COMPLEX REGIONAL PAIN SYNDROME 1

A STUDY ON PAIN AND MOTOR IMPAIRMENTS

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Complex Regional Pain Syndrome 1: a study on pain and motor impairments

Complex Regionaal Pijn Syndroom 1:

een studie naar pijn en motorische stoornissen.

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Contents

Chapter 1

Introduction

This thesis is compiled of publications on reflex sympathetic dystrophy (RSD) or Complex Regional Pain Syndrome type 1 (CRPS 1), as it was renamed by the committee on taxonomy of the International Association for the Study of Pain (IASP).[1] It is a puzzling syndrome both from a clinical point of view as well as in the perspective of basic pain science. Therapies rendered may vary and include physical therapy, occupational therapy, physical immobilization, surgical or chemical sympathectomies, pharmacotherapy and psychological treatment.[2] A well accepted treatment algorithm is lacking and treatment regimens hardly seem driven by the progress made in basic pain science.[3] The leading thread of this thesis is the concept of CRPS 1 as a neuropathic pain syndrome of unknown etiology involving multiple and time-dependent mechanisms. It is discussed that besides the affected extremity also spinal and suprapinal structures may become involved. The scope of the publications varies from clinical studies on pain management performed in the context of an interdisciplinary rehabilitation team, to experimental studies on motor impairments and immunology. The clinical and experimental work was at least partly performed before the introduction of the term complex regional pain syndrome 1. It is for this reason that the reader may encounter the term reflex sympathetic dystrophy in some chapters.

Outline of this thesis

Chapter 2 is a review that addresses the question whether CRPS 1 should be considered as a peripheral disorder involving one or more affected extremities or whether spinal and supraspinal mechanisms may be involved, especially regarding chronic pain and motor impairments. As to the peripheral mechanisms involved, the focus of attention is drifting from sympathetic dysfunction to an exaggerated inflammatory process. However, a direct verification of an inflammation in the classical sense has never been established.[4] In **chapter 3** an evaluation of immune system function in patients suffering from CRPS 1 is described. A neurogenic inflammation does not only cause impuls generation

and propagation in somatosensory afferents but also axonal transport of chemicals that have the potential to alter the sensitivity of the peripheral and spinal circuitry (peripheral and central sensitization).[5] Within this perspective blocking the activity of afferents may contribute to the clinical management of CRPS 1. Blocking nociception may facilitate active and passive physical therapy and prevent peripheral and central sensitization. The chapters 4 and 5 represent clinical studies on this topic, describing infrequently used anesthetic techniques in CRPS 1. **Chapter 4** is a case report on a patient with CRPS 1 in an acute stage who was treated with topical capsaicin in combination with a stress loading program. In **chapter 5** six patients with CRPS 1 of varying duration are described. They were hindered in their treatment program by severe pain for which reason brachial plexus anesthesia was performed. **Chapter 6** addresses the question whether in chronic CRPS 1, besides peripheral and central sensitization, supraspinal motor processing may become involved. Functional recovery should at all times be the ultimate goal in treating patients with CRPS 1.[6] Pain may be the limiting factor in achieving progress in which case pharmacologic treatment is indicated. In **chapter 7** a preliminary theoretical framework for the pharmacologic treatment of pain in CRPS 1 is constructed. It is aimed to incorporate insights obtained in basic pain research in a model of clinical pain management. **Chapter 8** is a short overall conclusion.

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Chapter 2

The Reflex Sympathetic Dystrophy Syndrome: a review with special reference to chronic pain and motor impairments

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Summary

Reflex sympathetic dystrophy (RSD) is manifested by pain, vasomotor and trophic disregulation and by various motor impairments. Its course shows a large variability, but an acute stage can roughly be discriminated from a chronic stage. The aim of this paper is to review the literature on RSD with regard to diagnosis and pathophysiology, in particular referring to chronic pain and motor impairments. It will be demonstrated that complementary investigations are heplful in making a definite diagnosis. RSD appears to be multicausal. In the acute stage, overproduction of toxic free radicals, sympathetic nervous system disregulation and neurogenic inflammatory reactions predominate. In the more chronic stage, a shift from peripheral to central mechanisms seems to take place. This centralization is probably an essential factor in the development and maintainance of both pain and RSD-associated motor impairments such as tremor, dystonia, increased muscle tone, muscle spasms and weakness. It is concluded that insight into the mechanisms underlying chronic pain and motor impairments has clear implications, both for preventing disabilities and for developing rehabilitation strategies during the more chronic stages of RSD.

The reflex sympathetic dystrophy syndrome

The reflex sympathetic dystrophy syndrome (RSD) refers to a poorly understood and not well defined symptom complex formed by a combination of pain, trophic changes, vasomotor disturbances and motor impairments. Usually it results from a minor injury. Minor causalgia, posttraumatic pain syndrome, Sudeck's atrophy, shoulder-hand syndrome, reflex neurovascular dystrophy and algodystrophy are some examples of disorders that are incorporated under the term RSD.[1] Given the variety of disorders ranging under RSD, it is not surprising that definitional problems and diagnostic ambiguities arise and that epidemiologic data are hard to interpret. However, it can be stated that RSD is a significant problem worldwide with which many clinicians are faced.[2]

Severe pain, occuring suddenly or progressively, is the most disabling feature of RSD and is present in the majority of patients.[3] The severity of the pain seems disproportional in relation to the seriousness of the injury. It may have a burning character, mimicking a spreading neuralgia that is often called causalgia. Generally, it is accompanied by hyperpathia (lowered pain threshold and enhanced pain perception) and allodynia (pain from innocuous mechanical or thermal stimuli) and often by a hyper- or hypoesthesia in a stocking- or glove-like distribution. Early .in the clinical course of RSD, the pain may be sympathetically maintained and responsive to sympathetic blockade or sympathectomy. In later stages, it frequently becomes sympathetically independent.[2] If not responsive to treatment in the acute stage of RSD, the pain may become refractory to almost any form of treatment. It may then become a chronic pain problem with behavioural consequences as will be described later in this text.

Trophic changes may include all structures from skin to bone including tendons, aponeuroses, muscles and joint capsules.[4] Nails may become brittle and hair loss or increased hair growth may occur. The skin may have a scleroderma-like appearance.

Vasomotor disturbances may manifest themselves in several ways.[1] The red, warm and oedematous skin with vasodilation in the affected extremity reflects an inflammatory reaction. However, the skin may also be cold and mottled due to vasoconstriction with livedo reticularis, cold intolerance and induration.

Although epidemiological data on this matter are scarce, RSD-

associated motor impairments (such as muscle weakness, tremor, dystonia, spasms and difficulty in initiating movements) form a well known aspect of the syndrome. In the early stages of the disease, motor impairments may be present in very mild forms even without the patient being aware of them. During the later stages they may constitute, together with the pain, a major cause of disability. In a prospective study of 829 patients suffering from RSD, tremor in the affected arm was present in 49% and muscular incoordination in 54% of the subjects. Muscle spasms were present in 25% of the patients with RSD of longer duration, whereas 16% suffered from such severe weakness that no movements of the limbs were possible.[5] In a study of 200 RSD patients, all patients in stages II or III exhibited some combination of weakness, spasms, tremor, increased tone, increased reflexes, difficulty in initiating movement or dystonia. Furthermore, the movement impairments may spread to other body parts e.g. in a mirror-like distribution at the contralateral side.[6]

Initiating events and course

RSD may be caused by a large scatter of eliciting events, ranging from (hardly recognized) minor injuries to surgical lesions; from non-traumatic diseases of the locomotor apparatus (infectious, inflammatory, metabolic or neoplastic) to myocardial infarctions and pleuropulmonary diseases; from malignancies, endocrine diseases, the use of various drugs (barbiturates and antituberculous agents) to central neurological disorders such as traumatic spinal cord injury, acute stroke and multiple sclerosis.[7,8,9] In about 25% of the adult cases, however, no inciting event can be identified, whereas in children such is even the rule.[10,11,12,13]

RSD is supposed to progress according to three stages: acute (stage I), dystrophic (stage II) and atrophic (stage III).[14] In stage I there is a history of persistent pain with hyperpathia, hyperesthesia or allodynia in the affected part, with at least two of the following physical findings: increased hair or nail growth, oedema, livedo reticularis, temperature change, hyperhidrosis, or piloerection. In stage II dystrophic changes of soft tissue or nails or hair loss are added to the stage I criteria. In stage III the features of stages I and II are present as well as atrophy of skin, soft tissue, muscle and

bone. However, these stages form a rather schematic and crude representation of the clinical course, because they are of variable length (ranging from weeks to years) and do not always emerge in a fixed order. In 5% of the RSD patients a cold extremity is even the first symptom.[5] Nevertheless, it appears that two extremes of a continuum can be distinguished: the acute stage during which inflammatory signs predominate and the chronic stage characterized by atrophy, chronic pain and motor impairments.

Diagnosis

The diagnosis of RSD is often solely based on the clinical presentation. In 1981 a classification system has been proposed that distinguishes four levels of probability of a positive diagnosis.[15] This classification is still being used nowadays. When pain and tenderness in the distal extremity are accompanied by swelling and vasomotor instability, the diagnosis of RSD is *definite*. If accompanied by swelling or vasomotor instability, the diagnosis is *probable*. RSD is considered *possible* when there is tenderness (but no pain) associated with vasomotor instability and/or swelling. In the case of merely unexplained pain and tenderness, diagnosis is *doubtful*. Recently presented criteria include excercise-induced occurrence of or increase in the following symptoms or signs: unexplained pain, oedema, changes in skin temperature or colour, or limited active range of motion. In addition, these signs and symptoms have to be present in an area larger than the area of primary injury, including the area distal to it.[5] Despite the clinical relevance of RSD-associated motor impairments, they are hardly ever incorporated in clinical diagnostic criteria.
Each clinical sign of RSD may be suggestive of such diagnosis as septic, inflammatory, or tuberculous arthritis, metabolic arthropathy, tumor processes, osteonecrosis, arthrosis, stress fractures, etc. Therefore, although the diagnosis in its typical complete form is primarily a clinical one, it should be confirmed by laboratory, radiologic and scintigraphic evidence.[16] Besides, complementory investigations may add to treatment evaluation and advance diagnosis to an earlier phase, thus improving therapeutical perspective.
Studies on biochemical constants in RSD are scarce. The non-

specific parameters of inflammation (erythrocyte sedimentation rate (ESR), proteinelectrophoresis and fibremia) show no deviations. This absence of biochemical signs of inflammation is even considered of crucial importance for a positive diagnosis, which is remarkable because the stage I symptoms clearly suggest an inflammatory reaction.[17] Hypercalcemia, hypercalcuria and increased alkaline phosphatase levels have been described but are of no diagnostic importance, nor do they relate to the severity of RSD.[17] Being a parameter of bone metabolism, the urinary excretion of hydroxyproline has received some attention. Hyperhydroxyprolinuria may support the diagnosis but is an inconstant finding because bone atrophy is not an obligatory symptom.

Only after considerable demineralization (30-50% of bone calcium) manifestations of RSD can be observed on plain radiographs. Radiological manifestations are not pathognomic and are usually preceded by clinical signs by 4 to 6 weeks. Sometimes bone demineralization does not appear until after several months. It may even remain absent during the entire evolution of the disease.[9] The typical pattern of spotty osteopenia is mainly seen in the epiphysis of the short bones of the hands and feet. Subchondral bone may virtually disappear, sparing the subchondral bony plate that thus may give a higher contrast. However, it may also result in unsharp bone contours of the joint. Subperiosteal resorption may cause thinning of diaphysial cortical layers. These röntgenographic signs should not be considered useful for early diagnosis but should be regarded as non-specific support for a positive diagnosis of RSD.

Since the seventies, several studies on radionuclide bone imaging techniques in the assesment of metabolic bone disease have been conducted. A growing number of these studies concern RSD. The three-phase bone scanning technique (TPBS) has proven a valuable diagnostic and treatment evaluative aid that is more sensitive and specific than plain radiography in RSD.[18,19,20,21] TPBS objectifies three parameters. The hemovelocity and bloodpool asymmetries are the two hemodynamic indices. They may demonstrate an asymmetrical perfusion of the limbs or an asymmetrical distribution of the bloodpool in either limb. Bone fixation is the third parameter and represents the bone calcium metabolism. Paralelling the clinical stages, three scintigraphic stages of RSD are distinguished. In stage I, bone fixation is invariably increased, the hemodynamic indices are increased in 80% of the cases and normal

in the rest. The bone fixation remains increased in the second stage, but the hemodynamic parameters may decrease, normalize or remain increased. In the third and last stage, bone fixation normalizes or decreases in about 60% of the subjects. The hemodynamic parameters are usually decreased in phase three, reflecting vasoconstriction. Bone fixation is an important and sensitive diagnostic aid in stage I and helps to evaluate the persistence of the disease in stage III. Normalization of the hemodynamic indices in stages II and III may reflect therapeutical success. As argued before, a clear separation of RSD in three stages is a crude representation of its clinical course. The scintigraphic characteristics of these stages may overlap and therefore, even with TPBS, a clear division into three stages remains difficult. Usually in children, instead of an increased bone uptake, a diffusely decreased bone uptake at the symptomatic site can be observed.[10] The cause of this remarkable incomparison with adults has not yet been explained.

Pathophysiology

A historic overview

The symptom complex ranging under the term RSD is known for over a hundred years. Mitchell (1872) introduced the term "causalgia" (burning pain) and suggested that it is caused by peripheral as well as central pathophysiological mechanisms.[22] He argued that "inexplicable reflex transfers" in the spinal cord might be responsible for the severe pain experienced in tissues remote from the injured nerve area. Shortly after Röntgen's discovery of X-ray techniques, Sudeck (1900) employed this novel method for studying the bony manifestations of several disorders. He was the first to link osteoporosis to RSD and to stress the inflammatory aspect of the syndrome.[23] Leriche (1939) introduced the hypothesis of the "vicious circle" in which peripheral mechanisms cause vasospasms and secondary ischemic pain.[24] On the basis of spinal reflexes, the sympathetic nervous system is activated through nociception, causing progression of vasospasms and ischemia. Livingston (1944) expanded the concept of the vicious circle into a theory of "reverberating circuits".[25] In Livingston's concept closed self-sustaining loops are triggered in the internuncial pools of the

spinal cord by peripheral mechanisms. These self-sustaining loops spread to the ventral horns (causing muscle spasms), trigger an increase in sympathetic activity and activate spinal ascending neurons that subserve nociception. Doupe et al (1944) suggested a peripheral mechanism in which efferent sympathetic impulses depolarize afferent somatosensory fibres.[26] Nathan (1947) indicated that somatosensory afferents are abnormally stimulated by efferents.[27] He introduced the concept of artificial synapses that allow ephaptic transmission between efferent and afferent fibres. More recently, Melzack (1971) postulated that both causalgia and phantom pain are the result of a decreased inhibitory influence of a "central biasing mechanism" in the brainstem reticular formation due to a lowered sensory input.[28] As a result self-sustaining activity in closed neuronal loops at all neural levels increases. Melzack's theory differs from others in the assumption that a decreased sensory input and not an increased nociceptive afference is at the basis of spinal disregulation in RSD. Much in resemblance to Livingston's reverberating circuits, Sunderland (1976) suggested a disregulation of the dorsal horn cells leading to self-sustaining hyperactive foci spreading along transmission pathways in the spinal cord ("turbulance hypothesis").[29]

This short historic overview illustrates that most of the proposed concepts focus on pain perception and trophic disturbances through either peripheral or central mechanisms. Nevertheless, the theories of Leriche, Livingston, Melzack and Sunderland already embrace some interactionistic ideas. Also in the present paper such an interactionistic concept is adopted and expanded to the pathophysiology of motor impairments. RSD is conceptualized as the result of a disturbed interaction between central and peripheral mechanisms leading to a centralization of pathological processes. In the acute stage with inflammatory signs, peripheral mechanisms predominate. In later stages, a gradual shift towards a disregulation of the central nervous system takes place. This process of centralization is assumed to be at the basis of chronic pain, trophic disturbances and RSD-associated motor impairments. This interactionistic viewpoint will be further elaborated in the following sections, starting with the pathophysiology of pain and trophic changes (see Fig.1), followed by the mechanisms underlying motor impairments (see Fig.2). It will become clear that this differentiation is somewhat artificial and made for a pragmatic

reason. For the same reason, peripheral mechanisms are consistently discussed before central mechanisms.

