A CRPS triptych : studies on diagnosis, pathogenesis and treatment of the Complex Regional Pain Syndrome

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A CRPS TRIPTYCH

**studies on diagnosis, pathogenesis and
treatment of the Complex Regional Pain
Syndrome**

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A CRPS TRIPTYCH

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and **treatment** of the
Complex Regional Pain Syndrome

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aan de Universiteit Maastricht
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“You are as healthy as you feel”
Robert de Niro, Taxi Driver

To my mother† and father

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Complex Regional Pain Syndrome, Pathogenesis, Diagnosis and Treatment

Introduction

This thesis focuses on the Complex Regional Pain Syndrome (CRPS), a neuropathic pain syndrome.

In recent years CRPS has gained considerable research interest: in the Netherlands, seven Ph.D. theses have been recently published on the subject by respectively Kurvers (1997), Geertzen(1999), van der Laan (1999), Oerlemans (1999), Kemler (2000), van de Beek (2001) en Ribbers (2001). Despite all research, CRPS or Reflex Sympathetic Dystrophy remains a controversial diagnosis.

This is also reflected in the great number of disciplines treating CRPS patients.

This introduction limits itself to describe the larger models and theories concerning the pathogenesis, diagnosis and treatment of CRPS. The following chapters are dedicated to studies in these three problem fields in CRPS.

DIAGNOSIS

The Diagnosis of Complex Regional Pain Syndrome.

'CRPS Type 1 is a syndrome that usually develops after an initiating noxious event, is not limited to the distribution of a single peripheral nerve, and is apparently disproportionate to the inciting event. It is associated at some point with evidence of edema, changes in skin blood flow, abnormal sudomotor activity in the region of the pain, or allodynia or hyperalgesia.'- *Definition of CRPS-I in IASP's 'Classification of Chronic Pain' by Merskey and Bogduk.*¹

Complex Regional Pain Syndrome is a consensus-based name for a complex of signs and symptoms, which should be present to an certain extent to meet this diagnosis. Its name and definition were established in 1993 by the leading pain organization the 'International Association for the Study of Pain (IASP).^{2,3} It was meant to replace other terms like Reflex Sympathetic Dystrophy (RSD) and causalgia, but this new terminology has not gained wide acceptance yet.⁴ RSD has no established neural damage in contrast to causalgia, but it is claimed that no essential differences can be found in its clinical presentation.⁵⁻⁷ The term causalgia was first described by Weir Mitchell in 1864, RSD by Evans in 1947.⁸ The term 'Sudecks' atrophy comes from a description of Sudeck in 1900 of acute post-traumatic atrophy of bone in the extremity.⁹

In the IASP terminology, RSD was renamed as CRPS type 1 and causalgia as CRPS type 2. Although the older names are still being used clinically and in scientific literature, CRPS will be used in this thesis.

Subtypes

CRPS has two official subtypes; CRPS type 1 and CRPS type 2.

The difference between the two is that CRPS type 2 patients have proven nerve damage. Boas proposed the addition of a third type of CRPS, in which there was idiopathic pain with some sensory, motor and autonomic dysfunction, but not enough to meet the criteria for CRPS type 1.³

Others noticed the existence of patients with one single affected limb and those with CRPS spread to more than one extremity. It is found that these *multiple CRPS* patients were younger and more often female, more often reported a difference in skin temperature between the diseased and the healthy opposite limb at the onset of symptoms and had less often upper extremity CRPS.^{10,11}

Multiple CRPS is associated with its own HLA subtype, HLA subtype association in single CRPS is described in chapter 5.¹²

Differential diagnosis

The differential diagnosis of CRPS is not well established. Until recently, no study has been published to unravel CRPS' s differential diagnosis. Clinical observations have resulted in a list of more or less rare diagnoses that are normally easily distinguishable from CRPS.

Tendosynovitis, lymphedema, atrophy of disuse, senile or postmenopausal osteoporosis, tuberculous or pyogenic osteomyelitis, peripheral neuritis, radiculitis, peripheral vascular disease, hysteria, and rheumatoid arthritis were already mentioned by Hartley in 1955.¹³ Boas added occupational overuse syndrome, tennis elbow, bursitis, nerve entrapment, myofascial pain syndrome and CRPS type III as potential differential diagnoses.³ Also neuropathies, root compression and polyneuropathies should be taken in

consideration.¹⁴ A rather unknown, but important differential diagnosis is erythromelalgia.¹⁵ Absences of common features such as sensory disturbances, inciting events, therapy resistance to NSAID's and edema, discoloration or pain that does not increase in intensity during exercise, increase the chance on existence of other pathology. Also, CRPS can be distinguished from many of aforementioned diagnoses by normal blood values, its acute start, and asymmetry in body distribution. If one focuses on CRPS differential diagnosis, one should not limit the discussion to these syndromes. One should also clarify the vague boundaries of CRPS. There are patients with enigmatic chronic pain syndromes who do not meet sufficient severity, duration or distribution criteria to provide a sound CRPS diagnosis.³ The question how to diagnose CRPS should be followed by the question how to diagnose the remaining 'CRPS-like' pain patients. Chapter 3 discusses the role of idiopathic pain and somatoform pain syndromes in the differential diagnosis in CRPS

Clinical tools in diagnosis

The IASP definition of CRPS may work well as an informative description, but it is an insufficient tool for diagnosing patients. It is both a clinical and research problem how to diagnose patients, as there are no pathognomic clinical or laboratory abnormalities in CRPS. Since diagnosis is difficult and subjective, no clear estimates on incidence and prevalence of CRPS are yet possible. In general, one can only say that dysfunction of the neural system seems to be present in CRPS, which may result in different and fluctuating signs like pain, edema, motor disorders, hypesthesia, hyperesthesia, changed skin color, changed perspiration, changed temperature, and changed blood flow in skin, muscle and bone. Different tests have been developed to quantify these changes, but none has succeeded to gain enough support to reach golden standard in diagnosis.¹⁶⁻²² None of these changes are consistently present through the different phases of CRPS or through the entire patient population.

Radiographic and bone scan tests

Sometimes bone demineralization can be manifest in CRPS, but it might as well be absent in either early or late phases. Sudeck reported osteoporosis in 1900 after X-ray examination in CRPS patients.⁹ Meanwhile three-phase scanning is well established in CRPS diagnosis, although there are contradictory reports on its validity.²³⁻²⁵ Especially in the chronic phase of CRPS, bone metabolism might normalize or even decrease.^{26,27} Different results are often found in children.²⁸ Interesting for future research can be Kozin et al's finding that a positive scintigraph might predict treatment outcomes. If this duality is also found in other clinical tools, possibly pain patients without positive scintigraphs resemble a different diagnostic group.²⁹ But until now, these results have not been reproduced.³⁰

Skin temperature and cutaneous blood flow tests

A subpopulation of CRPS patients does have abnormalities in temperature regulation.^{16,31,32} CRPS patients can be divided in primary warm and primary cold patients. Primary cold CRPS patients also appear to have a higher chance on refractory complaints or complications.^{10,33} Skin temperature measurement reveals problems of sensitivity and specificity, even if vasomotor tone was determined by measuring skin blood flow with laser Doppler flow meters and skin temperature by infrared thermometry.¹⁷ Disuse and inflammation can lead to temperature difference too. Healthy women in general have different vascular responses compared to men.³⁴ Also in CRPS patients changes over time have been found.^{35,36}

Sweat output tests

Sweat production is claimed to be important in diagnosing definite CRPS from controls.^{17,18,37,38}

Without doubt, 'sweat tests' can diagnose a subgroup in CRPS patients. But one can expect that there are CRPS patients without sweat symptoms. Therefore it is not yet possible to determine the final diagnostic value of sweat tests for the diagnosis of CRPS.³⁹

Therapy results of sympathetic blocks in CRPS patients did correlate with disturbed sweat output.⁴⁰

What this mean is yet unknown since sympathetic blocks are no longer considered effective in CRPS therapy.⁴¹

Histopathological findings

In several small studies disturbances were found pointing to perivascular inflammatory infiltration ⁴², increased neuropeptides ⁴³ and possible other signs of inflammation and oxidative stress ^{44,45} it has not resulted in diagnostic tests.

Criteria systems

In general, diagnostic criteria systems are developed to compensate the lack of unique symptoms in clinical syndromes. The vast amount of different possible combinations of signs and symptoms in CRPS and the change of signs during the different stages of the syndrome complicates the process of reaching consensus upon clinical criteria in the CRPS field. To achieve a more or less reliable diagnosis, criteria systems have been developed to weight the importance of the different CRPS signs and symptoms. The absence of consensus in scientific literature for these clinical criteria to diagnose CRPS, limits research in general and in specific the development of better diagnostic tests.³⁹

In recent years different criteria systems have been developed for RSD or CRPS (appendix I).

None of these were a result of scientific research, but all were based on clinical experience and consensus. Since no standard criteria exist in CRPS diagnosis, physicians and researchers can differ considerably in their judgment of possible CRPS patients. In the end, all differences in diagnosis can be summarized as 'how many signs and/or symptoms are needed to establish the diagnosis of CRPS?' Therefore, as long as there is no consensus, experienced based diagnosis in CRPS will not be valid (see chapter 2). Even if contemporary criteria systems are used in diagnosis, it appears that CRPS diagnosis is not a valid diagnosis.^{7,46,47}(see also chapter 2). To construct a reliable diagnostic system in CRPS, reliability of patient reports of symptoms and validity of signs in CRPS needs to be studied. Also, strategies of CRPS physicians to establish CRPS diagnosis and their differential diagnosis need to be clarified to find better ways to standardize and validate the CRPS diagnostic process.(see Chapter 2-4).

PATHOGENESIS

Sympathetic involvement

There is enough proof of changed blood flow in CRPS in skin, subcutis, muscles and bone ^{21,31,36,48,49}. This can explain the dystrophic aspect of many CRPS limbs. Increased sympathetic tone might change peripheral blood flow. This would explain why women are more prone to develop CRPS, since they have a different sympathetic tone compared to men. ³⁴

It was suggested in German scientific literature that people with vegetative vulnerability or 'sympathetic hyperreactors' were predisposed to CRPS ⁵⁰⁻⁵², but this model has not received many followers. Nevertheless, several authors have speculated about a central component in sympathetic dysfunction ^{49,53-56} and some even have found proof for central sympathetic dysfunction prior to the development of CRPS. ⁵⁷ More circumstantial evidence for a role of the central sympathetic system is that CRPS preceding events, such as post stroke hemiplegia, myocardial infarct and physical trauma might change sympathetic tone and therefore predispose to CRPS. A role for habitual smoking as a risk factor in CRPS could, although known for its sympathetic stimulating effect and decrease of cutaneous nutritious flow, has not been established. ^{58,59}

Figure 1. Possible pathogenetic process in CRPS

Leriche was the first to claim that trauma elicited an increased sympathetic vasomotor reflex.⁶⁰ This would result in ischemic pain, which might enhance vasomotor reflexes and therefore would initiate a vicious circle of ischemia and pain. Although at several stages this theory can be of value, its validity is limited, since CRPS pain is often not sensitive to anti-sympathetic treatment (especially post-ganglionic treatment by local perfusion) and seldom to vasodilatory treatment.⁶¹⁻⁶³ Relatively often though, CRPS pain is prone to increase by cold, dependency or emotional stress. This can be viewed as sympathetically dependent pain mechanisms. This sympathetic pain can physiologically be explained by trauma induced artificial synapses in the neural system between afferent sensory nerves and efferent sympathetic nerve fibers. These new synapses, also called ephapses, would increase nuncial interneuron activity.⁶⁴ Another substrate for sympathetic pain could be the impulses of the sympathetic strain leading to local vasoconstriction in the dorsal root ganglion. The reduced blood flow would lead to ectopic ganglionic impulses.⁶⁵ These ectopic impulses are suggested to play a role in the maintenance of neuropathic pain, paresthesias⁶⁶ and increase of the pain during cooling, dependency of the affected limb and increased emotions (figure 1). This would explain, that peripheral anti-sympathetic treatment with e.g., intravenous guanethedine has no proven effect and blocks of the paravertebrally located sympathetic ganglia clinically appear to have some, though yet insufficiently proven, pain reducing effect. With this last therapy though, transiently working local anesthetics are used, which also might have additional regional pain relieving effect. In line with this ganglionic theory of sympathetically maintained pain, Kurvers postulated that sympathetic impulses might be increased proximally, instead of distally, to the injury.⁶⁷ A vicious circle might exist in CRPS where acute pain in predisposed patients, causes reflex ganglionic ischemia, enhanced ectopic ganglionic impulses and therefore chronic pain. Breaking this circle might explain how in some patients a sympathetic block with local anesthetics can give prolonged pain relief extending the time expected based on immediate pharmacological action. Vulnerability to re-enter this vicious circle would remain and therefore would predict recurrence of CRPS in 'cured' patients. Animal research suggests that nerve damage might change adrenergic sensitivity by changed membrane properties of neurons in the dorsal root ganglion (DRG) and induced neuropathic pain can also be related to new connections formed between efferent sympathetic fibers and afferent sensory fibers.⁶⁸⁻⁷¹ These structural changes might also explain why in 'cured' CRPS patients chronic pain can return after a renewed minor trauma of the affected limb. Other animal research suggests that evoked excitations (in the peripheral terminal regions) and adrenergic receptor changes in DRG⁷² might explain why 'cured' patients can still have pain upon injection with noradrenalin in contrast to non CRPS patients.⁷³ It appears that many cured CRPS patients still have different neurophysiological properties than non-CRPS patients. However, it is now clear there is no increased sympathetic activity, but hyposympathetic activity in the distal extremity.⁷⁴ It is possible that after a period of hyposympathetic activity peripheral adrenergic sensitization occurs.⁷⁵⁻⁷⁷ This would explain how many patients shift from warm CRPS (hyposympathetic response) in the acute phase to a cold CRPS (hyperreactive sympathetic response) in the chronic phase of their disease. However, despite all these hypotheses, a definitive role for the sympathetic nervous system in the pathogenesis of CRPS, is not established.

Central pain mechanisms, spinal overload and sensitization

CRPS pain cannot be explained by peripheral mechanisms alone.⁷⁸⁻⁸⁰ As mentioned above, different peripheral neurophysiological changes might occur in CRPS e.g. polymodal nociceptor neuron sensitization⁸¹ and ephapse formation, which are supposed to increase afferent sensory input to the spinal cord. This might cause secondary central (read: spinal) sensibilization. Hyperhidrosis is probably of central origin since it cannot be explained by sensitization of sweat glands or high circulating amount of catecholamins.⁸²

Livingston proposed in 1943 that sympathetic input might result in increasing activity of the internuncial pools in the spinal cord.⁸³ This increased spinal activity results in increased sympathetic activity, which completes this vicious circle. Spinal overload might cause ipsilateral pain and dystonia, but also mirror phenomena of pain and motor manifestations in the contralateral limb.⁸⁴⁻⁸⁶

There are other theories concerning changed spinal activity. For example the gate-control theory, which describes that loss of central inhibition might facilitate pain.⁸⁷ Although the gate-control theory was published in 1965, in 1955 Noordenbos already theorized that disproportional loss of thick fibers caused central facilitation and pain.⁸⁸ Livingston's vicious circle hypothesis was continued by Bonica.⁸⁹ Sunderland proposed a mechanism of retrograde changes in sympathetic ganglia resulting in spinal cord changes to explain the continuous pain.⁹⁰ Important in the current opinion on CRPS was the article of Roberts on sensitization on central level^{65,91}, and later by Dotson et al (1993) who postulated that the increased expression of peripheral 1-adrenergic receptors preceded activation of afferent somatic nerves and mechanoreceptors leading to tonic firing and therefore pain.⁷² The physical substrate for touch evoked pain or allodynia would be spinal 'wide dynamic range neurons' (WDR) activated by a persistent painful stimulus and sympathetic efferent actions. Sensitization of WDR neurons and nociceptive-specific neurons is possible and is referred to as plasticity of pain pathways. This is supposed to be partially NMDA (N-methyl-D-aspartate) dependent.⁹²⁻⁹⁶ Mechanical stimulation of A-fiber mechanoreceptors would not only lead to perception of touch, but through WDR sensitization also lead to pain. This is called mechanical allodynia. At spinal level long-lasting excitatory postsynaptic potentials are produced by central release of neuropeptides and excitatory amino acids. These summate and depolarize a population of dorsal horn interneurons. These decrease the Mg²⁺ block of NMDA ion channels of the central pain projecting neurons. This facilitates the central signal transmission. Contemporary NMDA antagonists reduce neuropathic pain, but have too many side effect to be clinically useful.

