Complex regional pain syndrome related movement disorders : studies on pathophysiology and therapy.
Munts, A.G.

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Studies on pathophysiology and therapy

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For my parents

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Chapter 1

General introduction and aims

Trauma to a limb (often minor) is occasionally followed by severe pain and trophic changes characteristic of sympathetic algodystrophy (Sudeck's atrophy). The pathophysiology of the condition is unknown. Even more rarely minor trauma may provoke not only Sudeck's atrophy but also involuntary movements. The clinical picture is so unusual that such patients may be labeled as "hysterical," particularly when compensation is being considered. We, however, have seen four similar cases of muscle spasms associated with Sudeck's atrophy after mild trauma in three different countries. We believe this to be a distinct clinical syndrome, although of unknown pathophysiology.[1]

These words date back to 1984. Since this recognition by professor C. David Marsden and colleagues, a number of case series[2-7] were reported on what is nowadays called 'complex regional pain syndrome (CRPS) related dystonia'.

Dystonia

In general, dystonia is characterized by an abnormal control of movement, with involuntary muscle contractions causing twisting movements and abnormal postures.[8] In CRPS, dystonia typically presents with predominant flexor postures of the fingers (in less severe cases only the third to fifth finger), wrists, and feet. Progression to the proximal part of the extremity as well as spread to muscles outside the affected limb may occur. Because of the presence of postures, which are typically not mobile, this dystonia is called 'fixed'.

What is CRPS?

In 1994, the International Association for the Study of Pain (IASP) introduced the term CRPS, which was the new name for sympathetic algodystrophy (or Sudeck's atrophy or reflex sympathetic dystrophy).[9] It was defined by a combination of sensory and autonomic disturbances which are often preceded by a limb trauma (Table 1.1). It is noteworthy that the presence of a preceding trauma is not a necessary requirement. The IASP made a distinction between two types of CRPS: without nerve injury (type 1) and with nerve injury (type 2). In 2003, new diagnostic criteria for CRPS were proposed by an international consensus group (Table 1.2).[10,11] The validity of these criteria were reconfirmed in a recent study,[11] however, until now these were not formally approved by the IASP.

Table 1.1. IASP diagnostic criteria for CRPS, type 1[9]

Criterium	
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 oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain
4	This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction

Note: criteria 2-4 must be satisfied.

Table 1.2. Proposed clinical diagnostic criteria for CRPS[11]

Criterium	
1	Continuing pain, which is disproportionate to any inciting event
2	Must report at least one symptom in *three of the four* following categories: – *Sensory:* reports of hyperesthesia and/or allodynia – *Vasomotor:* reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry – *Sudomotor/oedema:* reports of oedema and/or sweating changes and/or sweating asymmetry – *Motor/trophic:* Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3	Must display at least one sign at time of evaluation in *two or more* of the following categories: – *Sensory:* evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement) – *Vasomotor:* evidence of temperature asymmetry and/or skin colour changes and/or asymmetry – *Sudomotor/oedema:* evidence of oedema and/or sweating changes and/or sweating asymmetry – *Motor/trophic:* evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4	There is no other diagnosis that better explains the signs and symptoms

The pathophysiology of CRPS-related dystonia

The pathophysiology of both CRPS and its dystonia is only partly understood. Each (micro-) trauma that leads to activation of local nociceptors results in neurogenic inflammation, i.e. the release of inflammatory mediators. This process causes inflammatory signs, induces sensitisation of the nociceptors as well as sensitisation at the spinal cord level.[12] It is supposed that this process is out of balance in both type 1 and 2 CRPS. Against this background, it was suggested that inflammatory mediators are involved in the pathophysiology of CRPS. Indeed, increased levels of the pro-inflammatory interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were found in artificially obtained blister fluid of CRPS patients with a mean disease duration of 8 months (range 4-12 months).[13] At three years follow-up,[14] but not at six years follow-up,[15] these levels remained elevated. Neurogenic inflammation induces functional changes at the spinal cord level which play a key role in the maintenance of the pain (central sensitisation).[16]

Dystonia is considered to be a consequence of perturbed sensorimotor processing.[8] Lack of central inhibition plays a key role in the pathophysiology of dystonia in general.[17] In CRPS, the altered processing of noxious, tactile and thermal input has been suggested to be an important factor in the development of fixed dystonia.[18] Central sensitisation is associated with disinhibition of sensory circuits leading to spontaneous pain, allodynia and hyperalgesia. In CRPS patients with and without dystonia, pathophysiological studies have provided evidence of central disinhibition on different levels of the nervous system, ranging from the spinal cord[19] to cerebral cortex[20,21]. The role of central disinhibition in CRPS-related dystonia is further supported by a small placebo-controlled study in which about half of the patients had a marked and sustained reduction of the dystonia severity after administration of intrathecal baclofen, a specific gamma aminobutyric acid (GABA) B agonist. This drug enhances the presynaptic and postsynaptic inhibition of afferent input on neurons in the spinal cord.[22]

CRPS-related tremor and myoclonic jerks

In CRPS, tremor and myoclonic jerks have also been reported, however, information on these movement disorders is scarce.[18]

A hysterical label?

To date, there are a number of neurologists who consider CRPS-related dystonia a psychogenic movement disorder.[23,24] Though these are expert opinions, and as such meaningful, a scientific approach would be more appropriate. In a study with 27 CRPS-related dystonia patients, no psychological abnormalities were found in comparison with a control population.[25] In a recent study, that was performed at the Leiden University Medical Centre, no unique disturbed psychological profile was found in 46 CRPS patients with dystonia.[26] Nevertheless, in comparison to patients with affective disorders, the level of somatoform dissociative experiences (medically unexplained analgesia, anesthesia, motor disturbance, alternating preferences for tastes and smells, pain, and loss of consciousness) was elevated. Early traumatic experiences were found to be moderately related to somatoform dissociative experiences which may indicate that early traumatic experiences are a predisposing factor for the development of CRPS-related dystonia.[26] Of course, if psychological or psychiatric abnormalities are present, they also might be part of the syndrome instead of the cause.

Epidemiology

A recent Dutch population-based study[27] found an estimated overall incidence rate of CRPS of 26.2 per 100,000 person years (95% CI 23.0-29.7). Women are affected 3.4 times more often than men. The highest incidence occurred in women in the age category of 61-70 years. Considering a life expectancy at birth of 77.6 years for men and 81.9 years for women (Statistics Netherlands, 2006), the life time risk for CRPS is 0.9% for men and 3.3% for women.

Generally, it is assumed that 14-30% of the CRPS patients may develop dystonia.[28] In comparison with CRPS, the female to male ratio is further increased in patients with CRPS-related dystonia: the ratio was 6.2 in a study that was performed at the Leiden University Medical Centre.[6]

Course

Of 74 CRPS patients that were identified in a population study in the United States, 55 patients (74%) underwent resolution, often spontaneously.[29] In a more recent Dutch study, it was shown that at a minimum of 2 years since onset 65 of 102 CRPS patients (64%) still fulfilled the IASP criteria for CRPS.[30] The course of CRPS-related dystonia was studied in the 185 patients who visited the Department of Neurology of the Leiden University Medical Centre between 1998 and 2004.[6] It was found that the presence of dystonia in the affected limb increased the hazard of developing dystonia in a second limb with 2.29 (95% CI 1.67-3.14). Furthermore, dystonia in two extremities increased the hazard of developing dystonia in the third to 2.15 (95% CI 1.33-3.48), and dystonia in three extremities increased the hazard of developing dystonia in the fourth to 7.4 (95% CI 3.74-14.65). In contrast, as the number of extremities with only non-motor CRPS symptoms increased, which occurred in 21 patients (11.4%), the hazard of developing dystonia decreased. However, this study investigated a highly selected population, and these findings may not be generalised.

Treatment

The Dutch Institute for Healthcare Improvement (CBO) developed the evidence-based 'Guideline Complex Regional Pain Syndrome type I'.[31] The scientific support for most treatments in CRPS is limited. Figure 2.1 shows the proposed treatment algorithm which includes the treatment of dystonia. Clearly, the treatment of CRPS-related dystonia is still in its infancy. Intrathecal baclofen is considered a promising therapy for severe dystonia.[22] However, until now, treatment was restricted to the experimental setting.

Aims of this thesis

First aim was to study the pathophysiology of CRPS-related movement disorders. Neurologists differ in their opinions on whether CPRS-related dystonia is psychogenic or not. *Chapter 2* describes, from a historical point of view, the sway between organic and psychogenic explanations for dystonia including CRPS-related dystonia. The sensory system in CRPS-related dystonia patients was evaluated by means of quantitative somatosensory thermotesting, which is described in *chapter 3*. *Chapter 4* describes the clinical characteristics of CRPS-related dystonia. These findings were used in a neuromuscular model of the wrist to investigate a possible role of disrupted proprioceptive reflexes. The results from cerebrospinal fluid analysis are described in *chapter 5*. We used coherence analysis to investigate myoclonic jerks that occurred in CRPS patients with or without dystonia. The findings are described in *chapter 6*.

Second aim was to find new treatments for CRPS-related movement disorders. Two chapters describe studies that evaluated continuous administration of intrathecal baclofen (*chapter 7*) and glycine (*chapter 8*). Both these agents have the potential to reverse the lack of inhibition in the central nervous system. A study that evaluated intrathecal methylprednisolone in CRPS is described in *chapter 9*. We found a high incidence and prolonged course of post-dural puncture headache after implantation of the pump for intrathecal administration. This observation and, moreover, its implications, are described in *chapter 10*.

Figure 2.1 (next page). CBO treatment algorithm for CRPS in adults (printed with permission from Van Zuiden Communications).[31]

Primary prevention:
• in the case of wrist fractures, vitamin C

Secondary prevention (for existing or past CRPS-I):
• postpone surgery until CRPS-I symptoms have almost disappeared
• keep the operation as short as possible and try to prevent to operate without removing blood from the operated extremity
• adequate pre- and perioperative pain control
Consider:
• perioperative stellate ganglion block or administer regional i.v. anaesthesia (clonidine)
• anaesthesia with sympathicolytic effect
• perioperative calcitonin

Treatment:
Paramedical:
• physiotherapy according to a protocol
• occupational therapy according to a protocol

In the event of a discrepancy between symptoms that can be objectively described and the patient's pain-related behaviour, if treatment stagnates, or if the patient is experiencing extreme suffering:
• consult a psychologist

Treatment of children with CRPS-I:
• In addition to drug treatment, physiotherapy and/or occupational therapy
• if necessary, psychological support from a paediatric/adolescent psychologist

Drug treatment:
• pain medication according to the WHO ladder (up to step 2)
• 50% DMSO / n-acetylcysteine

In the case of allodynia/hyperalgesia:
• gabapentin
• carbamazepine
• amitriptyline/nortriptyline

In the case of dystonia, myoclonia or muscle spasms:
• oral baclofen, diazepam or clonazepam

If ineffective:
• intrathecal baclofen at a specialised clinic

In the case of cold CRPS-I:
• vasodilating medication

If ineffective:
• percutaneous sympathetic block

Communication and information:
• verbal and written
• involve relatives
• put patients in touch with patient association for CRPS-I
CRPS-I and work:
• have the patient's working conditions assessed by the company doctor
• consult the patient's company doctor / doctor treating him or her to establish how much strain he or she can bear

Other therapies:
If other therapies prove ineffective, you may consider:
• spinal cord stimulation at a specialised clinic
If recurrent infections occur, you may consider:
• amputation at a specialised clinic

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Chapter 2

How psychogenic is dystonia? Views from past to present

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Abstract

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

Introduction

For many years, physicians have observed and discussed the remarkable signs of what we nowadays call dystonia. The introduction of the term dystonia as an abnormality of tone with coexistent hypo- and hypertonia goes back to 1911 when the well-known Berlin neurologist Hermann Oppenheim (1858-1919) introduced *dystonia musculorum deformans*, which was later renamed early-onset generalised torsion dystonia.[1] In 1967, Wolfgang Zeman (1921-2001) and Paul Dyken reported the presence of milder forms of dystonia in dystonia musculorum deformans families, including cases of isolated writer's cramp.[2] In 1976, David Marsden (1938-1998) proposed the term focal dystonia for blepharospasm, oromandibular dystonia, dystonic writer's cramp, and torticollis, as well as for axial dystonias, arguing that these were closely related to generalised dystonia.[3] Up to the present, this view has not changed. Over the years, however, there has been a discussion on whether the aetiology of dystonia is either organic or psychogenic. In this paper we study the evolution of ideas with respect to dystonia, in particular whether or not it was considered an organic or psychogenic affliction. We will put the historical evolution against the background of present-day knowledge resulting from functional imaging and neurophysiological studies, and of the blurred border between organic and psychogenic.

Methods

We started our search on dystonia history using two standard books on the history of medicine.[4,5] Furthermore, we used the PubMed database by entering the term 'dystonia' with limitation to 'history of medicine'. In addition, we used medical and neurological textbooks from the 19th and 20th century written in English, French, German, or Dutch.[6-16] In the tables of contents and subject indexes we searched for dystonia, spasm(s), spasmodic contortion or contraction, torticollis, wryneck, (writer's) cramp, scrivener's palsy, occupational neurosis (English); dystonie, torticolis (mental), spasme clonique (du sterno-mastoïdien), spasme fonctionel (du sterno-mastoïdien), crampe fonctionelle, crampes des écrivains (French); Dystonie, Torticollis, Schreib(e)krampf, Funktionskrämpfe, Beschäftigungsneurose (German); dystonie, torticollis, (ver)kramp(ing), and schrijvers-kramp (Dutch). In addition, we searched for relevant literature in the reference lists of consulted books and papers. As many nineteenth- and early twentieth-century primary textbooks refer to the work of Duchenne and Bell, we chose to discuss their descriptions in more detail. When dealing with the question whether a particular author considered a disorder psychogenic or organic, we assumed a spectrum from organic to psychogenic between which ideas of the individual authors could be placed, as far as could be derived from the text.

Definition of dystonia

The word *dystonia* was introduced in 1911.[1] Later its meaning was changed several times. For example, Derek Denny-Brown (1901-1981) considered dystonia a disorder with a fixed posture or oscillation between two or more fixed postures (Denny-Brown, 1965; Denny-Brown, 1966). The modern definition is "a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures".[17] In this article, we use the latter definition.

Definitions of neurosis and hysteria

In the late 18th and early 19th century, neurosis was defined as the category of clinically well-characterised nervous diseases without known pathological substrates.[18,19] Throughout the 19th century, this category became smaller when neuropathological substrates of several of these diseases were established.[20] Hysteria was a subcategory within the neuroses, in which neurological signs were similar to those in patients who suffered from nervous diseases with known anatomic lesions, although somewhat different and usually more extensive. In the late 19th century, Charcot assumed that hysteria arose from a lesion of an undetermined structural or functional nature and he expected that the pathological basis would be found in due course. The neurological defect was believed to result from a combination of hereditary predisposition and an environmental, provocative factor, which usually was a physical or emotional shock.[21] Therefore, throughout history the term psychogenic cannot always be considered equal to non-organic, in particular in the pre-Freudian period. After this period non-organic mostly did mean psychogenic. The meanings of neurosis and hysteria changed and finally the terms were used solely in descriptions of psychiatric diseases. At present, the terms are used less often, and no longer listed in the Diagnostic and Statistical Manual of Mental Disorders.[22] In this article, where needed, we clarify the context of these words.

Results

Primary generalised dystonia

In 1871 William Hammond (1828-1900) reported on three patients "in which the most characteristic symptoms are an inability to retain the fingers and toes in any position in which they may be placed, and their continual motion".[23] He mentioned the acquired disorder 'athetosis' and hypothesised on a striatal lesion. Hammond's patients may not be considered dystonic patients – although today most authors consider athethosis part of the dystonia spectrum[24] but it is important to mention Hammond's coining of the term athetosis. In 1897, the Spanish physician Lluis Barraquer I Roviralta (1855-1928) reported another patient with athetosis, which later was considered the first description of generalised torsion dystonia.[25,26] In 1908, the German Marcus Walter Schwalbe (1883-1927) described hysterical symptoms in the siblings Fanny, Heimann, and Wulf Levin, suffering from tonic cramps, which is now recognised as early-onset generalised torsion dystonia (Figure 2.1).[27,28] Among the most important hysterical characteristics there was the presence of pressure points (called 'hysterogenic zones' in Charcot's work[21]), i.e. body areas in which cramps may be provoked by pressure.

Familial involvement was another feature. In 1911 Oppenheim launched the term *dystonia musculorum deformans* for the same disorder.[1] He reported on four patients, who were Jewish children. Illustrative is the description of a 14-year old girl with a 'dromedary gait' "indem der sättelformige ausgebuchtete Rücken in eine fast horizontale Lage kommt, und zwar fällt die Rumpfbeugung zusammen mit dem Aufsetzen des linken Beins, während der Rumpf sich hebt beim Schwingen des linken Beins" [because the saddle-shaped back acquires an almost horizontal position, in which the left leg posture phase is accompanied by trunk flexion, and the swing phase by trunk elevation]. He was convinced that it was an organic disease without concomitant hysteria.

Subsequently, dystonia musculorum deformans became a collective term for a variety of neurologic disorders.[29] There was a continuing discussion on the characteristics of the disorder, and a pathological substrate was still unknown. For these reasons, the concept of dystonia as a disease was demolished during the tenth Réunion Neurologique Internationale Annuelle in Paris (1929). Subsequently, the Danish physician Auguste Wimmer (1872-1937) concluded that dystonia was no more than a syndrome.[30] In the meantime, a psychogenic explanation had emerged for various nervous disorders without anatomic lesions. One of the founders of psychogenesis was Sigmund Freud (1856-1939). From 1888 to 1910 he described several patients who suffered from hysteria and in whom symptoms were related to conflicts and psychological defence.[31] The effectiveness of psychological intervention supported this new and revolutionary theory. Exploring and resetting the unconscious mind, by means of 'psychoanalysis', became a successful therapy in many cases of hysteria. Since then, many patients with generalised dystonia underwent this or other forms of psychotherapy.

In 1944, Ernst Herz (1900-1965) published three frequently cited articles on his studies of dystonia cases. He considered dystonia a "clinical entity" with "characteristic irregular, involuntary motor phenomena", "a peculiar distribution of 'excess of motion' and 'excess of tension'", and "without recognizable etiologic factors at onset".[32-34] In 1959 the hereditary nature of dystonia musculorum deformans was demonstrated[35] and ten years later a report was published on the limited efficacy of psychotherapy in 44 patients with torsion dystonia.[36] In the same year, Irving Cooper (1922-1985) reported on a 77% success rate after unilateral or bilateral surgery of the thalamus or globus pallidus in 144 dystonia musculorum deformans patients.[37] In the 1960s Denny-Brown reported his landmark studies on dystonia. He caused selective lesions in monkey brains which led to uncontrollable abnormal postures and movements resembling dystonia. It was remarkable

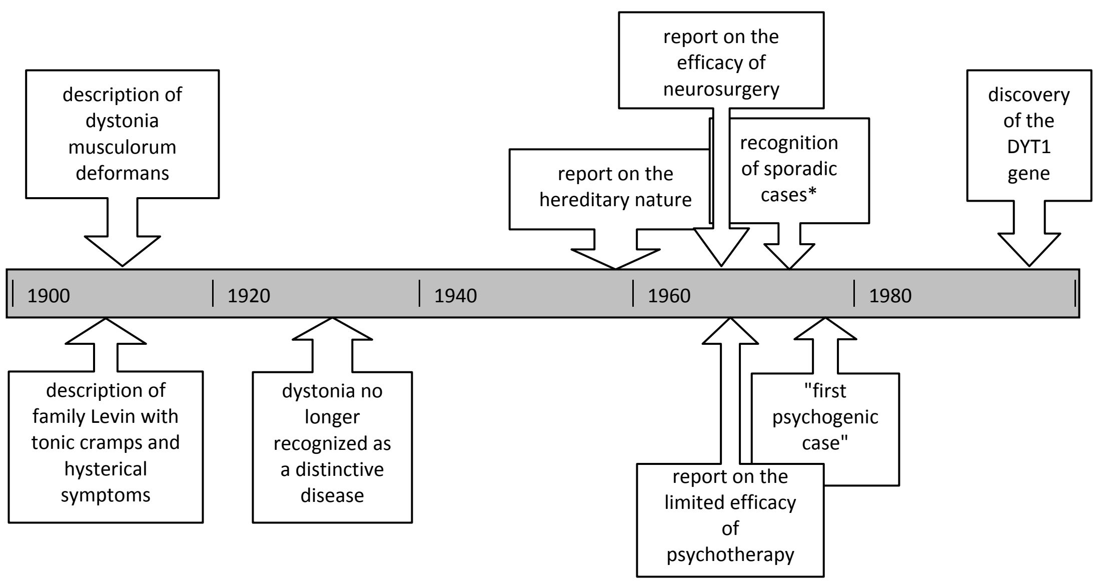

Figure 2.1. Developments on generalised dystonia in the 20th century. See the text for references.
*Not for the first time but more convincing than ever before.

to observe that damage in different anatomical structures might have the same consequences. Denny-Brown assumed that dystonia resulted from an imbalance of reflex responses in the central nervous system.[38-40] In 1975, an International Symposium on Dystonia was organised. In the preface of the conference book, Eldridge and Fahn wrote:

> In the past, many victims of dystonia and their families have been caused anguish and hardship over and above that caused by the disease itself owing to the frequent misdiagnosis of the symptoms as manifestations of a psychiatric ailment. We hope that the present volume will facilitate accurate diagnosis, assist practicing physicians in treating their dystonic patients, encourage them to report their observations and results, and stimulate clinical and basic research workers in efforts to elucidate the causes and eventual treatment of dystonia and related disorders.[41]

At this symposium, Marsden emphasised the existence of sporadic torsion dystonia.[42] Fahn and Eldridge stated that psychologically based dystonia was a rare or non-existent condition.[43] However, three years after the symposium (1978), the "first case of psychogenic dystonia" was reported[44] and in 1983, at the 35th annual meeting of the American Academy of Neurology, another five followed.[45] The first patient was a 15-year-old girl who had simulated her dystonic symptoms and signs. She was admitted after a failed suicide attempt and told that she had faked her symptoms: "she discarded her leg brace, and the sustained contractions in her leg and arm immediately improved". The histories of the other five patients were not included in the publication.

In 1984, an *ad hoc* committee, consisting of members of the Scientific Advisory Board of the Dystonia Medical Research Foundation, re-defined dystonia as "a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures".[17] Four years later a classification for psychogenic dystonia followed (Table 2.1).[46] The first locus (9q32-34 region) for idiopathic dystonia (DYT1) was found in 1989[47] and ten years later the same group identified the gene, describing a unique 3-base pair deletion in the coding region, which was responsible for almost all their cases with early-onset, but for only a few with late-onset idiopathic torsion dystonia.[48]

Table 2.1. Definitions on the degree of certainty of the diagnosis of a psychogenic dystonia[46]

Documented	Persistent relief by psychotherapy, by the clinician utilizing psychological suggestion including physiotherapy, or by administration of placebos (again with suggestion being a part of this approach), or the patient must be witnessed as being free of symptoms when left alone supposedly unobserved
Clinically established	The dystonia is inconsistent over time or is incongruent with classical dystonia, plus at least one of the following features: - other neurologic signs are present that are definitely psychogenic, e.g. false weakness, false sensory findings, and self-inflicted injuries - multiple somatizations are present - an obvious psychiatric disturbance is present

Probable	- The dystonia is inconsistent over time or is incongruent with classical dystonia, but there are no other features, or
	- The dystonia is consistent and congruent with organic dystonia, however at least one of the following features is present:
	  - other neurologic signs are present that are definitely psychogenic, e.g. false weakness, false sensory findings, and self-inflicted injuries
	  - multiple somatizations are present

Possible	The dystonia is consistent and congruent with organic dystonia, however, an obvious emotional disturbance is present

Cervical dystonia (Table 2.2)

One of the earliest descriptions of cervical dystonia was given by the Swiss physician Felix Platerus, also known as Plater (1536-1614).[49,50] He described a case of 'spasmi species, in qua caput in sinistrum latus torquebatur' [a kind of spasm in which the head was turned to the left side]. The Dutch Nicolaas Tulp, or Tulpius (1593-1674), well-known from the famous Rembrandt painting *The Anatomy Lesson* of 1632, described dissection of the sternocleidomastoid muscle as a therapy for what he called 'obstipi capitis' [crooked head] in his *Observationes medicae*.[51,52] However, this patient had had torticollis from childhood and the origin was probably mechanical.

Table 2.2 (continued on next pages). Historical descriptions on cervical dystonia

Year	Author	City	Terminology	O/P	Comments
1614	Plater[49,50]	Basel (CH)	spasmi species, in qua caput in sinistrum latus torquebatur	O	case report; explained as a disorder of the muscle and surrounding tissue
1641	Tulp[51,52]	Amsterdam (NL)	obstipi capitis	O	probably mechanic origin; dissected the involved muscle
1765	Lorry[50,53]	Paris (FR)	colli singularem omninò distortionem	P	case report in a monography on melancholia; explained as due to boredom and therefore aversion to life
1768	Boissier de Sauvages[54,55]	Montpellier (FR)	obstipitas spasmodica	O	classified as partial tonic spasms, together with strabismus, tics, contractures, ankylosis, cramps and priaprism
1822	Dupuytren[56]	Paris (FR)	torticolis, caput obstipum	O	divided the sternocleidomastoid muscle
1825	Middlesex Hospital[57]	London (UK)	spasmodic affection of the muscles of the neck	U	case report
1825	Gilby[58]	Bristol (UK)	contraction of the muscles of the neck	O?	efficaciously used electricity in the corresponding contralateral muscles
1838	Stromeyer[59]	Hannover (DE)	Krampf des Kopfnickers	O	dissected the involved muscle(s)
1844	Bell[60]	Edinburgh (UK)	spasmodic contortion of the head and neck	O	suspected a diseased nerve
1846	Romberg[61]	Berlin (DE)	Halsmuskelkrampf	U	in most cases unknown cause, sometimes due to physical strain; described that some think that it may be

					due to intense emotions
1861	Duchenne[62]	Paris (FR)	spasme du sternomastoïdien	O	may be cured by continuous stretch to the antagonists by means of an apparatus; no success with electricity
1867	Middlesex Hospital[63]	London (UK)	spasmodic contraction of cervical muscles	O?	case report; spinal accessory nerve was dissected, although without efficacy
1872	Jaccoud[64]	Paris (FR)	hyperkinésie de l'accessoire de Willis	O	clonic form: rare, unknown cause; tonic form: either congenital, vertebral disorder or due to pressure on sensible nerve (reflex cramp)
1873	Charing Cross Hospital[65]	London (UK)	clonic torticollis	O	case report; improvement by electricity together with rhythmical exercise
1888	Charcot[66]	Paris (FR)	spasme clonique du sterno-mastoïdien et du trapèze	O ≈ P	case report; improvement with electricity to the atrophied contralateral muscle
1888	Gowers[10]	London (UK)	spasmodic wry-neck	O + P	'not-organic' variant (= hysterical = partly moral, partly physical) tends to spread from the neck to the trunk
1889	Freud[67]	Vienna (AT)	Genickkrämpfe	O	case report (Frau Emmy v. N…); hysteria patient who underwent hypnosis; Genickkrämpfe were not considered hysterical
1890	Keen[68,69]	Philadelphia (US)	spasmodic wry neck	U	divided the dorsal rami of the C1-C3 spinal nerves in a patient in whom

					spinal accessory nerve division was unsuccessful; some improvement
1893	Brissaud[70]	Paris (FR)	torticolis mental	P	believed that torticolis was a tic (P), not a spasm (O); the touch that was able to correct proved the psychic nature
1894	Voisin[71]	Paris (FR)	torticolis intermittent	P	case report; cured with suggestion during hypnosis
1894	Oppenheim[13]	Berlin (DE)	Krämpfe im Bereich der Halsmuskeln	O ≈ P	hereditary or congenital instability of kinetic centres in the cerebral cortex
1896	de Quervain[72]	La-Chaux-de-Fonds (CH)	torticolis spasmodique	O?	efficaciously dissected involved muscles and nerves (method from Kocher); treatment effect might be due to suggestion of a cortical center
1900	Babinski[73]	Paris (FR)	torticolis spasmodique	O	case report with extensor toe response
1902	Meige & Feindel[74]	Paris (FR)	torticolis mental	P	the 'geste antagoniste efficace' is characteristic; careful and prolonged observation is needed to distinguish it from 'torticolis-spasme' (O)
1905	Kollarits[75,76]	Budapest (HU)	torticollis mentalis	P	geste antagoniste was named "Brissauds Handgriff"
1907	Curschmann[77]	Mainz (DE)	spasmodischen torticollis	O	vestibular disorder; quinine was efficacious
1914	Mohr[12]	Koblenz (DE)	Torticollis mental	O < P	often in neuropathic patients; organic causes must be excluded (ocular, auricular; cervical spine, or brain

					disease)
1914	New York Neurological Society[78]	New York (US)	mental torticollis	P	Clark reported on the efficacy of psychotherapy; was criticised by others
1923	Wartenberg[79]	Freiburg im Breisgau (DE)	Torticollis	O > P	pathophysiological description on the influence of sensible input in extrapyramidal disorders (including the geste antagoniste)
1923	Cushing[80]	Boston (US)	spasmodic torticollis	U	performed surgery with unilateral division of the spinal accessory nerve and ventral and dorsal 1st to 3rd roots, with success
1935	Yaskin[81]	Pennsylvania (US)	spasmodic torticollis	O < P	psychotherapy before surgery
1938	Critchley[82] at the Annual Meeting of the British Medical Association	London (UK)	spasmodic torticollis	O or P	distinguished: psychogenic; postencephalitic; associated with an extrapyramidal disease; and progressive spasm of doubtful nature
1940	Kinnier Wilson[11]	London (UK)	torticollis	O or P	distinguished: neuralgic, occupational (P), spasmodic, paralytic, hysterical (P) and congenital torticollis and torticollis tic (P)
1943	Patterson and Little[83]	Ann Arbor (US)	spasmodic torticollis	O >> P	103 cases; promoted surgery
1945	Paterson[84]	Edinburgh (UK)	spasmodic torticollis	O or P	21 cases; psychotherapy is the treatment of choice
1949	Herz and Glaser[85]	New York (US)	spasmodic torticollis	O	43 cases; though organic in nature, the clinical picture may be

					influenced by psychogenic factors
1965	Denny-Brown[38,39]	Boston (US)	torticollis	O	performed experiments in monkeys; described that torticollis arises from damage to the pretectal region, and is due to distortion of optokinetic reflexes
1967	Brierley[86]	Newcastle-upon-Tyne (UK)	spasmodic torticollis	O or P	efficaciously used behaviour therapy with conditioning through electric shocks
1971	Mitscherlich[87]	Düsseldorf (DE)	spasmodic torticollis	P	psychoanalytical treatments in 60 patients; >5,000 hours; severe ego-regression in all cases
1974	Brudny *et al*.[88]	New York (US)	torticollis	O?	improvement with sensory feedback therapy (13 cases); also improvement in spasticity patients
1976	Marsden[3]	London (UK)	torticollis	O	focal dystonia; suspected an abnormality in the extrapiramidal system
1985	Tsui *et al*.[89]	Vancouver (CA)	spasmodic torticollis	O	first report on the efficacy of botulinum toxin
1987	Rentrop and Straschill[90]	Berlin (DE)	spasmodic torticollis	O + P	stated that in some cases psychotherapy is indicated

O = organic; P = psychogenic; O > P = majority of cases is organic; O or P = cause is organic in some cases and psychogenic in other cases; O + P = cause is a combination of organic and psychogenic factors in every; U = unknown cause.