Pain and trophic disturbances in RSD, a peripheral notion I: toxic free radicals

An important peripheral aspect of RSD, viz. the inflammatory aspect of the affected area, has already been stressed by Sudeck.[23] This idea has received little attention until the notion of RSD as an inflammation could be linked to the hypothesis that toxic free radicals can mediate inflammatory reactions.[30] Free radicals posess an unpaired electron and can be considered as fragments of molecules that generally are very reactive. Oxygen and its radical derivates (superoxide and hydroxyl radical) are important examples of free radicals. They are produced continuously in cells either as accidental by-products of metabolism or deliberately e.g. during phagocytosis, in which case their function is to suppress noxious stimuli by activating the immune respons.[31,32] However, reactive free radicals formed within cells can oxidize biomolecules and lead to cell death and tissue injury. Hence, a well-controlled balance between the production and breaking down of free radicals is critical to maintain the integrity of cells and tissues. It has been suggested that an excessive production of free radicals can be responsible for cell and tissue damage and progression of the inflammatory reaction in RSD. The fact that a number of patients with inflammatory signs have been successfully treated with radical scavengers such as mannitol and dimethylsulfoxide, is a preliminary support of this notion.[33] However, free radicals are extremely reactive and short lived. Currently available techniques to measure free radicals are limited to semi-quantitative assays of damage to biomolecules, which is the main reason that a causal role of free radicals in RSD is yet hard to verify.[34]

Pain and trophic disturbances in RSD, a peripheral notion II: the sympathetic nervous system

Because of the vasomotor disturbances and positive reactions to sympathectomies, the sympathetic nervous system is thought to play an important pathophysiological role in RSD. There is ample evidence that in lower vertebrates efferent sympathetic activity modulates depolarization of myelinated (Aδ) and unmyelinated (C)

cutaneous afferents.[35,36] Three ways in which sympathetic post-ganglionic nerve fibres may affect cutaneous afferent fibres have been described.[35]

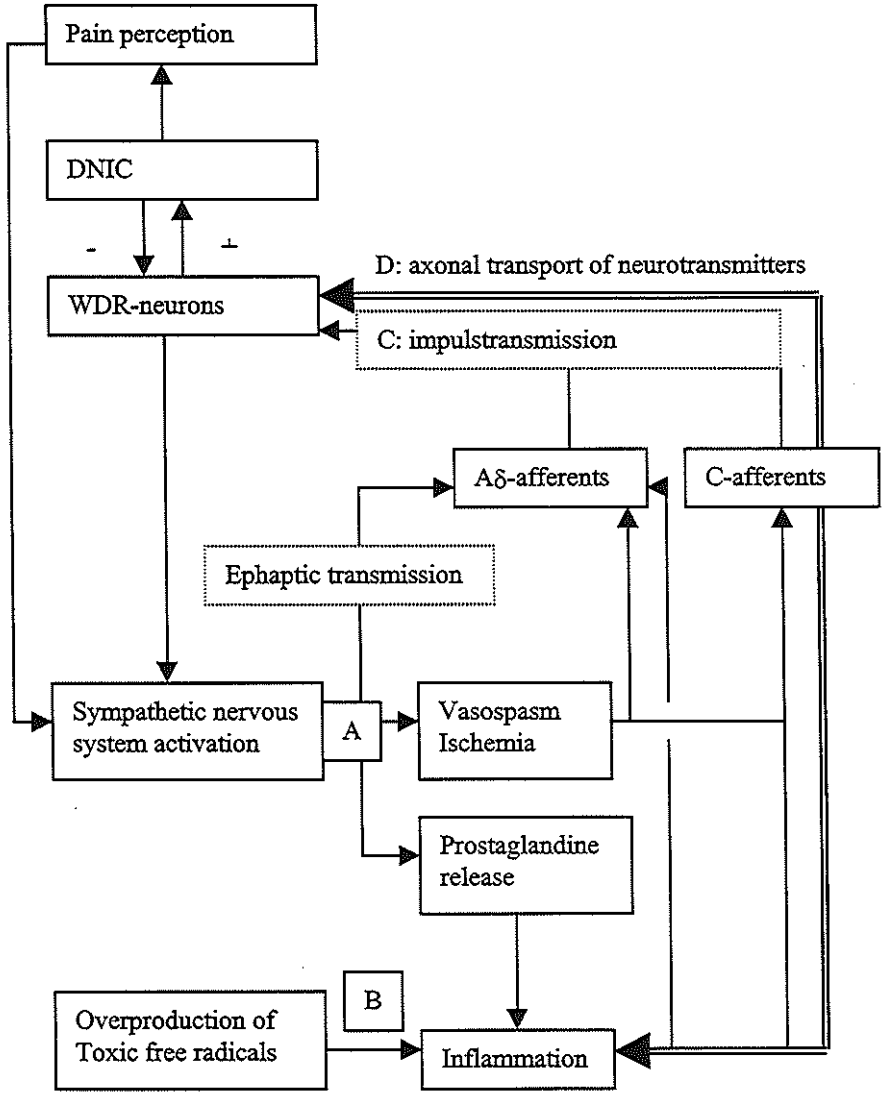

Figure 1
Depolarization of myelinated A-delta and unmyelinated C-afferents is modulated by the

sympathetic nervous system (a: ephaptic transmission, changed micro-environment of primary afferents due to vasospasm and prostaglandine release) and through an inflammatory reaction. The inflammatory reaction is mediated by an overproduction of toxic free radicals (b) or by a neurogenic release of inflammatory substances caused by altered axonal transport of neurotransmitters (d). Axonal transport of neurotransmitters is antero- and retrograde (double bars). Therefore, besides a peripheral neurogenic inflammatory reaction, this mechanism may cause sensitization of spinal Wide Dynamic Range (WDR) neurons. When stimulated, WDR neurons activate the diffuse noxious inhibitory controls (DNIC) that serve as an amplifier of a nociceptive stimulus (c). Allodynia is explained by stimulation of sensitized WDR neurons by innocuous activation of A-mechanoreceptors.

The first way refers to ephaptic transmission. This abnormal cross-talk between fibres may occur among cutaneous afferents but also between autonomic postganglionic efferent fibres and cutaneous afferents. The second way refers to the fact that noradrenaline-releasing postganglionic sympathetic axons change the micro-environment of primary afferents, thus causing altered chemo-sensitivity. Thirdly, there is evidence that noradrenaline acts presynaptically on α-2 adrenergic receptors on the sympathetic post-ganglionic terminals.[37] This causes a release of prostaglandine that contributes to an inflammatory reaction and leads to decreased thresholds of cutaneous afferents for nociceptive stimuli. A study of Arnold et al (1993) provided in-vivo evidence of increased responsiveness of venous α-adrenoreceptors to locally infused noradrenaline in limbs affected by RSD.[38] This increased responsiveness was also present in the contralateral unaffected extremity, which is compatible with the the clinical finding that RSD may spread from one affected limb to other extremities. This mirror distribution of increased responsiveness to infused noradrenaline supports the notion that central changes in autonomic outflow are relevant in RSD. RSD may spread from a lower extremity to an upper extremity or vice versa, which suggests that the central influence is not confined to one or adjacent segments of the spinal cord, but that more rostral structures can be involved.[39]

Pain and trophic disturbances in RSD, an interactional notion: neurotransmitters

Several neurotransmitters such as excitatory amino acids (L-

glutamate, L-aspartate and L-homocysteate), neurokinins (substance P, neurokinin A, neurokinin B) and other peptide neurotransmitters such as calcitonine gene-related peptide and vaso-active intestinal peptide are involved in linking peripheral (inflammation and sympathetic activity) to central mechanisms.[40] In the case of nerve injury, not only the impuls transmission between the peripheral and central nervous system is disrupted, but also anterograde and retrograde axonal transport of neurotransmitters. These transmitters are produced in the spinal ganglia and transported both to the spinal cord and to the periphery. The axonal transport routes are important in establishing and maintaining peripheral and central connections of afferent and efferent fibres. In particular the unmyelinated C-afferent fibres subserve this trophic function. Altered antero- and retrograde axonal transport may result in a changed state of axons e.g. sprouting, ephaptic transmission, partial deafferentation and even permanent cell loss. These processes may lead to peripheral reactions such as neurogenic inflammatory reactions (local vasodilatation, chemotaxis and extravasation due to the local influence of the neurotransmitters) as well as central changes such as shifting of receptive fields in neural networks and unmasking of synaptic connections. Transneural chemical changes spreading from peripheral afferents to the spinal cord and even to the supra-spinal regions have been reported in the case of deafferentation.[41,42,43] This finding underlines that the central nervous system is adaptive to peripheral influences. Within this perspective, Roberts formulated a hypothesis in which wide dynamic range (WDR) neurons in the dorsal horn of the spinal cord serve as an interface between central and peripheral processes.[40] Cutaneous afferents (unmyelinated C-afferents and myelinated Aδ-afferents) project both to nociceptor-specific and to WDR neurones. The axons of the WDR neurons ascend to supraspinal centres for pain identification and localization. WDR neurones are in fact convergent. The centres of their receptive fields are responsive to noxious and innocuous stimuli, whereas the peripheral areas are only responsive to noxious stimuli.[44] Depolarization of C-afferents induces sensitization of WDR neurons through axonal transport of neurotransmitters. Enlarged cutaneous receptive fields, a lowered threshold to fire and a greater responsiveness are the neurophysiological manifestations of central sensitization.[2] Sensitized WDR neurons may cause pain perception after innocuous stimulation of A-mechanoreceptors explaining allodynia.

Spontaneous pain results from altered central processing and is maintained dynamically by an ongoing peripheral input such as inflammatory reactions and sympathetic activity.[45] WDR neurons activate the Diffuse Noxious Inhibitory Controls (DNIC) which seem to be an analogue of Melzacks central biasing mechanism.[40] When activated, the DNIC inhibit all background activity of the remaining spinal and trigeminal WDR neurons. In reducing the background firing, the DNIC allow the extraction of a meaningful nociceptive message from non-specific activities of WDR neurons. The DNIC thus serve as a filter or amplifier with an important alarm function, in which psychological mechanisms such as arousal or mood disorders may be involved.

Motor impairments in RSD

The pathophysiology of RSD-associated motor impairments is still a matter of controversy. Much like the discussion on pain and trophic disturbances in RSD, the discussion on motor impairments focuses on such mechanisms as oxydative stress, sympathetic nervous system disregulation, the excitatory influence of neuropeptides on spinal motor neurons as well as possible supraspinal mechanisms. Finally, the possibility of a psychopathological basis is mentioned. The remaining part of this paper will further elaborate the possible causes of RSD-associated motor impairments (see Fig. 2).

Motor impairments in RSD, a peripheral notion: oxidative stress

It has recently been argued that peripheral oxidative stress due to impaired oxygen extraction in the affected extremity explains for the loss of motor control in RSD. Heerschap et al (1993) investigated the lower leg skeletal muscles at rest in 11 RSD-patients by ^{31}P nuclear magnetic resonance spectroscopy.[46] The results were compared with similar investigations of unaffected legs in patients and volunteers. An increase in average tissue pH in the muscles of the affected legs and an increase in the average inorganic phosphate/phosphocreatine ratio (Pi/PCr) was observed. These observations are attributed to oxidative stress in the limbs affected by RSD.

However, although oxidative stress may explain an increase in pain during movement and perhaps muscle weakness, it remains hard to

understand how it may cause dystonia, tremor, involuntary movements, spasms or spreading of motor impairments to other body parts.

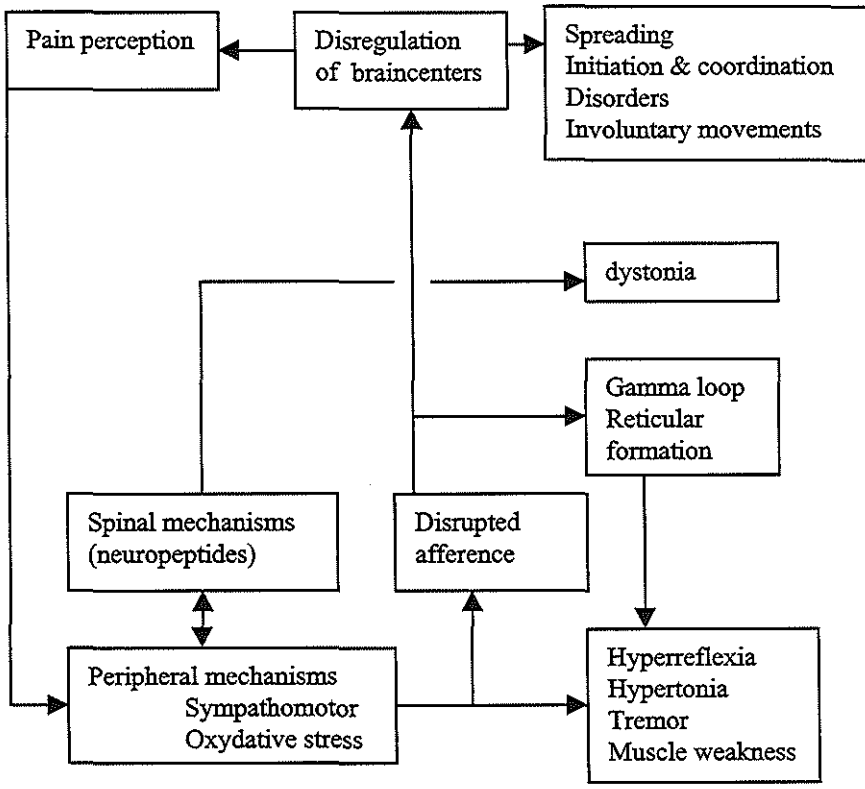

Figure 2

Schematic overview of the mechanisms that underlie RSD-associated motor impairments (for discussion see text).

Motor impairments in RSD, an interactional notion I: sympathomotor interaction and neuropeptides

Disregulation of the sympathetic nervous system may also be a possible cause of motor impairments in RSD. Sympathetic innervation of intrafusal and extrafusal fibres of the muscle spindle and ventral horn efferent fibers has been demonstrated and may underlie the sympathomotor interaction.[47] Sympathomotor

disregulation may be at the basis of muscle weakness, tremor, increased muscle tone, increased reflexes and dystonia in RSD.
Yokata et al (1989) described four RSD-patients with muscle weakness that improved dramatically after sympathetic blocks and worsened by catecholamine loading.[48] This was thought to be due to abnormally increased sympathetic tone and was called "sympathetic motor paresis".
Tremor in RSD is regarded as an enhanced physiological tremor that is sympathetically maintained or even induced and that may normalize after sympatholytic interventions.[49] It has been argued that sympathetic sensitization of muscle spindles is at the basis of tremor in RSD. Sensitized muscle spindles cause a gain of proprioceptive reflexes. Enhanced proprioceptive reflexes are a major peripheral input causing synchronous discharges of motor units and thereby enlarged tremor amplitudes.[50]
Besides muscle weakness and tremor, other RSD motor manifestations such as increased muscle tone, increased reflexes and dystonia may also be sympathetically induced.[2] Firstly, sympathetic nerve stimulation increases the firing rate of muscle spindle afferents, which increases muscle tone and deep tendon reflexes. Secondly, as argued before, sympathetic stimulation modifies the activity of myelinated and unmyelinated cutaneous afferents, which activates the gamma loop via the reticular formation, thus increasing muscle tone. Thirdly, sympathetic stimulation of unmyelinated afferents causes altered axonal transport of neuropeptides. Neuropeptides, such as Substance P, are transported to different parts of the spinal cord and produce longlasting depolarization of anterior horn cells in vitro. The interaction between substance P and the sympathetic nervous system is thought to underlie the intense and prolonged depolarization of anterior horn cells causing dystonia in RSD.[2,49]

Motor impairments in RSD, an interactional notion II: centralization

Although the automic nervous system may play a crucial role in mediating RSD-associated motor impairments, they may persist after the recovery of autonomic disregulation and may become irresponsive to sympathetic blockades. Futhermore, RSD motor impairments may spread beyond the original site in a hemiplegic, transverse or crossed distribution. This spreading of motor

impairments cannot be explained on the basis of a peripheral origin and is also difficult to relate to invoking segmental changes in the spinal cord. Bathia et al. (1993) argued that, at the spinal level, a hemiplegic distribution can only be explained on the basis of propriospinal pathways that control axial muscles, whereas RSD motor impairments are usually restricted to the distal extremities.[51] The same is true for a possible site of origin of motor impairments at the brainstem, because brainstem motor pathways also control the axial muscles. Hence, it appears that in an early stage the sympathomotor interaction is fundamental, whereas in later stages higher central mechanisms may be involved.

Indeed, there is some support for the notion that the process of centralization expands to higher brain structures. For instance, the case reports by Marsden et al (1984) and Robberecht et al (1988) provide direct support for the possibility of cerebral involvement.[52,53] Firstly, Marsden et al (1984) reported a patient suffering from RSD after fracturing a metacarpal bone in a fall.[52] One year after the injury abnormal involuntary movements of the hand developed, initially intermittently but over a few months only disappearing during sleep. After failure of treatment with various drugs and a stellate ganglion block, a thermocoagulation of the thalamic ventral intermediate nucleus was performed. This procedure abolished the motor impairment and reduced the pain. Secondly, some additional support for cerebral involvement is based on electro-encephalography. Altered cortical potentials preceding involuntary movements in RSD have been registered.[53] In one patient there was even no difference between the cortical potential preceding the involuntary movement and the readiness potential occurring before voluntary flexion of the contralateral extremity.

Although these studies are not conclusive, they indicate that cerebral mechanisms may be involved. It can therefore be hypothesized that cerebral involvement after peripherally induced motor impairments is the final state of a progressive centralization process. This is certainly not a new idea. Jankovic and van der Linden (1988) described 23 patients with focal dystonia, tremor or both occurring after acute peripheral injury.[54] Ten of these patients had RSD. Those with psychogenic motor impairments were excluded. In addition to a detailed neurological examination, neurophysiological investigations including nerve conduction velocities, electromyography and somatosensory evoked potentials

were performed. They concluded that central mechanisms are fundamental in RSD-associated motor impairments and that "a specific central susceptibility to altered afferent input may be required for the movement disorders to occur". They assumed that e.g. perinatal problems and the use of neuroleptic medications may lead to such a central susceptibility. Schott has also emphasized the role of central mechanisms in motor impairments after peripheral trauma in a syndrome called "painful legs and moving toes".[55,56,57]
Outside the field of RSD research there is growing evidence of a strong central-peripheral interaction that may underlie a process of centralization after peripheral injury. Reorganisation of spinal and cerebral neural networks due to altered input has been observed after sectioning peripheral nerves, after anesthetic blocks, after amputation of body parts and after section of the dorsal roots of peripheral nerves.[58,59,60,61,62] Reorganisation at a spinal level has already been reported by Wall (1980) who sectioned peripheral nerves depriving a population of spinal cord cells from their normal input.[63] It was shown that large numbers of cells in a region of the cord that were normally dominated by afferents from the foot and the toes began to respond to other areas of the leg in several days or weeks after the peripheral deafferentation. Levine et al (1985) emphasized the neural basis that underlies the spreading of acute inflammation from a site of injury to a remote uninjured site in which the spinal cord, nociceptive afferents and sympathetic efferents are involved.[64] He described that in rats an injured hind paw elicited a contralateral inflammatory response even though pure humeral mechanisms were excluded. They referred to this phenomenon as "reflex neurogenic inflammation". As for the role of the nervous system in mediating inflammatory reactions, neuronal plasticity following tissue injury has also been reported by Dubner and Ruda.[65]
Merzenich and co-workers focused their attention on cerebral plasticity. They showed that the spatial representation of body parts on the primary somatosensory cortex of monkeys can be significantly changed by manipulations of peripheral input.[66,67] In a series of experiments, they sectioned median nerves in monkeys and showed that immediately after this section most of the cortical territory, that was previously activated by the cut nerve, became unresponsive to stimulation. Besides this neural decay, in most monkeys small islands within the "silent" cortex became responsive to stimulation from neighbouring dermal areas. Several weeks after

the nerve section, the previously silent cortical regions were totally reorganized now responding to input from intact peripheral nerves. Identical cortical reorganizations have been observed after amputation of digits of the hands of racoons.[68] In humans, Pascual-Leone and Torres (1993) showed that reading Braille is associated with expansion of the sensorimotor cortical representation of the reading finger.[69] Even interhemispheric transfer of plasticity has been reported. Calford and Tweedale (1990) showed that in adult flying foxes a small peripheral denervation causes a receptive field expansion on the primary somatosensory cortex.[70] This induced plasticity in one hemisphere was immediately mirrored to the contralateral hemisphere.

