleptic treatments), other medical or psychiatric concomitant disorders that could affect the surgical risk or completion of the trial, pregnancy and spinal deformities that could interfere with implantation of the pump/catheter system. Physicians throughout the Netherlands referred patients to our department. Patient consent was obtained in accordance with the Declaration of Helsinki and the local Ethics Committee approved the study.

Dose-escalation study

A single-blind, placebo-run-in, dose-escalation study with continuous infusion of baclofen was conducted. This design was chosen for the following reasons. Firstly, our increasing experience of ITB in CRPS patients with dystonia indicates that bolus injections may result in effects lasting several days. These prolonged effects suggest that the previously used cross-over design[19] with baclofen and placebo on alternate days is inappropriate. We therefore chose to administer placebo before baclofen. Patients were blind as to which days they received placebo. Secondly, bolus injections with ITB are less effective than continuous infusions with ITB[22].

Baclofen or placebo was administered via a percutaneous catheter that was introduced into the subarachnoid space (L3-4) and advanced to the lower thoracic region. The other end of the catheter was tunneled subcutaneously to the flank and connected to an external micro-infusion pump. Two days of placebo infusion were followed by the start of ITB infusion on the third day at a rate of 200 μg per day, which was increased daily according to a fixed schedule (200-250-300-375-450-525-600-700-800 μg) until the responder criteria (see below) were reached. If a baclofen-related side effect occurred, the dose was decreased or maintained, depending on the severity of the side effect.

Open-label study

A programmable pump (SynchroMed Infusion system, Medtronic INC, Minneapolis, MN) for ITB administration was implanted subcutaneously in the lower abdominal wall in patients who met the responder criteria. The catheter was introduced in the subarachnoid space (L2-L3) under X-ray guidance with placement of the distal tip of the catheter in the midthoracic region. The catheter was placed in the same position in all

patients, irrespective of upper or lower extremity involvement of dystonia. The catheter was then tunneled subcutaneously and connected to the pump.
ITB was started at a rate of 150 μg per day and increased in 10-20% steps until 1) patients experienced a satisfactory reduction of dystonia, 2) a maximum daily dose of 1300 μg was reached, or 3) dose-limiting side effects occurred. Pump-catheter system integrity was verified postoperatively in all patients and again in patients who showed no effect when a minimum daily dose of 1000 μg was reached or who deteriorated after an initial positive response.

Outcome
Patients completed Global Dystonia Severity (GDS) and Dystonia-related Functional Limitations (DFL) ratings at hourly intervals at home for five consecutive days and also for the duration of the dose-escalation study. GDS was assessed using a numeric rating scale (NRS) ranging from 0 (absent) to 10 (most severe). DFLs involved four items (transfers, general mobility, left/right arm functions) with four response options, ranging from 0 (no limitations) to 3 (severe limitations).
Patients participating in the open-label study were evaluated at baseline and 3, 6, 9, and 12 months after surgery. Primary outcome measures included the GDS and DFL scores. All other outcome measures were considered secondary. Dystonia severity was rated using the Burke-Fahn-Marsden (BFM) Dystonia Rating Scale [23], which is the sum of the scores of the individual body regions. Pain severity was evaluated using a numeric rating scale, ranging from 0 (no pain) to 10 (worst possible pain). The Rivermead Mobility Index (RMI) was used to assess mobility and includes 15 questions addressing a wide range of activities, from turning over in bed to running. The items are scored dichotomously (0-1) and summated, with a higher score reflecting better mobility (0-15) [24]. Activities of daily living were scored using the Barthel index (range 0-20) [25], while the Rankin Scale was used to determine global disability (0: no symptoms to 4: severe disability) [26]. Health-related quality-of-life was assessed with the EuroQol-5D [27]. The EuroQol-5D includes five items with three response options, from which a health state value (EQ-Tariff) is calculated, which ranges from 0 (death) to 1 (perfect health), although negative values for health states considered worse than death are possible. It also includes a visual analog scale for general health (ranging from 0; worst imaginable to 100; best imaginable). Higher scores in the RMI, the Barthel Index and the EuroQol-5D correspond to better mobility, ADL and quality of life, respectively. Higher scores in all other measures indicate symptoms with a higher degree of severity or poorer function.
Safety was evaluated by recording the frequency and severity of adverse events, which included any new symptom or worsening of a pre-existing symptom.

Statistical analysis

Dose-escalation study. The scores of six hourly intervals from the home evaluation (11:00-16:00) were summed (range 0-60) for each of the five days. The selection of these six time points was based on the fact that these were the hours that patients were active and able to record their evaluations. Sleeping, bathing and other activities often caused a larger number of missing values in the earlier and later parts of the day. The mean of these 5 days was used as the baseline score. A mean sum score was similarly calculated for the two placebo days and each baclofen day. Missing values in the diary were replaced with the value of the previous hour if this concerned two scores or less per day. A day was excluded from analysis if three or more values were missing. The placebo and baclofen responses were expressed as the percentage change from baseline (i.e, home evaluation). The GDS score was used as the primary outcome. The responder criteria were set at a ≥ 25% difference between the $GDS_{baclofen}$ and $GDS_{placebo}$ responses on two consecutive baclofen days.

Open-label study. The primary outcome measures were the changes in the GDS and DFL from baseline to 12 months. Missing data in the primary outcome measures were handled in the same way as in the dose-escalation study. Secondary outcome was defined as changes from baseline on all other scales. Data from any particular patient's scale were excluded from statistical analyses if 25% or more of the data were missing from the scale. The results were analyzed both on an "intention-to-treat" and on an "on-treatment" basis. Score differences between baseline and 12 months were compared using the paired-samples t-test or Wilcoxon-signed-rank test. The relationship between the results from the various scales was assessed using a Spearman's rho test. A logistic regression analysis was performed to evaluate which patient characteristics or screening parameters predicted responsiveness to treatment in the open-label study, where a ≥ 25% reduction in patient-reported dystonia was considered a positive response. Statistical analyses were performed using SPSS (version 14.0). A 95% confidence interval (CI) excluding 0 indicated a significant difference at an alpha level of 0.05 (two-sided). No adjustments were made for multiple testing.

Results

Dose-escalation study

Fifty-seven CRPS patients were assessed for eligibility between January 2002 and January 2007, of which 42 patients (40 women) with a mean disease duration of 10.3 (standard deviation 6.1) years participated in the study (tables 1 and 2). Nineteen percent of study patients had CRPS in two extremities, another 19% in three extremities and 62% had symptoms in four extremities. Three percent of patients suffered from dystonia in one extremity while two, three and four extremities were affected by dystonia in 31, 21 and 45 percent of patients, respectively. Demographic and dystonia characteristics of the 15 excluded patients did not differ significantly from the included patients (figure 1). Three patients dropped-out due to intolerable side effects (n=1), CSF leakage (n=1) and because the study was considered too demanding (n=1). The number of missing data from the primary outcome never exceeded 2 scores per day. Thirty-seven patients followed the fixed-dose schedule; side effects required adjustment of the schedule for 5 patients. Blinding in the dose-escalation study was generally successful until patients perceived an improvement in their dystonia, after which blinding could not be maintained successfully. The mean $GDS_{placebo}$ response was 7% (95% CI: 3 to 12). One patient did not respond to ITB. A dose-effect of baclofen on dystonia severity was observed in doses up to 450 μg. Thirty-one patients reached the responder criteria at this dose (figure 2). A total of 38 patients showed a ≥ 25% difference between the baclofen and placebo responses on two subsequent baclofen days. The mean difference between placebo and baclofen response was 38% (95% CI: 34 to 43) in favor of baclofen for responders on the first response day and 41% (95% CI: 36 to 46) on the second day. The responder criteria were reached at a mean baclofen dose of 415 μg/day (SD 139, range 200-800). The total $DFL_{placebo}$ response score showed a worsening of 2% (95% CI: -3 to 7%). The mean difference between $DFL_{placebo}$ and $DFL_{baclofen}$ response was 25% in favor of baclofen (95% CI: 17 to 33) on the first response day and 25% (95% CI: 17 to 31) on the second day.