The well-known Scottish surgeon-anatomist Charles Bell (1774-1842) stated that the origin of 'spasmodic contortion of the head and neck' was nerve rather than muscle dysfunction.[60] One of his patients, Mary Preston, developed the disease following a hard and protracted labour. In Bell's view, a disorder of the accessory nerve but not other nerves, due to strain, might lead to unbalanced muscle drive and thus to the disease. Interestingly, the same case was also reported elsewhere,[57] but according to these authors, the disease was not limited to the distribution of the accessory nerve. Their disagreement with Bell was underlined by their commentary "We have frequently had occasion to notice the very ingenious manner in which Mr. Bell perverts facts, in order to meet his own particular views of a case". The French physician Guillaume-Benjamin Duchenne (1806-1875), who applied electricity for a variety of disorders in Paris hospitals, reported that 'spasme fonctionnel du sterno-mastoïdien' is quite resistant to treatment.[62] Instead, he advised therapy by applying continuous stretch of the antagonists with the use of an instrument.

During one of his well-known Tuesday Lessons, on June 26, 1888, Charcot presented a 63-year old man with 'spasme clonique du sterno-mastoïdien et du trapèze' [clonic spasm of the sternocleidomastoid and the trapezius muscles], which had been present for eight months.[66] The disorder started after the patient, who was a stockbroker, had lost all his money. On July 10, 1888, he was presented again after being successfully treated with electricity. Five years later, one of Charcot's former students, Edouard Brissaud (1852-1909), introduced the term 'torticolis mental'.[70] In his view, the condition was psychogenic, which was evident from the fact that the patient was able to correct the powerful muscle activity by simply touching the head, later named the 'geste antagoniste efficace'.[74] Emphasizing the psychogenic nature again, the Hungarian Jenö Kollarits (1870-1940) reported on six 'torticollis hystericus' cases in 1905.[75] Therapeutic dissection of the involved muscles or nerves, as performed by the Swiss surgeon Fritz de Quervain (1868-1940),[72] was considered malpractice according to Kollarits, who, instead, stated that therapy should be based on suggestion.

In this period, there was much discussion on torticollis in the scientific community. At the New York Neurological Society (1914), Pierce Clark (1870-1933) presented an adult man with 'mental torticollis' which, he said, was the consequence of pleasurable stroking movements by his mother, before the age of six.[78] In reaction, Bernard Sachs (1858-1944) said, "if this indicated the future trend for our present-day neurology, then the less we hear of it, the better". The debate went on for several decades. In 1935 Joseph Yaskin (1891-1955) wrote that before surgery, every case of 'spasmodic torticollis' should receive a trial of psychotherapy.[81] In 1943 Patterson and Little reported on 103 cases with spasmodic torticollis,[83] stating that the aetiology was usually organic and that surgery, intradural rhizotomy in particular, was very satisfactory. However, in 1945 the Scottish physician Paterson presented 21 cases, concluding that psychotherapy was the treatment of choice unless gross signs of neurological disease were present.[84]

At the 1975 International Symposium on Dystonia *(vide supra)*, Marsden presented arguments that spasmodic torticollis, as well as blepharospasm, oromandibular dystonia and dystonic writer's cramp *(vide infra)*, were focal dystonias with an organic aetiology. He summarised the reasons why they had been regarded psychogenic (Table 2.3),[3] and subsequently explained his ideas about functional abnormalities in the extrapyramidal motor system.[3] Obvious arguments were their occurrence in early-onset generalised torsion dystonia and the similarities with late-onset generalised torsion dystonia: both focal dystonia and late-onset generalised torsion dystonia had a comparable age of onset and were usually neither progressive nor hereditary. A new name was introduced in the 1980s: 'cervical dystonia'. In 1985 the Canadian Tsui reported for the first time the successful use of botulinum toxin injections in 12 patients,[89] which eventually became the standard treatment. During the past few decades hardly any reports on psychogenic cervical dystonia cases have been published.

Table 2.3. Seven reasons why focal dystonias were regarded as psychogenic[3]

1	The bizarre nature of the dyskinesias
2	Their appearance frequently only on certain actions, other motor acts employing the same muscles being carried out normally
3	Their relief by certain inexplicable trick actions
4	Their exquisite sensitivity to social and mental stress
5	The failure so far to find any anatomical, physiological, or biochemical abnormality in any of these conditions
6	The belief that such patients show overt psychiatric disturbance
7	A psychopathological interpretation of the significance of, for example, eye closure or neck turning

Writer's cramp

In 1713 the Italian physician Bernardino Ramazzini (1633-1714) recognised intense fatigue of the hand and arm, which resulted in failure of power, as an occupational disorder in professional writers.[91] In 1844 (published posthumously), Bell most probably described writer's cramp when he reported on an ambiguous condition in which writing had become impossible while the arm strength remained normal.[60] In 1861 Duchenne reported on 'crampe des écrivains' in which electricity was not a very successful therapy. However, he advised an ingenious prosthesis.[62] He preferred the names 'spasme fonctionnel' and 'paralysie musculaire fonctionelle' because the disorder was not restricted to cramps and could be provoked not only by writing but also by other manual actions.

> En résumé, les faits et les considérations exposés précédemment démontrent, comme je l'ai dit au commencement de cette note, qu'il existe une maladie caractérisée par un spasme douloureux ou indolent (contracture, contractions clonique, tremblements), ou par une paralysie musculaire; que ces troubles se manifestent seulement pendant l'exercice de certains mouvements volontaires ou instinctifs; enfin, qu'ils peuvent siéger dans des régions fort diverses.[62] [In summary, the former findings and considerations show, as I described in the beginning of this report, that there is a disease which is characterised by painful or painless spasms (contracture, jerks, tremor) or paralysis in which the signs only occur during certain (in-)voluntary actions; the involved body parts are diverse.]

Similar to the situation in cervical dystonia, the debate on aetiology started in the early 20th century. In 1914 the German Fritz Mohr (1874-1957) summarised the two conflicting theories in Lewandowsky's *Handbuch der Neurologie*.[12] Writer's cramp was explained by some authors as a purely organic disorder, e.g. as a reflex cramp through motor nerves that was initiated by painful sensory input**.** The German physician Moritz Romberg (1795-1873) was mentioned as one of the early advocates (with reference to the 1853 edition of Rombergs *Lehrbuch der Nervenkrankheiten des Menschen*[92]). Others, including Mohr himself, believed that only people with certain personality characteristics were prone to develop the disorder, a psychological factor possibly being involved. From that view, accurate psychoanalysis would be the best therapy for patients with writer's cramp. Kinnier Wilson's (1878-1937) 1940 edition of *Neurology*, described 'writers' cramp' as an occupational neurosis, physiologically akin to hysteria, and assumed a cortical dysfunction.[11] Prevention by excluding people prone to develop 'spasms' from certain occupations, was considered the best treatment.

As in other focal dystonias, Marsden advocated the organic nature of writer's cramp *(vide supra)*,[3] which he and Sheehy further demonstrated in a report on 29 patients, (1982).[93] However, in 1983 Cottraux (France) *et al*. reported on the success of behavioural therapy and biofeedback in 9 of 15 patients with writer's cramp,[94] and the 1985 edition of John Walton's *Brain's Diseases of the nervous system* stated:

> I find the conclusions of Sheehy and Marsden inherently implausible and unacceptable. In my experience even subtle physical signs are absent in the many 'simple' cases that I have seen and neither focal dystonia nor any other organic disorder could in my view impair movements only when they take part in one co-ordinated act while leaving totally unaffected all other precise and complex voluntary actions involving the affected member.[95]

The 1993 edition stated that writer's cramp had "in the past been attributed to psychological factors, but there is now good evidence that this is not so". Interestingly, the author referred to the same single publication of Sheehy and Marsden.[93,96] In 1991 Rivest *et al*. reported for the first time on the use of botulinum toxin for writer's cramp,[97] which is currently considered the most effective treatment.

Fixed dystonia related to complex regional pain syndrome

In 1864 Silas Weir Mitchell (1829-1914) described a series of American Civil War (1861-1865) victims with gunshot wounds who developed burning pain and a shiny red skin after nerve injury.[98,99] He suspected that traumatic nerve irritation was the cause and named the condition 'causalgia'. He recognised that patients might come into an unendurably painful hyperaesthetic state. In 1892, Charcot demonstrated another entity in two patients: 'oedème bleu des hystériques', a painful condition with oedema and blue discoloration of the skin, which may occur in combination with an hysterical limb contracture or paralysis.[100]

> L'historique de cette affection n'est pas bien long. Je l'ai pour la première fois mentionnée et distinguée à propos d'un malade de cet hospice [with reference to the *Leçons du Mardi* from 1889], que je suis d'ailleurs à même de vous présenter de nouveau. Puis, à plusieurs reprises je l'ai observée chez des personnes de la ville, combinée tantôt avec des altérations de la sensibilité (anesthésie ou hyperesthésie), tantôt avec des troubles du mouvement (paralysies et contractures). Il s'agissait presque toujours de sujets marqués, par la présence des stigmates, au sceau de l'hystérie la mieux caractérisée.[100] [This disorder has a short history. For the first time [in 1889], I reported on a patient from this hospital [Hospice de la Salpêtrière]. From then, I recognised more cases. In a number of them, I observed sensory abnormalities (anesthesia or

hyperesthesia) or movement disturbances (paralysis and contractures). Mostly, patients were extraordinary persons having characteristics which may be considered hysterical.]

In 1946, Evans renamed the latter disorder 'reflex sympathetic dystrophy', because he suspected involvement of spinal reflexes as well as sympathetic efferent fibres.[101] It was different from causalgia in that it occurred in the absence of major nerve trauma. However, in 1994, the International Association for the Study of Pain introduced the name CRPS for both conditions: type 1 (reflex sympathetic dystrophy) and type 2 (causalgia).[102] The diagnostic criteria for CRPS type 1 were: (i) presence of an initiating noxious event, or a cause of immobilization (not obligatory item); (ii) continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event; (iii) evidence at some time of oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain; and (iv) no other condition that would account for the degree of pain and dysfunction. CRPS type 2 has the same characteristics, but is accompanied by nerve injury.[102]

In 1984 Marsden *et al*. reported on four 'reflex sympathetic dystrophy' patients who had dystonia, characterised by fixed, predominantly flexion, postures.[103] They believed it to be 'a distinct clinical syndrome'. Six years later Schwartzman *et al*. reported on motor disturbances in 43 patients with 'reflex sympathetic dystrophy', in whom the most dramatic characteristic was a dystonic posture in all patients.[104] The authors hypothesised on a spinal cause. In 1993, a series of 18 patients with similar characteristics was reported.[105] However, it was remarkable that many patients met the criteria for psychogenic dystonia from 1988 *(vide supra)* (Table 2.1). They concluded that the aetiology of this disorder, psychogenic or organic, was unknown.[105] In 2004 it was reported that many patients with features of CRPS and dystonia also had features of psychogenic dystonia.[106] In the same year it was stated that a very large proportion had a primary psychogenic disorder.[107] In a more recent paper on 110 CRPS type 1 patients with dystonia predominantly characterised by tonic flexion postures, the authors hypothesised that maladaptive plasticity with disinhibition of spinal mechanisms might be the cause.[108]

Discussion

There has been a continuous vacillation between psychogenic and organic explanations for (i) primary generalised dystonia; (ii) cervical dystonia; (iii) writer's cramp; and (iv) CRPS-related fixed dystonia. Although at first sight the attributions of the terms psychogenic and organic in Table 2.2 seem quite obvious, it seems more realistic to assume a spectrum with two ends between which attributions were moving. Moreover, the discussion between an organic and psychogenic aetiology has not always been explicit (particularly in the 19th century). The opinions of several authors could only be derived or interpreted from their hypotheses on aetiology and their therapies.

An example is Schwalbe's description of hysterical symptoms in siblings with generalised dystonia. In the late 19th century, Charcot considered hysteria a neurosis, similar to paralysis agitans, epilepsy and chorea, which were diseases without known pathology. For paralysis agitans he expected that the lesion would be discovered.[109] Hysteria appeared a more difficult obstacle for Charcot's clinical-anatomic method and, when describing male traumatic neurosis, he moved towards a psychological conception of hysteria.[109] This was further elaborated by Freud and his followers.[110] Hysteria evolved from a disease in which an organic pathophysiology was suspected but not found, to a psychogenic disease in the late 19th and early 20th century. Recent functional imaging studies in these patients have shown specific cerebral abnormalities.[111,112] From these studies, it is suspected that affective or stress-related factors modulate cerebral sensorimotor representations through interactions between limbic and sensorimotor networks. It is hypothesised that primitive reflexive mechanisms of protection and alertness, which are partly independent of conscious control, are involved.

Primary generalised dystonia

The patients of Oppenheim made him move to the organic end of the spectrum, whereas Freud and his followers in psychoanalysis, moved in an opposite direction. The improved description of the 'clinical entity' in the 1940s (Herz), the new hereditary cases described in the 1950s (Zeman), and the limited efficacy of psychotherapy in torsion dystonia, as well as the effects of surgical treatments and the lesion studies in the 1960s (Eldridge, Cooper, and Denny-Brown respectively) pushed the explanatory ideas back into the organic again. This culminated in Eldridge's & Fahn's 1975 statement (published in 1976). However, a new movement towards psychogenesis soon followed with the recognition of psychogenic dystonia. Meanwhile, the remaining dystonias kept their position on the organic side of the spectrum, not in the least because of the discovery of the DYT1 gene. Nevertheless, one cannot be too rigid because dystonic disorders with a genetic origin can be triggered by emotional stress.[113]

Cervical dystonia

Bell and Duchenne probably assumed an organic cause for cervical dystonia (Table 2.2). Not much later Charcot, and certainly his student Brissaud, moved to the psychogenic view, in which the interpretation of observing the 'geste antagoniste' played an important role. At the time, such terms as 'torticolis mental' and 'torticollis hystericus' were used on both sides of the Atlantic and dealt with likewise. Psychological and surgical treatments were applied simultaneously in different patients at different places around the 1940s. After Marsden's 1975 presentation, the aetiological ideas on cervical dystonia clearly moved away from the psychogenic to the organic side of the spectrum.

Writer's cramp

To explain writer's cramp, Ramazzini used such terms as 'fatigue' and 'failure of power'. These should be interpreted in the humoral pathophysiological concepts of the time, i.e. animal spirits that flow through the nerves with less power than usual. One would be inclined to consider an organic aetiology here; however, we may question whether Ramazzini was concerned with this question at all. From Bell's description a century later and also from Romberg's work, an organic viewpoint may be recognised. Duchenne again used the term 'functional', which, however, does not necessarily imply that he meant a psychogenic aetiology. A clearer distinction came about in the early 20th century, when Mohr mentioned personality characteristics and a psychological factor, and suggested psychoanalysis for treatment. An interesting position was taken by Kinnier Wilson, assuming cortical dysfunction but comparing it to hysteria. Once more, Marsden's 1975 presentation pushed the aetiology of writer's cramp toward the organic side, with a few exceptions in the 1980s.

Fixed dystonia related to complex regional pain syndrome

Charcot's demonstration of two patients with 'oedème bleu des hystériques' occurred in a period in which he was moving towards a psychological explanation of hysteria. Marsden *et al*. expressed the opinion that the similarities between CRPS cases with dystonia over the world suggested its existence as a distinct clinical syndrome.[103] In contrast, Sa *et al*. stressed that most cases satisfied the criteria for psychogenic dystonia, and should, therefore, be considered as such.[107] But these are based on expert opinion. Such statements are not like a gold standard and should, therefore, be used with caution. Moreover, it is remarkable that the reasons why CRPS-related fixed dystonia is considered psychogenic are at least partly the same as the arguments that were used in the past to explain why focal dystonia was psychogenic (Table 2.3): (i) the dystonia in CRPS may be considered incongruent with classical dystonia; (ii) may be inconsistent over time; (iii) weakness, described in the majority of CRPS cases, might be interpreted as false; (iv) sensory abnormalities, which fit the diagnosis of CRPS, might be interpreted as false sensory findings; and (v) sometimes, psychiatric abnormalities are present. In recent times significant motor cortex abnormalities were found in CRPS.[114,115]

It is clear that the discussions on the psychogenic or organic aetiology of dystonia have been emotional. In some of the periods, particularly during the 20th century, strong believers as well as non-believers may be recognised. Charcot isolated hysterical disorders from other neurologic diseases. In his view, environmental factors ('agents provocateurs') were involved in its pathogenesis. The rise of the psychoanalytic movement, following the work of Freud at the beginning of the 20th century, caused important disagreements between supporters of organic and psychogenic explanations. This was not specific to the interpretation of dystonia, but more generally reflected the division between biologically and psychoanalytic oriented neuropsychiatrists at the time. The success and popularity of psychoanalysis, as well as the lack of an organic substrate for dystonia, encouraged psychogenic theories. As the 20th century proceeded, knowledge in favour of a somatic origin of early-onset generalised dystonia accumulated. Marsden, a leading neurologist in movement disorders, convinced the neurological community in the 1970s and 1980s that both generalised and focal dystonia were somatic entities. However, psychogenic dystonia re-emerged, but as a special category. Nowadays, psychogenic dystonia is thought to be "common" in specialised movement disorders clinics.[116]

The recognition of the hereditary character of dystonia played an important role in attributing an organic nature in the first as well as the last decades of the 20th century. If dystonia had existed as an entity and its hereditary character had been recognised previously, it would probably have been interpreted in a different way, because of the particular concepts of the late 19th century. In this period several neuroses were considered hereditary, in fact a favourite subject in the interpretation models of Charcot.[117] Similar to contemporary psychiatrists (the French Benedict-Augustin Morel (1809-1873) and Valentin Magnan (1835-1916)), he assumed that degeneration was a constitutional factor in certain families ('neuropathic families') in which neuroses including hysteria, alcoholism, and epilepsy could be transformed during the passage from one generation to the next. Hysteria in a parent could be inherited as epilepsy in the child.[109,118] In the 20th century, following delineation of dystonia as an entity and following new discoveries in genetics, the hereditary character led to new insights. Today it is recognised that more than 14 genes are implicated in different monogenic dystonia syndromes, which are frequently inherited as autosomal dominant conditions with reduced penetrance. Most cases of early-onset torsion dystonia are associated with the DYT1 gene mutation.[113] Familial occurrence of cervical dystonia or writer's cramp has been described but appears to be rare.[119]

Medical problems nearly always unravel because of the advent of a new technology, skill, or understanding of a hitherto unknown system of disease. One example is the unravelling of the electric nature of nerve action in the 18th and 19th century. Ideas on whether or not animal electricity existed and played a role in the nature of nerve conduction, were put forward at the end of the 18th century by Galvani and denied by Volta.[120,121] The confirmation had to await more sophisticated sensitive measuring devices such as the galvanometer invented by Du Bois-Reymond in the 1840s, after which observation of the action potential became possible.

What will be the future 'sophisticated sensitive measuring device' that will finally lead to the understanding of dystonia? We believe that the increasing knowledge resulting from neurophysiological and imaging studies, combined with genetic methods, will provide the insight that the explanation of dystonia cannot just be interpreted in terms of organic or psychogenic. These modern methods may show that the interaction of genetic and environmental factors is more complex than was previously thought. When reviewing the pathophysiology of primary adult-onset focal dystonia, Defazio *et al.* suggest that in human focal dystonia there may be an overload of a predisposed sensory system resulting from peripheral injury or repetitive motor activity in a certain part of the body, or both, causing sensory receptive changes in the corresponding cortical brain areas and leading to abnormal regulation of inhibitory interneuronal mechanisms at brainstem or spinal cord level.[119] There seems to be an abnormality of sensorimotor integration and cortical excitability beyond the symptomatic body part. In both generalised and focal dystonia neurophysiological and functional imaging studies indeed point towards abnormalities in the sensorimotor circuitry, which result in a vulnerable central nervous system. Some of these phenomena have been found in asymptomatic gene carriers, as well as in representations of unaffected body parts. It is suspected that a 'second hit' is needed to bring the central nervous system out of balance, which leads to dystonia.[113,119] Musician's dystonia is an interesting example. In a transcranial magnetic stimulation study, cortical changes were found in musicians compared to healthy controls, and these changes were more marked in those with musician's dystonia. It is hypothesised that musician's dystonia is a form of training-induced dystonia.[122]

These suggestions, in particular the assumption of abnormal regulation of inhibitory interneuronal mechanisms at brainstem or spinal cord level, bring us back to Sherringtonian neurophysiology as already suggested by Denny-Brown in the 1960s, when he found that damage in different anatomical structures could have the same consequence, pointing to a basic neurophysiological principle, the final common path, that had been conceived around the turn of the 19th to the 20th century by his teacher Charles Scott Sherrington (1857-1952).[123,124] This may still be a valid explanation of the phenomenology, if not the underlying causation of dystonia in modern terms.

Today, psychogenic dystonia is considered a disorder that results from an underlying psychiatric illness. Its diagnostic criteria have remained unchanged for decades (Table 2.1). In the meantime, however, the border between neurology and psychiatry has been less well defined. For example, schizophrenia,[125] autism,[126] and primary dystonia[113] are now considered neurofunctional disorders. Additionally, it has been shown recently that patients with cervical dystonia or blepharospasm have distinct neuropsychiatric and personality profiles of the anxiety spectrum.[127] Another study shows high psychiatric comorbidity in cervical dystonia, which is unlikely to be a mere consequence of chronic disease and disfigurement.[128] It is attractive to see psychogenic disorders as the consequence of functional crashes in anatomically normal brains. In these disorders, abnormalities found in neurophysiological and functional imaging studies may be interpreted as signs of organic dysfunction. We have only traced two transcranial magnetic stimulation studies on psychogenic dystonia. Interestingly, one of these found similar abnormalities in both organic and psychogenic dystonia: reduced short and long-interval intracortical inhibition and cortical silent period, and an increased cutaneous silent period.[116] The other detected difference: patients with organic dystonia had an increased response to paired associative stimulation compared to patients with psychogenic dystonia.[129] The authors of the latter study concluded that abnormal plasticity is a hallmark of organic dystonia in contrast to psychogenic dystonia.

If we hypothesise further, assuming abnormal regulation of inhibitory interneuronal mechanisms as mentioned above, neurophysiological and functional imaging studies may help to explain dystonia in CRPS due to peripheral injury leading to similar sensory receptive changes. Such mechanisms may also be in play in dissociation disorders, including conversion disorder,[111,112,130-132] thereby associating primary dystonia, CRPS-related fixed dystonia, and sensory and motor disorders in conversion disorder.

Conclusions

Opinions on whether dystonia is either organic or psychogenic continuously changed on a spectrum between the two extremes over the described period. Genetic studies, the limited efficacy of psychotherapy, the effects of surgical treatments, lesion studies, and the recognition that focal dystonias may be minor forms of generalised dystonia pushed the explanatory ideas in the direction of organic. We have seen how insights were influenced by contemporary general pathophysiological concepts (humoral pathophysiology in the pre-1800 period, solid pathophysiology reflected by the clinical-anatomical method thereafter, psychological pathophysiology after about 1900, and genetic and molecular pathophysiology in recent decades), as well as by various research methods, from which we have learn to be prudent with the interpretation of results and to reflect on epistemological mechanisms. Nevertheless, with these reservations in mind, modern neurophysiological and imaging studies may open new ways for the interpretation of dystonia. In both generalised and focal dystonia, studies point towards abnormalities in the sensorimotor circuitry, resulting in a vulnerable central nervous system. They indicate that the old distinction between psychogenic and organic is not easily applicable and perhaps should be abandoned. Similar mechanisms may be in play in CRPS-related fixed dystonia and sensory and motor disorders in conversion disorder. Hypotheses made on the basis of neurophysiological and functional imaging studies need further testing in these groups of patients. In addition, genetic studies may provide further insight. Until more knowledge is available, we must keep in mind the lessons from history and remember 1975:

> In the past, many victims of dystonia and their families have been caused anguish and hardship over and above that caused by the disease itself owing to the frequent misdiagnosis of the symptoms as manifestations of a psychiatric ailment.[41]

Once hurt, twice shy.

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Chapter 3

Thermal hypesthesia in patients with complex regional pain syndrome related dystonia

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Abstract

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

Introduction

Complex regional pain syndrome (CRPS) is characterised by various combinations of sensory, autonomic and motor disturbances, and is usually preceded by a trauma. Patients with CRPS often experience spontaneous pain along with allodynia, hyperalgesia and hyperesthesia.[1,2] In addition, negative sensory phenomena, such as hypesthesia and hypalgesia may be present, especially in chronic cases with longer disease duration.[1,3-5] Autonomic signs include changes in skin temperature and colour, and hyperhidrosis.[1,2] About 25% of the patients develop movement disorders, especially dystonia.[6-8] In contrast to the twisting and repetitive movements generally encountered in primary dystonia, dystonia in CRPS is typically characterised by fixed flexion postures of the distal extremities.

In primary dystonia, there is compelling evidence of altered sensory processing[9] which includes abnormalities in temporal and spatial discrimination and vibration-induced illusion of movements as well as higher-order sensory processing. In CRPS-related dystonia, sensory integration of proprioceptive afferent input was found normal.[10] Until now, small nerve fiber (i.e., C and Aδ) as opposed to large nerve fiber function, has not been studied in this type of dystonia.

The quantitative thermal test is a non-invasive clinical test which assesses the function of small fibers and their central connections.[11,12] The technique quantifies temperature sensation by testing minimally detectable temperature changes ('thresholds') for cold (CDT) and warmth detection (WDT), as well as for heat-induced (HPT) and cold-induced pain (CPT).

In this study we applied the quantitative thermal test to evaluate C and Aδ fiber dysfunction in CRPS patients with dystonia. Since CRPS patients with dystonia may sometimes have three or even four affected extremities, and because an unaffected extremity may be involved on a subclinical level, we chose to compare results primarily with those of healthy controls. Whenever possible, comparisons were also made between affected and unaffected sides

Patients and methods

We studied 44 consecutive CRPS patients (41 women; mean age (SD) 36 (13) years; mean disease duration (SD) 10 (6) years) who were candidates for a study on intrathecal baclofen treatment (Table 3.1). This study was published in detail elsewhere.[13] Severity of pain was evaluated with a numeric rating scale (NRS) ranging from 0 (no pain) to 10 (worst imaginable pain). Severity of dystonia was assessed with the Burke-Fahn-Marsden (BFM) dystonia rating scale,[14] which ranges from 0-120 with higher scores reflecting more severe dystonia.

Table 3.1. Characteristics of the 44 CRPS patients with dystonia

Characteristic	**Value**
Gender (F/M)	41/3
Age (yr; mean, SD)	36 (13)
Duration of CRPS (yr; mean, SD)	10 (6)
Severity of pain (NRS; mean, SD)	7.7 (1.4)
Number of affected extremities, *n* (%)	
1	0
2	8 (18)
3	7 (16)
4	29 (66)
Number of affected arms, *n* (%)	
1	9 (20)
2	33 (75)
Number of affected legs, *n* (%)	
1	9 (20)
2	34 (77)
Number of extremities with dystonia, *n* (%)	
1	2 (4)
2	11 (25)
3	9 (21)
4	22 (50)
Severity of dystonia (BFM; mean, SD)	50 (21)
Sensory abnormalities, *n* (%)	43 (98)
Mechanical hypesthesia or hypalgesia	37 (84)
Mechanical hyperesthesia, hyperalgesia or allodynia	25 (57)

BFM = Burke-Fahn-Marsden dystonia rating scale (range 0 - 120, with 0 = no dystonia)[14]; CRPS = complex regional pain syndrome; IQR = interquartile range; NRS = numeric rating scale (range 0 - 10, with 0 = no pain).

For control purposes, 35 healthy controls with a similar age and gender distribution, who had no diseases of the central nervous system and did not receive any neuroactive drugs were also investigated (35 women; mean age (SD) 40 (13) years). Controls were partners, relatives or friends of patients, or were recruited among the hospital staff. Informed consent was obtained from all subjects according to the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the Leiden University Medical Centre.