The results of these studies all indicate a functional unity between peripheral and central neural mechanisms which has clear implications for the study of reorganization processes after sensorimotor damage. Because such a unity is not at all specific for any kind of disorder but a common characteristic of the nervous system, it can safely be assumed that also in RSD long-term central alterations result from prolonged peripherally distorted input. Such a centralization process may thus involve both spinal and cerebral structures. Cerebral involvement may be at the basis of poorly understood phenomena such as involuntary movements, initiation problems and spreading of motor impairments far from the primarily affected area. It can be speculated that even the premotor and parietal association cortices can be disregulated in persons with an enhanced central susceptibility to a distorted afference, causing all types of complex motor programming impairments. Such an interactionistic notion is in accordance with recent motor control theories.[71]

Psychopathological mechanisms

The possibility of a psychopathological etiology of RSD continues to receive support in clinical practice and the medical literature.[72,73] An interesting study (one of the few if not the only one with a prospective design) has been conducted by von Zachariae (1964).[74] One hundred patients with a Dupuytren's contracture were operated and followed during the post-operative course. Based on a psychological examination, 47 patients were classified as being at

risk for developing RSD. The surgeon had no knowledge of this prediction. In 43 out of 47 patients the prediction proved to be correct. Still, how remarkable this result may be, there is hardly any other support for a psychological basis in RSD. Bathia et al (1993) reported 18 patients with causalgia and dystonia.[51] They all suffered, besides the "causalgia-dystonia syndrome", from vasomotor, sudomotor and trophic changes in combination with hyperpathia and allodynia. No one had a family history of dystonia or a history of neurological or psychiatrical illness. All patients had normal cognitive and higher mental functions. Formal psychometry was carried out in 9 cases and was normal. Lynch (1992) performed a complete study of the literature from the late 1800's to 1991 containing any psychological information with respect to RSD.[75] She concluded that, due to definitional errors, semantic problems and other methodological shortcomings such as lacking control groups, the currently available data are insufficient for inferences regarding causality of psychopathological mechanisms in RSD.
However, there is agreement that behavioural and emotional issues in patients suffering from RSD are important and can be profound. This aspect has recently been underlined by Geertzen et al (1994) who emphasized the importance of early stress management training in RSD.[76] From a behavioural point of view, Fordyce (1979) and Vlaeyen et al (1989) described that when pain becomes chronic the relationship between organic pathology and pain experience becomes less direct.[77,78] Chronic pain can no longer be conceptualized as a pure sensory modality but should be considered as a "pathological emotion". In the biomedical model, nociception is controlled by somatic factors: a nociceptive stimulus is followed by a so-called respondent pain reaction. The value of the biomedical model becomes limited in the case of chronic pain. At this point, the direct relationship between a nociceptive stimulus and pain behaviour attenuates because an operant pain reaction has developed. Such an operant pain reaction is no longer related to the antecedent nociceptive stimulus but is controlled by the consequences of the exposed pain behaviour. In other words, merely anticipating the effect of the pain behaviour will trigger such behaviour without a direct relationship with a nociceptive stimulus. Hence, an operant reaction pattern must be regarded as the result of a learning process leading to a vicious circle of decreasing activity and increasing pain behaviour. In any chronic pain patient, the question is not whether an operant reaction is

present but rather the extent to which such is the case. A treatment policy that strongly focuses on pain avoidance, particularly in the chronic stage of RSD, is a strong reinforcer of this vicious circle. Besides an operant aspect, there is also a cognitive-evaluative dimension in chronic pain. How is the pain interpreted by the patient? These interpretations are called "causal attributions". Causal attributions can be characterized by three dimensions: locus (is the cause of pain located inside or or outside the person?), stability (is the cause of pain lasting or not?) and controllability (is the cause of pain subject to volitional control or not?). Based on these causal attributions the patient will try to reduce his suffering. In this perspective, it is important to prevent irrational or distorted inferences by means of education and cognitive treatment.

Conclusions and Implications

Although RSD as a symptom complex is recognized for over a hundred years, it remains a controversial subject with many open questions regarding diagnostic criteria, pathophysiology and treatment. The diagnosis of RSD is primarily based on clinical grounds. Nevertheless, complementary technical investigations can be very helpful in making an early diagnosis, excluding other pathologies and evaluating treatment. In this perspective, particularly the three-phase bone scanning technique should be mentioned.

The clinical picture of RSD stage I resembles an inflammatory reaction. It is, therefore, surprising that immunological data on RSD are scarce. This topic needs further investigation. Converging lines of research on the pathophysiology of RSD strongly suggest that, as a result of the adaptivity of the central nervous system to peripheral pathology, a process of centralization may occur in time. In the early stage, peripheral processes such as overproduction of toxic free radicals, sympathetic nervous system disregulation and neurogenic inflammatory reactions predominate. In later stages, spinal and supraspinal processes seem to prevail. It is argued here that such a centralization process may be at the basis of both chronic pain and motor impairments in RSD. From this viewpoint, it can also be understood that some of the RSD-associated motor impairments may become irresponsive to sympathetic blocks and

may spread to other parts of the body. Indeed, it has been convincingly demonstrated that a prolonged distortion of normal input patterns causes central adaptations in related neural networks. These central alterations of sensorimotor representation might be (in)directly responsible for complex motor programming impairments e.g. initiation and coordination problems or the spreading of such loss of motor control to remote body parts.
In view of the above-mentioned considerations, it seems essential to re-establish as early as possible a normal afference to the central nervous system. Therefore, early diagnosis and aggressive treatment of RSD in its initial stages are obligatory. Inflammatory reactions should be treated e.g. with radical scavengers (such as mannitol or dimethylsulfoxide) or corticosteroids, trophic disturbances and vasospasms with sympathetic blocks and vasodilating medication, whereas pain and swelling should be reduced by analgetics (e.g. NSAID, calcitonine or anaesthetic blocks). Only when input can be normalized in an early stage, excitation of spinal and supraspinal centres might be prevented.
Because in stage I of RSD complaints and symptoms are exercise-induced or -dependent, one is inclined to prescribe physical rest to prevent exacerbation of inflammation. Physical therapy should be given without increasing pain and swelling. However, during later stages a regime dictated by preventing pain perception may easily enhance the possibility of developing a chronic pain problem, characterized by a vicious circle of decreasing physical activity and increasing pain behaviour. Hence, stimulating activity during RSD stages II and III may help to prevent the development of such a vicious circle. Naturally, physical therapy should be well-dosed with a focus on active rather than passive movements. In this way, also normal proprioception is promoted. At all costs, chronic disuse with the possibility of a virtual disappearance of the affected extremity from the normal body scheme should be prevented.
From a psychological viewpoint, it seems relevant to strengthen the patient's coping style and to reduce as many external stressful factors as possible. For this reason, psychological counseling can be useful. Moreover, a behaviourally trained psychologist can educate and train both the patients family and the entire rehabilitation team to adapt their judgements and behaviour in such a way that normal use and experience of the affected extemity is reinforced whenever possible. It is only through a well-coordinated and theory-based rehabilitation strategy that also the patients in the

more chronic stages of RSD may eventually prove to have a fair chance of recovery from the severe disabilities that often result from RSD.

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Chapter 3

Complex regional pain syndrome I: is the immune system involved?

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Summary

Objectives: evaluation of immune-system function in patients suffering from the complex regional pain syndrome (CRPS) 1
Design: survey on bloodsamples obtained from patients and from a randomly selected control group. The lymphocyte populations (T, B, NK cells), and the activated T cells (CD25, and HLA-DR positive CD4 and CD8 cells) were analyzed by flow-cytometry with dual colour direct immunofluorescence after whole-blood lysis. Clinical chemistry parameters were analysed in additional serum samples.
Setting: tertiary care centre (out-patient rehabilitation clinic)
Subjects: 13 patients (9 women) and a control group of 21 healthy individuals.
Main outcome measures: The results of the flow-cytometry analysis of patients were related to those of the control subjects. Means were analysed and confidence intervals for differences of the means were calculated. The means of the clinical chemical analysis were related to local reference values.
Results: The flow cytometry analysis did not differ between patients and healthy controls. Although in some patients an individual parameter of clinical chemical analysis differed from its reference value, all of the mean values were within reference limits. Stratification on medications with immunomodulatory effects and on probability on a definite diagnosis had no influence on the results.
Conclusion: No association between immunological indices and CRPS 1 was found. This finding is relevant as recent theories stress that it is not the sympathetic nervous system but a local inflammatory reaction that is fundamental in the pathogenesis of CRPS 1. The results of this study do not support this notion.

Introduction

Pain, vasomotor and trophic disregulation and various motor impairments form the key elements of reflex sympathetic dystrophy (RSD). It typically follows minor peripheral injuries. Also central neurological disorders such as acute stroke and spinal cord injury, endocrine diseases as well as e.g. myocardial infarctions may cause RSD.[1] Despite the fact that RSD has been known as a symptom complex for over a hundred years and forms an important clinical problem worldwide, there still is active debate on its etiology, the effectiveness of treatment modalities and even on diagnostic criteria.[2] Theories regarding the etiology of RSD focus on the question whether it is caused by sympathetic disregulation or by an inflammatory reaction. In view of this scientific debate the lack of quantitative data on immune system function in RSD is surprising. When a local inflammatory response is present immune system involvement should be expected. Therefore, this study aims to evaluate major non-specific and specific characteristics of immune-system function in RSD. The results are discussed against the background of the debate on the etiology of RSD.

Design of the study

The study was set up after scanning of references in recent articles and after performing a Medline search (key words: reflex sympathetic dystrophy, complex regional pain syndrome type 1, immunology, neuroimmunology, psychoneuroimmunology, laboratory; languages: English, German, French) disclosed no publications with quantitative data on immunology in RSD since 1966. 13 consecutive patients (4 males, 9 females; median age 45 years, range 29-66) were studied (table 1). All patients were referred to the out-patient rehabilitation clinic of the Sint Maartenskliniek or the Canisius Wilhelmina Hospital, both situated in Nijmegen, the Netherlands.

Patients were enrolled in the study if they could be classified as "definite" or as "probable" RSD according the diagnostic criteria formulated by Kozin (1981).[3] In this classification four levels of

probability of a positive diagnosis RSD are distinguished. When pain and tenderness in the distal extremity are accompanied by swelling and vasomator instability, the diagnosis RSD is definite; if accompanied by swelling or vasomotor instability, the diagnosis is probable. Subjects were not included in the study if the diagnosis RSD was classified as "possible" or as "doubtful". In our sample of 13 patients, 9 had a definite (3 males, 6 females) and 4 a probable (1 male, 3 females) diagnosis. All patients met the criteria that were introduced in 1994 when the term RSD was replaced by "chronic regional pain syndrome (CRPS), type 1".[4] Patients had been suffering from CRPS 1 for 3 months to 8 years. Exclusion criteria were: fever within 48 hours before taking the blood sample, recent surgery (within the preceding two months), immune-compromising diseases such as human immunodeficiency virus seropositivity and auto-immune diseases. The randomly selected control group consisted of 21 healthy individuals working in the Canisius-Wilhelmina hospital or Sint Maartenskliniek. Individual data were coded and correlated with the clinical status after the results had been tabulated.

Table 1. Patient characteristics

No	gender	age (years)	duration (months)	diagnosis*	CRPS 1**
1	F	45	79	definite	+
2	F	44	11	probable	+
3	F	53	5	definite	+
4	F	48	5	probable	+
5	F	66	0.2	probable	+
6	F	66	3	definite	+
7	M	29	5	definite	+
8	M	29	1	definite	+
9	F	49	1	definite	+
10	F	50	2	definite	+
11	F	41	1	definite	+
12	M	42	2	definite	+
13	M	41	3	probable	+

* criteria formulated by Kozin et al (1981)[5]

** IASP criteria (1994)[4]

The results of the clinical chemical analysis were related to local reference values. The results of the flow-cytometry analysis of patients were related to those of the control subjects. The study was approved by the medical ethical commitees of both the Canisius-Wilhelmina hospital and the Sint Maartenskliniek.

Measurements

In the present study, flow-cytometry and several monoclonal antibodies recognising T, B, and natural killer cell populations as well as activation markers were used. Furthermore, clinical chemical analysis was performed.
Before further describing the applied techniques the characteristics of the T, B and natural killer cell populations will be briefly summarized.[5] B lymphocytes express the CD19 cell-surface molecule and produce antibodies (IgG, IgA, IgM). T lymphocytes represent the cell mediated immunity and are devided into helper T (T_H) cells and cytotoxic T (T_C) cells. T_H cells are characterized by a CD4 cell-surface molecule. They are partitioned in two subsets, one promoting cellular immunity and one promoting humoral immunity. T_C cells are characterized by a CD8 cell-surface molecule and demonstrate either cytotoxic or downregulatory activity. B and T cells are the repositories of specific immunity. Natural killer (NK) cells are non-specific hunter-killers that express CD16 and CD56 cell-surface molecules but lack the typical T-cell markers.
Blood samples of anticoagulated blood (K3-ethylenediamine tetra-acetic acid) were collected for flow cytometric studies, white blood cell counts and differential counts.[6] Additional serum samples were taken for clinical chemistry parameters. Lymphocyte populations were analysed by flow cytometry with dual colour direct immunofluorescence after whole-blood lysis. The panels of fluorescein isothiocyanate (FITC) or phycoerythrin (PE) labeled monocloclonal antibodies used are represented in table 2.
A single laser flow cytometer ("FACScan", Becton Dickinson Immunocytometry systems, San Jose, California), which can discriminate forward and side scatter as well as three fluoro-

chromes, was used with the "Simulset" and "Lysis II" computer software.

Table 2. Panel of monoclonal antibodies

Celll subsets	*Antibody specifity*
CD3	Total T
CD3 CD4	T helper/inducer
CD3 CD8	T cytotoxic/suppressor
CD3 CD 16+56	Natural Killer
CD 19	B cell
Activation markers	
CD25 CD4[1]	Activated T helper/inducer
HLA-DR CD4[1]	Activated T helper/inducer
CD25 CD8[1]	Activated T cytotoxic/suppressor
HLA-DR CD8[1]	Activated T cytotoxic/suppressor
CD8 CD38	Activated cytotoxic/suppressor

By convention, the FITC conjugated antibody is listed first and the PE Conjugated antibody second. Antibodies from Becton Dickinson unless stated differently.
[1] Dako, Glostrup, Denmark

Briefly, 100 μl of whole blood was placed into tubes, 10 μl of each monoclonal antibody added, and incubated for 15 minutes at room temperature in the dark. Red cells were lysed and fixed with 2 ml "FACS" lysing solution (Beckton Dickinson) for 10 minutes, spun down 5 minutes at 450g, and washed with phosphate buffered saline ("FACSflow" Becton Dickinson). Cells were resuspended in 0.5 ml wash buffer. Lymphocyte gates were set automatically in the Simulset program ("Leucogate" with CD45 and CD14, Becton Dickenson).

Data analysis and statistics

Data analysis was performed with the SPSS-package. Means were analysed with t-tests for independent samples. Confidence intervals for differences of the means of the independent samples were calculated.

Table 3. Patients result of clinical chemical analysis (n=13).

	mean (range)	reference value	
ESR	13 (2-50)	<20	mm/hr
Leucocytes	7.2 (4-13)	4.5-10	$x10^9/l$
AF	64 (38-141)	30-95	U/l
CPK	67 (14-290)	10-130	U/l
TAP*	67 (56-74)	60-80	g/l
SPE¶: albumine	44 (33-50)	35-50	g/l
alfa-1	2.1 (2-3)	1-4	g/l
alfa-2	7.3 (5-11)	5-10	g/l
beta	7.6 (5-11)	6-12	g/l
gamma	6.8 (4-12)	6-16	g/l
IgG	12.0 (9-19)	5.6-17.6	g/l
IgM	1.9 (0.5-3.0)	0.8-3.9	g/l
IgA	1.9 (1-3.8)	0,5-3,8	g/l

*TAP: total amount of proteins, ¶SPE: serum protein electrophoresis

Results

All the mean values of the indices derived from clinical chemical analysis were within reference values (table 3). In some individual cases a single value differed from its reference value. One patient showed an ESR of 50 mm/h, one patient's leucocyte count was 13.00 U/L (10 U/L), in one case the alkaline phosphatase was 141 (30-95 U/L), in one patient the creatine phosphokinase level was 290 U/L (10-130 U/L) and in one patient the fraction of α-2 protein was 11 g/L (5-10 g/L). In all individual cases the total amount of proteins, serum protein electrophoresis and levels of IgG, IgM and IgA were within reference value (table 3).
The phenotyping of the major lymphocyte populations (T, B, NK cells), percentage and absolute number of CD4 and CD8 T cells, and presence of activation antigens (CD25 and HLA-DR) on CD4 or CD8 positive T cells did not differ between patients and healthy controls (table 4).

Medications with immunomodulatory effects were recognized as confounders in this study. One patient used steroids, five patients used a non-steroid-anti-inflammatory drugs (NSAID) and 1 patient used a β blocking agent. However, stratification according to the use of medication did not influence the results of the study (data not presented). Although all patients met the diagnostic criteria of CRPS type 1, we also stratified for patients with "definite" RSD (conformable to the criteria formulated by Kozin[3]), thus excluding those with a "probable" RSD. This had no influence on the afore mentioned results (data not presented).

Table 4. Mean fluorescence (SD) of the markers in patients (n=13) and controls (n=21), with the difference between patients and controls and 95% confidence interval (CI) of the difference.