Table 1. Demographic and clinical characteristics of patients (n=42)

Characteristic	Value
Age - mean (SD), years	35.7 (12.8)
Sex - male / female, no.	2 / 40
Disease duration - mean (SD), years	10.3 (6.1)
Trauma preceding first affected extremity - no. (%)	
Soft tissue injury	23 (55)
Fracture	11 (26)
Surgery	8 (19)
Extremities affected by CRPS – no. (%)	
2	8 (19)
3	8 (19)
4	26 (62)
Extremities affected by dystonia – no. (%)	
1	1 (3)
2	13 (31)
3	9 (21)
4	19 (45)
Dystonia in upper and lower extremities - no. (%)	
Only upper	3 (7)
Only lower	1 (2)
Upper and lower	38 (91)

Open-label study

Thirty-six of the 38 patients who met the responder criteria participated in the open-label study. Two patients declined to proceed to implantation, due to catheter-induced back pain and persistent partial improvement of dystonia after the dose-escalation study. Missing data never exceeded the predefined criteria. All dystonia scores had improved significantly between baseline and 12 months (table 3). GDS improved by a mean of 2.9 (SD 3.0) points (40%). The BFM-score showed a similar improvement of 18.8 (27.1) points (38%). BFM subscores for the upper extremities improved by 45%, while dystonia in the lower extremities improved by 33%. GDS and BFM scores decreased during the first six months and remained stable thereafter (Fig 3A and B). Pain severity measured by the NRS decreased from 7.7 to 5.7 (26%) and there was a correlation between the reduction of pain and the improvement in the GDS score (Spearman's rho

Table 2. Signs and symptoms of CRPS in affected extremities

Variable	Affected extremity			
	1st (n=42)	2nd (n=42)	3rd (n=34)	4th (n=26)
Pain present/ absent/ unknown, no.	42 / 0 / 0	42 / 0 / 0	34 / 0 / 0	26 / 0 / 0
Hypoalgesia present/ absent/ unknown, no.	38 / 4 / 0	32 / 9 / 1	26 / 8 / 0	19 / 5 / 2
Hyperalgesia/allodynia present/ absent/ unknown, no.	28 / 14 / 0	22 / 20 / 0	17 / 17 / 0	11 / 15 / 0
Edema present/ absent/ unknown, no.	39 / 3 / 0	29 / 13/ 0	17 / 17 / 0	12 / 14 / 0
Temperature changes present/ absent/ unknown, no.	40 / 2 / 0	36 / 4 / 2	25 / 8 / 1	18 / 6 / 2
Color changes present/ absent/ unknown, no.	40 / 1 / 1	38 / 3 / 1	24 / 10 / 0	19 / 6 / 1
Hyper/hypohidrosis present/ absent/ unknown, no.	31 / 10 / 1	25 / 15 / 2	19 / 14 / 1	13 / 11 / 2
Hair and nail growth changes present/ absent/ unknown, no.	35 / 6 / 1	32 / 8 / 2	23 / 8 / 3	15 / 9/ 2

Variables were deemed to be present if a symptom, a sign or both were reported or observed.

0.50). The DFL total, mobility, transfers, and left/right arm function scores improved by 31, 19, 38, 35 and 33%, respectively. The Rivermead mobility index improved by 44%. Out of six patients who were completely confined to bed, four changed to using a wheelchair (two of which were able to walk short distances with or without walking aids) and one patient became fully ambulatory. One explanted patient remained confined to bed. Three of four patients who were partially bed-bound changed to full-time wheelchair use. Of the 14 patients who were wheelchair-bound, 10 remained unchanged, two still needed a wheelchair but were able to walk short distances, and two became fully ambulatory. All four patients with part-time wheelchair use remained unchanged. Of five patients who needed walking aids, four improved to walking without aids. One of three ambulatory patients became part-time wheelchair-dependent due to worsening of CRPS symptoms. The other two patients remained ambulatory. The Barthel index improved by 26%. Distribution of the Rankin Scale improved; 26 patients had moderate to severe disability at baseline, compared to 15

patients during follow-up. The EuroQol-index improved from 0.21 to 0.45 while the health state improved from 42 to 54. The pump was explanted in six patients before the endpoint was reached (figure 1, mean duration of ITB administration = 6 months, range 2-11). Results of the intention-to-treat analysis (n=36) did not differ from the on-treatment analysis (n=30). Apart from a slight improvement in GDS score, none of the outcome measures in the off-treatment group changed significantly. Seventy percent of patients on treatment improved by ≥ 25% on the primary outcome, whereas 47% of the patients improved by ≥ 50%, and 20% improved by ≥ 75%.

Figure 1. Enrollment of patients in dose-escalation and open-label studies.

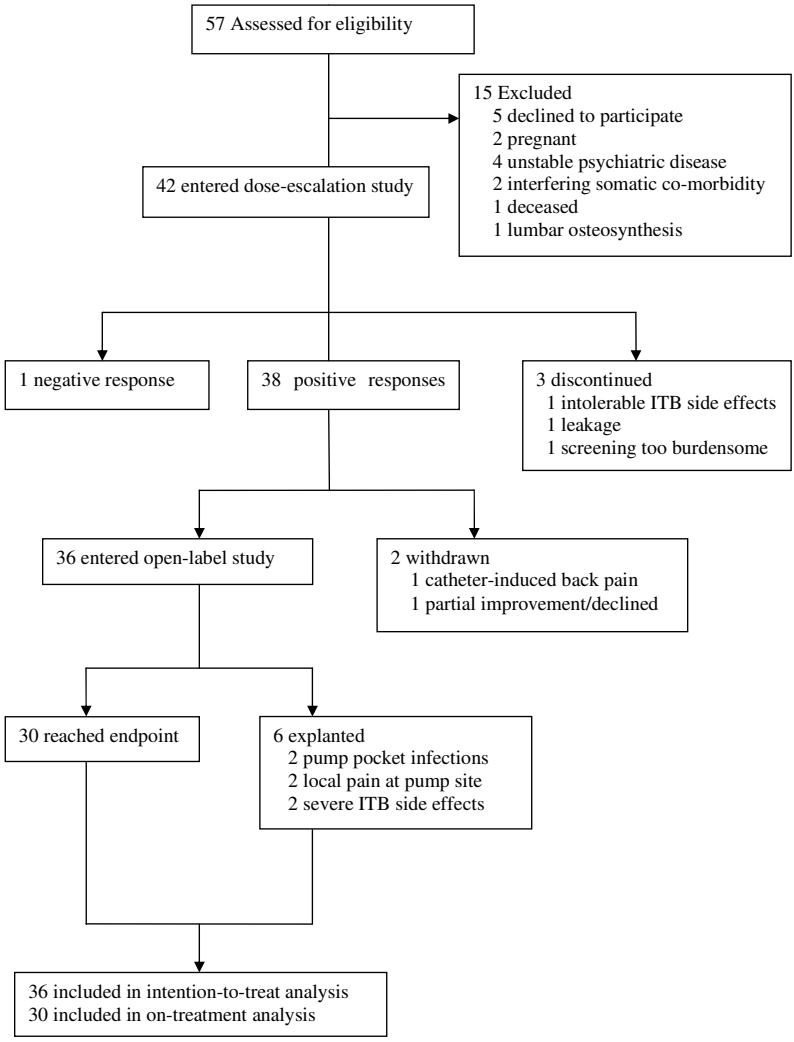
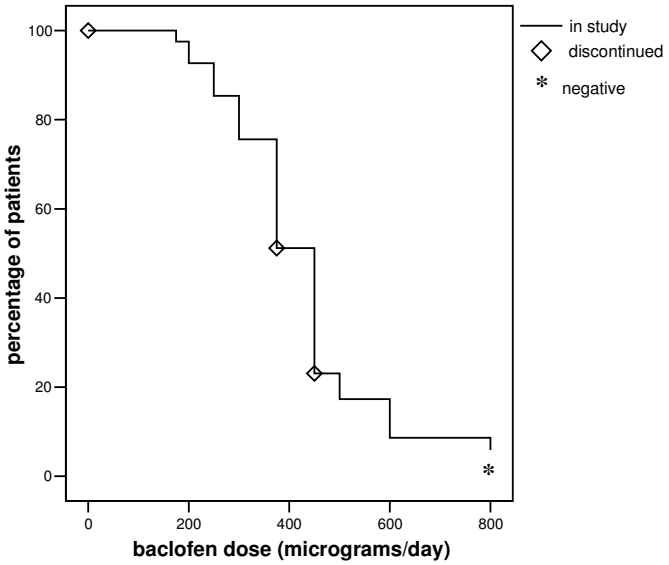


Figure 2. Dose-escalation study: baclofen dose at which the responder criteria were reached.