Pain, as with most chronic pain, is spread outside the original area of trauma in CRPS. This is explained because of wrong cortex interpretation, due to summation of impulses from increased activity in the internuncial pool.⁸⁶ Another explanation is that activated peripheral ephapses cause referred pain to the entire area of distribution of that sensory nerve.⁹⁷ The last explanation for spreading of pain and hypesthesia outside the original area of trauma is by the concept of referred pain. Numbness or mechanical hypesthesia is a frequently found complaint for approximately 75 % of patients, which can improve in time spontaneously and after placebo treatment.^{98,99} For some authors, there is no neurological explanation for hypesthesia (in CRPS) when it is not limited to a single peripheral nerve and somatosensory evoked potentials are normally unaffected.¹⁰⁰ Others have described reversible mechanical hypesthesia in (experimental) muscle pain, without any nerve damage.^{101,102} One new finding is the improved cutaneous sensitivity in CRPS when gabapentin users are compared to placebo users (chapter 7) Reversal of sensory deficit during the use of gabapentin was already suggested by 3 case reports

in other neuropathic pain syndromes.¹⁰³ CRPS patients usually report hypersensitivity and pain to non-painful stimuli, but CRPS pain also mimics experimental referred pain by intramuscular hypertonic saline infusion in most aspects. Both are diffuse, unpleasant and felt in structures at a mostly distal, but sometimes proximal, distance of the original site of either trauma or saline infusion. Besides referred pain, hypertonic saline induces deep tissue hyperalgesia. Similarly induced deep tissue hyperalgesia and referred pain are found upon i.m. injection of capsaicin, serotonin and bradykinin.^{104,105} Referred pain is a rather common phenomenon in neurology. It is possible that all the somatosensory findings and pain outside the original area of trauma in CRPS, which often has been addressed as non-neurological, can be attributed to referred pain mechanisms. Other research showed that referred pain is more extensively inducible in chronic pain patients with fibromyalgia or post whiplash syndrome.^{106,107} It is possible that some fibromyalgia patients turn out to have a CRPS subtype¹⁰⁸, nevertheless referred pain in CRPS patients has not been studied yet. Gabapentin has been reported to alleviate referred pain.¹⁰⁹ Since many CRPS patients have mechanical hypesthesia, we suggest that gabapentin by the same way it decreases pain, it might also decreases mechanical hypesthesia.

Systemic pain mechanisms

Melzack proposed that an increased stress reaction around the moment of trauma caused an increased catabolic reaction, through, e.g., cortisol. Therefore minor neural deficits would remain, which leads to prolongation and thereby centralization of pain.¹¹⁰ This mechanism possibly underlies several similar disorders like CRPS, irritable bowel disease, chronic fatigue syndrome and fibromyalgia in which a strong female predisposition is often coupled with common clinical features like fatigue, stiffness and sleeplessness³ of which sleeplessness appears to be related to increased cortisol levels.¹¹¹ A common mechanism of sensitization to stimuli in these syndromes of 'subjective health complaint' is also hypothesized by several other authors.^{112,113} Others focus in these syndromes on the signs of dysregulation of the hypothalamic-pituitary-adrenal axis^{112,114,115}. Whatever the relationship is between sustained stress reaction and these 'subjective health complaints', the relationship itself was already suggested in 1859 as Briquet described hysteria or asthenia as an overload of a weak ("asthenic") system.¹¹⁶ The past 150 years has brought us new concepts as burnout and posttraumatic stress disorder and more detailed models to hypothesize on the pathogenesis of their symptoms. Clinically however, not much has changed as physicians still warn their patients not to overload their 'weak system' in e.g., CRPS, chronic fatigue syndrome, idiopathic low back pain and fibromyalgia.

Disuse

To maintain good limb function one should periodically use a limb. Some scientists has proposed that CRPS patients for unknown reasons do not use their affected limb enough, thereby creating secondary problems. Disuse in pain syndromes is proposed as a possible cause of osteoporosis and the nutritional disturbances in the skin^{13,117,118}. It is a small step to suggest that disuse is a possible cause of CRPS. Some are suggesting disuse as an important factor by assessing and publishing the vast amount of disuse of affected limbs in CRPS patients.¹¹⁹ An argument against this possible etiological factor is that CRPS (pain) often starts immediately after trauma, without several weeks of disuse before. The association between disuse and CRPS was wrongly suggested when, like in several other painful limb syndromes, false positive or at least indirect signs of disuse were found on X-ray films of CRPS patients.^{48,120-}

¹²² Firstly, it was not proven that these changes were disuse related, and secondly no cause-effect relationship had been established. There are no scientific arguments to claim that disuse in CRPS is not a result of pain and dystonia. The claim of disuse in pathogenesis of CRPS without further evidence should be avoided, since it unnecessarily stigmatizes patients by its association with inactivity and malin-gering.

Nevertheless, unnecessary disuse should be avoided in CRPS. An article on posttraumatic osteoporosis indicates that good fixation is necessary to improve weight bearing capacity and therefore related to the use of and osteogenesis in the affected limb.¹²² Maybe all movement-induced pain should be avoided through strict fixation to minimize avoidable disuse. This would improve osteogenesis and therefo-re might enhance recovering. Another reason to promote immobilization above painful movement is the suggestion that CRPS might be maintained by activity of deep somatic structures ¹²³ and that pain-ful physiotherapy often appears to lead to aggravations of symptoms.¹²⁴

Genetic susceptibility

Besides a discussion on direct preceding events leading to CRPS, one may wonder which persons are prone to development of CRPS. An indirect clue for the existence of a predisposition to CRPS might be that a subpopulation of patients with CRPS in one limb have a relative high chance to develop CRPS in another limb too.¹²⁵ It might be that changes in the immunological system whether or not caused by stress reactions, predispose to the development of chronic pain. Also, a genetically based theory could explain why only a small group is susceptible for developing chronic neuropathic pain. Perhaps changes in the central nervous system as for example in the descending inhibitory pathways, predispose to CRPS.¹²⁶ A possible association of a human leukocyte antigen (HLA) subgroup DR15(2) with CRPS not responding on treatment was described in 1994.¹²⁷ In 2000, a prevalence of HLA DR13 was increased from 27% in controls to 46% in a group of refractory CRPS patients with tonic dystonia spreaded to two or more limbs.¹² Recently, genetic susceptibility loci associated with auto- immune diseases have been described in a all female CRPS population with dystonia.¹²⁸ More research is needed in a general CRPS population (see chapter 5).

Chronic inflammation

The concept of neurogenic inflammation is old.¹²⁹ In neurogenic inflammation, neurons produce sub-stances generating inflammatory (skin) responses. Goris published the idea that this inflammation is involved in CRPS, attributing a crucial role for free radicals.¹³⁰ Free radicals play a role in macrophage and neutrophil mediated inflammatory processes. They cause tissue damage, a trigger for macrophage action and new radical formation. This free radical mediated processes result in edema, tissue damage by oxidative stress, but primarily antimicrobial activity.¹³¹ Circumstantial microscopic evidence of free radical induced changes, congruent to the chronic insufficient nutritious flow has been found. ^{132,133} Other circumstantial evidence for cellular hypoxia has been found by measuring phosphocreatin meta-bolism, arterial-venous oxygen saturation ratio, increased capillary permeability of macromolecules, lipu-fuscin deposition, lactate flux, clubbing of fingers and immediately increasing complaints upon exercise and adrenalin injection.^{45,132,134-137} It is not clear to which extent neuropeptides as substance P, and calcitonin gene-related peptide (CGRP) or cytokines are involved in pain and vasodilatation in acute CRPS, but the cytokines profile of chronic patients is not abnormal.¹³⁸ A role for pain inducing vasoac-

tive substances in CRPS was proposed in 1942.¹³⁹ Both increased and decreased skin blood flow can be explained by C-fiber stimuli through interaction of antidromic neurogenic inflammation and sympathetic vasomotor outflow.^{140,141} One study found increased levels of the neuropeptides bradykinin as well as CGRP in all their patients, suggestive for inflammation.⁴³ Other results also suggest an increased releasability of cytokines and neuropeptides in CRPS.¹⁴²⁻¹⁴⁵ No evidence has been found for mobilization of neutrophils or macrophages, although there is one case-report on the existence of increased inflammation and CGRP associated, Langerhans cells.^{146,147} Nevertheless, the expected increase in antimicrobial activity has not been found. Instead, CRPS patients are extremely vulnerable for infections, which sometimes lead to amputation of the affected limb. Some physicians advocate the use of free radical scavengers in CRPS treatment. Mannitol has been given as a hydroxyl scavenger in CRPS, but in therapeutic doses its capacity to reduce free radical damage is doubted.¹⁴⁸ The suggested action mechanism of mannitol would be an increased nutritive flow, which corrects the decreased oxygen extraction in CRPS.^{137,149} However, its clinical effects have never been proven in a controlled trial. The mechanism behind chronic inflammation has not yet been elucidated. So for now, the most likely explanation for the laboratory findings is a decreased nutritive flow itself that causes oxidative stress and tissue damage. This mechanism is comparable to similar findings in diabetes mellitus.¹⁵⁰⁻¹⁵³ In CRPS this reduced nutritive flow could be caused by a chronic inflammation, but as well so by metabolic or neurogenic processes.

Inflammatory characteristics like bone atrophy, edema and redness are far less often explained in literature maybe because they are clinically seen as less relevant, but are sometimes explained as signs of tissue inflammation, either neurogenic or oxidative stress induced.^{9,129,146,154,155} The role for oxidative stress is further established after the publication of the preventive effect of antioxidants in a placebo controlled study, although CRPS incidence in the placebo control group of the study was extremely high.¹⁵⁶ In rat models of neuropathic pain a role for free radicals has been established.^{157,158}

Post-infectious pain

Several neuropathies like the Guillain-Barré syndrome and its variant, Miller-Fisher syndrome are probably post-infectious diseases. Support has been found for the molecular mimicry hypothesis as a mechanism for the induction of cross-reactive pathogenic antibodies in possible post infectious neuropathic syndromes as Bell's palsy^{159,160}, certain forms of Guillain-Barré syndrome¹⁶¹⁻¹⁶³ and even multiple sclerosis¹⁶⁴⁻¹⁶⁶ or Alzheimer's dementia¹⁶⁷. Mimicry of body tissue and pathogens may lead to cross-reactive autoimmunological processes leading to tissue damage, redness, swelling and pain. Neuropathic pain is viewed by some as a possibly autoimmunological disease, since immunoactive blood cells, increased glial activity and increased MHC class II can be found in a rat model of neuropathic pain.¹⁶⁸

Theoretically, it is possible that the blood-nerve barrier prevents contact of several neural molecules. After minor trauma it might be that blood-nerve barrier is disturbed and that a cross reactivity starts between post viral antibodies and neural tissue. This has already been theorized for e.g., Parsonage-Turner syndrome (neuralgic shoulder amyotrophy, plexus neuritis). The Parsonage-Turner syndrome is comparable to the CRPS syndrome.¹⁵⁹ The Parsonage-Turner etiology can sometimes be related to a minor trauma or recent infection, with e.g., Parvovirus B19.¹⁶⁹ They differ so far that the former is always self-limiting, associated with motor dysfunction and EMG proven nerve damage. The role of Parvovirus B19 virus and other possible involved pathogens in CRPS is discussed in chapter 6.

The psychological issue

Some clinicians are convinced of the existence of psychological features, which predispose to CRPS.¹⁷⁰⁻¹⁷⁶ Although it is described and generally accepted that pain in CRPS changes patient's behavior and mood, evidence for psychopathology preceding CRPS or continuing after resolving of the painful features has, despite many publications, not been established yet.¹⁷⁷⁻¹⁸⁰

Recently, the "psychological discussion" was started again after a study suggested that CRPS patients relatively often have a significant life event in the year preceding the symptoms.^{181,182} but this study did not correct for events and physical traumas usually preceding CRPS e.g., strokes, operations, bone fractures and car accidents. The conclusion that psychological traumas or stress may lead to CRPS cannot be drawn. Whether psychological pathology may or may not lead to CRPS, physicians should always remember that somatoform patients are often wrongly diagnosed as CRPS patients. A group of people considering themselves as CRPS patients will also be falsely positive diagnosed somatoform patients. This was already predicted^{118,183}, but more circumstantial evidence for this claim has been found in a small subpopulation of presumed CRPS patients with additional positive motor signs as spasms, jerks and tremors.¹⁰⁰ A second bias in the conception of a role for the psyche in CRPS etiology is the diagnosis of psychogenic disturbances in these patients. This does not exclude the coexistence of CRPS. Many CRPS patients get involved in legal proceedings in which they are confronted with skepticism and disbelief. This might stimulate patients' exaggerations of clinical symptoms.¹⁸⁴

So conclusively, overdiagnosis and secondary psychological symptoms might bias the physicians view on the patient population, the presumed effect of therapies and the presumed psychological involvement of CRPS.

TREATMENT

The number of therapies available for a complaint is apparently correlated with therapy resistance in this complaint. For CRPS more than 50 treatments are described in literature.¹⁸⁵ In general, CRPS treatment can be divided in their presumed activity: mobilizing, desensibilising, antisympathetic activity, blood vessel dilating, anti-inflammatory, free radical scavenging, edema decreasing, voltage channel stabilizing, bone tissue increasing, pain killing by NSAIDS or opiates, neuromodulating, neurosurgically (vital sensibility) and miscellaneous like ECT and non-medical therapies like acupuncture and color therapy. Several therapies are capable of multiple action properties.

Therapies should still be judged on its merits. Physical therapy, for example, is possibly the most advocated and practised therapy in CRPS. It is meant to be activating and desensitizing. Its effect is doubtful. In chronic CRPS patients it results in increased complaints in more than 50%.^{33,124} Also patients may benefit in short terms, it appears that this effect subsides and when evaluated after one year no pain relieving effect can be found in comparison to controls.¹⁸⁶ The other main CRPS treatment was sympathetic block, since Leriche advocated its use in 1916. In the 1993 workshop the term Reflex Sympathetic Dystrophy was left, because it was doubted whether the sympathetic nervous system was important in CRPS patients. Nowadays, it is clear not to promote regional sympathetic blocks anymore for CRPS treatment.^{61,187} But it is also questionable whether CRPS patients without allodynia should still have paravertebral sympathetic blocks.^{63,188-190} Placebo controlled randomized controlled studies are available for calcitonin¹⁹¹⁻¹⁹⁴, corticosteroids^{195,196}, acupuncture¹⁹⁷⁻¹⁹⁹, guanethidine^{193,200-202}, reserpine²⁰⁰, epidural clonidine²⁰³, DMSO²⁰⁴, biphosphonates²⁰⁵, phentolamine²⁰⁶ epidural neuromo-

dulation²⁰⁷ and gabapentin (chapter 7). Acupuncture, phentolamine, reserpine and guanethidine and sympathetic blocks do not appear to be beneficial. Standardized meta-analysis of RCT's has been performed.

The most recent analyses showed only enough results in CRPS therapy of calcitonin^{208,209}, but its clinical effect is small and many experience unpleasant, mostly gastroenterological, side-effects.²¹⁰ One study did not show a pain relieving effect.²¹¹ Its presumed action is stimulating bone activity, but more recently its claimed pain diminishing effect in phantom pain, Raynaud's phenomenon and diabetic neuropathy suggests other action mechanisms.²¹²⁻²¹⁵ In fact, calcitonin redistributes bloodflow in favor of cutaneous flow and probably enhances responsiveness to opioids.^{212,216} It is also claimed to stabilize neuronal membranes and inhibit neuronal calcium influx.²¹⁷ Also serotonergic and catecholaminergic mechanisms, protein phosphorylation, endorphin production, cyclooxygenase inhibition and histamine interference has been proposed as antinociceptive mechanism.²¹⁸

The presumed action of corticosteroids on CRPS has not been established. It is supposed that corticosteroids have an inhibitory effect on spontaneous neural discharge.²¹⁹ Its use is limited, since the effect is only proven in the acute phase of CRPS.

Taken together, none of the used therapies for CRPS appears to be evidence-based.

Aim of this thesis

We sought to answer the following questions:

- 1 Is CRPS type I a valid diagnosis?
 - a What is the interobserver reliability of CRPS type I signs and symptoms?
 - b Do patient reports on symptoms in CRPS predict signs upon physical examination?
 - c What are main differential diagnoses in CRPS type I?
- 2 Are neurotropic viruses/bacteria involved in CRPS type I pathogenesis?
- 3 Is there a HLA subtype association with CRPS type I?
- 4 Is gabapentin useful as a treatment in CRPS type I?

Our studies on diagnosis are outlined in chapters 2-4 of this Ph.D. thesis. Our study focussed on reliability of patients' reports of symptoms, physical examination and diagnostic criteria systems in chronic CRPS patients; we assessed relevant differential diagnoses of CRPS. Our studies on pathogenesis of CRPS are described in chapter 5-6. We studied HLA associations and involvement of microbial pathogens in the development of CRPS. With a placebo controlled study of gabapentin in CRPS we evaluated a possible CRPS treatment, as described in chapter 7.

Appendix I

Examples of criteria systems in CRPS

IASP Diagnostic criteria in Complex Regional Pain Syndrome type I 2
as also published by Merskey and Bogduk (1994)¹:

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

Note: Criteria 2-4 must be satisfied¹

Kozin (1981)²²⁰

Proposed Clinical Diagnostic criteria for RSDS:

Definite RSDS

Pain and tenderness in the distal extremity
Signs and/or symptoms of vasomotor instability
Swelling in the extremity—often with periarticular prominence
(Dystrophic skin changes usually present)

Probable RSDS

Pain and tenderness
AND
Vasomotor instability OR swelling
(Dystrophic changes often present)

Possible RSDS

Vasomotor instability OR/AND swelling
No pain, but mild-moderate tenderness may be present
(dystrophic skin changes occasionally present)

Doubtful RSDS

Unexplained pain and tenderness in a extremity

Consensus report of an Ad Hoc committee of the American Association for Hand Surgery on the Definition of Reflex Sympathetic Dystrophy Syndrome (1990)²²¹ :

1. Diffuse pain
hyperalgesia, hyperpathia OR allodynia
2. Loss of hand/foot function
any activity or motion impairment associated with the pain
3. Sympathetic dysfunction
objective evidence of significant autonomic dysfunction, as reflected by skin, soft-tissue, or blood flow changes, such as temperature increase or decrease, sweating increase or decrease, hair growth increase or decrease, nail growth increase or decrease, atrophy of skin or subcutaneous tissue, edema, blood flow increase or decrease, Sudeck's osteoporosis, or characteristic bone scan

Bonica (1990)⁸⁹ :

History of recent or remote accidental or iatrogenic trauma or disease
Presence of a persistent pain that is burning, aching and/or throbbing in character
One or more of the following:
a) vasomotor and sudomotor disturbances
b) trophic changes, edema of the limb, sensitivity to cold, muscle weakness or atrophy, or trophic changes
Relief of pain and modification of signs after regional sympathetic blockade

Holder(1992)²²² criteria resembles a lot the criteria of Bonica >s

Diffuse non anatomical pain
Autonomic-vasomotor signs (warm or cool skin temperatures, moist-sweaty or dry- scaly skin)
Positive response on (lumbar) sympathetic block.