	Patients	Controls		
Variable	Mean (SD)	Mean (SD)	difference	95% CI
HLADR	23.9 (9.1)	21.6 (6.6)	2.3	-3.4 - +7.9
CD3	66.6 (7.1)	67.0 (7.4)	-0.4	-5.8 - +5.0
CD3 CD4	41.9 (5.8)	42.2 (9.6)	-0.3	-6.5 - +5.9
CD3 CD8	26.5 (5.5)	27.2 (8.5)	-0.7	-6.3 - +4.8
CD3 CD16+56	16.6 (6.6)	14.8 (6.2)	1.9	-2.9 - +6.6
CD19	11.4 (5.2)	12.1 (4.7)	-0.8	-4.4 - +2.9
CD25 CD4	12.7 (3.9)	10.5 (3.6)	2.3	-0.5 - +5.0
HLADR CD4	2.5 (1.1)	2.8 (1.0)	-0.3	-1.1 - +0.5
HLADR CD8	3.5 (1.7)	3.9 (2.9)	-0.4	-2.2 - +1.5
CD25 CD8	1.4 (1.2)	2.6 (2.7)	-1.3	-2.9 - +0.4
CD8 CD38	12.5 (4.5)	15.4 (8.4)	-2.9	-8.1 - +2.4

Discussion

The discussion whether CRPS 1 is an inflammatory disease or whether the sympathetic nervous system is involved goes back until the turn of the century. Sudeck stressed the inflammatory aspect of the syndrome.[7] Leriche described a patient in whom

resection of the adventitia of the brachial artery caused relief of pain.[8] He suspected an important etiologic role of the sympathetic nervous system and sympathectomies were adopted world wide as first choice treatment. However, the dominant role of the sympathetic nervous system is unclear and the effectiveness of sympathectomies is questioned.[2] Microneurography studies show normal sympathetic outflow to the skin of CRPS 1 patients and low venous plasma concentrations of noradrenaline (suggesting sympathetic efferent hypofunction) in the affected area have been demonstrated.[9,10] The lack of conclusive evidence as to the involvement of the sympathetic nervous system lead to the introduction of the descriptive diagnosis CRPS type 1, thus avoiding the mechanistic term reflex sympathetic dystrophy in 1994.[11] Some investigators point out the inflammatory aspects of this syndrome.[12] The symptoms of RSD in the acute stage resemble an inflammatory reaction and the effectiveness of steroids also supports the existence of a certain type of inflammatory process. Furthermore, extravasation of macromolecules (suggesting increased microvascular permeability) and perivascular cellular infiltrations in synovial biopsies in acute CRPS 1 also point to an inflammatory process.[13,14] Three mechanisms that explain an inflammatory process have been described. First, there is evidence that noradrenaline acts presynaptically on α-2 adrenoreceptors on the sympathetic post-ganglionic terminals.[15] This causes a release of prostaglandine that contributes to an inflammatory reaction. Secondly, overproduction of oxygen free radicals has been suggested as a possible cause of a peripheral inflammatory reaction.[12,16] Oxygen and its radical derivates (superoxide and the hydroxyl radical) are extremely reactive and capable of oxidizing biomolecules leading to cell death and tissue damage. Overproduction of free radicals may thus cause an inflammatory reaction. This notion is supported by a placebo controlled study in which the radical scavenger dimethyl-sulfoxide 50% in a fatty cream proved an effective treatment modality.[17] Thirdly, a peripheral neurogenic inflammatory reaction seems involved.[18] Somatosensory afferents and the immune system are closely interrelated. Classically, nociceptors are defined as afferent fibres that signal injury-threatening stimuli or the presence of chemical irritants, including many inflammatory mediators. However, nociceptors may subserve a unique dual afferent-effector function.[19,20] Besides the afferent function they also have efferent actions in the

tissue that they innervate. This is a relatively novel concept in which peripheral sensory nerves and immune cells are interrelated.[for reviews see 21,22] Following nociceptive stimulation neuropeptides such as the neurokinins (substance P, neurokinin A), calcitonine-gene-related-peptide (CGRP), and vasoactive intestinal peptide (VIP) are released and cause a neurogenic inflammatory reaction. The most extensively studied compound mediating interactions between nociceptors and immunocytes is substance P (SP).[23] SP is a neural regulator of inflammatory processes that induces local and systemic responses to inflammation and injury.[24] It evokes vasodilation and vascular permeability, induces the release of histamine by mast cells and potentiates the activities of vasoactive amines such as histamine. SP stimulates cell mediated immunity and augments immunoglobulin secretion in rheumatoid arthritis. CGRP is also released from primary afferent nerves. It inhibits cellular immune functions and it is speculated to be a natural endogenous antagonist of the pro-inflammatory action of SP.[22] Vasoactive Intestinal Peptide and Somatostatin are other examples of neuropeptides that are involved in neuro-immunoregulation. Furthermore, there is a growing body of evidence that opioid peptides are synthesised by immune cells and opioid receptors have been demonstrated on the peripheral terminals of Aδ- and C-fibres.[25] Opioid peptides exert an antinociceptive action in inflamed tissue and have an anti-inflammatory influence by inhibiting the release of excitatory neuropeptides from central and peripheral nerve endings. Also the sympathetic nervous system may exert immunomodulatory effects. Adrenoreceptors have been demonstrated in T and B lymphocytes and the immune system is a target of sympathetic innervation.[26] In humans a single injection of epinephrine causes an increase in the the number of circulating blood lymphocytes and monocytes with increased NK cells and reduced CD4 T_H-cells.[27,28]

Conclusion

The focus of attention in the discussion on the etiology of CRPS 1 is shifting from the sympathetic nervous system to inflammatory processes. As illustrated above, immune system activation should be expected when an inflammatory respons underlies CRPS 1.

However, there is a remarkable lack of quantitative data on immune system function in CRPS 1. This might be the result of an information bias as negative results are infrequently published. This study does not support the hypothesis of an inflammatory process underlying CRPS 1. However, although it is clear that neuropeptides play an important role in immunoregulation, many aspects of this complicated biological system remain unclear. A major problem is that the results of in vitro experiments cannot be easily extrapolated to the in vivo situation let alone to pathological conditions.[21] Furthermore, it might be argued that a local inflammatory response in the affected extremity is not perse reflected in systemically measured immune parameters. However, the symptoms presented by the selected patients were impressive, resembling acute arthritis. It seems unlikely that in these cases immune system activation is strictly peripheral and not reflected systemically.

The etiology of CRPS 1 remains unsolved. It seems that only through an integrated approach of basic scientists and of clinicians of various fields more insight will be gained in this complex multimodal syndrome. On this basis theory driven treatment modalities can be developed and implemented, aiming to improve the outcome of this sometimes very disabling condition. Further immunological studies should be part of this approach and should broaden the knowledge from the fundamental single-cell level to the tissue level in vivo and in pathological conditions.

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Chapter 4

Complex Regional Pain Syndrome type 1 treated with topical capsaicin: a case report.

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Summary

This report describes a multitrauma patient who underwent an amputation of the left arm and had a complicated left crural fracture with a delayed union. He was treated in an inpatient setting for preprosthetic training for a myoelectric prosthesis and to regain walking abilities. After consolidation of the crural fracture, CRPS 1 developed of the left foreleg, which hindered mobilization. Topical capsaicin 0.075% was prescribed and a stress loading mobilization schema was instituted. No other treatment modalities directed at CRPS 1 were added. After six weeks no signs or symptoms of CRPS 1 were present and capsaicin was discontinued. It is discussed that capsaicin is a well accepted and documented treatment modality in neuropathic pain states such as postherpethic neuralgia. However, it has scarcely been described in CRPS 1. Capsaicin is discussed within the framework of recent insights in the neurobiology of nociception and it is concluded that it may provide a theory driven treatment modality in CRPS 1, especially in the acute stage, that facilitates physical therapy and prevents peripheral and spinal sensitization.

Introduction

In 1994 the International Association for the Study of Pain (IASP) replaced the mechanistic term Reflex Sympathetic Dystrophy (RSD) by the descriptive term Complex Regional Pain Syndrome (CRPS) 1, underlining its unknown etiology and that pain is a key symptom.[1] The pain may be spontaneous and continuously present or be manifested by allodynia or hyperalgesia. Furthermore, edema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain have had to be present at some time. Typically, these symptoms are disproportionate to the inciting event and cannot be accounted for by other conditions. The treatment of CRPS 1 is a challenging problem and may include oral corticosteroids, anesthetics, local application of the radical scavenger dimethylsulfoxide, oral or nasal calcitonin, intravenous bretylium or intrathecal clonidine, sympathectomy, various forms of physical therapy and psychological counseling.[2-5] The effectiveness of these treatments has scarcely been demonstrated in controlled clinical trials, and a well accepted algorithm for treatment of CRPS 1 has not yet been developed. This lack of consensus may be related to the complexity and interactivity of the underlying mechanisms of CRPS 1.
The present case report describes a patient with CRPS 1, who was succesfully treated with a topical application of capsaicin. Capsaicin, a derivate of red hot chilli peppers, has been tested and is being used in several neuropathic pain states such as postherpetic neuralgia and diabetic neuropathy.[6,7] Capsaicin as a potential treatment modality in CRPS 1, will be discussed within the context of recent insights in the neurobiology of nociception.

Case report

A 26-year-old man was submitted to our rehabilitation center. Eight months earlier, he was run over by a fork-lift truck and transfered to the university hospital with multiple luxation and crush fractures of the left arm and a complicated left crural fracture. The left arm had to be amputated above the elbow and an external fixation was placed on the left tibia. The external fixation was removed two months postoperatively and replaced by an osteosynthesis. However, after three months no consolidation of the fractured tibia had occurred and the wound appeared infected. A surgical nettoyage, including fibulotomy, was performed followed by

plastercast immobilization. Weightbearing on the left leg was not allowed during seven weeks. The patient, being single and therefore unable to follow an outpatient rehabilation programme, was transferred to the inpatient rehabilitation clinic to continue (pre-)prosthetic training for the myoelectric prosthesis, and for mobilization after fracture consolidation. After nearly six weeks of plaster cast immobilization, the patient complained of persisting pain in the left foreleg and foot. The plaster cast was removed and the left foot appeared warm and swollen, up to about three inches above the ankle joint. The entire foot showed a marked allodynia that scored 8 on a VAS score. Clinical examination did not point to a peripheral neuropathy, blood tests excluded an inflammation, plain X-ray examination revealed a patchy osteoporosis of the ankle, tarsal and metatarsal bones without signs of osteomyelitis, and showed consolidation of the fracture. Three-phase bone scanning revealed an increased crural bone fixation, including the foot, with increased hemodynamic parameters. CRPS 1 was diagnosed. Weightbearing on the left leg was permitted, because of fracture consolidation, but was poorly tolerated due to pain. After discussing several treatment options with the patient, topical capsaicin two times daily was prescribed in a commercially available dose of 0.075%. A stress loading mobilization schema with increasing weight bearing, was started under strict clinical surveillance. Intolerable subjective pain experience, and an increase of the sudomotor disturbances or edema on daily clinical examinations, were defined as limiting parameters for the mobilization schema. No other co-treatment variables amed at CRPS 1, such as antialgesics, desensitization techniques or psychologial counseling were instituted and the (pre-)prosthetic training was continued. After three weeks the allodynia had decreased to a VAS score of 4, the spontaneous pain had improved and the swelling diminished. Topical capsaicin was discontinued after six weeks. At that time the allodynia had further improved (VAS score 2), the spontaneous pain had disappeared, and edema and sudomotor disturbances were absent. At that moment walking and daily care activities were sufficient to continue treatment in an outpatient setting. The myoelectric prosthesis was successfully introduced and walking ability returned to normal.

Discussion

In 1916 Leriche described a patient with a brachial plexus nerve injury in whom resection of the adventitia of the brachial artery led

to relief of the causalgic pain.[8] Sympathectomy was adopted worldwide as first choice treatment in causalgia and sympathetic disregulation was considered to be at its basis. Sympathectomy was also introduced for use in a syndrome with similar symptoms to those of causalgia, but without the nerve damage. This latter syndrome was given different names over time, including minor causalgia, algodystrophy, RSD and finally CRPS 1. Since that time both the cause and the underlying mechanisms of CRPS 1 have remained largely unresolved. An inflammatory reaction, disregulation of the sympathetic nervous system, and even psychopathology have been suggested.[9] However, definite evidence for any one of these mechanisms is lacking. With recent insight in the neurobiology of pain, CRPS 1 is considered a multimodal pain state, in which predominant mechanisms may vary with time, from the acute stage to the chronic stage, and in location, from the affected extremity to the spinal cord and possibly supraspinal structures.
The classic model of nociception was hard-wired and line labeled, in which a modality specific, single pathway led from stimulus to sensation.[10] This model is now considered far too simplistic to reflect the dynamic, interactive mechanisms involved in nociception. The central nervous system is informed of the presence of tissue damage, in two different ways.[11] The first is by nerve impulses produced in sensory fibers that are in contact with damaged and inflamed tissue. The second is chemical signalling, the relatively slow antero- and retrograde transport of chemicals along axons. Chemicals, such as neurotrophins, may actually change the phenotype of the cell and thereby its chemistry and physiology. This may have consequences both postsynaptically in the central nervous system, and in the peripheral tissue. Neurotrophins, such as Nerve Growth Factor (NGF) may cause an increase of the neurokinins substance P and neurokinin A in sensory nerves, allowing vasodilatation, plasma extravasation and mast cell degeneration, all elements of a neurogenic inflammation. This may cause "sleeping" nociceptors, unresponsive even to intense sensory (thermal or mechanical) stimuli, to exhibit spontaneous activity or to become sensitized to sensory stimuli, the phenomenon of peripheral sensitization. Furthermore, chemical signalling may cause sprouting of sympathetic fibers around the dorsal root ganglion and an increase of synaptic activation of dorsal horn neurones via excitatory amino acid (EAA) receptors (spinal sensitization).

Topical application of capsaicin provokes a concentration-dependent burning pain, pricking and itching and a flare response.

However, with repeated application these sensory responses are followed by hypalgesia, refered to as desensitization or nociceptor inactivation, a loss of responsiveness of the neuron to other stimuli. The membrane ion channel specifically activated by capsaicin, the vanilloid receptor-1 (VR1), is found on polymodal nociceptors.[12] This the most abundant class of nociceptors, responsive to various stimuli such as noxious pressure, heat and chemical irritants. NGF is involved in the upregulation of the VR1 and a low pH (rise in proton concentration), such as in ischemic or inflamed tissue, activates the VR1. NGF and a low pH cause an increase in membrane permeability to cations, particularly calcium and sodium ions. The desensitization effect of capsaicin is explained by an elevated intracellular concentration of the calcium ion, causing inactivation of voltage-activated calcium channels. Capsaicin is also a selective neurotoxin, long-term treatment can cause selective loss of epidermal C-fibers.[13] Furthermore, repeated topical application of capsaicin prevents the antero- and retrograde release of neuropeptides and glutamate. Thus, not only nociceptive afference to the spinal cord is inhibited but also chemical signalling, involved in peripheral and central sensitization.

Controlled clinical trials on topical capsaicin in neuropathic pain have been performed in diabetic neuropathy and postherpetic neuralgia.[4] In these latter studies capsaicin proved to be effective without side effects. The topical application of capsaicin in CRPS 1 has scarcely been documented, is not evidence based and is not commonly used.[14] However, as discussed, it seems a theory-driven treatment modality that may have a place in treating the acute stage of CRPS 1. Its hypalgesic effects may enhance active and passive physical therapy, and peripheral and central sensitization may be prevented reducing the chance of chronicity. To enable patients to tolerate even larger dose treatments, a combination of topical capsaicin with regional anesthesia, has been described.[15] However, it may take days to weeks to develop the anti-algesic effect. Compliance may be low due to the burning pain following application in the intial phase of treatment. Therefore a controlled clinical trial should be on an intention-to-treat basis and, preferably, the placebo should evoke an initial burning sensation similar to that of capsaicin. Mustard oil has the qualities to be an acceptable placebo.

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Chapter 5

Axillary brachial plexus blockade for the reflex sympathetic dystrophy syndrome

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Summary

The reflex sympathetic dystrophy syndrome (RSD) is a neurogenic pain syndrome that is characterised by pain, vasomotor and dystrophic changes and often motor impairments. Although the exact pathogenesis of RSD is unknown, for long the sympathetic nervous system was thought to play a dominant role and pharmacological and surgical sympathectomies have been a mainstay in treatment procedures. However, there is growing evidence of a pivotil role of C- and Aδ-fibres in the etiology of RSD. These fibres subserve a dual sensory-effector function. Besides the initiation of afferent impulses, they release neuropeptide mediators that cause a peripheral neurogenic inflammatory reaction and central neuroplastic reactions. Brachial plexus blockade (BPB) with local anesthetic drugs interferes with the conduction of action potentials along both sympathetic efferents and the somatosensory C- and Aδ-afferents and therefore seems a potential treatment modality in RSD. The aim of this study was to draw attention on this regional anesthetic technique that is not commonly used in RSD. In this study 6 patients with severe RSD of an upper extremity in varying stages were treated with BPB in the multidisciplinary setting of an out-patient rehabilitation clinic with a follow-up of 12 to 21 months. The study was not placebo controlled. Three patients responded well. In these cases the treatment interval varied from 3 to 6 months, one case had RSD stage 1 and the two others stage 2. Three patients showed poor respons. In one of these patients the initial effect was good but due to an infection at the insertion site of the catheter, BPB had to be discontinued. The other 2 poor-responders had treatment intervals of 7 and 25 months and both had stage 3 RSD. We conclude that there is theoretical and clinical support to further evaluate the effect of BPB as a treatment modality in the early stages of RSD.

Introduction

The reflex sympathetic dystrophy syndrome (RSD) is a neurogenic pain syndrome that is characterized by a combination of pain, trophic changes, vasomotor disturbances and motor impairments. Most often there is a precipitating factor such as a trivial peripheral trauma but also non-traumatic diseases of the locomotor apparatus, myocardial infarction, pleuropulmonary disease and central neurological disorders (e.g. acute stroke and spinal cord injury) may cause RSD.[1,2,3,4] Two extremes of a continuum can be distinguished in the clinical course of RSD: the acute stage during which inflammatory signs predominate (stage 1) and the chronic stage with atrophy, chronic pain and motor impairments (stage 3 or the atrophic stage). Stage 2 is classified as the dystrophic stage.[5] The different stages are of variable length, do not correspond to different treatment modalities and do not occur in a fixed order. RSD is a descriptive diagnosis with criteria that are not unequivocal. Bone scanning can be used to confirm the clinical diagnosis in which case the three-phase bone scanning technique (TPBS) is the most specific and sensitive investigation.[2] It antecedes any radiological changes and may be used in treatment evaluation. Theories on the pathogenesis of RSD are hypothetical and there is little objective evidence on which to base a rational treatment plan. Sympathetic nerve blocks (surgical sympathectomies and regional (Bier) or epidural blocks) have been a mainstay in the treatment of RSD. As will be discussed later, the predominant role of the sympathetic nervous system in RSD is subject to debate and there is growing evidence that sensitised somatosensory afferents (low-threshold Aδ-mechanoreceptors and C-nociceptors) are pivotil in the etiology of RSD. This study is aimed at focusing attention on the use of axillary brachial plexus blockade (BPB) in RSD. Brachial plexus blockade with local anesthetics decreases the conduction of both sympathetic efferent fibres and somatosensory afferents and therefore seems a potential treatment modality for RSD. The effect of BPB on pain, vasomotor disturbances, range of motion of affected joints and hand function was evaluated in six patients with various stages of RSD of one upper extremity. After describing the applied methods as well as the individual and general results, the use of this regional anesthetic technique will be discussed within the framework of recent insights in the pathogenesis of RSD.

Methods

Six patients were studied in the time period from december 1994 until september 1996 (table 1). All patients received a standard out-patient rehabilitation programme including physical therapy, occupational therapy and psychosocial interventions with a frequency of three to five times per week. Moreover, common medical interventions such as pain medication, intra-articular injections, radical scavengers (such as dimethyl sulfoxide (DMSO) 50% ointment) and vasomediators were administered in individual regimes. BPB was added in those patients in which the severity of the pain in the affected extremity was so intense that active or passive exercises were not possible.
After standard neurological and orthopedic physical examination, patients were enrolled in the study if they were classified as definite or probable RSD of (a part of) one upper extremity according to the diagnostic criteria formulated by Kozin et al.[6] According to these criteria the diagnosis RSD is considered definite when pain and tenderness in the distal extremity are accompanied by swelling *and* vasomotor instability. If pain is accompanied by swelling *or* vasomotor instability the diagnosis RSD is probable. Patients who met the following criteria were excluded: allergy for local anesthetics, immune compromising diseases, hemorrhagic diathesis, severely limited abduction and exorotation in the shoulder of the affected arm, lack of cooperation and mental or psychiatric disorders. Informed consent with respect to the use of BPB was obtained from all patients. Plexus blockade was performed after placing an indwelling catheter within the neurovascular sheath. Regional anesthesia was performed continuously by infusing bupivacaine (0,50%, 3 ml/hour) by means of a portable pump (BPB^1) or by daily single dosis of 20 ml bupivacaine (0,25%) 30 minutes before therapy (BPB^2). The BPB-treatment was always given for maximally two weeks, after which one week "rest" was given in order to prevent complications such as infection and fibrosis. The time period of two weeks treatment and one week rest will be referred to as one "session". If necessary these sessions were repeated until the pain and other symptoms were reduced to a level that allowed active or passive exercises. The choice for BPB^1 or BPB^2 was a pragmatic one and dictated by the availability of financial support of a pump in the individual cases. The effect of the treatment was evaluated by an experienced physician in physi-

cal medicine and rehabilitation, with a follow-up of 12 to 21 months.