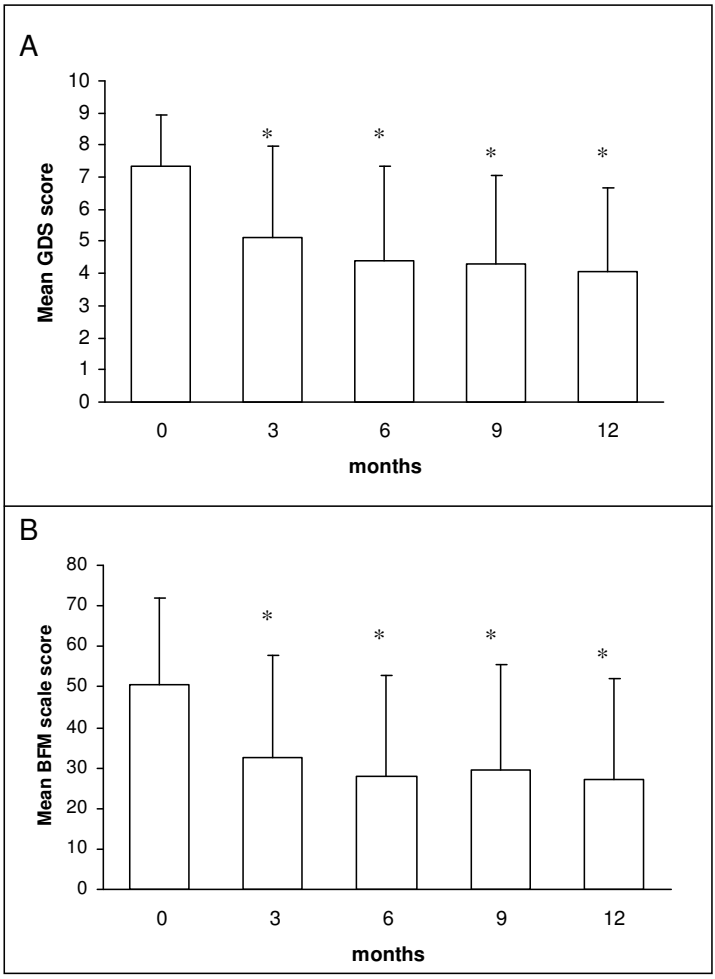
Kaplan-Meier curve of 42 patients showing the baclofen dose at which patients reached the responder criteria. ◊ denotes three patients that dropped out because of intolerable side effects, CSF leakage and the fact that the study was too burdensome. * denotes one patient who did not respond to ITB.

Table 3. Open label study: primary and secondary outcomes at baseline and 12 months follow-up

Outcome (range)	Intention to treat (n=36)				On treatment (n=30)				Off treatment (n=6)			
	0 Mo	12 Mo	Change from baseline	95% CI	0 Mo	12 Mo	Change from baseline	95% CI	0 Mo	12 Mo	Change from baseline	95% CI
Global dystonia severity (0-10)	7.3	4.4	-2.9	-3.9;-1.9	7.3	4.1	-3.2	-4.4 ; -2.1	7.1	6.1	-1.0	-1.8 ; -0.2
Burke-Fahn Marsden Scale (0-120)	48.9	30.1	-18.8	-28.0;-9.6	50.5	27.2	-23.3	-33.3 ; -13.3	40.8	44.8	3.9	-12.0 ; 20.4
Pain - numeric rating scale (0-10)	7.7	5.7	-2.0	-3.0;-1.0	7.7	5.4	-2.3	-3.4 ; -1.2	7.4	7.4	0	-1.5 ; 1.5
Dystonia-related functional limitations												
Total score (0-12)	8.5	5.9	-2.6	-3.8;-1.5	8.6	5.3	-3.3	-4.5;-2.1	8.2	8.8	0.6	-1.1;2.3
Mobility (0-3)	2.1	1.7	-0.4	-0.6;-0.1	2.1	1.6	-0.5	-0.8;-0.2	2.1	2.4	0.3	-0.2;0.8
Transfers (0-3)	2.1	1.3	-0.8	-1.1;-0.4	2.1	1.2	-0.9	-1.3;-0.5	2.0	2.1	0.1	-0.5;0.7
Right hand function† (0-3)	2.3	1.5	-0.8	-1.2;-0.4	2.3	1.3	-1.0	-1.4;-0.6	2.3	2.3	0	-0.6;0.7
Left hand function† (0-3)	2.1	1.4	-0.7	-1.1;-0.4	2.1	1.2	-0.9	-1.3;-0.5	1.8	2.0	0.2	-0.3;0.7
Rivermead Mobility Index (0-15)	5.5	7.9	2.4	0.5;4.4	5.7	8.3	2.7	0.4;4.9	4.6	5.6	1.0	-1.8;3.8
Barthel index (0-20)	11.8	14.9	3.1	1.3;5.0	11.6	15.3	3.7	1.7;5.8	13.0	13.0	0	-4.4;4.4
EuroQol-5D												
Index (EQ-Tariff) (0-1)	0.21	0.45	0.24	0.12;0.36	0.24	0.50	0.26	0.13;0.41	0.04	0.10	0.06	-0.03;0.14
Health state (0-100)	42.2	53.8	11.6	4.4;18.7	43.5	54.5	11.0	3.1;18.8	34.6	49.8	15.2	-10.9;41.3

†Right and left hand functions were only assessed in affected hands. Absolute values are given in means. 95% CI denotes 95% confidence interval. Differences in global dystonia severity were tested with the paired samples T-test. For all other outcome parameters the paired Wilcoxon signed rank test was used.

Figure 3. Dystonia severity during open-label study.



Mean (SD) scores of Global Dystonia Severity (GDS, panel A) and the Burke-Fahn-Marsden scale (BFM scale, panel B) before and after 3, 6, 9, 12 months of ITB infusion in the on-treatment group (n=30). * denotes a significant difference compared to baseline values ($p<0.001$).

None of the variables tested in the logistic regression analysis (including patient characteristics and screening characteristics, such as time to response and dose at which the patient met the responder criteria in the screening phase) predicted the response to ITB in the open-label study. The median ITB dose in the follow-up study increased from 450 μg/day (range 150-1250) after 3 months to 615 μg/d (range 150-1500) after one year.

Adverse events

Nineteen ITB-related adverse events were reported in 14 patients (table 4). Most frequent ITB-related adverse events were nausea, vomiting, headache, and short-term urinary retention at the start of the treatment. Three patients developed baclofen intoxication with somnolence, nausea and vomiting, which required temporary discontinuation of baclofen. Persistent baclofen-related headache and vomiting, which cleared after lowering ITB dose to a minimum rate, led to pump explantation in one patient. Three patients had psychiatric adverse events (two with psychosis and one with depression), which were probably caused by ITB, as symptoms cleared after lowering or stopping ITB. This led to explantation in one of these patients.

Device-related complications were common: 43 catheter-related complications occurred in 33 patients, with post-dural puncture headache (n = 31) as the most frequent complication.

Five patients, who initially responded to ITB, experienced a gradual worsening of dystonia over a period of 1-2 weeks. Catheter dysfunction was found in these patients and dystonia improved after a variable delay of days to months after catheter revision.

Nine pump-related adverse events occurred in eight patients. Two patients experienced refractory pain at the site of the pump pocket, which led to explantation in one of these patients. The pump was explanted in three of four patients who developed a pocket infection. The pump was not re-implanted in two of these patients due to a questionable effect of ITB. The third patient improved to her former level after re-implantation.