Gibbons (1992) ²²³

(Not useful, because of division in possible and probable RSD. Thereby are the last 4 changes not as important any more as before, because of lack of sensitivity/specificity.)

RSD score < 3 : no RSD

„ „ 3-5: possible RSD

„ „ >6: probable RSD

one point for positive; half-point for equivocal

1. Allodynia or hyperpathia
2. Burning pain
3. Edema
4. Color or hair growth changes
5. Sweating changes
6. Temperature changes
7. Radiographic changes (demineralization)
8. Quantitative measurement of vasomotor/sudomotor disturbance
9. Bone scan consistent with RSD
10. Response to sympathetic block

Veldman (1994) ^{124,224,225}; based on Goris ³³

*4 out of 5:

Unexplained diffuse pain

Difference in skin color relative to other limb

Diffuse edema

Difference in skin temperature relative to other limb

Limited active range of motion

*Occurrence or increase or above signs and symptoms after use

*Above signs and symptoms present in an area larger than the area of primary injury or operation, including the area distal to the primary injury

Wilson (1996) ²²⁶

- history of pain
- allodynia, hyperalgesia or hyperesthesia

2 signs:

- edema
- vasomotor changes: color, temperature instability, asymmetry
- sudomotor changes
- trophic changes in skin, joint, nail, hair
- impaired motor function (may include components of dystonia and tremor)

Bruehl (1999): proposed modified research diagnostic criteria for CRPS 7

(1) Continuing pain which is disproportionate to any inciting event

(2) At least one symptom in each of the following categories

Sensory: reports of hyperesthesia

Vasomotor: reports of temperature asymmetry and/or

skin color changes and/or skin color asymmetry

Sudomotor/edema: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

(3) At least one sign in two or more of the following categories

Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch)

Vasomotor: evidence of temperature asymmetry and/or skin color changes and/or asymmetry

Sudomotor/edema :evidence of edema and/or sweating changes and/or sweating asymmetry

Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

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Interobserver Reliability of Diagnosis in Patients with Complex Regional Pain Syndrome

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Summary

Complex Regional Pain Syndrome type I (CRPS-I), formerly reflex sympathetic dystrophy (RSD), is a chronic pain syndrome of unknown aetiology. Its diagnosis is a clinical one, for which several criteria systems have been defined. Despite their widespread use, the reliability of these criteria has never been studied.

In this inter-observer study twenty-five CRPS patients were interviewed and examined by six physicians. Through structured questionnaires signs, symptoms, and diagnosis were recorded, after which observer agreement for these was calculated with kappa statistics.

Physicians' agreement in assessment of signs and symptoms in CRPS patients varied greatly. More importantly, final diagnosis of CRPS showed poor observer agreement (kappa: 0.20). Kappa values were higher, had physicians applied IASP criteria, but still insufficient. The application of Bruehl's criteria results in a fair kappa of 0.38, but then frequency of CRPS diagnosis in our study population decreased from 73% to 43% in comparison with physicians' own diagnosis. We conclude that, using current criteria systems, the diagnosis of CRPS is not reliable.

Introduction

Complex Regional Pain Syndrome type I (CRPS-I), formerly reflex sympathetic dystrophy (RSD), is a chronic pain syndrome of unknown aetiology. It is usually characterised by pain, swelling, autonomic dysregulation and chronic functional impairment after a trauma of the affected limb. The diagnosis of CRPS is a clinical one. A gold standard in the form of an objective test is not available.¹⁻¹² Although diagnostic criteria for CRPS have been formulated¹³⁻¹⁵, none is generally used. The International Association has developed the most official criteria system for the Study of Pain, IASP¹⁶. As far as we know three validation studies on these CRPS criteria have been published¹⁷⁻¹⁹. These studies address the validity of IASP criteria as to their specificity in delineating CRPS from other neuropathic pain syndromes. However, the distinction between CRPS and other neuropathic pain syndromes, e.g. postherpetic neuralgia and diabetic polyneuropathy, is not a diagnostic problem in daily clinical practice. The main clinical problem is inter-physician variability in CRPS diagnosis. This is due to the variability in observed signs, symptoms and the amount of signs, symptoms and credibility in patients needed to reach the diagnosis CRPS. Until now, inter-physician agreement studies of diagnosis in CRPS patients have not been done. Herein we report a study with 6 physicians examining 25 patients, to assess inter-observer variability in diagnosing CRPS.

Subject and methods

Subjects

Twenty-five patients who visited our outpatient clinic for pain management in the preceding four years participated in the study. They had been at random selected from a database with patients once diagnosed as CRPS or Reflex Sympathetic Dystrophy. All patients were informed about this diagnosis and had received some treatment for it and remained to have pain and other symptoms despite CRPS treatment. All patients gave informed consent. The Institutional Review Board of the University Hospital Maastricht approved the study.

Study design

Six physicians (three anaesthesiologists, two surgeons and one neurologist) with known experience on CRPS participated in the study. They were instructed to take a semi-structured interview and perform a physical examination of the patient scoring absence or presence of signs and symptoms by yes/no.²⁰ The observers were free to ask additional questions to obtain adequate information. Finally they estimated the patient's pain and filled in a diagnosis according to their own clinical view. No instructions were given about CRPS diagnostic criteria. Physicians were not allowed to discuss any aspect of the study with each other. The items for interview and physical examination had been selected by collecting symptoms and signs from published RSD criteria^{13-15,21}, the IASP classification of pain¹⁶ and the Neuropathic Pain Scale²² (list available upon request). After interview and examination physicians were asked to give their diagnosis. They were instructed to select one of the following: CRPS 1, CRPS 2, CRPS 3 (pain and sensory, motor and/or tissue abnormalities not otherwise specified), (diabetic) polyneuropathy, radiculopathy, myofascial pain, nerve entrapment²³, somatoform pain disorder, (idiopathic) pain not otherwise specified. The questionnaire contained 35 CRPS symptoms and 27 CRPS signs (See tables 1 and 2). The study was set up in three sessions with six patients and one session with seven patients. To limit the fluctuation in time of signs between successive physical examination, the six observers successively saw all patients within approximately 2 hours, but examination varied from 10-20 minutes per patient. Because some patients had more than one affected extremity, physicians were asked to focus on the most affected limb. Test results like EMG, laser Doppler flow-metry, and three-phase bone scanning were not provided. Temperature difference of the skin of both extremities was measured manually.

Diagnostic criteria for CRPS type I are identical to CRPS type II in which nerve damage is proven. Therefore we consider CRPS patients in this report as patients with either CRPS type I or type II. Preliminary data suggest that CRPS type I patients do not differ from CRPS type II patients in signs, symptoms and therapy results^{19,24}. We compared expert-based diagnosis with diagnosis using criteria systems (the official IASP criteria and the most recently proposed CRPS criteria of Bruehl et al).^{16,19}

Statistical analysis

Data were analysed in the following steps.

1. Analyses of inter-observer agreement on signs and symptoms by group kappa and percentage of agreement, measured by a generalised kappa statistics for more than two raters (group kappa).²⁵ In the group kappa coefficient, the average observed agreement is compared to the average chance agreement, with the average taken over all pairs of expert-physicians and over all patients. Kappa values range from -1 to 1. Positive values show certain agreement beyond chance agreement. Kappa values were classified as slight (kappa= 0.00-0.20), fair (kappa= 0.21-0.40), moderate (kappa= 0.41-0.60), substantial (kappa= 0.61-0.80) and almost perfect agreement (kappa=0.81-1.0).²⁶
2. Analysis of interobserver agreement in expert-based diagnosis (group kappa).
3. By applying the official IASP criteria¹⁶ and the CRPS criteria of Bruehl et al.¹⁹ on our data sets we compared criteria-based diagnosing with expert-based diagnosing (see appendix I and II for criteria sets). IASP and Bruehl diagnostic criteria were applied in the 150 data sets.^{16,19} This resulted in new interobserver agreement values for criteria-based diagnosing and CRPS prevalences. These were compared with kappa value for inter-observer agreement in expert-based CRPS diagnosis.²⁷
4. IASP and Bruehl diagnostic criteria were applied to the 150 data sets containing signs and symptoms.¹⁹ This resulted in new frequencies of CRPS diagnoses. These were compared with expert-based CRPS frequencies.
5. The value of patient's symptoms in CRPS diagnosis is unknown. We analysed the effect on the frequency of CRPS diagnosis, when reported symptoms instead of objective signs were applied in criteria systems.

Results

Twenty-five patients with a mean age of 42.3 yrs (23-65 yrs) participated of whom eighteen had upper extremity involvement and seven lower extremity involvement. Twenty-three patients were women. Duration of symptoms had a median of 39 months (range 5-168 mo.). Therefore some of these patients will be considered by some as late stage CRPS, although it is unclear how to differentiate between acute stage and late stage CRPS. All patients would consider themselves as having CRPS, because at least once a physician considered them as having CRPS and treated him/her as such.

All patients were diagnosed as CRPS-I by at least one observer. CRPS type I was diagnosed in 99 (67%) assessments, CRPS II in 11 (7%), CRPS III in 15 (10%), somatoform disorder in 17 (11%), and myofascial pain or idiopathic pain not otherwise specified in 8 cases.

Observer agreement in signs and symptoms

Kappa values, observer agreements and frequencies of potential diagnostic criteria are shown in table 1 (interview) and table 2 (physical examination). Kappa values of signs and symptoms ranged from fair to moderate. Kappa value has not been calculated in those instances with a prevalence of findings being less than 10% or more than 90%. These kappa values would have been affected by the extreme prevalences. In these cases, only percentages of agreement uncorrected for chance agreement are given.²⁸

Interobserver agreement in CRPS diagnosis

We expected kappa values would increase if experts had applied criteria systems. To evaluate the validity of these criteria systems, we applied physicians' findings in the interview and examination to diagnose according to IASP and Bruehl's diagnostic criteria. Table 3 shows that kappa values for diagnosing CRPS and idiopathic, CRPS-like, pain syndromes between the different pairs of observers resulted in a group kappa of 0.20 (CI: 0.06-0.33) in expert-based diagnosis, but if IASP was applied, kappa value rose to 0.29 (CI: 0.03-0.55). If Bruehl's diagnostic criteria were applied kappa value rose to 0.38 (CI: 0.18-0.58) (see table 3).

Frequency of CRPS diagnosis

Since signs in CRPS can fluctuate in time, physicians, in general, use both reported symptoms and physical examination for diagnosis. We analysed the validity of the use of subjective reported symptoms (symptom-based) in diagnosing. Bruehl's diagnostic criteria consist of two parts: symptoms and sign-based criteria. We applied these Bruehl's criteria, but we both calculated CRPS-frequency when the signs and symptom criteria were synchronously applied, when only reported symptoms were applied and when only the sign-based criteria were applied (table 4). Symptom-based IASP criteria resulted in a CRPS frequency of 98%. Frequency of CRPS diagnosis with Bruehl's criteria did not change much, if besides sign-based criteria also the symptom-based criteria were applied. When Bruehl's criteria were applied on our 150 data sets, 65 times CRPS-I/II would be diagnosed, but symptoms were essential in only 2 out of 150 patient assessments (1.3 %) to meet the Bruehl's diagnostic criteria for CRPS.

Discussion

CRPS is a clinical diagnosis for which criteria have been formulated. Until now inter-physician agreement of the diagnostic process had not been studied. In this study we tried to assess the reliability and validity of CRPS diagnostic criteria. To this end we asked 6 different experienced physicians to interview and examine 25 possible CRPS patients. We felt that this set-up most closely resembles daily practice, although certain biases cannot be ruled out. One possible bias is caused by patient selection: all patients were chronic CRPS patients. Another bias may be caused by repetitive examination of the affected limb by different observers. We do not think that they seriously affected our conclusions, as the last examination in each session did not differ significantly from the first ones (data not shown).

We found that interobserver agreement is reasonable for symptoms, but low for signs in our population with possible CRPS patients. Assessments of edema, hair growth and mechanical allodynia showed moderate agreement. Kappa values for signs should preferably be more than 0.40 (moderate agreement), when dealing with criteria for a diagnosis.²⁹ Kappa value for edema in our population was comparable with kappa value (0.47) for edema in juvenile rheumatoid arthritis.³⁰ Perhaps kappa values would have been higher in a population of recent CRPS patients, although Oerlemans et al were not able to find agreement in subjective reports of skin temperature and objective measurements in patients with more acute CRPS.³¹

Reaching a final diagnosis of CRPS, according to the experts, reached a kappa value of only 0.20 (Table 3). Diagnosing CRPS in our study was thus as reliable as diagnosing pneumonia with stethoscope and percussion, but without X-ray.³² This poor observer agreement is less than other difficult clinical diagnoses as medical fitness for a job (kappa=0.37) and shoulder disorders (kappa=0.45).^{33,34} The application of standardized instruments to measure for example edema, skin temperature or sensory abnormalities might improve diagnostic reliability further, but until now these results have been disappointing.³⁵

Since the application of criteria systems often improves observer agreement in diagnosis, we calculated kappa's for diagnosis when IASP and newly proposed criteria of Bruehl were applied to the data (Table 3). Agreement did indeed rise to almost moderate level if IASP or Bruehl's criteria were applied. Bruehl's criteria resulted in a fair kappa value of 0.38 and the specificity of CRPS diagnosis increased too. CRPS frequency decreased to 43% in comparison to frequency of CRPS (73%) in experts' diagnosis (Table 4). Therefore, the option to increase specificity might be beneficial for research goals, but the concordant decrease in sensitivity probably limits the clinical value of Bruehl's criteria. In an effort to identify signs and symptoms with a major impact on the CRPS diagnostic process, we performed a logistic regression analysis on our data-set (data not shown). We were not able to find any signs or symptoms crucial for the diagnosis of CRPS. This accords with Veldman who found that sympathetic signs and symptoms (like hyperhidrosis, hypertrichosis, and changed nailgrowth) as single entities do not contribute significantly to the diagnosis of CRPS.²¹

The remaining question is whether, with our current knowledge, valid CRPS criteria for clinical practice can be developed at all. Further studies are needed to develop other methods to diagnose CRPS. Until that time it might be appropriate to restrict clinical trials of CRPS to patients who fulfill Bruehl's criteria.

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Appendix I IASP Diagnostic criteria in CRPS

Diagnostic criteria in Complex Regional Pain Syndrome type I (Stanton Hicks et al. 1995)

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

Note: Criteria 2-4 must be satisfied (Merskey and Bogduk 1994)

Appendix II Criteria of Bruehl: research diagnostic criteria for CRPS

1. Continuing pain which is disproportionate to any inciting event
2. At least one symptom in each of the following categories
Sensory: reports of hyperesthesia
Vasomotor: reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry
Sudomotor/oedema: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. At least one sign in two or more of the following categories
Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch)
Vasomotor: evidence of temperature asymmetry and/or skin colour changes and/or asymmetry
Sudomotor/oedema: evidence of oedema and/or sweating changes and/or sweating asymmetry
Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

Table 1 Group kappa, interobserver agreement for CRPS symptoms and frequency of symptoms in experts' diagnosis (%)

	group kappa	observer agrmnt	frequency in subjects
continuous (spontaneous) pain	-	0.97	0.94
dysesthesia	-	0.93	0.96
functional impairment	-	0.94	0.96
cold or warm sensation in affected limb	-	0.94	0.97
pain aggravates with cold and/or heat	-	0.92	0.94
decreased range of motion	-	0.91	0.96
start after phys.l trauma or relevant disease	-	0.90	0.95
pain outside original affected area	-	0.90	0.95
loss of strength	-	0.97	0.99
aggravation of pain with stress	0.86	0.94	0.36
anhidrosis/hyperhidrosis	0.80	0.91	0.67
changed nailgrowth	0.79	0.90	0.65
superficial pain	0.73	0.88	0.67
burning pain	0.71	0.86	0.60
sympathetic block diminished complains	0.69	0.90	0.21
pain upon soft touch (mechanical allodynia)	0.67	0.85	0.65
throbbing pain	0.66	0.86	0.70
(spontaneous pain) in one extremity	0.65	0.87	0.75
changed hair growth	0.59	0.82	0.31
spontaneous sensations (paresthesias)	0.58	0.80	0.60
color changes	0.57	0.86	0.79
deep pain	0.55!	0.90	0.88
hypersensitivity to touch (hyperesthesia)	0.51	0.81	0.73
sharp pain	0.50	0.80	0.72
cold pain	0.47	0.75	0.63
swelling (edema)	0.40	0.75	0.72
tremor	0.37	0.72	0.32
start after immobilization	0.35	0.72	0.31
skintemperature asymmetry	0.33!	0.81	0.83
concentrate to move (motor neglect)	0.30	0.70	0.69
guarding' of affected extremity	0.29!	0.83	0.87
provoked pain last longer (hyperpathia)	0.28!	0.85	0.89
hypesthesia	0.25!	0.77	0.81
limbmovements are painful (acute)	0.25!	0.82	0.86
the use of limb aggravates pain (delayed)	0.21!	0.81	0.86

Dash(-) indicates kappa cannot be calculated (frequency of <10% or >90 of patients).

