Complex Regional Pain Syndrome – Diagnosis, Treatment and Future Perspectives

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Abstract

Complex regional pain syndrome (CRPS) is a pain syndrome of the extremities that can result in severe disability. CRPS is diagnosed using diagnostic Budapest criteria based on signs and symptoms, whereby sensory, autonomic, vasomotor, motor and trophic disturbances are assessed. Many pathophysiological mechanisms are proposed in the development and disease course of CRPS, starting with exaggerated inflammation and resulting in vascular deregulation, central sensitisation and cortical reorganisation. Treatment is based primarily on reducing inflammation by using medicinal anti-inflammatory therapy and increasing motor function by physiotherapy. Furthermore, pain reduction, normalisation of vasomotor and motor function, and psychological interventions might be needed. Future research should focus on the efficacy of anti-inflammatory therapy, effective rehabilitation programmes, modulating neuropathic pain and cortical reorganisation.

Complex regional pain syndrome (CRPS) is a painful disorder of the extremities, characterised by sensory, autonomic, vasomotor, motor and trophic disturbances (see *Figures 1* and *2*). CRPS mostly occurs after a trauma, such as a fracture or an operation, but can also develop without a preceding event.[1,2] In the Netherlands, approximately 4,300 patients develop CRPS each year, whereby females are affected three times more than males and the highest incidence is found between the age of 61 and 70 years.[3]

Diagnosing Complex Regional Pain Syndrome

The diagnosis of CRPS is based on clinically observed signs and symptoms reported by the patient. Additional laboratory or radiological assessments provide insufficient basis for diagnosing CRPS, but should be used to exclude other pathologies (such as an unresolved fracture or active infection).[4] Several sets of diagnostic criteria have been proposed over the past decades, some of which are still being used concurrently. The criteria of Veldman et al.[5] are based on the identification of a limited amount of signs and symptoms, which are present predominantly in the acute phase of CRPS. The International Association for the Study of Pain (IASP)-Orlando criteria[6] allow for the diagnosis to be made almost exclusively based on anamnestic information and appear to be more sensitive than the Veldman et al. criteria.[7] More specific criteria have been developed by Bruehl and Harden[8] requiring both anamnestic and observed information regarding sensory, vasomotor, motor,

sudomotor and motortrophic disturbances. An adapted version of the latter criteria set has been validated internationally, resulting in a diagnostic tool that combines good specificity with excellent sensitivity for diagnosing CRPS: the Budapest criteria (see *Table 1*).[9] These criteria have recently been adopted by the IASP as the international standard for diagnosing CRPS.

To maximise the comparability of studies of CRPS and ensure agreement between clinicians involved in diagnosing and treating CRPS, a uniform and internationally accepted criteria set such as the Budapest criteria is necessary. Uniform diagnosis and assessment of CRPS could be further improved by identification of disease markers of CRPS Type 1 (CRPS-1) and development of objective assessment tools.

Pathophysiological Mechanisms of Complex Regional Pain Syndrome

Neurogenic and immune-mediated inflammation, disproportional oxidative stress, autonomic dysfunction, vasomotor dysfunction, increased neuronal excitation, central sensitisation, cortical reorganisation and psychological predisposition have been proposed as possible disease mechanisms for CRPS. This variety in pathophysiological perspectives combined with possible simultaneous occurrence of different mechanisms in a single patient, might provide an explanation for the heterogeneity of phenotypes described in CRPS literature in recent years.

Neurogenic Inflammation

A trauma can easily result in micro-injury of small nerve fibres, which in turn triggers the release of neuropeptides, such as substance P (SP) and calcitonin gene-related peptide (CGRP) in the periphery.[10,11] This excessive release of neuropeptides, called neurogenic inflammation, induces vasodilatation and increases vascular permeability, leading to plasma extravasation and attraction of immune mediators to the site of injury, resulting in an inflammatory response. Neurogenic as well as immune-mediated inflammation contribute to the generation of pain, whereby features of neuropathic sensitisation, such as allodynia or hyperesthesia, are observed. In patients with CRPS, elevated levels of CGRP have been found, suggesting a contribution of neurogenic inflammation to the development and maintenance of in this condition.[12]

Immune-mediated Inflammation

Especially during the early stages of the disease course, CRPS signs and symptoms resemble the classic clinical presentation of inflammation: rubor, calor, dolor and functio laesa. Increased levels of inflammatory markers and markers of mast cell activity have been found in blister fluid (e.g. interleukin [IL]-6, tumour necrosis factor [TNF]-α and tryptase) and serum (IL-8, soluble TNF receptors and SP) obtained from the affected extremity of patients with CRPS, compared with both the unaffected extremity and healthy controls.[10,13,14] Indications for central inflammatory activity can be found in increased pro-inflammatory cytokines (IL-6) and decreased anti-inflammatory cytokines (IL-4 and IL-10) in cerebrospinal fluid.[15] Furthermore, markers of increased glial cell activation (glial fibrillary acidic protein [GFAP] and monocyte chemoattractant protein 1 [MCP1]) found in CRPS, might provide support for neuronal-driven immune activation.[16]