Discussion

Dystonia is characterized by impaired inhibition of sensorimotor circuitry at multiple levels of the central nervous system[28-30]. Findings on dystonia in CRPS are in line with this and showed a loss of spinal and cortical inhibition[28,31,32]. The dose-escalation study showed that ITB reduces dystonia in patients with CRPS. The fact that baclofen is infused around the spinal cord where it is known to stimulate presynaptic $GABA_b$ and possibly postsynaptic receptors[20,21], may indicate that loss of spinal GABAergic inhibition is an important mechanism in this type of dystonia. However, since baclofen may diffuse more rostrally, we cannot rule out that part of the effect is mediated at a supraspinal level. The open-label study showed marked improvement of patient and assessor-rated dystonia after one year. The largest improvement in dystonia was seen after three months, with a smaller further improvement after 6 months after which dystonia remained stable (Figure 2). A similar response pattern was observed in deep brain stimulation (DBS) in patients with primary generalized dystonia[33] and contrasts with the more rapid

Table 4. Adverse events in open-label study.

Adverse events	Type of event	N
ITB-related (N=19)	Urinary retention	3
	Somnolence	3
	Psychiatric[1]	3
	Nausea, vomiting	2
	Headache	2
	Fatigue	1
	Dysesthesia	1
	Hypotension, bradycardia	1
	Other[2]	3
Device–related, catheter (N=43)	Post-dural puncture headache	31
	Dislodgment	5
	Subcutaneous fluid collection/CSF leak	3
	Occlusion/kink	2
	Compression spinal cord or root	2
Device–related, pump (N=9)	Pump pocket infection	4
	Pain at pump site	2
	Migration of pump	2
	Ulcerations at pump site during pregnancy	1
Other (N=18)	Worsening CRPS symptoms	3
	Psychiatric[3]	4
	Excessive weight loss	2
	Gastro-intestinal problems (unrelated to ITB)	3
	Infections (unrelated to device)	3
	Internal complications[4]	

[1] psychosis: n=2, depression and anxiety disorders: n=1
[2] diplopia, dizziness, anorgasmia
[3] confusional state: n=2, reactive depression: n=1, reactive psychosis: n=1
[4] anemia, elevated liver enzymes, electrolyte changes

response to DBS of other movement disorders, possibly indicating a typical response characteristic of dystonia. A direct antinociceptive effect of baclofen cannot be ruled out since pain reduction was only partly explained by a decrease in dystonia severity[20]. The median baclofen dose of 615 **µg/d a**fter one year of follow-up was similar to doses used in other types of dystonia[22,34], but higher than those reported for spasticity (mean 290 µg/d)[35,36], possibly due to differences in the pathophysiology of both disorders. We found improvement in arm function (DFL, 35/33%), transfers (DFL, 38%), and mobility (DFL 19%, Rivermead Mobility Index 44%) on the disability level.

The largest changes in mobility were observed in patients confined to bed. The improvements in the impairment and disability levels paralleled those in the quality-of-life. The efficacy of ITB in CRPS-related dystonia is emphasized by the observation that, contrary to the on-treatment group, the off-treatment group failed to change significantly in all measures but the GDS. However, the small change in GDS was not paralleled by a change in the BFM dystonia rating scale.

One may postulate that the benefits reported by the patients on ITB reflect placebo effects, but we consider this unlikely for the following reasons. Firstly, all patients had long-term, progressive dystonia despite numerous interventions, including rehabilitation programs and invasive procedures (e.g. spinal cord stimulation). Secondly, only a small placebo response (7%) was found in the dose-escalation study, which was similar in magnitude to our earlier study[19]. Thirdly, catheter dysfunction led to obvious worsening of dystonia in initial responders when these patients were unaware of the immediate cause. This worsening of dystonia also highlights that ITB acts on a symptomatic level.

All patients had met the 25% responder criteria in the dose-escalation study, but only 70% of the on-treatment patients experienced a ≥ 25% reduction in dystonia, which was not anticipated. Malfunctioning of the pump-catheter system or a subtherapeutic dose of ITB could not explain this failure to respond. Pump-catheter system integrity was verified postoperatively in all patients and again in non-responders when a minimal dose of 1000 microgram per day was reached. The cause of the discrepancy between both our studies therefore remains uncertain. A possible explanation is the difference in ITB flow rates between both studies since the flow rate during the dose-escalation study was almost six times higher than the rate in the open-label study. Flow-rate dependent effects of intrathecal administration may influence the drug's distribution along the spinal canal [37] and are currently being evaluated in a new study. We encountered a high percentage of adverse events during the follow-up period, which were related to the surgical procedure, drug delivery system and to baclofen. Particularly, post-dural puncture headache (PDPH) occurred more frequently (86%) than commonly reported for pump implantation in other disorders (up to 42%,[38]). A previous study reported high frequency of CSF leakage in patients with dystonia[22]. CSF leakage related to PDPH was evident in three of our implanted patients, but we cannot rule out CSF leakage at a subclinical level in those patients lacking clear signs of CSF leakage. Migration of the pump leading to failure of drug delivery occurred in two patients with a body mass index of over 30. ITB likely caused psychosis in two patients and depression in one, since lowering the dose resulted in symptoms clearing. The higher number of device-related adverse events compared to ITB-treated patients with spasticity, can possibly be explained by the greater mobility in patients with CRPS-related dystonia.

Although the female to male ratio of CRPS is 3-4 in most studies, our patient group included a very high percentage (95%) of female patients. This finding is in line with other studies in patients with CRPS-related dystonia where the percentage of females is much higher (84-86%)[14,17,39]. To date, no satisfactory explanation has been provided for this female predominance.

There is an ongoing controversy over whether dystonia related to peripheral trauma with or without CRPS is caused by organic or psychogenic factors. Seventy-four percent of patients in our study also participated in a case-control study, in which their psychological characteristics were compared with those of patients with affective and conversion disorders[40]. In line with other case-control studies[16,39], this study found no evidence to support a distinct psychological profile in patients with CRPS-related dystonia.

In conclusion, this placebo-controlled dose-escalation study showed that ITB reduces dystonia in CRPS and lends further support to the role of GABAergic mechanisms in this cause of dystonia. ITB also improved disability and Qol and remained efficacious over a period of one year. However, ITB is associated with a high complication rate and therefore methods to improve patient selection and catheter-pump integrity are warranted to enhance its therapeutic potential.

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9

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 set[1]. 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 diseases[2]. CRPS may occur in a familial form and these patients develop the disease at younger age and have a more severe phenotype than sporadic cases[3], 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 50[6]. Finally, a genetic predisposition is apparent from genetic associations that were found with different human leukocyte antigen (HLA) factors[7-10].

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 rare[11]. 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 patients[12-14] 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 approach[17]. 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 accellerated disease course are characteristics of maladaptive neuronal plasticity and have been documented for clinical manifestations of other diseases[24-27]. 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 Aδ 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 CPRS 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 condition[35]. 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 pain[36]. 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 CRPS[37]. A recent fMRI study on pediatric CRPS patients reports on Blood-Oxygen-Level-Dependent (BOLD) responses during fulminating CRPS and again following their clinical recovery[38]. 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 dystonia[39-42]. For focal dystonia several researchers have provided evidence for abnormal cortical plasticity in susceptible individuals[43].

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 everyone[48]. 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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Samenvatting, conclusies en toekomstplannen

Dit proefschrift beschrijft de resultaten van aan aantal studies naar bewegingsstoornissen bij patiënten met Complex Regionaal Pijn Syndroom (CRPS). Ten eerste onderzochten we de klinische karakteristieken en het ziektebeloop van bewegingsstoornissen bij CRPS (in het bijzonder dystonie) bij patiënten met meerdere aangedane extremiteiten. Vervolgens bestudeerden we de pathofysiologie van de aandoening door middel van neurofysiologisch onderzoek en functionele beeldvorming van de hersenen. Tenslotte evalueerden we de veiligheid en effectiviteit van behandeling met intrathecaal baclofen bij CRPS-gerelateerde dystonie.