Results

Patient 1 is a 31-year-old woman who underwent handsurgery because of a morbus Quervain of the right hand. Post-operatively the forearm was immobilized with a plaster cast for 3 weeks. After removal of the cast the forearm remained swollen, cold and she perceived an ongoing burning pain in the entire right arm. She was diagnosed as having RSD. At first she was treated with physical therapy, non-steroid anti-inflammatory drugs and intra-articular infiltrations with corticosteroids in the wrist. Her complaints persisted and in second instance the radical scavenger DMSO (50% ointment) and verapamil (120 mg daily) were prescribed without effect. Transcutaneous electrostimulation and amitriptyline also proved ineffective. The pain persisted and the arm lost all active functions. A cock-up splint for the wrist provided some pain relief. One-and-a-half year after onset she was referred to our out-patient clinic. At that time, the entire right arm was cold with a severe allodynia and an ongoing burning pain that worsened with active or passive movement of the arm. Hair and nail growth were increased and skin and muscles were atrophied with severe muscle weakness. Contractures were present in the right shoulder, elbow, wrist and hand joints. X-ray examination of the hand and wrist showed the typical patchy osteoporosis. For two months BPB[2] was added to the rehabilitation programme. The treatment was aimed at reduction of pain and ischemia and redression of contractures. The initial effect was fair both on pain and contracture reduction. Due to local irritation at the insertion place the catheter had to be removed after one week. After a replacement of the catheter one week later, the effect improved dramatically. Only hours after the replacement, the right arm became warm, the pain decreased and the active and passive range of motion of the affected joints returned to almost normal. Despite three sessions on BPB[2], it was not possible to achieve a definite break through in turning the vicious circle of pain and disabilities caused by RSD. All symptoms reoccurred only weeks after the last infusion which remained so during the follow-up period of 14 months.

Table 1. Patient Characteristics

	Age/sex	*Cause*	*Site*	*Stage*	*Interval*
1	31/F	hand surgery	right arm	3	25
2	39/F	shoulder luxation	left arm	1	2
3	41/F	reconstructive surgery	right arm	2	2
4	52/F	hand surgery	right arm	2	3
5	57/F	Colles fractures	right arm	2	6
6	41/F	spontaneous	right arm	3	7

Interval: time period passed between diagnosing RSD and first session of brachial plexus anesthesia (months).

Patient 2 is a 39-year-old woman who had her first (ideopathic) epileptic seizure on which occasion she traumatized her left shoulder. 14 hours after admission to hospital a left glenohumeral luxation was recognized and repositioned. After 3 days the left arm progressively started to swell and a burning diffuse pain developed. Initially she was treated with paracetamol 500 mg 6 times daily, levomepromazine 12,5 mg and carbamazepine 300 mg daily. Because there was no treatment effect she was referred to our outpatient clinic after six weeks. At that time she suffered from severe allodynia and ongoing burning pain in the entire left arm, which was aggravated by any active or passive motion. The left arm was swollen, red and warm with hyperhydrosis and could not be actively moved. Contractures were developing in the left shoulder and the elbow. The ranges of motion of the left hand were severely reduced and painful on examination. Electroneuromyography was performed and revealed minor signs of left brachial plexus lesion, in particular impaired motor and sensory conduction velocity of the ulnar nerve. A three-phase bone scanning confirmed the diagnosis RSD. Treatment was started with prednison 20 mg daily, DMSO (50% ointment), a cock-up splint for the wrist (during the night) and an arm-supporting orthosis to stabilize a minor subluxation in the left glenohumeral joint. At several times an intra articular injection was given in the left glenohumeral joint. After one month the effect of this regime was unsatisfying and BPB[2] was started. Immediately after the first injection of bupivacaine, there was a substantial improvement in pain, swelling as well as active and passive mobility. Hand function gradually improved and

bimanual activities could be performed. After two sessions of BPB[2] a definite tendency towards pain reduction and improvement of hand functions and manual abilities was achieved, also without BPB. The effects remained present during a follow-up period of 14 months.

Patient 3 is a 41-year-old woman who cut four extensor tendons at the dorsum of the right wrist due to a fall while carrying bottles. After reconstructive surgery her forearm was immobilized with a plaster cast. Almost immediately after immobilization the forearm started to swell and it alternately became red and warm or cold and blue. Also, a fierce allodynia and ongoing burning pain developed and the cast had to be removed. Active or passive exercises were not tolerated due to the severe pain. Initially she was treated with the radical scavenger mannitol (10% intravenously, 1 liter daily) and with verapamil 240 mg daily. The mannitol infusion was stopped after one week because of phlebitis. After two months this patient was referred to our out-patient clinic because of persisting complaints. At that time she suffered from a cold forearm with allodynia, ongoing burning pain, oedema, increased hair and nail growth and a dystrophic skin. She was unable to allow any active or passive movements of the wrist or fingers. X-ray examination showed a patchy osteoporosis of the wrist and the hand. A three-phase bone scanning confirmed the diagnosis RSD. Only a few hours after starting BPB[1] the right forearm and hand became warm, with a substantial reduction in nociception and swelling. Physiotherapy was easily tolerated. However due to a local infection at the insertion site of the catheter with expansion to a subcutaneous abcess, BPB had to be stopped after three sessions and all symptoms reoccurred. During a follow up of 12 months a slight improvement of the contractures remained. However, no gain was achieved in the functional use of the hand in activities of daily life.

Patient 4 is 52-year-old woman who had undergone surgery for Dupuytren contractures in the right hand. After two months she had to be reoperated due to poor functional results. After the second operation she developed severe burning pain in the entire right arm hindering sleep and household activities and forcing her to stop playing the piano. She was refered to our out-patient clinic four

months after the second operation. There was some oedema in the right hand with hyperpathia and hypoesthesia. Severe contractures were present in the right shoulder, wrist and hand joints as well as marked proximal and distal muscle weakness. There were no local trigger points in the scar and a possible neuroma could be excluded by soft- tissue echoscopy. X-ray examination revealed patchy osteoporosis of the right shoulder and hand and a three-phase bone scan confirmed the diagnosis. The right glenohumeral joint was treated with several injections of corticosteroids with excelent results. Contracture reduction of the right wrist and hand proved impossible due to severe pain. BPB[1] was given during three sessions. With this regime she was free of pain during therapy sessions and arm and hand function could be restored. Minor contractures in the distal and proximal interphalangeal joints of the digits III and IV of the right hand persisted but muscle strength fully recovered. After 12 months follow up, this patient was not completely satisfied with the outcome because the contractures in digits III and IV remained bothersome while playing the piano.

Patient 5 is a 57-year-old woman who sustained bilateral Colles fractures which were treated with plaster cast immobilization. The fracture on the right side was complicated by a delayed union and the hand remained painful. At first she was unsuccesfully treated with physiotherapy and the radical scavenger N-acetyl cystein 3 times 600 mg daily. Seven months after her injury she attended our out-patient clinic with a stage 2 RSD that was confirmed by a three-phase bone scan. The right hand was too painful to be used. Active and passive movements were limited due to severe contractures. In order to allow mobilization BPB[2] was applied during four sessions. There was a major reduction in pain as well as in muscle strength. Physiotherapy and finger splinting aimed at contracture reduction were well tolerated. After two months the pain had disappeared and the contractures had improved with exception of the digits IV and V. The hand could be used in all daily life activities and writing. This effect remained present during the follow up period of 21 months.

Patient 6 is a 43-year-old woman, already known with a stage 3 RSD of the right leg that had developed seven years before. Without a clear cause, the right hand became red, warm, swollen

and painful. She was diagnosed as RSD and treated with DMSO (50% ointment), NSAID, cock-up splint for the wrist, arm sling, regional intravenous sympathetic blocks, transcutaneous electrostimulation as well as physical and occupational therapy aimed at prevention of contractures and chronic disuse. Because the symptoms did not improve she was referred for the BPB-trial after seven months. At that time the right forearm was cold with allodynia, ongoing burning pain, atrophy of skin, nails and muscles. There were slight contractures in the right shoulder and elbow, severe contractures had developed in the wrist and hand joints. The hand could not be used in activities of daily life. There was an immediate good respons to BPB^2. The hand became warm, the pain subsided, contractures improved and bimanual activities were regained after three sessions of BPB. However, long term effects were disappointing. Only weeks after cessation of BPB the pain and vasomotor disturbances reappeared, again hindering manual activity. After 21 months a slight improvement in pain and contractures remained present but bimanual activities were not possible.

General results

Three out of six patients responded poor to treatment. Patient 3 (RSD stage 2, treatment interval 2 months, BPB^1) showed a good initial respons but due to an infection the catheter had to be removed. The other two patients with a poor respons (patient 1 and 6) both had RSD stage 3 and were treated with PBB^2 after long treatment intervals (respectively 25 months and 7 months). Despite the fact that patient 6 had a stage 3 RSD that was irresponsive to sympathectomies and showed poor long term results, BPB initially proved effective in reducing pain, vasomotor disturbances and contractures. Three patients responded well. Patient 5 (RSD stage 2, treatment interval 6 months, BPB^2) showed an excellent immediate respons with disappearance of pain and vasomotor disturbances, full regainment of handfunction with exception of remaining slight contractures in digits IV and V. Patients 4 (RSD stage 2, treatment interval 3 months, BPB^1) and 2 (RSD stage 1, treatment interval 2 months, BPB^2) responded well on all modalities.

Discussion

During the American Civil War in 1864 Weir Mitchill introduced the term causalgia when he described the typical burning pain that followed peripheral nerve injuries from gunshot wounds.[7,8] In 1916 Leriche described a patient with a lesioned brachial plexus nerve in whom resection of the adventitia of the brachial artery of the affected arm caused relief of pain.[9] He suspected an important pathogenetic role of the sympathetic nervous system in causalgia. Sympathectomies were adopted worldwide as first-choice treatment in causalgia without adequate evaluation of the effect of this technique.[10] It appeared that many patients with similar clinical findings as in causalgia showed no evidence of a vascular or neural lesion and many different names such as minor causalgia, post-traumatic pain syndrome or algodystrophy were introduced for this syndrome. Currently, RSD is the most commonly used term. Because of the similarities in the clinical presentations of causalgia and RSD, sympathectomies were adopted in the treatment of RSD. Again, the physiological responses to these interventions remained unclear because of lacking placebo controlled studies. Nowadays, the notion of predominant sympathetic involvement in RSD is questioned.[11,12,13] Sensitized peripheral nociceptors (C-afferents) and low-threshold mechanoreceptors (Aδ-afferents) seem to play a pivotal role in RSD and may implicate central mechanisms.[14] Sympathetic activity, tissue destruction due to overproduction of toxic free radicals and a neurogenic inflammatory reaction all have been suggested to cause nociceptive afference. Firstly, in lower vertebrates it has been demonstrated that efferent sympathetic activity modulates depolarization of the myelinated Aδ- and unmyelinated C-cutaneous afferents.[15,16] However, microneurography studies show that sympathetic outflow to the skin of RSD patients appears normal.[13] Furthermore, low venous plasma concentrations of noradrenaline in the painful area even suggest sympathetic efferent hypofunction.[17] Secondly, cell destruction and tissue damage due to an overproduction of oxygen free radicals have been suggested as possible underlying cause of RSD.[18] A placebo controlled study on the effect of the radical scavanger dimethylsulfoxide (DMSO) 50% in a fatty cream as treatment in RSD supports this hypothesis.[19] Thirdly, it has become evident that a substantial portion of primary afferent neurons with C- or Aδ-fibres form a separate subset of the peripheral nervous system.

They subserve a dual afferent-efferent function. These *sensory-effectors* are suitable both for afferent impuls initiation to the central nervous system and for peripheral and central release of neuropeptide mediators.[20] The neuropeptide mediators may cause a peripheral neurogenic inflammation (allowing the sensory fibres to increase their sensitivity for detecting and responding to adverse conditions) and enhance central neuroplastic reactions. Chronic nociceptive afferent activity induces transient or long-lasting alterations in membrane excitability as well as changes in cellular biochemistry and even structural modification of cytoarchitecture and connectivity. These changes may be transneural involving wide dynanamic range (WDR-) neurons in the spinal internuncial pool.[14] Sensitized WDR-neurons continuously stimulate sympathetic and motor efferent fibers resulting in a vicious self-sustaining cycle. Also, it has become evident that transneural changes may spread beyond the spinal internuncial pool to other spinal and supraspinal regions (centralization).[21] Within this theoretical framework blocking nociceptive afferents seems a logic procedure as it not only relieves nociception but also prevents centralization. Cicala et al (1990) presented a case in which lumbar sympathetic blocks only temporarily eliminated vasomotor disturbances and hyperesthesia in the affected limb, without reducing a constant burning pain.[22] In contrast, a 72 hours continuous epidural block with 0,125% bupivacaine relieved all symptoms. In this concentration bupivacaine induces a pharmacologic sympathectomy and relieves nociceptive afference. The authors conclude that interruption of a pathologic afferent to efferent nerve conduction loop might be responsible for relieving the patients causalgia. Becker et al (1995) report two cases of chronic and therapy resistent RSD that responded well to intrathecal morphine infusion by means of an implanted pump.[23] Only a few casuistic reports have outlined the benifits of BPB in RSD and it is not a commonly applied technique in RSD. Murray (1995) reports a single case in which a series of continuous axillary brachial plexus blocks was succesfully used in a patient with chronic RSD.[24] Earlier case-studies have outlined the benifits of the sequential use of single dosis blocks.[25,26]

Like the former studies this study has important methodological shortcomings; it is not placebo controlled, the small mumber and heterogeneity of patients allows no statistics and it might even be argued that we observed the natural history of the disorder. However, in all patients pain and vasomotor disturbances improved within hours after BPB which seems to weaken this argument.

Despite the fact that this study doesn't allow any definite conclusions, the results are hopeful. Patients 2, 4 and 5 illustrate that early treatment with BPB, in otherwise irresponsive cases, may improve functional outcome. It is hypothesized that blocking the somatosensory afferents in an early stage of RSD, prevents the process of centralization and thereby chronicity. Murray's study illustrates that chronicity in RSD does not per se warrants therapeutic nihilism.[24] Patient 6 with RSD stage 3 also illustrates that blocking somatosensory afferents in a chronic stage can facilitate contracture reduction through physical therapy. However, hand function in activities of daily life did not improve in this patient. Perhaps this is due to the fact that this patient received intermittently administered regional anesthesia with BPB^2. Would continuous pain reduction with BPB^1 have resulted in better functional use of the affected hand in activities of daily life and thereby improve long term effect? BPB^1 seems more effective than BPB^2 in interrupting an afferent-efferent vicious circle and in preventing centralization and seems first choice when BPB is considered in treating severe RSD of an upper exteremity in which active and passive exercises are not tolerated. To prevent the possible severe disabilities that may result from RSD, treatment should start as early as possible. BPB does not affect the glenohumeral joint. When the glenohumeral joint is involved in RSD of an upper extremity, intra-articular infiltrations or suprascapular blocks should be considered. Furthermore antibiotic prophylaxis may reduce the number of complicating infections. Brachial plexus lesions should be documented before BPB is applied in order to exclude iatrogenic damage. BPB should not be applied in the case of lack of cooperation or insight, in immune compromising diseases or in hemorrhagic diathesis.

Although insights in the pathogenesis of RSD are still hypothetical, a monocausal or strictly peripheral origin of this potentially very disabling disorder should be rejected. Because of the multiplicity of the mechanisms underlying RSD, the treatment of these patients remains a challenge and should be performed in multidisciplinary setting. This study illustrates that there is theoretical and clinical support that BPB may add to an effective multimodal intervention in severe RSD of the upper extremity. However, further studies are needed to evaluate this.

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Chapter 6

Reflex Sympathetic Dystrophy of the left hand and motor impairments of the unaffected right hand: impaired central motor processing?

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Abstract

Objective: To test whether central motor processing can be impaired in chronic reflex sympathetic dystrophy (RSD).
Design: Experimental two-group analysis.
Setting: Tertiary care centre.
Subjects: Five patients with stage 3 RSD of the left forearm, free of symptoms and complaints of the right forearm, and 10 healthy control subjects. Exclusion criteria: illiteracy and visual, neurologic, psychiatric or musculoskeletal disorders.
Main outcome measures: On a digitizer three sequences of graphemes of different complexity had to be drawn with the (unaffected) dominant right hand by RSD patients and healthy control subjects. The drawing tracks were segmented in time periods between points of velocity minima of the pen tip. Mean velocity, coefficients of variation of both length and movement time per segment, and mean intersegmental pausing time were calculated for each sequence.
Results: A repeated measures analysis of variance using the multivariate method yielded a 35% lower mean velocity ($F(1,13)=5.83$, $p=.031$), a 110% larger segment length variability ($F(1,13)=9.72$; $p=.008$) and a 60% larger variability of movement time per segment ($F(1,13)=5.78$; $p=.032$) in RSD patients. No group difference for intersegmental pausing time or any interaction effect with the type of task was found.
Conclusion: The results suggest that patients with chronic RSD have a normal ability to preprogram sequential movements of the unaffected hand, however, with impaired temporospatial coding and movement execution. It is concluded that cortical mechanisms may be involved in motor impairments in patients with chronic RSD.

Introduction

Reflex sympathetic dystrophy (RSD) is a syndrome formed by a combination of pain, trophic changes and vasomotor disturbances. Motor impairments such as muscle weakness, tremor, dystonia, spasms, difficulty in initiating movements or incoordination occur in a majority of patients. In a chronic stage motor impairments may constitute, together with pain, a major cause of disability in RSD patients.[1,2] The underlying mechanisms of motor impairments in RSD are still a matter of debate. Attention has been focused on mechanisms such as oxydative stress, sympathomotor dysregulation and a prolonged depolarization of anterior horn cells caused by substance P release in the spinal cord.[3,4,5,6] However, none of these mechanisms can account for all of the possible motor impairments in RSD.[7] Furthermore, RSD motor impairments may spread in a hemiplegic, transverse or crossed distribution, which is hard to explain solely on the basis of a peripheral origin or segmental changes in the spinal cord.[8] Therefore, a disruption of motor processing in the brain should be considered.[7] Indeed, clinical observations provide preliminary support for this idea. Marsden et al (1984) described a RSD patient whose involuntary movements disappeared after thermocoagulation of the thalamic ventral intermediate nucleus and Robberecht et al (1988) recorded altered cortical potentials preceding involuntary movements in a RSD patient.[9,10] Furthermore, Rommel et al (1999) found hemisensory deficits in RSD patients comparable to those observed after large lesions of the parietal cortex or after thalamic lesions.[11] Because the hemisesensory deficits were significantly correlated with motor impairments, it is concluded that the motor as well as the sensory impairments in RSD probably reflect "functional alterations in central processing". The present article describes an exploratory study on this topic.

It has been demonstrated in numerous experiments that motor processing at its highest level, is abstract and global rather than aimed at individual effector systems such as joints and muscles.[12,13,14,15,16,17] For example, the writing patterns of the left and right hand of an individual, share relevant temporospatial

characteristics.[17] This notion formed the basis of the present experiment. If it can be shown that in RSD patients motor control of the unaffected dominant hand differs, in terms of specific kinematic parameters, from healthy control subjects, this may be seen as support for the idea that motor control may be affected at the level of effector independent motor processing.