Oxidative Stress

Excessive, non-self-limiting release of free oxygen radicals leading to oxidative stress has been proposed as a pathophysiological mechanism underlying CRPS. Studies based on animal models have shown that infusion with free radical-inducing agents results in features that resemble clinical signs of CRPS, such as swelling, impaired function, increased temperature, redness and increased pain sensitivity.[17] A role for increased oxidative stress is also supported by the observation of elevated levels of oxidative markers in the serum and saliva of patients with CRPS-1.[18] Furthermore, leukocyte accumulation in the affected extremity has been observed in patients with CRPS, probably resulting from increased vascular permeability owing to oxidative stress.[19] Tissue hypoxia, as shown by the poor oxygenation of skin in patients with CRPS,[20] lends further support to this observation. The efficacy of free radical scavengers, such as dimethylsulfoxide and N-Acetylcysteine,[21,22] in the treatment of CRPS-1 and the preventive effect of vitamin C after fractures[23,24] in the development of this disease provide indirect evidence for the oxidative stress hypothesis.

Autonomic Disturbances

Hyperactivity of the sympathetic nervous system has long been thought to be the primary pathophysiological mechanism of CRPS-1, resulting in increased vasoconstriction, increased sweating and trophic disturbances. However, studies have shown lower levels of sympathetic neurotransmitters in the affected limb[25–27] compared with the unaffected limb, indicating decreased sympathetic activity. Presumably, increased sensitivity of α-adrenergic receptors, probably resulting from reduction of sympathetic neural traffic, would explain

Figure 1: Patient with Complex Regional Pain Syndrome (Florid Clinical Type) of the Left Hand

Characteristics of complex regional pain syndrome: red (vasomotor), swollen (sudomotor) and increased hair growth (trophic disturbance).

Figure 2: Patient with Complex Regional Pain Syndrome and Dystonia of the Left Foot

this phenomenon.[28] The extent in which autonomic disturbances are observed can differ depending on the stage of the disease course.[29]

Vascular Dysfunction

An alternative hypothesis for the vasomotor instability observed in patients with CRPS is based on endothelial dysfunction resulting in hypoxia, a decrease in nitric oxide (NO) synthase and an increase in endothelin-1.[30] This dysfunction leads to clinical features, such as a cold affected extremity and discolouration (pale, blue skin), and other features of CRPS associated with oxygen deprivation.

Neuronal Excitation and Central Sensitisation

Clinical features displayed in CRPS, such as allodynia, hyperalgesia and wind-up, have been related to the process of central sensitisation.[31] This process is triggered by the release of SP, CGRP and glutamate after tissue damage, which in turn activate the normally dormant N-methyl-D-aspartic acid (NMDA) receptor.[32] Elevated levels of glutamate found in the serum and cerebrospinal fluid of patients with CRPS are suggestive of the involvement of NMDA receptor responses.[33] Central sensitisation might also influence the

Table 1: Diagnostic Criteria for Complex Regional Pain Syndrome (CRPS) Type 1

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

spinal motor circuitry, resulting in movement disorders associated with CRPS, such as dystonia, tremor or myoclonia.[34]

Cortical Reorganisation

Pain and sensory disturbances in CRPS often spread from the location of the initial trauma to a larger area, sometimes even to another extremity, which might indicate plastic changes of the central nervous system owing to neurogenic inflammation.[35] In patients with CRPS, reorganisation of the primary somatosensory cortex (S1) has been observed, which correlated with the amount of pain and hyperalgesia experienced by the patients.[36,37] Cerebral representation and motor processing in the brain are also reported to be disturbed, possibly leading to movement disorders in CRPS-1 and distorted visualised representation of the affected limb.[38–41]

Psychological Factors

Psychological disturbances have often been proposed to be involved in complex conditions, such as chronic pain and CRPS. However, little evidence has emerged to support this hypothesis. No relation has been found between psychological dysfunction, disease-related fear or personality and the development of CRPS.[42–44] One study reports that stressful life events are more common in patients with CRPS than in controls,[45] but other studies could not confirm this finding.[42,43,46,47] Once patients have developed CRPS, pain-related fear and fear of re-injury are proposed to be risk factors for a poor prognosis relating to pain reduction and functional improvement.[48,49]

Treatment Options

Treatment of CRPS-1 is challenging, because of the variety of symptoms and the variable disease course exhibited by patients. A multimodal approach consisting of pharmacological treatment and physiotherapy, sometimes in combination with invasive therapy or psychological support, is required. An overview of systematic reviews and guidelines providing an evidence-based approach to treatment of CRPS is presented in *Tables 2* and *3*.[50–60]