Exclamation point (!) indicates frequency of 10%-20% or 80%-90% (see Methods).

Table 2 Group kappa, interobserver agreement for CRPS signs and frequency (%) of signs in experts diagnosis

	group kappa	observer agrmnt	frequency in subjects
functional impairment	-	0.96	0.95
decreased range of motion	-	0.94	0.93
no dermatome related symptoms	-	0.93	0.96
changed reflexes	-	0.88	0.08
cervical, or in case of legpain lumbar,			
ipsilateral pressure pain paravertebrally	0.58	0.79	0.53
changed hair growth	0.54!	0.88	0.16
tremor	0.53!	0.91	0.11
pain after with movement (passive/active)	0.51!	0.90	0.89
pain upon soft touch (mechanical allodynia)	0.50	0.77	0.64
edema	0.41	0.73	0.35
changed nailgrowth	0.37	0.70	0.39
hypersensibility	0.34	0.67	0.58
color changes	0.33	0.67	0.54
sympathetic disregulation	0.28	0.67	0.65
dysesthesia	0.27	0.71	0.73
thoracal paravertebral pressure pain	0.25!	0.81	0.14
anhidrosis/hyperhidrosis	0.23	0.65	0.33
skintemperature asymmetry	0.23	0.62	0.59
dystrophy or atrophy cutis/subcutis/muscles	0.22	0.61	0.47
guarding of affected extremity	0.20	0.67	0.73
dystonia	0.15	0.63	0.30
pain aggravates with cold and/or heat	0.11	0.68	0.80
sensory deficit	0.11	0.66	0.75
hyperpathia	0.10	0.66	0.77
hypesthesia	0.08	0.54	0.57
loss of strength	0.02!	0.77	0.87
neurological disorder in affected extremity	0.02	0.47	0.49
credibility of patients' complaints	0.22	0.71	0.76
pain behavior	0.12	0.56	0.40
diagnosis	0.20	0.57	0.73

Dash(-) indicates kappa cannot be calculated (frequency of <10% or >90 of patients). Exclamation point (!) indicates frequency of 10%-20% or 80%-90% (see Methods).

**Table 3 Kappa value in CRPS diagnosis. C.I. is confidence interval.
Observ. agreement is observer agreement**

	Kappa	C.I.(95%)	observ. agreement
Expert-based diagnosis	0.20	0.06- 0.33	0.57
IASP sign-based criteria	0.29	0.03- 0.55	0.74
Bruehl sign-based criteria	0.35	0.15- 0.55	0.68
Bruehl sign and symptom based	0.38	0.18- 0.58	0.74

Table 4 Frequency of CRPS diagnosis in 150 datasets.

Expert-based diagnosis*	110/150=	CRPS I/II (73%)
IASP-symptom based	147/150=	CRPS I/II (98%)
IASP-sign based	114/150=	CRPS I/II (76%)
Bruehl-symptom based	130/150=	CRPS I/II (87%)
Bruehl-sign based	67/150 =	CRPS I/II (45%)
Bruehl complete	65/150 =	CRPS I/II (43%)

**expert (view) based diagnosis is an experience-based diagnosis without any application of criteria systems.*

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Interobserver Agreement on Differential Diagnosis of Complex Regional Pain Syndrome type 1

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Summary

Complex Regional Pain Syndrome type I (CRPS I) is a controversial clinical diagnosis. It is unknown which differential diagnoses are important in chronic pain patients suspected of having CRPS I. In this study 25 patients with possible CRPS I were interviewed and examined by 6 CRPS-experts. On average, one out of four CRPS-experts disagreed with the diagnosis when CRPS I was diagnosed by a colleague. CRPS I could not be diagnosed with much certainty. Idiopathic and somatoform pain syndromes are important differential diagnoses in CRPS I.

Keywords: Reflex Sympathetic Dystrophy; Interobserver agreement; Somatoform Disorders; Differential Diagnosis

Introduction

Complex Regional Pain Syndrome type I (CRPS I) is a clinical diagnosis. It is controversial because a gold standard for diagnosis in the form of an objective test is not available.¹⁻¹² The main clinical problem is interphysician variability in CRPS diagnosis. This is due to interphysician differences of interview and physical examination, but also due to disagreement about which signs and how many signs are needed to reach the diagnosis of CRPS. A diagnostic problem in chronic CRPS is that signs are often less prominent in comparison to the acute phase.^{13,14} We sought to answer the following question: when doctors do not agree on the diagnosis CRPS I, which differential diagnoses are involved? Many diagnoses have been proposed as possible differential diagnoses (table 1), but it has not been studied to which extent they are clinically relevant in the daily practice of diagnosing CRPS I.

In this study we describe how six CRPS experts diagnose 25 chronic pain patients suspected for CRPS I and upon which they differ. We designed the study to test the extent of agreement in diagnosing possible and definite CRPS patients and to find out which differential diagnoses are important in this.

Patients and methods

Six physicians (3 anesthesiologists, 2 surgeons and 1 neurologist) with known experience on CRPS I were invited to participate in the study. The physicians, who all worked in a university outpatient pain or CRPS-clinic, saw each patient during 10-20 minutes for a semi-structured interview and a physical examination; details of the study set-up have been described previously.^{15,16} Although dichotomous questions were used to assess signs and symptoms, the observers were free to ask additional questions to obtain adequate information after which they filled in the most adequate diagnosis according to their own clinical view. No instructions were given about criteria to diagnose CRPS.

Twenty-five patients were at random selected from a tertiary care database with patients at least once diagnosed and informed about CRPS I or reflex sympathetic dystrophy (RSD). All patients had received treatment, though remained to have complaints. They all gave informed consent.

Physicians were able to choose from CRPS I and 8 differential diagnoses: CRPS II (CRPS with evidence of nerve damage) CRPS III (idiopathic pain with sensory, motor and/or tissue abnormalities not other-

wise specified), myofascial pain, peripheral neuropathy (e.g. diabetic), radiculopathy, nerve entrapment, somatoform (pain) disorder, 'pain not otherwise specified'.^{17,18} Also, an open answer possibility for other diagnoses was given.

The study was set up in three sessions with six patients and six physicians each session and one session with seven patients and six physicians.^{15,16} To limit the variation of signs between successive physical examination, every patient was seen within 90 minutes by the six observers successively. Physician assessment was standardised by a semi-structured interview and physical examination on 52 possible signs and symptoms.

Physicians in this study focussed on clinical signs as in bedside evaluation and had no access to any laboratory test results like electromyogram, laser Doppler flowmetry or three-phase bone scanning. Frequency distributions of diagnoses were calculated to assess most important differential diagnoses. To measure interphysician agreement in diagnosis we calculated kappa values.^{15,19}

CRPS experts diagnose CRPS with yet unknown mechanisms. These might be helpful in future criteria systems. We applied logistic analysis (stepwise, forward procedure) of expert-based diagnosis to find significantly predicting signs and symptoms for CRPS, CRPS-III and somatoform disorder. All signs and symptoms were taken as independent variables.

Results

In this study twenty-five patients participated with a mean age of 42.3 years (23-65 yrs). Twenty-three of them were women. Duration of symptoms had a median of 39 months (5-168 mo.) and record based searches revealed that the patients had been seen by at least five physicians (5-13) prior to participation and no serious other pathology like diabetes mellitus, arthritis or vascular pathology had been found to explain the symptoms. Because some patients had possibly more than one affected extremity, they were asked to focus on the most affected limb. Eighteen patients with upper extremity pain and concomitantly seven patients with lower extremity pain were included.

All patients were diagnosed as having CRPS I by at least one observer. In table 2 the frequency distributions of the diagnoses are shown for the six physicians. In 150 assessments, patients were diagnosed as CRPS I in 67% (N=99). The two surgeons diagnosed CRPS in 80%, which is more than the four others who diagnosed CRPS I in 59% ($p < 0.05$, chi-square analysis). Sometimes patients were diagnosed as idiopathic pain patient with sensory, motor and/or tissue abnormalities (CRPS III) or somatoform pain disorder, while CRPS II and the other diagnoses were diagnosed even less frequently. The category 'other' was formed by differential diagnoses: idiopathic pain not otherwise specified (N=7) and myofascial pain (N=1).

In order to assess which regional pain syndrome is most difficult to distinguish from the others we calculated the frequency distribution of diagnosis (table 3). As one observer diagnosed CRPS III or a somatoform pain syndrome, simultaneously the other observers agreed in a mean of respectively 13% and 25%. When CRPS I was diagnosed, 75% agreement in diagnosis was found. When an observer diagnosed CRPS II (N=11), none of the five colleagues assigned a somatoform syndrome in the same patient and vice versa, when an observer diagnosed a somatoform syndrome, none of the other colleagues diagnosed CRPS II.

Kappa values for interphysician agreement ranged from 0.05 to 0.30 (table 4).

It is unknown which signs and symptoms mainly influence diagnostic judgment in CRPS specialists. A logistic regression was applied to reveal significant factors. The fifty-three items measure were analyzed, which included 35 reported symptoms and 28 signs.¹⁵ Besides CRPS signs, physicians were also asked to rate patients's pain, to judge pain behavior and credibility of patients' complaints and answer whether the pain was located to one extremity and if they had seen the patient before. These factors were also included in the logistic regression analysis. Figure 1 and 2 show which factors contribute significantly in CRPS I/II and CRPS III. No symptom or sign is exclusively present in either form of CRPS. As expected, sympathetic dysfunction, dystrophic change and severity of complaints are important contributors to the CRPS diagnosis.

Sensibility changes as hypersensitivity, dysesthesia and a discrepancy between reported and objective hypesthesia are the other significant factors for the CRPS diagnosis. More logistic regression analyses (Fig. 3) revealed that reported burning pain, reported color differences, lack of spontaneous pain, lack of sympathetic dysregulation, lack of sensory dysfunction and lack of credibility are important predictors for the diagnosis of 'somatoform disorder'.

Discussion

CRPS is a clinical diagnosis for which criteria have been formulated. Until now, interphysician agreement of the diagnostic process had not been studied. Our study population consisted of possible CRPS patients, by at random inviting patients who had ever been diagnosed as CRPS/ RSD.

Our results show that differential diagnoses are important in CRPS I, because CRPS I cannot be diagnosed with much reliability.^{15,16} In our population of patients suspected of having CRPS I, patients were also diagnosed as having CRPS II (5%), CRPS III (7%) or somatoform disorders (9%). Physicians differ in their clinical differential diagnosis in patients suspected of CRPS I. Especially idiopathic pain with sensory, motor and/or tissue abnormalities (CRPS III) and somatoform disorders are diagnosed unequally by the participating physicians, which might reveal differences between medical disciplines. It appeared that in some patients physician 6 (neurologist) preferred to diagnose somatoform disorders, where physician 4 (anesthesiologist) preferred to diagnose CRPS III. The surgeons, both working at the CRPS clinic, diagnosed CRPS I more often than the other physicians who worked at a general pain clinic. The latter are presumably more familiar with other chronic, (e.g., idiopathic and somatoform) pain patients than surgeons. Kappa values for interphysician agreement showed low agreement in CRPS diagnosis with a range of 0.05-0.30, where only a kappa value of more than 0.40 can be considered as moderate.²⁰ Kappa values in our study population cannot be directly extrapolated to a general population, but the complaints of patients about disbelief and contradictory information from their own physicians can be understood and explained by these low kappa values. If one considers that CRPS patients are often seen by physicians, who are probably less focused on CRPS than the experts in this study, even more disagreement can be expected at other settings.

In an effort to identify signs and symptoms with a major impact on the CRPS diagnosis, we performed a logistic regression analysis. We can conclude as Veldman¹⁴ that sympathetic signs and symptoms (like hyperhidrosis, hypertrichosis and changed nailgrowth) as single entities do not contribute significantly to the diagnosis of CRPS in our population.

The diagnosis of somatoform pain syndrome (range 0-24%) and a rarely used non-official diagnosis as 'CRPS III-idiopathic pain with sensory, motor and/or tissue abnormalities' (range 0-28%) were in this study more often assigned than one would expect.^{21,22} Somatoform disorder is normally a diagnosis, which cannot be assigned by one physician after one examination.¹⁸ Therapy is often unsuccessful. We think it is therefore underreported in favor of other (less stigmatizing) diagnoses. Because this study asked physicians explicitly for the most likely diagnosis, we think that the large representation of idiopathic and somatoform diagnoses in possible CRPS patients, reveals the true opinion of pain experts. The concept of CRPS III^{17,21,22} should be re-evaluated as some physicians might want to use an 'escape diagnosis' to represent a group of patients which have symptoms and signs that cannot be explained by any neurological or mental entity.

In this population more than 10% of the diagnoses were assigned as a somatoform disorder. We did not find patients simultaneously diagnosed as

CRPS II and somatoform pain syndrome. This is logical as a diagnosis of CRPS II can only be reached in the context of proven nerve damage¹⁷, thus ruling out a somatoform pain syndrome. This accords with recent findings by Ochoa and co-workers^{23,24}, who found that signs of nerve damage argue against and the presence of movement disorders argues in favour of a somatoform disorder in patients suspected of having CRPS.

Chronic idiopathic pain is a burden for patient, physician and society as treatment is, per definition, unsatisfactory. Treatment results and patient satisfaction might improve with better diagnosing. In the future more attention should be focused on how to distinguish CRPS I from somatoform²⁵ and idiopathic pain syndromes, for example by focusing on differences in diagnosis between medical disciplines.

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table 1. Differential diagnosis in CRPS of the extremities as mentioned in the literature

<i>neuropathic pain syndrome</i>	peripheral polyneuropathy (e.g. diabetic) neural entrapment radiculopathy CRPS type III postherpetic neuralgia deafferentation pain
<i>myofascial pain syndrome</i>	myofascial pain NOS occupational overuse tennis elbow repetitive strain injury fibromyalgia
<i>inflammation</i>	inflammation NOS bursitis seronegative arthritis rheumatologic disease
<i>vascular</i>	acrocyanosis atherosclerosis Raynaud's phenomenon erythromelalgia
<i>psychogenic involvement</i>	somatoform pain disorder Münchhausen syndrome NOS = Not Otherwise Specified

table 2. Frequency distributions of diagnosis of the 6 CRPS specialists

<i>physician</i>	<i>CRPS I</i>	<i>CRPS II</i>	<i>CRPS III</i>	<i>Somatoform</i>	<i>Other</i>
1 (anesthesiologist)	.60	.12	.08	.20	.00
2 (surgeon)	.80	.08	.08	.04	.00
3 (surgeon)	.80	.08	.12	.00	.00
4 (anesthesiologist)	.52	.00	.28	.04	.16
5 (anesthesiologist)	.76	.08	.04	.12	.00
6 (neurologist)	.52	.08	.00	.24	.16
Total	.67	.07	.10	.11	.05

CRPS III is idiopathic pain with sensory, motor and/or tissue abnormalities.

table 3. Frequency distribution (%) of the clinical diagnosis of 5 observers, conditional on the judgment of the other observer

	Cases (N=150)	CRPS I	CRPS II	CRPS III	Somatoform	Other
CRPS I	99	75%	5%	7%	9%	4%
CRPS II	11	44%	40%	11%	0%	5%
CRPS III*	15	47%	8%	13%	21%	11%
Somatoform	17	49%	0%	19%	25%	7%
Other	8	55%	8%	20%	12%	5%

* CRPS III is 'pain and sensory, motor and/or tissue abnormalities not otherwise specified'. Somatoform is somatoform disorder

table 4. Kappa values between physicians in diagnosing patients suspected for having CRPS

	physician 2 (surg.)	physician 3 (surg.)	physician 4 (anesth.)	physician 5 (anesth.)	physician 6 (neur.)
physician 1 (anesth.)	0.27	0.12	0.15	0.29	0.30
physician 2 (surg.)		0.30	0.07	0.05	0.15
physician 3 (surg.)			0.13	0.26	0.17
physician 4 (anesth.)				0.18	0.25
physician 5 (anesth.)					0.23

Anesth is anesthesiologist. Surg. is surgeon. Neur. is neurologist

Figure 1. Signs and symptoms relevant in expert-based CRPS diagnosis as found after logistic regression. The frequencies of these signs and symptoms in CRPS, CRPS type III and somatoform disorder as diagnosed by experts is given. CRPS I/II is the lower bar

Figure 2. Signs and symptoms relevant in expert-based CRPS type III diagnosis as found after logistic regression. The frequencies of these signs and symptoms in CRPS, CRPS type III and somatoform disorder as diagnosed by experts is given. CRPS type III is represented by the bar in the middle.

Figure 3. Signs and symptoms relevant in expert-based somatoform disorder as found after logistic regression. The frequencies of these signs and symptoms in CRPS, CRPS type III and somatoform disorder as diagnosed by experts is given. Somatoform disorder is represented by the upper bar.

