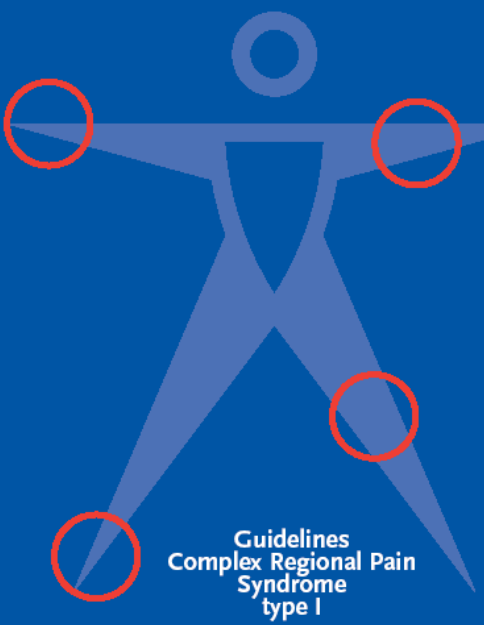


Posttraumatische
Dystrophie



Guidelines
Complex Regional Pain
Syndrome
type I

Guidelines
Complex Regional Pain Syndrome
type I

Evidence Based Guideline Development

Evidence Based Guidelines for Complex Regional Pain

Syndrome Type I

Complex Regional Pain Syndrome type I (CRPS-I) is a condition that often starts in an arm or leg, usually following a trauma of some kind, and is characterised by a combination of autonomic, sensory and vasomotor symptoms.

It usually requires long-term, intensive medical assistance and is therefore a considerable drain on available healthcare budgets. Many patients who have had CRPS-I are no longer able to perform their usual (social) role in everyday life; this means that the condition has a significant effect on their quality of life.

The CRPS-I guidelines contain recommendations for efficient diagnosis and medical and paramedical treatment. They also look at risk factors and prevention, especially as regards the workplace.

The guidelines were developed for use in GP clinics, rehabilitation medicine, anaesthesiology, neurology, paediatrics, surgical disciplines (surgery, neurosurgery, plastic surgery, orthopaedic surgery), vocational and industrial medicine, insurance medicine, psychology and paramedical professions (physiotherapy and occupational therapy).

These EBGD guidelines were developed as a result of an initiative taken by the Netherlands Society of Rehabilitation Specialists (VRA) and the Netherlands Society of Anaesthesiologists (NVA). The development of these guidelines was made possible by the Order of Medical Specialists (umbrella organisation for all medical specialists) with methodological support from the Institute for Healthcare Improvement CBO. EBGD guidelines are designed for use by healthcare professionals in preventing, diagnosing and treating disease and in organisational issues. They aim to (1) improve the quality of healthcare, (2) assist in clinical decision-making, (3) promote coordination between healthcare professionals in their interventions and (4) give an insight into the background of care. The term EBGD stands for Evidence-Based Guideline Development. EBGD guidelines are based on the best scientific evidence available. The strength of evidence is guaranteed according to the principles of evidence-based medicine.

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The Utrecht-based Institute for Healthcare Improvement (CBO) works to support individual healthcare practitioners, their professional associations and healthcare institutions in improving patient care. The CBO runs programmes and projects to support and assist with the systematic and structured assessment, improvement and maintenance of high-quality patient care.

The Netherlands Society of Rehabilitation Specialists (VRA) is the national society for doctors specialising in rehabilitation medicine. The core activities of a rehabilitation specialist are: providing diagnosis, treatment, advice and consultation for patients who have experienced a loss of function following illness, accident or a congenital condition. The aim of rehabilitation treatment is to help patients play a more active part in society and reduce the impact on their social life.

The Netherlands Society of Anaesthesiologists (SA) is a society made up of and working on behalf of anaesthesiologists. It promotes its members' interests and helps create a positive image for anaesthesiology and anaesthesiologists in the Netherlands. It supports high-quality and appropriate performance of anaesthesiology by developing and implementing policies in the field of scientific research, medical technology, quality assurance and inspections.

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Guidelines

Complex Regional Pain Syndrome type 1

Initiative

Netherlands Society of Rehabilitation Specialists

Netherlands Society of Anaesthesiologists

With the support of:

Institute for Healthcare Improvement CBO

In cooperation with:

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Dutch College of General Practitioners

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Dutch Orthopaedic Association

Dutch Multidisciplinary Association for the Study of Pain

Netherlands Society of Neurosurgeons

Netherlands Association of Posttraumatic Dystrophy Patients

Netherlands Association for Occupational and Industrial Medicine

Dutch Association of Occupational Therapy

Netherlands Society of Surgery

Netherlands Society of Paediatric Medicine

Netherlands Society of Neurology

Netherlands Society for Plastic Surgery

Netherlands Society of Rheumatology

Netherlands Society for Insurance Medicine

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Summary of recommendations

Diagnosis

- The clinical diagnosis of CRPS-I can be established using the criteria drawn up by Veldman et al. and the IASP (International Association for the Study of Pain). The project group prefers to use Veldman et al's criteria for clinical purposes in the Netherlands. For scientific research purposes, it is recommended that patient groups be described using the criteria drawn up by Veldman et al. and/or the IASP and/or Bruehl et al.
- In the day-to-day course of diagnosing CRPS-I patients, none of the additional diagnostic methods described in this chapter offer any added value in diagnosing CRPS-I. This applies to: imaging techniques (X-ray diagnosis, MRI, functional MRI, PET, SPECT, three-phase bone scan, bone density measurements, indium 111 IgG scans), general blood tests (haematology, chemistry), specific blood tests (immune parameters, neurotropic virus titres, inflammation parameters), skin tests (inflammation parameters, histochemical markers), skin temperature (absolute skin temperature measurements, thermography), sympathetic and sudomotor function tests (laser Doppler fluxmetry, 'computer-assisted' venous impedance plethysmography, resting sweat output, thermoregulatory sweat test and quantitative sudomotor axon reflex test, sympathetic skin response), neurophysiological tests (nerve conduction, electromyography, SSEP, transcranial magnetic stimulation, H reflex, polysomnography and magnetic encephalography) and quantitative sensory tests.
- The aforementioned conclusion does not apply to general blood tests and neurophysiological research if another diagnosis is suspected.
- Test methods that have been developed solely to quantify and objectify clinical findings in CRPS-I patients have no additional diagnostic value in respect of actually diagnosing CRPS-I. However, the test methods can be important in the context of meeting CRPS criteria, and can serve as a parameter for progress in the context of investigations. This applies to: absolute temperature measurement using an infrared thermometer, quantitative sensory testing, resting sweat output, thermoregulatory sweat test, quantitative sudomotor axon reflex test, sympathetic skin response, volumetry and finger diameter in the case of limb oedema, visual analogue scale (VAS pain), total score on impairment level, capabilities questionnaire, upper limb activity monitor, Radboud skills test, walking stairs questionnaire & questionnaire rising and sitting down and foot function test.

Epidemiology

- There is no need to consider the possibility of a greater risk of CRPS-I when deciding whether to apply an external fixator.

Drug treatment and invasive treatment

- A sub-anaesthetic dose of ketamine should be considered for patients with CRPS-I who are experiencing pain symptoms. The project group asserts that pain medication should be administered in accordance with the WHO pain ladder up to and including step 2. Strong opioids should not be administered to this patient group.
- The project group also recommends that further research should be carried out into the specific effect of pain medication on CRPS-I.
- Administration of gabapentin should be considered for patients with CRPS-I. This should be discontinued if no clear reduction in pain symptoms, allodynia or hyperaesthesia occurs within an eight-week trial period.
- A trial course of carbamazepine, pregabalin or other anti-epileptic drugs can be considered for patients with CRPS-I suffering significant attacks of neuropathic pain.
- A trial course of amitriptyline or nortriptyline can be considered for patients with CRPS-I who are suffering continuous neuropathic pain.
- Capsaicin has no place in the treatment of CRPS-I.
- A three-month course of 50% DMSO (dimethylsulphoxide) cream five times a day (for local application on skin) is recommended for patients who have had CRPS-I for less than a year.
- A one-month trial course of DMSO applied locally can be considered for patients who have had CRPS-I for more than a year. If the results are favourable, the treatment can be continued for three months.
- A three-month course of 600 mg of N-acetylcysteine 3 times a day can be considered for patients with CRPS-I who have a primary cold skin temperature.
- Until trials have found mannitol to be effective in reducing oedema, the project group is of the opinion that this medicine should only be administered in the context of a trial.
- The members of the project group recommend that CRPS-I patients suffering from dystonia, myoclonias or muscle spasms should be started on 1) oral baclofen according to the standard dose increase pattern, 2) diazepam or clonazepam, which should be slowly titrated in the light of the effect and side-effects.
- The project group considers that botulin toxin has no place in the treatment of CRPS-I-patients with dystonia.