Pharmacological Treatment

Analgesics

Pain medication according to the WHO analgesic ladder has been suggested in therapeutic guidelines, although evidence supporting the efficacy of paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDS) is limited. Tramadol has been shown to be effective in neuropathic pain disorders, therefore it can be considered for severe pain accompanying CRPS, although evidence for its effects in CRPS is lacking.[4,50,51,55,61–63]

Treating CRPS with strong opioids should only be considered as crisis management for a limited period of time.[51,55] Furthermore, gabapentin has proven efficacy in CRPS-1;[50,51,55,62,64] however, amitryptiline and carbamazepine or newer tricyclic antidepressants (TCAs), such as duloxetine or venlafaxine, can also be considered, because of their shown effectiveness in other neuropathic pain disorders.[50,55,62]

Intravenous administration of the NMDA receptor antagonist ketamine can be considered; however the full scope of its therapeutical potential (including a risk–benefit assessment) has not yet been established.[50,60,65,66] Lidocaine patches have been proposed for treatment of localised sensory deficits, such as allodynia in CRPS.[67]

Anti-inflammatory Therapy

The free radical scavenger dimethyl sulfoxide (DMSO) has been shown to be effective in patients who have had CRPS-1 for less than a year.[58] N-Acetylcysteine (NAC) shows comparable efficacy to DMSO, but proved superior to DMSO for primary cold CRPS in subgroup analyses.[68] Vitamin C has established efficacy in the prevention of CRPS after wrist fractures.[23,24] Furthermore, corticosteroids can provide significant pain reduction in CRPS; however, there is no consensus on the dosage or duration of treatment.[50,58,62,63] Both types of intervention have so far only been evaluated in early-stage CRPS.[51,55]

Calcium-regulating Drugs

The use of bisphosphonates has been proposed as a treatment option for CRPS. Although limited support for their ability to reduce pain (associated with bone loss) has been reported, additional research with regard to their dosage, frequency and duration of treatment is required.[21,50,53,55,56,62,69,70]

Vasodilatory Medication

For treatment of patients with CRPS and vasomotor disturbances, α-1 adrenergic blockers, phenoxybenzamine and terazosin, or calcium influx blockers, such as nifedipine, can be considered.[4,55,71] No reduction in temperature asymmetry was found for NO-regulating medication (e.g. tadalafil or isosorbide dinitrate) in primary cold CRPS, although tadalafil is superior to placebo in reducing pain for this subgroup.[72,73] Likewise, intravenous administration of ketanserine is reported to reduce pain in CRPS.[50,74]

Spasmolytics

Movement disorders in CRPS-1, such as dystonia, myoclonia and tremor, might benefit from treatment with baclofen or benzodiazepines.[4,50,63] Treatment with anti-cholinergics has not shown to be beneficial for CRPS-related movement disorders over a longer period of time.[34]

Table 2: Systematic Reviews of Interventions for Complex Regional Pain Syndrome Type 1

Review	Topic
Kingery, 1997[50]	Oral corticosteroids, DMSO, calcitonin (intranasal and subcutaneous), regional blocks, intravenous ketanserine and phentolamine, and epidural clonidine in CRPS compared with other neuropathic pain disorders
Stanton-Hicks et al., 1998[51]	NSAIDs, opioids, antidepressants, calcium blockers, corticosteroids, bisphosphonates, capsaicin, adrenergic drugs, local anaesthetic blocks, neuromodulation, physical therapy, psychiatric and psychological measures, and treatment of children with CRPS
Raja et al., 2002[52]	Oral, topical and intravenous analgesics, bisphosphonates, free radical scavengers, corticosteroids, alpha blockers, blockades, epidural and intrathecal therapies, physiotherapy, neuromodulation, psychotherapy and invasive treatment options
Foroufanzar et al., 2002[53]	Blocks, intravenous ketanserine, calcium-regulating drugs, free radical scavengers, corticosteroids, complementary therapies and prevention of CRPS
Cepeda et al., 2002[54]	Local anaesthetic sympathetic blockade
Harden, 2005[55]	TCAs, anticonvulsants, anti-inflammatory drugs, opioids, clonidine, nifedipine, calcitonin, bisphosphonates, adrenergic antagonists, topical treatments and local anaesthetic block therapies
Brunner et al., 2009[56]	Bisphosphonates
Daly and Bialocerkowski, 2009[57]	Physiotherapy
Fischer et al., 2010[58]	Anti-inflammatory drugs
Perez et al., 2001[59]	Anti-inflammatory drugs, free radical scavengers, beta blockers, calcitonin, stellate ganglion blocks, intravenous treatment with lidocaine and ketanserine, clonidine and bisphosphonates
Collins et al., 2011[60]	NMDA receptor antagonists

CRPS = complex regional pain syndrome; DMSO = dimethyl sulfoxide; NMDA = N-methyl-D-aspartic acid; NSAIDs = non-steroidal anti-inflammatory drugs; TCA = tricyclic antidepressant.