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Discrepancy between Complaints and Objective Signs in Complex Regional Pain Syndrome: a multi-observer study

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Summary

Complex Regional Pain Syndrome of Reflex Sympathetic Dystrophy (CRPS) is a controversial diagnosis based on clinical criteria, i.e. signs and symptoms. Symptoms are reported complaints of the patient. Signs are features found by physical examination. The clinical impression in CRPS is that symptoms cannot always be confirmed upon physical examination. We studied the predictive value of symptoms for the presence of signs.

6 CRPS experts saw a study population of 25 patients, in the past diagnosed as having reflex sympathetic dystrophy. In these patients physicians were often not able to confirm CRPS symptoms by physical examination. Signs, which can be exaggerated by the patient, like pain and limb function related signs were found more often than behaviourally independent signs like oedema.

The discrepancy in prevalence of signs and symptoms in CRPS has important implications for the applicability of clinical diagnostic criteria for CRPS.

Introduction

Complex Regional Pain Syndrome (CRPS) or Reflex Sympathetic Dystrophy (RSD) is a controversial diagnosis. Its symptoms are usually continuing pain, swelling, autonomic dysregulation and chronic functional impairment after a trauma of the affected limb. Diagnostic criteria are identical to causalgia in which additionally nerve damage is proven. The diagnosis of CRPS is based on clinical observations. A gold standard in the form of an objective test is not available despite many efforts¹⁻¹². A main clinical problem is inter-physician variability in CRPS diagnosis. This is due to the variability in observed signs, symptoms and the amount of signs, symptoms and credibility in patients, needed to reach the diagnosis CRPS.

In CRPS patients one often sees a clinical mismatch between symptom presentation and objective findings¹³. As this mismatch is a prerequisite for the diagnosis of somatoform disorder, this might be the most important differential diagnosis of CRPS.¹⁴ The possibility of a somatoform pain disorder emerges when one can conclude that the symptoms are in excess of what would be expected from the physical findings, especially when credibility of the patient is doubtful.^{15,16} The aim of this study was to formally assess the possible discrepancy between signs and symptom presentation in a chronic pain patient population suspected of CRPS.

Patients and methods

We here report a study where six physicians with known experience on CRPS examined 25 patients during four afternoon sessions. By doing so we aimed to reduce the impact of temporal changes in signs (recurrences) and observer-bias in physical signs. We chose to study inter-observer reliability among 6 different physicians, as it can be doubted whether predictive values of CRPS symptoms analyzed in a single-observer study have sufficient external validity.¹⁷ To minimize inter-observer variability the six participating physicians used a semi-structured interview containing 18 signs and symptoms. Assessment by sex specialists in this study of 25 possible CRPS patients resulted in a collection of 150 data sets. All patients gave informed consent.

Patient selection

Patients were selected at random from a database of patients ever diagnosed as CRPS at the Maastricht University Hospital Pain Management and Research Centre, a tertiary outpatient clinic of

pain management. The only criterion was that patient's pain syndrome had ever been diagnosed as Complex Regional Pain Syndrome type one or Reflex Sympathetic Dystrophy and was informed about their diagnosis. Despite treatment, all patients continued to have complaints. To check whether all patients still had CRPS complaints, physicians were asked to assign a diagnosis to each patient after finishing the interview and examination.

Statistical analysis was conducted with SPSS (SPSS 7.5 for Windows). Predictive power for absence and presence of subjective symptoms to predict the presence or absence of objective signs in physical examination was conducted. Positive predictive value (PPV) was defined as true positive plus false-positive rates. This indicates the probability that the presence of a CRPS-symptom in the interview is followed by positive findings in physical examination.

Results

Twenty-five patients with a mean age of 42.3 years (23-65 years) participated of whom eighteen had upper extremity involvement and seven lower extremity involvement. Twenty-three patients were women. Duration of symptoms had a median of 39 months (range 5-168 months). A retrospective patient file search revealed that the patients had visited a mean of at least eight physicians (range 5-13) prior to participation.

In our study all patients were diagnosed as CRPS by at least one physician¹⁶. In 67% of the total number of assessments CRPS was diagnosed. All six physicians diagnosed eight patients (32%) as CRPS. Another eight patients were diagnosed as CRPS by four or five physicians, and six CRPS by only two or three physicians and three remaining patients by only one physician. Other diagnoses were causalgia (CRPS-II), pain and sensory/motor/tissue abnormalities not otherwise specified (CRPS-III), somatoform pain syndrome, and more rarely pain 'not otherwise specified' and myofascial pain syndrome (Table 1).¹⁸

We studied how often symptoms coincided with findings in physical examination. Mainly pain related symptoms as pain during movement, after touch and hyperpathy were confirmed in physical examination, as represented by the positive predictive value (Table 2). Supposedly 'objective' symptoms as tremor, edema, discoloration of the skin and hyperhidrosis were less often substantiated upon examination (Table 2).

Discussion

CRPS is a difficult clinical diagnosis lacking a gold standard laboratory test. Criteria- systems may have a high sensitivity, but specificity remains a problem.¹⁹ For as far as we know this is the first published study on predictive values of symptoms in possible CRPS patients in relation to their signs. Also it is one of the few studies in which physicians saw patients 'in vivo', instead of via videotapes or patient's records, at almost the same time. Because patients were interviewed six times, this study aimed to give more insight in general practice where patients are also seen by several physicians during their illness. This study material has limitations. All patients were diagnosed as CRPS by at least one observer and 88% by at least two physicians. The study population was small with 25 patients. The study population might be representative for chronic pain patients strongly suspected of CRPS, but not for acute CRPS patients. Frequency of signs and symptoms were probably lower than in patients with acute CRPS. Frequencies of signs were, besides oedema, similar or higher than in one comparable study in which CRPS patients were diagnosed according to IASP criteria.¹⁴

We show here that the value of symptoms in predicting CRPS signs is low. Symptom exaggeration might be a partial explanation. Since sign exaggeration is also possible in CRPS, CRPS-signs were divided in pain behaviour related signs as allodynia, pain upon movement, functional impairment, dysesthesia etc. and in more objective signs as discoloration, swelling, nail-growth, hyperhidrosis and tremor. Pain and limb function related symptoms had a reasonable positive predictive value between 79.2% and 96.5%, but the other symptoms like changed skin temperature, edema, hyperhidrosis and discoloration of the skin did predict objective findings in only 46.0%-66.9%. One can deduct from table 2 that positive predictive value is highest in those signs where patient pain behaviour possibly could influence its observer's opinion where lowest values are found in behaviour independent signs.

The relative lack of objective signs in most patients gives difficulties in CRPS diagnosis. If one decides to focus on objective signs for diagnosing CRPS, one often chooses to ignore patients' complaints. This may lead to underdiagnosis of CRPS. Fluctuating signs like edema and skin temperature and colour change may as well cause the discrepancy between signs and symptoms. Clinical physicians will therefore not always avoid symptom-based diagnosis in case of negative findings in a patient. Even patients with rheumatoid arthritis reported 'excessively swollen' or 'stretched' joints, while the physician was not able to find swollen joints.²⁰

Nevertheless, the discrepancy between symptom presentation and objective findings together with a low specificity of criteria put CRPS back in line with other much criticised syndromes as somatoform pain disorder, fibromyalgia, carpal tunnel syndrome, chronic fatigue syndrome and perhaps irritable bowel syndrome.²¹ In particular, somatoform pain disorder is potentially the principal differential diagnosis of CRPS, as the discrepancy between sign and symptom presentation is actually the main diagnostic criterion for somatoform pain disorder.¹⁵ Putting CRPS next to this syndrome explains at least partially the debate and scepticism around this diagnosis.²²

Where exclusive sign-based diagnosis may lead to underdiagnosis and undertreatment, focussing on CRPS symptoms in diagnosis renders the diagnostic outcome vulnerable for suggestion, malingering and overdiagnosis. Future CRPS criteria will be widely available in our present information society and patients will be seen by several physicians. This gives the patient often more knowledge on symptom presentation than physicians and leaves him/her more vulnerable for suggestion. This may lead to overrepresentation of symptoms.

Our results indicate that in CRPS the most objective signs are the least likely to be found in physical examination. So theoretically, one wonders whether a subgroup of patients with CRPS symptoms do consciously or subconsciously, exaggerate their symptoms and several signs. It is too early to conclude that a subgroup of CRPS patients has a psychological problem, just because CRPS signs are often absent or possibly exaggerated.²³ For the moment we only know that many CRPS patients have symptoms and signs that cannot be explained by any neurological, inflammatory or even psychiatric entity. More research should be done to evaluate any fluctuation in CRPS signs in individual patients to explain the sign/symptom discrepancy.

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Table 1 **Assigned diagnoses in study population**

CRPS	99
Causalgia	11
Pain and sens./motor/tissue-abnormalities NOS	15
Pain NOS	6
Somatoform pain syndrome	17
Myofascial pain syndrome	1
Two pain syndromes	1
Total	150

Frequencies of 150 diagnosis in population (N=25). NOS is 'not otherwise specified'.

Table 2 Positive predictive value (PPV, %) and negative predictive value (NPV, %) of subjective CRPS symptoms (%) for CRPS signs (%).

	symptoms	signs	PPV	NPV	sensitivity	specificity
Functional impairment	0.96	0.95	96.5	50	97.9	37.5
Impairment of movement	0.96	0.93	96.5	83.3	99.3	50
Limb movements are painful (acute)	0.86	0.89	94.5	47.6	91.7	58.8
Loss of strength	0.99	0.87	89.1	100	100	15.8
Pain upon soft touch (mechanical allodynia)	0.65	0.64	88.5	81.1	89.5	79.6
Pain aggravates with cold and/or heat	0.94	0.80	83.6	77.8	98.3	23.3
Provoked pain last longer (hyperpathia)	0.89	0.77	83.5	76.5	96.5	37.1
Guarding of affected extremity	0.87	0.73	79.2	70	94.5	34.1
Hypersensitivity	0.73	0.58	72.5	82.5	91.9	52.4
Dysesthesia	0.96	0.73	69.7	85.7	99	12.2
Changed skin temperature	0.83	0.59	66.9	80	94.2	33.3
Hypesthesia	0.81	0.55	64.8	78.6	92.9	33.8
Discoloration of skin	0.79	0.54	61.9	80.6	92.4	35.7
Changed nail growth	0.65	0.39	58.2	98.1	98.3	55.4
Swelling (edema)	0.72	0.35	54.4	92.9	94.2	39.8
Changed hair growth	0.31	0.16	48.9	99	95.8	81
Anhydrosis/hyperhidrosis	0.67	0.33	46	92	92	46
Tremor	0.32	0.11	31.3	99	93.8	75.4

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HLA-DQ1 associated with reflex sympathetic dystrophy

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Summary

Reflex sympathetic dystrophy (RSD) is a relatively common invalidating disorder of unknown pathophysiology. From a cohort of 52 patients, carefully selected to fulfill the recently formulated diagnostic criteria for RSD, venous blood samples were taken for typing of class I and II major histocompatibility antigens. The frequency of HLA-DQ1 was found to be significantly increased compared with control frequencies. The association provides an indication for an organic basis of RSD.

Introduction. Reflex sympathetic dystrophy (RSD) is a disabling disease of unknown pathophysiology that usually starts following trauma to an extremity. The affected limb is characterized by pain, impaired function and shows signs like oedema, skin colouring changes, hypoesthesia, allodynia, and altered growth of hairs and nails. Genetic factors are likely to be involved. In a rat model of RSD, sensitiveness of rats to develop neuropathic pain has been found inheritable.¹ To test the hypothesis that there is a genetic predisposition to RSD, we investigated the relationship between RSD and the human leucocyte antigen (HLA) system.

Methods.

Fifty-two unrelated Dutch patients with a definite diagnosis of RSD according to the criteria given by the International Association for the Study of Pain were selected for study. The criteria are listed in Table 1. Serological HLA typing was performed by the standard microcytotoxicity assay for both class I and class II major histocompatibility (MHC) antigens 3,4. Class I typing was routinely carried out for 18 A-locus, 33 B-locus and 8 C-locus antigens. Class II typing detected DR1 to DR16 and DQ1 to DQ4. The results obtained in the patient group were compared to the frequencies in a random control group of 295 unrelated healthy individuals, representative of the Dutch population overall. They were mainly recruited from hospital staff and blood donors. The presence of a particular HLA type does not depend on age or sex, but is dependent on race. All patients and controls were of Caucasian origin.

Results.

The frequency of DQ1 was found to be increased from 42% in the normal population to 69% among patients with RSD (Bonferroni corrected 2, $p = 0.02$). All other MHC antigens did not differ significantly from control frequencies (Table 2).

Discussion.

Previously, an association between RSD and DR15(2) has been found in a small sample of patients⁵. This association is compatible with our observation since DQ1 is closely linked with DR15(2). The biological significance of this association is not clear and we do not know whether the association is due to the serologically detectable HLA antigens themselves or whether other genetic factors linked to the MHC region but different from the antigens may be more directly involved in determining the susceptibility to RSD.

The linkage shown by our results between the MHC and RSD suggests an organic basis of this disorder. It is of interest that the neurologic disorders multiple sclerosis and narcolepsy are associated with the same HLA antigens⁶. These HLA antigens possibly relate to factors involved in repair of damaged neural tissue. The demonstrated association should prompt further research to better understand how RSD could be linked to a particular HLA antigen and how this association could be shared with other neurological disorders such as multiple sclerosis and narcolepsy.

Table 1. Diagnostic criteria for reflex sympathetic dystrophy

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

Diagnostic criteria for reflex sympathetic dystrophy as stated by the International Association for the Study of Pain. 2 Criteria 2 to 4 must be satisfied.

Table 2. Frequencies of class I and II major histocompatibility antigens of patients with reflex sympathetic dystrophy and controls

antigen					antigen				
n = 52		n = 295			n = 52		n = 295		
	n	%	n	%		n	%	n	%
A1	22	41	85	29	B35	9	17	54	18
A2	20	39	131	44	B37	1	2	13	4
A3	14	26	98	33	B60 (40)	5	9	33	11
A23 (9)	2	4	19	6	B61 (40)	0	0	11	4
A24 (9)	12	23	51	17	B41	0	0	6	2
A25 (10)	1	2	9	3	B42	0	0	0	0
A26 (10)	3	6	16	5	B46	0	0	1	0
A34 (10)	0	0	0	0	B47	0	0	2	1
A66 (10)	0	0	2	1	B48	0	0	0	0
A11	8	15	25	9	B53	0	0	5	2
A29 (19)	1	2	21	7	B70	0	0	0	0
A30 (19)	2	4	20	7	B73	0	0	0	0
A31 (19)	3	6	18	6					
A32 (19)	3	6	22	8	Cw1	2	4	15	5
A33 (19)	1	2	4	1	Cw2	10	19	44	15
A74 (19)	0	0	0	0	Cw3	15	29	103	35
A28	5	9	29	10	Cw4	9	17	82	28
A36	0	0	0	0	Cw5	8	15	40	14
					Cw6	6	12	51	17
B51 (5)	6	11	34	12	Cw7	30	58	153	52
B52 (5)	0	0	4	1	Cw8	2	4	13	4
B7	13	25	62	21					
B8	10	19	62	21	DR1	8	15	52	18
B44 (12)	14	27	62	21	DR15 (2)	13	25	38	13
B45 (12)	0	0	7	2	DR16 (2)	3	6	4	1
B13	1	2	16	5	DR3	9	17	40	14
B14	3	6	13	4	DR4	17	32	52	18
B62 (15)	8	15	36	12	DR11 (5)	6	11	40	14
B63 (15)	1	2	6	2	DR12 (5)	2	4	10	3
B75 (15)	0	0	1	0	DR13 (6)	11	20	50	17
B38 (16)	3	6	11	4	DR14 (6)	4	7	15	5
B39 (16)	5	9	14	5	DR7	14	26	43	15
B57 (17)	5	9	14	5	DR8	8	15	17	6
B58 (17)	0	0	3	1	DR9	1	2	4	1
B18	6	11	26	9	DR10	2	4	8	3
B49 (21)	2	4	10	3					
B50 (21)	0	0	5	2	DQ1	36	69	124	42
B55 (22)	3	6	14	5	DQ2	15	29	69	23
B56 (22)	0	0	7	2	DQ3	30	58	106	36
B27	6	11	17	6	DQ4	7	13	11	4

Data given as numbers of patients and percentages. Only DQ1 frequencies of RSD patients and controls differed statistically significant at the Bonferroni corrected $p < 0.05$ level.

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Screening of patients with complex regional pain syndrome type I for antecedent infections

Screening of Patients with Complex Regional Pain Syndrome type I for Antecedent Infections

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Summary

This study was designed to investigate whether Complex Regional pain syndrome type I (CRPS I) could be linked to any previous infection.

Fifty-two patients with CRPS I of one extremity were screened for the presence of antibodies against mostly neurotropic microorganisms.

Of these 52 patients none had antibodies against *Treponema pallidum*, *Borrelia burgdorferi* or HTLV-1.

Only four patients were positive for *Campylobacter jejuni*. For cytomegalovirus, Epstein-Barr virus, herpes simplex virus and *Toxoplasma gondii*, seroprevalences were similar to control values. The total seroprevalence of parvovirus B19 was 77%, which was significantly higher than in an independent Dutch population group (59%). Seroprevalence in lower extremity CRPS I (94%) was significantly higher than in upper extremity CRPS I patients (68%). In this study all patients were seropositive for varicella zoster virus (VZV) antibodies, but a high prevalence of VZV antibodies is similar to its prevalence in a normal population (>90%).