Quantitative thermal test

A TSA-II NeuroSensory Analyzer (Medoc Ltd., Ramat Yishai, Israel) was used to determine CDT, WDT and HPT of both hands (thenar eminence) and both feet (dorsal aspect of the first metatarsal bone). CPT was not tested to minimize discomfort. These tests were performed by trained technicians in a quiet room at a temperature of 20 - 22°C. Subjects were measured in supine position and were not allowed to watch the computer screen. The 'method of levels' algorithm was used, in which the thermode returns to its baseline temperature (32°C) after each temperature change. After each stimulus period subjects are asked whether a change was perceived. The amplitude of the next temperature change is based on the response given after a stimulus: when no change of temperature has been perceived, the temperature change for the next step is doubled. If a change was perceived, the amplitude for the next step was halved. The procedure was continued until the step size reached 0.1°C. To alert the subject that a stimulus was imminent each stimulus was preceded by an auditory cue. Lower and higher temperature limit were 15.0° and 50.0°C, respectively; rate of temperature change 1.0°C/s (CDT, WDT) and 4.0°C/s (HPT); stimulus duration 5 s; return rate 10°C/s; and interstimulus interval 5 s (CDT, WDT) and 9 s (HPT).

Statistical analysis

The data were not distributed normally (Kolmogorov-Smirnov statistics for raw and log-transformed CDT and WDT data, and raw HPT data, $P<0.05$) and therefore non-parametric tests were used. The significance threshold was set at $P<0.05$. For all tests, the SPSS software package version 14.0 (SPSS Inc., Chicago, IL) was used.

Results

Patients versus controls

Thermal thresholds were evaluated in 37 hands of 28 patients, and in 48 feet of 37 patients; testing on the other sites was not feasible due to dystonia or pain. The CDT and WDT were abnormal in the patients' affected limb in comparison with the controls' non-dominant limbs (Table 3.2). There was a strong positive correlation between CDT and WDT in patients (Spearman rho = 0.66, $P<0.001$) and a trend towards significant association in controls (Spearman rho = 0.33, $P=0.05$). HPT did not differ between patients and controls (HPT hand: $P=0.50$, HPT foot: $P=0.53$).

Compared with the non-dominant limbs of controls, CDT and WDT of patients' unaffected limbs were increased, although the difference was not significant (Table 3.2). There were no significant differences in thresholds between non-dominant and dominant limbs in controls (data not shown).

Within and between patients comparisons

Nine patients had one affected arm, and also nine patients had one affected leg (Table 3. 1). The affected limbs showed elevated CDT and WDT in comparison with their unaffected counterparts, but this was only significant for WDT in the hands (Table 3.2).

Table 3.2. Comparison of thermal thresholds between CRPS patients' affected and controls' non-dominant extremities and between patients' affected and unaffected side

	Hand			Foot		
	CDT (ΔT)	**WDT (ΔT)**	**HPT**	**CDT (ΔT)**	**WDT (ΔT)**	**HPT**
Patients vs controls						
Patients, *n*=44	-1.0 (-2.4 to -0.5)	1.7 (0.7 to 5.6)	43.0 (35.0 to 48.8)	-5.1 (-8.9 to -1.9)	10.2 (3.7 to 13.2)	44.0 (36.5 to 49.0)
Controls, *n*=35	-0.2 (-0.5 to -0.1)	0.5 (0.3 to 0.7)	44.0 (43.0 to 46.8)	-0.5 (-1.5 to -0.4)	2.6 (1.8 to 5.6)	45.8 (42.8 to 47.0)
P value	<0.0005	<0.0005	0.50	<0.0005	<0.0005	0.53
Patients[a]						
Affected limb, *n*=7	-0.5 (-1.4 to -0.4)	2.0 (0.8 to 5.4)	41.5 (35.0 to 48.5)	-3.3 (-8.4 to -0.1)	10.4 (3.1 to 11.7)	46.5 (45.5 to 47.0)
Unaffected limb, *n*=7	-0.4 (-0.6 to -0.1)	0.7 (0.3 to 1.5)	47.0 (42.8 to 47.3)	-1.3 (-2.3 to -0.6)	4.4 (2.3 to 11.8)	46.0 (43.5 to 47.8)
P value	0.24	0.01	0.46	0.25	0.18	0.46

Data represent median values (°C) with interquartile ranges shown in parentheses.
CDT = cold detection threshold (difference from baseline temperature); CRPS = complex regional pain syndrome; HPT = heat-induced pain threshold; WDT = warmth detection threshold (difference from baseline temperature); ΔT = difference with baseline temperature.
[a]Note that most patients were excluded because they had two affected hands or two affected feet; number of patients is slightly different from Table 3.1 because testing was impossible in two patients due to dystonia or pain (both for hands and feet).

Relations between clinical characteristics and thermal thresholds

There was no significant correlation between the severity of pain (NRS) and any threshold (data not shown), nor between dystonia (BFM) and any threshold. Although disease duration varied considerably between patients, none of the thresholds showed significant associations with this variable. There were no significant differences in thermal thresholds between patients who used analgesics versus those who did not.

Discussion

Although thermal thresholds have previously been examined in CRPS patients without dystonia,[3,15-17] this issue has not been addressed in CRPS patients with dystonia. These earlier studies have yielded variable findings that most likely are explained by differences in applied methods and population characteristics. The general picture that arises from these studies is that CDT and WDT are elevated in patients with disease durations up to 4 years, with the possible exception of CDT in patients with short disease duration (6 months); findings on CPT and HPT are contradictory. In the present study we found cold and warmth hypesthesia together with normal HPT in the affected arms and legs of CRPS patients with dystonia.

Thermal hypesthesia may be caused by disturbances at multiple levels of the nervous system. First, small fiber pathology has been demonstrated in CRPS[18-20] and may explain our findings. In addition, it is known that impairment of C and Aδ fibers typically leads to thermal hypesthesia while sparing heat-induced pain, due to differences in spatial summation requirement.[11] Second, C fiber activation by capsaicin injection elicited reversible tactile hyperalgesia and hypesthesia at the site of injection, but also in the adjacent tissue.[21] This was attributed to rerouting of somatosensory input from non-nociceptive into nociceptive pathways in the spinal dorsal horn. Therefore, plasticity-related changes of sensory processing at the spinal level may also be an explanation for our findings. Third, in a population of 40 CRPS patients with one affected extremity, neurological examination showed hemisensory deficits including the face in 15 (38%).[17] The authors suggested that functional changes in the thalamus may play an important role in the pathogenesis of sensory abnormalities. Fourth, a shrunk representation area of the affected hand was found in the primary somatosensory cortex of CRPS patients.[22-24] Reduced activation of the contralateral primary and secondary somatosensory cortex after tactile stimulation has also been reported in CRPS[24] and similar cortical changes may underlie thermal hypesthesia.

In conclusion, we found thermal hypesthesia in CRPS patients with dystonia. Whether this sensory abnormality is a secondary phenomenon or is in fact involved in the causal pathway to dystonia is uncertain. For a further understanding, clinical studies on the efficacy of sensory rehabilitation in CRPS-related dystonia are warranted.

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Fixed dystonia in complex regional pain syndrome: a descriptive and computational modelling approach

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Abstract

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

Background

Dystonia is characterised by sustained muscle contractions, frequently causing repetitive twisting movements or abnormal postures.[1] The aetiological classification of dystonia discriminates primary (idiopathic) dystonia, in which dystonia is the only clinical sign without any identifiable exogenous cause, from secondary forms in which dystonia is a symptom of an identified neurological condition, such as a focal brain lesion, exposure to drugs or chemicals.[2] Primary dystonia is associated with disturbances of higher order processing including sensory temporal-spatial discrimination, multisensory integration for example between visual and tactile input, and movement representation.[3] These disturbances have been attributed to dysfunction of basal ganglia cortico-striatal-thalamo-cortical motor circuits.[1,4–6]

One example of secondary dystonia is the so-called peripherally-induced dystonia which may develop following peripheral tissue or nerve injury.[7] Whereas primary dystonia is typically characterised by prolonged twisting and repetitive movements, peripherally-induced dystonia features abnormal postures (fixed dystonia), the underlying cause of which is unknown.[8]

These fixed dystonias occur in about 25% of the patients with complex regional pain syndrome (CRPS) which is usually triggered by a limb injury. CRPS is characterised by persistent pain, autonomic and trophic features[9–11] which reflect the various involvement of mechanisms that underlie inflammation[12,13] and vasomotor dysfunction.[14,15] Fixed dystonia in CRPS may spread to other limbs[16,17] and its prognosis is poor[18,19]. Psychological or personality-based factors have been proposed as predisposing factors for CRPS-related dystonia, but the rationale underpinning this proposal is not clear and evidence is lacking.[20]

One hypothesis underpinning CRPS-related fixed dystonia is that noxious input might interfere with joint and muscle proprioception of the affected body part, which in turn distorts segmental and polysegmental muscle activation during voluntary and reflex movements.[21] Disturbed proprioceptive reflexes have been found in patients with CRPS-related dystonia demonstrated by impaired inhibition of H-reflexes on tendon vibration,[22] and disturbed proprioceptive reflexes in posture maintenance experiments using a robot manipulator.[23] We therefore hypothesised that fixed dystonia may result from aberrant proproceptive reflex strengths of position, velocity or force feedback. Although several independent reports appear to describe similar postures,[24–26] a formal categorisation of CRPS-related dystonia has not been undertaken. We aimed to fill this critical gap by characterising the nature of CRPS-related dystonia in 85 patients with CRPS-related dystonia. We subsequently used a neuromuscular model to evaluate whether specific disruptions of the musculotendinous system and reflex loops originating from muscle spindles and Golgi tendon organs (GTO) could produce fixed dystonia as observed in patients with CRPS.

Methods

Clinical evaluation

Eighty-five patients with arm or leg pain who presented to the Neurology department of the Leiden University Medical Centre and were diagnosed with CRPS type 1 and dystonia in one or more extremities, participated (Table 4.1). CRPS was diagnosed according to the criteria of the International Association for the Study of Pain: patients must have (i) continuing pain, allodynia or hyperalgesia, in which the pain is disproportionate to any inciting event; (ii) evidence at some time of oedema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain; and (iii) no condition that would otherwise account for the degree of pain and dysfunction.[27] It is convention to categorise patients as having CRPS type 2 if a nerve lesion is demonstrable and CRPS type 1 if a lesion is not demonstrable. This study involved only CRPS type 1 patients with dystonia of at least one extremity.

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.

All patients provided informed consent before they were filmed in sitting or standing so that footage of each limb, sufficient to characterise its posture, was obtained. Footage of CRPS patients who exhibited fixed dystonia at rest on clinical examination between 1994 and 2007 was examined by one investigator (T.M.). The severity of dystonia in the affected extremities was evaluated using the severity factor of the Burke-Fahn-Marsden scale (slight, mild, moderate or severe).[28] Patterns of fixed posture were evaluated in four joints of the arms (fingers, wrist, elbow and shoulder) and legs (toes, ankle, knee and hip). Medical records were evaluated to verify that the posture observed in the footage was consistent with clinical presentation.

Table 4.1. Demographic and clinical characteristics (*n*=85)

Characteristic	Value
Gender, *n* (%)	
Female	80 (94.1)
Male	5 (5.9)
Age (yr; mean, SD)	41.3 (13.5)
Duration of CRPS (yr; mean, SD)	11.7 (8.6)
Preceding psychiatric history, *n* (%)	8 (9.4)
Duration of dystonia (yr; mean, SD)	9.9 (8.6)
Number of extremities with dystonia, *n* (%)	
1	8 (9.4)
2	26 (30.6)
3	26 (30.6)
4	25 (29.4)
Severity dystonia most affected extremity, *n* (%)	
Slight	10 (11.8)
Mild	35 (41.2)
Moderate	21 (24.7)
Severe	19 (22.3)
Sensory abnormalities, *n* (%)	
Mechanical hypesthesia or hypalgesia	74 (87.1)
Mechanical hyperesthesia, hyperalgesia or allodynia	51 (60.0)

Neuromuscular model simulation of fixed dystonia

The neuromuscular model used to simulate dystonia consists of two antagonistic muscles attached to hand inertia, with Hill-type activation & contraction dynamics[29] based on the Winters and Stark muscle model.[30] Two parameter sets for the wrist and shoulder muscles were adopted from Winters and Stark.[30] The model contains explicit contributions of the musculotendinous system and reflex pathways originating from muscle spindles and GTO with subsequent time delays to represent neural latencies. In the model, three reflex pathways are included that excite the contractile element of the muscle: (i) velocity-dependent pathways initiated by activation of type Ia afferents from the muscle spindles; (ii) position-dependent pathways initiated by activation of type II afferents from the muscle spindles; and (iii) force-dependent pathways initiated by activation of type Ib afferents (GTO) (Table 4.2). The model enables determination of the contribution of each of these pathways to muscle activity in the arm.

Table 4.2. Proprioceptive feedback pathways in humans

Feedback pathway	Proprioceptive sensory organ	Afferent nerve type	Physical measure	Sensitive to muscle shortening or lengthening
Position	Muscle spindle	Mainly II	Muscle stretch	Only lengthening (unidirectional)
Velocity	Muscle spindle	Mainly Ia	Muscle stretch velocity	Only lengthening (unidirectional)
Force	Golgi tendon organ	Ib	Muscle force	Both (bidirectional)

There was one reference scenario with normal reflexes and three scenarios with abnormal reflexes (Figure 4.1): (i) increased reflex sensitivity, increased sensitivity of both the agonistic and antagonistic reflex loops, i.e. 'hyperreflexia'; (ii) imbalanced reflex sensitivity, increased sensitivity of only the agonistic reflex loop; and (iii) imbalanced reflex offset, an offset to the reflex output in only the agonistic proprioceptors. Each scenario was applied to each of the three reflex pathways to produce nine aberrant conditions.

Although under normal conditions, reflex strength adapts during external force and voluntary movement[31] and reflexes are suppressed to enable unimpeded voluntary movements, we excluded reflex adaptation so that both external forces and voluntary movements elicited reflexes. Each simulation had the same set-up: five seconds of continuous external force were followed by five seconds of rest, and then, five seconds of continuous voluntary contraction followed by again five seconds of rest.

Figure 4.1 shows that the model reflex strengths were set up as (over) excitatory to agree with neurophysiologic studies in patients with CRPS that have demonstrated reduced central inhibition - so-called 'disinhibition'.[17,22,32,33] Behaviour of the resultant model in each of the aberrant reflex scenarios was scored (0-5) according to the following characteristics, which are typical of CRPS-related dystonia:[17,34] (i) abnormal posture; (ii) sustained contraction; (iii) increased stiffness; (iv) worsening with activity; and (v) loss of voluntary control.

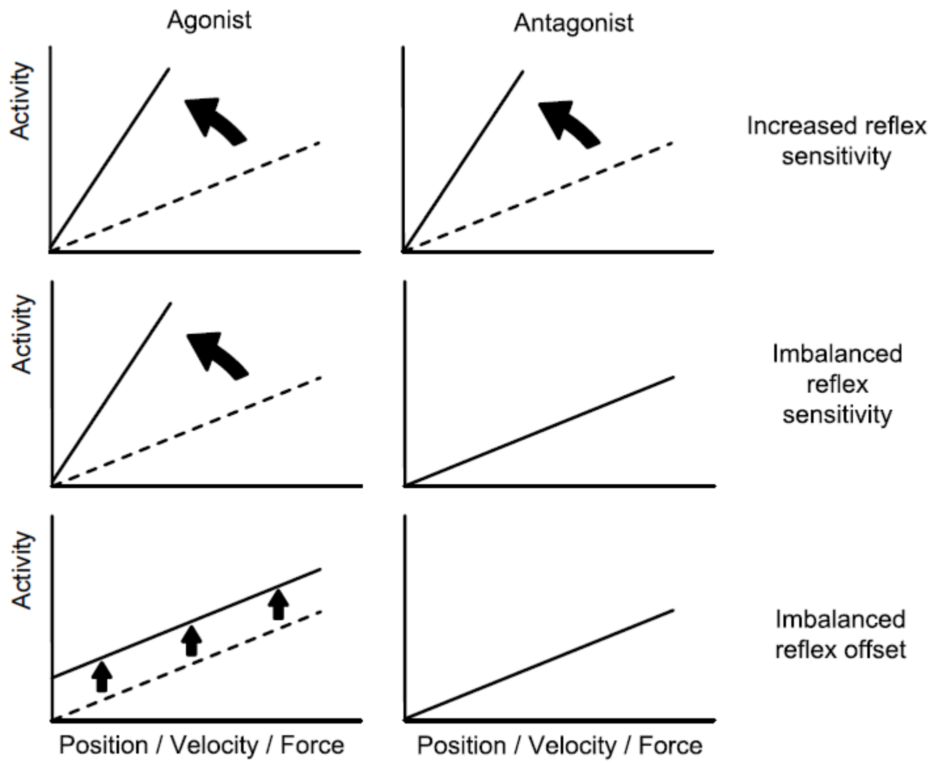

Figure 4.1. Schematic representation of the aberrant reflex scenarios tested with the neuromuscular model.
Increased reflex sensitivity, i.e. increased sensitivity of both the agonistic and antagonistic reflex loops; imbalanced reflex sensitivity, i.e. increased sensitivity of only the agonistic reflex loop; and imbalanced reflex offset, i.e. an offset to the reflex output in only the agonistic proprioceptors.

Results

Eighty-five patients with CRPS and fixed dystonia (80 female) participated. Mean (SD) age was 41 (13) with a range from 16-69 years. Mean duration of CRPS was 11.7 (8.6) years, mean duration of dystonia was 9.9 (8.6) years and median number of dystonic extremities was 3.

Arms

Fixed dystonia was apparent in 123 arms of 77 patients (both arms were affected in 46/77 patients). The dominant pattern of fixed dystonia was flexion. This fixed flexion dystonia was more often present in distal joints than in proximal joints, affecting mostly the fingers (116/123) but also the wrist (41/123), and elbow (38/123). Shoulder adduction was observed in 12/123 arms (Figure 4.2). One or more of these joint postures were found in 118 arms (Table 4.3A). Other fixed dystonias were observed, although they were much less common. Extension of the fingers was observed in 5/123 arms, extension of the wrist in 1/123, and pronation of the elbow in 3/123.

The extent and nature of fixed dystonia did not vary between left and right arms (P=0.95, Fisher's exact test). The 60 arms in which at least two segments were involved showed a gradual spread of dystonia from distal to more proximal regions of the limb.

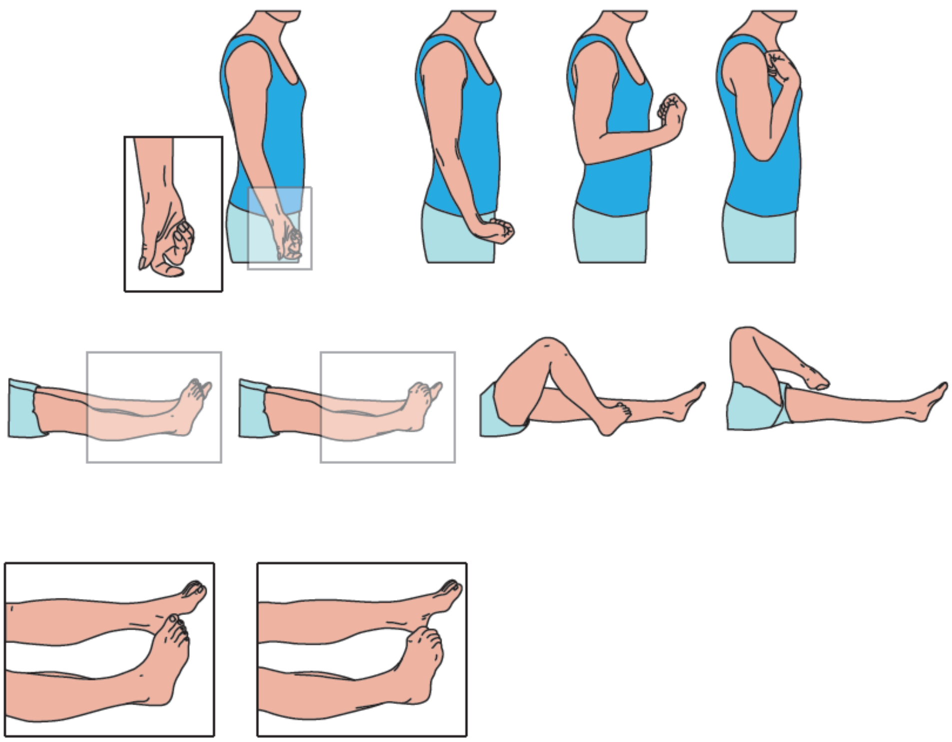

Figure 4.2. Most common postures in arm and leg in CRPS-related dystonia arranged to the severity from left to right. Drawings were made by S. Blankevoort.

Table 4.3. Combinations of most common arm (A) and leg postures (B) in patients with CRPS-related dystonia

A

Number of arms	Flexion fingers	Flexion wrist	Flexion elbow	Adduction shoulder
60	X			
20	X	X	X	
15	X	X		
9	X		X	
4	X		X	X
4	X	X	X	X
3	X			X
1	X	X		X
1		X		
1			X	
118	116	41	38	12

B

Number of legs	Plantar flexion toes	Plantar flexion or inversion ankle	Flexion knee	Endorotation hip
42		X		
24	X	X		
17	X	X	X	
6	X			
6		X	X	
6		X		X
4			X	
3	X	X		X
3	X		X	
2	X	X	X	X
113	55	100	32	11

Most common arm postures were present in 74 patients and most common leg postures in 77 patients. Column totals are presented in the bottom row. Note that for clarity reasons, other postures that occurred with or without these most common postures are not shown.

Legs

Fixed dystonia was present in 114 legs of 77 patients. Only the right leg was involved in 21/77, only the left in 19/77 and both legs in 37/77. Also in the legs, fixed dystonia was more often seen in distal than in proximal joints. The most common postures were plantar flexion and inversion of the ankle (73/114 legs); plantar flexion without inversion (11/114 legs), and inversion without plantar flexion (16/114 legs). Other common postures were plantar flexion in the toes (55/114 legs), flexion of the knee (32/114), and internal rotation in the hip (11/114) (Figure 4.2). One or more of these postures were observed in 113 legs (Table 4.3B).

Other postures were rarely observed: dorsal flexion of the ankle (2/114 legs), eversion (2/114), dorsal flexion and inversion (1/114), and plantar flexion and eversion (2/114); dorsiflexion of the toes (4/114), and knee extension (7/114).

As for the arm, there was no difference in the number or nature of fixed dystonias between the left and right legs (P=0.90, Fisher's exact test). The 73 legs in which at least two segments were involved showed also a gradual spread of dystonia from distal to more proximal regions of the limb.

Simulating CRPS-related dystonia by modelling aberrant proprioceptive reflexes

We used a neuromuscular model to simulate the dominant postures observed in patients. This model incorporates the interaction between mechanical properties of the limb and spinal proprioceptive reflexes. Figure 4.3 shows the movement and muscle torques of the wrist in the reference condition with (arbitrary) normal reflexes. Figure 4.1 shows the aberrant reflex scenarios, i.e. (i) increased reflex sensitivity; (ii) imbalanced reflex sensitivity; and (iii) imbalanced reflex offset, which were successively applied to proprioceptive feedback pathways originating from muscle spindles and GTO (Table 4.2).

The increased reflex sensitivity scenario (i.e. 'hyperreflexia') resulted in motor dysfunction, varying from rigidity (in case of increased reflex sensitivity to force) to fast oscillatory movements (in case of increased reflex sensitivity to velocity or position), but did not cause an abnormal posture (Figure 4.4). The imbalanced reflex offset scenario resulted in abnormal postures, however, without other characteristics of fixed dystonia such as sustained contraction, increased stiffness and loss of voluntary control (Figure 4.4). For both the wrist and the shoulder parameter sets the simulation of the imbalanced reflex sensitivity to muscle force was the only condition that resulted in behaviour that closely resembled all clinical characteristics of fixed dystonia (Figure 4.4). The upper plot in Figure 4.5 shows the deviant joint angles (abnormal posture) that resulted from imbalance of muscle force feedback. The degree of imbalance determined the severity of the deviation, since the force imbalance is counteracted by force contributions from muscle stretch in the antagonist. The increased co-contraction is evident from the high muscle torques in agonist and antagonist in Figure 4.5. After attaining the abnormal posture, the joint movement induced by external force and voluntary contraction is smaller due to the co-contraction and excitatory force feedback.

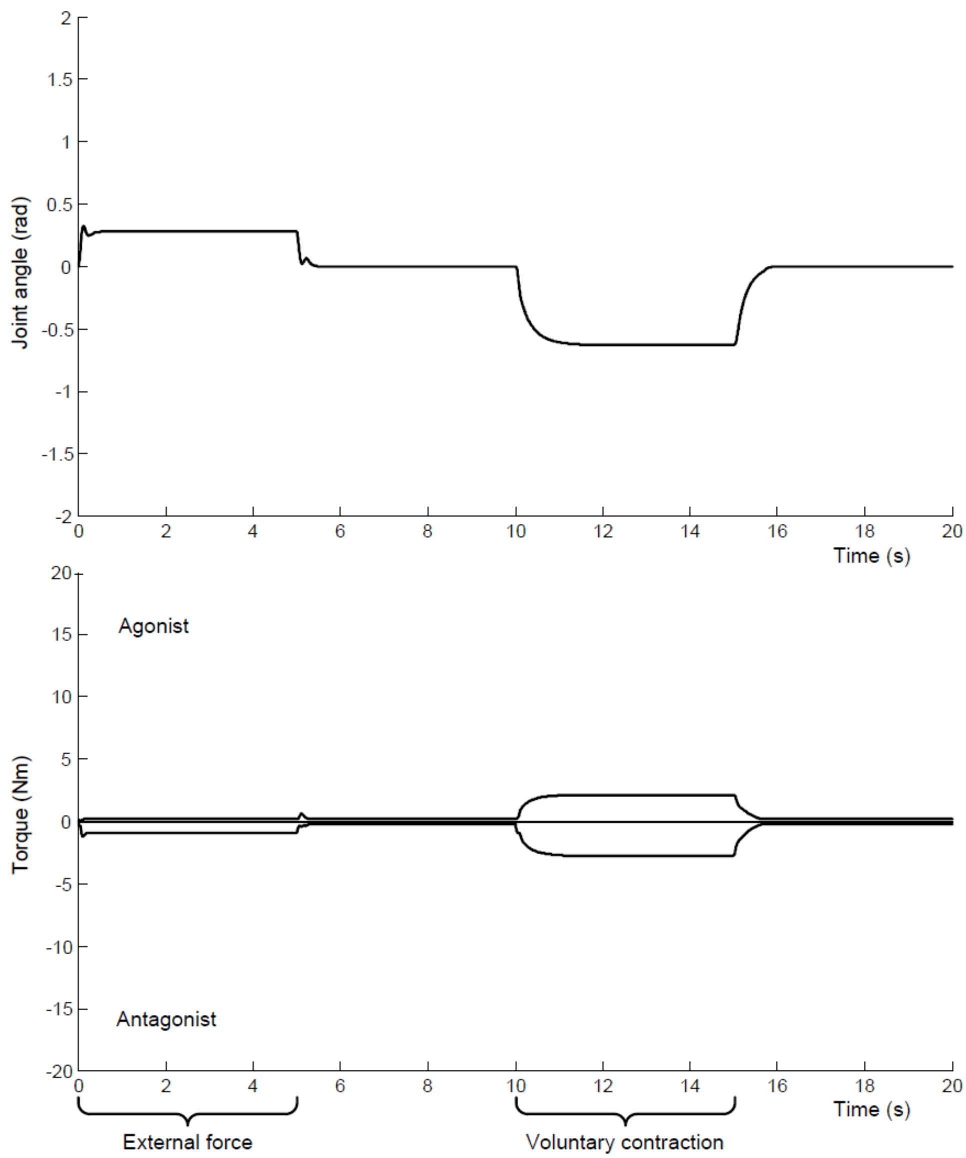

Figure 4.3. Model simulation results with normal reflexes.
Joint angle (top panel) and muscle torques (bottom panel) at the wrist in response to external force (0-5 s) and voluntary contraction (10-15 s) with normal reflexes. In periods of rest (5-10 and 15-20 s) the muscle contractions subside and the hand returns to its neutral position.

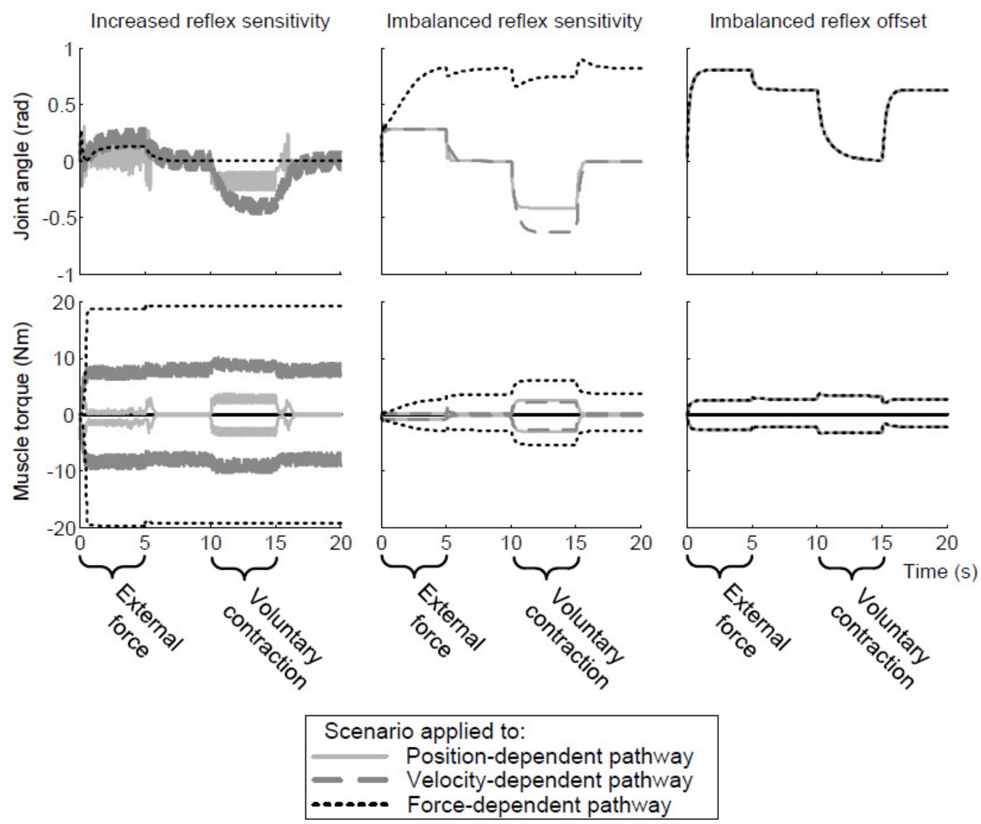

Figure 4.4. Model simulation results with the three aberrant reflex scenarios applied to the three reflex pathways.