- Intrathecal baclofen has no place in the treatment of patients with CRPS-I. Intrathecal baclofen can only be considered for patients with CRPS-I if dystonia is a major problem and conventional therapy has proven ineffective. This treatment must be administered in the context of a trial.
- Routine administration of corticosteroids has no place in the treatment of CRPS-I patients.
- The project group is of the opinion that in view of the conflicting results of research, it is impossible to give any clear advice as to the use of calcitonin in patients with CRPS-I.
- As there is little experience with the use of bisphosphonates in patients with CRPS-I, it is currently advised that these drugs should only be considered in the context of a trial.
- A calcium channel blocker can be prescribed for patients with a cold CRPS-I. The effect must be assessed a week after administration. The drug must be discontinued if it has no effect.
- Intravenous sympathetic blockade has no place in the treatment of patients with CRPS-I.
- Intravenous administration of 10-20 mg of ketanserine can be considered for the treatment of CRPS-I patients.
- Routine administration of reserpine, droperidol and atropine is not recommended for CRPS-I patients.
- Treatment with percutaneous sympathetic blockade using local anaesthetics may be considered for patients with cold CRPS-I who do not respond adequately to vasodilating medication.
- If a trial blockade has proved successful, definitive sympathetic blockade using radiofrequent lesions, phenol or alcohol can be considered in the context of a study.
- Pain control with spinal cord stimulation is a sound option for carefully selected CRPS-I patients who have not responded to other treatments. Spinal cord stimulation should ideally only be administered to other CRPS-I patients in the context of a trial.
- Amputation for CRPS-I patients can only be considered in order to improve the quality of life in the case of severe, recurrent infections and severe functional disorders. This intervention should be performed at a specialised centre.
- Extreme caution is vital when considering surgical sympathectomy for pain control in CRPS-I. The procedure should be conducted in the context of a trial in order to ascertain the efficacy and potential risks.

Paramedical, rehabilitation medicine and psychological treatment methods

- It is recommended that physiotherapy aimed at restoration of function be started as soon after the onset of CRPS-I as possible.
- TENS (transcutaneous electrical nerve stimulation) can be tried out without risk in CRPS-I patients as an additional treatment. It is only sensible to continue with the treatment if it is found to be effective.
- The project group recommends that patients with upper-limb CRPS-I be referred for occupational therapy.

- Where a number of practitioners are treating a CRPS-I patient at the same time, it is advisable that one of them acts as case manager.
- The project group advises that CRPS-I patients should consult a psychologist if the practitioner observes a discrepancy between clinical symptoms and the patient's (pain-related) behaviour, if stagnation in (somatic) treatment occurs, if the burden of suffering caused by the symptoms is great, or if the patient requests this.

Treatment of children with CRPS-I

- The project group considers that further research is needed to determine the effects of drug treatment and invasive treatment on children with CRPS-I. Caution is advised when applying the treatments described in these guidelines to children. Particular attention must be paid to measurement of the dose and giving (medical) support to the child.
- The project group recommends that children with CRPS-I should have physiotherapy.
- The project group advises that occupational therapy should be a component of multidisciplinary treatment for children with CRPS-I.
- Psychological diagnosis and treatment of children with CRPS-I should ideally be carried out by a child psychologist.

Communication, information and prevention

- The project group is of the opinion that all doctors and other medical professionals engaged in consultation with CRPS-I patients should actively inform and listen for physical symptoms, behaviour and social factors, and offer targeted and appropriate information.
- Written information should be given in addition to verbal information provided by the medical professional, and must not be used as a substitute for such verbal information.
- Company doctors should assess whether workplace adjustments or organisational measures are needed to allow a patient with CRPS-I to work without damaging his or her health, and if such adjustments or measures are needed what form they should take. This process involves assessing the exertion involved in a job and the ability of the patient to bear such exertion.
- The project group recommends that the diagnosis of complex regional pain syndrome type I (with the secondary terms 'Sudeck's atrophy' and 'posttraumatic dystrophy') should be added to the occupational health & safety (ARBO) and social insurance scheme's classification system under 'Disorders of the nervous system' (this applies specifically to the Netherlands).
- If it appears that the company doctor will be unable to see a CRPS-I patient within a short time, or if insufficient information is

available to allow him or her to assess the amount of exertion that the patient can bear, then he or she should consult the doctor treating the patient.

- Consideration should be given to prescribing 500 mg of vitamin C to be taken orally for 50 days in order to reduce the risk of CRPS-I in adults who have had a wrist fracture.
- Perioperative administration of intravenous guanethidine is not advised for primary prevention of CRPS-I.
- Perioperative administration of subcutaneous calcitonin is not advised for primary prevention of CRPS-I.
- Timing of surgery: It is recommended that surgery of the (previously) affected limb be postponed until the signs and symptoms of CRPS-I have almost disappeared. This does not apply to operations intended to eliminate an underlying factor that may be responsible for the CRPS-I.
- It is recommended that the duration of the operation and blood removal be minimised.
- Adequate pre-, per- and postoperative pain control is recommended.
- Perioperative blockades of the ganglion stellatum or IV regional blockades using clonidine 1 µg/kg (not guanethidine) can be considered in the case of upper-limb surgery on patients who previously suffered from CRPS-I.
- The use of regional anaesthesia with a sympatholytic effect (epidural/spinal analgesia, plexus brachialis blockade), either alone or in combination with general anaesthesia, can be considered in the case of surgery on patients who previously suffered from CRPS-I.
- The perioperative use of calcitonin can be considered.
- The perioperative use of mannitol to prevent CRPS-I is not recommended.

General introduction

Background

It is estimated that between 5,000 and 8,000 people are diagnosed with Complex Regional Pain Syndrome Type I (CRPS-I) in the Netherlands each year. However, we do not have any concrete epidemiological figures on incidence and prevalence. This condition usually requires long-term, intensive medical assistance and is therefore a considerable drain on available budgets. It is estimated that 20% of patients who have had CRPS-I are no longer able to fulfil their usual (social) role in everyday life, which contributes to the present debate on unemployment and disability benefits. The condition also has a marked impact on the quality of life of these patients.

As there is not yet a consensus in the Netherlands on the diagnosis and strategy for treating CRPS-I, the syndrome is often undertreated or sometimes overtreated. Various sets of diagnostic criteria are used alongside each other, and many different therapies are applied to this group of patients, some of which are of dubious efficacy. The diagnostic criteria and optimum treatment strategy for CRPS-I are subjects of discussion at the national and international levels.

The complexity of this problem, the fact that various disciplines are involved in treatment, and the consequences for the patient's psychosocial functioning mean that a clear, uniform set of guidelines is essential; such guidelines would also make it easier to provide patients with unambiguous information.

The development of such guidelines has also raised issues relating to the funding of various treatments for CRPS-I.

It is in the light of the foregoing considerations that the Netherlands Society of Rehabilitation Specialists and the Netherlands Society of Anaesthesiologists have decided to draw up a set of multidisciplinary evidence-based guidelines for CRPS-I policy. In this context, the Institute for Healthcare Improvement CBO offered its methodological expertise.

Objective

These guidelines contain recommendations to back up everyday practice. They are based on the results of scientific research and further discussion on how to establish good medical, paramedical and psychological treatment. The guidelines indicate what care is generally most appropriate for patients with CRPS-I, and contain recommendations on the diagnosis, treatment, after-care, follow-up and information and support for children and adults with CRPS-I.

The guidelines can be used to give information to patients. They can also act as a springboard for other arrangements, such as transmural arrangements or local protocols in support of implementation.

The specific aims of these CRPS-I guidelines are to achieve uniformity in respect of diagnosis and treatment in the various centres and to define the contexts in which multidisciplinary care should be provided to patients with CRPS-I. In particular, the guidelines will address the indications for treatment of symptoms and the role of the various medical and paramedical disciplines in this respect.

The development of guidelines should also improve communication between practitioners and widen opportunities for assessing individual types of treatment and their effects.

Target group

The guidelines are intended for use by all medical practitioners involved in treating patients with CRPS-I, such as GPs, rehabilitation specialists, rheumatologists, anaesthesiologists, neurologists, paediatricians, surgeons, neurosurgeons, plastic surgeons, orthopaedic surgeons, company doctors, insurance doctors, psychologists, physiotherapists and occupational therapists.

Description of the problem and fundamental questions

The multidisciplinary committee that compiled the guidelines formulated a number of fundamental questions (see pages 21-23) that cover everyday practice in relation to the diagnostic, therapeutic and support policy for patients with CRPS-I.

They describe the incidence, pathogenesis, symptomatology and factors affecting the future course of the condition, diagnostic and treatment options together with their efficacy and influence on quality of life. Several chapters also address what kind of psychosocial support should be provided for patients with this condition. The fundamental questions form the basis for the various chapters in these guidelines. We do not therefore claim that the guidelines are completely comprehensive. Some of the chapters are more directional in nature. These guidelines do not deal with branches of alternative medicine.

Composition of the project group

A multidisciplinary project group was set up in the autumn of 2003 to work on these guidelines. It was made up of representatives of all medical and paramedical disciplines engaged in diagnosing and treating patients with CRPS-I, epidemiologists, a representative of the Netherlands Association of Posttraumatic Dystrophy Patients and the Institute for Healthcare Improvement

CBO (see *Composition of the project group*). The project group was established with a view to ensuring an even spread between geographical locations, balanced representation of the various societies and bodies involved, and a fair division between members with an academic background and those from a non-academic background. A file containing details of the members of the project group and covering possible financial conflicts of interest can be inspected at the offices of the Institute for Healthcare Improvement CBO. No particular forms of conflict of interest have been reported.

Approach taken by the project group

In view of the size of the task, a number of sub-groups with representatives of relevant disciplines were set up. A group of core editors, comprising the Chairman, the Secretary, the CBO Advisor and P.U. Dijkstra and M.A. Kemler, from the project group, was responsible for coordination and consultation between the subgroups. The project group spent approximately two years working on the text of the draft guidelines. They produced texts, either individually or in subgroups, that were discussed at plenary meetings and approved after comments had been taken into account. The plenary project group met ten times to discuss the results of the sub-groups. The subgroups' texts were integrated into a single document, the draft guidelines, by the core editors. These guidelines were presented for comment at a national guidelines meeting held on 7 October 2005. Once the comments had been taken into account, the guidelines were adopted by the full project group and sent to the relevant professional bodies for approval.