In this study we found a significantly higher seroprevalence of Parvovirus B19 in CRPS I and this is most striking in lower extremity CRPS I patients. Further serologic research in other geographic areas is needed to provide additional information about a potential role of Parvovirus B19 or other microorganisms in the etiopathogenesis of CRPS I.

Introduction

Complex regional pain syndrome type I (CRPS I) is a seriously disabling neuropathic pain syndrome. Its etiopathogenesis remains an enigma.¹ Antecedent infections have been implicated in its pathogenesis, because some of its key features (e.g., edema, pain, vasomotor abnormalities) point to an ongoing inflammatory process.^{2,3} Also, its association with human leucocyte antigen DQ1 suggests an involvement of the immunological system⁴. In other neurological disorders of unknown origin progress has been made as to the role of infections like in Bell's palsy^{5,6}, multiple sclerosis⁷⁻⁹, and Alzheimer's dementia¹⁰. The role of *Campylobacter jejuni*, cytomegalovirus (CMV) and Epstein-Barr virus (EBV) in the onset of certain forms of Guillain-Barré syndrome is a recent example of research along these lines.^{11,12}

Antecedent infections may have predisposed patients in such a way that a minor trauma resulted in CRPS I. A systematic analysis of the serologic status of CRPS I patients as to antecedent infections has to our knowledge not been carried out. We report herein a systemic serological screening for 10 different microbiological organisms, of 52 strictly diagnosed CRPS I patients.

Patients and results

Sample and data collection

All medical specialists known to treat patients with CRPS I (such as anesthesiologists, surgeons, and neurologists) working in the south of The Netherlands were asked to refer patients fulfilling the standardized diagnostic algorithm (table 1) to the Maastricht University Hospital. The algorithm closely resembles the criteria for Chronic Regional Pain Syndrome type 1 as stated by the International Association for the Study of Pain (IASP).¹³ The final decision whether patients could enroll the study

was based on rechecking the diagnostic criteria. A physical examination was conducted by two physicians separately, as well as a psychological test (SCL-90).¹⁴ Patients with CRPS I (n=52) were asked to supply venous blood for further research. The patients, mostly sent by other centers, suffered from chronic CRPS I in one extremity in which no therapeutic modality had yielded resolution of the symptoms. The diagnosis was made by two physicians separately.¹³ In addition patients were selected who had suffered from CRPS I for at least 6 months, during which period the symptoms had been unresponsive to all conventional treatments, such as nonsteroidal antiinflammatory drugs, opioids, antidepressants, anticonvulsants, sympathetic blocks, transcutaneous electric nerve stimulation, and physical therapy. Pain, as measured on a 10 cm Visual Analogue Score had to be at least 5 cm.¹⁵

Patients with other conditions affecting function were not included in the study. Informed consent was obtained from all patients according to the Declaration of Helsinki. The study protocol had been approved by the Ethical Committee of our institution.

Eventually, 54 patients were considered eligible for the study and 56 were excluded, 40 were not eligible and 16 refused to participate. No blood was drawn from two of the patients included in the study. The reason for this is not known. All 52 remaining patients were white, Dutch-speaking adults (18-65 years of age) suffering from severe CRPS I affecting either one arm (n = 34) or one leg (n = 18).

Possibly involved pathogens were identified by a Medline search from 1966 - 1997 (keywords: serological, virus, infection, serology and dystrophy; neurotropic and infection or virus), based upon the hypothesis that neurotropic microorganisms could play a role in the etiopathogenesis of CRPS I. Ten ml of serum was frozen and stored at a temperature of -20°C. Serological status was measured according to standard laboratory procedures of our microbiology department. Detection of IgG-antibodies was done with microimmunofluorescence for herpes simplex virus (HSV), varicella zoster virus (VZV) and EBV-virus capsid antigen (each distributed by Gull, 's Hertogenbosch, The Netherlands). Screening was done with dilution 1:10. Quantification was done with dilutions 1:100, 200, 400, 800 and 1600. For anti-Parvovirus B19 IgG antibodies a qualitative immunofluorescent assay (Biotrin, Dublin, Ireland) with dilution 1:64 was done. Campylobacter serology was done with complement fixation and with ELISA methodology (both from Virion, W, rzburg, Germany). Anti-CMV and Toxoplasma gondii IgG antibodies were quantitatively measured by AxSYM (Abbott, Hoofddorp, The Netherlands). TPHA for Treponema pallidum and anti-human T-lymphocyte virus -1 (HTLV- 1) antibodies were investigated by agglutination (Fujirebio, Tokyo, Japan) and anti -Borrelia burgdorferi IgG antibodies with ELISA (IDEIA Dako, Cambridgeshire, United Kingdom).

Statistical analysis on CRPS I extremity subgroup seroprevalences was performed using either a two-tailed Chi square or a Fisher's Exact Test (SPSS, p<0.05).

Results

Fifty-two patients (37 females and 15 men) participated, with a mean age of 38.9 years (21-65 yrs) and a mean CRPS I duration of 37.7 months (9-120 months). Thirty-four had CRPS I of their arm and 18 had CRPS I of their leg. The CRPS I was precipitated by trauma in 25 patients, by surgery in 23 patients and had started spontaneously in the last four patients. All patients suffered severe pain and functional impairment, which made them unfit for work. Of 34 patients with an affected hand, 20 were unable to use their hand for any daily activity; 13 were using a splint. Of 18 patients with an affected foot, 7 were wheelchair-dependent and 8 were using crutches.

All patients were seropositive for VZV and 50 patients (96%) were seropositive for EBV. For parvovirus B19 and for HSV the prevalence of antibodies in this group of patients was 77% and 73% respectively. A lower prevalence was found for CMV (40%), *T. gondii* (23%) and *C. jejuni* (8%). All patients were negative for *T. pallidum*, *B. burgdorferi* and HTLV-1 antibodies. Data are given in table 2 and 3.

For levels of detectable antibodies, the median immunofluorescence titer was 100 (range 10-800) for VZV, 200 (range 10-1600) for HSV and 400 (range 100-1600) for EBV. For VZV, HSV and EBV respectively 21, 18 and 15 patients had an above-median titer. The median results for CMV and Toxoplasma were >250 IU/ml and 23 IU/ml, respectively. Prevalence of Parvovirus B19 infection in lower extremity CRPS is 94% and higher than expected. The prevalence is significantly more than the 68% seroprevalence of B19 parvovirus in patients with upper extremity CRPS I ($p = 0.04$). The total seroprevalence in our CRPS population is 77%. This is partially due to the high prevalence in lower extremity CRPS, significantly higher than the 59% seroprevalence of Parvovirus B19 in a Dutch population group ($n = 353$, $p = 0.01$).¹⁶

Discussion

CRPS I is a seriously disabling neuropathic pain syndrome of unknown pathophysiology. Although (neurogenic) inflammation has been hypothesized to play a role in the pathogenesis of the disorder^{17,18}, a systemic search for a microbiological infection as a possible causative mechanism has, to our knowledge, not been performed. In the past, studies along these lines have probably been hampered by lack of diagnostic criteria and budgetary restrictions. We report a systematic serologic analysis of 52 carefully diagnosed CRPS I patients. Our ratio of lower versus upper extremity CRPS I patients (18:34) is comparable to the normal ratio of 1:2.¹⁹⁻²¹ There is an extensive list both of possible neurotropic infections in the Western World (northwestern Europe) and of pathogens ever associated with CRPS I or neurologic diseases. Most of these infections are longlasting or latent infections, often present since childhood. Also, in our study group the duration of the CRPS I had been so long that the IgM antibodies were not expected anymore. For both these reasons, only IgG serology was done. For epidemiological reasons, we did not screen for pathogens as rabies, JC virus, poliovirus, mumps and HIV. Ethical reasons also kept us from screening for HIV.

No association was found between CRPS I and *T. pallidum*, *B. burgdorferi* or HTLV-1 since all patients were seronegative. In contrast, IgG antibodies against VZV (100%) and EBV (96%) were present in almost all patients. However, this high seroprevalence is not significantly different from the high seroprevalence (>90%) worldwide^{22,23} or from a seroprevalence of about 75% in an independent Dutch control group¹⁶. Because of this high seroprevalence, much larger studies or studies in other geographic areas would have to be done to prove or even exclude an eventual correlation between CRPS I and VZV or EBV. The seroprevalence of HSV in the CRPS I patients was 73%, which is almost the same as the seroprevalence of 68% in the Dutch control group.¹⁶ The percentages are also comparable with a seroprevalence of 30-50 % in higher socioeconomic groups and increased prevalence to 80-100 % in lower socioeconomic groups.²³ In female CRPS I patients, the seroprevalence of EBV, HSV and parvovirus B19 was 9-14% higher than in male patients. For CMV and for *Toxoplasma gondii* the seroprevalence was higher in men. These differences are not statistically significant, possibly because of the low number of patients.

The worldwide seroprevalence of antibodies against CMV ranges from 40 to 100 percent depending on

the socioeconomic composition of the population.²³ The prevalence of 40% found in our CRPS I patients is lower than a prevalence of 51% found in the Dutch control group.¹⁶ Although in our study only 21 (40%) CRPS I patients were positive for specific anti-CMV antibodies, the titer distribution was skewed by high anti-CMV antibody titers. Thirteen patients had a level of more than 250 IU/ml and six patients had a level between 120 and 250 IU/ml. Only two young women (age 27 and 29 years) had levels of 16 and 59 IU/ml. The high anti-CMV antibody levels in CRPS I patients probably does not indicate an etiological role. It is more likely that these high antibody levels are a reflection of a potential reactivation of a latent CMV infection during acute or chronic clinical CRPS I.

The worldwide variation in prevalence of anti-*T. gondii* antibodies ranges from only 3 to more than 90% of healthy adults depending of the selected population.²³ Again, the seroprevalence of 23% for anti-*T. gondii* antibodies in our CRPS I patients is comparable to a prevalence of 22% found in all patients investigated in our hospital in 1997 (unpublished data). Also, the level of antibodies was in accordance with the normal distribution mentioned in unpublished data from Abbott, Hoofddorp, The Netherlands.

Only four patients had detectable antibodies against *C. jejuni*. However, in two patients this was accompanied with a high titer (128) of complement binding antibodies, suggesting a recent infection in patients with an already pre-existing CRPS I. This means that at the onset of CRPS I probably only two patients were seropositive for anti-*C. jejuni* antibodies.

The seroprevalence of parvovirus B19, in our patient population of 77% is higher than the 30%- 60% mentioned in literature²²⁻²⁴ and the 59% found in patients from the Dutch control group.¹⁶ Strikingly, we found in patients with lower extremity involvement (table 3) that the seroprevalence for parvovirus B19 is more than 94%. This is significantly more ($p = 0.039$) than the 68% seroprevalence of B19 parvovirus in patients with upper extremity CRPS I. In the lower extremity CRPS I group there is a predominance of women. Women have a slightly higher seroprevalence of anti- parvovirus B19 antibodies than men.²⁵ However, this female overrepresentation does not completely explain this difference, because similarly higher seroprevalences for EBV and HSV in women did not result in significant differences between upper and lower extremity subgroups.

The most common manifestation of Parvovirus B19 is an erythema infectiosum, also known as fifth disease, with a mild febrile illness and a maculopapular rash ("slapped cheek" appearance) of variable intensity. Besides the erythema, prodromal symptoms and influenza-like illness are also possible, as are arthropathy, transient aplastic crisis, and pregnancy complicated by hydrops fetalis or fetal death. There is evidence that Parvovirus B19 infection induces the production of autoantibodies.^{26,27} It may be associated with rheumatoid arthritis²⁸ and transient systemic lupus erythematosus-like symptoms.²⁹

Central nervous system involvement is a rare but well-documented complication of Parvovirus B19 infection in children and adults. Parvovirus B19 has been associated with encephalitis³⁰, encephalopathy³¹⁻³³, aseptic meningitis^{34,35}, ocular neuropathy³⁶, and fetal brain infection.³⁷ In addition, brachial plexus neuropathy^{32,38-40}, recurrent paresthesias⁴¹, and numbness and tingling of fingers⁴² are associated with Parvovirus B19 infection.

A possible role of Parvovirus B19 in the etiopathogenesis of CRPS I is also suggested by a case report.²⁸ The prevalence of symptoms in Parvovirus infection is unknown. Parvovirus infection can manifest in subclinical infection or clinical arthralgia. Because many CRPS I patients report diffuse pain without sympathetic dysregulation before CRPS onset, Parvovirus might be a direct precursor of CRPS

I. A prospective study for antecedent arthralgias in CRPS I would be interesting. A subclinical Parvovirus infection may well precede CRPS by a period of several months or even years, because auto-immunological mechanisms through tissue mimicry can manifest slowly.

Conclusion

In this study we did not find a clear association between CRPS I and any of the investigated microorganisms. For parvovirus B19 we found a significantly higher seroprevalence in CRPS I and this is most striking in lower extremity CRPS I patients. Because of high seroprevalences of VZV, EBV and HSV in CRPS I patients as well as in a control group, an association between herpesviridae and CRPS I could not be excluded. CMV has probably no etiological role in CRPS I, but reactivation of a foregoing latent CMV infection during CRPS I is possible. Low seroprevalences were found for *T. gondii* and *C. jejuni*. No antibodies were found against *T. Pallidum*, *B. burgdorferi* and HTLV-1. Further serological research in other geographic areas will have to give additional information about a potential role of parvovirus B19 or other microorganisms in the etiopathogenesis of CRPS I.

Table 1. CRPS I criteria for study inclusion**Absolute criteria:**

pain (Visual Analogue Score >5)
 impaired function *
 expansion of symptoms outside the area of trauma *
 cold, warm or intermittent cold-warm feeling in affected extremity

Relative criteria (3 of 9)

edema
 increased nail growth
 increased hair growth
 hyperhidrosis
 abnormal skin coloring
 hypesthesia
 hyperalgesia
 mechanical and/or thermal allodynia
 patchy demineralization of bone

* Indicates those additional to those of the International Association for the Study of Pain

Table 2. Qualitative and quantitative serologic screening in Reflex Sympathetic Dystrophy

Age, y	No. of patients	CJ	Toxo -plasma (%)	CMV (%)	HSV (%)	P-B19 (%)	EBV (%)	VZV
20 - 30	11	1	0	4 (36%)	7 (64%)	9 (82%)	9	11
30 - 40	18	0	2 (11%)	7 (39%)	13 (72%)	14 (78%)	18	18
40 - 50	12	1	5 (42%)	4 (33%)	8 (67%)	10 (83%)	12	12
> 50	11	2	5 (45%)	6 (55%)	10 (91%)	7 (64%)	11	11
Total,%	52	4	12 (23%)	21 (40%)	38 (73%)	40 (77%)	50 (96%)	52 (100%)
Median titer	-	-	23	> 250	200	-	400	100
Range			14 - 88	16- >250	10-1600		100-1600	10-800

CJ, *Campylobacter jejuni*; CMV, cytomegalovirus; HSV, herpes simplex virus; P-B19, parvovirus B19; EBV, Epstein-Barr virus

Table 3. Percentage of seroprevalence in CRPS I subgroups

	no.of patients	Toxopl.	CMV	HSV	P-B19	EBV	VZV
women (%)	37	3	6 (16%)	28 (76%)	30 (81%)	37 (100%)	37 (100%)
men (%)	15	1	6 (40%)	10 (67%)	10 (67%)	13 (87%)	15 (100%)
lower extremity (%)	18	3 (17%)	12 (50%)	14 (78%)	17 (94%)*	18 (100%)	18 (100%)
upper extremity (%)	34	9 (28%)	12 (35%)	24 (71%)	23 (68%)*	32 (94%)	34 (100%)

*Significance : $p < 0.04$ (two-tailed Fisher's Exact Test)

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Randomised controlled trial of gabapentin in Complex Regional Pain Syndrome type 1

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Article abstract

To study the efficacy of the anticonvulsant gabapentin as treatment for pain in patients with complex regional pain syndrome type 1 (CRPS1).

We did a randomized double blind placebo controlled crossover study with two three-weeks treatment periods with gabapentin and placebo separated by a two-weeks washout period. Patients started at random with gabapentin or placebo, which was administered in identical capsules three times daily. We included 58 patients with CRPS type 1.

Patients reported significant pain relief in favor of gabapentin in the first period. Therapy effect in the second period was less; finally resulting in no significant effect combining results of both periods. The CRPS patients had sensory deficits at baseline. We found that this sensory deficit was significantly reversed in gabapentin users in comparison to placebo users.

Gabapentin had a mild effect on pain in CRPS I. It significantly reduced the sensory deficit in the affected limb. A subpopulation of CRPS patients may benefit from gabapentin.

INTRODUCTION

Complex Regional Pain Syndrome type one (CRPS I) or formerly Reflex Sympathetic Dystrophy (RSD) is a disabling syndrome, in which a painful limb is accompanied by varying symptoms like edema, hyperhidrosis, hypertrichosis, allodynia, coloring of the skin and, over time, atrophy of the involved tissue. Spontaneous recovery does occur and several therapies have been described, but for some patients CRPS I is a chronic disabling disease.¹ Neuropathic pain is a prominent feature of CRPS I, occurring in 75% of cases, and many researchers go as far as classifying CRPS I as a neuropathic pain syndrome.²⁻⁶ Gabapentin (Neurontin®, Pfizer) is an anticonvulsant with a proven analgesic effect in various neuropathic pain syndromes.⁷⁻¹⁵ Anecdotal reports suggest that gabapentin may also be an effective analgesic in CRPS patients.^{3,8,16-27} To study this hypothesis, we conducted a double blind, placebo-controlled crossover trial of gabapentin in 58 patients with Complex Regional Pain Syndrome type I.