Joint angles (top panels) and muscle torques (bottom panels) at the wrist in response to external force (0-5 s) and voluntary contraction (10-15 s) with the three aberrant reflex scenarios applied to the three reflex pathways. Left panels show the increased reflex sensitivity scenario, middle panels show the imbalanced reflex sensitivity scenario, and right panels show the imbalanced reflex offset scenario. The three traces within a panel represent the results of the scenario applied to the velocity-, position- and force-dependent pathways.

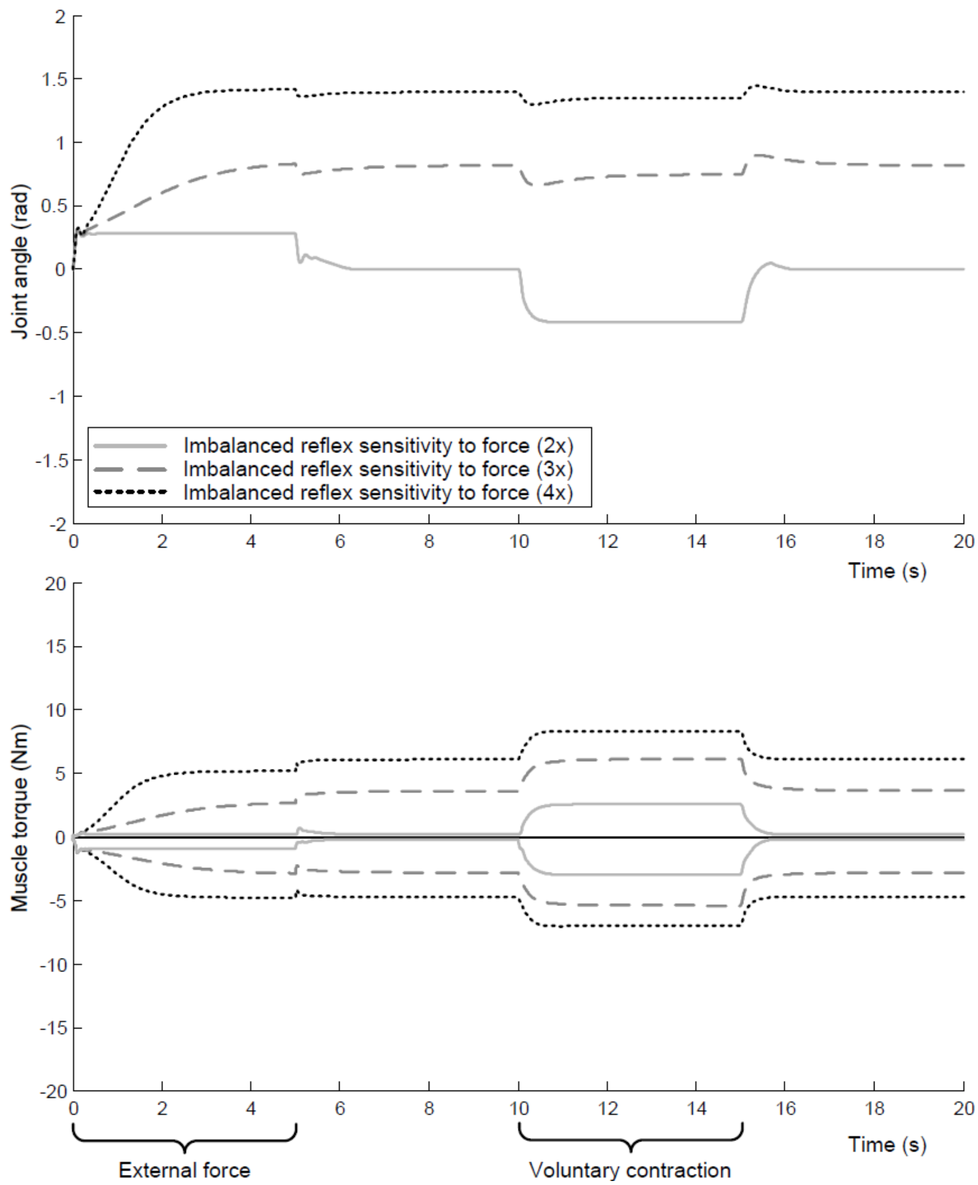

Figure 4.5. Model simulation results with several degrees of imbalanced reflex sensitivity to muscle force.

Joint angles (top panel) and muscle torques (bottom panel) at the wrist in response to external force (0-5 s) and voluntary contraction (15-20 s) with several degrees of imbalanced reflex sensitivities to muscle force. The motor behaviour resembles fixed dystonia.

Discussion

By systematically evaluating 123 affected arms and 114 affected legs, of 85 patients with CRPS-related dystonia, we identified a dominant pattern of fixed dystonia that would be predicted on the basis of proprioceptive disruption as an underlying cause. Symptoms are more often present in distal than in proximal joints, and more in flexor than in extensor muscles. In fact, Table 4.3A shows that proximal joint involvement was always found to be accompanied by more distal dystonia. From the 12 arms with an affected shoulder joint all had affected fingers. In legs the same relation was found between the hip and ankle, from the 11 legs with an affected hip joint all had affected ankles. In contrast, distal dystonias without involvement of proximal joints occurred often: only the fingers were affected in 60 out of 118 arms and only the ankle in 42 out of 113 legs.

The conspicuous involvement of flexor muscles in fixed dystonia in CRPS has been attributed to disinhibition of spinal circuitry involved in mediating nociceptive withdrawal reflexes (NWR).[17] The character of the NWR represents the most appropriate movement for a withdrawal of the stimulated area from an offending stimulus.[35] If disinhibition of NWR played a role in our findings, one would generally expect a stereotypical pattern of multi-segmental muscle involvement. However, only in the most severely affected cases did we encounter such multi-segmental patterns. In the majority of cases there was a selective distal muscle involvement which thus raises the need for an alternative explanation for fixed dystonia.

Flexor motor neurons and associated interneurons which mediate depolarisation of primary afferent fibres, receive more sensory input than their extensor counterparts. The release of gamma aminobutyric acid (GABA) by spinal interneurons produces primary afferent depolarisation and reduces transmitter release (presynaptic inhibition), which in turn modulates reflex gains. The synaptic effectiveness of Ib afferent feedback ending in the spinal cord of vertebrates can thus be modulated by means of specific sets of GABA-ergic interneurons.[36] Dysfunction of GABA-ergic interneurons, which is a key component of central sensitisation, has been shown to compromise the specificity of afferent processing.[37] Several studies have found evidence of disinhibition along the neuraxis in CRPS patients with and without dystonia.[22,33] Dystonia in CRPS patients responds to the $GABA_B$ receptor agonist, baclofen, which enhances spinal GABA-ergic inhibition[38,39] but not to the administration of the inhibitory neurotransmitter glycine.[40] Collectively, these findings highlight a specific role of GABA-ergic mechanisms in CRPS patients with dystonia.

Since separate sets of GABA-ergic interneurons allow for selective control of muscle length and muscle tension, the predominant flexor postures in dystonia of CRPS may implicate imbalanced control of functionally coupled muscles.[41]

We tested three types of aberrant reflex patterns using a neuromuscular model that captures the interaction between proprioceptive reflexes, the mechanical properties of the limb and its load. The aberrant reflex pattern that most closely mimicked the fixed dystonia in patients with CRPS was imbalanced reflex sensitivity to muscle force feedback. The severity of the abnormal posture varied according to the degree of imbalance. In contrast, increased and imbalanced reflex sensitivity to position and velocity feedback only caused oscillatory motions, which likely can be explained by consecutive reflexive contractions leading to decreased stretch in one of the antagonistic muscles, but increased stretch in the other. Increased reflex sensitivity to muscle force caused behaviour that exhibited all the characteristics of dystonia, except for the abnormal posture due to the balanced force feedback. Our findings therefore implicate possible involvement of GTO afferent input. GTO functions as the sensor in the feedback system that regulates muscle force and accurately signals active contractile force.[42–44] Stretch of the tendon, which is proportional to the force in the muscle during active contraction, activates GTO and thereby increases type Ib afferent input onto inhibitory interneurons subserving primary afferent depolarization. These in turn inhibit α-motor neurons that supply the muscle from which they arise.[45] Finally, since time delays destabilise feedback systems and the delay is greater distally than proximally, disruption of GTO feedback would most likely be associated with fixed dystonias that arise distally and then progress proximally. Hence, central sensitisation may impair the processing of GTO afferent input and thus contribute to the development of fixed dystonia.

Alternatively, peripheral factors that influence the torque at the joint, such as changes of the contractile properties of the muscles, may introduce imbalances in force feedback independent of reflex settings. In fact, differences in agonistic and antagonistic muscle strength and moment arms may already introduce imbalances and possibly only become symptomatic with disturbed feedback control. Speculatively adequate control of reflexes may be required to actively balance feedback control. The most common ankle postures in our patients were plantar flexion or inversion, and indeed, the contributing muscles have greater strength compared to their antagonists. It may also explain the greater diversity in shoulder and hip postures, because the proportional strength of the contributing muscles is more variable between subjects and postures.

In conclusion, findings derived from a neuromuscular model suggest that aberrant force feedback regulation from GTO involving an inhibitory interneuron may underpin the typical fixed flexion postures in CRPS patients with dystonia.

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Chapter 5

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

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Abstract

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

Introduction

Complex regional pain syndrome (CRPS) is a disorder that usually occurs after trauma and is more common in women.[1-3] The initial clinical features of CRPS, which include persistent pain, changes in skin colour and temperature, sweating and swelling, have led several investigators to suggest an aberrant inflammatory response to trauma in these patients.[3,4] Various studies have reported involvement of a perturbed function of both C and Aδ fibres of sensory nerves (neurogenic inflammation) and the local immune system in the skin.[5-8] Following the acute phase of CRPS, patients may develop chronic pain, allodynia, hyperalgesia and movement disorders, which may include dystonia, myoclonus and tremor.[2,9] There is compelling evidence that these clinical features are associated with aberrant processing of spinal and supraspinal sensorimotor neural networks.[10]

In recent years evidence was obtained indicating that the immune system influences central sensitisation. A wide range of inflammatory mediators including cytokines, chemokines, adhesion molecules, endothelins, nitric oxid and complement are involved in the cascade of central events that play a role in the development and maintenance of pain.[11,12] Furthermore, several lines of evidence have implied involvement of lactoferrin and hypocretins in nociceptive processing.[13,14]

Because cerebrospinal fluid (CSF) is in close proximity of the central nervous system, it may reflect biochemical changes that are associated with mechanisms that underlie immune system involvement in central sensitisation. In this perspective, increased levels of interleukin-1β (IL-1β) and interleukin-6 (IL-6) have been found in CSF of patients with chronic CRPS.[15]

In the present study we first aimed to confirm our earlier findings of increased levels of IL-1β and IL-6 in patients with CRPS and secondly searched for additional inflammatory mediators involved in chronic CRPS with dystonia.

Materials and methods

Patients and controls

We used CSF from patients with CRPS-related dystonia who participated in clinical trials with intrathecal administration of medication. CRPS was diagnosed if patients met the CRPS type 1 criteria of the International Association for the Study of Pain,[16] either at the time of disease onset or at the time of presentation at the clinic. Because we focussed on CRPS type 1, nerve conduction studies were performed in those cases where on the basis of history or the distribution of sensory abnormalities, dystonia was possibly associated with CRPS type 2. Additionally, imaging studies were performed in those cases where history or neurological exam yielded atypical findings.

CSF acquisition and processing

CSF samples (5 mL) of 20 patients were collected prior to the administration of intrathecal medication. Control CSF samples (1-2 mL) were obtained from subjects who underwent spinal anaesthesia for surgical interventions including urologic (e.g. transurethral resection of urinary bladder tumour), orthopaedic (e.g. total knee prosthesis), vascular (femoropopliteal bypass), gynaecologic (vulvectomy) and general (e.g. lipoma excision) surgery. Otherwise, controls did not suffer from pain or neurological diseases. CSF was always sampled before surgery had started. Neither patients nor controls had any ongoing or recent infection at the time of the sample collection.

After CSF was obtained, a small amount was used for leukocyte and erythrocyte count. Subsequently, CSF was centrifuged at 1790 x*g* for 5 min and the supernatant collected. Thereafter, supernatants were frozen in aliquots and stored at -80° C. The complete procedure was performed within 2 h. CSF containing >1000 erythrocytes/µL was excluded from the study. The medical ethics committee approved the study (MEC P01.098 and P03.027) and all subjects gave written informed consent.

Assays

Each test was performed on thawed aliquots, which were not re-frozen for further testing. If available, commercial assays were used and performed following the manufacturer's protocol. *IL-1β* and *IL-6* concentrations were measured using enzyme-linked immunosorbent assays (ELISA; respectively R&D Systems, Minneapolis, MN, USA, high sensitivity assay, and BioSource, Nivelles, Belgium, ultrasensitive assay). Furthermore, ELISA (R&D Systems) were used to determine CSF levels of chemokines *interferon-γ inducible protein-10 (IP-10)* and *RANTES (regulated upon activation, normal T-cell expressed and secreted)*. Complement *C1q* and *C3* levels were determined by radial immunodiffusion using monospecific polyclonal rabbit antisera. Concentrations of *mannose-binding lectin (MBL)*, involved in the lectin pathway of the complement system, were measured using ELISA as described in an earlier study.[17] *Soluble intercellular adhesion molecule-1 (sICAM-1)* as well as e*ndothelin-1 (ET-1)* levels were measured by ELISA (R&D Systems) and *nitric oxide (NO)* levels were measured using a colorimetric activity assay (R&D Systems). Lactoferrin concentrations were quantified with a human lactoferrin-specific ELISA as described by Van Berkel *et al.*[18] using a microplate reader (BioTek Instruments, Winooski, VT, USA). Detection limits of these assays are reported in the table. *Hypocretin-1* was measured with a standardised radioimmunoassay with a detection limit of 100 pg/mL (Phoenix Pharmaceuticals Inc, Belmont, CA, USA); levels were measured in unextracted samples.

Statistics

Group differences were analysed using a Mann-Whitney *U* test (SPSS version 12.0). *P* values <0.05 were considered significant.

Results

Twenty female patients with a mean (range) age of 42 (22-57) years and mean (range) disease duration of 10 (2-20) years were included. They reported mean visual analogue scale pain scores of 8 on a scale of 0-10 (range 4-9) and most of them used analgesics as medication. Allodynia and hyperalgesia were present in 13/20, hypesthesia and hypalgesia in 13/20; spread of CRPS to other limbs occurred in 18/20 and spread of dystonia in 16/20 patients. Controls (13 females, 16 males) had a mean age of 59 (range 31-78 years).
Median leukocyte count was 1/µL (range 0-10) in patients and 0/µL (0-9) in controls; median erythrocyte count was 11/µL (0-587) in patients and 1/µL (0-501) in controls.

Control levels for IL-1β ranged from <0.125-0.83 pg/mL (median <0.125). This was not significantly different from that published earlier (Figure 5.1A). While in our earlier study a significant increase of IL-1β in CRPS patients was found, in the present study these differences between patients and controls were not obvious (*P*=0.10). In a similar fashion, IL-6 was analysed and again not significantly different between the two groups (Figure 5.1B). Elevated CSF levels of IL-1β (4.6 and 7.4 pg/mL) were measures in two patients and in none of the controls. CSF IL-6 was elevated in one other patient (5.9 pg/mL) and in none of the controls. The clinical features of these three patients were similar to those of the other patients.

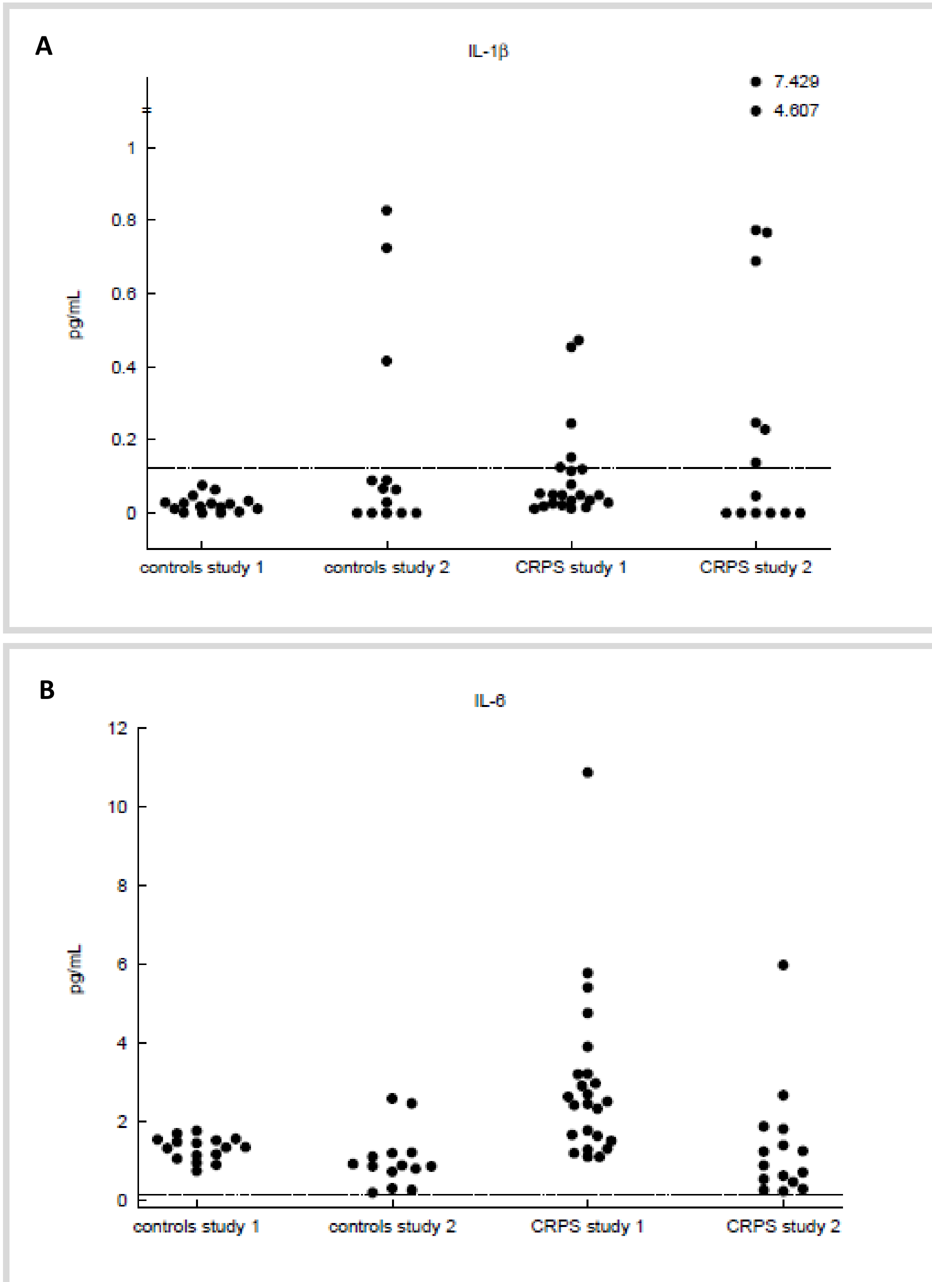

Figure 5.1. Dot plots of CSF levels of IL-1β (A) and IL-6 (B) in CRPS patients and controls in the current study (study 2). For comparison, levels measured in an earlier study[15] (study 1) are also shown. According to the ELISA manuals, inter-assay coefficient of variation is 8.2-19.2% for IL-1β and 6.7-10.0% for IL-6. The dotted lines mark the lowest detectable levels of the ELISAs.

Table 5.1. CSF assays in chronic CRPS patients and healthy controls

Assay	**Measurement unit**	**Lowest detectable level**	**CRPS patients**		**Healthy controls**		***P* value (Mann-Whitney *U* test)**
			median	**range (*n*)**	**median**	**range (*n*)**	
IL-1β	pg/mL	0.125	0.14	<0.125 – 7.43 (*n*=15)	< 0.125	<0.125 – 0.83 (*n*=14)	0.10
IL-6	pg/mL	0.16	0.89	0.23 – 5.98 (*n*=15)	0.88	0.20 – 2.59 (*n*=14)	0.74
IP-10	pg/mL	7.8	70.7	29.4 – 385.6 (n=20)	140.2	41.1 – 293.9 (*n*=19)	0.08
RANTES	pg/mL	31.2	ND	ND (*n*=20)	ND	ND (*n*=19)	-
C3	ng/mL	10	2213	1511 – 3271 (*n*=15)	2534	1775 – 2953 (*n*=6)	0.59
C1q	ng/mL	0.1	184	132 – 293 (*n*=15)	231	148 – 322 (*n*=6)	0.16
MBL	ng/mL	0.1	ND	ND (*n*=15)	ND	ND (*n*=6)	-
sICAM-1	ng/mL	0.35	2.1	1.3 – 3.6 (*n*=15)	2.8	1.1 – 6.7 (*n*=14)	0.08
ET-1	pg/mL	0.064	<0.064	<0.064 – 0.3 (*n*=15)	<0.064	<0.064 – 0.3 (*n*=13)	0.71
NO	µmol/L	0.54	3.0	0 - 15.0 (*n*=15)	3.5	1.7 - 7.0 (*n*=13)	0.68
Lactoferrin	ng/mL	0.4	4.9	<0.4 – 15.8 (*n*=15)	3.8	0.6 – 8.8 (*n*=11)	0.62

ND = not detectable.

CSF levels of C3 and C1q in patients were not significantly different from controls. MBL was undetectable in both groups. sICAM-1, ET-1, NO and lactoferrin CSF levels were not significantly different between patients and controls (Table 5.1). Hypocretin-1 (orexin A) levels were measured in 15 patients and were all in the normal range (197-391 pg/mL, median 346 pg/mL).

Discussion

The clinical spectrum of CRPS is heterogeneous and most likely reflects a mixture of symptoms and signs that are linked to differentially involved peripheral and central biological pathways. Identification of biomarkers that are related to particular biological pathways may provide clues to the pathogenesis of CRPS and perhaps contribute to improving therapeutic strategies. In this study we found no differences between patients and controls for any of the evaluated mediators of inflammation or hypocretin-1. Although patients and controls had a different age and gender distribution, these variables were not controlled because they were not related to the various mediators and could therefore not have acted as confounders.

Recently, in a collaborative study, we found elevated CSF levels of IL-1β and IL-6 in chronic cases of CRPS.[15] In the current study we could not confirm these findings, which may have at least two reasons. First, IL-1β and IL-6 levels in the controls of the present study were more heterogeneous (Figure 5.1A and B). This finding was unexpected because, contrary to the controls in the previous study, our controls did not have a history of neurological disease. Review of the medical records of the three controls with an elevated level of IL-1β (Figure 5.1A) revealed no explanation for these findings. Controls in the present study did not have neurological symptoms or signs and consequently are unlikely to have CSF abnormalities; therefore they better represent a normal population than those in the previous study. Second, inter-assay variation (IL-1β 8-19%; IL-6 7-10%) may have contributed to the different findings. Nonetheless, inspection of the IL-1β and IL-6 data of both studies shows that the majority of patients have values in the same range as controls.

We additionally evaluated the presence of several other inflammatory molecules in CSF of patients and controls, because of their presumed role in neuropathic pain.[7,12,15,19-21] Unfortunately, the results again revealed no difference in CSF levels between both groups. RANTES and MBL were not detectable in both patients and controls. Hence, our study does not support a role of a variety of inflammatory mediators in these patients, but absence of evidence is not evidence of absence.[22] Because our patients represent an extreme dystonic phenotype with long disease duration, we cannot exclude a role of these inflammatory mediators in the early inflammatory phase where they may be a prerequisite to develop CRPS[23,24] For both neuropathic pain and dystonia aberrant neuroplasticity is considered to be the pivotal underlying mechanism.[25-28] Hence, a search for CSF biomarkers involved in molecular pathways that play a role in the ability of the CNS to re-organize its neural circuits may be more fruitful in chronic cases with the dystonic phenotype.[29]

Finally, neuroplasticity may involve a coordinated up and down-regulation of multiple protein complexes within the activated circuits.[30] As a consequence, in future research a more global proteomics-based approach may be more informative than studies that focus on changes in CSF levels of inflammatory proteins.

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Chapter 6

Clinical and neurophysiological characterisation of myoclonus in complex regional pain syndrome

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Abstract

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

Introduction

Complex regional pain syndrome (CRPS) may follow trauma and is characterised by sensory and autonomic features. Symptoms and signs of the acute phase reflect aberrant inflammation.[1,2] Subsequently, patients may develop chronic pain, allodynia, or hyperalgesia, and movement disorders.[3] In CRPS patients, dystonia is found in 14-30% and myoclonus in 11-36%.[4]

The nature of CRPS and its associated movement disorders has been subject of debate. Views supporting a role of somatic[3,5,6] and psychogenic[7-9] factors have been reported. Currently, for dystonia in CRPS there is compelling evidence implicating disinhibition on the spinal and cortical level.[3]

In the present study, eight CRPS patients with myoclonus as a predominant movement disorder were clinically characterised and evaluated. Electromyography (EMG) was performed and analysed using coherence analysis, including entrainment during tapping. Coherence analysis is used for the evaluation of functional coupling between cerebral cortex and muscles (corticomuscular coherence) and central circuits linking individual muscles (intermuscular coherence).[10] Abnormal or increased normal oscillatory drives have been described in different types of hyperkinetic movements, and are thought to indicate involvement of different CNS structures.[10]

Subjects and methods

Subjects

All CRPS patients with myoclonus of at least one extremity were selected from the CRPS database (399 records) of the Leiden University Medical Centre (department of Neurology). Thirteen patients had myoclonus as predominant movement disorder. Of them, three were lost to follow-up and two refused participation. The remaining eight patients (seven women; mean age 41 years, range 35 - 59 years) were investigated (Table 6.1). CRPS was diagnosed according to the definition of the International Association for the Study of Pain: patients must have (i) continuing pain, allodynia or hyperalgesia, in which the pain is disproportionate to any inciting event; (ii) evidence at some time of oedema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain; and (iii) no condition that would otherwise account for the degree of pain and dysfunction.[11] Medication use was stable over a period of a month prior to the investigations. The ethics committee of the Academic Medical Centre of Amsterdam approved the study and all participants gave written informed consent.

Clinical evaluation

Nature, distribution and severity of movement disorders were assessed by two authors (A.M. and M.T.) at the day of coherence analysis using items 5-8 of the abnormal involuntary movements scale (AIMS),[12] which rates severity of dyskinesia on a scale of 0-4 in the upper extremities, lower extremities, trunk, and overall (total score ranging from 0-16).

Coherence analysis

Recordings were performed at the Academic Medical Centre Amsterdam. Surface electro-encephalogram (EEG) and EMG were recorded with silver-silver chloride electrodes. EEG electrodes were placed according to the international 10-20 electrode system. Bipolar EMG was recorded from three muscles of both the symptomatic extremity and the asymptomatic or less symptomatic contralateral arm. A typical montage in the arm was first dorsal interosseus (FDI) and wrist extensor (Ext) and flexor (Flex) muscles, and in the leg gastrocnemius (GA), vastus medialis (VM) and tibialis anterior (TA) muscles. Measurements were performed with BrainlaB (OSG, Rumst, Belgium). Sampling rate was 1 kHz. Involuntary movements were recorded with uniaxial accelerometry (CPU gauge 9500 series, Aikoh Engineering, Japan).

Participants were measured in the supine position during: (1) rest; (2) posture: in case of a most affected arm, both arms were simultaneously extended; in case of a most affected leg only that leg was raised; (3a) force 1: 25 percent of maximal voluntary contraction against resistance of the most affected extremity and; (3b) force 2: 25 percent of maximal voluntary contraction against resistance of the unaffected or less affected hand; and (4) entrainment test: tapping with the unaffected or less affected hand at a metronome-guided rate during rest and posture of the most affected extremity. The metronome frequency was set between 2 and 4 Hz, at a rate different from the patient's involuntary movements. Each condition had a total duration of 3 min; conditions (2) to (4) were performed in periods of 30-60 s separated by 10 s of rest.