Hoofdstuk 1 is de introductie van dit proefschrift. Hierin worden kort de naamgeving van het syndroom en de symptomatologie beschreven. De symptomen bestaan uit pijn en verschillende combinaties van sensibele stoornissen, autonome kenmerken en sudomotore en trofische veranderingen. Daarnaast kunnen patiënten met CRPS bewegingsstoornissen ontwikkelen waarbij dystonie het meeste voorkomt. CRPS-gerelateerde dystonie kan zich voordoen in meerdere extremiteiten, is vaak moeilijk te behandelen en lijkt een slechte prognose te hebben. Er is gebrek aan betrouwbare informatie over de aard, het beloop en de klinische karakteristieken van dystonie bij CRPS patiënten. Deze informatie zou een beter inzicht kunnen verschaffen in onderliggende pathofysiologische mechanismen. Momenteel wordt CRPS gezien als een multifactoriële aandoening waarbij complexe interacties tussen het immuunsysteem en het (perifere en centrale) zenuwstelsel een rol spelen. Meerdere ziekteconcepten worden in dit hoofdstuk besproken. Er zijn slechts een paar studies gepubliceerd die de mogelijke mechanismen die aan CRPS-gerelateerde dystonie ten grondslag liggen als onderwerp hebben. Uit neurofysiologisch onderzoek zijn er aanwijzingen voor een gebrek aan inhibitie in het ruggenmerg en de motore cortex, wat verder ondersteund wordt door de resultaten van een kleine studie die een gunstig effect liet zien van een behandeling met intrathecaal baclofen, een middel dat inhibitie bevordert.

In **hoofdstuk 2** werden spreidingspatronen en de hiermee samenhangende klinische karakteristieken bestudeerd bij patiënten met CRPS in meerdere extremiteiten. Honderdvijfentachtig CRPS patiënten werden retrospectief geëvalueerd. Negenentachtig patiënten vertoonden CRPS in meerdere extremiteiten. Spreidingspatronen werden bestudeerd bij 72 patiënten bij wie CRPS begon in één extremiteit en uitbreidde naar een volgende. Hierbij werd contralaterale spreiding gevonden in 49%, ipsilaterale spreiding in 30% en diagonale spreiding in 14% van de patiënten. Er was sprake van een voorafgaand trauma bij respectievelijk 37, 44 en 91%. Spreidingspatronen verschilden significant tussen patiënten met spontane spreiding en patiënten met spreiding na een voorafgaand trauma. In vergelijking met patiënten met

één aangedane extremiteit, waren patiënten met meerdere aangedane extremiteiten gemiddeld zeven jaar jonger en hadden tevens vaker bewegingsstoornissen. De 'hazard' op spreiding van CRPS nam toe met het aantal aangedane extremiteiten. Concluderend kan gesteld worden dat bij patiënten met CRPS in meerdere extremiteiten, spreiding van symptomen veelal spontaan verloopt volgens een contralateraal of ipsilateraal patroon, en dat diagonale spreiding zeldzaam is en meestal vooraf wordt gegaan door een trauma. Spreiding van symptomen hangt samen met een jongere leeftijd bij ontstaan van CRPS en met de aanwezigheid van bewegingsstoornissen. Zowel processen in het ruggenmerg als supraspinale veranderingen zijn mogelijk verantwoordelijk voor spontane spreiding van CRPS.

Hoofdstuk 3 beschrijft de resultaten van een retrospectieve studie waarbij we de klinische en temporele karakteristieken van bewegingsstoornissen bij CRPS onderzochten. Een Cox proportional hazards model werd gebruikt om factoren die het ontstaan van bewegingsstoornissen beïnvloedden te evalueren. Honderdvijfentachtig patiënten hadden CRPS in één of meerdere extremiteiten. Honderdéénentwintig van deze patiënten hadden bewegingsstoornissen waarbij dystonie het meeste voorkwam (91%). Tweeënzestig procent van deze patiënten vertoonde dystonie in meerdere extremiteiten. Patiënten met dystonie waren gemiddeld elf jaar jonger dan patiënten zonder dystonie en hadden ook vaker CRPS in meerdere extremiteiten. Het interval tussen het ontstaan van CRPS en dystonie in de eerste aangedane extremiteit varieerde van minder dan een week in 26% van de patiënten tot meer dan één jaar in 27%. De hazard op het ontwikkelen van dystonie in andere extremiteiten nam toe met het aantal extremiteiten dat al dystonie had ontwikkeld. Uit deze resultaten kan worden geconcludeerd dat dystonie bij CRPS een zeer variabele latentietijd kent, geassocieerd is met een jongere leeftijd bij ontstaan van CRPS en tevens een verhoogd risico geeft op het ontwikkelen van dystonie in andere extremiteiten. Het bestaan van een interval tussen ontstaan van de eerste CRPS symptomen en het ontstaan van dystonie en het progressieve beloop kan wijzen op de betrokkenheid van een ander onderliggend mechanisme welke mogelijk geassocieerd is met maladaptieve neuroplasticiteit.

Het doel van de studie beschreven in **hoofdstuk 4** was het evalueren van psychologische kenmerken bij ernstig aangedane patiënten met CRPS-gerelateerde dystonie. Bij 46 patiënten werden persoonlijkheidskenmerken, psychopathologie, dissociatieve ervaringen, het aantal traumatische ervaringen en kwaliteit van leven bestudeerd. De bevindingen bij deze groep werden vergeleken met twee historische controlegroepen (54 patiënten met een conversiestoornis en 50 patiënten met een affectieve stoornis) en met normatieve populatie data. Bij CRPS patiënten was er sprake van verhoogde scores

op de metingen voor somatoforme dissociatie, traumatische ervaringen, algemene psychopathologie, en lagere scores voor kwaliteit van leven vergeleken met data voor de algemene populatie. In vergelijking met patiënten met een conversiestoornis of een affectieve stoornis lieten CRPS patiënten significant lagere scores zien op de metingen voor persoonlijkheidskenmerken, recente levensgebeurtenissen en algemene psychopathologie. Het algemene niveau van psychopathologie bij CRPS patiënten was evenveel verhoogd als dat van patiënten met chronische pijn, maar het niveau was significant lager dan dat van beide psychiatrische controlegroepen. Het aantal vroege traumatische ervaringen was vergelijkbaar met dat van conversiepatiënten maar verhoogd in vergelijking met patiënten met een affectieve stoornis. Vroege traumatische ervaringen werden gerapporteerd bij 87% van de CRPS patiënten en lieten een matige correlatie met somatoforme dissociatieve ervaringen zien. Dit zou erop kunnen wijzen op dat vroege traumatische ervaringen een predisponerende, maar niet noodzakelijke factor zijn voor het ontwikkelen van CRPS-gerelateerde dystonie. Hoewel het psychologisch profiel van patiënten met CRPS-gerelateerde dystonie enkele afwijkingen laat zien, is een uniek afwijkend psychologisch profiel op groepsniveau niet aantoonbaar.

In **hoofdstuk 5** werden het voorkomen en de karakteristieken van hyperacusis bij patiënten met CRPS-gerelateerde dystonie onderzocht. Ernstig aangedane patiënten zouden mogelijk vaker hyperacusis hebben, hetgeen centrale betrokkenheid kan suggereren. Het voorkomen van hyperacusis en het niveau van spraakwaarneemdrempels (SRT), pure toon drempels (PTT) en onaangename luidheid (UCL) werden geëvalueerd bij 40 patiënten met CRPS-gerelateerde dystonie. PTT en SRT waren bij alle patiënten normaal. Vijftien patiënten (38%) rapporteerden hyperacusis en dit was geassocieerd met allodynie/hyperalgesie en met de aanwezigheid van meerdere aangedane extremiteiten. UCLs van patiënten met hyperacusis waren significant lager dan UCLs van patiënten zonder hyperacusis. De resultaten laten zien dat hyperacusis frequent voorkomt bij ernstig aandane patiënten met CRPS-gerelateerde dystonie, wat kan wijzen op de uitbreiding van centrale sensitisatie naar auditieve circuits.