METHODS

Study population

This study complied with the Declaration of Helsinki regarding investigations in humans after approval of the protocol by the Institutional Review Board of University Hospital Maastricht, the Netherlands. Patients were recruited from a database with patients who, in recent years, had been diagnosed with complex regional pain syndrome type I in our hospital. All patients had been treated in our pain management and research center (dept. of Anesthesiology, University Hospital Maastricht, The Netherlands) and had received treatments like sympathetic blocks,²⁸ mannitol infusions,^{29,30} transcutaneous neuromodulation. All participating patients fulfilled the IASP criteria³² for the diagnosis of CRPS type I and were included when aged between 18 - 75 years old and when they had a visual analog score (VAS) for pain > 3. Apart from IASP criteria, all patients had functional loss and pain outside the original traumati-

zed area. Patients were excluded in case of a possibility of health risk or confounding by other diseases of syndromes, like e.g., pregnancy, known kidney and/or severe liver disease, another (2nd) chronic pain syndrome, known nerve damage in the affected area, active infection or diabetes mellitus. Patients were participating in 8-week periods from 19-11-1998 until 2-12-1999. Gabapentin was not registered as a drug in the Netherlands before or during the trial. After the trial the producing pharmaceutical company supplied gabapentin for compassionate use if indicated.

Treatment

Since our patient population consisted of chronic CRPS I patients with a multiple years' duration of pain complaints refractory to various treatments, we assumed that their pain complaints would be more or less stable. We therefore undertook a double blind, randomized crossover study.

Randomization of patients took place after baseline measurements and written informed consent. The assignment scheme was generated by our hospital pharmacy from a table of random numbers. The closed envelopes containing the assignments were prenumbered and kept at the pharmacy. The first treatment group received gabapentin, followed by a washout period and placebo treatment. The second treatment group received placebo treatment, which was followed by a washout period and gabapentin treatment. Each medication period lasted three weeks separated by the two-weeks washout period.

Medication was stocked and delivered to the patient at the hospital pharmacy. Both the gabapentin capsules and the identical placebo capsules were delivered immediately before the start of the two medication periods. Left over medication was recollected and counted.

The gabapentin (GBP) dose was slowly increased to reduce adverse side effects:

600 mg's GBP AN once a day on day 1-2

600 mg's GBP b.i.d. on day 3-4

600 mg's GBP t.i.d on day 5-21

Placebo dose was identically titrated. Patients were allowed to take their usual analgesics and were told preferably not to change the usual dose.

Follow-up measurements

The patients were reevaluated at the hospital three weeks (T1), five weeks (T2) and eight weeks (T3) after randomization. During the trial, the patient noted her/his pain rate of the past 24 hr (VAS) and the use of additional analgesics in a diary. During each hospital visit the following assessments were done:

Global perceived effect (GPE) on pain indicating: worst ever; much worse; somewhat worse; not improved/not worse; somewhat improved; much improved and best ever.

GPE on function was scored on an analogous scale.

Neuropathic pain scale (NPS), a 10 item qualitative evaluation of neuropathic pain.³³

Sensibility through Von Frey monofilament skin application each on 9 areas corresponding to cutaneous nerve branches and dermatomes of either both hands or both feet.³⁴ Stimulus placement of filaments was as follows: one second for placement, one second for bending and one second for removal. (hand-set with resp. 0.0677, 0.4082, 2.052 and 3.632 grams calculated force, North Coast Medical, Inc., San José, USA).

Mechanic allodynia test with brush strokes and static pressure with the finger tip,³⁵ on 9 areas corres-

ponding to cutaneous nerve branches and dermatomes of either both hands or both feet.

Edema, discoloration, and changed skin temperature were scored after physical examination on a three point scale indicating no, some or overt presence of each sign, the latter two signs in comparison to the healthy or healthiest limb. Physical examination in CRPS is well comparable to instrumental evaluation of signs with volumeter, infrared thermometer and goniometer.³⁶

Impairment and disability tests: Symptom Checklist-90-Revised (SCL-90-R),³⁷ Brief Pain Inventory,³⁸ adapted for CRPS to measure the influence of CRPS in general on daily life by 0-10 scale ranging from 0 ('CRPS has not interfered') to 10 ('CRPS completely interfered'), 'range of motion' as a parameter of limb function.

Side effects during treatment

A blinded independent investigator (SSvdB) tested sensibility, allodynia and range of motion tests. A physician (AvdV), who examined each patient, did all the other measurements throughout the trial. Patient, investigator and physician were unaware of the treatment received. We tested blinding by questioning physician and participants after each medication period.

Statistical Analysis

The statistical analysis of VAS-scores was determined per patient using estimating medication and period effect through linear regression analyses. Possible relationship of patient characteristics and outcome was tested by Pearson R's test. Mann-Whitney analyses were used for monofilament sensitivity on log-transformed data. Three point scales and seven point scales were dichotomized and like the SCL-90-R, NPS and CRPS-Brief Inventory questionnaires intra-individual paired tested (McNemar, t-test, Bonferroni-Holm corrected for multiple tests). Student t-tests and regression analysis were used to test treatment effect, which is calculated in crossover studies as $((AT1-AT0)-(AT3-AT2))/2+((BT3-BT2))-BT1-BT0)/2$, where A represents data of placebo starters and B data of gabapentin starters both before (T0,T2) and after (T1,T3) treatments.³⁹ Blinding was tested with Chi-square analyses. Possible related factors to therapy effect were analyzed with forward stepwise logistic regression. Data analyses required complete data sets. Patients who were not completing one or two treatments were excluded for analyses. We tested two-tailed, with $\alpha=0.05$ as a level of significance (Excel 2000, SPSS 10.0 for Windows).

RESULTS

Demographics

After randomization 58 patients were enrolled, with a mean age of 44.0 (range 24-75) resulting in 29 patients in the gabapentin-placebo arm and 29 patients in the placebo-gabapentin arm; 49 patients completed the gabapentin period, 50 patients the placebo period, 46 patients completed both periods and were used for further within-patient paired analysis (Table 1). Twelve patients discontinued treatment of which 6 during the placebo treatment, 2 during washout and 4 during GBP treatment. Three of these four GBP users discontinued due to side effects (Table 1). Between randomization and start of (placebo) medication one patient withdrew after rereading the information letter about possible side effects.

These patients were excluded from analysis, since intra-individual testing was necessary for most of the data-analyses. Patients, who could not be used for analysis, did not differ in their characteristics from the total group nor comparing between the two arms of treatment (Tables 2 and 3). When comparing the placebo-GBP arm and GBP-placebo arm on sexes, age and pain level before period 1 or 2, duration of illness, SCL-90-R score, we could not find a difference between the two arms (Tables 2 and 3). SCL-90-R score revealed increased values on any subscale comparing to standard norms, indicating personal distress (Table 3). We found relative higher scores on somatic and sleeping complaints. The SCL-90-R scores were identical to control chronic pain patients (N= 143), besides higher score on sleeping complaints (T. Forouzanfar, data not published). Trial medication was returned and counted afterwards, but revealed no lack of compliance in any patient.

Blinding

After each medication period both patient and physician were asked about their ideas concerning study medication in the past period. The treating physician guessed the used medication correctly more often after both phases than can be explained by coincidence ($p=0.000$). Blinding for patients was sufficient in the first phase, but not anymore after the second phase ($p=0.2$ versus $p=0.000$).

Response to Treatment

Pain

Comparing gabapentin and placebo users in terms of pain relief, there was a significant pain relief in favor of gabapentin in the first period. Therapy effect in the second period was less, finally resulting in no significant effect combining results of both periods. There was an unexpected increase of pain level above baseline in the washout period for both the gabapentin starters and placebo starters (Figure 1). Global perceived pain relief as measured by the seven-point scale showed a significant effect for gabapentin, and also more pronounced in the first period. This measurement also found a significant effect in the second period, with an effect being defined as a patient scoring 'much improvement'. Statistical analysis of global perceived effect showed significant more treatment effect ($p=0.002$) with 43 % versus 17 % reported pain relief respectively during gabapentin compared to placebo treatment. 13 % of patients reported aggravation of pain during gabapentin vs. 9 % during placebo treatment (Figure 2 and table 4). Stepwise forward logistic regression analysis of baseline value of pain level, age, sex, duration of illness, location of illness, mono- or bilateral CRPS, trial arm and all items of CRPS-BI, NPS and SCL-90-R was performed. Only the level of self care was related to perceived pain relief during GBP. The neuropathic pain scale, indicating different aspect of pain, improved significantly in terms of less hot and more comfortable, but not when corrected for multiple tests (Bonferroni-Holm correction). We found that during gabapentin use, patients reported equal use of co-medication comparing to baseline assessment and placebo-use with a non-significant trend towards less medication during GBP use.

Sensory tests

Each participant was tested throughout the study on response to mechanical stimuli with von Frey filaments. The CRPS patients had sensory deficits at baseline. Application of smaller filaments was not felt in multiple skin areas. We found, with Mann-Whitney analyses, that this sensory deficit was significantly reversed in gabapentin users in comparison to placebo users ($p=0.027$). This difference was found in

patients with upper and lower extremity CRPS, but was still significant in the subgroup of lower extremity CRPS ($p=0.011$) as seen in table 5.

Mechanical allodynia to static and dynamic stimuli (soft touch and brush) was measured by a mean of 11-point scales (range 0-10) of 9 areas of the hand/feet corresponding to cutaneous nerve branches. We found no effect of gabapentin on allodynia in comparison to placebo.

Other symptoms

No difference was found on the parameters edema, discoloration, range of motion of wrist/ankle and fingers/toes between placebo and GBP. 10 patients out of 45 improved in relative skin temperature during placebo use compared to 18 patients out of 45 in gabapentin, which is two sided tested not significantly different (McNemar analysis, $p=0.096$).

Limb dysfunction and quality of life

The reported function improvement was, with 10 positive responders during GBP versus 7 positive responders during placebo, not significantly different ($N=46$) between the two treatments. The SCL-90 showed no significantly better scores during gabapentin treatment. CRPS-BI showed improvement of sleep between placebo treatment and gabapentin treatment, but this effect disappeared after Bonferroni-Holm correction.

Adverse effects

Dizziness, somnolence and lethargy were significantly more often reported during gabapentin use than during placebo. Before washout 95 % of patients ($n=21$) reported side effects during gabapentin use versus 58 % in placebo treatment ($n=14$). After washout this was respectively 63% ($n=15$) in GBP and 32% ($n=7$) in placebo use. For more details on side effects see table 6. Since a high incidence of side effects can produce a stronger placebo effect, we analyzed the possible correlation between side effects and pain relief. There was a small relation between perceived side effects and pain relief in placebo users in period 2 ($p=0.04$, Pearson's R value is 0.4), but, whether in period 1 or period 2, no relationship was found during the use of gabapentin ($p=0.2$ in period 1, $P=0.4$ in period 2).

DISCUSSION

To evaluate gabapentin treatment as a treatment for pain in CRPS, we conducted a placebo-controlled crossover study. We conclude from our trial that overall, gabapentin did not relieve pain as compared to placebo on pain visual analogue scores, our primary outcome measure. Gabapentin relieved pain in a subgroup of patients and gave a significant global perceived pain relief. The effect was mild and there was no patient in which gabapentin completely eliminated pain.

Moreover, the frequency of side effects as dizziness, somnolence and lethargy was higher during gabapentin treatment than with placebo. These side effects probably also account for the relative lack of blinding we observed in our study. This does not mean that the study was biased: our population were chronic CRPS patients who all had undergone numerous unsuccessful treatments, and clearly wanted

the drug to work. Any possible bias would therefore have been positive towards gabapentin. Although we did not find a significant pain reducing effect when analyzing the complete trial, we did find a significant effect in the first half of the trial. In fact, the difference in outcome between the two trial halves is striking. There was a reverse carry-over effect resulting in increasing pain above baseline after the washout period for both gabapentin and placebo starters. The increase of pain intensity above baseline level in the second period (before the start of placebo treatment) cannot be explained pharmacologically. Gabapentin has no known biological dependency or tolerance mechanism. It can be a period effect, although this would more likely result in a regression to the middle instead of increasing pain. Perhaps this is a reversed placebo effect in which the expectation and/or the actual perception of not receiving gabapentin anymore might increase pain intensity. Kemler and de Vet found that treatment allocation in a trial can influence pain intensity in CRPS.⁴⁰ The decreasing therapy effect after washout is found in other crossover pain trials.⁴¹ Expectation and attention have been shown to be powerful influences on pain pathways in the brain,⁴² and perhaps a crossover design is not suited to study treatments in chronic pain patients.

We found a decreased sensory deficit in gabapentin users compared to placebo users. We did not expect this, but found in the literature several cases in which gabapentin decreased the area of hypesthesia in neuropathic pain syndromes.⁴³ This has, to our knowledge, never been described for any other medication. Numbness or mechanical hypesthesia is a frequently found complaint for approximately 75 % of CRPS patients, which can improve in time spontaneously and after placebo treatment. It is possible that the somatosensory findings and pain outside the original area of trauma can be attributed to referred pain mechanisms. Gabapentin has been reported to alleviate referred pain.⁴⁵ Since many CRPS patients have mechanical hypesthesia, we hypothesize that gabapentin influences some common neural pathway for 'referred' sensations, whether mechanical sensation or pain.

Gabapentin had a mild effect on pain in patients with CRPS I. It significantly reduced the sensory deficit in the affected limb. A subpopulation of CRPS patients may benefit from gabapentin, but then for each individual patient the benefit has to be weighed against the frequently occurring side effects.

Acknowledgements

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Conflicts of interest:

Parke-Davis (now a Warner-Lambert/Pfizer division) has had no role in the writing of this manuscript. Drs. Van de Vusse and Weber have received financial support from Parke-Davis to attend one congress.

Table 1 Selection of patients participating in the trial

Table 2. Patient characteristics

	Placebo starter	GBP starter	Excluded from analysis	
			Placebo starter	GBP starter
	N=24	N=22	N=5	N=7
Sex (F/M)	21/ 4	18/ 4	3/ 2	6/ 1
Age in years	42($\pm$ 13)	47($\pm$ 14)	40 ($\pm$ 11)	43 ($\pm$ 11)
Duration in months	43 ($\pm$ 36)	44 ($\pm$ 21)	83 ($\pm$ 39)	45($\pm$ 30)
VAS0	64.2 ($\pm$ 16)	62.5 ($\pm$ 18)	62 ($\pm$ 10)	67 ($\pm$ 12)
VAS2	67 ($\pm$ 20)	64 ($\pm$ 21)		
upper extremity pain	3R 8L 3RL=14	8R 7L 4RL=18	2R 0L 1RL	2R 4L 0RL
lower extremity pain	2R 7L 4RL=13	3R 3L 0RL=6	2R 1L 0RL	1R 1L 1RL

R/L/RL represents no. of patients that report pain in resp. right, left or bilateral extremities.

A few patients had upper and lower extremity pain. VAS is pain level on visual analogue scale. VAS0 is day 1, VAS2 is day 35 (post wash-out)

Table 3. Basic characteristics of participating patients on neuropathic pain scale (NPS), CRPS brief inventory and SCL-90-R ($\pm$ standard deviation).