Table 3: Guidelines for the Treatment of Complex Regional Pain Syndrome Type 1

Treatment Guidelines	Description
CBO Guidelines, Complex Regional Pain Syndrome type 1, 2006 (www.cbo.nl/thema/Richtlijnen/ Overzicht-richtlijnen/Overig)	Dutch guidelines for CRPS considering analgesics, local and intravenous anaesthetics, anticonvulsants, antidepressants, capsaicin, free radical scavengers, oral muscle relaxants, local botulinum, intrathecal baclofen, corticosteroids, calcitonin, bisphosphonates, calcium channel blockers, invasive treatment, paramedical intervention, treatment options for children with CRPS and recommendations for the prevention of CRPS
AWMF: Leitlinien der Deutschen Gesellschaft für Neurologie, 2008 (German) (www.awmf.org/leitlinien/ detail/ll/030-116.html)	German guidelines for the treatment of CRPS considering bisphosphonates, calcitonin, corticosteroids, free radical scavengers, physio- and occupational therapy, analgesics, psychotherapy, blockades, spinal cord stimulation and intrathecal treatment
RSDSA, Complex Regional Pain Syndrome Treatment Guidelines, 2010 (www.rsds.org/3/clinical_guidelines/ index.html)	American guidelines on the effects of anti-inflammatory drugs, anticonvulsants, neuromodulators, antidepressants, anti-anxiolytics, opioids, NMDA receptor antagonists, anti-hypertensives and α-adrenergic antagonists, calcitonin, bisphosphonates, topical treatment, psychological interventions and invasive interventions
Van Eijs et al, 2011[4]	Dutch guidelines for anaesthesiologists on physical therapy, psychological support, anti-inflammatory therapy, analgesic therapy, vasodilatory therapy, spasmolytic therapy, regional blocks, intrathecal and epidural treatment and neurostimulation

AWMF = Association of the Scientific Medical Societies in Germany; CBO = Central Accompaniment Organization; CRPS = complex regional pain syndrome; NMDA = N-methyl-D-aspartic acid; RSDSA = Reflex Sympathetic Dystrophy Syndrome Association.

Physical Therapy

An important modality for treatment of CRPS is physical therapy directed at increasing control over pain and improving skills.[57,75] Motor imagery and mirror therapy have been proven effective, both of which are applied to counter disturbed cortical motor processing, resulting in improvement of pain and function.[41,76,77] Transcutaneous electrical nerve stimulation (TENS) might be beneficial for treatment of pain in a subgroup of patients and might therefore be a suitable adjunctive non-invasive therapy. However, evidence for the latter is limited.[4]

Invasive Treatment

Spinal cord stimulation with an implantable generator can be considered for patients with chronic CRPS; however, the high incidence and severity of complications following spinal cord stimulation warrant careful patient selection.[78] Spinal cord stimulation should not be considered in early stages of CRPS.[79] Studies of intrathecal administration of baclofen show that patients with CRPS dystonia can experience marked improvement in pain and disability levels, paralleled by improvement in quality of life.[80,81] However, as with other intrathecal approaches, complications can be severe and, therefore, should be limited to patients who are refractory to conventional therapy and be conducted by physicians with ample experience with intrathecal devices.[81]

Psychological Treatment

Although studies with regard to psychological interventions for CRPS are limited, treatment by a psychologist can be considered in cases where disease burden is high or there is a discrepancy between noted pain behaviour and observed signs and symptoms of CRPS.[63] Graded exposure is a promising therapy to reduce fear of pain and to regain functionality of the affected extremity.[49]

Future Perspectives

In recent decades, much research effort has been directed to unravelling the underlying mechanisms of CRPS, and improving strategies for its prevention and treatment, alongside the unification of diagnostic procedures. An important issue to be addressed is the identification of prognostic factors for disease development, which could lead to a more targeted approach and therewith improve the prognosis of patients with CRPS. Prospective cohort studies on the development of CRPS are necessary to gain a better understanding of prognostic factors related to disease onset and disease course.[82] The recently developed CRPS severity score (CSS) as a derivation of the Budapest diagnostic criteria[83] might be helpful in improving the systematic follow up of patients; however, validation of this tool is ongoing. CRPS remains a clinical diagnosis, and the patient population is heterogeneous. Although it has been proposed that CRPS comprises different disease subtypes or stages of the disease, this has not led to further subcategorisation of the disease.[8] A targeted approach based on the identification of CRPS subtypes and specific mechanisms prevailing in an individual patient is therefore still warranted.

The many available treatment options suggest that the optimal therapy for CRPS has not yet been identified. Given the heterogeneous nature of CRPS, an optimal therapy seems unlikely; therefore, a mechanism-directed approach to treatment of CRPS appears preferable. With regard to interventions targeting inflammation, comparative studies of established interventions (e.g. prednisolone and DMSO) and novel anti-inflammatory agents, such as intravenous administration of immunoglobulin,[84] should be performed. Furthermore, alternative approaches, such as targeting the cholinergic anti-inflammatory pathway,[85] whereby activating the parasympathetic nervous system to inhibit inflammatory activity and autonomic dysregulation in CRPS, could be pursued. Promising interventions addressing sensory disturbances related to peripheral and central sensitisation, such as NMDA receptor antagonists[86] and the N-type calcium channel blocker ziconotide,[87] are worthwhile targets for further research.