Data were processed off-line using BrainVision Analyzer software (Brain Products GmbH, München, Germany). Bipolar derivations were calculated for EEG data. EEG was high-pass filtered at 2 Hz, and EMG at 10 Hz, and a 50 Hz notch filter was applied. Subsequently, EMG was rectified thus enhancing the firing rate information of the signal.[13] Frequency analysis was performed using Matlab (The MathWorks Inc., Cambridge, UK) and NeuroSpec software (http://www.neurospec.org). Fourier transform of disjoint sections of 1,024 data points, applying a Hanning window, was used to construct autospectra of EEG and EMG. Coherence is an extension of Pearson's correlation coefficient. It measures the correlation between autospectra and ranges from 0 (no linear association) to 1 (perfect linear association) and is the absolute square of the cross-spectrum normalized by the autospectra. Coherence was estimated between EEG and EMG and between EMG and EMG in the 2-50 Hz range. Cumulant density estimates (inverse Fourier transform of the cross-spectrum) and phase plots (defined as the argument of the cross-spectrum) were calculated, providing information on the time delay between two signals (lags and leads). Confidence limits were calculated.[14] Phase plots were visually inspected; phase was formally assessed when there was a constant slope over the band of significant coherence that extended over at least five data points. Only significant findings (exceeding the 95% confidence level) are reported. Coherence entrainment is considered to be present when significant intermuscular coherence exists between affected extremity and contralateral arm at the tapping frequency together with corresponding peaks in both autospectra.[15]

Results

Results for the individual patients are described below and listed in Table 6.1. The interval between onset of CRPS and hyperkinetic movements ranged from 0-10 years. There were no particular events preceding the onset of the hyperkinetic movements. In four patients, therapy with oral baclofen, diazepam, tiapride or magnesium had led to a reduction of severity. At neurological examination, all patients showed hyperkinetic movements at rest that increased during action. All patients had combinations of irregular jerks with tremulousness or dystonia in the affected extremities as specified below and in Table 6.1. Dystonia spread to other extremities in two of them (patient D and E). Myoclonus was multifocal in 4 and focal in 4 patients (Table 6.1). AIMS scores are shown in Table 6.2.

Table 6.1 (next pages). Characteristics of the CRPS patients

Patient	Age, y/ gender/ CRPS duration, y	Initiating noxious event or cause of immobilization	Distribution of CRPS	Latency between onset of CRPS and myoclonus	Distribution of jerks	Tremulous-ness?	Dystonia?
A	54/F/7	L CTS surgery	LA	6 months	LA > RA; dist > prox	Y	Y
B	45/F/12	L + R hallux valgus surgery	RA, LA, RL + LL	10 years	RA > LA	Y	N
C	59/M/5	Contusion R hand	RA + RL	1 week	RL > RA	Y	N
D	35/F/10	Strain/sprain	RA, LA, RL + LL	6 years	LA	N	Y
E	51/F/5	Strain/sprain	RA + RL	Immediate	RA + LA; dist > prox	N	Y
F	48/F/11	Strain/sprain	RA + RL	7 years	RL	Y	Y
G	43/F/14	R wrist fracture	RA + LA	10 years	RL	Y	Y
H	51/F/8	Spontaneously	LA + LL	3 years	LA	Y	Y

AIMS = abnormal involuntary movements scale; CRPS = complex regional pain syndrome; CTS = carpal tunnel syndrome; dist = distal; LA = left arm; LL = left leg; prox = proximal; RA

Distribution of jerks	Tremulous-ness?	Dystonia?	Burst duration (action), ms/ frequency, Hz	AIMS (items 5-8)	Current medication
LA > RA; dist > prox	Y	Y	90-130/4-5	6	Meloxicam, Metoclopramide, Distigmine, Bisacodyl, Macrogol
RA > LA	Y	N	120-180/ 5-6	4	Tiapride, Diazepam, Baclofen, Oxycodone, Acetaminophen, Furosemide, Magnesium, Bisacodyl, Conjugated estrogens
RL > RA	Y	N	120-150/6-8	3	Propranolol, Magnesium
LA	N	Y	30-60/10-14	5	Morphine, Amitriptyline, Metoclopramide, Naproxen, Ketanserin, Pantoprazole
RA + LA; dist > prox	N	Y	70-100/9-11	8	Baclofen, Pantoprazole, Ethinylestradiol/Levonorgestrel
RL	Y	Y	25-75/14-16	9	Magnesium, Amlodipine, Levothyroxine, Furosemide
RL	Y	Y	40-100/8-11	8	Acetaminophen, Codeine, Naproxen, Amitriptyline
LA	Y	Y	25-50/15-20	2	Amitriptyline

= right arm; RL = right leg.

EMG recording and coherence studies were feasible in all patients. Five patients (A, C, D, E and G) had difficulty to tap rhythmically with their contralateral hand, nevertheless, EMG autospectrum peaks of the tapping muscles were at the metronome frequency. It was noticed that coherence was predominantly seen in a lower, 6-12 Hz band, and a higher 15-30 Hz band. Table 6.1 summarises EMG findings and Table 6.2 summarises the maximum coherence values per patient for the different channels per condition for these two bands.

Table 6.2. Significant intermuscular coherence in 5 patients

Subject	Muscle pairs	Intermuscular coherence				
		Frequency band (Hz)	**Rest**	**Posture**	**Force 1**	**Force 2**
B	FDI R-Ext R	6-12	+ (0.28)	+ (0.04)	-	+ (0.44)
	FDI R-Flex R	6-12	+ (0.15)	-	+ (0.03)	+ (0.54)
	FDI R-FDI L	6-12	-	-	+ (0.05)	-
	FDI R-Ext L	6-12	-	+ (0.02)	-	-
	Ext R-FDI L	6-12	-	+ (0.05)	-	-
	Ext R-Ext L	6-12	-	+ (0.06)	-	-
	Flex R-FDI L	6-12	-	+ (0.10)	-	-
	FDI L-Ext L	6-12	-	+ (0.10)	+ (0.04)	+ (0.12)
E	Ext R-Tri R	6-12	-	-	+ (0.04)	-
	FDI R-FDI L	6-12	-	-	+ (0.04)	-
	Ext R-FDI L	15-30	-	-	-	+ (0.02)
	Ext R-Ext L	6-12	-	-	+ (0.02)	-
	Tri R-FDI L	15-30	-	-	-	+ (0.02)
	Ext L-Tri L	15-30	-	-	-	+ (0.02)
F	GA R-VM R	6-12	-	+ (0.29)	NP	-
	TA R-VM R	6-12	-	+ (0.05)	NP	-
G	GA R-VM R	6-12	+ (0.20)	+ (0.18)	+ (0.17)	+ (0.11)
	TA R-VM R	6-12	+ (0.10)	+ (0.29)	+ (0.10)	+ (0.04)
H	FDI R-Ext R	15-30	+ (0.05)	+ (0.04)	+ (0.02)	+ (0.04)
	FDI R-Flex R	15-30	-	-	+ (0.03)	+ (0.03)
	Ext R-Ext L	15-30	+ (0.02)	-	-	-
	Flex R-Flex L	15-30	+ (0.02)	-	-	-
	FDI L-Ext L	15-30	+ (0.02)	-	+ (0.02)	+ (0.03)
	FDI L-Flex L	15-30	+ (0.03)	-	+ (0.04)	+ (0.02)

Force 1 = 25% maximal voluntary contraction of the (most) affected extremity; Force 2 = 25% maximal voluntary contraction of the contralateral extremity; FDI = first dorsal interosseus; Ext = forearm extensor; Flex = forearm flexor; GA = gastrocnemius; VM = vastus medialis; TA = tibialis anterior; NP = not possible.

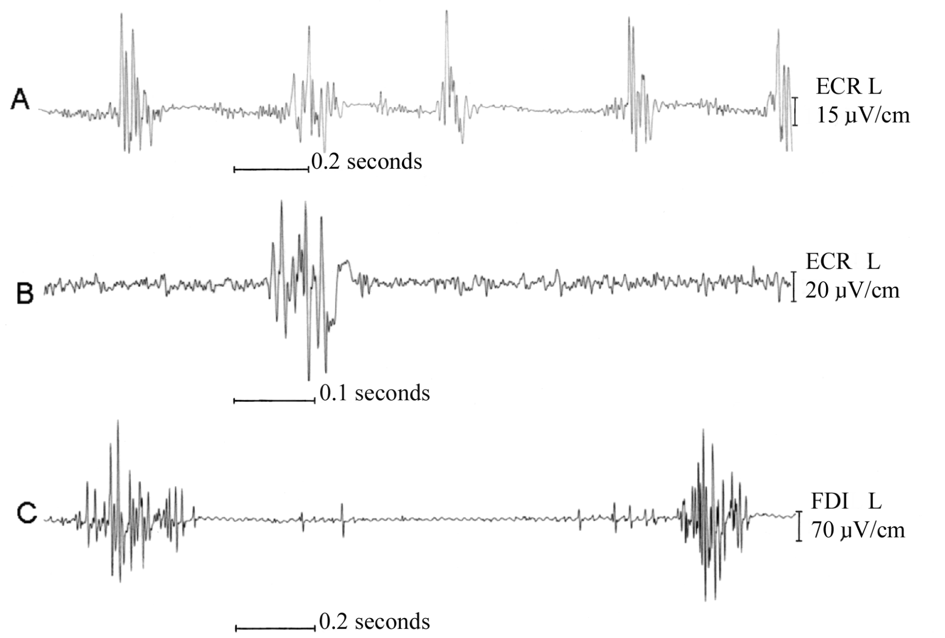


Figure 6.1. Raw EMG data from patient A (A), patient D (B) and patient E (C), at rest. ECR = extensor carpi radialis, FDI =first dorsal interosseus.

Patient A showed jerks, tremulousness and dystonia in both arms, left more than right. The raw EMG showed 90-130 ms bursts with frequency 4-5 Hz during action (Figure 6.1A). During rest, bursts were present, but less frequently. Intermuscular and corticomuscular coherence were not detected. There was no coherence entrainment (Figure 6.2).

Patient B showed jerks and tremulousness in both arms, right more than left. Intermuscular coherence in the 5-10 Hz range was found between muscles of the right arm, between muscles of the left arm and between muscles of both arms (Table 6.2). Corticomuscular coherence was found around 6 Hz (C3Cz-Ext R and C3Cz-Flex R; posture); phase was ambiguous. During tapping with the left hand, the frequency was adopted by the right arm. This patient showed coherence entrainment between both forearm extensors with a coherence of 0.45 (Figure 6.2).

Patient C showed jerks and tremulousness in the right leg and, to a lesser extent, in the right arm. Intermuscular and corticomuscular coherence were not detected. Left hand tapping altered the frequency of the hyperkinetic movements on visual inspection and coherence entrainment with magnitude 0.06 was found.

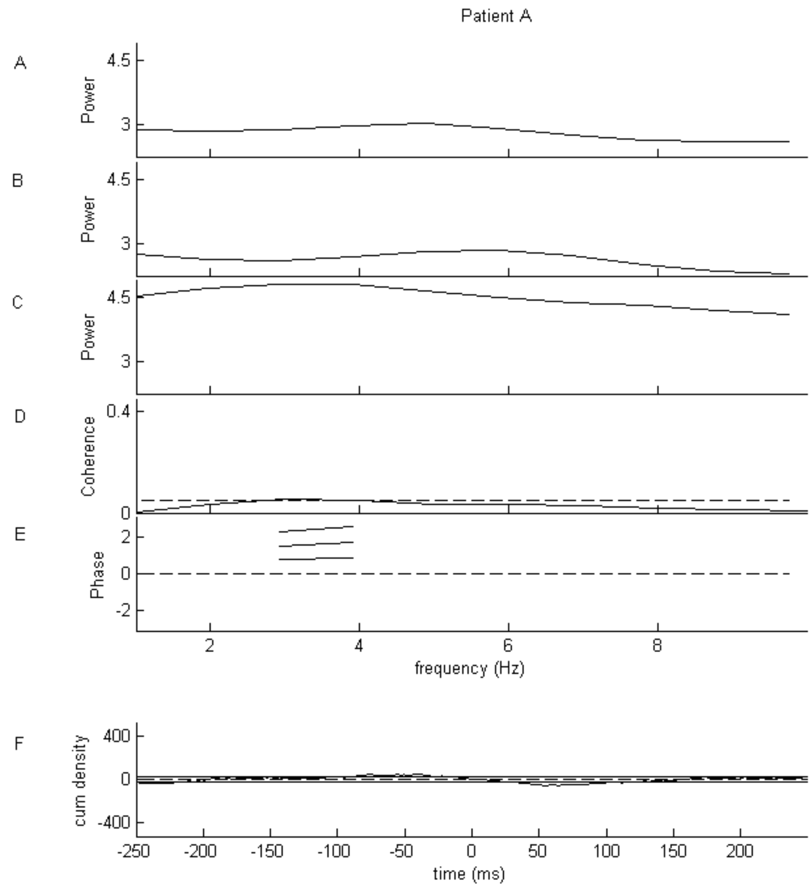
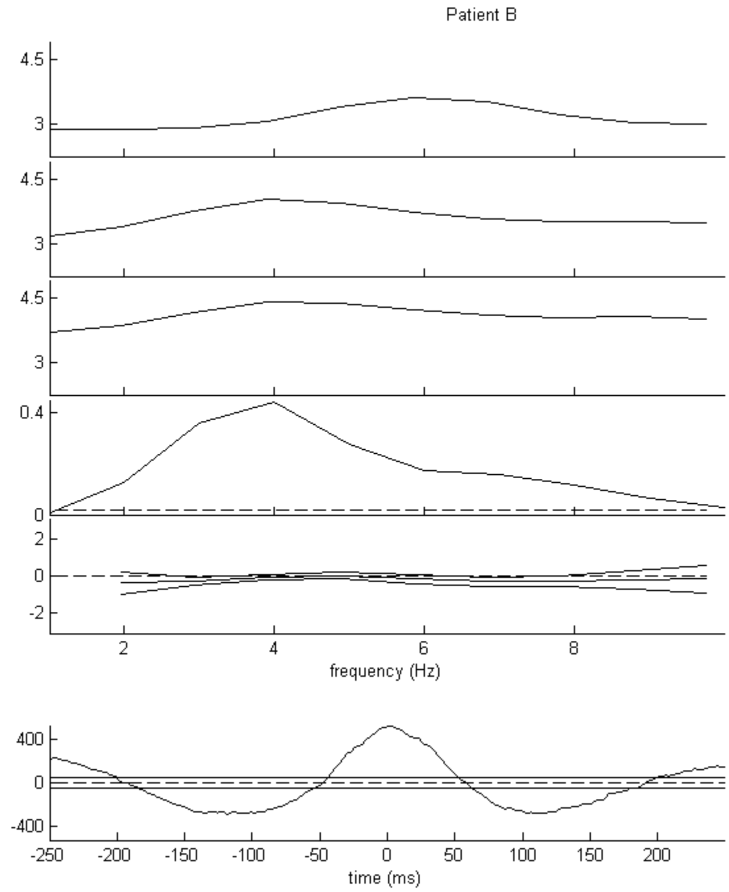


Figure 6.2 (continued on next page). Results of coherence entrainment test is shown for patients A and B: EMG autospectrum of the affected forearm extensor (Ext) during posture of both arms (A) and during posture of the affected arm and tapping with the contralateral hand (B), EMG autospectrum of the Ext of the tapping arm (C), coherence spectrum between (B) and (C) with 95% confidence limit (D), phase between them with 95% confidence limits (E) and cumulant density estimate (F).

Patient D showed jerks in the left arm, increasing during action and less in rest (Figure 6.1B), and dystonia in both arms. Intermuscular and corticomuscular coherence were not detected. Right hand tapping altered the frequency of the hyperkinetic movements on visual inspection and coherence entrainment (0.17) was found.



Patient E showed jerks and dystonia in both arms. During rest jerks decreased (Figure 6.1C). Coherence in the 7-11 Hz range was found between muscles of the right arm and between muscles of both arms (Table 6.2). Furthermore, intermuscular coherence was present in the 15-16 Hz range. Left hand tapping altered the frequency of the hyperkinetic movements on visual inspection and coherence entrainment (0.29) was found.

Patient F showed jerks, tremulousness and dystonia in the right leg. Coherence ranging from 9-10 Hz was found between muscles of the right leg (Table 6.2). Corticomuscular coherence was found around 9-10 Hz (C3F3-GA R, C3Cz-GA R, C3Cz-TA R, C3F3-VM R and C3Cz-VM R; posture); phase was ambiguous. The coherence entrainment test failed because of the occurrence of dystonia.

Patient G showed jerks, tremulousness and dystonia in the right leg. Coherence between 8 and 10 Hz was found between muscles of the right leg (Table 6.2). Left hand tapping altered the frequency of the hyperkinetic movements on visual inspection and coherence entrainment (0.03) was found.

Patient H showed jerks, tremulousness and dystonia in the left arm. Both intermuscular (Table 6.2) and corticomuscular coherence were detected in the 17-23 Hz range. The coherence entrainment test failed because of the short and intermittent presence of the hyperkinetic movements.

Discussion

CRPS is associated with presence of movement disorders like tremor and dystonia.[3] Myoclonus is also frequently mentioned but detailed information is scarce. In the current study, we investigated the clinical and electrophysiological characteristics in eight patients with CRPS-related myoclonus.

Clinically, the myoclonus in our eight patients was diverse. Jerks were present at rest and worsened during action in all patients. Combination with tremulousness was present in most of them. Five of our patients developed myoclonus only several years after the onset of CRPS, as also described in dystonic features in CRPS patients.[16] EMG registration revealed burst durations ranging from 25 ms-240 ms with a frequency ranging from 4-20 Hz during action.

Significant intermuscular coherence was detected most often during isometric contraction of the affected extremity (posture, force 1; Table 6.2). In patients B, E, F and G, intermuscular coherence in the 6-12 Hz band was detected. Furthermore, significant corticomuscular coherence in the 6-10 Hz range was present in two of them (B and F) during the posture condition. Both these coherence bands are most likely related to the hyperkinetic movements recorded in the same muscles, as the accelerometer peak frequency was in the same range. In dystonia, an abnormal drive can be detected in the 4-7 Hz frequency band.[17] The detected coherence in the current patients did not, however, correlate with clinical dystonic features. Moreover, in our dystonia patients, coherence was present at another frequency band.

Deuschl *et al.*[18] performed tremor recordings in 21 CRPS patients and found enhanced physiological tremor (EPT) with a mean tremor frequency of 7.2 (SD 0.4) Hz in 12 of them. The rhythmic hyperkinetic movements in our CRPS patients share some characteristics with EPT. However, two of them also showed side-to-side intermuscular coherence, which is uncommon for EPT.[19] Side-to-side coherence has been reported in three patients with bilateral postural and kinetic tremors resembling EPT; in those patients there was no known cause for their tremor and there was a significant asymmetry in tremor amplitude in two of them.[19] It was suggested in that study that these unclassified tremors originated from brainstem generators. Side-to-side coherence has also been described in three patients with persistent mirror movements, possibly originating at the level of corticospinal tracts projecting both contra- and ipsilaterally.[20] A common drive for the bilateral involuntary movements in our patients seems likely.

Coherence around 20 Hz was seen in patient E during both force conditions, and in patient H during rest and posture. Significant coherence in this band is considered physiological during submaximal voluntary contraction.[10]

Coherence entrainment was present in five patients. Entrainment has been suggested as clue for psychogenic movement disorders.[21] However, none of our patients had a psychiatric history before the onset of CRPS or otherwise indications of psychogenic movement disorders[21] in line with a previous study on CRPS patients with dystonia.[22] In general, phase and frequency of oscillatory movements are prone to entrainment by rhythmic movements occurring elsewhere in the same individual.[23] Coupling between spinal pattern generators has been implicated in interlimb entrainment by movement-elicited afference.[24] Therefore, presence of entrainment may reflect a normal physiological phenomenon. On the other hand, entrainment may share similarities with mirror movements, which are defined as visible involuntary movements of the relaxed hand that appear to replicate the timing and type of movement being carried out by the voluntary activated hand.[25] Overflow of central motor drive as occurs in mirroring may support the concept of central disinhibition in CRPS and its movement disorders. Further studies towards the value of detected entrainment are warranted.

On visual inspection five patients were unable to tap rhythmically with their contralateral hand, suggesting a more elaborate impaired voluntary motor control. Ribbers *et al.*[26] performed kinematic analysis on the nonaffected dominant arm in CRPS patients. During a drawing task, CRPS patients showed poorer execution of movement and impairment of temporospatial coding, suggesting impairment of central motor processing.

To summarise, myoclonus in CRPS has a distinct clinical presentation. Clinically, jerks are associated with tremulousness and dystonia, are present at rest and aggravate during action. The current study shows some similarities and differences with other movement disorders, highlighting the need for future studies to clarify the mechanism underlying motor dysfunction of CRPS.

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Chapter 7

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 colour 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 Aδ 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 characterised 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 generalised 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 (i) to further elucidate the efficacy of ITB in a dose-escalation study of a large group of patients with CRPS-related dystonia and (ii) 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 1 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 (i) the presence of an initiating noxious event or a cause of immobilization;

(ii) continuing pain, allodynia or hyperalgesia with which the pain is disproportionate to any inciting event; (iii) evidence at some time of oedema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain; and (iv) absence of a condition that would otherwise account for the degree of pain and dysfunction. Criteria ii-iv 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 (i) patients experienced a satisfactory reduction of dystonia; (ii) a maximum daily dose of 1300 μg was reached; or (iii) 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). DFL 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 (QoL) 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 QoL, 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% CI excluding 0 indicated a significant difference at an α 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 (SD) disease duration of 10.3 (6.1) years participated in the study (Tables 7.1 and 7.2). 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 7.1).

Table 7.1. Demographic and clinical characteristics of patients (*n*=42)

Characteristic	Value
Gender (F/M)	40/2
Age (yr; mean, SD)	35.7 (12.8)
Duration of CRPS (yr; mean, SD)	10.3 (6.1)
Trauma preceding first affected extremity (%)	
Soft tissue injury	23 (55)
Fracture	11 (26)
Surgery	8 (19)
Number of affected extremities (%)	
2	8 (19)
3	8 (19)
4	26 (62)
Number of extremities with dystonia (%)	
1	1 (3)
2	13 (31)
3	9 (21)
4	19 (45)
Dystonia in upper and lower extremities (%)	
Only upper	3 (7)
Only lower	1 (2)
Upper and lower	38 (91)

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.

Table 7.2. 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, *n*	42 / 0 / 0	42 / 0 / 0	34 / 0 / 0	26 / 0 / 0
Hypalgesia				
Present / absent / unknown, *n*	38 / 4 / 0	32 / 9 / 1	26 / 8 / 0	19 / 5 / 2
Hyperalgesia/allodynia				
Present / absent / unknown, *n*	28 / 14 / 0	22 / 20 / 0	17 / 17 / 0	11 / 15 / 0
Oedema				
Present / absent / unknown, *n*	39 / 3 / 0	29 / 13 / 0	17 / 17 / 0	12 / 14 / 0
Temperature changes				
Present / absent / unknown, *n*	40 / 2 / 0	36 / 4 / 2	25 / 8 / 1	18 / 6 / 2
Colour changes				
Present / absent / unknown, *n*	40 / 1 / 1	38 / 3 / 1	24 / 10 / 0	19 / 6 / 1
Hyper-/hypohidrosis				
Present / absent / unknown, *n*	31 / 10 / 1	25 / 15 / 2	19 / 14 / 1	13 / 11 / 2
Hair and nail growth changes				
Present / absent / unknown, *n*	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.

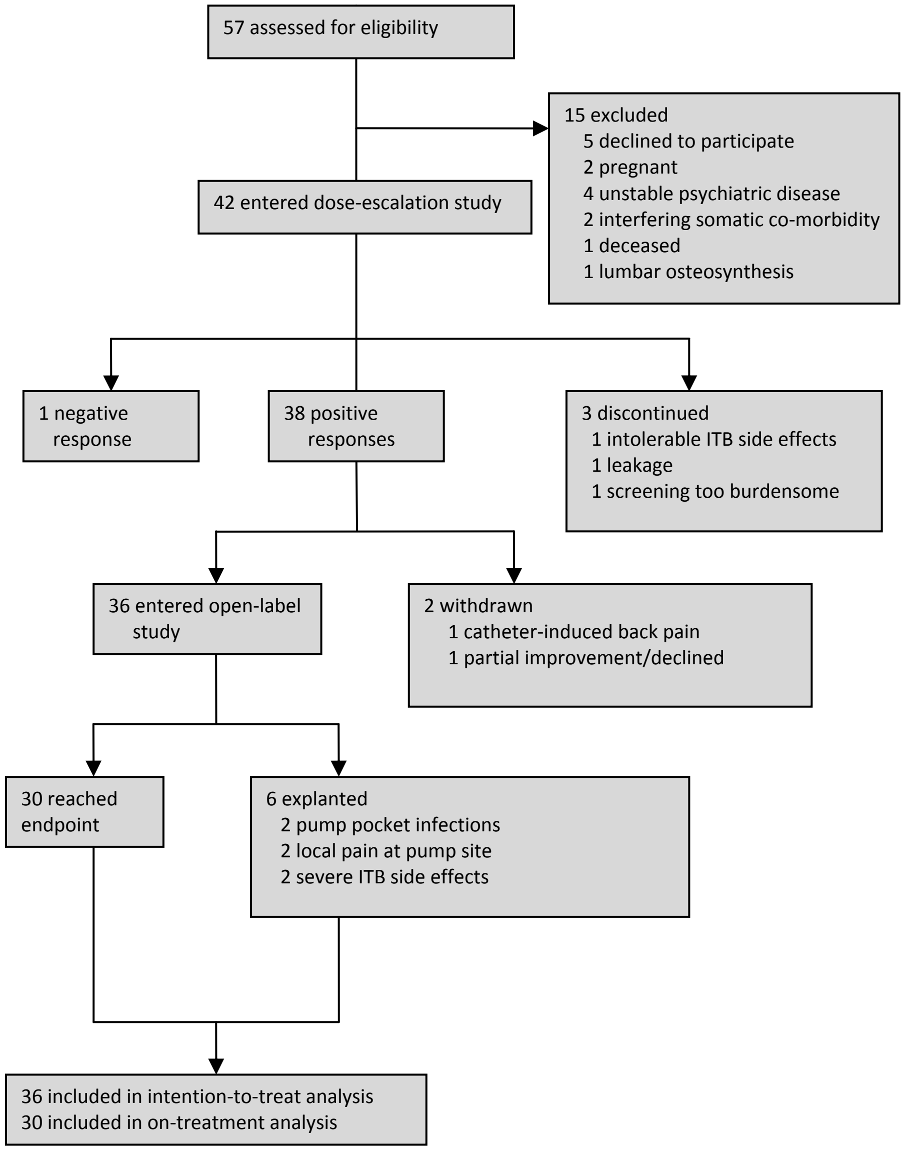

Figure 7.1. Enrollment of patients in dose-escalation and open-label studies.

The mean $GDS_{placebo}$ response was 7% (95% CI 3-12). One patient did not respond to ITB. A dose-effect of baclofen on dystonia severity was observed in doses up to 450 µg/day. Thirty-one patients reached the responder criteria at this dose (Figure 7.2). 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 34-43) in favor of baclofen for responders on the first response day and 41% (95% CI 36-46) 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 -3-7). The mean difference between $DFL_{placebo}$ and $DFL_{baclofen}$ response was 25% in favor of baclofen (95% CI 17-33) on the first response day and 25% (95% CI 17-31) on the second day.

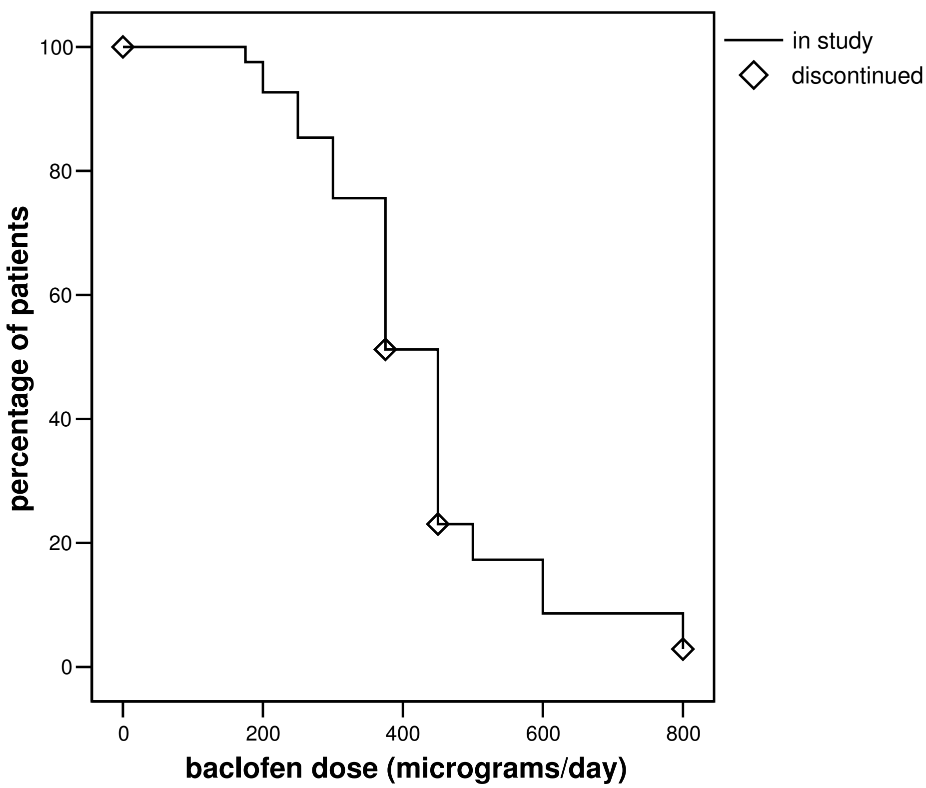

Figure 7.2. Dose-escalation study: baclofen dose at which the responder criteria were reached.
Kaplan-Meier curve of 42 patients showing the baclofen dose at which patients reached the responder criteria. ◊ denotes three patients that dropped out because of intolerable side effects, aanpassen. *denotes one patient who did not respond to ITB.

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 7.3). 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 (Figure 7.3A 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 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 7.1, 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%.