NPS description of pain in terms of 1. intensity 2. sharpness 3. hot 4. aching 5.cold 6. sensitive7. itching 9.comfortability 10a. intensity deep pain 10b. intensity superficial pain. Item 8 is a nominal scale left out of analysis.										
Symptom Checklist-90-Revised (SCL-90-R) subscale on anxiety, phobic anxiety, depression, somatization, obsessive compulsive, interpersonal sensitivity, hostility, insomnia and psychoneuroticism. CRPS BI : influence of CRPS on 1. general activity 2. mood 3. mobility 4. normal work 5. personal relationships 6. sleep 7. enjoyment of life 8. self care 9. recreational hobbies 10. social activities. CRPS BI and NPS on a 0-10 scale.										
NPS										
mean AB n=24	7,3 ($\pm$ 1,8)	7,3 ($\pm$ 1,5)	6,0($\pm$ 3,2)	7,0($\pm$ 2,4)	6,0($\pm$ 3,2)	6,6($\pm$ 2,5)	2,8($\pm$ 2,5)	7,8($\pm$ 1,6)	7,6($\pm$ 1,3)	6,0($\pm$ 2,7)
mean BA n=22	7,3($\pm$ 1,4)	7,4($\pm$ 1,5)	5,9($\pm$ 3,1)	7,2($\pm$ 1,6)	5,9($\pm$ 3,1)	7,2($\pm$ 2,5)	3,7($\pm$ 3,1)	7,7($\pm$ 1,4)	7,8($\pm$ 1,2)	6,8($\pm$ 2,4)
lost AB n=5	7,6 ($\pm$ 0,5)	8 ($\pm$ 1,2)	6,2 ($\pm$ 3,8)	6,8 ($\pm$ 1,8)	8,2 ($\pm$ 0,8)	8,4 ($\pm$ 0,9)	2,8 ($\pm$ 3,8)	7,3 ($\pm$ 1,7)	8,2 ($\pm$ 1,3)	7,4($\pm$ 1,1)
lost BA n=7	7,7($\pm$ 1,4)	7 ($\pm$ 1,3)	5,7 ($\pm$ 3,3)	8,3 ($\pm$ 1,0)	8,4 ($\pm$ 1,7)	8,6 ($\pm$ 1,1)	2,3 ($\pm$ 2,9)	8,8 ($\pm$ 1,0)	8,3 ($\pm$ 1,1)	8,6 ($\pm$ 0,8)
SCL-90-R										
totalAB n=24	15,9($\pm$ 5,8)	10,9($\pm$ 4,0)	31,1($\pm$ 11,4)	26,2($\pm$ 8,3)	19,2($\pm$ 7)	26,8($\pm$ 10,1)	10,2($\pm$ 5,4)	10,1($\pm$ 3,9)	163,0($\pm$ 47,5)	
total BA n=21	15,9($\pm$ 5,8)	11,2($\pm$ 6,3)	33,6($\pm$ 14,4)	25($\pm$ 8)	19,7($\pm$ 6,0)	28,1($\pm$ 10,5)	8($\pm$ 1,9)	10,3($\pm$ 3,5)	163,8($\pm$ 44,9)	
lost AB n=5	18,4($\pm$ 11,2)	13,4($\pm$ 8,3)	27,8($\pm$ 10)	26,8($\pm$ 7,8)	21($\pm$ 2,9)	26($\pm$ 2)	9,2($\pm$ 2,8)	11,6($\pm$ 2,1)	166,8($\pm$ 41,2)	
lost BA n=6	19,7($\pm$ 11,1)	12,2($\pm$ 4,4)	33($\pm$ 17,5)	29,17($\pm$ 11,5)	22,3($\pm$ 9,8)	33,5($\pm$ 18,0)	11,7($\pm$ 7,5)	12,8($\pm$ 2,1)	189,7($\pm$ 80,1)	
CRPS brief inventory										
	1	2	3	4	5	6	7	8	9	10
meanAB n=24	7,4($\pm$ 1,7)	6,5($\pm$ 2,1)	6,3($\pm$ 3,1)	7,6($\pm$ 2,0)	4,2($\pm$ 2,6)	7,0($\pm$ 2,8)	6,4($\pm$ 2,2)	4,3($\pm$ 3,4)	7,2($\pm$ 2,2)	5,6($\pm$ 2,5)
meanBA n=22	7,0($\pm$ 2,0)	5,0($\pm$ 3,0)	6,3($\pm$ 3,0)	7,8($\pm$ 2,3)	4,8($\pm$ 2,9)	7,7($\pm$ 2,1)	5,1($\pm$ 3,1)	5,1($\pm$ 2,7)	6,8($\pm$ 2,5)	5,5($\pm$ 2,5)
lostAB n=5	7,4($\pm$ 1,8)	7,2($\pm$ 1,6)	7,8($\pm$ 0,4)	9($\pm$ 1)	4,6($\pm$ 1,5)	8,2($\pm$ 0,8)	6($\pm$ 2,6)	6,4($\pm$ 2,6)	7,2($\pm$ 3,6)	6,8($\pm$ 1,1)
lost BA n=7	8,6($\pm$ 1,4)	6($\pm$ 3)	6,4($\pm$ 3,9)	9($\pm$ 1,2)	5($\pm$ 2,9)	8($\pm$ 1,6)	7($\pm$ 2,8)	6,7($\pm$ 1,8)	7,3($\pm$ 2,3)	6,6($\pm$ 2,4)

Table 4 Patients (%) with global perceived effect on pain
a in the four arms of treatment and
b totals for the two treatments.

treatment period	GBP- 1	placebo-1	wash-out	GBP- 2	placebo-2
% some improvement (n)	45 % (10)	13 % (3)	1	8 % (2)	13 % (3)
% much improvement (n)	14 % (3)	5 % (1)	0	21 % (5)	4 % (1)
% total (n/N)	59 % (13/22) ^a	17 % (4/24)	1	29 % (7/24)	18 % (4/22)
	total GBP	total placebo			
% some improvement	26 % (12/46)	13 % (6/46)			
% much improvement	17 % (8/46) ^b	4 % (2/46)			
% total (n/N)	43 % (20/46) ^a	17 % (8/46)			
worsened	13 % (6/46)	9 % (4/46)			

GBP-1 is gabapentin treatment before wash-out. GBP-2 is gabapentin treatment after wash-out. 'α' is significant, $P < 0.005$, 'β' is $P < 0.10$ McNemar two sided tested gabapentin versus placebo.

Table 5. Mann-Whitney scores of monofilament application in CRPS patients testing cutaneous sensibility thresholds

	Mean ranking		
	hand	feet	total
placebo	12.0(N=12)	5.5(N=10)	16.8 (N=22)
gabapentin	15.6(N=15)	12.0*(N=3)	25.0* (N=18)

Significant different values ($p < 0.05$) are marked with *.

Table 6. Side effects as mentioned after treatment

adverse effects	Gabapentin (N=54) n (%)	Placebo(N=51) n (%)	significance
dizziness	20 (37.0)	2 (3.9)	P=0.0000
somnolence	15 (27.8)	3 (5.9)	P=0.003
lethargy	11 (20.4)	1 (2.0)	P=0.003
nausea	10 (18.5)	5 (9.8)	n.s.
headache	8 (14.8)	3 (5.9)	n.s.
stomach problems	4 (7.4)	3 (5.9)	n.s.
'drunken'	4 (7.4)	0 (0)	n.s.
disturbed gait	4 (7.4)	0 (0)	n.s.
water retention	1 (1.9)	3 (5.9)	n.s.

Data on all patients who started treatment and returned for assessment after 3 weeks, with or without completing 3 weeks of treatment. n.s. is 'not significant'

Figure 1 VAS for pain in both groups at start (T0), three weeks (T1), five weeks (T2), and eight weeks (T3) after randomization. T0-1 is the first treatment period, and T2-3 the second

Figure 2 Global perceived pain relief (on a seven-point scale) as reported by patients. GBP-1 and -2 denote patients receiving GBP in the first and second period; placebo-1 and -2 are analogously denoted.

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Summary and conclusions

Complex Regional Pain Syndrome (CRPS) is being called Reflex Sympathetic Dystrophy. There are many synonyms for this syndrome, and even more definitions. In general, one can say that CRPS is a chronic pain syndrome with sensory, autonomic and motor dysfunction. Chapter 1 summarizes the contemporary view on its diagnosis, treatment and hypotheses on etiopathogenesis. The scientific relevance of chapter 2 - 7 of this thesis is pointed out by comparing our studies with the literature.

Numerous signs and symptoms are being attributed to the CRPS syndrome. So far, there is no agreement which and in which way these need to be found in a patient to diagnose CRPS. CRPS, as a diagnosis, is not valid. Chapter 2 describes our study on this problem. We found that this is not only caused by different definitions for CRPS, but that also the assessment of signs and symptoms in patients is problematic. Important signs like edema, dystrophic changes and changed hair growth have a low interobserver agreement, even between CRPS experts (chapter 2).

There is also a discrepancy between signs and symptoms in CRPS patients. Many patients complain about swelling, discoloration and heat/cold sensations without these being confirmed by a physician during physical examination. The most objective signs like swelling or changed hair and nail growth are the least often confirmed in comparison with behaviour dependent signs like hypersensitive skin and limb dysfunction (chapter 4). This discrepancy between outcomes of patient interview and physical examination is also described in other diagnoses like irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome and somatoform disorder.

Physicians are being taught implicitly to consider psychopathology as a differential diagnosis when a patient is presented with chronic, idiopathic pain with relatively few objective symptoms, changing signs in time and multiple diagnoses being addressed to in the past by other physicians. It therefore thinkable this diagnosis is sometimes being given to CRPS patients and vice versa. In our study with 6 CRPS specialists (surgeons, anaesthesiologists and a neurologist) somatoform disorder was an important differential diagnosis for chronic CRPS patients (chapter 3), especially for those physicians who also often treated other chronic pain patients. Of course, this is no proof for CRPS being a subtype somatoform disorder, but it is likely that patients with a somatoform disorder sometimes are misdiagnosed as having CRPS.

Clinical research in CRPS is not very useful as long as there are no generally accepted diagnostic criteria. For the time being, CRPS criteria in research need to be thorough, even though it may minimize the possible study population.

Chapter 5 describes a study on HLA antigen subtypes. We found an association of CRPS with MHC class II antigen HLA-DQ1. This antigen was prevalent in 42% of the controls in comparison to 69% in CRPS patients. This implies a possible genetic predisposition for (a subtype) of CRPS and this predisposition might involve the immune system. An association for HLA-DQ1 is also described for narcolepsy and multiple sclerosis.

Chapter 6 describes the study of antibodies to viruses and bacteria in CRPS. An association between CRPS and Parvovirus B19 infection was found. It is speculated that this virus might start an immune reactivity in predisposed patients, and thus result in a painful post infectious reaction after a trauma of a limb (read: after disposing antigen to the immune system). This would partially explain why only some people develop this syndrome after trauma. Of course, this model is incomplete as not every patient with HLA DQ1 and Parvovirus B19 infection develops CRPS and our results are not yet confirmed by

other researchers. Now only symptomatic treatment is possible, with limited effect.

In this thesis' last chapter a patient study on gabapentin treatment is described. In a placebo controlled research we found that in chronic CRPS patients gabapentin can fulfil a small part in pain management, but can also reverse sensory deficit.

Conclusions

These study results show that CRPS is a syndrome with vague boundaries. The physical examination is not valid on most relevant aspects. An important differential diagnosis of CRPS is somatoform disorder. Nevertheless, it should not be forgotten that CRPS is an invalidating illness, which has huge impact on daily life. There are findings that points toward a genetic and/or inflammatory cause. A good therapy is not yet available. Gabapentin can be a possible aid in pain management and reversing of sensory deficits.

Samenvatting en conclusie

Complex Regional Pain Syndrome (CRPS) is een chronisch pijnsyndroom dat gekenmerkt wordt door sensibele, autonome en motorische afwijkingen en wordt momenteel in Nederland vaak posttraumatische dystrofie genoemd. Behalve de veel gebruikte synoniemen Sympathische Reflex Dystrofie en posttraumatische dystrofie zijn er nog verschillende namen, en zelfs meer definities voor dit ziektebeeld. Hoofdstuk 1 geeft een overzicht over de huidige stand van zaken omtrent de diagnose, behandeling en hypothesen over de etiopathologie.

Er zijn tientallen klachten en symptomen bij CRPS patiënten beschreven. Er is (nog) geen overeenstemming welke hiervan en in welke mate deze aanwezig moeten zijn om de diagnose te kunnen stellen.

Hoofdstuk 2 beschrijft onze studie naar dit probleem. We vonden dat dit niet alleen veroorzaakt wordt door verschillende gehanteerde definities, maar ook het medisch onderzoek naar klachten en symptomen bij een patient is problematisch.

Belangrijke klinische symptomen zoals oedeem, dystrofe veranderingen en veranderde haargroei, hebben een lage interobserver overeenstemming, zelfs bij CRPS experts (hoofdstuk 2).

Het blijkt dat deze gerapporteerde klachten relatief niet goed overeenkomen met de bevindingen bij lichamelijk onderzoek. Vaak klagen patienten over zwelling, verkleuring en warmte/koude sensaties zonder dat de arts deze afwijkingen kan vaststellen. De meest objectiveerbare afwijkingen zoals toegenomen zwelling, haargroei of nagelgroei worden het minst vaak aangetroffen in vergelijking met relatief gemakkelijk na te bootsen afwijkingen als een overgevoelige huid of een functiebeperking van de aangedane ledemaat (hoofdstuk 4). Deze discrepantie tussen anamnese en lichamelijk onderzoek bij CRPS is in vergelijkbare mate aanwezig bij diagnoses zoals het prikkelbare darm syndroom, fibromyalgie, chronisch vermoeidheidssyndroom en somatoforme stoornis.

Omdat artsen impliciet geleerd wordt om psychopathologie in de differentiaal diagnose op te nemen als een patient zich presenteert met chronische onbegrepen pijnklachten met relatief weinig objectieve afwijkingen, is het denkbaar dat bij sommige CRPS patiënten deze diagnose gesteld wordt. In ons onderzoek met 6 CRPS specialisten (chirurgen, anesthesiologen en een neuroloog), bleek bij chronische CRPS patienten een somatoforme stoornis een belangrijke differentiaal diagnostische overweging (hoofdstuk 3), met name voor artsen die andere chronische pijn patienten beroepsmatig zagen. Dit is geen bewijs om CRPS als een variant-somatoforme stoornis te beschouwen. Wel is het waarschijnlijk dat er binnen de populatie CRPS patienten zich patienten met een somatoforme stoornis bevinden.

In hoofdstuk 5 wordt een onderzoek beschreven naar HLA antigeen subtypes. Wij vonden een associatie van CRPS met MHC klasse II antigeen HLA-DQ1. Dit antigeen was aanwezig in 42% van de controlegroep in vergelijking met 69% in de groep CRPS patienten. Dit impliceert dat er mogelijk een genetische aanleg voor (een subtype van) CRPS bestaat en dat deze aanleg mogelijk betrokken is bij het immunologische afweersysteem van het lichaam. Een HLA-DQ1 associatie is binnen de neurologie eerder beschreven voor narcolepsie en multiple sclerose.

In hoofdstuk 6 wordt een verslag gegeven van onderzoek bij CRPS patienten naar antistoffen tegen virussen en bacteriën die neurologische verschijnselen kunnen geven. Er wordt een gevonden associatie beschreven tussen CRPS en Parvovirus B19 besmetting. De verklaring wordt geopperd dat een Parvovirus B19 besmetting bij gepredisponeerde mensen een immuunreactie zou opwekken, waardoor een kwetsuur van een ledemaat een pijnlijke postinfectieuze auto-immuun reactie zou opwekken. De resultaten zijn niet alomvattend, want niet ieder persoon met HLA-DQ1 en Parvovirus B19 ontwikkelt

CRPS en de resultaten zijn nog niet bevestigd door andere onderzoekers.

Momenteel is er geen adequate therapie voor CRPS omhanden. Er zijn alleen symptomatische therapieën mogelijk, alle met een beperkt effect.

In het laatste hoofdstuk wordt een placebo gecontroleerd gerandomiseerd onderzoek beschreven naar de behandeling van CRPS pijn met gabapentine. We vonden dat bij chronische CRPS patiënten gabapentine een aanvullende rol kan spelen in de pijnbestrijding, maar ook de verminderde tastzin bij CRPS patiënten significant kan verbeteren.

Conclusie

Deze studieresultaten laten zien dat CRPS een syndroom is met onscherpe grenzen. Het lichamelijk onderzoek is op de meeste relevante symptomen niet valide. Een belangrijke differentiaal diagnose is de somatoforme stoornis. Desondanks mag niet vergeten worden dat CRPS een invaliderende aandoening is met een grote impact op het dagelijks leven van de patient. Er zijn aanwijzingen voor een genetische en/of inflammatoire oorzaak van de klachten. Een goede therapie is vooralsnog niet voorhanden. Gabapentine zou een mogelijke bijdrage aan de pijnvermindering en herstel van verminderde tastzin kunnen geven.

Curriculum Vitae

Anton Cornelis van de Vusse werd op 20 augustus 1969 geboren te Poortugaal. Hij behaalde zijn VWO diploma in 1987 op het Christelijk Lyceum Veenendaal. Hierna ging hij studeren aan de Universiteit Maastricht, toen nog Rijksuniversiteit Limburg geheten. Hij behaalde in 1988 zijn propaedeuse Gezondheidswetenschappen en in 1989 zijn eerste jaar van Verplegingswetenschappen (FdGW) welke hij afbrak om in 1989 aan zijn doctoraalstudie Geestelijke Gezondheidskunde (FdGW) te beginnen. Hij behaalde zijn doctoraal examen in 1993 na een klinische stage neuropsychologie aan de CVA afdeling van Revalidatie Centrum Hoensbroeck en een wetenschappelijke studie naar cognitieve revalidatie bij patiënten met traumatisch hersenletsel. Ondertussen was hij in 1990 gestart met de studie Geneeskunde, wat resulteerde in 1994 in een Doctoraal Geneeskunde (Cum Laude). In 1995 volgde hij een stage aan Harvard University/ Beth Israel Hospital te Boston, USA op de afdeling Neurologie en in 1997 behaalde hij zijn artsexamen (Met Genoegen). Hierna heeft hij van 1997 tot 2000 als klinisch arts-pijnbestrijder/onderzoeker gewerkt aan het Academisch Pijncentrum Maastricht, afdeling Anesthesiologie, Academisch Ziekenhuis Maastricht (hoofd: dr. W. E. J. Weber). Na een jaar 'perifere' Neurologie in het Slotervaart Ziekenhuis (opleider: dr. J. van der Sande) te Amsterdam was hij van oktober 2001 tot mei 2003 als arts-assistent aangesteld bij de afdeling Neurologie van het Leids Universitair Medisch Centrum (opleider Prof. dr. R. A. C. Roos). Momenteel volgt hij de Huisartsopleiding aan de Vrije Universiteit te Amsterdam, welke hij medio 2006 hoopt te voltooien.

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De tientallen 'dystrofie' patienten die meegedaan hebben aan alle screeningsprocedures en testbatterijen wil ik hierbij van harte bedanken. Ik hoop dat het onderzoek bijdraagt aan uw erkenning en beterschap.