Therapy directed at the stimulation of adaptive cortical reorganisation involving brain-training programmes, such as mirror therapy[76] and motor imagery,[77] merit implementation in daily practice. Continuing this line of thought, a strong point can be made for increasing patients' awareness and knowledge regarding mechanisms underlying the development of chronic pain and CRPS.[88] Further research within the field of exercise and occupational therapy should be focused on the distinction between pain and time-contingent approaches. Positive initial results have been found for pain exposure physical therapy (PEPT), which is based on progressive-loading exercises and desensitisation beyond the patients' pain limits.[89] Cognitive behavioural aspects are taken into account, with the goal to motivate patients to use the affected limb in daily activity despite experiencing pain. Likewise, for patients with CRPS with pain-related fear, research is ongoing into the effects of graded exposure therapy (GEXP), comprising provision of information about CRPS, observational learning and 'flooding' of feared movements and activities.

Repetitive transcranial magnetic stimulation (rTMS), whereby the motor cortex is stimulated to treat neuropathic pain, has been shown to provide short-term pain relief in patients with CRPS-1.[90] However, issues related to placebo response and ways to prolong its efficacy need to be addressed.

For each of the interventions discussed in this article, long-term studies of sufficient sample size, with specific attention to patient selection, timing and dosage of therapies, are required to establish risks and benefits of each intervention for patients with CRPS. ■

1. De Mos M, Huygen FJ, Dieleman JP, et al., Medical history and the onset of complex regional pain syndrome (CRPS), *Pain*, 2008;139(2):458–66.
2. De Rooij AM, Perez RS, Huygen FJ, et al., Spontaneous onset of complex regional pain syndrome, *Eur J Pain*, 2010;14(5):510–3.
3. De Mos M, De Bruijn AG, Huygen FJ, et al., The incidence of complex regional pain syndrome: a population-based study, *Pain*, 2007;129(1–2):12–20.
4. Van Eijs F, Stanton-Hicks M, Van Zundert J, et al., Evidence-based interventional pain medicine according to clinical diagnoses. 16. Complex regional pain syndrome, *Pain Pract*, 2011;11(1):70–87.
5. Veldman PH, Reynen HM, Arntz IE, Goris RJ, Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients, *Lancet*, 1993;342(8878):1012–6.
6. Merskey K, Bogduk N, Descriptions of Chronic pain syndromes and definitions of pain terms. In: *Classification of Chronic Pain*, Seattle: WA IASP Press, 1994:41–3.
7. Perez RS, Collins S, Marinus J, et al., Diagnostic criteria for CRPS I: differences between patient profiles using three different diagnostic sets, *Eur J Pain*, 2007;11(8):895–902.
8. Bruehl S, Harden RN, Galer BS, et al., Complex regional pain syndrome: are there distinct subtypes and sequential stages of the syndrome? *Pain*, 2002;95(1–2):119–24.
9. Harden RN, Bruehl S, Perez RS, et al., Validation of proposed diagnostic criteria (the 'Budapest Criteria') for Complex Regional Pain Syndrome, *Pain*, 2010;150(2):268–74.
10. Schinkel C, Gaertner A, Zaspel J, et al., Inflammatory mediators are altered in the acute phase of posttraumatic complex regional pain syndrome, *Clin J Pain*, 2006;22(3):235–9.
11. Schinkel C, Scherens A, Koller M, et al., Systemic inflammatory mediators in post-traumatic complex regional pain syndrome (CRPS I) - longitudinal investigations and differences to control groups, *Eur J Med Res*, 2009;14(3):130–5.
12. Birklein F, Schmelz M, Neuropeptides, neurogenic inflammation and complex regional pain syndrome (CRPS), *Neurosci Lett*, 2008;437(3):199–202.
13. Huygen FJ, De Bruijn AG, De Bruin MT, et al., Evidence for local inflammation in complex regional pain syndrome type 1, *Mediators Inflamm*, 2002;11(1):47–51.