Table 7.3 (continued on next page). Open label study: primary and secondary outcomes at baseline and 12 months follow-up

Outcome (range)	Intention to treat (*n*=36)			
	0 Mo	**12 Mo**	**Change from baseline**	**95% CI**
Global Dystonia Severity (0-10)	7.3	4.4	-2.9	-3.9 to -1.9
Burke-Fahn Marsden Scale (0-120)	48.9	30.1	-18.8	-28.0 to -9.6
Pain - numeric rating scale (0-10)	7.7	5.7	-2.0	-3.0 to -1.0
Dystonia-related Functional Limitations				
Total score (0-12)	8.5	5.9	-2.6	-3.8 to -1.5
Mobility (0-3)	2.1	1.7	-0.4	-0.6 to -0.1
Transfers (0-3)	2.1	1.3	-0.8	-1.1 to -0.4
Right hand function[a] (0-3)	2.3	1.5	-0.8	-1.2 to -0.4
Left hand function[a] (0-3)	2.1	1.4	-0.7	-1.1 to -0.4
Rivermead Mobility Index (0-15)	5.5	7.9	2.4	0.5 to 4.4
Barthel Index (0-20)	11.8	14.9	3.1	1.3 to 5.0
EuroQol-5D				
Index (EQ-Tariff) (0-1)	0.21	0.45	0.24	0.12 to 0.36
Health state (0-100)	42.2	53.8	11.6	4.4 to 18.7

[a]Right and left hand functions were only assessed in affected hands. Absolute values are given in means. 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.

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/day (range 150-1500) after one year.

Adverse events

Nineteen ITB-related adverse events were reported in 14 patients (Table 7.4). 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

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**
7.3	4.1	-3.2	-4.4 to -2.1	7.1	6.1	-1.0	-1.8 to -0.2
50.5	27.2	-23.3	-33.3 to -13.3	40.8	44.8	3.9	-12.0 to 20.4
7.7	5.4	-2.3	-3.4 to -1.2	7.4	7.4	0	-1.5 to 1.5
8.6	5.3	-3.3	-4.5 to -2.1	8.2	8.8	0.6	-1.1 to 2.3
2.1	1.6	-0.5	-0.8 to -0.2	2.1	2.4	0.3	-0.2 to 0.8
2.1	1.2	-0.9	-1.3 to -0.5	2.0	2.1	0.1	-0.5 to 0.7
2.3	1.3	-1.0	-1.4 to -0.6	2.3	2.3	0	-0.6 to 0.7
2.1	1.2	-0.9	-1.3 to -0.5	1.8	2.0	0.2	-0.3 to 0.7
5.7	8.3	2.7	0.4 to 4.9	4.6	5.6	1.0	-1.8 to 3.8
11.6	15.3	3.7	1.7 to 5.8	13.0	13.0	0	-4.4 to 4.4
0.24	0.50	0.26	0.13 to 0.41	0.04	0.10	0.06	-0.03 to 0.14
43.5	54.5	11.0	3.1 to 18.8	34.6	49.8	15.2	-10.9 to 41.3

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 (PDPH) (*n*=31) as the most frequent complication.

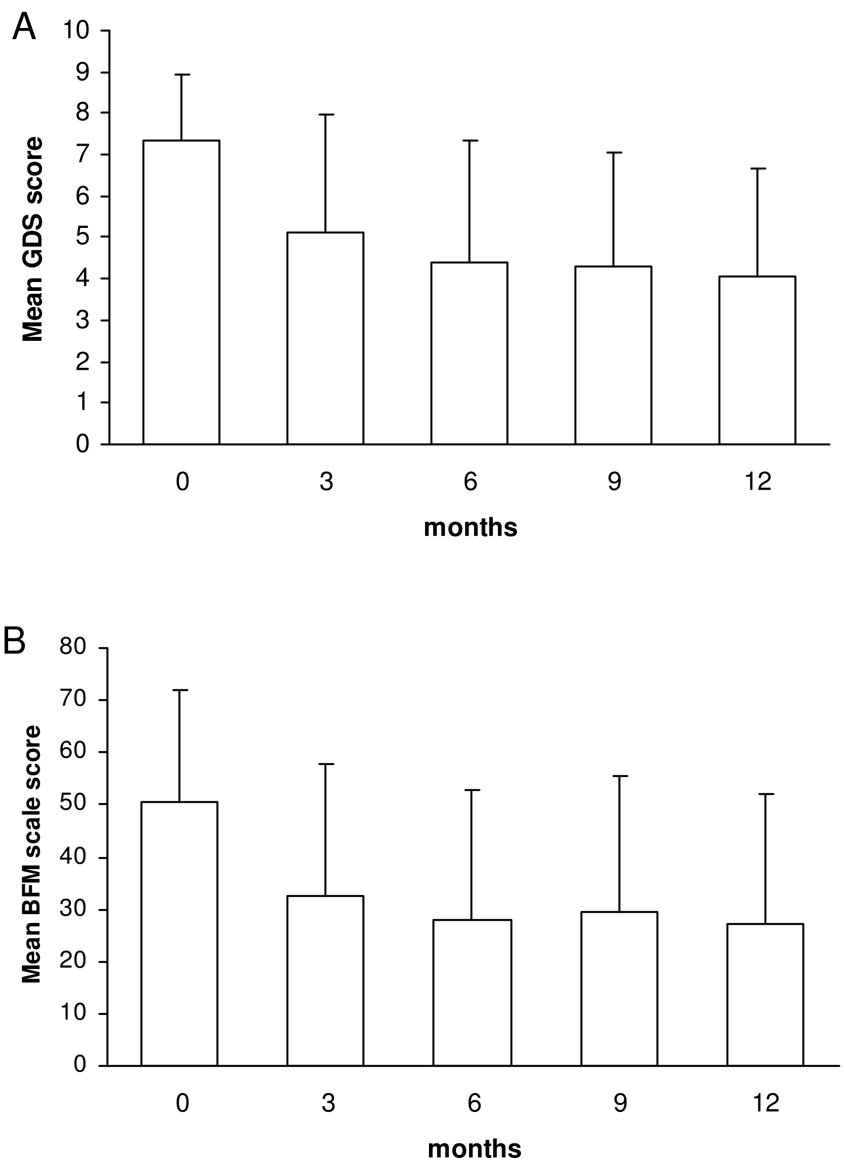

Figure 7.3. Dystonia severity during open-label study.
Mean (SD) scores of Global Dystonia Severity (GDS, panel A) and the Burke-Fahn-Marsden scale (BFM scale, panel B) before and after 3, 6, 9, 12 months of ITB infusion in the on-treatment group (n=30). *denotes a significant difference compared to baseline values (P<0.001).

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.

Table 7.4. Adverse events in open-label study

Adverse events	**Type of event**	***n***
ITB-related (*n*=19)	Urinary retention	3
	Somnolence	3
	Psychiatric[a]	3
	Nausea, vomiting	2
	Headache	2
	Fatigue	1
	Dysesthesia	1
	Hypotension, bradycardia	1
	Other[b]	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[c]	4
	Excessive weight loss	2
	Gastro-intestinal problems (unrelated to ITB)	3
	Infections (unrelated to device)	3
	Internal complications[d]	3

[a]psychosis: *n*=2, depression and anxiety disorders: *n*=1
[b]diplopia, dizziness, anorgasmia
[c]confusional state: *n*=2, reactive depression: *n*=1, reactive psychosis: *n*=1
[d]anemia, elevated liver enzymes, electrolyte changes

Discussion

Dystonia is characterised 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.[30-32] 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 GABA-ergic 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 7.2). A similar response pattern was observed in deep brain stimulation (DBS) in patients with primary generalised dystonia[33] and contrasts with the more rapid 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/day after 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/day),[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 QoL. The efficacy of ITB in CRPS-related dystonia is emphasised 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, 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 GABA-ergic 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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Intrathecal glycine for pain and dystonia in complex regional pain syndrome

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Abstract

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

Introduction

Complex regional pain syndrome type 1 (CRPS), which is more common in women and often preceded by a trauma, is characterised by spontaneous pain, oedema, changes in skin temperature and colour, hyperhidrosis, and motor disturbances.[1,2] The latter mainly include fixed dystonia of the distal extremities.[3,4] The pathophysiology of CRPS is still unclear but over the last decade there is increasing evidence showing that different mechanisms may contribute to its broad clinical spectrum.[1,5,6]

The initial symptoms of CRPS have been attributed to a perturbed regulation of inflammation in which both C and Aδ sensory nerve fibers (neurogenic inflammation) and the immune system of the skin are involved.[7-10] Peripheral inflammation or injury may in turn lead to profound changes in the processing of sensory input at the spinal level, a process known as central sensitisation.[11,12] As a result, pain may become chronic and allodynia and hyperalgesia may develop. Additionally, these central changes may corrupt the normal control of motor circuits.[13,14]

Compelling evidence from neurophysiological studies that focused at the spinal or cortical level in patients show that disinhibition is a key characteristic in the involvement of the central nervous system in CRPS patients with and without dystonia.[15-18] Cutaneous C and Aδ afferents are linked to spinal interneuronal circuits that mediate nociceptive withdrawal reflexes (NWRs).[19] Interestingly, both sensitised NWRs in animal models and pain and dystonia in CRPS patients respond to the intrathecal administration of the $GABA_B$ agonist baclofen (ITB), which enhances spinal GABA-ergic inhibition.[20-22]

In addition to GABA-ergic circuits, glycinergic circuits may also be involved in central sensitisation. In rats, peripheral inflammation-induced central sensitisation has been associated with loss of glycinergic inhibition.[23] Following peripheral inflammation or spinal PGE_2 injection, mice with a glycine receptor deficiency showed a reduced pain sensitisation.[24,25] In animal models of neuropathic pain, intrathecal glycine (ITG) reduced[26,27] or prevented[28] hyperalgesia. Besides involvement in afferent processing, glycine may play a prominent role in the control of motor functions. Strychnine is a glycine receptor antagonist, and poisoning with this drug results in overwhelming muscle spasms, rigidity and tremor.[29] Glycine receptor mutations in both humans and animals result in spasms, tremor and myoclonia,[30,31] motor features that bear a remarkable similarity to those reported in CRPS.

In view of the important role of disinhibition in chronic CRPS and the potential role of glycinergic mechanisms in pain and motor processing, drugs such as glycine that enhance glycinergic inhibition may provide a new mode of treatment in CRPS. Because glycine is abundantly present in food, it would seem plausible that this potentially dangerous inhibitory neurotransmitter has limited access to the CNS. Indeed, two animal studies have reported a poor blood-brain barrier (BBB) passage of glycine.[32,33] As a consequence, glycine requires intrathecal administration (ITG) to explore its role in the management of pain and dystonia in CRPS.

Aims of the current study were to evaluate the safety and efficacy of ITG in patients with CRPS. We here report the results of a double-blind randomised placebo-controlled crossover trial evaluating 4weeks of ITG treatment in 20 chronic CRPS patients.

Methods

Subjects were male or female out-patients, at least 18 years of age, with a clinical diagnosis of CRPS with dystonia who were referred to the movement disorders outpatient clinic of the Department of Neurology and were candidates for ITB treatment. Patients who qualified for ITB treatment were requested to participate in the current study, which was performed in the period before ITB treatment started. Patients were referred by physicians throughout the Netherlands. Inclusion criteria were CRPS 1 according to the diagnostic criteria of the International Association for the Study of Pain,[34] clinically significant fixed dystonia in one or more extremities, and symptoms for at least 1 year. Exclusion criteria were satisfactory relief of symptoms with conventional treatments including oral baclofen, pregnancy, breastfeeding, childbearing potential without using effective contraception, clinically significant psychiatric illness, suspicion of poor compliance, or involvement in legal proceedings concerning compensation for CRPS. All patients were evaluated by a psychiatrist to exclude psychiatric comorbidity. In all subjects a programmable SynchroMed pump (Medtronic, Minneapolis, MN) for continuous IT administration was implanted. The catheter was introduced in the subarachnoid space (L2-L3) under X-ray guidance with the distal tip of the catheter placed in the midthoracic region. The catheter was then tunneled subcutaneously and connected to the pump. Pump-catheter system integrity was verified post-operatively. We aimed to recruit 20 patients, which was considered a reasonable sample size for a first safety study. Patient consent was obtained according to the Declaration of Helsinki and the study was approved by the Ethics Committee of the Leiden University Medical Centre.

N=1 experience

To date no published studies on ITG in humans are available. The dose schedule of ITG in the current study was based on our experiences in one CRPS patient who progressed to generalised dystonia and did not respond to ITB. After consent was obtained from both the local Ethics Committee and the patient, a last resort therapy with ITG was started. We noted a sustained and prominent decrease in pain with moderate effects on dystonia at a dose of 30 mg/24 h. ITG was administered for 1 year and no side-effects occurred.

Study design

We used a double-blind randomised placebo-controlled crossover design. Randomization was done by a computer-generated list and took place at the Department of Pharmacy. Treatment allocation remained concealed from patients and investigators (including those who performed the assessments) throughout the study. Every subject received two intrathecal treatments: 21 mg/mL glycine solution during 4 weeks, and sodium chloride 0.9% (w/v) during 4 weeks (placebo), with a tapering and wash-out period in-between both treatments: tapering in 1 week (3 equal dose reductions with an interval of 48 h), followed by a wash-out period of 1 week. The carry-over between treatments was considered minimal because the plasma half-life of IV glycine ranges from 30-60 min[35] (the half-life of ITG is unknown). Placebo and ITG have the same watery appearance, which made unblinding by inspection of the administered substances impossible. Treatment was started at 8 mg/24 h and was increased weekly with 8 mg/24 h. Unless side-effects occurred, glycine administration reached a daily dose of 32 mg/24 h in the last week of the glycine period. Higher dose administrations were not studied because of the associated short filling interval (<1 month) of the pump, which was considered not feasible in clinical practice.

An independent data safety board monitored the study. The committee monitored the safety of the patients by evaluating the treatment-emergent adverse events (AEs). The study is registered with the Netherlands Trial Register, number NTR499.

Outcome measures

Safety assessments included history taking, physical examination and routine blood assessments (every other week) and electrocardiograms (every other week). Pain was evaluated with a numeric rating scale (NRS) for pain, and the McGill pain questionnaire.[36] A TSA-II thermal sensory analyzer (Medoc Ltd., Ramat Yishai, Israel), using a thermode placed on both hands (thenar eminences), was used to assess detection thresholds of temperature change (method of limits).[37] Efficacy on movement disorders was studied with the Burke-Fahn-Marsden (BFM) dystonia rating scale,[38] unified myoclonus rating scale (sections 2, 3, and 4)[39] and tremor research group rating scale (items 1-8).[40] Assessment of activity level included the Radboud skills questionnaire[41] (if arms were involved) and the walking ability questionnaire[42] (if legs were involved). Change of CRPS signs and symptoms was rated on a global impression scale: both the investigator (clinical global impression, CGI) and the patient (patient's global impression, PGI) assessed the change during treatment on a scale ranging from -3 (very poorly) to +3 (very well).

Success of the blinding was investigated by asking both the patient and investigator to guess which treatment was administered.

Plasma glycine and growth hormone analysis

Blood samples for glycine measurement were taken at the last day of treatment (before tapering). Blood was collected in EDTA (ethylene diamine tetraacetic acid) tubes and directly cooled with melting ice. Plasma was isolated after centrifugation at 20°C for 7 min at 1,500*g* and stored at -20°C until analysis. Glycine was determined on a Biochrom 30 automated amino acid analyzer (Biochrom, Cambridge, UK) as previously described;[43] however 250 µM L-methionine sulfone (Sigma, St Louis, MO) was used as the internal standard and a short buffer program of 50 min was used.

Because in a previous study in children, IV glycine increased growth hormone (GH) levels,[44] blood levels of GH were monitored at baseline and at the last day of each of the interventions.

Statistical analysis

To study differences between 4 weeks of ITG treatment and 4 weeks of placebo treatment, the paired *t*-test (if data were normally distributed) or Wilcoxon test (if not) were used. Significance was assumed at the 0.05 level. For all tests, the SPSS software package version 14.0 (SPSS Inc., Chicago, IL) was used.

Results

No patients refused to participate in the study in the period before their ITB treatment started. Patients were aged 26-58 years (19 women, 1 man). One patient withdrew her consent after implantation. The remaining 19 patients entered the study (Table 8.1). In one patient, the study was ended prematurely because participation was experienced as too burdensome (she received ITG during 21 days, and no placebo).

Table 8.1. Baseline characteristics - before pump implantation (*n*=19)

Characteristic	**Value**
Gender (F/M)	18/1
Age (yr; median, IQR)	41 (34-51)
Duration of CRPS (yr; median, IQR)	9 (5-17)
Number of dystonic extremities (%)	
1	0
2	6 (31)
3	3 (16)
4	10 (53))
Modified Rankin scale (%)[45]	
No significant disability	0
Slight disability	7 (37)
Moderate disability	5 (26)
Moderately severe disability	7 (37)
Severe disability	0

CRPS = complex regional pain syndrome type 1; IQR = interquartile range.

Safety

Treatment-emergent AEs were found in 15 patients. The most frequently reported AEs were drowsiness, headache, dysesthesia and nausea and vomiting (Table 8.2). The proportion of patients with one or more AEs was similar during ITG (12/19 = 63%; 18 AEs) and placebo treatment (9/18 = 50%; 13 AEs; χ^2 = 0.23, df = 1, *P*=0.63).

Serious AEs did not occur. Other AEs during ITG treatment were categorized as mild to moderate. In one patient, a mild but persistent exacerbation of pain and dystonia occurred, which began at the first day of ITG treatment.

Plasma glycine and GH measurements

Mean plasma glycine concentrations were not different between ITG treatment (242 µM, range 106-461) and placebo treatment (241 µM, range 105-499) at 28 days of treatment (*P*=0.75, paired *t*-test).

Table 8.2. Treatment-emergent adverse events

Adverse event	ITG (*n*=19)	Placebo (*n*=18)
Drowsiness	3	2
Headache	2	2
Dysesthesia	1	3
Dysgeusia	1	-
Photopsia	-	1
Restless legs	1	-
Nervousness	1	-
Emotional liability	2	-
Nausea or vomiting	1	3
Palpitations	-	1
Polyuria	1	-
Unpleasant feelings	1	2
Myalgia	2	-
Fever (1 day)	1	-
CRPS exacerbation	2	-
Total	**19**	**14**

CRPS = complex regional pain syndrome type 1; ITG = intrathecal glycine.

At baseline, four patients had GH values (8.8, 9.8, 25.9 and 70.6 mU/L) above the normal range (0.0-5.0 mU/L). GH was significantly increased at day 29 of ITG treatment (median 2.1, interquartile range [IQR] 0.7-5.3, maximum 30.7 mU/L) compared to day 29 of placebo (median 0.9, IQR 0.5-4.2, maximum 13.4 mU/L; *P*=0.031, Wilcoxon test). There were no significant abnormalities in other clinical laboratory tests or electrocardiograms.

Efficacy

There were no significant differences in any of the outcome measures, between ITG and placebo treatment (table 8.3). During ITG treatment, one patient reported improvement (PGI +2), and nine reported worsening (PGI -3 in one patient, -2 in four, and -1 in four). The CGI score showed improvement in one patient during ITG treatment (+2), and worsening in five (-3 in one, and -1 in four). During placebo treatment, two patients reported improvement (PGI +2), and four reported worsening (-2 in three, and -1 in one), the CGI showed improvement in none, and worsening in one (-1). The effect of placebo was 0% for the pain NRS and -15% for the BFM dystonia rating scale.

Table 8.3. Summary of secondary outcome events (medians (interquartile ranges) are presented)

Outcome event	Range scale[a]	Intrathecal glycine		Placebo		*P*[b]
		Baseline	4 weeks	Baseline	4 weeks	
Pain (numeric rating scale)	0-10	6 (4-8)	6 (5-8)	7 (5-8)	7 (5-7)	1.0
McGill pain questionnaire						
Number of words chosen	0-20	12 (7-13)	13 (8-14)	12 (8-14)	12 (8-14)	0.20
Pain rating index	0-63	21 (11-28)	20 (13-32)	22 (14-28)	19 (13-31)	0.49
Thermal sensory analyzer (°C)						
Cold detection threshold (ΔT)	0.1-17.0	1.3 (0.3-4.7)	1.0 (0.3-3.8)	1.0 (0.4-5.6)	1.0 (0.4-4.2)	0.70
Heat detection threshold (ΔT)	0.1-18.5	1.4 (0.5-5.1)	1.8 (0.9-4.3)	2.3 (1.2-6.1)	2.0 (0.8-4.0)	0.23
Burke-Fahn-Marsden dystonia rating scale	0-120	32 (14-44)	35 (12-48)	27 (12-41)	31 (16-48)	0.60
Unified myoclonus rating scale						
Myoclonus at rest	0-128	0 (0-8)	0 (0-5)	0 (0-1)	0 (0-1)	0.35
Stimulus sensitivity	0-17	0 (0-1)	0 (0-0)	0 (0-1)	0 (0-1)	0.13
Myoclonus with action	0-160	10 (0-20)	0 (0-16)	3 (0-20)	4 (0-17)	0.96
Tremor research group rating scale (items 1-8)	0-76	2 (0-6)	2 (0-6)	1 (0-6)	2 (0-6)	0.96
Radboud skills questionnaire (total)	1-5	4 (3-5)	4 (3-4)	4 (3-4)	4 (3-4)	0.18
Walking stairs questionnaire						
Walking in the house	0-10	9 (8-10)	9 (6-10)	9 (6-10)	9 (7-10)	0.77
Walking outside	0-10	10 (7-10)	10 (7-10)	10 (9-10)	10 (8-10)	0.23
Patient's global impression	-3-+3		0 (-1-0)		0 (0-0)	0.32
Clinical global impression	-3-+3		0 (-2-0)		0 (0-0)	0.74

[a]Best score is underlined.

[b]ITG at 4 weeks versus placebo at 4 weeks (Wilcoxon signed rank test).

Patient's and investigator's guesses of which treatment was administered were incorrect in 57% and 59%, respectively. There was no significant effect of sequence (ITG-placebo or placebo-ITG) on the pain NRS and BFM dystonia rating scale baseline scores.

Discussion

Central disinhibition plays an important role in CRPS and enhancing the GABA-ergic inhibitory status through intrathecal administration of baclofen has proven beneficial in the treatment of dystonia and to a lesser extent on pain.[21,22,46] Against this background, we were interested if similar results could be obtained by enhancing glycinergic inhibition in CRPS patients. Because no information is available on the tolerability of this mode of glycine administration in humans, this study firstly focussed on the safety of ITG and secondly evaluated its efficacy in doses up to 32 mg/24 h. No major AEs occurred in 19 CRPS patients treated with ITG over 4 weeks. The proportion of most frequently reported AEs (drowsiness, headache, dysesthesia and nausea and vomiting) was similar for ITG and placebo treatment. Compared to placebo, median GH values increased during ITG treatment (0.9 versus 2.1 mU/L). GH levels still remained in the normal range of 0-5.0 mU/L, and were smaller than the increases that are observed with intravenous GH. Notably, the absence of functional disturbances in our patients is at best only a surrogate marker for the absence of neurotoxicity of ITG.[47] Evolving deficits may not be revealed by functional indices for an extended period of time, whereas histological examination demonstrates a continuing event.[48] Consequently, our findings are insufficient to assume that ITG is not associated with neurotoxicity and further studies are required to address this issue.

Over the dose-escalation period of 4 weeks with doses up to 32 mg/24 h we did not find evidence of efficacy of ITG. Several explanations for this lack of efficacy of ITG are possible. First, it is possible that not glycinergic but GABA-ergic mechanisms play a key role in central disinhibition of CRPS. Second, ITG may have been administered in an insufficient dose, although GH-increases indicate that the doses were pharmacologically active. Third, effective synaptic concentrations of glycine are regulated by glycine transporters which mediate its uptake into nerve terminals and adjacent glial cells.[49] Hence, the lack of efficacy of ITG could result from a compensatory ITG-mediated increased activity of glycine reuptake transporter mechanisms. In this case, selective inhibitors of glycine transporter could be more efficacious. Finally, however, our patient and clinician-based impression scores may hint at another explanation. Although the primary outcomes showed no difference, there was a trend on the patient and clinician-based impression scores to show deterioration during ITG. Nine patients worsened during ITG, versus four during placebo treatment according to the patient-based PGI score. In line with this, the investigator-based CGI indicated that five patients got worse during ITG, versus one patient during placebo treatment. Although, the PGI and CGI were not significantly different from zero, the trend towards a deterioration of signs and symptoms with ITG suggests that glycine may play a pathophysiological rather than a therapeutic role in CRPS. This could be caused by the dual action of glycine, which serves both as an obligatory co-activator of the spinal excitatory *N*-methyl-D-aspartate (NMDA) receptor, and as a neurotransmitter at the inhibitory strychnine-sensitive glycine receptor.[50,51] It is possible that the excitatory effects prevailed in the applied dose range. In CRPS, chronic pain, allodynia, and hyperalgesia, are assumed to result from central sensitisation, a state reflecting enhanced synaptic transmission efficiency of neurons in the dorsal horn of the spinal cord.[11] In central sensitisation, the NMDA receptor is upregulated, and open studies using NMDA antagonists memantine and ketamine have reported beneficial effects on pain in CRPS .[52-54] Hence, ITGs efficacy could depend on the state of the NMDA receptor and stimulation of the excitatory glycine receptor of the upregulated NMDA receptor may potentially worsen symptoms such as pain, explaining the trend of poorer ratings of patients and physicians when patients were using ITG.[55-57] Interestingly, intrathecal administration of 2-amino-5-phosphonopentanoate, an NMDA receptor antagonist, unmasked the analgesic action of glycine in rats.[58] Hence, future studies could analyze whether or not NMDA inhibition, administered prior to or simultaneously with ITG may enhance its therapeutic potential under circumstances of central sensitisation. Because intrathecal administration of NMDA inhibitors is neurotoxic,[59] this hypothesis can only be tested with orally or intravenously administered agents.

We studied a population of severely affected CRPS patients with long disease duration. Consequently, this patient sample involved a selection of treatment refractory patients, who are not representative for all CRPS patients. However, it would be unethical to evaluate ITG in acute stage patients, in whom symptoms might resolve spontaneously or following less invasive treatment options.

There is no data on the magnitude of the placebo responses in trials evaluating chronic treatment in CRPS patients with dystonia until now. In our previous study, placebo responses to two intrathecal saline injections were 4% and 8%, respectively.[21] Interestingly, there was no detectable placebo response in the current study during 4 weeks of intrathecal treatment. This finding might be useful for designing future trials on this subject.

In conclusion, ITG in doses up to 32 mg/24 h during four weeks was not associated with serious adverse events, but further studies are required to rule out potential neurotoxicity of ITG. Although results from animal studies were promising, this study did not find efficacy on pain or dystonia in patients with chronic CRPS. Several potential explanations for this finding could be addressed in future studies.

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Appendix

The data safety board consisted of Prof.dr. H.J. Guchelaar (Department of Clinical Pharmacy, Leiden University Medical Centre), Dr. R.J.E. Grouls (Department of Clinical Pharmacy, Catharina Hospital, Eindhoven) and Dr. G.J. Lammers (Department of Neurology, Leiden University Medical Centre).

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

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Abstract

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

Introduction

Complex regional pain syndrome type 1 (CRPS) is usually preceded by tissue injury and characterized by pain, oedema, skin discoloration, altered temperature, hyperhidrosis, and movement disorders.[1,2] The initial symptoms of CRPS have been attributed to aberrant inflammation in which both C and Aδ sensory nerve fibers and the immune system of the skin contribute.[3-5] This peripheral inflammation may lead to profound changes in spinal processing resulting in allodynia, hyperalgesia, and the chronification of pain (central sensitisation).[6,7] In turn this process may corrupt sensorimotor network function causing motor dysfunction.[8,9]

The mechanisms underlying central sensitisation in CRPS are still largely unknown. Activation of spinal microglia has been implicated in the development and maintenance of neuropathic pain states.[5,10,11] In this process, a range of immune mediators is released, among which prostaglandin E_2 (PGE_2) plays a crucial role.[12] Cyclooxygenase-2 (COX-2), induced by spinal interleukin-1β (IL-1β), is the major limiting factor in the production or release of PGE_2.[13]

Glucocorticoids have powerful anti-inflammatory effects throughout the whole body with COX-2 repression as one of the mechanisms of action.[14] In CRPS, glucocorticoids may be beneficial early in the course of the syndrome,[15] which most likely is explained by the suppression of peripheral inflammation. Because of the poor spinal bioavailability,[16] oral corticosteroids may lack efficacy with respect to the chronic features of CRPS caused by central sensitisation. A possible method to circumvent this problem is intrathecal administration. In chronic postherpetic neuralgia, another neuropathic pain syndrome, intrathecal methylprednisolone (ITM) was shown to be effective.[17]

The aim of this study was therefore to evaluate the efficacy and safety of a single administration of ITM in chronic patients with CRPS.

Methods

Subjects were male or female outpatients, with a clinical diagnosis of CRPS type 1 who were referred to the Movement Disorders outpatients clinic of the Department of Neurology. In all cases patients were referred by neurologists and anesthesiologists throughout the Netherlands. Patients had to fulfill the diagnostic criteria of the consensus report of CRPS 1,[18] had to be 18-75 years old, have experienced symptoms for more than 6 months and less than 6 years, and report spontaneous pain of at least five on a pain intensity numeric rating scale (PI-NRS; on which 0 represents no pain, and 10 the worst imaginable pain). Patients were excluded if they had experienced satisfactory relief of symptoms with conventional treatments, had contraindications for steroid therapy or lumbar puncture, were pregnant or breast-feeding women or women of childbearing potential not using effective contraception, had clinically significant psychiatric illness, were suspected of poor compliance, or were involved in legal proceedings claiming compensation for their CRPS.

A review of the literature showed that methylprednisolone acetate (Depo-Medrol) was administrated intrathecally in patients in more than 5,900 occasions (see the discussions in The Medical Journal of Australia,[19-27] Archives of Neurology[28-35] and The Clinical Journal of Pain[36-38]). Serious adverse events were reported in 31 of these occasions and involved cerebral hemorrhage,[39] meningitis,[39-47] conus syndrome,[48] progressive weakness,[49] reversible bladder dysfunction,[39] paresthesia,[22] adrenal insufficiency[50] and hypercortisonism[39]. Most of these side effects were reported in patients with multiple sclerosis who received repeated administrations.