Healthy control subjects and patients with chronic RSD of the non-dominant hand had to perform drawing tasks of varying complexity with their dominant hand. Following former studies on effector independence in motor control, the preparation of the movement, the temporospatial coding and execution of the movement were studied.[17,18] It is known that movement preprogramming becomes more time consuming when the movement increases in complexity, as in shifting between different types of movements.[19] It was argued here that a distortion in preprogramming would be reflected in an extension of the time interval between the end of a movement segment and the start of a next movement segment. Shifting between different types of movement was considered to stress preprogramming and would therefore result in disproportionally extended pausing times between movement segments in the case of impaired preprogramming capacities. A distortion in movement implementation would result in an impaired ("noisy") temporospatial coding of the movement (less fluent, slower and more variable). Hence, the main kinematic parameters in the present study are the length of the time interval between separate movement segments, movement velocity and movement variability. The key question of this experiment is whether (and if so on which kinematic parameters) RSD patients differ from healthy control subjects in performing a drawing task with the unaffected dominant hand.

Methods

Subjects

Five right-handed RSD patients participated with informed consent (see table 1 for patient characteristics). The patients suffered from

chronic RSD of the left hand and forearm and were free of any symptoms and complaints in the dominant right hand. All patients met the criteria of Complex Regional Pain Syndrome, type 1 (RSD) formulated in 1994[20] and showed motor disorders such as involuntary movements, initiation disorders, dystonia or muscle spasms in the affected extremity on clinical examination. Furthermore, writing with the right hand did not provoke any pain in the left hand. Exclusion criteria were: illiteracy, visual disturbances other than corrected refraction disorders, and neurologic, psychiatric or musculoskeletal disorders of any kind. The kinematic characteristics of the drawing tracks of the 5 RSD patients were compared with those of 10 healthy control subjects of a similar age and educational level, working in the rehabilitation center.

Table 1: Patient characteristics

sex	age	duration	cause	motor impairments
F	24	2,5 years	surgery ganglion dorsum left hand	movement initiation muscle weakness involuntary movements
F	46	1.2 years	fracture 3rd meta-carpel left hand	movement initiation muscle weakness
M	29	10 months	bee sting left forearm	tremor movement initiation muscle weakness
F	44	3.5 years	surgery ganglion dorsum left hand	tremor dystonia movement initiation involuntary movements
F	46	9 years	contusion left hand	tremor movement initiation

Equipment

The drawing tasks were performed with a pen, that left a normal ink trace, on a large sheet of paper covering a Calcomp 9600 digitizer that was connected to an IBM compatible computer. The equipment has been used and described before.[21,22] The digitizer

sampled the horizontal and vertical coordinates of the pen tip at a frequency of 110 Hz with a spatial accuracy of 0.2 mm and a temporal accuracy of 0.1 ms. The signals were filtered by means of a Fast-Fourier analysis using a cut-off frequency of 10 Hz.

Figure 1: Drawing sequences

Open triangle (OT-task)

Arch (A-task)

Open triangle-Arch (OT-A-task)

Procedure

Subjects were seated at a table in a comfortable position for drawing. The display screen, on which the drawing tracks were presented online, was not visible for the subjects. Three figures representing either open triangles (OT-task), arches (A-task) or alternating open triangles and arches (OT-A-task) (see Fig. 1) were presented in the left margin of the paper that covered the digitizer. Subjects were instructed to draw a sequence of each presented figure with the dominant hand, as fast and accurately as possible. Each individual trial started when the experimenter pressed a key

on the computer's keyboard which generated an acoustic starting signal. Subjects were unaware that sampling actually started 2 seconds after this signal, thus eliminating the first few graphemes from the registration. The effective sampling period lasted 30 seconds. No scores or other systematic feedback about the performance were given to the subjects during or after the individual trials. The experimental trials were preceded by practice trials to ensure that all subjects understood the task. All trials were performed once and in a fixed order. Hence, every subject performed at least six trials of 30 seconds: at least one practice trial for each task, followed by experimental trials of subsequently the OT-, A- and OT-A-task.

Data analysis

The drawing sequences were divided into segments, whereby a segment represented the time period between two points of zero velocity of the pen tip. The mean intersegmental pausing time per sequence was calculated, reflecting the phase of motor preprogramming. Segment length, movement time per segment and velocity were considered kinematic parameters of movement implementation.[19] Although these parameters are interrelated, the movement time and the length per segment are the more invariant characteristics of movement implementation.[18,22] Velocity is the more variable parameter. Therefore, the intrasubject variability of both length and movement time per segment was expressed in a coefficient of variation for each sequence, whereas velocity was expressed as an average for each sequence.

Statistics

For each individual task performance, the mean velocity, the coefficients of variation of the length and movement time per segment and the mean intersegmental pausing time were calculated. A repeated measures analysis of variance using the multivariate method (MANOVA) was performed, using a standard SPSS package, with 'Group' (2 levels: controls and RSD patients) as a between subjects factor and 'Task' (3 levels: OT, A and OT-A) as a within subjects factor. A contrast parameter was constructed in

order to test for possible differences between the OT-A-task and the weighed sum of the seperate OT- and A-tasks. A main effect of task would indicate that any of the kinematic parameters would be significantly affected by task complexity, irrespective of the group. Likewise, a main effect of group would indicate that drawing performance would be significantly affected by RSD, irrespective of the task. A group by task interaction would implicate that the effect of task complexity on drawing performance would be different for each group.

Table 2 Results

		OT-task*	A-task*	OT-A-task*	Average
MiPT	Controls	0.31 (0.87)	1.17 (1.36)	1.99 (1.22)	1.16 (0.97)
	Patients	0.84 (0.90)	1.28 (1.04)	2.25 (1.13)	1.46 (0.67)
CV Lps	Controls	17.88 (7.05)	16.49 (7.05)	22.60 (12.82)	18.99 (6.68)
	Patients	37.56 (17.35)	36.24 (19.02)	47.05 (12.28)	38.56 (18.81)
CV MTps	Controls	24.60 (13.67)	20.57 (7.33)	29.82 (11.99)	25.00 (7.43)
	Patients	35.86 (17.23)	33.51 (19.42)	50.02 (8.18)	39.80 (16.95)
MVps	Controls	6.27 (2.63)	5.97 (1.65)	4.86 (1.04)	5.70 (1.61)
	Patients	3.43 (1.26)	3.75 (1.87)	3.86 (1.42)	3.68 (1.31)

CV MTps: coefficient of variation of the movement time per segment; CV Lps: coefficient of variation of the length per segment; MVps: mean velocity per segment in millimeters per second; MiPT: mean intersegmental pausing time in seconds; ( ) standard deviations; * see text

Results

Table 2 reflects the group means and standard deviations of each parameter for the three individual tasks as well as averaged over three tasks and tables 3a and 3b represent the multivariate and

univariate results from the MANOVA. The intersegmental pausing time showed a significant Task-effect ($F(2,12)=22.391$; $p=.000$) due to a significant difference between the OT-A-task versus the weighed sums of the OT- and A-tasks ($1,13)=12.355$; $p=.004$). However, no Group-effect ($F(1,13)=.37$; $p=.554$) or Group by Task interaction effect was present ($F(2,12)=.622$; $p=.553$) for this parameter. The coefficients of variation of the length per segment were on average 110% larger in the RSD patients than in the control subjects ($F(1,13)=9.72$; $p=.008$) and the coefficients of variation of the movement time per segment of the RSD patients exceeded those of control subjects by 60% ($F(1,13)=5.78$; $p=.032$). Furthermore, the RSD patients had a 35% lower mean movement velocity than the control subjects ($F(1,13)=5.83$; $p=.031$). No Group by Task interactions were found for any of these parameters.

Discussion

The goal of this study was to explore motor processing in patients with chronic RSD. The results showed that intersegmental pausing times increased with increasing task complexity, both in RSD patients and in control subjects. However, no significant Group-by-Task-interaction could be obtained, indicating that at the level of motor preprogramming no differences existed between the RSD patients and the healthy control subjects. RSD patients appear to have a normal ability to plan the sequential drawing movements ahead, even with increasing task complexity. It should be noted, however, that the discrete and hierarchical model of preprogramming, in which the planning of a movement foregoes the execution of a movement, is subject to debate. A continuous model, in which programming occurs both before and online during movement execution, is supported for more complex sequences.[23] In this case a decrease in movement velocity would allow additional online processing time. Indeed, the RSD patients were slower in task performance than the healthy control subjects in this experiment. Furthermore, specific aspects of movement implementation were distorted in RSD patients. Compared to control subjects, RSD patients were characterized by impaired

temporospatial coding (higher segment length variability and higher variability of movement time per segment) and slower movement execution.

How may these results contribute to the discussion on the underlying mechanisms in RSD? It is becoming increasingly clear that traditional views on nociception, in which a modality specific, single pathway leads from stimulus to sensation, is too simple to reflect the dynamical, interactive mechanisms involved.[24] The sensitivity of the peripheral terminal is not fixed. Repeated stimulation or changes in the chemical milieu as in inflammatory reactions, cause alterations in activation thresholds, known as the phenomenon of peripheral sensitization. In addition, nociceptive input to the spinal cord induces both an immediate pain sensation and an increase in membrane excitability of spinal neurons that outlasts the nociceptive stimulus (spinal sensitization).[25] As discussed, peripheral and spinal mechanisms are also considered to underlie motor impairments in RSD but cannot account for all of the observed motor problems.[4,5,6,7] Supraspinal mechanisms, on nociception and especially on motor processing, hardly have been studied in RSD. Although it is beyond the scope of the present study to determine what neural structures might be involved in the observed motor deficits in RSD patients, cortical areas should be taken into account. The parietal cortex plays a crucial role in the integration of extrapersonal spatial information with intrapersonal temporospatial properties of effectors. An extensive interconnectivity exists between the parietal and frontal cortex, which places the frontal cortex in a strategic position for accessing the temporospatial representations of motor responses.[26,26,27,28,29]

RSD is considered a multimodal syndrome and it might be speculated that a process of centralization may occur, involving spinal and supraspinal structures. In the initial stage of the syndrome, mechanisms in the affected extremity, such as oxydative stress and a (neurogenic) inflammation cause peripheral senstization.[25,30]

Table 3a: multivariate statistics

	Hypothesis Df	Error Df	Hotellings Trace	F value	P value
MiPT#					
Task	2	12	3.73	22.39	**.000**
Task by Group	2	12	.10	.62	.553
CV Lps#					
Task	2	12	.45	2.69	.108
Task by Group	2	12	.24	1.46	.271
CV MTps#					
Task	2	12	1.36	8.81	**.006**
Task by Group	2	12	.11	.67	.531
MVps#					
Task	2	12	.15	.89	.433
Task by Group	2	12	.22	1.34	.299

see legend Table 2

Table 3b: univariate statistics

	Hypothesis			*Error*				
	Df	sums of squares	mean square	Df	sums of squares	mean square	F value	P-value
MiPT[#]								
Group	1	.87	.87	13	30.59	2.35	.37	.554
OT/A vs OT-A	1	13.34	13.34	13	14.04	1.08	12.35	**.004**
CV Lps[#]								
Group	1	10277.49	10277.49	13	13740.83	1056.99	9.72	**.008**
OT/A vs OT-A	1	5090.75	5090.75	13	12661.51	973.96	5.22	**.040**
CV MTps[#]								
Group	1	2194.19	2194.19	13	4938.74	379.90	5.78	**.032**
OT/A vs OT-A	1	1134.21	1134.21	13	1358.93	104.53	10.85	**.006**
MVps[#]								
Group	1	40.82	40.82	13	91.04	7.00	5.83	**.031**
OT/A vs OT-A	1	5.22	5.22	13	23.61	1.82	2.88	.114

see legend table 2

In a later stage, spinal sensitization may occur in the dorsal horn due to the release of e.g. excitatory amino acid and neuropeptide transmitters.[25] If treatment is unsuccessful in these stages, peripheral and spinal sensitization may cause a chronically altered input to the somatosensory cortex, involved in temporospatial coding of movements. Neuroplastic reactions in the somatosensory cortex due to input alterations, have been demonstrated in many experiments.[31-36]
Although this is only a speculative explanation of our data, it seems to underline the importance of early diagnosis and treatment of RSD. Pain treatment should be a pillar, aiming to prevent peripheral and central sensitisation, and physical therapy should be aimed at active rather than passive movements, however without provoking pain. Physical immobilization, such as with a cast or splint, should not be used on a routine basis as it may stimulate chronic disuse. However, a well accepted treatment algorithm is lacking and treatment strategies may vary and depend on local customs. Therefore, the construction of an evidence based or at least theory driven treatment algorithm, should be in the focus of future clinical research on RSD. More effort should be made in evaluating in individual patients which pathophysiological mechanisms may underly the presenting symptoms, so that treatment can be targetted to the underlying mechanisms rather than to the symptoms.

Some potential fallacies of this study should be noted. Firstly, it is possible that the exposed differences between RSD patients and healthy control subjects are not specifically related to RSD, but to a "specific central susceptibility" due to which individuals may develop motor impairments after a peripheral noxe of any kind.[37] The association of peripheral lesions, unassociated with RSD, and involuntary movements has been discussed before.[38] Within this perspective, it remains the question, whether impaired motor control is a key-characteristic of chronic RSD or an epiphenomenon caused by a chronic distorted input in "susceptible" individuals. Secondly, pain is a topic that deserves further attention. Drawing did not provoke pain in the affected arm and patients did not feel hindered by the affected arm while drawing. However, the presence of spontaneous ongoing pain was not systematically

evaluated and it may be a confounder of our results. Thirdly, although all selected patients were free of RSD symptoms and complaints of the dominant right hand, it cannot completely be excluded that some form of subclinical RSD, undetectable by clinical examination, was present. Finally, it might be stated that our data have been influenced by psychopathology or even malingering. The literature on this this topic provides insufficient data to support the notion of psychopathology as a cause of RSD[39,40] and a history of psychiatric or psychological problems requiring treatment was an exclusion criterium in the present experiment. Furthermore, the standard deviations of all chosen parameters hardly differed between subjects and controls, which would be an unlikely finding in the case of malingering.

Conclusion

This experiment is one of the first attempts to compare kinematic aspects of motor processing between RSD patients and healthy control subjects. The fine motor performance of the unaffected hand of RSD patients clearly differed from the performance of healthy controls. The kinematic analysis seems to suggest that in chronic RSD, motor processing may be impaired at the level of movement implementation, not at the level of motor preprogramming. These findings might support cortical involvement as the end stage of a centralization process in chronic RSD. However, more research is needed to obtain better insight into the role of the disturbed sensory input in the control of movement in RSD patients. In future research, techniques such as functional magnetic resonance imaging or positron emission tomography may be helpful in establishing whether cortical structures are actually involved.

In 1939 Livingston argued that peripheral irritative lesions could trigger activity in the central nervous system "with an intrinsic momentum that continues when the peripheral excitatory cause is removed".[38] Sixty years later, clinical and experimental evidence supporting this view, is slowly emerging.

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Chapter 7

Pharmacologic treatment of Complex Regional Pain Syndrome 1: a conceptual framework

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Abstract

This article represents some elements for the construction of a conceptual framework for the pharmacologic treatment of Complex Regional Pain Syndrome 1 (CRPS1). Pharmacotherapy in CRPS 1 forms part of an individually tailored interdisciplinary treatment regimen. The aim of this treatment regimen is functional restoration. Pharmacotherapy may be needed when pain hinders achieving this aim. CRPS 1 is considered a neuropathic pain syndrome with three main aspects; (1) a prolonged regional inflammatory reaction, (2) peripheral sensitization and (3) central sensitization. In clinical evaluation these mechanisms are represented by (1) the classical inflammatory symptoms rubor, dolor, calor, tumor and functio laesa, (2) by stimulus independent pain and (3) by stimulus evoked pain. The underlying mechanisms are described in some detail and pharmacotherapeutic options are discussed. It is concluded that pharmacologic treatment in CRPS 1 may need polytherapy rather than monotherapy and should result from a careful clinical evaluation of the individual patient as the dominant mechanisms may vary across individual patients with different time profiles. The presented framework is crude and incomplete. Yet it is seems to be a necessary first step from a mainly empirical treatment paradigm towards more theory oriented treatment procedures.

Introduction

Reflex sympathetic dystrophy (RSD) is a pain syndrome associated with vasomotor and sudomotor abnormalities. In the past numerous names have been attributed to this syndrome, all sharing a lack of formal, standardized diagnostic criteria. In response to this problem the International Association for the Study of Pain (IASP) in 1994 introduced the term Complex Regional Pain Syndrome 1 (CRPS 1) (table 1).[1]

Table 1 IASP criteria for Complex Regional Pain Syndrome 1 (RSD)

1. The presence of an initiating noxious event, or a cause of immobilization.
2. Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event.
3. Evidence at some time of edema, changes is skin bloodflow, or abnormal sudomotor activity in the region of pain.
4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

Whereas the criteria 2-4 have to be satisfied, this is not the case for the presence of an initiating event. Atrophy (of hair, nails, and other soft tissues), alterations in hairgrowth, loss of joint mobility, impairment of motor function and sympathetically-maintained pain may be associated signs and symptoms but are not used for diagnosis.

These new diagnostic criteria are consensus based and have not yet been adequately validated.[2,3] Treatment regimens are highly variable and may include physical therapy, sympathetic nerve blocks, tricyclic antidepressants, opiates, anticonvulsives and psychological treatment.[4] Also, physical immobilization, such as with a cast or splint, is frequently used. Yet, animal and clinical studies demonstrate that immobilizing a limb may result in the development of CRPS 1 symptoms and signs.[5]
In a consensus meeting, aimed to counterbalance the heterogeneous approach of CRPS 1, it was stated that time contingent functional recovery through a measured pace should at all times be the ultimate goal of treatment.[6] It was stated that initially desensitization and overcoming fear of movement are important, allowing the limbs to be touched and the patient to start moving. This phase should be followed by isometric strengthening, stress loading techniques and general aerobic conditioning. The last step

should be aimed at complete functional recovery. Psychological management may be focused on overprotection, fear of movement, irrational inferences or psychiatric problems such as depression. If pain is a limiting factor in achieving progress, pharmacologic treatment is indicated. However, adequate guidelines for the choice of pharmacotherapy are still lacking. The present article describes a conceptual framework in which the mechanisms underlying pain in CRPS 1 are discussed in relation with pharmacologic treatment. Firstly, the pain in CRPS 1 is discussed in the context of the underlying mechanisms of neuropathatic pain. Secondly, clinical aspects of neuropathic pain are related to the underlying pain mechanisms. Finally, it will be discussed how the clinical evaluation of pain may guide pharmacotherapy in individual patients.