14. Huygen FJ, Ramdhani N, van Toorenenbergen A, et al., Mast cells are involved in inflammatory reactions during Complex Regional Pain Syndrome type 1, *Immunol Lett*, 2004;91(2–3):147–54.
15. Alexander GM, van Rijn MA, van Hilten JJ, et al., Changes in cerebrospinal fluid levels of pro-inflammatory cytokines in CRPS, *Pain*, 2005;116(3):213–9.
16. Alexander GM, Perreault MJ, Reichenberger ER, Schwartzman RJ, Changes in immune and glial markers in the CSF of patients with Complex Regional Pain Syndrome, *Brain Behav Immun*, 2007;21(5):668–76.
17. Van der Laan L, Ter Laak HJ, Gabreels-Festen A, et al., Complex regional pain syndrome type I (RSD): pathology of skeletal muscle and peripheral nerve, *Neurology*, 1998;51(1):20–5.
18. Eisenberg E, Shtahl S, Geller R, et al., Serum and salivary oxidative analysis in Complex Regional Pain Syndrome, *Pain*, 2008;138(1):226–32.
19. Tan EC, Ter Laak HJ, Hopman MT, et al., Impaired oxygen utilization in skeletal muscle of CRPS I patients, *J Surg Res*, 2010;16:1–8.
20. Koban M, Leis S, Schultze-Mosgau S, Birklein F, Tissue hypoxia in complex regional pain syndrome, *Pain*, 2003;104(1–2):149–57.
21. Perez RS, Pragt E, Geurts J, et al., Treatment of patients with complex regional pain syndrome type I with mannitol: a prospective, randomized, placebo-controlled, double-blinded study, *J Pain*, 2008;9(8):678–86.
22. Zuurmond WW, Langendijk PN, Bezemer PD, et al., Treatment of acute reflex sympathetic dystrophy with DMSO 50% in a fatty cream, *Acta Anaesthesiol Scand*, 1996;40(3):364–7.
23. Zollinger PE, Tuinebreijer WE, Kreis RW, Breederveld RS, Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomised trial, *Lancet*, 1999;354(9195):2025–8.
24. Zollinger PE, Tuinebreijer WE, Breederveld RS, Kreis RW, Can vitamin C prevent complex regional pain syndrome in patients with wrist fractures? A randomized, controlled, multicenter dose-response study, *J Bone Joint Surg Am*, 2007;89(7):1424–31.
25. Drummond PD, Finch PM, Smythe GA, Reflex sympathetic

dystrophy: the significance of differing plasma catecholamine concentrations in affected and unaffected limbs, *Brain*, 1991;114(Pt 5):2025–36.
26. Vogel T, Gradl G, Ockert B, et al., Sympathetic dysfunction in long-term complex regional pain syndrome, *Clin J Pain*, 2010;26(2):128–31.
27. Wasner G, Schattschneider J, Binder A, Baron R, Complex regional pain syndrome – diagnostic, mechanisms, CNS involvement and therapy, *Spinal Cord*, 2003;41(2):61–75.
28. Drummond PD, Sensory disturbances in complex regional pain syndrome: clinical observations, autonomic interactions, and possible mechanisms, *Pain Med*, 2010;11(8):1257–66.
29. Drummond PD, Involvement of the sympathetic nervous system in complex regional pain syndrome, *Int J Low Extrem Wounds*, 2004;3(1):35–42.
30. Groeneweg JG, Huygen FJ, Heijmans-Antonissen C, et al., Increased endothelin–1 and diminished nitric oxide levels in blister fluids of patients with intermediate cold type complex regional pain syndrome type 1, *BMC Musculoskelet Disord*, 2006;7:91.
31. Janig W, Baron R, Complex regional pain syndrome is a disease of the central nervous system, *Clin Auton Res*, 2002;12(3):150–64.
32. Guo H, Huang LY, Alteration in the voltage dependence of NMDA receptor channels in rat dorsal horn neurones following peripheral inflammation, *J Physiol*, 2001;537(Pt1):115–23.
33. Wesseldijk F, Fekkes D, Huygen FJ, et al., Increased plasma glutamate, glycine, and arginine levels in complex regional pain syndrome type 1, *Acta Anaesthesiol Scand*, 2008;52(5):688–94.
34. Van Hilten JJ, Movement disorders in complex regional pain syndrome, *Pain Med*, 2010;11(8):1274–7.
35. Maleki J, LeBel AA, Bennett GJ, Schwartzman RJ, Patterns of spread in complex regional pain syndrome, type I (reflex sympathetic dystrophy), *Pain*, 2000;88(3):259–66.
36. Juottonen K, Gockel M, Silen T, et al., Altered central sensorimotor processing in patients with complex regional pain syndrome, *Pain*, 2002;98(3):315–23.
37. Maihofner C, Handwerker HO, Neundorfer B, Birklein F, Patterns of cortical reorganization in complex regional pain

syndrome, *Neurology*, 2003;61(12):1707–15.

38. Geha PY, Baliki MN, Harden RN, et al., The brain in chronic CRPS pain: abnormal gray-white matter interactions in emotional and autonomic regions, *Neuron*, 2008;60(4):570–81.

39. Lewis JS, Kersten P, McPherson KM, et al., Wherever is my arm? Impaired upper limb position accuracy in complex regional pain syndrome, *Pain*, 2010;149(3):463–9.

40. Maihofner C, Baron R, DeCol R, et al., The motor system shows adaptive changes in complex regional pain syndrome, *Brain*, 2007;130(Pt 10):2671–87.

41. Mccabe CS, Haigh RC, Ring EF, et al., A controlled pilot study of the utility of mirror visual feedback in the treatment of complex regional pain syndrome (type 1), *Rheumatology*, 2003;42(1):97–101.