Patients in our study were orally and written informed about these facts. Patient consent was obtained according to the Declaration of Helsinki and the study was approved by the medical ethics committee of the Leiden University Medical Centre.

Study design

We used a double-blind randomised placebo-controlled parallel-group design. Randomization was done with a computer-generated list and took place at the Department of Pharmacy. Treatment allocation remained concealed from patients and investigators (including those who performed the assessments) throughout the study. Lumbar puncture (20 or 22 gauge needle) was performed by physicians experienced in performing lumbar punctures (A.M. or A.P.). Subjects received 60 mg methylprednisolone acetate (Depo-Medrol 40 mg/ml) or 1.5 ml sodium chloride 0.9% (placebo). Study medication was distributed in opaque syringes, which made unblinding impossible. Clinical assessments were scheduled at baseline (1 week before administration of study treatment), at 6 weeks and 12 weeks follow-up.

An independent data monitoring committee was instituted to monitor safety and to perform an interim analysis on efficacy halfway during the study. At the interim analysis, this committee assessed the probability that efficacy of ITM could be demonstrated at the end of the study. The study is registered with the Netherlands Trial Register, number NTR61.

Outcome measures

Pain was evaluated with the PI-NRS,[51] and the McGill pain questionnaire[52] and were computed as the means of the scores at 09:00, 13:00, 17:00 and 21:00 h at one day. The effect of ITM on movement disorders was studied with the Burke-Fahn-Marsden dystonia rating scale (BFM),[53] unified myoclonus rating scale (UMRS; sections 2-4)[54] and tremor research group rating scale (TRGRS; items 1-8)[55]. Change of CRPS signs and symptoms was rated on a global impression scale: both the investigator and the patient assessed the change from baseline at the end of the study period on a scale ranging from -3 (very much worse) to +3 (very much improved).[51,56]

The integrity of the blinding procedure was investigated by asking both the patient and investigator to indicate which treatment they thought had been administered.

Safety assessments included history taking and physical examination at each follow-up visit.

Statistical analysis

The primary outcome measure was the change in pain on the PI-NRS at six weeks. It was estimated that 21 patients in each treatment group would provide a 90% power to detect a mean difference in the mean PI-NRS of ≥2 points between the two groups, which was considered clinically relevant,[51] with a type I error rate of 5%. Based on previous studies,[51,57] an SD of 2 was assumed. Independent-samples *t*-tests were used to compare the PI-NRS change between the two groups after 1, 6 and 12 weeks. Mann-Whitney *U* tests were used to compare the patient's and investigator's global impression scores between both groups. One-way between groups analyses of covariance (ANCOVA) with the baseline scores of the various outcome measures entered as covariates, were used to compare the efficacy of ITM to placebo while adjusting for baseline differences between the two groups. For the ANCOVA, preliminary checks were conducted to ensure that there was no violation of the assumptions of normality, linearity, homogeneity of variances, homogeneity of regression slopes, and reliable measurement of the covariate. The relation between the patient's and investigator's global impression score was investigated using Spearman rank correlation coefficient. Significance was assumed at the 0.05 level. For all tests, the SPSS software package version 14.0 (SPSS Inc., Chicago, IL) was used.

Results

Participant characteristics

Twenty-eight patients were screened for enrollment, seven of whom were ineligible: two did not meet the inclusion criteria, and five refused to participate (in whom clinical characteristics were not different from the remaining patients; Figure 9.1). The other 21 patients (16 females, 5 males) were randomised; their mean (SD) age was 46 (11) years and their mean (SD) duration of CRPS 4.5 (2.2) years. One randomised patient (who had received placebo) withdrew from the study because she developed severe post-dural puncture headache as well as a major depressive disorder. All male patients (n=5) received placebo. Twelve patients had two or more affected extremities, of which eight received ITM. Other baseline characteristics were similarly distributed between treatment groups (Table 9.1).

Efficacy

The study was ended prematurely because the interim analysis showed that the chance of reaching efficacy on the pre-established primary outcome measure was <1%.

There was no significant difference in PI-NRS change score between the ITM and the placebo group after 6 weeks (t = 0.65, df = 18, P=0.53; difference in means 0.3, 95% CI -0.7-1.3). PI-NRS change scores in the ITM group were in the range between -0.75 and +1.75, thus indicating that none of the patients met the predefined criteria of clinically significant improvement. Additionally, adjusting for baseline PI-NRS scores did not yield a significant difference (F (1,17) = 0.33, P=0.57, partial eta squared = 0.02) (Table 9.2). There was a strong relation between the PI-NRS at baseline and 6 weeks (partial eta squared value = 0.73). Contrary to the placebo group, myoclonus deteriorated in the ITM group, leading to a significant difference between the groups (F (1,17) = 6.17, P=0.02, partial eta squared = 0.27) (Table 9.2). There were no significant differences between ITM and placebo treatment in any of the remaining outcome measures. In the ITM group, two patients reported improvement (global impression score +1), and three reported worsening (-3, -2, and -1), whereas the other 5 remained unchanged. The investigator's global impression score showed improvement in one patient in the ITM group (+2) and worsening in two (-3, and -1), whereas the other seven remained unchanged. In the placebo group, one patient reported improvement (+2), and six reported worsening (-3 in one patient, -2 in three, and -1 in two), the investigator's global impression score showed improvement in one patient (+2), and worsening in three (-2 in one, and -1 in two). There was a strong positive correlation between patient's and investigator's global impression scores (Spearman rho = 0.75, $P<0.0005$).

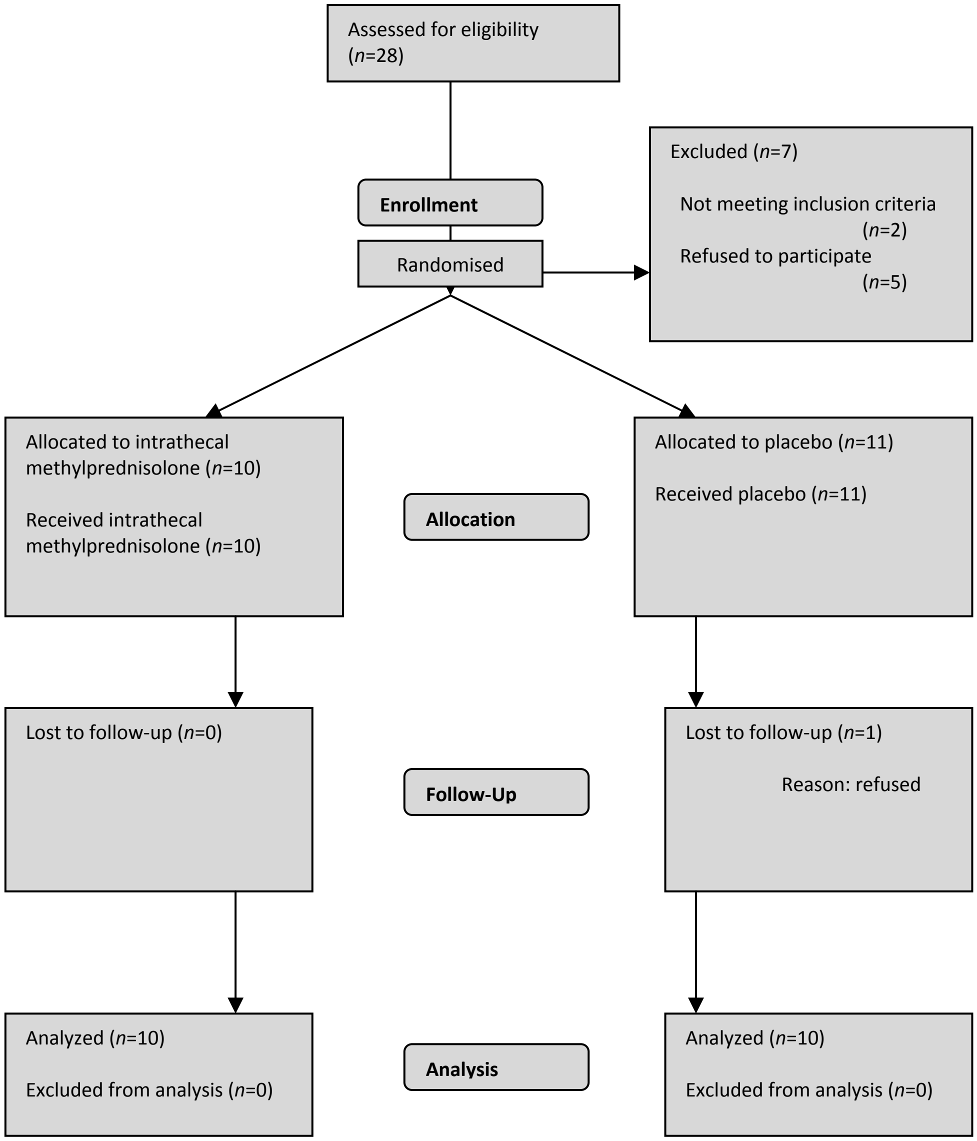

Figure 9.1. Patient disposition.

Table 9.1. Baseline characteristics of the 21 patients

Characteristic	**Methylprednisolone (*n*=10)**	**Placebo (*n*=11)**
Gender (F/M)	10/0	6/5
Age (yr; mean, SD)	45 (7)	46 (15)
Duration of CRPS (yr, mean, SD)	5 (2)	4 (2)
Preceding trauma, *n*		
Contusion	5	5
Fracture	1	2
Surgery	0	4
Other	4	0
Affected extremity		
Right/left arm	6/7	5/7
Right/left leg	7/8	5/4
Mean PI-NRS (SD)	6.9 (2.1)	7.3 (1.7)
McGill Pain Questionnaire (SD)		
NWC	12.2 (6.3)	11.5 (6.0)
PRI	24.2 (17.7)	25.5 (18.4)
Autonomic abnormalities, *n*	9	10
Oedema	9	7
Skin discoloration	8	7
Altered temperature	9	10
Hyperhidrosis	7	7
Sensory abnormalities, neurological examination, *n*	9	11
Tactile hypesthesia or hypalgesia	5	7
Tactile hyperesthesia, hyperalgesia or allodynia	9	7
Movement disorders, *n*	10	11
Dystonia	9	9
Myoclonus	5	6
Tremor	5	5

CRPS = complex regional pain syndrome; NWC = number of words chosen; PI-NRS = pain intensity numeric rating scale; PRI = pain rating index.

Data at 1 and 12 weeks follow-up showed no significant differences compared to baseline (data not presented). Both patient's and investigator's guesses of which treatment was administered, were correct in 52%.

Table 9.2. Summary of outcome measures at six weeks

Outcome measures means, (SD)	Range scale[a]	Methylprednisolone		Placebo		*P* value[b]
		Baseline	**Follow up**	**Baseline**	**Follow up**	
PI-NRS (SD)	0-10	6.9 (2.1)	6.9 (2.0)	7.3 (1.7)	6.8 (1.9)	0.57
McGill pain questionnaire (SD)						
NWC	0-20	12.2 (6.3)	11.9 (5.7)	11.5 (6.0)	9.7 (6.1)	0.35
PRI	0-63	24.2 (17.7)	22.3 (17.2)	25.5 (18.4)	19.5 (18.4)	0.53
BFM (SD)	0-120	15.7 (17.5)	14.6 (16.5)	7.3 (7.6)	9.3 (12.4)	0.28
UMRS (SD)	0-305	9.3 (17.3)	15.5 (21.0)	2.7 (3.6)	2.3 (3.5)	0.02
TRGRS, items 1-8 (SD)	0-76	2.9 (4.2)	2.5 (3.4)	1.4 (2.1)	1.7 (2.1)	0.89
PGI	-3-+3	-0.4		-0.9		0.42[c]
CGI	-3-+3	-0.3		-0.2		0.83[c]

BFM = Burke-Fahn-Marsden dystonia rating scale; CGI = clinician's global impression; NWC = number of words chosen; PGI = patient's global impression; PI-NRS = pain intensity numeric rating scale; PRI = pain rating index; TRGRS = tremor research group rating scale; UMRS = unified myoclonus rating scale.
[a]Best score is underlined.
[b]Analysis of covariance (with adjustment for baseline value).
[c]Independent-samples *t*-test.

Table 9.3. Treatment-emergent adverse events

Adverse event	Methylprednisolone (*n*=10)	Placebo (*n*=11)
Post-dural puncture headache	5	3
Tension-type headache	-	1
Backache	5	4
Major depressive disorder	-	1
Constipation	1	-
Diarrhea	-	1
Flushing	1	-
Oedema	-	2
Vasovagal syncope	-	1
Decubitus	-	1
Abnormal skin odor	1	-
CRPS exacerbation[a]	-	1
Total	**13**	**15**

CRPS = complex regional pain syndrome.
[a]In this patient, worsening of CRPS-related pain occurred.

Safety

Serious AEs did not occur. Non-serious AEs occurred in 16 patients: 13 events in 8 patients who received ITM and 15 events in 8 patients who received placebo (Table 9.3). Post-dural puncture headache occurred in eight patients (38%), with durations ranging from 2 days to the complete study period of 84 days (median 9 days, persistent in three patients). Three epidural blood patches were administered in two patients, though, without effect. Backache occurred in nine patients (43%), the duration of which ranged from 2 days to the whole study period (median 14 days, persistent in four patients).

Discussion

Despite the extensive evidence for a role of the immune system in chronic pain disorders,[5,10,12,13] and the favourable findings of ITM in postherpetic neuralgia,[17] we did not find a positive effect of ITM in chronic CRPS patients. Moreover, none of the patients met the predefined criteria of clinically significant improvement. There may be several explanations for this lack of efficacy. Firstly, the role of the immune system in pain in CRPS may be different from other chronic pain disorders. The evidence suggesting increased levels of inflammatory mediators in CSF of chronic CRPS patients is inconsistent.[58,59] Secondly, the lack of effect of ITM in chronic CRPS may indicate that it is much too late to expect effects on glia cell activation mechanisms since these occur early in the process of chronification of pain. Patients in Kotani *et al.*'s study[17] had a mean (SD) duration of postherpetic neuralgia of 3 (2) years. Thirdly, one administration of ITM may have been insufficient since Kotani *et al.*[17] applied four intrathecal administrations. However, since after a single intrathecal administration of methylprednisolone acetate, CSF levels of the drug remain measurable for at least 2 weeks, some improvement of symptoms can be expected.[60] In view of the risks associated with repeated ITM administrations (see above), a study with repeated intrathecal administrations would only be appropriate if some improvement had occurred after a single administration. Finally, it is possible that the efficacy of ITM in postherpetic neuralgia is overestimated. Until now, replication of the results from Kotani *et al.*[17] have not been reported.

We did not find any difference in treatment-emergent AEs between the ITM and placebo group, which is in line with the earlier study on ITM[17]. Post-dural puncture headache developed in 38% of patients (*n*=8), and no relation with the administered treatment was found. Additionally, post-dural puncture headache extended beyond the follow-up period of 12 weeks in 14% (*n*=3), which is unusual as compared to published findings in other diseases.[61] Indeed, we used fairly wide-bore needles (20 or 22 Gauge) which is common at neurology departments, at least in The Netherlands. Although the use of small-bore needles may have led to lower rates of post-dural puncture headache, recent observations suggest that other mechanisms besides intracranial hypotension may contribute to the development of post-dural puncture headache in CRPS.[62]

We cannot rule out that patient selection may have influenced the findings. This partly results from the fact that this study was performed at a neurology department, where the majority of the randomised patients had movement disorders. However, all patients had typical features of CRPS including prominent chronic pain. Since there are no indications for a different pain pathophysiology in CRPS patients with or without movement disorders, there is no clear reason to assume that patient selection negatively influenced our findings. Because all men in this study received placebo, the efficacy of ITM in male patients remains unknown, although there are no arguments to assume gender specificity. Furthermore, since the mean duration of symptoms in our patients was five years, we cannot exclude that ITM may have been efficacious in an earlier phase of the condition. The meaning of the significant deterioration of myoclonus in the ITM group is uncertain.
In conclusion, a single bolus administration of ITM is not efficacious in chronic CRPS patients, which may indicate that spinal immune activation does not play an important role in this phase of the syndrome.

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Appendix

The data monitoring committee consisted of Prof.dr. A. Dahan (Department of Anesthesiology, Leiden University Medical Centre), Prof.dr. A.F. Cohen (Centre for Human Drug Research, Leiden) and Prof.dr. R. Brand (Department of Medical Statistics and Bioinformatics, Leiden University Medical Centre).

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Chapter 10

Post-dural puncture headache in complex regional pain syndrome: a retrospective observational study

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Abstract

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

Introduction

Complex regional pain syndrome type 1 (CRPS) is characterized by combinations of chronic pain, allodynia, hyperalgesia, changes in skin colour and temperature, sweating and swelling.[1] The syndrome predominantly develops in women and usually occurs following a tissue injury, for example a fracture or surgery.[1-3] Approximately 20% of the patients with CRPS develop dystonia, which is characterized by fixed flexion postures.

Treatment of dystonia is difficult,[4] although continuous administration of intrathecal baclofen (ITB) was shown to be beneficial in some patients with multifocal or generalised dystonia.[5] Inherent to this mode of drug delivery is the requirement of placement of an intrathecal catheter. As a consequence of the catheter's perforation of the spinal dura, cerebrospinal fluid (CSF) leakage may occur. Subsequent to this procedure, 0-42% of the patients develop headache over the frontal and occipital areas radiating to the neck and shoulders.[6-10] Exacerbation of the headache by adoption of the upright posture, and improvement of the pain by lying down is the sine qua non of post-dural puncture headache (PDPH).[10] PDPH is often associated with nausea and vomiting, neck stiffness, tinnitus, hypacusia, and photophobia, and after a single small diameter puncture rarely lasts longer than a week.[11] Although a low CSF pressure and meningeal inflammation have been suggested to play a role, the actual mechanism producing the complaints in PDPH is unclear.[10,12,13]

We have treated patients with CRPS-related dystonia with ITB since 1996. Over this period we have noticed an unusual high frequency and prolonged duration of PDPH after pump implantation in these patients. Here, we present our experiences and propose a mechanism, distinct from CSF hypotension, as a potential alternative cause of PDPH in this population.

Methods

The medical records of all CRPS patients who underwent pump implantation in the course of studies addressing the efficacy and safety of ITB in CRPS-related dystonia between May 1996 and December 2005 were evaluated. Therefore, the current study is retrospective, not-controlled and observational. All patients met the CRPS type 1 criteria of the International Association for the Study of Pain,[14] either at the time of disease onset or at the time of presentation at the clinic. Subjects were included if they had dystonia in at least two extremities, and experienced insufficient relief from oral baclofen or if this treatment caused dose-limiting side effects. Before implantation, patients were subjected to a screening procedure to determine responsiveness to ITB.[5,15] The SynchroMed EL or SynchroMed II programmable drug infusion system (Medtronic, Minneapolis, MN) was implanted under general anesthesia by an experienced neurosurgeon (J.V.). One end of the catheter was placed in the intrathecal space through a 17 gauge Tuohy needle (direction of the bevel parallel to the longitudinal axis of the spine), with the catheter tip placed at the midthoracic level. The other end of the catheter was tunneled into the subcutaneous space to the pump, which was positioned in the lower abdomen.

PDPH was diagnosed according to the definition of the International Headache Society: (i) headache that worsens within 15 min after sitting or standing and improves within 15 min after lying, with at least one of the following: neck stiffness, tinnitus, hypacusia, photophobia and nausea; (ii) dural puncture had been performed; and (iii) headache developed within 5 days after dural puncture.[11] It is assumed that the headache resolves spontaneously within 1 week or within 48 h after effective treatment of the spinal leak (usually by epidural blood patch (EBP)) in 95% of cases.[11]

PDPH during the post-operative course was treated with bed rest in horizontal position, pain killers (acetaminophen or non-steroidal anti-inflammatory drugs), EBP or intravenous (IV) ketamine (the latter as from 2004). EBP was administered by experienced anesthesiologists who injected 10-20 mL autologous blood one level caudal to the dural puncture site. This level was chosen to prevent damaging of the inserted spinal catheter. Dose of the ketamine infusion was based on a study from Correll *et al*.[16] Instead of racemic ketamine, we used S(+) ketamine because (at half the dose) this optical isomere has been suggested to be as efficient in reducing pain with fewer cognitive side effects.[17] The infusion rate was started at a dose of 4 mg/h and increased with increments of 2 mg/h or less three times a day if pain relief was insufficient and side effects were acceptable to the patient. The maximum dose was 20 mg/hr. Duration of the treatment was 7-14 days, or shorter if PDPH symptoms disappeared earlier or severe adverse events (as judged by patient or physician) occurred.

Presence, characteristics and duration of PDPH, effectiveness of treatment, as well as occurrence of CRPS exacerbation were recorded on a case report form. Exacerbation was

defined as a serious increase in CRPS-related pain as judged by the patient, or an increase in dystonia or autonomic signs (oedema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain) as observed by the physician.
The frequency of PDPH in patients with and without CRPS exacerbations was compared using a, where a *P* value <0.05 was considered significant.

Two patients who were evaluated for CSF leakage with radionuclide studies, by injecting indium^{111} diethylenetriaminepentaacetic acid (DTPA) into the drug reservoir of the pump,[18,19] are described in more detail.

Table 10.1. Baseline characteristics (*n*=54)

Characteristic	**Value**
Gender (%)	
Male	4 (7)
Female	50 (92)
Age	
Mean, SD (yr)	38.6 ± 12.4
Median, IQR (yr)	40.3 (26.8-49.0)
Duration of CRPS (yr; mean, SD)	10.1 (6.8)
Number of affected extremities (median, IQR)	3 (2 - 4)
Number of extremities with dystonia (median, IQR)	3 (2 - 4)
Preceding trauma, n (%)	
Contusion	19 (35)
Fracture	10 (19)
Surgery	7 (13)
Soft tissue injury	2 (4)
Distorsion	1 (2)
Spontaneously	15 (28)
VAS pain (mean, SD)	7.4 (1.8)
Sensory abnormalities, *n* (%)	
Hyperesthesia, hyperalgesia or allodynia	28 (52)
Hypesthesia or hypalgesia	39 (72)

IQR = interquartile range.

Results

Fifty-four CRPS patients (50 female) who underwent a pump-catheter implantation were identified (7 patients, in whom clinical characteristics where not different from the remaining patients, had dropped out during the screening procedure). Mean (SD) age was 39 (12.4) years with a range from 17-64 years. The median number of extremities affected by CRPS was 3: both sides of the body were involved in 44 patients, only right in 7, and only left in 3; upper and lower extremities were involved in 47 patients, only upper in 3, and only lower in 4 (Table 10.1). PDPH occurred in 41 patients (76%) after the implantation procedure (Figure 10.1). A history of migraine was present in 9 patients. Forty-four percent of the migraine patients developed PDPH, against 82% of the patients without migraine.

Three patients (7%) showed signs of CSF leakage (i.e., subcutaneous swelling). In one of these patients, the subcutaneous swelling with PDPH disappeared spontaneously after 5 weeks. Because this patient rated the symptoms of PDPH severity as mild, no treatment was started. In the second patient, PDPH resolved within 48 h after an EBP that was administered 11 days after implantation. In the third patient, PDPH persisted for 12 months after implantation, in spite of the disappearance of subcutaneous swelling after two EBPs administered at 10 and 17 days after implantation. Radionuclide imaging was performed three months after pump implantation and showed no signs of CSF leakage. PDPH was of such severity that she was confined to bed till six months after implantation. At this stage, two IV ketamine treatments were administered over a three week period which resulted in a gradual decrease of PDPH allowing the patient to become wheelchair-bound. Subsequently, PDPH gradually decreased. At 12 months post-implantation PDPH had resolved.

Thirty-eight of the 41 PDPH patients (93%) had PDPH without signs of CSF leakage. Duration of PDPH in these patients varied from 2 days-36 months, with a median of 18 days and an interquartile range of 8 days-3 months. Of the 24 cases who received an EBP, PDPH resolved within 48 h in 13 (54%). In 9 patients with enduring complaints of PDPH, EBPs were repeated once (*n*=5) or twice (*n*=4) without any result. One of these patients experienced PDPH for 16 months and 3 EBPs were unsuccessful. One month after pump implantation, radionuclide imaging was performed which showed no signs of CSF leakage. She was not treated with IV ketamine because PDPH resolved before 2004 (when IV ketamine was introduced at our department).

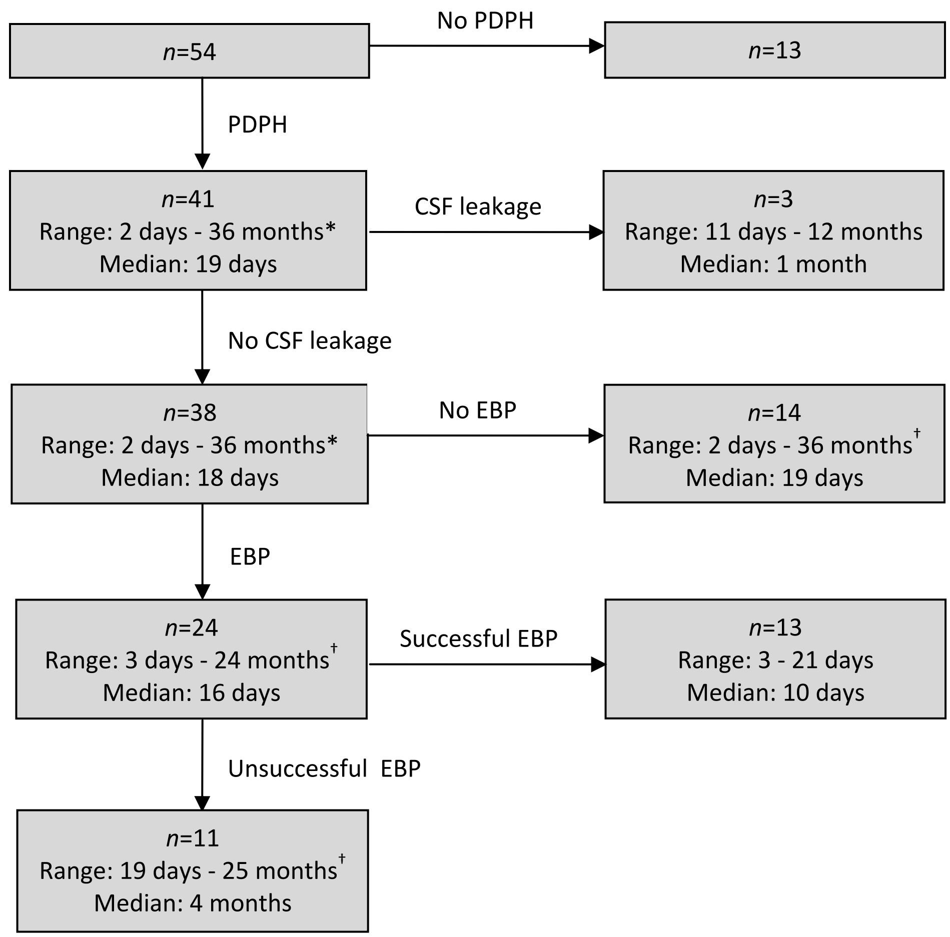

Figure 10.1. Study population flow chart.
CRPS = complex regional pain syndrome; CSF = cerebrospinal fluid; PDPH = post-dural puncture headache.
*Persistent symptoms in 2; †persistent symptoms in 1.

Six patients with PDPH but without overt signs of CSF leakage received IV ketamine (Table 10.2). PDPH resolved in four patients (67%) during 2-10 days of treatment. In two of these patients a prior EBP had had no effect. IV ketamine gave no improvement in two patients, one of whom also had had a prior EBP without effect. Non-serious adverse events related to IV ketamine including feeling high (*n*=2), malaise (*n*=1) and nausea (*n*=1), occurred in 3 patients.

Table 10.2. Ketamine IV in PDPH patients without signs of CSF leakage (*n*=6)

Patient	Duration from surgery to ketamine	Ketamine succesful?	Earlier EBP?	Duration PDPH	Also CRPS exacerbation?	Duration CRPS exacerbation
A	4 days	+	-	8 days	+	24 months[a]
B	4 days	-	+	4 months	+	3 months
C	7 days	+	-	17 days	-	NA
D	9 days	-	-	3 months	+	3 months
E	12 days	+	+	19 days	+	32 months[a]
F	13 days	+	+	19 days	+	unknown

CRPS = complex regional pain syndrome; EBP = epidural blood patch; NA = not applicable; PDPH = post-dural puncture headache.
[a]Persistent symptoms.

Following pump implantation, 15 patients (28%) experienced an exacerbation of CRPS. Fourteen of these patients also had PDPH without signs of CSF leakage. One patient had an exacerbation of CRPS without PDPH. Compared to patients without PDPH, patients with PDPH, but without signs of CSF leakage (*n*=51), more often experienced an exacerbation of CRPS (χ^2 = 3.964, df = 1, *P*=0.046, difference in proportions 29%, 95% CI 0.2-46.2%). The exacerbation lasted 7 days-51 months, with 4 patients still experiencing symptoms at a recent follow-up visit.

Discussion

In this study, 76% of the CRPS patients developed PDPH after pump implantation for intrathecal drug delivery. In 38 of the 41 PDPH patients, there were no overt clinical signs of CSF leakage. The duration of symptoms clearly exceeded the usual duration of PDPH known for patients that have been implanted, with 50% of the cases experiencing PDPH that lasted between 18 days to 36 months.
An EBP was effective in 54% of the patients. An explanation for the high incidence of PDPH in our population may be that needles with a large diameter, which are associated with a greater risk for PDPH,[20] were used. This explanation seems less likely because several earlier studies that used a catheter for ITB with a similar diameter, have reported PDPH in 0-42%,[6-9] which clearly differs from the 76% encountered in our population.