In **hoofdstuk 6** wordt een studie naar somatosensore verwerking van perifeer toegediende stimuli bij CRPS patiënten met dystonie beschreven. Bij 33 patiënten met CRPS en dystonie en 19 gezonde controles werden “somatosensory evoked potentials” (SSEPs) bestudeerd. N9, N14, N20 en N35 amplitudes werden geregistreerd na gepaarde stimulatie van de n. medianus en n. ulnaris (“spatiëel”), en na stimulatie van beide zenuwen met enkelvoudige stimuli en inter-stimulus intervallen van 20 en 40 ms (“temporele” stimulatie). Tenslotte werden beide methoden geïntegreerd, wat resulteerde

in “spatiotemporele” stimulatie. De statistische analyse werd uitgevoerd met behulp van een “linear mixed model” variantie analyse. SSEP amplitudes waren significant lager na spatiële en temporele stimulatie. Er was geen verschil tussen patiënten en gezonde controles. Bij spatiotemporele stimulatie werd in beide groepen geen additioneel onderdrukkend effect gezien. Concluderend kunnen deze bevindingen erop wijzen dat proprioceptieve sensore verwerking bij CRPS-gerelateerde dystonie ongestoord is en dat inhibitie mogelijk beperkt is tot de motore cortex. Met het oog op het concept van dystonie als een stoornis van neurale circuits, is het de vraag of een bevinding als motore disinhibitie moet worden gezien als de “”kip” of het “ei”. Gezien de perifere initiatie van de aandoening lijkt een spinale origine van CRPS-gerelateerde dystonie met secundaire veranderingen op het supraspinale niveaus het meest waarschijnlijk.

Hoofdstuk 7 beschrijft de bevindingen van ‘functionele magnetic resonance imaging’ (fMRI). Het doel van deze studie was het bepalen van de cerebrale-netwerk-functie bij CRPS patiënten met dystonie. Bij patiënten en controles werd de cerebrale verwerking van zowel het uitvoeren als visualiseren van handbewegingen met fMRI gemeten. Acht CRPS patiënten met dystonie van de rechter bovenste extremiteit en 17 gezonde, op leeftijd gematchte controles werden onderzocht. Vergeleken met controles werd bij patiënten bij het visualiseren van bewegingen van de aangedane hand aan de ipsilaterale zijde verminderde activatie gezien in de premotore en de aangrenzende prefrontale cortex, als ook in een cluster bestaande uit het frontale operculum, het anterieure deel van de insula en de gyrus temporalis superior. Aan de contralaterale zijde werd verminderde activatie gezien in de inferiore pariëtale en aangrenzende primaire sensore cortex. Bij het uitvoeren noch het visualiseren van bewegingen van de niet-aangedane hand was er verschil tussen patiënten en controles. Er kan geconcludeerd worden dat patiënten met CRPS-gerelateerde dystonie bij visualisatietaken verminderde activatie laten zien in gebieden die betrokken zijn bij het plannen van beweging, multimodale sensomotore integratie, autonome functie en pijn. Mogelijk resulteert pijn in veranderingen in de cerebrale organisatie van beweging door functionele interactie tussen deze gebieden.

In **hoofdstuk 8** wordt een studie naar de effectiviteit en veiligheid van behandeling met intrathecaal baclofen (ITB) bij CRPS-gerelateerde dystonie beschreven. Om de respons van dystonie op ITB te onderzoeken werd een enkelblinde, placebo-run-in, dosis-escalatie studie uitgevoerd bij 42 CRPS patiënten. Zesendertig van de 38 patiënten die aan de responscriteria voldeden, kregen een pomp voor continue toediening van ITB en zij werden gedurende 12 maanden gevolgd om de langetermijneffectiviteit en -veiligheid vast te stellen (open-label studie). Primaire uitkomstmaten waren de globale dystoniescore (beide studies) en de score voor dystonie-gerelateerde functionele

beperkingen (open-label studie). Bij doseringen tot 450 µg per dag liet de dosis-escalatie studie bij 31 patiënten een dosis-effect van baclofen op de dystoniescore zien. Eén patiënt reageerde niet op behandeling in de dosis-escalatie studie en drie patiënten vielen uit. Zesendertig patiënten stroomden door naar de open-label studie. Intention-to-treat analyse van de data van 12 maanden liet een substantiële verbetering zien van dystoniescore, pijn, beperkingen en kwaliteit van leven. De respons in de dosis-escalatie studie bleek de respons op ITB in de open-label studie niet te kunnen voorspellen. Bij 26 patiënten traden in totaal negenentachtig bijwerkingen op die gerelateerd waren aan baclofen (n=19) of aan defecten van het pomp/kathetersysteem (n=52). De overige bijwerkingen (n=18) konden niet worden duidelijk worden toegewezen. Bij zes patiënten werd de pomp in de follow-up fase geëxplanteerd. Samenvattend kan men stellen dat ITB behandeling resulteert in verbetering van dystonie, pijn, beperkingen en kwaliteit van leven en dat deze interventie effectief blijft gedurende een follow-upperiode van één jaar. Behandeling met ITB gaat echter gepaard met veel complicaties en het is belangrijk om de patiëntenselectie en de functie van het pomp/kathetersysteem te verbeteren.

Conclusies

In de laatste twee decennia is de kennis over bewegingsstoornissen bij CRPS langzaamaan toegenomen. De realisatie dat CRPS patiënten ook bewegingsstoornissen kunnen ontwikkelen heeft geresulteerd in een voorstel van een 'expert consensus panel' om deze klinische categorie aan de nieuwe criteria set toe te voegen[1]. Een goede beschrijving van klinische, pathofysiologische en therapeutische aspecten van bewegingsstoornissen bij CRPS kan mogelijk bijdragen aan betere behandelstrategieën voor deze invaliderende symptomen van het syndroom, en deze drie onderwerpen zullen worden bediscussieerd in het nu volgende deel van het proefschrift.

Klinische karakteristieken

Het eerste doel van deze studie was het uitbreiden van onze kennis over de klinische karakteristieken en het ziektebeloop van aan CRPS gerelateerde bewegingsstoornissen en van die welke samengaan met het voorkomen van deze aandoening in meerdere extremiteiten. Wij onderzochten dus patiënten met een ernstig fenotype met invaliderende kenmerken. We realiseren ons dat deze subgroep van patiënten niet de "gemiddelde" CRPS patiënt representeert, maar het grote aantal van deze patiënten die in de loop der jaren op onze afdeling zijn gezien toont aan dat een dergelijk fenotype niet zeldzaam is. Patiënten met een ernstig CRPS fenotype met dystonie

en/of meerdere aangedane extremiteiten waren significant jonger bij het ontstaan van de CRPS symptomen in vergelijking met patiënten met een milder fenotype. Deze bevinding suggereert een genetische susceptibiliteit zoals ook bij andere aandoeningen is aangetoond[2]. CRPS blijkt daarnaast voor te kunnen komen in families en zulke patiënten ontwikkelen de ziekte op een jongere leeftijd en hebben een ernstiger fenotype dan sporadische gevallen[3], wat tevens kan wijzen op een verhoogde vatbaarheid om de ziekte te krijgen[4,5]. Een andere studie liet een verhoogd risico zien voor broers en zussen van CRPS patiënten die de ziekte voor het vijftigste jaar ontwikkelden, en ook dit wijst op een mogelijke genetische component[6]. Tenslotte is een genetische predispositie waarschijnlijk gezien de associaties die werden gevonden met verschillende "human leukocyte antigen" (HLA) factoren[7-10].