42. Beerthuizen A, van 't Spiker A, Huygen FJ, et al., Is there an association between psychological factors and the Complex Regional Pain Syndrome type 1 (CRPS1) in adults? A systematic review, *Pain*, 2009;145(1–2):52–9.

43. Beerthuizen A, Stronks DL, Huygen FJ, et al., The association between psychological factors and the development of complex regional pain syndrome type 1 (CRPS1) – A prospective multicenter study, *Eur J Pain*, 2011;15(9):971–5.

44. Ciccone DS, Bandilla EB, Wu W, Psychological dysfunction in patients with reflex sympathetic dystrophy, *Pain*, 1997;71(3):323–33.

45. Geertzen JH, de Bruijn H, de Bruijn-Kofman AT, Arendzen JH, Reflex sympathetic dystrophy: early treatment and psychological aspects, *Arch Phys Med Rehabil*, 1994;75(4):442–6.

46. Monti DA, Herring CL, Schwartzman RJ, Marchese M, Personality assessment of patients with complex regional pain syndrome type I, *Clin J Pain*, 1998;14(4):295–302.

47. Rose MJ, Klenerman L, Atchison L, Slade PD, An application of the fear avoidance model to three chronic pain problems, *Behav Res Ther*, 1992;30(4):359–65.

48. Den Hollender M, de Jong JR, Volders S, et al., Fear reduction in patients with chronic pain: a learning theory perspective, *Expert Rev Neurother*, 2010;10(11):1733–45.

49. De Jong Jr, Vlaeyen JW, Onghena P, et al., Reduction of pain-related fear in complex regional pain syndrome type I: the application of graded exposure in vivo, *Pain*, 2005;116(3):264–75.

50. Kingery WS, A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes, *Pain*, 1997;73(2):123–39.

51. Stanton-Hicks M, Baron R, Boas R, et al., Complex Regional Pain Syndromes: guidelines for therapy, *Clin J Pain*, 1998;14(2):155–66.

52. Raja SN, Grabow TS, Complex regional pain syndrome I (reflex sympathetic dystrophy), *Anesthesiology* 2002; 96(5):1254–60.

53. Forouzanfar T, Köke AJ, van Kleef M, Weber WE, Treatment of complex regional pain syndrome type I, *Eur J Pain*, 2002;6(2):105–22.

54. Cepeda MS, Lau J, Carr DB, Defining the therapeutic role of local anesthetic sympathetic blockade in complex regional pain syndrome: a narrative and systematic review. *Clin J Pain* 2002;18(4):216–33.

55. Harden RN, Pharmacotherapy of complex regional pain syndrome, *Am J Phys Med Rehabil*, 2005;84(3 Suppl.):S17–S28.

56. Brunner F, Schmid A, Kissling R, et al., Biphosphonates for the therapy of complex regional pain syndrome I – systematic review, *Eur J Pain*, 2009;13(1):17–21.

57. Daly AE, Bialocerkowski AE, Does evidence support physiotherapy management of adult Complex Regional Pain Syndrome Type One? A systematic review, *Eur J Pain*, 2009;13(4):339–53.

58. Fischer SG, Zuurmond WW, Birklein F, et al., Anti-inflammatory treatment of Complex Regional Pain Syndrome, *Pain*, 2010;151(2):251–6.

59. Perez RS, Kwakkel G, Zuurmond WW, de Lange JJ, Treatment of reflex sympathetic dystrophy (CRPS type 1): a research synthesis of 21 randomized clinical trials, *J Pain Symptom Manage*, 2001;21(6):511–26.

60. Collins S, Sigtermans MJ, Dahan A, et al., NMDA receptor antagonists for the treatment of neuropathic pain, *Pain Med*, 2010;11(11):1726–42.

61. Duhmke RM, Cornblath DD, Hollingshead JR, Tramadol for neuropathic pain, *Cochrane Database Syst Rev*, 2004;(2):CD003726.

62. Mackey S, Feinberg S, Pharmacologic therapies for complex regional pain syndrome, *Curr Pain Headache Rep*, 2007;11(1):38–43.

63. Perez RS, Zollinger PE, Dijkstra PU, et al., Evidence based guidelines for complex regional pain syndrome type 1, *BMC Neurol*, 2010;10:20.

64. Serpell MG, Neuropathic Pain Study Group, Gabapentin in neuropathic pain syndromes: a randomised, double-blind, placebo-controlled trial, *Pain*, 2002;99(3):557–66.

65. Correll GE, Maleki J, Gracely EJ, et al., Subanesthetic ketamine infusion therapy: a retrospective analysis of a novel therapeutic approach to complex regional pain syndrome, *Pain Med*, 2004;5(3):263–75.

66. Sigtermans M, Noppers I, Sarton E, et al., An observational study on the effect of S+-ketamine on chronic pain versus experimental acute pain in Complex Regional Pain Syndrome type 1 patients, *Eur J Pain*, 2010;14(3):302–7.