Scientific evidence

Where possible, the recommendations in these guidelines are based on evidence taken from published scientific research. Relevant articles were sourced from systematic searches in the Cochrane Library, Medline, Embase, Cinahl and Psychinfo. We looked only for articles written in English, German, French, Italian or Dutch. Manual searches were also conducted, and we selected articles quoted in the bibliographies of articles that had already been found. We also consulted recent guidelines on CRPS-I. The search covered the period from 1980 to June 2004, and we also considered some articles that appeared after this date. We used the following patient population key words: Reflex-Sympathetic-Dystrophy, Complex-Regional-Pain-Syndromes; reflex sympathetic dystrophy; Sudecks atrophy; algodystrophy; posttraumatic dystrophy as MESH (Medical Subject Heading) term and as a free text word. The key selection criteria were: comparative studies with significant evidential force, such as meta-analyses, systematic reviews, randomised controlled trials (RCTs) and controlled trials (CTs). Where these were not available we sought further for comparative cohort research, comparative patient control trials or non-comparative trials. Other important criteria

were: adequate size, adequate follow-up, adequate exclusion of selection bias, and whether the results obtained can be translated to the situation in the Netherlands.

The members of the project group assessed the quality of these articles on the basis of evidence-based guidelines development (EBGD) assessment forms. Articles of moderate or poor quality were excluded. After this screening process we were left with the articles that form the basis for the various conclusions put forward in the guidelines. The articles were then graded according to their evidential strength, classifying them as described below.

Table 1 Classification of the literature consulted, according to evidential strength

For articles on intervention:

- A1 systematic reviews that comprise at least several A2 quality trials whose results are consistent;
- A2 high-quality randomised comparative clinical trials (randomised, double-blind controlled trials) of sufficient size and consistency;
- B randomised clinical trials of moderate quality or insufficient size, or other comparative trials (non-randomised, comparative cohort study, patient control study);
- C non-comparative trials;
- D opinions of experts, such as project group members.

For articles on diagnosis:

- A1 research into the effects of diagnosis on clinical outcomes in a prospectively monitored well-defined patient group with a predefined policy on the basis of the test outcomes that are to be investigated, or operational investigation into the effects of diagnosis on clinical outcomes, where the results of A2-quality research are used as the basis and sufficient account is taken of the interdependency of diagnostic tests;
- A2 research relating to a benchmark test where criteria for the test to be investigated and for a benchmark test are defined beforehand, with a good description of the test and the clinical population to be investigated; a sufficiently large series of consecutive patients must be involved, predefined upper limits must be used, and the results of the test and the 'gold standard' must be assessed independently. Interdependence is normally a feature of situations involving multiple diagnostic tests, and the analysis must be adapted accordingly (by means of logistic regression, for example);

- B comparison with a benchmark test, description of the test and population under review, but without the other features mentioned under A;
- C non-comparative trials;
- D opinions of experts, such as project group members.

Level of evidential strength

- 1 at least one systematic review (A1) or two grade A2 studies conducted independently of each other;
- 2 at least two grade B studies conducted independently of each other;
- 3 at least one grade A2, B or C study;
- 4 opinions of experts, such as project group members.

The description and evaluation of the various articles are given in the individual texts under the heading *Scientific support*. The scientific evidence is summarised in the *Conclusions*. The main published sources on which these conclusions are based are listed at the end of the conclusions along with the *Evidential strength*.

The description and evaluation of the articles are also summarised for each subject in an evidence table. The evidence tables are not included in the printed version of the guidelines but can be found on the CBO's website: www.cbo.nl .

How the recommendations were produced

Various other aspects are often important in the production of a recommendation alongside scientific evidence, such as patients' preferences, availability of special techniques or expertise, organisational aspects, social consequences and costs. These aspects are discussed after the *Conclusions*. The conclusions based on publications are set into the context of daily practice here, and we weigh up the advantages and disadvantages of the various possible policies. The definitive recommendation is the result of the evidence available in combination with these considerations. The purpose of following this procedure and drawing up the guidelines in this 'format' is to increase their transparency. It offers room for an efficient debate between project group meetings, and also makes the guidelines easier for users to understand.

Implementation and evaluation

At the various stages of development of the draft guidelines, we have taken account, where possible, of their implementation and the practical feasibility of the recommendations. The guidelines are going to be sent to all general and university hospitals and to all relevant scientific associations. A summary of the guidelines will also be submitted for publication to the *Nederlands Tijdschrift voor Geneeskunde* [Dutch Journal of Medicine], and various specialist journals will report on the guidelines. The complete text of the guidelines will also be published on the CBO website. In order to encourage implementation and evaluation of these guidelines, the project group intends to devise an implementation plan and develop a list of indicators which can be used to monitor implementation. Indicators generally enable healthcare providers to see whether they are providing the desired care and, as such, can identify areas in which healthcare provision could be improved.

The guidelines will be tested with end users in the various regions and scientific associations. The tests will involve medical audits to the institutions concerned.

Legal status of guidelines

Guidelines are not statutory requirements, but views and recommendations which are soundly based in science and enjoy broad support. Healthcare providers should comply with them in order to offer good quality care. As guidelines are based on 'average patients', healthcare providers may deviate from the recommendations in individual cases. If the patient's condition requires, it may even be essential to deviate from established guidelines. However, any deviations should be justified, documented, and where necessary discussed with the patient.

Revision

The guidelines will be tested against scientific developments once a year by a multidisciplinary committee that has yet to be set up. The Chairman of this multidisciplinary committee will be drawn from the ranks of the Netherlands Society of Rehabilitation Specialists or the Netherlands Society of Anaesthesiologists, being the groups most closely involved in these guidelines. The committee will be responsible for contacting professional associations in the meantime to find out whether they consider that the current guidelines are in need of revision. In the event of essential changes, it may be decided following consultation with the CBO to produce an updated electronic version and distribute it to the various professional bodies. Where necessary, a new project group will be set up to revise (parts of) the guidelines. The committee will establish a new multidisciplinary project group by 2010 at the latest, which will be tasked with producing a fully revised version of the guidelines.

Fundamental questions relating to CRPS-I

Diagnosis and epidemiology

Diagnosis

- How is CRPS-I diagnosed?
- Is CRPS-I a purely clinical diagnosis?
- Is an indication needed to carry out additional tests for CRPS-I?

Epidemiology

- What is the incidence of CRPS-I?
- Can any predisposing factors for developing CRPS-I be identified?
- Are there any sub-groups within CRPS-I?
- When can a patient be considered cured?
- How can a relapse of CRPS-I be defined?

Course of the condition

- Are there different categories of severity?
- Does the condition progress through distinct stages?
- What is the natural course of the syndrome?
- What prognostic factors affect the course of the syndrome?
- What parameters/measuring instruments are used to monitor patients?

Drug treatment and invasive treatment

Drug treatment

- What drug treatments are available (subdivided into 'scavengers', calcium antagonists, paracetamol/NSAIDs/opioids, antidepressants/anti-convulsants, anaesthetics/muscle relaxants, etc.)?
- What degree of proof exists for these drug treatments?
- What is the role of these drug treatments within the CRPS-I treatment spectrum?
- Are there any specific requirements relating to drug treatment of (young) children with CRPS-I?

Invasive treatments

- What forms of invasive treatment are available for CRPS-I (subdivided into blockade techniques, intrathecal treatments, spinal cord stimulation, local infiltration, etc.)?
- What degree of proof exists for these forms of invasive treatment?
- What is the role of these invasive treatments within the CRPS-I treatment spectrum?
- Is there an indication for surgery in CRPS-I?
- What surgical procedures are available for CRPS-I and what degree of proof exists for them?
- Is there an indication for amputation in CRPS-I?
- What is the role of these specific surgical procedures within the CRPS-I treatment spectrum?
- Are there any specific requirements relating to invasive treatment of (young) children with CRPS-I?

General aspects

- Are there any contraindications for the various treatments?
- How cost-effective are the various treatment options?

Paramedical, rehabilitation medicine and psychological treatment methods

Paramedical and rehabilitation medicine treatment methods

- What physiotherapy, occupational therapy and rehabilitation medicine treatments are available?
- What degree of proof exists for these interventions?
- What is the role of these treatments within the CRPS-I treatment spectrum?
- Are there any specific requirements relating to physiotherapy treatment of (young) children with CRPS-I?

Psychological treatment methods

- What psychological treatments are available for CRPS-I?
- What degree of proof exists for these treatments?
- What is the role of these psychological treatments within the CRPS-I treatment spectrum?
- Are there any specific requirements relating to psychological treatment of (young) children with CRPS-I?

General aspects

- Are there any contraindications for the treatments?
- How cost-effective are the various treatment options?

Communication and information

- What general advice can be given to CRPS-I patients and their families (support, ability to bear exertion, (resuming) work)?
- What is the role of information in the treatment of CRPS-I (preventing aggravation of the condition)?

Prevention

- What preventive measures are available to prevent CRPS-I (following trauma, pre- and perioperative)?
- What degree of proof exists for these measures?

- What is the role of these measures within the CRPS-I treatment spectrum?

Implementation of the guidelines

- How will the guidelines be implemented (information to patients, practitioners, professional bodies; using which media)?
- Should a decision tree or flowchart be drawn up to guide practitioners in the choice of treatments?