CRPS 1 as a neuropathic pain syndrome

Pain is a leading symptom in CRPS 1 and its treatment is underevaluated. [7] CRPS 1 has been categorized as a neuroimmune disorder with a genetic predisposition.[8] However, its actual cause remains obscure. When dealing with a pain syndrome "instead of emphasizing or categorizing the patient primarily or exclusively on the diagnosis of the primary disease, an attempt should be made to identify the mechanisms responsible for pain".[9] The relation between the etiology of pain, its mechanisms and presenting symptoms is very complex. Diseases of different etiologies may have common pain mechanisms, a single mechanism may explain different symptoms and, furthermore, a similar symptom in separate patients may be caused by different mechanisms.[10] The capacity to experience pain has a protective role: it warns us of tissue damage and elicits behavioral responses that may limit the damage to a minimum. However, persistent pain syndromes do not offer such biological advantage. Neuropathic pain is initiated or caused by a primary lesion *or dysfunction* in the nervous system and forms a well known example of a pain state that may become persistent.[1,10] Normal sensory function depends on a critical equilibrium between neurons and their environment and any disruption of this equilibrium can initiate profound changes in sensory function. Per definition neuropathic pain in CRPS 1 is not determined by an anatomical lesion in a nerve, since in the case of an injured nerve the diagnosis CRPS 2 is appropriate.[1] In CRPS 1 functional alterations in the complex interactions between neurons and their environment seem to play a pivotal role. The complex

interplay of primary afferents, spinal cord neurons and sympathetic efferents are reviewed and discussed in the context of the clinical evaluation of neuropathic pain.

Peripheral sensitization

Noxious messages arise from free unmyelinated terminal arborisations in cutaneous, muscular and joint tissues. Some of these fibers specifically act as nociceptors and various types have been identified, such as polymodal nociceptors (responsive to thermal, mechanical, and chemical stimuli), Aδ mechanothermal nociceptors and high threshold Aδ mechanoreceptors.[11] Others are activated by non-noxious stimuli with increasing activity as the intensity of the stimulus increases. The sensitivity of this complex and heteromodal peripheral terminal of afferents is not fixed.[12] Under pathological conditions, such as in inflammation, the responsiveness of the primary afferents may increase (peripheral sensitization). Although a direct verification of an inflammation in the classical sense has not yet been established, an excessive inflammatory response in CRPS 1 has been suggested.[13-17] Preclinical evidence of neuroimmune interactions in peripheral sensitization has been established mainly in cases of axons with anatomical lesions. However, recently neuroimmune interactions have been demonstrated in an animal model without such a lesion, which is more alike the model of CRPS 1.[18] A wide variety of chemical mediators present in the "inflammatory soup" surrounding the primary afferents, are involved in this process.[19] These mediators are of vascular origin or are produced by the damaged tissue, afferent fibers themselves, sympathetic fibers and various immune cells. The reactive oxygen species (ROS), such as hydrogen peroxide, superoxide and hydroxyl species, may cause oxidative stress and enhance the effects of other inflammatory mediators such as bradykinin and prostaglandin.[20,21,22] Nitric oxide (NO), another reactive molecule with pro-inflammatory actions, may contribute to ectopic discharges in primary afferents. These and many other mediators (such as protons, kinins, prostanoids, serotonin, histamine and adenosine triphosphate) take part in a series of responses that cause changes in local bloodflow, vascular permeability, activation and migration of immune cells as well as in changes in the release of growth and trophic factors from surrounding tissue. These processes induce a state of hyperexcitability causing local defense mechanisms and contributing to the prevention of (re-)traumatisation. Several ion channels may be involved in this state of hyperexcitability. Sodium channels, especially the one ones insensitive to tetradotoxin,

calcium channels and the capsaicin or vanilloid receptor are the most prominent ones.[23-26]

Central sensitization

In addition to impuls generation and propagation, C fibers display axonal transport of chemicals such, as glutamate and substance P, that mediate an increased responsiveness of dorsal horn neurons to all forms of input (central sensitization). Especially the N-methyl-D-aspartate (NMDA) receptor is important in this process.[27,28,29] A change in phenotype and anatomy of afferents may also contribute to the increased sensitivity of spinal cord neurons.[30] In the case of inflammation Aβ fibers start expressing substance P and calcitonine gene-related peptide. These transmitters are involved in central sensitization and are normally only produced by C and Aδ fibers in transmitting nociceptive signals. Via this route non-noxious stimuli may start contributing to central sensitization. Furthermore, sprouted Aβ fibers invade lamina II where they interact with neurons that normally receive nociceptor input via C fibers. The sprouting causes lamina II to start receiving non-noxious stimuli, offering an anatomical substrate in which non-noxious stimuli may be misinterpreted as noxious.

Sympathetically maintained pain

For long pain relief after sympathectomy was considered pathognomonic for CRPS 1 and sympathectomies have been used as diagnostic tests and were considered first-choice treatment.[31] Nowadays, the pivotal role of sympathetic vasoconstrictor hyperactivity in regional vasomotor and sudomotor abnormalities in CRPS 1 is questioned.[32,33,34] Nevertheless, the contribution of the sympathetic nervous system to neuropathic pain is under constant review. Under pathological conditions activity in the sympathetic neurons may or may not generate pain, sympathetically maintained pain (SMP) or sympathetically independent pain (SIP).[35,36] Almost any type of pain disorder, such as phantom pain, metabolic neuropathies, herpes zoster and also CRPS 1, may manifest with elements of SMP or SIP. Pain may be mixed SMP and SIP and the relative contribution of SMP may vary over time. Animal models with partially lesioned nerves have revealed several mechanisms that may explain how sympathetic discharge may lead to neuropathic pain. These include the sprouting of sympathetic efferents to the axons and dorsal root ganglia of the primary afferents (basketformation) and the expression of α adrenoreceptors on injured and uninjured axons.[37] Sympathetic

outflow also triggers depolarization of uninjured C fibers, however only when these afferents are embedded in an inflamed skin.[38,39,40] Furthermore, activated α-2 adrenergic autoreceptors on the sympathetic terminal evoke the synthesis of prostaglandin, involved in the sensitization of the C afferents.[41,42] The responsiveness of C afferents to sympathetic outflow is to be considered physiological and should subside when the inflammation subsides. The pathology (SMP) appears when the inflammation persists or when the adrenergic responsiveness does not disappear.[43]

How the mechanisms of neuropathic pain relate to the symptoms

As discussed, multiple mechanisms underlying pain may operate at different sites simultaneously or on different time scales. It is the clinician's challenge to identify the mechanisms operating in an individual patient and to target treatment to them. Woolf and co-workers have developed a preliminary framework in which two clinically identifiable aspects of neuropathic pain are related to the mechanisms discussed above.[9,10]

Stimulus-independent pain

An inflammatory reaction may cause functional and even phenotypical changes in primary afferents resulting in altered discharge patterns (peripheral sensitization). Spontaneous depolarization of primary afferents, independent of any sensory stimulus, is a key characteristic of peripheral sensitization. In C fibers this may cause persistent burning pain, in Aδ afferents a sharp lancinating pain and in Aβ fibers, normally signalling non-noxious stimuli, a dysesthetic tingling sensation.

Spontaneous activity of sensory neurons may depend on several mechanisms. Firstly, an accumulation or activation of specific ion channels (sodium, calcium and the vanniloid receptor). Secondly, SMP may be a component of stimulus-independent pain. A decreased inhibitory input at a spinal level may be a third contributor to stimulus-independent pain. Descending control of pain is manifested via pathways that originate at the level of the cortex, the thalamus and the brainstem.[44] Serotonin, noradrenaline, gamma-aminobutyric acid (GABA) and the endogenous opiods are the main transmitters that are involved in the descending modulation of pain.

Stimulus-evoked pain

In physiological conditions pain is only elicited by intense mechanical, thermal, or chemical stimuli. In pathological conditions a state of an exaggerated sensitivity to mechanical, thermal or chemical stimuli occurs with two key features: hyperalgesia and allodynia.[10] Hyperalgesia is an increased pain response to what would normally be a suprathreshold noxious stimulus and results from abnormal processing of nociceptor input. Allodynia is a pain response caused by what would normally be a non-noxious stimulus. Allodynia can be caused both by decreased thresholds of peripheral C afferents, as in pheripheral sensitization, and by a state of hyperexcitability in the dorsal horn of the spinal cord, as in central sensitization. Since these two different causes of allodynia cannot be distinguished clinically assessing allodynia does not contribute to target treatment to peripheral or central sensitization. Hyperalgesia on the other part, represents an NMDA mediated state of hyperexcitability with increased responses of dorsal horn neurons to peripheral stimuli (central sensitization). It is characterized by tactile or dynamic hyperalgesia, cold hyperalgesia and pin prick hyperalgesia and may manifest in three ways: enlargement of the area in the periphery where a stimulus will activate neurons, increased responses to suprathreshold stimuli, and previously subthreshold inputs that initiate action potentials.

Clinical implications

A prolonged regional inflammation may underly neuropathic pain by inducing peripheral and central sensitization. Pharmacologic treatment of neuropathic pain may therefore be aimed at the regional inflammation, at peripheral and central sensitization.[45] Since these aspects of neuropathic pain may be present in each patient in a unique individual mix and with different time profiles individually tailored treatment regimens are required.

Regional inflammatory reaction

The presence of neuroimmune interactions suggests that neuropathic pain might be responsive to immunosuppressive therapy. Indeed, there is some preclinical evidence with cyclosporine, thalidomide and methotrexate, that supports this argument.[43,46] Immunosuppressives are not used in the clinical management of neuropathic pain, although other drugs are used to

treat the inflammatory symptoms of CRPS 1 such as non-steroid-anti-inflammatory drugs (NSAIDs), corticosteroids and free radical scavengers. In a recent critical review on controlled clinical trials in CRPS, oral corticosteroids proved to be the only drug effective with long term result.[47] A similar result was obtained in a systematic review on treatment of post-stroke shoulder hand syndrome, often associated with CRPS 1.[48] Furthermore, corticosteroids are known to relieve neuropathic pain in animal models.[43] Corticosteroids may be administered systemically as oral prednisolone or injected locally as soluble dexamethasone and methylprednisolone with lidocaine in the affected area, similar to a Bier's block.[45] Fluorinated corticosteroids such as triamcinolone or dexamathasone are reported to have an increased risk of severe muscle wasting, and methylprednisolone is thus probably preferable.[49] A well accepted regimen on oral steroids in CRPS 1 is lacking. Kozin and co-workers evaluated a regimen using enteric-coated prednisolone 15 to 20 milligrams on a 6 hourly basis during 4 days building down in maximally four weeks to finally 5 milligrams once daily after wich treatment is discontinued.[50] This schema is still frequently used in daily clinical practice. NSAIDs share the ability to inhibit the cyclooxygenase-mediated synthesis of prostaglandins. Prostaglandins are important mediators of inflammatory hyperalgesia, which may explain the anti-inflammatory effects of NSAIDs.[19] Besides the peripheral anti-inflammatary action of NSAIDs, an analgesic action by blocking spinal nociceptive processing has been emphasized.[51] However, the results of NSAIDs in several neuropathic pain trials are mixed and studies in CRPS 1 are still lacking. In a scintigraphic study Rico and co-workers compared the course of CRPS 1 in a treatment regimen with NSAIDs to one with calcitonin and calcium.[52] In their study NSAIDs failed to show any effect. The IASP consensus report states that NSAIDs should be considered especially when treating the early manifestation of the inflammatory signs of CRPS 1.[6] ROS are known to be involved in inflammatory processes and are suggested to cause oxydative stress in CRPS 1. Studies on the scavangers dimethylsulfoxide (DMSO) and vitamin C seem to support this hypothesis.[53,54] In a randomized clinical trial (RCT) DMSO 50% in a fatty cream significantly reduced inflammatory symptoms in CRPS 1 patients without contributing to pain relief.[53] Another RCT suggests that the prophylactic administration of vitamin C reduces the frequency of CRPS 1 after a wrist fracture.[54]

Stimulus independent pain

When pain is stimulus independent pharmacologic treatment should be aimed at the mechanisms underlying peripheral sensitization. Ion channel blockers, sympathectomy or drugs that facilitate spinal inhibitory mechanisms such as opiates and clonidine may be used.[55] Also sodium channel blockers, such as local anesthetics, tricyclic antidepressants (TCAs), antiarythmic and antiepileptic drugs, are commonly used in neuropathic pain. TCAs are the first drugs proven effective in neuropathatic pain.[56] They are not only potent sodium channel blockers, but may also act as NMDA receptor blockers and some have sympatholythic effects. However, TCAs are also well known because of their side-effects so that a careful monitoring of the patient is necessary. The newer antidepressents, such as the serotonin-selective re-uptake blockers, have a more favorable side effect profile but lack experimental support as analgesics in neuropathic pain.[55] They may stimulate the descending modulatory pathays in the spinal cord. Nerve conduction blocks with local anesthetics, such as in brachial plexus anesthesia, do not only block nociceptive signals but also central sensitization, as they stop chemical signalling.[57] Inadequate anchoring of the catheter, infections at the insertion site and phrenic blocks are complications of continuous brachial plexus anesthesia. In this perspective the topical application of lidocaine with patches might be considered in CRPS 1. The effectiveness of lidocaine patches has been demonstrated in post herpetic neuralgia.[55] Although treatment with lidocaine patches in post herpetic neuralgia is approved by the Food and Drug Administration, it has not been studied in CRPS 1. Anticonvulsives are frequently used in neuropathic pain, e.g. carbamazepine because of its sodium channel blocking effects and valproic acid because of its GABAergic (gamma-amino butyric acid) effect on neurotransmission and its effect on levels of excitatory amino acids in the brain.[55] The novel anticonvulsant gabapentin, a blocker of the voltage gated calcium channel in the terminals of the primary afferents, is frequently used in neuropathic pain syndromes.[24,58] Its effectiveness in CRPS 1 has been described in a case study.[59] However, a recent systematic review in the Cochrane database demonstrated surprisingly few trials showing analgesic effectiveness of anticonvulsives in neuropathic pain.[60] Finally, the capsaicin or vanniloid recepter may serve as a possible target for ion channel blockade. When activated it allows calcium influx and consequently depolarization and the release of neuropeptides that are involved in a neurogenic inflammatory process.[25] The vanniloid receptor is activated by capsaicin. However, repeated application of capsaicin blocks both the nociptive afference as well as the release

of neurogenic inflammatory mediaters. A meta analysis on five studies on the topical application of capsaicin (three in diabetic neuropathy and two in post herpetic neuralgia) demonstrated a significant effect.[47] Case studies support its potential use in CRPS 1.[26] Sympathectomy in CRPS 1 remains a controversial subject. In a double blind comparison of the effectiveness of guanethidine, reserpine and normal saline no significant differences in pain relief in the three groups were observed. It was suggested that a tourniquet-induced analgesia was at the basis of this finding.[61] A meta-analysis showed poor outcome with sympathectomies.[47] Alternatives to regional intravenous treatments with substances mimicking guanethidine have been studied. A RCT comparing bretylium in combination with lidocaine to lidocaine alone demonstrated a significant effect on pain relief and baseline temperature.[62] Droperidol proved ineffective and caused serious side effects.[63] The intravenous administration of phentolamine, an α-adrenergic blocking agent, may predict whether a SMP component is present in CRPS 1 and thus if sympathectomy should be considered.[64] Serotonin is involved in autonomic transmission and the serotonergic antagonist ketanserin is reported effective, even in treating CRPS 1 patients in a chronic stage.[65] There is some evidence to support that the efficacy of ketanserin may be improved when combined with carnitine.[66] Carnitine, involved in the oxydation of long chain fatty acids in the mitochondrial matrix, is thought to effect the cellular metabolism. Reduced inhibitory inputs, from the spinal cord or descending from the brain, may also be involved in spontaneous pain. Opiates, gabapentin, tricyclic antidepressants, GABA-enhancing drugs or drugs such as clonidine that mimic descending inhibition may be useful in augmenting central inhibition.[67] Intrathecal clonidine alleviates allodynia in neuropathic rats and its use has been described in CRPS 1.[68,69] Clonidine has also been administered transdermally with patches in diabetic polyneuropathy and orally in post herpetic neuralgia. Until now, its effectiveness has not been convincingly demonstrated.[47] The intrathecal administration of a mixture of clonidine and morphine proved more effective than either drug alone in neuropathic pain after spinal cord injury.[70] Effective long term treatment with intrathecal morphine alone has been reported in two cases of CRPS 1.[71] However, the role of opioids in neuropathic pain remains controversial.[47,72]

Stimulus-evoked pain

When pain is stimulus-evoked treatment should be aimed at central sensitization. In this case opioid analgia may possibly be enhanced

when combined with NMDA antagonists.[73] NMDA receptors are involved in central sensitization and several studies report of the analgesic effects of clinically available NMDA receptor antagonists, such as ketamine and amantadine.[28,29,74,75] NMDA receptors are widely distributed throughout the central nervous system and their antagonists are known for side effects such as hallucinations, vivid dreaming, auditory and visual disturbances. The side effect profile of amantadine is better than ketamine and long term effects of amantadine, lasting beyond the drug presence in body tissues, have been described.[28,76]

Conclusion

Pharmacotherapy forms only one aspect of an individually tailored multidisciplinary treatment regimen in CRPS 1 and depends on the signs and symptoms present in an individual patient. Poly- rather than monotherapy is needed, e.g. aimed at peripheral sensitization with sodium channel blockers and at augmenting inhibitory modulation with opiates. It is highly unlikely that a single "magic bullet" will do the job. Operational criteria for determining which patient may profit from what (combination of) therapeutical intervention(s), are lacking. The present conceptual framework focuses on a prolonged regional inflammation, and on stimulus dependent and independent pain. The mechanisms involved are highly complex with transmitters and receptors widely distributed throughout the nervous system, involved in multiple physiological functions that have been studied mainly in animal or laboratory models.[77] The clinical diagnostic tools to identify pain mechanisms in an individual patient are limited and, finally, available drugs are of a limited specificity and may have various side effects. Therefore the presented framework is incomplete and may serve only as a startingpoint for formulating a more rational pharmacologic treatment of CRPS 1. Nevertheless, if the gap between basic pain science and clinical pain management in CRPS 1 is ever to be bridged, the approach in which clinical aspects of pain are related to the underlying mechanisms is necessary. This will need an intense and ongoing collaboration between clinicians, preclinical and clinical researchers.