An EBP to reduce CSF leakage is the standard treatment of PDPH, but evidence of its efficacy (in comparison with a sham procedure) is still lacking.[11,21] Although the loss of CSF and subsequent decrease of CSF pressure is not disputed, the actual mechanism underlying the symptoms in PDPH is still unclear.[10] CSF leakage related PDPH was evident in some of our implanted patients and we cannot exclude that CSF leakage occurred at a subclinical level in those patients without overt signs of CSF leakage. However, both prevalence and duration of symptoms of PDPH in CRPS patients without CSF leakage deviated conspicuously from the values that are reported in patients implanted for other indications. Additionally, in two of our cases with long-lasting (12-16 months) PDPH, radionuclide studies did not reveal CSF leakage. Together, our findings suggest that, in CRPS at least, other causes than a reduced CSF pressure may underlie the initiation or maintenance of PDPH.

Compared to patients without PDPH, patients with PDPH more often experienced an exacerbation of CRPS. This may suggest that biological mechanisms involved in CRPS play a role in the initiation or maintenance of PDPH as well. Compelling evidence suggests that aberrant inflammation, in which both neurogenic and immunogenic components play a role, underlie the clinical features of the acute phase of CRPS.[22-24] Patients with CRPS may also develop symptoms and signs of vasomotor dysregulation, in which both a decreased central sympathetic activity and disturbed endothelium mechanisms play a role. As a consequence, vessels show a reduced vasomotor tone.[25-27] According to the Monro-Kellie doctrine, the sum of volumes of the brain, CSF and intracranial blood is constant with an intact skull.[10] It has been suggested that in PDPH a loss of CSF is compensated by vasodilatation[28] which has been illustrated by pachymeningeal gadolinium enhancement on magnetic resonance imaging.[12] Surgery or needle punctures are both well-known triggers of CRPS, but may also incite an exacerbation in patients with established disease.[29,30] If, and to what extent CRPS may cause an inflammatory response as well as a vasomotor dysregulation of meningeal structures is unknown. Nevertheless, increased pooling of blood in possibly sensitised meningeal vessels with disturbed vasomotor regulation may have contributed to PDPH in CRPS.

IV ketamine had a beneficial effect on PDPH in four of our six patients. This finding may suggest that ketamine elevated CSF pressure, as has been reported previously,[31] which consequently leaded to resolution of PDPH. However, this explanation is unlikely because there is compelling evidence to suggest that even in larger dosages, ketamine does not effect or even lower CSF pressure.[32,33] Our patients had long-lasting CRPS with sensory and motor features reflecting central involvement. Allodynia and hyperalgesia, present in half of our patients, are well-known features of central sensitisation.[34] Dystonia in CRPS has been attributed to a disinhibition of nociceptive withdrawal reflexes, likely also a reflection of central sensitisation.[34] Key in central sensitisation, is the activation of the *N*-methyl-D-aspartate (NMDA) receptor[35] and ketamine is a powerful suppressor of central sensitisation.[36] In CRPS patients, several open studies using ketamine have found beneficial effects on pain.[16,37,38] So, the beneficial response of PDPH to ketamine could be explained by its action as a non-competitive NMDA receptor antagonist in reversing central sensitisation. Alternatively, meningeal inflammation has been demonstrated in PDPH[12,13] and ketamine has an anti-inflammatory effect.[39-41] This may suggest that PDPH in CRPS reflects an aberrant meningeal inflammatory response induced by the insertion of an intrathecal catheter.

Obviously, there are a number of limitations in this study. First, we performed radionuclide imaging to exclude CSF leakage in only two patients and the reliability of this technique in demonstrating or excluding a leakage has not been established. However, this limitation is applicable for any other method used for this purpose. The most appropriate diagnostic study for evaluating intracranial hypotension would probably be measurement of CSF opening pressure. However, additional lumbar punctures potentially may further exacerbate the condition and were therefore not considered. Otherwise, PDPH is a clinical diagnosis.[11] Second, the efficacy of EBP and IV ketamine was evaluated in a small population (n=6) and in a non-randomised way, which may have led to bias. Third, retrospective studies are subject to misclassification and information on the exact duration of symptoms is less accurate than those that would have been obtained in a prospective study.

Nevertheless, our observations on PDPH may suggest that other mechanisms besides low CSF pressure play a role in the initiation and maintenance of PDPH in CRPS and stimulate new directions of research on this topic.

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Chapter 11

Summary and conclusions

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

Chapter 1. General introduction and aims

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

Chapter 2. How psychogenic is dystonia? Views from past to present

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

Chapter 3. Thermal hypesthesia in patients with complex regional pain syndrome related dystonia

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

Chapter 4. Fixed dystonia in complex regional pain syndrome: a descriptive and computational modelling approach

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

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

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

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

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

Chapter 7. Intrathecal baclofen for dystonia of complex regional pain syndrome

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

Chapter 8. Intrathecal glycine for pain and dystonia in complex regional pain syndrome

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

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

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

Chapter 10. Post-dural puncture headache in complex regional pain syndrome: a retrospective observational study

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

Conclusions

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

Studies on pathophysiology

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

By systematically evaluating the extremities of 85 patients with CRPS-related dystonia, we identified a dominant pattern of fixed dystonia. Fixed flexion of the fingers was observed in 95% of affected arms and a multisegmental pattern of finger flexion, wrist and/or elbow flexion and shoulder internal rotation/adduction, was observed in 66% of affected arms. A similar pattern was observed in affected legs: plantar flexion/inversion of the ankle was observed in 88% of affected legs, and a multi-segmental pattern of ankle plantar

flexion/inversion, toe and knee flexion, internal rotation of the hip, was observed in 66% of affected legs. Our modelling study showed that aberrant force feedback from Golgi tendon organs may be related to these postures.
Our CSF findings did not support a role of a variety of inflammatory mediators in chronic CRPS patients with dystonia. A search for CSF biomarkers involved in molecular pathways that play a role in neuroplasticity may be more fruitful.

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

Studies on intrathecal therapy

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

Future studies

Hitherto, studies on the pathogenesis of dystonia in CRPS have focused on the role of single biochemical CSF components and distinct neurophysiological characteristics.
Instead, modern 'omics' approaches are able to measure the overall metabolic or proteomic content of biological samples. The output of these experiments may be interpreted as a signature, or 'endophenotype', of the disease. Extrapolation on other 'omics' data potentially uncovers mechanisms of disease. Currently, such studies using different body fluids from CRPS patients with dystonia are ongoing.
The central nervous system controls the behaviour of the musculoskeletal system through many feedback loops. Their dynamic behaviour can be quite unpredictable from the individual components. The results from our modelling study suggest that it may be

worthwhile to study dystonia with closed loop system identification techniques. Currently, such studies are employed in the evaluation of CRPS-related dystonia.

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

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

Chapter 12

Samenvatting en conclusies (Dutch)

Dit proefschrift beschrijft de resultaten van een aantal studies naar de pathofysiologie en behandeling van complex regionaal pijnsyndroom (CRPS) gerelateerde bewegingsstoornissen.

Hoofdstuk 1. Algemene inleiding en doelen

Een korte samenvatting van de huidige kennis over CRPS gerelateerde bewegingsstoornissen wordt gegeven in hoofdstuk 1. Het syndroom komt meestal in combinatie met sensibele en autonome stoornissen voor. Het wordt vaak voorafgegaan door een trauma aan een ledemaat. De huidige theorie is dat het syndroom wordt veroorzaakt door een combinatie van trauma gerelateerde perifere en centrale neuro-immunologische factoren. Een belangrijk neurofysiologisch kenmerk is gebrek aan inhibitie. CRPS is een ernstige en invaliderende aandoening en de behandelingsmogelijkheden zijn beperkt.

Hoofdstuk 2. Hoe psychogeen is dystonie? Inzichten van vroeger naar nu

In de afgelopen eeuwen waren er afwisselend organische en psychogene verklaringen voor dystonie. In hoofdstuk 2 onderzoeken we deze geschiedenis en gaan daarbij uit van een spectrum van organisch naar psychogeen. We hebben ons gericht op (i) primair gegeneraliseerde dystonie; (ii) cervicale dystonie; (iii) schrijverskramp; en (iv) gefixeerde dystonie gerelateerd aan CRPS. We bestudeerden medische teksten vanaf de 19e eeuw inclusief de referenties. Jean-Martin Charcot was aanhanger van het concept van hysterie: stoornissen waarin naast predispositie omgevingsfactoren een belangrijke rol spelen. Sigmund Freud introduceerde de psychoanalyse: een inzichtgevende therapie voor psychische stoornissen. Deze ontwikkelingen, tezamen met de afwezigheid van een organisch substraat voor dystonie, waren destijds aanleiding voor een nadruk op psychogene verklaringen. Dientengevolge werd vele dystonie patiënten verteld dat ze leden aan psychologische conflicten en werd hun behandeling daarop gericht. Echter, door nieuwe beschrijvingen van families met meerdere aangedane personen in de jaren 50, de teleurstellende resultaten van psychotherapie bij torsie dystonie, de effectiviteit van chirugische behandelingen en de lesie-studies in de jaren 60, raakten meer en meer artsen overtuigd van de organiciteit van dystonie. Het ultieme moment was de ontdekking van het *DYT1* gen in 1997. Inmiddels hadden experts de neurologische gemeenschap al overtuigd dat focale dystonieën zoals cervicale dystonie en schrijverskramp partiële uitingen van generaliseerde dystonie waren en dus een organische basis hadden. De pathofysiologie van CRPS gerelateerde gefixeerde dystonie bleef echter controversieel.

Kennis van deze ontwikkelingen die zich afspeelden op de grens tussen neurologie en psychiatrie is leerzaam en toont hoe ingewikkeld het is een onderscheid te maken. Vandaag de dag laten functionele imaging en neurofysiologische studies zien hoe onzeker het verschil tussen neurologische en psychiatrische stoornissen is en vervaagt de grens tussen organisch en psychogeen. Tegenwoordig wordt verondersteld dat gestoorde sensomotorische integratie en corticale exciteerbaarheid een belangrijke rol spelen in het ontstaan van dystonie. In feite verklaart het alle onderzochte dystonie varianten en brengt het ons terug naar de fysiologie van Sherrington.

Hoofdstuk 3. Thermische hypesthesie bij patiënten met complex regionaal pijnsyndroom gerelateerde dystonie

De kwantitatieve thermische test toonde koude en warmte hypesthesie zonder toegenomen hitte pijn sensitiviteit in de aangedane ledematen van CRPS patiënten met tonische dystonie (n=44) in vergelijking met gezonde controles met een zelfde leeftijds- en geslachtsopbouw (n=35). De mate van koude en warmte hypesthesie was onderling sterk gecorreleerd. Deze bevindingen vormen een aanwijzing voor gestoorde verwerking van dunne zenuwvezel (dat wil zeggen C en Aδ vezels) informatie bij patiënten met CRPS gerelateerde dystonie.

Hoofdstuk 4. Gefixeerde dystonie bij complex regionaal pijnsyndroom: een beschrijvende en een modelmatige benadering

CRPS kan optreden na een trauma, meestal van een ledemaat, en wordt gekenmerkt door pijn en stoornissen in bloeddoorstroming, temperatuurregulatie en motorische controle. Ongeveer 25% van de patiënten ontwikkelt een gefixeerde dystonie. Betrokkenheid van dysfunctionele GABA (gamma-aminoboterzuur)-erge interneuronen wordt verondersteld, echter, de mechanismen zijn onzeker. De hypothese in deze studie was dat de dystonie het gevolg is van afwijkende proprioceptieve reflexen namelijk een gestoorde terugkoppeling van positie, snelheid of kracht. We onderzochten de dystone patronen bij 85 CRPS patiënten met dystonie systematisch door de houdingen van de gewrichten van de aangedane ledemaat te bestuderen. We vergeleken de patronen met een neuromusculair computer model dat gestoorde proprioceptieve reflexen simuleerde. Het computer model bestaat uit twee antagonistische spieren met een expliciete bijdrage van het musculotendineuze systeem, reflexpaden vanuit de spierspoeltjes en Golgi peeslichaampje en met tijdsvertragingen die neurale latentietijden vertegenwoordigen. Drie scenario's werden met het model gesimuleerd: (i) verhoogde reflex sensitiviteit (verhoogde sensitiviteit van de reflexboog van zowel agonist als antagonist; (ii) onevenwichtige reflex sensitiviteit (verhoogde sensitiviteit van de reflexboog van de agonist); en (iii) onevenwichtige reflex uitgangswaarde (verhoogde uitgangswaarde van de proprioceptor van de agonist). Gefixeerde houdingen werden gevonden in 123 armen van 77 patiënten. Het dominante patroon bestond uit flexie van de vingers (116/123), de polsen (41/123) en de ellebogen (38/123). Gefixeerde houdingen werden gevonden in 114 benen van 77 patiënten. Het dominante patroon was plantairflexie van de tenen (55/114), plantairflexie en inversie van de enkel (73/114) en knieflexie (55/114). Alleen de simulaties met onevenwichtige reflex sensitiviteit voor kracht, afkomstig van Golgi peeslichaampjes, leidden tot patronen die veel gelijkenis vertoonden met de houdingen bij patiënten. In parallel experimenten met robotarmen is aangetoond dat dystonie patiënten minder goed in staat zijn de grootte van de krachtterugkoppeling aan te passen. De bevindingen van het huidige neuromusculaire model suggereren dat afwijkende regulatie van krachtterugkoppeling van Golgi peeslichaampjes, met betrokkenheid van een inhiberend interneuron, ten grondslag liggen aan de karakteristieke gefixeerde flexie houdingen bij CRPS patiënten met dystonie.

Hoofdstuk 5. Analyse van ontstekingsmediatoren in de liquor cerebrospinalis bij chronische complex regionaal pijnsyndroom gerelateerde dystonie

Er is overtuigend bewijs voor betrokkenheid van het centrale zenuwstelsel bij neuropathische pijn en bewegingsstoornissen bij patiënten met CRPS. Eerder werden verhoogde liquorconcentraties van interleukine-1β en interleukine-6 gevonden bij CRPS patiënten met of zonder bewegingsstoornissen. Het doel van de studie in hoofdstuk 5 was om deze liquor bevindingen te bevestigen en om onderzoek te doen naar eventuele nieuwe liquor biomarkers bij chronische CRPS patiënten met dystonie. Liquormonsters van 20 patiënten en 29 mensen die spinale anesthesie ondergingen vanwege een chirurgische ingreep werden gebruikt. We bepaalden interleukine-1β, interleukine-6, interferon-γ induceerbare proteïne 10, RANTES ("regulated upon activation, normal T-cell expressed and secreted"), complement C3, mannose-bindend lectine, complement C1q, oplosbaar intercellulair-adhesiemolecuul-1, endotheline-1, stikstofoxide, humaan lactorferrine en hypocretine-1 concentraties in deze monsters. Er werd geen verschil in liquorconcentratie van deze effector mediatoren tussen patiënten en controles gevonden. Onze liquorbevindingen ondersteunen een rol van diverse ontstekingsmediatoren of hypocretine-1 bij chronische CRPS patiënten met dystonie niet.

Hoofdstuk 6. Klinische en neurofysiologische karakterisering van myocloniëen bij complex regionaal pijnsyndroom

De oorsprong van myocloniëen bij patiënten met CRPS is onbekend. Acht patiënten met CRPS gerelateerde myocloniëen werden klinisch geëvalueerd en bestudeerd met intermusculaire en corticomusculaire coherentieanalyse. De schokken waren in rust aanwezig, verergerden tijdens actie en waren vaak geassocieerd met tremor of dystonie. Electromyografie toonde een variabele burst duur van 25-240 ms met burst frequenties welke varieerden tussen <1 schok/s in rust tot 20 Hz tijdens actie. Coherentie studies toonden toegenomen intermusculaire coherentie in de 6-12 Hz band bij vier patiënten, zoals ook gerapporteerd is bij patiënten met een versterkte fysiologische tremor. Bij twee patiënten werd coherentie tussen de twee lichaamshelften gevonden, wijzend op een centrale oorzaak. Significante coherentie entrainment werd gevonden bij 5 patiënten. We concluderen dat kenmerken van myocloniëen bij CRPS anders zijn dat bij andere typen myocloniëen.

Hoofdstuk 7. Intrathecale baclofen voor dystonie bij complex regionaal pijnsyndroom

Dystonie bij CRPS reageert slecht op behandeling. Intrathecale baclofen (ITB) kan dit type dystonie doen verbeteren, maar de informatie omtrent effectiviteit en veiligheid is beperkt. Een enkel-blinde placebo run-in dosis-escalatie studie werd uitgevoerd bij 42 CRPS patiënten om te onderzoeken of de dystonie ITB-responsief was. Zesendertig van de 38 patiënten die voldeden aan de responder-criteria ontvingen een pomp voor continue ITB toediening en werden 12 maanden vervolgd om de lange termijn effectiviteit en veiligheid te onderzoeken (open-label studie). Primaire uitkomstmaten waren Globale Dystonie Ernst (beide studies) en Dystonie-gerelateerde Functionele Beperkingen (open-label studie). De dosis-escalatie studie toonde een dosis-afhankelijk effect van ITB op dystonie ernst bij 31 patiënten in doseringen tot 450 µg/dag. Eén patient reageerde niet op de behandeling in de dosis-escalatie studie en drie patiënten vielen uit. Zesendertig patiënten startten de open-label studie. Intention-to-treat analyse toonde een aanzienlijke verbetering bij de door zowel patiënt als onderzoeker gescoorde mate van dystonie, pijn, handicap en kwaliteit van leven na 12 maanden. De respons in de dosis-escalatie studie voorspelde de respons op ITB in de open-label studie niet. Negenentachtig bijwerkingen traden op bij 26 patiënten en waren gerelateerd aan baclofen (*n*=19), pomp/catheter systeem defecten (*n*=52), of konden niet worden gespecificeerd (*n*=18). De pomp werd geëxplanteerd bij 6 patiënten tijdens de follow-up fase. Dystonie, pijn, handicap en kwaliteit van leven verbeterde allemaal onder ITB en bleef stabiel over een periode van een jaar. Echter, bij ITB komen in deze patiëntengroep veel complicaties voor en verbetering van patiëntenselectie en pomp/catheter-integriteit zijn gewenst.

Hoofdstuk 8. Intrathecale glycine voor pijn en dystonie bij complex regionaal pijnsyndroom
Omdat glycinerge neurotransmissie een belangrijke inhiberende rol speelt bij het verwerken van sensibele en motorische informatie is intrathecale glycine (ITG) toediening een potentiële therapie voor zowel pijn als bewegingsstoornissen bij CRPS patiënten. Doelen van de studie beschreven in hoofdstuk 8 zijn het onderzoeken van de veiligheid en effectiviteit van ITG bij CRPS patiënten met dystonie. ITG behandeling gedurende 4 weken werd onderzocht bij CRPS patiënten met dystonie in de periode voorafgaand aan ITB behandeling. Twintig patiënten werden beoordeeld en na exclusie van één patiënt werden de overgebleven 19 patiënten gerandomiseerd in een dubbel-blinde placebo-gecontroleerde crossover studie. Veiligheid werd beoordeeld door klinische evaluatie, bloedonderzoeken en electrocardiogrammen. Effectiviteitsmaten waren pijn (numerieke beoordelingsschaal, McGill pain questionnaire), bewegingsstoornissen (Burke-Fahn-Marsden dystonia rating scale, unified myoclonus rating scale, tremor research group rating scale), activiteiten (Radboud skills questionnaire, walking ability questionnaire), en een clinical global impression (CGI) en patient's global impression score (PGI). ITG-gerelateerde bijwerkingen waren over het algemeen licht tot matig-ernstig en niet anders dan tijdens behandeling met placebo. Tijdens ITG behandeling waren de groeihormoon concentraties licht verhoogd. Hoewel er een trend naar verslechtering op de CGI en PGI tijdens ITG behandeling was, waren er geen significante verschillen tussen ITG en placebo behandeling in elk van de uitkomstmaten. ITG gedurende 4 weken was niet effectief op pijn en dystonie bij CRPS. Hoewel er geen ernstige bijwerkingen optraden zijn er meer studies nodig om potentiële neurotoxiciteit van ITG uit te sluiten.

Hoofdstuk 9. Effectiviteit en veiligheid van een eenmalige intrathecale methylprednisolon toediening bij chronisch complex regionaal pijnsyndroom
Geactiveerde immuuncellen in het ruggenmerg kunnen een belangrijke rol spelen in de ontwikkeling en instandhouding van neuropathische pijn, zoals gebeurt in reactie op een perifere ontsteking of weefselschade. Immuunactivatie kan daarom dienen als aangrijpingspunt voor immunomodulerende medicijnen zoals corticosteroïden. Deze dubbel-blinde gerandomiseerde placebo-gecontroleerde parallel-groep studie onderzocht de effectiviteit en veiligheid van een eenmalige intrathecale toediening van 60 mg methylprednisolon (ITM) bij chronische patiënten met CRPS. De primaire uitkomstmaat

was verandering in pijn (numerieke beoordelingsschaal; bereik 0-10) na 6 weken. Met 21 personen per groep had de studie een power van 90% om een klinisch relevant verschil (≥2 punten) te vinden. Nadat 21 patiënten (10 met ITM) waren geïncludeerd, werd de studie voortijdig beëindigd omdat de interim analyse had getoond dat ITM geen effect op pijn (verschil in gemiddelde numerieke beoordelingsschaal op 6 weken 0,3, 95% betrouwbaarheidsinterval -0,7 tot 1,3) of een van de andere uitkomstmaten had. We vonden geen verschil in bijwerkingen tijdens behandeling met ITM en placebo. We concluderen dat behandeling met een eenmalige toediening van ITM niet effectief is bij chronische CRPS patiënten, wat zou kunnen betekenen dat spinale immuunactivatie geen rol speelt tijdens deze fase van het syndroom.

Hoofdstuk 10. Post-punctie hoofdpijn bij complex regionaal pijnsyndroom: een retrospectieve observationele studie

Doel: beschrijving van het ongewone beloop van post-punctie hoofdpijn na een pomp-implantatie voor ITB toediening bij patiënten met CRPS gerelateerde dystonie. Opzet: Patiëntenserie gebaseerd op gegevens welke verzameld werden van 1996 tot 2005. Setting: polikliniek bewegingsstoornissen, academisch ziekenhuis. Patiënten: 54 patiënten met CRPS gerelateerde dystonie die behandeld werden met ITB. Resultaten: een hoge incidentie (76%) en langdurig beloop (mediaan 18 dagen, bereik 2 dagen-36 maanden) van post-punctie hoofdpijn werd gevonden. Radionuclide studies werden gedaan bij 2 patiënten met langdurige symptomen (12-16 maanden) waarbij geen lekkage van liquor cerebrospinalis werd gevonden. Bij patiënten zonder tekenen van liquor lekkage (*n*=38), werd een epidurale bloedpleister ('blood patch') aangebracht bij 24 patiënten welke niet effectief bleek bij 54%, terwijl ketamine infusie toegediend bij 6 patiënten effectief was bij 67%. Conclusie: Onze observaties suggereren dat andere mechanismen dan intracraniële hypotensie een rol spelen bij het ontstaan en instandhouden van post-punctie hoofdpijn bij CRPS en stimuleert nieuw onderzoek over dit onderwerp.

Conclusies

Voorafgaand aan de studies in dit proefschrift waren de mechanismen welke ten grondslag liggen aan CRPS gerelateerde bewegingsstoornissen slecht begrepen. Eveneens waren er geen gerandomiseerde gecontroleerde onderzoeken.

Pathofysiologische studies

Hoewel thermische hypesthesie eerder werd gevonden bij CRPS patiënten zonder dystonie, was dit niet eerder onderzocht bij CRPS patiënten met dystonie. We vonden thermische hypesthesie bij CRPS patiënten met dystonie. Kennelijk is er een gestoorde verwerking van dunne zenuwvezel (dat wil zeggen C en Aδ vezels) informatie bij deze patiënten. Omdat dezelfde afwijkingen werden gevonden bij CRPS zonder dystonie is het onzeker of deze afwijking een causale relatie met het ontstaan van dystonie heeft.

Door de ledematen van 85 patiënten met CRPS gerelateerde dystonie systematisch te evalueren, vonden we een dominant patroon van gefixeerde dystonie. Gefixeerde flexie van de vingers werd gevonden bij 95% van de aangedane armen en een multisegmentaal patroon van vinger, pols- en/of elleboogflexie en endorotatie/adductie van de schouder werd gevonden bij 66% van de aangedane armen. Een vergelijkbaar patroon werd gevonden bij aangedane benen: plantairflexie/inversie van de enkel werd gevonden bij 88% van de aangedane benen en een multisegmentaal patroon van enkel plantairflexie/inversie, teen- en/of knieflexie en endorotatie van de heup werd gevonden bij 66% van de aangedane benen. Onze modellering studie toonde dat afwijkende krachtterugkoppeling van Golgi peeslichaampjes gerelateerd kan zijn aan deze houdingen.

Onze bevindingen in liquor cerebrospinalis zijn geen ondersteuning van een rol van ontstekingsmediatoren bij chronische CRPS patiënten met dystonie. Een zoektocht naar liquor biomarkers welke betrokken zijn bij moleculaire paden die een rol spelen bij neuroplasticiteit is mogelijk meer succesvol.

We onderzochten ook acht patiënten met CRPS gerelateerde myocloniëen. Zowel de klinische als de neurofysiologische kenmerken waren gevariëerd. De significante coherentie entrainment die gevonden werd bij vijf patiënten kan duiden op een gebrek aan inhibitie van het centrale zenuwstelsel. Echter, coherentie entrainment wordt ook geduid als aanwijzing voor psychogene bewegingsstoornissen. Meer studies naar de waarde van entrainment zijn nodig.

Intrathecale therapie studies

Een eenmalige intrathecale toediening van 60 mg methylprednisolon was niet effectief bij chronische CRPS. Ook was continue ITG in doseringen tot 32 mg/24 u niet effectief bij CRPS gerelateerde dystonie. ITB verminderde wel de ernst van CRPS gerelateerde dystonie, verbeterde de kwaliteit van leven en bleef effectief gedurende een periode van een jaar (mediane dosis 615 µg/dag). Helaas was ITB geassocieerd met vele complicaties; voor een grotere toepasbaarheid is zowel een betere patiëntenselectie als een betere pomp/catheterintegriteit gewenst. De bevindingen van deze studies ondersteunen een rol van GABA-erge mechanismen bij het ontstaan van dit type dystonie.

Toekomstige studies

Studies naar de pathofysiologie van CRPS gerelateerde dystonie hebben zich tot nu toe gericht op bepaalde mediatoren in de liquor cerebrospinalis en een aantal neurofysiologische kenmerken.

In tegenstelling hiermee kunnen moderne 'omics technieken tegelijkertijd alle metabolieten of eiwitten van biologische monsters bepalen. De uitkomst kan beschouwd worden als handtekening of 'endofenotype' van een ziekte. Extrapolatie naar andere 'omics' data kan helpen bij het ontraadselen van ziektemechanismen. Momenteel worden deze studies met gebruikmaking van verschillende lichaamsvloeistoffen van CRPS patiënten met dystonie uitgevoerd.

Het centrale zenuwstelsel reguleert het gedrag van het bewegingsapparaat via vele terugkoppelingslussen. Het voorspellen van dat gedrag kan moeilijk zijn. De resultaten uit onze modellering studie suggereren dat het zinvol is dystonie te bestuderen met closed-loop systeem identificatie technieken. Momenteel wordt deze benadering gebruikt in klinische studies naar CRPS gerelateerde dystonie.

Via intrathecale toediening van medicatie, hebben we ons gericht op modulatie van voornamelijk spinale mechanismen bij CRPS gerelateerde dystonie. Resultaten van deze studies bevestigen de bevindingen van neurofysiologische onderzoeken dat disinhibitie een belangrijke rol speelt. Versterking van de centrale GABA-erge, maar niet glycinerge, inhibitie lijkt de ernst van de dystonie te kunnen verminderen. Echter, met het oog op de vele complicaties van het toedieningsmechanisme dat nodig is voor ITB, zijn GABA-erge medicijnen met een betere bloed-hersenbarrière passage wenselijk.

Pijn en dystonie zijn vermoedelijk stoornissen van neurale circuits en niet het gevolg van een enkel defect. Vandaar dat neuromodulatie technieken die aangrijpen op supraspinale structuren, zoals repetitieve transcraniële magneet stimulatie of epidurale corticale stimulatie, wellicht nieuwe therapeutische opties zijn voor CRPS gerelateerde bewegingsstoornissen.

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Curriculum Vitae

Alexander Gerard Munts was born in Dordrecht, The Netherlands, on June 12, 1973. He attended the Develstein College in Zwijndrecht for pre-university education and graduated in 1991. In the same year he started his medical study at the Erasmus University Rotterdam where he passed his "propedeuse" level examination cum laude. He obtained his Medical Degree in 1998. In that same year, he did a research project on transcranial Doppler sonography in TIA and stroke patients at the Department of Neurology of the Erasmus MC in Rotterdam (Prof.dr. P.J. Koudstaal and Prof.dr. D.W.J. Dippel). From 1998 to 1999, he worked as a resident at the Department of Internal Medicine of the Maasstad Hospital in Rotterdam (Dr. A. Berghout). From 1999 to 2000, he worked as a resident in child and adolescent psychiatry at Stichting De Jutters in Den Haag (H.A. Dekker). In 2000, he started as a resident in neurology at the Department of Neurology of the St. Antonius Ziekenhuis in Nieuwegein (Dr. H.M. Mauser). Later that year, he joined the Department of Neurology of the Atrium Medical Centre in Heerlen (Dr. C.L. Franke and Dr. P.J. Koehler) to start his training in neurology. In 2004, he started this PhD research at the Department of Neurology of the Leiden University Medical Centre, and continued his neurology training at this same Department (Prof.dr. R.A.C. Roos and Prof.dr. J.G. van Dijk). From 2009, he is working as a neurologist at the Kennemer Gasthuis in Haarlem.
Alexander lives together with Bastiaan Heijnen.

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