Complex Regional Pain Syndrome type 1

Complex Regional Pain Syndrome type I (CRPS-I) is a condition that causes multiple problems for both patients and practitioners. The condition often starts in an arm or leg, usually following a trauma of some kind, and is characterised by a combination of autonomic, sensory and vasomotor symptoms. Pain, temperature difference, impaired movement, change in skin colour, hyperaesthesia, hyperalgesia, hyperpathy, tremor, involuntary movements, muscle spasms, paresis, pseudoparalysis, skin, muscle and bone atrophy, hyperhidrosis and changes in hair and nail growth have been reported in patients with this syndrome (*table 1*). Much remains to be learned about this condition, which is characterised by a diverse range of symptoms and just as many treatment methods.

Table 1 Percentage of CRPS-I patients with the following symptoms after having had the condition for varying lengths of time

	0-2 months	2-6 months	6-12 months	> 12 months
Pain	92	88	97	97
Colour difference	97	96	90	84
Oedema	86	80	61	55
Temperature difference	98	91	89	91
Impaired movement	90	90	88	83
Symptoms worsened by exertion	87	95	96	97
Hyperalgesia	69	75	72	85
Hyperpathy	69	79	79	81
Coordination problems	53	47	55	61
Tremor	54	44	48	50
Involuntary movements	19	24	44	47
Muscle spasms	11	13	27	42
Paresis	98	93	91	97
Pseudoparesis	16	7	15	26
Skin atrophy	38	37	74	44
Nail atrophy	15	23	28	36
Muscle atrophy	40	50	56	67
Bone atrophy	7	41	48	52
Hyperhidrosis	57	56	42	40
Change in hair growth	54	56	42	40
Change in nail growth	58	60	59	52

Source: Veldman et al. 1993.

The way in which the syndrome is described has changed over the years. Around 72 different names are used in the literature: the most widely known are Sudeck's dystrophy, posttraumatic dystrophy and reflex sympathetic dystrophy². The latter designation highlights one of the problems associated with CRPS-I: the lack of a clear pathophysiological mechanism (see also *section 1.1* on pathophysiology). The term reflex sympathetic dystrophy refers to the assumption that following trauma the orthosympathetic nervous system is more active than normal as a result of damage to the sensory nerves³. This theory has recently been called into question following indications that the activity of the sympathetic nervous system is actually lower⁴⁻⁶.

In response to this, a consensus conference was held under the auspices of the Association for the Study of Pain (IASP), at which it was suggested that the descriptive term Complex Regional Pain Syndrome should be used. A distinction is drawn here between CRPS type I, formerly known as RSD, and type II, where a nerve lesion can be detected (formerly known as causalgia)^{7,8}.

The most recent IASP definition of the syndrome reads as follows:

*'Complex Regional Pain Syndrome is a term describing a variety of painful conditions following injury which appears regionally having a distal predominance of abnormal findings, exceeding in both magnitude and duration the expected clinical course of the inciting event, often resulting in significant impairment of motor function, and showing a variable progression in the course of time.'*⁸

The diagnostic criteria for CRPS-I is a matter of much debate (see *section 1.2* on diagnosis). The debate is further fuelled by the absence of any objective clinical test or clear pathophysiological mechanism for CRPS-I.

The current criteria for CRPS-I also make it difficult to establish when someone has been cured. A patient may no longer meet the criteria for CRPS-I, but still have residual symptoms of a past bout of CRPS-I.

The lack of clear diagnostic criteria, and the limited capacity of current diagnostic criteria to discriminate, make it hard to distinguish CRPS-I from conditions with comparable symptoms (see *table 2*). This is why we have decided to address the diagnosis issue before turning to epidemiology.

Shoulder-hand syndrome (SHS) occurring in cases of hemiplegia occupies a particular position^{9,10}. Although separate diagnostic criteria exist for SHS, this syndrome can also be regarded as a form of CRPS-I. As the project group considers that many of the symptoms of SHS are related to hemiplegia, we have ignored this syndrome in these guidelines.

Table 2 Differential diagnoses

Infections
Entrapment syndromes (CTS)
Costoclavicular compression syndrome (CCCS)
Compartment syndromes
Thrombosis
Rheumatism
Lymph oedema
Conversion/self-harm
'Dis-/non-use'

Various treatments for CRPS-I have been described, but few studies of high methodological quality have been carried out into the effects of those treatments.

It should be noted that most research has been conducted on patients at an early stage of the condition. Caution is essential when extrapolating these results to patients with a more advanced form of CRPS-I. Basically, treatments for CRPS-I can be divided into drug and/or invasive medical treatment, paramedical treatment and psychological treatment. There are indications that early diagnosis and treatment of CRPS-I leads to a better outcome in terms of symptom reduction¹¹. Little information is available on measures to prevent CRPS-I. The multidimensional nature of CRPS-I, and the fact that the effects of most treatment methods for CRPS-I have been investigated in combination with other treatments, confirm the importance of multidisciplinary treatment in both adults and children. Where a multidisciplinary approach is chosen, it is important for one practitioner to act as the case manager. However, there is no concrete evidence for the (added) value of multidisciplinary treatment for CRPS-I.

Providing information to patients and their families is a key part of treatment for CRPS-I. This matter is dealt with at greater length in *chapter 4*. The Netherlands Association of Posttraumatic Dystrophy Patients has an important role to play in providing information. References to this association can be found in *appendix 7*. The various forms of treatment discussed in these guidelines are summarised in a flowchart, which also suggests a possible sequence of treatment. However, it should be noted that the value of this flowchart has not yet been scientifically demonstrated either.

Chapter I

Diagnosis and epidemiology/aetiology

1.1 Pathophysiology

Introduction

As yet the pathophysiology of CRPS-I is not well understood. Most of the studies that have been carried out are observational in nature, with small numbers of patients taking part and, in most cases, without a control group. The conclusions of the studies are not always direct observations, but tend to be interpretations of the observations made by the investigators. The EBGD methodology does not contain any instrument capable of assessing these studies. We can draw a distinction between peripheral afferent, efferent and central mechanisms involved in the onset and continuance of the syndrome. So far we have found no clear explanation of how these various mechanisms are related to one another.

Peripheral afferent

It seems that a number of peripheral afferent mechanisms may be involved in the pathophysiology of CRPS-I. Indications point to an inflammatory process, a neuro-inflammatory process and tissue hypoxia. Anatomical changes have also been seen in CRPS-I patients. If a (neuro)inflammatory process is involved, then immunological predisposition may be relevant. There are indications that immunological acquired and/or genetic susceptibility may be involved in the onset of CRPS-I.

Inflammation

A number of arguments for and against the involvement of an inflammatory process in CRPS-I can be put forward. CRPS-I patients have been found to have disorders in high-energy phosphate metabolism (this was demonstrated by means of ³¹P-NMR spectroscopy). This can be caused by cellular hypoxia or diminished oxygen extraction. This phenomenon is also seen in inflammatory processes, and can point to an inflammatory process in cases of CRPS-I¹². Scintigraphs of CRPS-I patients show vascular leakage from macromolecules. This can also be a pointer to an inflammatory process¹³.

However, no activation of the immune system can be detected in the blood of CRPS-I patients¹³. No differences in levels of cytokines IL-1B, IL-6, IL-8, IL-10 and TNF alpha have been observed between CRPS-I patients and healthy subjects¹⁵. These observations are arguments against an inflammatory process being involved. More locally, however, fluid from blisters artificially produced on the skin are found to have significantly higher concentrations of IL-6 and TNF alpha in a limb affected by CRPS-I than in an unaffected limb¹⁶.

Tryptase is also significantly higher in blister fluid in the limb affected by CRPS-I than in the unaffected limb. This is an indicator of mast cell activity, a point in favour of an inflammatory process¹⁷.

Neuro-inflammation

There are some indications that a neuro-inflammatory process may be involved in CRPS-I. Concentrations of bradykinin, neuropeptide Y, Calcitonin Gene-Related Peptide (CGRP) and vasoactive intestinal peptide in the blood are higher in people with CRPS-I than in healthy control subjects¹⁸. Transcutaneous electrostimulation causes protein extravasation in CRPS-I patients but not in control subjects¹⁹. CGRP levels increase in cases of acute CRPS-I²⁰. Substance P-induced protein extravasation occurs in CRPS-I patients. This phenomenon does not take place in healthy controls. All this supports the theory that neurogenic inflammation may have a role to play in triggering CRPS-I²¹. However, levels of substance P and neurokinin A and B are the same in CRPS-I patients as in healthy volunteers²².

Tissue hypoxia

Some research findings point to tissue hypoxia in CRPS-I. Patients with the condition are more hyperalgesic than control subjects to fluids of low pH.

This applies not only to the skin but also to the deeper somatic structures²³. Patients with CRPS-I have higher skin lactate levels than controls, suggesting a rise in anaerobic glycolysis as a consequence of chronic tissue hypoxia²⁴.

Capillary haemoglobin oxygenation of the skin is normal in control individuals, lower than normal in the affected limb following surgery, and lower than normal in both affected and control limbs of people with CRPS-I. This suggests skin hypoxia in CRPS-I patients.

Reduced blood circulation leading to undernutrition of an affected limb may be a factor contributing to atrophy and ulceration²⁵.

Anatomical changes

Two studies have been carried out into anatomical changes in patients with CRPS-I. Histological examination shows that the efferent nerve fibres are not affected in individuals with chronic CRPS-I, while of the afferent fibres only the C fibres are affected.