Zesenvijftig procent van de patiënten in onze studie ontwikkelden dystonie meer dan een maand na het begin van CRPS, terwijl 27% dit na één jaar en drie patiënten dit zelfs na meer dan vijf jaar na het begin van de ziekte ontwikkelden. De klinische kenmerken van patiënten die binnen een jaar na het begin van CRPS dystonie ontwikkelden verschilden niet van die welke dit na meer dan een jaar ontwikkelden en dit suggereert een gemeenschappelijk achterliggend mechanisme bij deze patiënten. Het latere ontstaan van dystonie dat bij veel patiënten werd gezien, suggereert dat onderliggende mechanismen van de acute fase van CRPS verschillen van die van dystonie. In overeenstemming met een andere studie vonden we dat als dystonie later ontstaat dan de niet-motorische symptomen van CRPS, het optreden van een nieuw trauma voorafgaand aan het ontstaan van dystonie zeldzaam is[11]. De vraag of dystone symptomen die aan een perifeer trauma gerelateerd zijn een organische of psychogene oorzaak hebben is een voortdurend onderwerp van discussie. Echter, in overeenstemming met andere studies bij CRPS patiënten[12-14] en bij chronische CRPS patiënten met dystonie,[15] liet onze studie geen aanwijzingen zien voor de aanwezigheid van een uniek afwijkend psychologisch profiel. Ten opzichte van de algemene Nederlandse populatie liet het algemene niveau van psychopathologie bij CRPS patiënten een verhoging zien die vergelijkbaar is met die van patiënten met chronische pijn;[16] dit niveau was echter significant lager dan die van psychiatrische controlegroepen van patiënten met affectieve stoornissen of conversiestoornissen. Vroege traumatische ervaringen komen bij patiënten met CRPS-gerelateerde dystonie vaker voor dan bij studenten en de algemene populatie, en kunnen een mogelijke, hoewel niet noodzakelijke predisponerende factor voor CRPS-gerelateerde dystonie vormen. Zoals verwacht, rapporteerde de patiëntengroep een slechtere algemene gezondheid en lagere kwaliteit van leven dan de algemene populatie.

Het is belangrijk te benadrukken dat om een effectieve behandeling van CRPS te bewerkstelligen er aandacht dient te zijn voor psychosociale en gedragsmatige aspecten als onderdeel van de geïntegreerde multidisciplinaire benadering,[17] net zoals dat geldt voor andere groepen patiënten met chronische pijn, Co-existente psychiatrische stoornissen en belangrijke voortdurende stressoren moeten worden geïdentificeerd en behandeld om het succes van therapie te verbeteren.

Pathofysiologie

De resultaten van onze studies naar klinische en neurofysiologische aspecten van patiënten met CRPS in meerdere extremiteiten en patiënten met bewegingsstoornissen bij CRPS laten aanwijzingen zien voor afwijkingen op meerdere niveaus van het centrale zenuwstelsel (CZS).

Er bestaat overtuigend bewijs voor een initiërende rol van het immuunsysteem en het perifere zenuwstelsel bij CRPS, waarbij er sprake is van abnormale inflammatie[18,19]. Het uitbreiden van symptomen en het optreden van bewegingsstoornissen kan echter niet alleen worden verklaard door stoornissen op een perifeer niveau. De resultaten van de onderzoeken in dit proefschrift geven argumenten voor veranderingen op zowel spinaal als supraspinaal niveau.

Argumenten voor veranderingen op spinaal niveau:

- Spontane uitbreiding van CRPS-symptomen treedt vaak op volgens een contralateraal patroon, wat verklaard kan worden door afwijkende spinale verwerking van binnenkomende sensore informatie[20,21]. Hierbij zouden commissurale spinale interneuronen een rol kunnen spelen, en mogelijk zijn hierbij ook spinale gliacellen en pro-inflammatoire cytokinen betrokken[22,23].
- Veel CRPS patiënten ontwikkelden de dystonie later dan de andere symptomen. Zodra dystonie eenmaal aanwezig was, nam de hazard op dystonie in andere extremiteiten toe met het aantal extremiteiten dat reeds door dystonie was aangedaan. Op vergelijkbare wijze nam met de aanwezigheid van CRPS in meerdere extremiteiten de hazard op spreiding van symptomen naar volgende extremiteiten toe, zonder dat hiervoor een nieuwe trauma voor nodig was. Zowel het latere begin van dystonie als de versnelling van het ziektebeloop zijn kenmerken van maladaptieve neuronale plasticiteit en dit is ook een bekend fenomeen bij klinische manifestaties van enkele andere ziekten[24-27]. Dit overwegende, zou maladaptieve plasticiteit op spinaal niveau zich kunnen uiten in disinhibitie van spinale nociceptieve terugtrekreflexen (zie hierna). De bevindingen zouden echter ook kunnen worden verklaard door supraspinale veranderingen.

- Onze placebo-gecontroleerde dosis-escalatiestudie liet zien dat dystonie bij CRPS afneemt door behandeling met ITB. Dit ondersteunt de rol van spinale GABA-erge mechanismen bij deze aandoening; C en Aδ sensibele vezels spelen een rol bij neurogene inflammatie en zijn verbonden met spinale circuits die nociceptieve terugtrekreflexen moduleren. Een van de primaire mediatoren van neurogene inflammatie, Substance P (SP), kan ook SP receptoren activeren op neuronen in lamina I van de achterhoorn van het ruggenmerg en zodoende long-term potentiation (LTP) induceren, een vorm van neuronale plasticiteit. Diermodellen van neurogene inflammatie hebben laten zien dat SP terugtrekreflexen verstrekt[28]. Buigspieren spelen een prominente rol bij terugtrekreflexen en het is opvallend dat er bij CRPS-gerelateerde dystonie een prominente betrokkenheid is van flexiehoudingen[29,30]. Neurofysiologische studies bij CRPS patiënten met dystonie hebben een verminderde presynaptische GABA-erge inhibitie laten zien[31]. Zowel de SP gesensitiseerde nociceptieve terugtrekreflexen in diermodellen als de dystonie bij CRPS- patiënten reageren op intrathecale toediening van de $GABA_B$-agonist baclofen, welke spinale GABA-erge inhibitie verhoogt.[32] Onze bevindingen zouden kunnen wijzen op een disinhibitie van spinaal gemediëerde terugtrekreflexen als primair causaal mechanisme bij CRPS-gerelateerde dystonie als uiting van maladaptieve plasticiteit.

Argumenten voor veranderingen op supraspinaal niveau:

- Hyperacusis komt frequent voor bij patiënten met een ernstige vorm van CRPS-gerelateerde dystonie en is mogelijk een uiting van het uitbreiden van centrale sensitisatie naar auditieve circuits in de thalamus.
- Bij functionele beeldvorming van de hersenen met fMRI bij patiënten met CRPS en dystonie werd verminderde activatie tijdens visualisatietaken gezien in corticale gebieden die betrokken zijn bij het plannen van beweging, multimodale sensomotore integratie, autonome functie en pijn.
- Verschillende onderzoekers geven argumenten voor disinhibitie op het niveau van de motorische cortex bij CRPS-patienten[33,34]. De resultaten van de SSEP studie laten zien dat corticale sensore verwerking van proprioceptieve input normaal is bij patiënten met CPRS en dystonie. Als corticale inhibitie een rol spelt, zal dat waarschijnlijk beperkt zijn tot de motore cortex.