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Chapter 8
Conclusion

The complex regional pain syndrome (CRPS) type 1 presents as an amplified response to injury or immobilization with somatic, sympathetic and motor disregulations. Per definition CRPS 1 can not be related to nerve injury, whereas in CRPS 2 major peripheral nerve injury is identifiable. The clinical characteristics in both types of CRPS are similar.[1] Diagnostic criteria for CRPS 1 have been subject of debate since long. The latest criteria of CRPS 1 were formulated in a consensus meeting of the International Association for the Study of Pain in 1994 and are based on symptoms (subjective phenomena reported by the patient) and signs (phenomena observed by the examiner) concerning sensory changes such hyperesthesia and allodynia, vasomotor and sudomotor disorders, trophic changes and motor impairments. Laboratory testing may be used to monitor progress but does not contribute to the diagnosis.[2] CRPS 1 is a diagnosis of exclusion. Septic arthritis, acute trauma, insect bite, local allergy, factitious disorders, chronic vascular insufficiency (e.g. Raynaud's syndrome, scleroderma) all belong to its differential diagnosis. Substantial data that support the existence of three phases –acute, dystrophic and atrophic- are lacking and so is insight in its cause and therapy of choice. The advances of academic medicine in the past 200 years for a large part can be attributed to the insistence on identifying clearly defined causes for each disease. Yet, in many pain conditions e.g. trigeminal neuralgia, headache, backache and myofascial pain syndromes, causes remain obscure.[3] CRPS 1 is one of them. Diligent research on pathophysiological mechanisms is being performed but has not provided definite answers as to etiology or therapy. Some state that when there is no cause there is no disease and target the mind.[4] The importance of behavioral and emotional issues in chronic pain is undisputed but there is hardly any support for the concept of CRPS 1 as a psychiatric disorder or as a manifestation of malingering. Others point to the dynamic, interactive mechanisms involved in nociception.[5] These mechanisms may vary in time and in location, from the affected extremity to the spinal cord and supraspinal structures. The highly complex interactions between the somatic and autonomic nervous systems and local tissue factors are being unraveled at a high pace and insight is gained in the mechanisms underlying neuroplastic reactions in the spinal cord as well as in supraspinal structures.
However, the concept of CRPS 1 as a heteromodal syndrome involving the affected extremity as well as spinal and supraspinal

structures and with profound psychological consequences does not solve the problem of determining what patient may profit from what treament. As such, CRPS 1 remains a mystical concept, not related to a specific cause or treatment. Future research should aim to differentiate CRPS 1 in subsyndromes with specific pathophysiologic signatures and relate them to therapeutic interventions.[4]

The treatment of CRPS 1 should be aimed at functional restoration and may involve physical and occupational therapy and psychological counseling.[6] Pain treatment should be a pillar when pain hinders functional progress. The model of neuropathic pain may prove useful in targeting pharmalogic treatment of pain in CRPS 1. However, models on pain are often based on behavioral tests in which noxious stimuli are applied to healthy animals or on studies with transgenic mice with specific genes knocked out thus deleting receptors, channels or transmitters. These models do not necessarily reflect chronic pain states in humans. Furthermore, the transmitters, channels and receptors studied may be widely distributed throughout the nervous system and more than one neurotransmitter may be co-localized in a single neuron. Drugs may have a low specificity causing multiple side effects. Progress made in basic pain research therefore is not easily transfered to clinical pain management.[7] Nevertheless it may be concluded that polytherapy may be needed rather than monotherapy and it seems paramount to develop an approach in which treatment is targeted to the mechanisms underlying the pain in an individual patient at a specific moment.

Another major issue is the dilemma of rest versus movement in treating CRPS 1. Traditional approaches in medicine have been to promote rest in harmful conditions such as low back pain, soft tissue injuries and arthritis. However, rest seems to hamper healing.[8] Immobilization with plaster cast in a healthy individual may cause signs and symptoms of CRPS 1 and affects somatosensory representations in the cortex.[9] Nowadays exercise is being promoted after soft tissue injuries, in low back pain programs and following orthopedic procedures. In patients with active rheumatoid arthritis intensive exercise is effective in improving physical functioning.[10] The literature on CRPS 1 tends to agree that avoidance of activity and of tactile stimulation should be prevented as early as possible. Some promote a 'with pain no gain protocol', considering pain in CRPS 1 to result from disturbed oxygen

extraction.[11] Substantial experimental data to back up either one of these approaches are lacking. However, a treatment regimen solely dictated by subjective pain experience may easily enhance a chronic pain problem.

The clinical management of CRPS 1 and fundamental pain research are diverging. It seems no longer possible for the clinician to keep up an up to date critical knowledge of all the scientific disciplines which contribute to this highly specialised field. On the other hand, due the increasing complexity of scientific techniques basic scientists may lose sight on patient-oriented research.[12] A prolonged and intense collaboration between clinicians, clinical and basic researchers seems paramount to bridge this gap aiming at a more theory driven approach of CRPS 1 and to counteract the heterogeneity in its clinical management.

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Summary

This thesis is composed of a series of articles on Reflex Sympathetic Dystrophy (RSD) or Complex Regional Pain Syndrome type 1 (CRPS 1) as it was renamed by the International Association for the Study of Pain in 1994. The common theme is the concept of CRPS 1 as a neuropathic pain syndrome and as such as a heteromodal clinical problem of unknown origin in which predominant mechanisms may vary in time and location, involving the affected extremity but also spinal and suprapspinal structures.

Chapter 2 is a review of the literature on CRPS 1, in particular on chronic pain and motor impairments. In the acute stage a regional inflammatory reaction may predominate, whereas in later stages a shift to spinal and supraspinal structures seems to take place. This may be an essential factor in the development and maintenance of both pain and motor impairments. It is concluded that better insight into the mechanisms underlying the chronic pain and motor impairments in CRPS 1 is essential, both for preventing disabilities and for developing rehabilitation strategies during the more chronic stages.

Despite the fact that a prolonged regional inflammatory reaction may initiate CRPS 1, quantitative data on immune system function are scarcely published. **Chapter 3** is a descriptive study on this topic. Blood samples were obtained from 13 patients and from a randomly selected control group of 21 healthy individuals. The lymphocyte populations (T, B, NK cells), and the activated T cells (CD25, and HLA-DR positive CD4 and CD8 cells) were analysed by flow-cytometry with dual colour direct immunofluorescence after whole-blood lysis. Furthermore, clinical chemistry parameters were analysed in additional serum samples. The flow cytometry analysis did not differ between patients and healthy controls. Although in some patients an individual parameter of clinical chemical analysis differed from its reference value, all of the mean values were within reference limits. Possibly a regional inflammatory reaction is not reflected systemically. On the other hand however, caution is required in extrapolating experimental findings in cultured cells to the *in vivo* situation.

Secondary to a regional inflammatory reaction a cascade of events may take place. Primary and spinal afferents may become sensitized contributing to a neuropathic pain syndrome and motor disorders such as tremor and spasms may develop. To prevent chronicity, targeting treatment to neuropathic pain should be a pillar when dealing with CRPS 1.

Chapter 4 is a case study on a multitrauma patient with CRPS 1 of the left foreleg that hindered mobilization. A treatment regimen combining topical capsaicin 0.075% and a stress loading mobilization scheme proved to be successful. The topical application of capsaicin provokes burning pain, pricking and itching and a flare response. However, with repeated application a loss of responsiveness of primary afferents to stimuli occurs. This desensitization effect is attributed to an increased calcium ion influx and to a loss of epidermal nerve fibers. As such it is used and documented in treating neuropathic pain states such as postherpethic neuralgia. Topical capsaicin may provide a theory driven treatment modality in CRPS 1 that facilitates physical therapy and may prevent sensitization of primary afferents and spinal neurons.

In **chapter 5** Brachial Plexus Blockade (BPB) is applied in patients with severe CRPS 1 of an upper extremity in varying stages. The treatment took place in the interdisciplinary setting of an outpatient rehabilitation clinic with a follow-up of 12 to 21 months. Four patients responded well. In one of them the initial effect was good but due to an infection at the insertion site of the catheter, BPB had to be discontinued. In these cases the treatment interval varied from 3 to 6 months. One patient suffered from CRPS 1 with predominant inflammatory symptoms and in the others dystrophic symptoms were prominent. Two patients showed poor response. They had treatment intervals of 7 and 25 months, and presented with cold extremities with marked atrophy. It is discussed that BPB may improve functional outcome in CRPS 1, especially when instituted in the early stages, by facilitating physical therapy and by the prevention of peripheral and central sensitization.

The interplay between primary afferents, intrinsic spinal cord neurons and descending fibers determines the relation between the peripheral stimulus and the response. The processes of peripheral and central sensitization illustrate that this interplay is not static but

dynamic. In **Chapter 6** it is explored whether the dynamic interplay of neuronal mechanisms contributes to motor impairments in CRPS 1. Motor processing is compared between CRPS 1 patients and healthy control subjects. In an experimental two-group analysis the kinematic features of drawing tasks of five patients with chronic CRPS 1 of the left forearm and free of symptoms and complaints of the dominant right forearm and 10 healthy control subjects were compared. The results suggest that patients with chronic CRPS 1 have a normal ability to preprogram sequential movements of the unaffected hand, however, with impaired temporospatial coding and slower movement execution. It is concluded that supraspinal mechanisms may contribute to motor impairments in CRPS 1 patients. The assumption is that a chronic distorted input may cause neuroplastic reactions in neural networks involved in supraspinal motor processing.

The treatment of neuropathic pain in CRPS 1 therefore is important to facilitate physical therapy, to prevent peripheral and central sensitization and possibly to prevent motor impairments. However, experimental data to guide pharmacotherapeutic choices are scarce and consensus on prefered treatment regimens is lacking. **Chapter 7** represents a conceptual framework for the pharmacologic treatment of CRPS 1. The mechanisms underlying a prolonged regional inflammatory reaction, peripheral sensitization and central sensitization are discussed and related to the clinical evaluation of the patient. As such, findings from physical examination are related to pathophysiological mechanisms and to pharmacologic treatment. The presented model, although preliminary and still incomplete, is a theoretical basis to predict what patient may benefit from what treatment.

In **chapter 8** it is concluded that a large gap exists between basic pain science and the clinical management of CRPS 1. Not only local metabolic processes in the affected extremity determine the clinical picture of CRPS 1, but also functional and structural changes in spinal and supraspinal neural networks. However, this concept of CRPS 1 does not contribute to determine what patient may profit from what combination of therapy. As such, future research should aim to differentiate CRPS 1 in subsyndromes with specific pathophysiologic signatures and relate them to treatment regimens.

Samenvatting

Dit proefschrift is samengesteld uit een reeks van publicaties over Posttraumatische Dystrofie, het syndroom waarvoor in 1994 door de International Association for the Study of Pain (IASP) de term Complex Regionaal Pijn Syndroom (CRPS) type 1 werd geïntroduceerd. De rode draad in deze artikelen is dat CRPS 1 beschouwd wordt als een neuropathisch pijnsyndroom waarvan de oorzaak onbekend is en waarvan de onderliggende mechanismen kunnen variëren zowel in tijd als in locatie. Hierbij is niet alleen de aangedane extremiteit betrokken. Ook spinale en supraspinale mechanismen kunnen een rol spelen.

Hoofdstuk 2 is een literatuuronderzoek naar CRPS 1, met name gericht op chronische pijn en motorische stoornissen. Beschreven wordt dat de onderliggende mechanismen kunnen veranderen in de tijd. In het acute stadium lijkt een ontsteking in de aangedane extremiteit een rol te spelen terwijl in latere stadia spinale en mogelijk supraspinale structuren betrokken zijn, waarvoor de term centralisatie geïntroduceerd wordt. Hierbij kan sprake zijn van een verhoogde prikkelbaarheid van primaire afferenten en van neuronen in het centraal zenuwstelsel. Zowel functionele als neuroplastische veranderingen kunnen hieraan ten grondslag liggen. Besproken wordt dat deze mechanismen mogelijk bijdragen aan het ontstaan van een chronisch pijnsyndroom en aan motorische stoornissen.
In **hoofdstuk 3** wordt ingegaan op de ontstekingsreactie die verondersteld wordt in de zogenaamde "warme fase" van CRPS 1. Hoewel laboratorium onderzoek met *in vitro* celculturen en, in mindere mate, patiëntgebonden onderzoek de ontstekingstheorie ondersteunen, blijken kwantitatieve gegevens over immunologische parameters bij patiënten spaarzaam beschreven. In deze studie worden de lymfocytenpopulaties (T, B en NK cellen), de geactiveerde T cellen (CD25 en HLA-DR positieve CD4 en CD8 cellen) en aspecifieke ontstekingsparameters vergeleken tussen een groep van CRPS 1 patiënten en gezonde proefpersonen. Er werden geen verschillen gevonden. Enerzijds kan het zo zijn dat een lokaal proces niet te herleiden is uit systemisch gemeten parameters. Anderzijds wordt benadrukt dat onderzoeksresultaten uit *in vitro* onderzoek niet zondermeer vertaalbaar zijn naar de *in vivo* situatie.
Neuropathische pijn wordt door de IASP gedefinieerd als pijn die wordt veroorzaakt door een primaire laesie of *disfunctie* van het zenuwstelsel. Bij CRPS 1 liggen functionele en structurele veranderingen in primaire afferenten en centrale neuronen aan de

basis van een verhoogde gevoeligheid voor chemische, thermische en mechanische stimuli. Daarom kan CRPS 1 als een neuropathisch pijnsyndroom gezien worden. In dit kader zou de behandeling van pijn een fundament van de behandeling van CRPS 1 behoren te zijn.

Hoofdstuk 4 is de beschrijving van een multitraumapatiënt die met succes werd behandeld met capsicaïnecreme 0.075% vanwege CRPS 1 van het onderbeen. De patiënt doorliep een oefenprogramma met opbouwende belasting op geleide van het klinisch beeld. De lokale behandeling met capsicaïne is onder andere beschreven bij postherpetische neuralgie en slechts sporadisch bij CRPS 1. Het veroorzaakt een brandende pijn, jeuk en lokale hyperaemie. Echter bij herhaalde toediening treedt desensibilisatie op. Dit wordt toegeschreven aan een verhoogde influx van calciumionen en het verdwijnen van epidermale afferenten. De verlaagde pijnervaring faciliteert actieve oefentherapie en voorkomt sensibilisatie van primaire afferenten en spinale neuronen.

In **hoofdstuk 5** wordt een zestal patiënten beschreven bij wie de nociceptieve afferentie werd geblokkeerd door middel van een plexus brachialis anesthesie met bupivacaïne. Allen ondergingen poliklinische revalidatiebehandeling en werden belemmerd in actieve en passieve oefentherapie door pijnklachten. Vier patiënten reageerden goed, echter bij een patiënt moest de behandeling gestaakt worden vanwege een ontsteking ter plaatse van de insteekopening van de catheter. Bij twee patiënten had de behandeling geen bevredigend resultaat. Beiden hadden een koude extremiteit met contracturen en atrofie. Besproken wordt dat plexus brachialis anesthesie kan bijdragen aan een multidisciplinaire behandeling van CRPS 1 doordat de toegankelijkheid voor oefentherapie toeneemt en, indien vroegtijdig gestart, door het voorkomen van perifere en centrale sensibilisatie.

De interactie tussen primaire afferenten, intrinsieke en descenderende neuronen in het ruggenmerg bepaalt de relatie tussen de stimulus en de respons. Deze relatie is dynamisch en is van belang bij neuropathische pijn. In **hoofdstuk 6** wordt onderzocht of het dynamisch karakter van de interactie tussen primaire afferenten en neuronen in het centraal zenuwstelsel (mede) een rol speelt bij de motorische stoornissen die op kunnen treden bij CRPS 1. Het betreft een experimentele studie waarin een kinematische analyse plaatsvindt van tekentaken verricht met de niet-aangedane dominante hand door CRPS 1 patiënten in vergelijking met gezonde proefpersonen. De analyse richt zich op die variabelen die gerelateerd zijn aan supraspinale motorische sturingsprocessen. Vergeleken met gezonde proefpersonen lijken

CRPS 1 patiënten op een normale wijze bewegingssequenties te kunnen preprogrammeren, echter met een gestoorde temporospatiële bewegingscodering en trage bewegingsexecutie. Geconcludeerd wordt dat de motorische stoornissen bij CRPS 1 niet volledig verklaard kunnen worden uit lokale metabole processen en dat supraspinale mechanismen een rol kunnen spelen. Verondersteld wordt dat de chronisch veranderde afferentie neuroplastische reacties veroorzaakt in neurale netwerken betrokken in motorische sturingsprocessen.
De behandeling van pijn in CRPS 1 lijkt derhalve niet alleen van belang om actieve oefentherapie te faciliteren en om perifere en centrale sensibilisatie te voorkomen maar mogelijk ook ter preventie van motorische stoornissen. Echter er bestaat geen consensus over pijnbehandeling bij CRPS 1. In **hoofdstuk 7** wordt een theoretisch kader geschetst voor de farmacologische behandeling van pijn bij CRPS 1. De mechanismen die betrokken lijken te zijn bij de regionale ontstekingsreactie en bij perifere en centrale sensibilisatie worden beschreven en gerelateerd aan de klinische evaluatie van de patient. De bevindingen van het lichamelijk onderzoek worden dus gerelateerd aan onderliggende pathofysiologische mechanismen en daarmee aan de farmacologische behandeling. Dit model, hoewel voorlopig en incompleet, is een aanzet om tot een theorie gestuurd behandelplan voor een individuele patiënt te komen.
In **hoofdstuk 8** wordt geconcludeerd dat er een kloof bestaat tussen fundamenteel pijnonderzoek en de klinische behandeling van CRPS 1. Niet alleen lokale metabole stoornissen in de aangedane extremiteit lijken betrokken maar ook spinale en supraspinale structuren. Echter het model van CRPS 1 als een heteromodaal neuropathisch pijnsyndroom draagt niet bij aan het bepalen welke patiënt baat heeft van welke behandeling. Het lijkt noodzakelijk de syndroomdiagnose CRPS 1 verder te differentiëren in beelden die gerelateerd zijn pathofysiologische mechanismen.

Curriculum vitae

Gerard Ribbers was born on May 14, 1961 in Rotterdam. He graduated in 1979 from the "Hertog Jan College" in Valkenswaard. In 1980 he studied architecture at the Technical University in Eindhoven, and in 1981 and 1982 physical therapy at the Academy of Physical Therapy "West Brabant" in Breda. He continued his study at the medical faculty of the Katholic University of Nijmegen in 1982. During his study he worked as a research assistent at the department of Research and Development of the Sint Maartenskliniek in Nijmegen where Prof. dr. Th. Mulder infected him with his enthusiasm for research.
After receiving his medical degree in 1989 he worked at the department of neurosurgery at the Elisabeth Hospital in Tilburg. The traineeship in Physical Medicine and Rehabilitation (PM&R) started in 1991 at the Sint Maartenskliniek in Nijmegen (R.A.J. Rijken). During this time he was chairman of the "kerngroep revalidaticum" (a national forum for trainees in PM&R), guest speaker in several post academic teaching programmes, performed the experimental work that formed the fundaments of the present thesis and published his first articles. He was granted the "TOS-AGIO trophy" by the VRA (Dutch association for PM&R) in 1994.
Since 1995 he works at the Rehabilitation Center Rijndam, supervising a clinical ward for patients suffering from severe brain disorders and as chef of the clinical division. Furthermore, he is consultant for the "stichting Bureau Advies en Coördinatie Hersenaandoeningen" (a bureau for advice and coordination of short and long term consequences of brain disorders) and member of the "Samenwerkingsverband Onderzoek Revalidatie Rotterdam" (a board that stimulates and coordinates research activities of the Rehabililitation Center Rijndam Adriaanstichting and the Institute of Rehabilitation of the Erasmus University Medical Center Rotterdam).
Gerard Ribbers is married to Christianne Joossen. They have three children: Eva, Tessa and Pim.

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