Skeletal muscles show a variety of histopathological changes, including thickening of the capillary membrane²⁶. In cases of acute CRPS-I of the lower limb, no demonstrable disorders of the A-beta nerve fibre reflex have been observed²⁷.

Immunological acquisition

A study carried out into possible immunologically acquired changes found an association between seropositivity for parvovirus B12 and CRPS-I, pointing to the possibility of an immunologically acquired component in the onset of CRPS-I²⁸.

Genetic susceptibility

A number of studies have been carried out into genetic abnormalities in CRPS-I patients.

Genetic abnormalities may be involved in changes to the immunological response. Genetic abnormalities (HLA-DR2) in the Major Histocompatibility Complex region of the short arm of chromosome 6 are more common in patients with chronic CRPS-I²⁹. HLA-DQ1 is significantly more common in patients with CRPS-I than in control subjects³⁰. There are also associations with HLA-DR13³¹, the TNF2 allele in cases of warm dystrophy, and homozygosity in CRPS-I affecting two limbs³². These studies indicate that there may be a genetic predisposition to contracting the syndrome.

Peripheral efferent

Peripheral efferent mechanisms described in connection with CRPS-I are vasomotor and sudomotor changes in the central nervous system, changes at transmitter level and changes at receptor level.

Vasomotor disorder

A number of studies point towards vasomotor disorder. The vasoconstrictive response of thermoregulating skin circulation is slower in all phases of CRPS-I. This suggests sympathetic denervation, which may also explain the rise in thermoregulating skin circulation in the hot phase of CRPS-I compared to control subjects. As sympathetic denervation can lead to hypersensitivity to catecholamines in vascular structures, which may also be one reason why thermoregulating skin circulation declines in subsequent phases of the syndrome in comparison with control subjects^{4,33}.

Thermoregulating skin circulation and nutritive circulation observed by means of capillary microscopy are lower in later phases of CRPS-I³³. In the cold phase of CRPS-I, and in the phase in which heat and cold alternate, there is no decline in normal flow reserve capacity in spite of the reduction in skin circulation³⁴.

The sympathetic skin response is normal, lower or absent in patients with CRPS-I. The disorder in response is stronger in the first year after the trauma³⁵. The sympathetic skin response is stronger and faster in the acute stage of CRPS-I compared to a control limb³⁶.

The increase in thermoregulating skin circulation in the hot phase of CRPS-I may be caused by spinal vasodilator mechanisms initiated by peripheral nerve damage to the affected limb³⁷. The sympathetic dysfunction in the hot phase of CRPS-I is caused distal to the trauma by autonomous denervation; in the later stages by hypersensitivity to catecholamines. Sympathetic activity increases proximally in all stages³⁸. Sympathetic reflex vasoconstriction following central stimulation is impaired in patients with CRPS-I³⁹. Autonomous symptoms are seen in 98% of CRPS-I patients, but often change as the condition progresses⁴⁰. Additional changes must be taking place in the peripheral and central nervous system in CRPS-I patients compared to patients with an external fixation of a distal radius fracture. Impaired function of the sympathetic vasoconstriction reflex and hyperhidrosis are seen only in CRPS-I patients⁴¹.

Normal inhibition of pain during sympathetic activity is impaired in most CRPS-I patients. The increase in the vasoconstrictive response in an affected limb can be explained by adrenergic hypersensitivity⁴². In cases of acute CRPS-I, unilateral inhibition of the sympathetic vasoconstrictive neurons causes the limb to become warmer. Secondary changes in neurovascular transmission can lead to vasoconstriction and cold skin in patients with chronic CRPS-I.

Sudomotor disorder

A number of studies have pointed to sudomotor disorder. Sudomotor function is usually impaired in people with moderate to severe CRPS-I⁴³. Sudomotor stimulation causes increased and more rapid transpiration in limbs affected by CRPS-I than in control limbs⁴⁴. Control of vasomotor functions declines and control of sudomotor functions increases in the acute phase of CRPS-I. This can relate to a central disorder of thermoregulation, but peripheral mechanisms involved in vasomotor and sudomotor function can also play a part⁴⁵.

Transmitters

A number of studies show a disorder in the vasomotor and sudomotor efferent system at transmitter level.

Tests on the plasma of CRPS-I patients find that concentrations of 3,4-dihydroxyphenylethyleneglycol (DHPG), an intracellular metabolite of noradrenaline, are lower in the affected limb. Patients with extensive allodynia and hyperhidrosis also have lower noradrenaline concentrations in the affected limb. These observations suggest that transpiration and changes in the peripheral bloodstream are the result of hypersensitivity to sympathetic neurotransmitters⁶. Serum noradrenaline concentrations are significantly lower in the affected CRPS-I limb than in the unaffected limb. Serum adrenaline concentrations remain the same.

This suggests elevated peripheral receptor sensitivity with a pathological response to circulating catecholamines. Concentrations of neuropeptide Y (a vasoactive neurotransmitter that is associated with noradrenaline in sympathetic fibres) are lower in limbs affected by CRPS-I, particularly in cases of allodynia and warmer limbs⁴⁶.

Receptors

One study has also shown a possible disorder in the vasomotor and sudomotor efferent system at receptor level. The number of alpha-1-adrenergic receptors is greater in the hyperalgesic skin of CRPS-I patients⁴⁷.

Central mechanisms

The central mechanisms described for CRPS-I are functional changes, motor and sensory changes, and psychological factors. The effect of psychological factors on the development and progress of CRPS-I is described in greater detail in *section 3.4*; this chapter will therefore touch on this aspect only in passing.

Functional changes

Various studies have shown functional changes in patients with CRPS-I. Functional MRI highlights cortical regions that are specifically involved in pain in patients with chronic CRPS-I⁴⁸. There is a considerable variation in contralateral perfusion of the thalamus in CRPS-I patients⁴⁹.

This suggests changes to the thalamus.

Motor disorders

Motor dysfunction is common in patients with CRPS-I. Along with muscle weakness, patients can also develop 'neglect' syndrome. The limb feels strange ('cognitive neglect'), and mental and visual attention is needed to move a limb ('motor neglect')⁵⁰.

Sensory changes

There is no significant change in afferent C-fibres in patients with CRPS-I, but sensitisation of nociception does occur⁵¹. Almost half of all CRPS-I patients have disorders in spinothalamic, trigeminothalamic and corticospinal function. This can be a representation of medullary dysfunction. A third of the remaining CRPS-I patients have demonstrable spinal or cerebral pathology⁵². Sensory changes often occur in CRPS-I patients outside the area of the painful limb. The increased frequency of mechanical allodynia and movement disorders in patients with hemisensory or sensory changes in the upper quadrant points to central mechanisms being involved in the pathogenesis of CRPS-I⁵³. No hyperalgesia to heat occurs in acute CRPS-I. There is no mechanical hyperalgesia to

static stimuli, but there is mechanical hyperalgesia to phasic stimuli and a wind-up phenomenon⁵⁴. Patients with CRPS-I have altered central sensomotor response to tactile stimulation of the fingertip⁵⁵. 'Referred' sensations are a feature of CRPS-I, and this is evidence of central reorganisation⁵⁶.

Summary

Little is known about the pathophysiology of CRPS-I. We can draw a distinction between peripheral afferent, efferent and central mechanisms. The conclusions drawn from research are often interpretations of observations and must be treated with the necessary degree of caution.

The peripheral afferent mechanisms that have been described are: inflammation, neuroinflammation and tissue hypoxia. Anatomical changes have been observed. There are indications of immunologically acquired and/or genetic susceptibility to the development of CRPS-I. The peripheral efferent mechanisms that have been described are vasomotor and sudomotor changes, changes at transmitter level and changes at receptor level. The central mechanisms that have been described are functional changes, motor changes and sensory changes.

1.2 Diagnosis

Diagnosing CRPS-I

There is no uniform method of diagnosing CRPS-I, either in the Netherlands or internationally. Establishing a clinical diagnosis of a case of CRPS-I that is typical and acute in all its facets is often quite straightforward. However, in most cases CRPS-I does not present itself in the classic form with all the symptoms. A diagnosis may not be made at all, or it may be inaccurate or delayed. The literature does not contain any separate diagnostic criteria for children.

Scientific support

Over the years, various attempts have been made to clarify the diagnostic process^{1,7,57,58}. According to Amadio et al. and the American Association for Hand Surgery (AAHS)⁵⁷, pain without autonomic dysfunction and autonomic dysfunction without pain do not meet the definition of reflex sympathetic dystrophy (RSD). However, their preferred term,

Sympathetically Maintained Pain Syndrome, is rejected by Stanton-Hicks et al.⁸ as a variable phenomenon that should be seen as a symptom and is associated with various abnormalities, including CRPS-I.

In 1994 the IASP held a consensus conference⁷ at which the term Complex Regional Pain Syndrome (CRPS-I) was introduced along with corresponding diagnostic criteria (see *table 3*).

This classification is descriptive in nature, and not based on pathophysiology or scientific findings. Rather, it is the result of consensus based on expert opinion⁸. Pain is the *sine qua non* for this diagnosis.

This classification of CRPS-I has been criticised both inside and outside the IASP. Galer et al. examined 18 CRPS-I patients and found it to be insufficiently specific⁵⁹. Both Galer et al.⁵⁹ and Harden et al.⁶⁰ contend that the criteria need to be validated by empirical research. It seems that the IASP criteria have to date been used in only 15% of all recent research in this field^{61,62}.