67. Rowbotham MC, Pharmacologic management of complex regional pain syndrome, *Clin J Pain*, 2006;22(5):425–9.

68. Perez RS, Zuurmond WW, Bezemer PD, et al., The treatment of complex regional pain syndrome type I with free radical scavengers: a randomized controlled study, *Pain*, 2003;102(3):297–307.

69. Manicourt DH, Brasseur JP, Boutsen Y, et al., Role of alendronate in therapy for posttraumatic complex regional pain syndrome type I of the lower extremity, *Arthritis Rheum*, 2004;50(11):3690–7.

70. Varenna M, Zucchi F, Ghiringhelli D, et al., Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome. A randomized, double blind, placebo controlled study, *J Rheumatol*, 2000;27(6):1477–83.

71. Muizelaar JP, Kleyer M, Hertogs IA, DeLange DC, Complex regional pain syndrome (reflex sympathetic dystrophy and causalgia): management with the calcium channel blocker nifedipine and/or the alpha-sympathetic blocker phenoxybenzamine in 59 patients, *Clin Neurol Neurosurg*, 1997;99(1):26–30.

72. Groeneweg G, Niehof S, Wesseldijk F, et al., Vasodilative effect of isosorbide dinitrate ointment in complex regional pain syndrome type 1, *Clin J Pain*, 2008;24(1):89–92.

73. Groeneweg G, Huygen FJ, Niehof SP, et al., Effect of tadalafil on blood flow, pain, and function in chronic cold complex regional pain syndrome: a randomized controlled trial, *BMC Musculoskelet Disord*, 2008;9:143.

74. Hanna MH, Peat SJ, Ketanserin in reflex sympathetic dystrophy. A double-blind placebo controlled cross-over trial, *Pain*, 1989;38(2):145–50.

75. Oerlemans HM, Oostendorp RA, de Boo T, et al., Adjuvant physical therapy versus occupational therapy in patients with reflex sympathetic dystrophy/complex regional pain syndrome type I, *Arch Phys Med Rehabil*, 2000;81(1):49–56.

76. McCabe CS, Haigh RC, Blake DR, Mirror visual feedback for the treatment of complex regional pain syndrome (type 1), *Curr Pain Headache Rep*, 2008;12(2):103–7.

77. Moseley GL, Wiech K, The effect of tactile discrimination training is enhanced when patients watch the reflected image of their unaffected limb during training, *Pain*, 2009;144(3):314–9.

78. Kemler MA, de Vet HC, Barendse GA, et al., Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: five-year final follow-up of patients in a randomized controlled trial, *J Neurosurg*, 2008;108(2):292–8.

79. Cepeda MS, Acevedo JC, Alvarez H, et al., An N-of-1 trial as an aid to decision-making prior to implanting a permanent spinal cord stimulator, *Pain Med*, 2008;9(2):235–9.

80. Van Hilten BJ, van de Beek WJ, Hoff JI, et al., Intrathecal baclofen for the treatment of dystonia in patients with reflex sympathetic dystrophy, *N Engl J Med*, 2000;343(9):625–30.

81. Van Rijn MA, Munts AG, Marinus J, et al., Intrathecal baclofen for dystonia of complex regional pain syndrome, *Pain*, 2009;143(1–2):41–7.

82. Brunner F, Bachmann LM, Weber U, et al., Complex regional pain syndrome 1 – the Swiss cohort study, *BMC Musculoskelet Disord*, 2008;9:92.

83. Harden RN, Bruehl S, Perez RS, et al., Development of a severity score for CRPS, *Pain*, 2010;151(3):870–6.

84. Goebel A, Baranowski A, Maurer K, et al., Intravenous immunoglobulin treatment of the complex regional pain syndrome: a randomized trial, *Ann Intern Med*, 2010;152(3):152–8.

85. Tracey KJ, The inflammatory reflex, *Nature*, 2002;420(6917):853–9.

86. Collins S, Zuurmond WW, de Lange JJ, et al., Intravenous magnesium for complex regional pain syndrome type 1 (CRPS 1) patients: a pilot study, *Pain Med*, 2009;10(5):930–40.

87. Kapural L, Lokey K, Leong MS, et al., Intrathecal ziconotide for complex regional pain syndrome: seven case reports, *Pain Pract*, 2009;9(4):296–303.

88. Brunner F, Gymesi A, Kissling R, Bachmann LM, Disease-related knowledge of patients with chronic regional pain syndrome, *J Rehabil Med*, 2010;42(4):458–62.

89. Van de Meet H, Oerlemans M, Bruggeman A, et al., Safety of 'pain exposure' physical therapy in patients with complex regional pain syndrome type 1, *Pain*, 2011;152(6):1431–8.

90. Picarelli H, Teixeira MJ, de Andrade DC, et al., Repetitive transcranial magnetic stimulation is efficacious as an add-on to pharmacological therapy in complex regional pain syndrome (CRPS) type I, *J Pain*, 2010;11(11):1203–10.