Samengevat wijzen de resultaten van onze studies naar bewegingsstoornissen en spreiding bij CRPS op veranderingen in het CZS op zowel spinaal als supraspinaal niveau. Maladaptieve neurale plasticiteit is waarschijnlijk een belangrijk mechanisme dat ten grondslag ligt aan de bewegingsstoornissen. Neurale plasticiteit is een

eigenschap van het CZS die wordt gekarakteriseerd door het remodelleren van neuronale contacten in een poging om zich aan te passen aan een gewijzigde situatie[35]. Neurale plasticiteit kan gunstige effecten hebben en is nodig voor een normale ontwikkeling van het centrale zenuwstelsel en leren. Aan de andere kant kan abnormale plasticiteit aandoeningen veroorzaken zoals neuropathische pijn, tinnitus, en levodopa-geïnduceerde dyskinesiën[25,27,35]. Bij neuropathische pijn kan maladaptieve plasticiteit zich manifesteren door ectopische generatie van actiepotentialen, facilitatie en disinhibitie van synaptische transmissie, verlies van synaptische verbindingen, formatie van nieuwe synaptische circuits en gewijzigde neuroimmunologische interacties. Genetische polymorfismen, geslacht en leeftijd beïnvloeden allen de ontwikkeling van chronische pijn[36]. Bij de CRPS-symptomen chronische pijn en dystonie zou perifere neurogene inflammatie maladaptieve neurale plasticiteit in het ruggenmerg kunnen induceren (b.v. centrale sensitisatie) wat zich vervolgens kan uitbreiden naar meer rostraal (dus supraspinaal) gelegen structuren.
"Referred sensations", veranderingen in grootte en de organisatie van de somatosensore kaart, en veranderingen in representatie van de motorische cortex suggereren corticale betrokkenheid in CRPS[37]. Een recente fMRI studie bij kinderen met CRPS rapporteert over Blood-Oxygen-Level-Dependent (BOLD) responses tijdens fulminante CRPS en na klinisch herstel[38]. De auteurs vonden significante veranderingen in circuits van het CZS die ondanks het verdwijnen van de pijn persisteerden. De vraag op welk niveau van het CZS pathologische veranderingen primair hun oorsprong hebben, blijft dus onopgehelderd.
De aanwezigheid van verstoringen op meerdere niveaus van het CZS bij CRPS-gerelateerde dystonie komt overeen met recente hypothesen betreffende onderliggende mechanismen voor andere vormen van dystonie[39-42]. Bij focale dystonie hebben verschillende onderzoekers bewijs gevonden voor corticale plasticiteit in vatbare personen[43].

Therapie

Onze studie naar behandeling van patiënten met CRPS-gerelateerde dystonie met ITB liet een duidelijke verbetering zien van dystonie en pijnscores na één jaar. Verbeteringen op het niveau van stoornissen en beperkingen kwamen overeen met verbeteringen in kwaliteit van leven. De toename van dystonie na katheter- of pompdysfunctie laat zien dat ITB slechts op symptomatisch niveau werkt. Behandeling met ITB kon ernstige complicaties geven, welke onder andere bestonden uit infecties, draindysfuncties en psychiatrische symptomen die konden resulteren in explantatie van het pomp-katheter systeem. Deze therapie zou daarom alleen toegepast moeten worden bij patiënten die geen baat hebben bij conventionele therapieën en dient te worden uitgevoerd door

artsen met ruime ervaring met implanteren en instellen van intrathecale pompen. De patiëntenselectie blijft echter moeilijk aangezien we geen variabelen konden identificeren die een slechte respons of verhoogde kans op complicaties kunnen voorspellen.

Toekomstplannen

Prospectieve longitudinale epidemiologische studies zijn nodig om het natuurlijk beloop van CRPS te beschrijven en risicofactoren te identificeren die kunnen voorspellen bij welke patiënten de ziekte zal uitbreiden naar andere extremiteiten en welke patiënten bewegingsstoornissen zullen ontwikkelen. Genetisch onderzoek zal mogelijk aantonen welke personen gepredisponeerd zijn voor CRPS en bewegingsstoornissen in het bijzonder. Een van de andere toekomstige uitdagingen is het oplossen van het kip-of-ei vraagstuk betreffende de diverse pathofysiologische mechanismen op verschillende niveaus van het CZS; de volgorde en dynamiek van de veranderingen op perifeer, spinaal en supraspinaal niveau vereist nadere opheldering. Hier kunnen longitudinale neurofysiologische studies en biomarkerstudies in liquor bijdragen aan de ontwikkeling van geïndividualiseerde diagnostische en therapeutische strategieën, welke de uitbreiding van symptomen naar andere extremiteiten of de ontwikkeling van bewegingsstoornissen zouden kunnen voorkomen. Daarbij is ITB-behandeling een veelbelovende therapie voor bewegingsstoornissen bij CRPS, hoewel het selectief moet worden toegepast aangezien het een operatie vereist en vaak complicaties geeft. Daarnaast kan de effectiviteit van ITB verbeterd worden, bijvoorbeeld door onderzoek naar het effect van verschillende infusiesnelheden, de verfijning van katheters en pompsystemen en een betere identificatie van patiënten die waarschijnlijk goed zullen reageren op de therapie. Vanwege de achtergrond van CRPS verdienen niet-invasieve behandelstrategieën toegespitst op het moduleren van neurale plasticiteit de voorkeur. Zowel bij focale vormen van dystonie als bij CRPS zijn er ten aanzien van sensomotore trainingsprogramma's die gericht zijn op maladaptieve corticale veranderingen (bijvoorbeeld spiegeltherapie en transcraniële magnetische stimulatie) gunstige effecten gerapporteerd[44,45].

Perifeer-geïnduceerde bewegingsstoornissen (Peripheral Trauma induced Movement Disorders, PTMDs) kunnen een andere focus van toekomstig onderzoek vormen. Van alle bekende gevallen van PTMDs in de literatuur heeft vijftig procent CRPS (eigen data, ingediend ter publicatie). PTMDs zijn sinds lange tijd een controversieel onderwerp in de wereld van bewegingsstoornissen. De relatie tussen perifeer trauma en bewegingsstoornissen heeft in de loop der tijd aan acceptatie gewonnen en in 1995 werd door Cardoso en Jankovic een voorstel gedaan voor diagnostische criteria. Er is echter nog steeds een duidelijk gebrek aan consensus betreffende de pathogenese

van PTMDs. Sommige auteurs opperen dat PTMDs veroorzaakt worden door maladaptieve plasticiteit in het CZS[46,47] maar dit wordt niet door iedereen gesteund[48]. Studies naar de rol van perifeer trauma bij CRPS-geïnduceerde bewegingsstoornissen kunnen bijdragen aan een beter begrip van betrokken ziektemechanismen.
Samengevat kunnen toekomstige studies naar onderliggende mechanismen van neurale plasticiteit en studies naar modulatie van gestoorde neurale plasticiteit mogelijk leiden tot verbeterde behandelstrategieën bij CRPS-gerelateerde dystonie en op deze manier bijdragen aan een betere kwaliteit van leven en prognose van deze patiënten.

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List of abbreviations

AD	Affective Disorder
CD	Conversion Disorder
CRPS	Complex Regional Pain Syndrome
CGRP	Calcitonin Gene Related Peptide
CNS	Central Nervous System
DES	Dissociative Experiences Scale
DSM-IV	Diagnostic and statistical manual of mental disorders- Fourth edition
GABA	Gamma Amino Butyric Acid
HLA	Human Leukocyte Antigen
IASP	International Association for the Study of Pain
IQR	Interquartile Range
LTP	Long Term Potentiation
MD	Movement Disorder
fMRI	functional Magnetic Resonance Imaging
NWR	Nociceptive Withdrawal Reflexes
PDQ-R	Personality Diagnostic Questionnaire-Revised
RAND-36	Research and Development-36
RSD	Reflex Sympathetic Dystrophy
PTMDs	Peripheral Trauma induced Movement Disorders
PTT	Pure Tone Threshold
SCL-90-R	Symptom Checklist-90-Revised
SD	Standard Deviation
SDQ-20	Somatoform Dissociation Questionnaire-20
SMP	Sympathetically Maintained Pain
SP	Substance P
SRT	Speech Reception Threshold
SSEP	Somatosensory Evoked Potential
TEC	Traumatic Experiences Checklist
TREND	Trauma RElated Neuronal Dysfunction
UCL	Uncomfortable Loudness
VMIQ	Vividness of Movement Imagery Questionnaire
VRMG	"Vragenlijst Recent Meegemaakte Gebeurtenissen"(Recent Life Event Questionnaire)

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Curriculum vitae

Monica Adriana van Rijn (roepnaam: Monique) werd geboren op 23 juli 1973 te Rotterdam. In 1991 behaalde zij haar Atheneum diploma aan het Sint Laurens College in Rotterdam-Hillegersberg. Datzelfde jaar begon zij haar studie geneeskunde aan de Erasmus Universiteit te Rotterdam (EUR). Zij volgde wetenschappelijke stages op de afdelingen Klinische Genetica aan de EUR en Cel- en Moleculaire Biologie aan de Universiteit van Lund te Zweden. Het artsexamen behaalde zij in 1999.
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