Bruehl et al. conducted a study on 117 patients with CRPS-I and proposed a change to the criteria, rendering them more specific (*table 4*)⁵⁸. Unfortunately, this also results in a loss of sensitivity, as Van de Vusse et al. have confirmed⁶³.

The changes proposed by Bruehl et al.⁵⁸ have not so far been accepted or adopted by the IASP. However, these 'research-diagnostic criteria' put forward by Bruehl et al. might allow CRPS-I to be more clearly distinguished from other forms of neuropathic pain.

Baron et al.⁶⁴ produced a commentary suggesting another change to these diagnostic criteria (see *appendix 2*), but this has not yet been ratified either.

The objections against the IASP criteria are the small numbers of patients participating in the various trials and the requirement for pain and/or sensitivity disorders to be present. But the supporters of the criteria see the latter aspect as one of its advantages. No laboratory tests are needed in order to establish the diagnosis of CRPS-I on the basis of the aforementioned criteria, and there is also no need to ascertain whether the symptoms improve in response to nerve blockade (sympathetic blockade)⁵⁹. The use of these criteria allows practitioners to diagnose CRPS-I by means of anamnesis and physical examination alone⁶⁰. See also *section 1.3* on additional diagnosis.

The criteria drawn up by Veldman et al.¹ (*table 5*), widely used in the Netherlands, are also based on anamnesis and physical examination. The difference between these criteria and the IASP criteria is that pain is not a requirement *per se*. Veldman et al.¹ also reported that no causal noxa could be found in about 10% of 829 patients with RSD (spontaneous RSD). They therefore concluded that sensitivity disorders were not always a required feature.

There is a grey area of symptoms that can follow any surgery, wound or fracture-healing process. These are (mild) pain, swelling (oedema), redness and heat. We also know these signs as the classic symptoms dolor, calor, rubor, tumor and functio laesa in the case of inflammatory response. It is not always clear whether these fit into the normal boundaries of healing or signify the onset of CRPS-I^{1,65}.

Veldman et al. described the criteria for establishing a diagnosis in such a way that vague circumlocutions are avoided¹. The symptoms that can be seen during physical examination correspond to objective tests and render additional investigation for diagnosis superfluous⁶⁶.

Perez et al.⁶⁷ investigated the inter-investigator reliability of CRPS-I diagnoses drawn up according to Veldman et al.'s (modified) criteria¹. It was assessed as good, as was accuracy in ruling out CRPS-I.

In conclusion, we can state that the diagnosis of CRPS-I is made on the basis of clinical criteria. The lack of insight into pathophysiology and the absence of a good benchmark test, let alone a gold standard, leaves us no other option⁶⁴.

Conclusion

Level 4

The project group is of the opinion that CRPS-I can be diagnosed on the basis of anamnesis and the findings of physical examinations. The criteria drawn up by Veldman et al. and the IASP can be used for this purpose.

D Amadio 1997⁵⁷; Atkins 2003⁶⁵; Baron 2005⁶⁴; Van de Beek 2002⁶²; Bruehl 1999⁵⁸; Galer 1998⁵⁹; Harden 1999⁶⁰; Merskey 1994⁷; Oerlemans 1999⁶⁶; Perez 2002⁶⁷; Reinders 2002⁶¹; Stanton-Hicks 1995⁸; Veldman 1993¹; Van de Vusse 2003⁶³

Other considerations

There is no specific test or examination which can be used to establish a diagnosis of CRPS-I.

The current diagnostic criteria established by the IASP⁷ and Veldman et al.¹ appear to be sufficiently sensitive, although they can lead to overdiagnosis. Atkins et al.⁶⁵ do not regard this as a problem.

Stricter criteria such as those proposed by Bruehl et al.⁵⁸ could lead to underdiagnosis. Practitioners hesitating between a diagnosis of neuropathic pain and one of CRPS-I could use Bruehl's modified criteria.

The project group was unable to reach agreement on whether the IASP criteria or those established by Veldman et al. were preferable.

As various criteria are described in the literature, these guidelines contain a description of widely-quoted criteria (*appendix 2*).

Recommendation

The clinical diagnosis of CRPS-I can be established using the criteria drawn up by Veldman et al. and the IASP. The project group prefers to use Veldman et al.'s criteria for the situation in the Netherlands. For scientific research purposes it is recommended that patient groups be described using the criteria drawn up by Veldman et al. and/or the IASP and/or Bruehl et al.

Veldman diagnostic criteria for RSD (Veldman et al. 1993)

1. 4 or 5 of:
 - Unexplained or diffuse pain
 - Difference in skin colour relative to other limb
 - Diffuse oedema
 - Difference in skin temperature relative to other limb
 - Limited active range of motion
2. Occurrence or increase of above signs and symptoms after use
3. Above signs and symptoms present in an area larger than the area of primary injury or operation and including the area distal to the primary injury

IASP criteria for CRPS-I (Merskey et al. 1994)

1. Develops after an initiating noxious event (type I) or after a nerve injury (type II)
2. Spontaneous pain or allodynia/hyperalgesia that is not limited to the territory of a single peripheral nerve and is disproportionate to the inciting event

3. There is or has been evidence of oedema, skin blood flow abnormality, or abnormal sudomotor activity in the region of the pain since the inciting event
4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction

Proposed modified research diagnostic criteria for CRPS-I (Bruehl et al. 1999)

1. Continuing pain which is disproportionate to any inciting event
2. Must report at least one symptom in each of the four following categories
 - Sensory: reports of hyperesthesia
 - Vasomotor: reports of temperature asymmetry and/or skin colour change and/or skin colour asymmetry
 - Sudomotor/oedema: reports of oedema and/or sweating changes and/or sweating asymmetry
 - Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign 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)

1.3 Additional diagnosis and quantification of clinical symptomatology

Summary

- 1 In the day-to-day course of diagnosing CRPS-I patients, none of the additional diagnostic methods described in this chapter offer any added value in diagnosing CRPS-I.

This applies to:

- **imaging techniques:** X-ray diagnosis, MRI, functional MRI, PET, SPECT, three-phase bone scan, bone density measurements, Indium III IgG scans;

- **general blood tests:** haematology, chemistry;
- **specific blood tests:** immune parameters, neurotropic virus titres, inflammation parameters;
- **skin tests:** inflammation parameters, histochemical markers;
- **skin temperature:** absolute skin temperature measurements, thermography;
- **sympathetic and sudomotor function tests:** laser Doppler fluxmetry, computer-assisted venous impedance plethysmography, resting sweat output, thermoregulatory sweat test and quantitative sudomotor axon reflex test, sympathetic skin response;
- **neurophysiological tests:** nerve conduction, electromyography, SSEP, transcranial magnetic stimulation, H reflex, polysomnography and magnetic encephalography;
- **quantitative sensory tests**

2. The aforementioned conclusion does not apply to general blood tests and neurophysiological research if it is suspected that the patient may have another diagnosis.

3. Test methods that have been developed solely to quantify and objectify clinical findings in CRPS-I patients have no additional diagnostic value in respect of actually diagnosing CRPS-I. However, the test methods can be important in the context of meeting CRPS criteria and can act as a parameter for progress in the context of investigations. This applies to:
 - absolute temperature measurement using an infrared thermometer;
 - quantitative sensory tests;
 - resting sweat output, thermoregulatory sweat test and quantitative sudomotor axon reflex test;
 - sympathetic skin response;
 - volumetry and finger diameter in cases of limb oedema;
 - visual-analogue scale pain;
 - total score in terms of impairment;
 - capabilities questionnaire;
 - upper limb activity monitor;
 - Radboud skills test;
 - RSQ & questionnaire rising and sitting down;
 - foot function test.

Analysis of the literature

Our analysis of the various forms of additional diagnosis covered 135 studies. Inclusion criteria were mentioned in 57% of these, using 16 different CRPS-I or RSD criteria. This means that a considerable proportion of the studies (43%) did not mention any inclusion criteria for CRPS-I or RSD, or used criteria that were described in vague terms. The population size for the various studies varied considerably, with 56% of the studies being carried out on populations of 30 subjects or fewer.

The symptomatology of CRPS-I can be associated with the stage to which the syndrome has progressed, and this factor is therefore important if we are to compare studies within a single diagnostic modality. Forty percent of studies failed to mention the duration of the condition at all; and those that did mention it often had a broad spread of durations within the cohort.

Fifty-eight percent of the studies used a control group of healthy subjects or patients who had undergone different types of trauma. Only 5% of the studies featured a test-retest procedure of the diagnostic modality in healthy subjects in order to assess the reproducibility of the diagnostic test.

Data relating to sensitivity and specificity were reported in only 13% of cases. None of the studies included both a reference test and an index test carried out at the same time. In view of all these shortcomings, it is difficult to reach any firm conclusion from these studies as to the additional diagnostic value of the various tests used to diagnose CRPS-I.

1.3.1 Additional diagnosis for CRPS-I: imaging techniques

1.3.1.1 Three-phase bone scan

The three-phase bone scan (TPBS) is often used as an additional diagnostic tool in CRPS-I⁶⁸⁻⁷⁹. A rise in blood circulation in the affected limb, together with elevated diffuse activity in the blood pool phase and greater periarticular uptake in the late static (delayed) phase of TPBS are assumed to be pathognomonic for CRPS-I^{70,71}.

Inter-observer variability of TPBS indicates kappa values of 0.50 to 0.65, for a final diagnosis based on findings of all the individual phases of a TPBS. We have no information as to kappa values of the individual phases of TPBS⁷⁶ or intra-observer concurrence. One of the studies describes indium-III-IgG scans as being superior to TPBS¹³. However, no study has directly compared TPBS and indium-III-IgG scans performed on patients with CRPS-I.

Some of the studies contain data on specificity and sensitivity (see *background document, Evidence table Diagnosis: Bone scan* on www.cbo.nl).

None of the studies include a reference test in the analysis. One review of mediocre quality recommends that TPBS should not be used with CRPS-I patients⁷⁴.

It has not been possible to establish the discriminatory capacity and/or additional diagnostic value of TPBS in CRPS-I patients as a result of methodological shortcomings, such as unclear CRPS-I criteria, large spread of duration of the condition and the absence of reference tests from the studies.

Conclusion

Level 4

The additional diagnostic value of three-phase bone scans and indium-III-IgG scans for CRPS-I patients has not been demonstrated.

D Atkins 1993⁶⁸; Holder 1984⁶⁹; Intenzo 1989⁷⁰; Kozin 1981⁷¹; Kozin 2005⁷³; Lee 1995⁷⁴; O'Donoghue 1993⁷⁶; Oyen 1993¹³

Recommendation

The project group is of the opinion that three-phase bone scans and indium-III-IgG need not be used to diagnose patients with suspected CRPS-I.

1.3.1.2 Bone density measurements for CRPS-I

Only four studies of bone density measurement could be found; none of them contained data on specificity or sensitivity (see *background document, Evidence table Diagnosis: Bone density* on www.cbo.nl)⁸⁰⁻⁸³

In a prospective study of 60 tibia fractures, 18 patients developed CRPS-I and were found to have significantly lower bone density than the group of patients who did not develop CRPS-I⁸³. No CRPS-I criteria were defined in the course of this study. A cross-over study did not find bone density measurements to be of any diagnostic value⁸⁰.

It has not been possible to establish the discriminatory capacity and/or additional diagnostic value of bone density measurement in CRPS-I patients as a result of the small number of studies conducted and methodological shortcomings, such as unclear CRPS-I criteria, large spread of duration of the condition and the absence of sensitivity and specificity data.

Conclusion

Level 4

The additional diagnostic value of bone density measurement in CRPS-I patients has not been demonstrated.

D Chapurlat 1996⁸⁰; Kumar 2001⁸¹; Müller 2000⁸²; Sarangi 1993⁸³

Recommendation

The project group is of the opinion that bone density measurement need not be used to diagnose patients with suspected CRPS-I.

1.3.1.2 X-ray diagnosis for CRPS-I

Eight studies found abnormal X-ray results in CRPS-I patients^{43,73,75,78,83, 84,86,87}. Most of these were radiological abnormalities such as diffuse osteoporosis and spotty demineralisation, particularly in the periarticular regions, combined with subperiosteal bone resorption.

A small number of studies report data on specificity and sensitivity (see *background document, Evidence table Diagnosis: X-ray on www.cbo.nl*)^{78,84,86}.

It has not been possible to establish the discriminatory capacity and/or additional diagnostic value of X-ray images in CRPS-I patients as a result of the low degree of sensitivity of two studies^{78,86}, the small number of studies conducted and methodological shortcomings, such as unclear CRPS-I criteria and the lack of reference tests.

Conclusion

Level 4

The additional diagnostic value of qualitative assessment of X-ray images in CRPS-I patients has not been demonstrated.

D Bickerstaff 1991⁸⁴; Bickerstaff 1993⁸⁵; Gradl 2003⁸⁶; Kozin 2005⁷³; Moriwaki 1997⁷⁵; Plewes 2005⁸⁷; Rommel 1995⁴³; Sarangi 1993⁸³; Todorovic 1995⁷⁸

Recommendation

The project group is of the opinion that X-rays need not be used to diagnose patients with suspected CRPS-I.

1.3.1.4 MRI, f-MRI, PET and SPECT for CRPS-I

Four studies have been conducted on MRI examination of limbs affected by CRPS-I⁸⁸⁻⁹¹. Three of them reported specificity and sensitivity data⁸⁸⁻⁹⁰. MRI is not a suitable additional diagnostic tool for CRPS-I patients in view of the absence of a control group, data on the duration or stage of the condition, and CRPS-I criteria found to be most sensitive in one study⁹¹ and of low sensitivity in another study⁸⁹.

The same applies to other new imaging techniques such as functional MRI (f-MRI)^{48,92}, positron emission tomography (PET scan)^{93,94} and single photon emission tomography (SPECT)⁴⁹. However, these techniques are designed mainly to produce more information about pathophysiology rather than help diagnose CRPS-I (see *background document, Evidence table Diagnosis: MRI/PET scan/SPECT* on www.cbo.nl).

Conclusion

Level 4

The additional diagnostic value of MRI, functional MRI, PET scan and SPECT for CRPS-I patients has not been demonstrated.

D Apkarian 2001⁴⁸; Fukumoto 1999⁴⁹; Goldstein 2000⁹³; Grachev 2002⁹²; Graif 1998⁸⁸; Iadarolo 1995⁹⁴; Koch 1991⁸⁹; Schimmerl 1991⁹⁰; Schweitzer 1995⁹¹

Recommendation

The project group is of the opinion that MRI, functional MRI, PET and SPECT need not be used to diagnose patients with suspected CRPS-I.

1.3.2 Additional diagnosis for CRPS-I: blood tests

Various serum parameters have been studied in CRPS-I patients. General serum parameters, such as ESR, leukocytes, alkaline phosphatase, CPK, protein spectrum, IgG, IgA and IgM, are the same in CRPS-I patients as in healthy individuals¹⁴. The same applies to immune parameters such as lymphocyte and T-cell populations¹⁴, HLA typing^{14,29,30}, serum lactate²⁴, CRPG^{20,95}, adrenalin⁴⁶, bradykinin⁹⁵, cytokines, IL-6, IL-1 β and TNF- α ¹⁶ and titres of neurotropic viruses²⁸, catecholamines⁹⁶, and endothelin-I (see *background document, Evidence table Diagnosis: Laboratory parameters (serum)* on www.cbo.nl)⁹⁷.

No clear conclusions can be drawn with regard to the practical application of additional serum diagnosis for CRPS-I patients in view of methodological shortcomings, such as small subject populations, unclear CRPS-I criteria, large spread of duration of the condition and the lack of sensitivity and specificity data.

Conclusion

Level 4

The additional diagnostic value of general and specific blood tests in CRPS-I patients has not been demonstrated.

D Birklein 2000²⁴; Birklein 2001²⁰; Blair 1998^{as}; Drummond 1994⁴⁶; Eisenberg 2004⁹⁷; Figuerola 2002⁹⁶; Huygen 2002¹⁶; Kemler 2000³⁰; Mailis 1994²⁹; Ribbers 1998¹⁴; Van de Vusse 2001²⁸

Recommendation

The project group is of the opinion that blood tests need not be used to diagnose patients with suspected CRPS-I, unless another diagnosis is suspected and could be demonstrated by means of blood tests.

1.3.3 Additional diagnosis for CRPS-I: skin tests

Some investigations carried out in relation to CRPS-I are purely lab tests for various skin parameters such as lactate²⁴, interleukin 6 in blisters¹⁶, TNF- α in blisters¹⁶, elevated substance P-induced extravasation of proteins²¹, HbO₂,²⁵ and histochemical markers^{18,47}. The findings of most of the skin parameters assessed in the trials were not produced in other trials (see *background document, Evidence table Diagnosis: Laboratory parameters (skin)* on www.cbo.nl).

No clear conclusions can be drawn with regard to the practical application of additional skin diagnosis for CRPS-I patients in view of methodological shortcomings, such as small subject populations, unclear CRPS-I criteria, large spread of duration of the condition, the lack of sensitivity and specificity data, and the limited number of studies carried out.

Conclusion

Level 4

The additional diagnostic value of skin tests in CRPS-I patients has not been demonstrated.

D Birklein 2000²⁴; Calder 1998¹⁸; Drummond 1996⁴⁷; Huygen 2002¹⁶; Koban 2003²⁵; Leis 2003²¹

Recommendation

The project group is of the opinion that skin tests need not be used to diagnose patients with suspected CRPS-I.

1.3.4 Additional diagnosis for CRPS-I: skin temperature

The difference in skin temperature between the affected side and the unaffected side of patients with CRPS can be measured using an infrared thermometer or infrared thermography. Various stimuli, such as cold and heat stress, can be used when applying the latter technique.

1.3.4.1 Absolute temperature

The various studies carried out using an infrared thermometer found a range of differences in normative values for the absolute left/right temperature difference (L/R difference): 0.5 °C⁹⁸, 0.6 °C^{99,100}, 0.9 °C¹⁰¹ and 1.0 °C¹⁰². A difference of 1.5 °C is recommended as a way of differentiating between normal posttraumatic syndromes and patients with CRPS-I⁴⁰. Only two studies reported sensitivity and specificity data with regard to absolute L/R temperature differences (see *background document, Evidence table Diagnosis: Absolute temperature* on www.cbo.nl)^{103,104}.

Measuring an absolute L/R temperature difference is a process with a low sensitivity, which increases in the case of cold stimulus. This infrared thermometer method also presents the disadvantage that the temperature measured can vary from one spot to another within the same area; that the temperature on the back of the hand is different from the temperature on the palm; and that the temperature does not remain constant over time⁶⁶. The intra-observer reproducibility of the absolute temperature or different

sites on the hand using an infrared thermometer is high ($r = 0.96$ and $r = 0.94$ (two observers)). The L/R difference is also associated with very good inter-observer reproducibility ($r = 0.96$ and $r = 0.97$ (two observers))¹⁰⁵.

Although the subjective temperature difference can be adequately scored by CRPS-I patients by means of a visual analogue scale (VAS), this subjective method bears no relation to the absolute temperature measured using an infrared thermometer¹⁰⁶. The duration of the condition plays a critical part in the measurement of temperature differences in cases of CRPS-I. The sensitivity and specificity data reported in Wasner's study must be treated with caution in view of the large spread of durations¹⁰⁴.

1.3.4.2 Thermography

Infrared thermography is assumed to be a reliable method for measuring diffuse versus local temperature differences. Various stimuli, such as heat and cold stress, can also be applied when using this method^{41,99,107-110}.

Only three studies report sensitivity and specificity data (see *background document, Evidence table Diagnosis: Absolute temperature* on www.cbo.nl)^{99,108,109}.

The additional diagnostic value of skin temperature measurements with or without stimuli (labour-intensive) is limited in view of methodological shortcomings, such as small subject populations, unclear CRPS-I criteria, large spread of duration of the condition and the lack of reference tests.

Conclusion

Level 4

Absolute skin temperature measurements and thermography (with or without stimuli) offer limited additional diagnostic value in the case of CRPS-I patients.

These techniques can be important in quantifying temperatures in the context of CRPS-I criteria. A difference of 1.5 °C is recommended as a way of differentiating between normal posttraumatic syndromes and patients with CRPS-I.

D Birklein 2000⁴⁰; Birklein 2001⁴¹; Bruhl 1996⁹⁹; Chelimsky 1995¹⁰³; Cooke 1989¹⁰⁰; Feldman 1991¹⁰¹; Gulevich 1997¹⁰⁸; Huygen 2004¹⁰⁹; Karstetter 1991⁹⁸; Low 1994¹⁰²; Oerlemans 1999¹⁰⁵; Oerlemans 1999¹⁰⁶; Sherman 1994¹¹⁰; Wassner 2002¹⁰⁴

Recommendation

The project group is of the opinion that absolute skin temperature measurements and thermography (with or without stimuli) need not be used to diagnose patients with suspected CRPS-I.

1.3.5 Additional diagnosis for CRPS-I: sympathetic function tests

1.3.5.1 *Peripheral vasoconstriction reflex*

Laser Doppler fluxmetry is the most widely used method for evaluating blood circulation in the affected limb. Other techniques include dynamic vascular examination using $^{99}\text{Tc}^{\text{m}}$ HSA (human serum albumin)¹¹¹ and computer-assisted venous impedance plethysmography¹¹².

Most studies combine Doppler fluxmetry with various stimuli in order to assess the vasoconstriction response. We were able to identify fifteen studies (see *background document, Evidence table Diagnosis: Circulation* on www.cbo.nl)^{4,19,33,34,37,39,41,102,113,117}.

Seven of these studies used varying inclusion criteria, while eight did not mention their inclusion criteria at all or described them in vague terms. Rhythmic skin circulation was observed in healthy subjects but not in CRPS-I patients¹¹³.

It was striking to observe that one study found a diminished vasoconstriction response in the unaffected side¹¹⁸.

The fact that a normal vasoconstriction response measured by means of laser Doppler fluxmetry is found in posttraumatic patients with no signs of CRPS-I raises possibilities for this method as a diagnostic tool^{41,112}.

It is not yet proven that laser Doppler fluxmetry offers any additional diagnostic value in the case of CRPS-I in view of methodological shortcomings, such as unclear CRPS-I criteria, large spread of duration of the condition, and the lack of sensitivity and specificity data. However, there are indications that this method may help distinguish between CRPS-I patients and other posttraumatic patient populations.

Conclusion

Level 4

The additional diagnostic value of laser Doppler fluxmetry and computer-assisted venous impedance plethysmography in CRPS-I patients has not been demonstrated.

D Bej 2005¹¹³; Birklein 1998³⁹; Birklein 2001⁴¹; Block 1991¹¹¹; Kurvers 1994⁴; Kurvers 1995³³; Kurvers 1995³⁴; Kurvers 1996³⁷; Kurvers 1996³⁸; Low 1983¹¹⁴; Low 1994¹⁰²; Malcom O 1993¹¹⁶; Rosen 1988¹¹⁹; Schurmann 1999¹¹²; Schurmann 2000¹¹⁸; Wassner 2001¹¹⁵; Weber 2001¹⁹

Recommendation

The project group is of the opinion that laser Doppler fluxmetry and computer-assisted venous impedance plethysmography need not be used to diagnose patients with suspected CRPS-I.

1.3.5.2 Sudomotor function tests

In patients with CRPS-I the sympathetic function can be qualitatively assessed by investigating sweat secretion. This is done by determining the skin potential^{120,121}. However, we did not find any studies looking at this method by comparing healthy subjects and CRPS-I patients.

Basal sweat secretion can be quantitatively measured (Resting Sweat Output (RSO)), as can sweat secretion following heating of the body (Thermoregulatory Sweat Test (TST)). Local sweat secretion can be studied by applying carbachol to a particular area in order to influence the axon reflex (Quantitative Sudomotor Axon Reflex Test (QSART)) (see *background document, Evidence table Diagnosis: Sudomotor tests* on www.cbo.nl).

RSO can increase on the affected side and the unaffected side^{41,122}, or diminish¹⁰², or not change at all⁴⁴. No sensitivity or specificity studies on RSO in cases of CRPS-I are available. Both the TST^{41,44,123} and the QSART^{44,122,123} show that the sweat

response is significantly elevated in patients with CRPS-I. The latency time in which the sweat response occurs during TST or QSART is longer on the affected side of CRPS-I patients⁴⁴. The importance of the duration of the condition in TST and QSART was illustrated by a prospective study in which the TST result was still abnormal but the QSART result had been normalised after two years¹²³.

Only one study reported specificity data: the combination of an elevated RSO and diminished QSART had a specificity of 98%¹⁰³. However, this was a retrospective study using unclear inclusion criteria and with no indication of sensitivity data (see *background document, Evidence table Diagnosis: Sudomotor tests* on www.cbo.nl).

Conclusion

Level 4

The additional diagnostic value of the Resting Sweat Output Test, the Thermoregulatory Sweat Test and the Quantitative Sudomotor Axon Reflex Test in CRPS-I patients has not been demonstrated. However, these techniques may be important in quantifying sympathetic dysregulation in the context of CRPS-I criteria.

D Birklein 1997⁴⁴; Birklein 1999¹²³; Birklein 2001⁴¹; Chelimsky 1995¹⁰³; Cronin 1982¹²⁰; Knezevic 1985¹²¹; Sandroni 1998¹²²

Recommendation

The project group is of the opinion that the Resting Sweat Output Test, the Thermoregulatory Sweat Test and the Quantitative Sudomotor Axon Reflex Test need not be used to diagnose patients with suspected CRPS-I.

1.3.5.3 Sympathetic skin response

The sympathetic skin response (SSR) is a method that is thought to be capable of evaluating the function of the autonomic peripheral nervous system by measuring the skin's electrical resistance¹²¹. Standardisation and interpretation of the method is one of the problems associated with this technique¹²⁴. Percentages of subjects found to have an abnormal SSR vary markedly, from 0%⁹⁶ to 100%^{36,43}, though it must be pointed out that the number of subjects taking part in the studies was very low ($n < 10$) (see *background document, Evidence table Diagnosis: Sympathetic skin response (SSR)* on www.cbo.nl). This method is unsuitable for routine diagnosis in patients with suspected CRPS-I in view of the lack of standardisation and interpretation referred to above.

Conclusion

Level 4

Routine use of sympathetic skin response measurement in CRPS-I patients has not been shown to have any additional diagnostic value. However, this method may be significant to quantifying peripheral nerve injury in the context of the CRPS criteria.

D Arunodaya 1995¹²⁴, Clinchot 1996³⁶; Figuerola 2002⁹⁶; Knezevic 1985¹²¹; Rommel 1995⁴³

Recommendation

The project group is of the opinion that sympathetic skin response measurement does not need to be used to diagnose patients with suspected CRPS-I.

1.3.6 Additional diagnosis for CRPS-I: neurophysiological tests

1.3.6.1 Nerve conduction

Nerve conduction tests are vital when diagnosing CRPS-I in order to differentiate between type I and type II CRPS. Only a few studies of CRPS-I have featured nerve conduction tests^{35,58,125,126}. In Rommel's study, 16 of the 35 patients were found to have impaired nerve conduction (ten in one peripheral nerve and six in various peripheral nerves)¹²⁵. In eight patients meeting the criteria for CRPS-I, nerve conduction tests found various abnormalities not more than 10% above normal values. A peripheral nerve condition or CRPS-II must be assumed if values are 20% above the norm (see *background document, Evidence table Diagnosis: Neurophysiology, nerve conduction on www.cbo.nl*)¹²⁷.

1.3.6.2 SomatoSensory Evoked Response

The SomatoSensory Evoked Response (SSEP) evaluates the entire somatosensory trajectory from the peripheral nerve to the cerebral cortex. Both normal¹²⁸ and abnormal^{55,125,126,129} SSEP results have been found in patients with CRPS-I. These abnormal SSEPs are normally attributable to a peripheral nervous system condition or to CRPS-II. However, abnormal SSEP results have been observed in some patients meeting the criteria for CRPS-I¹²⁵.

SSEP is indicated for CRPS-I patients if a central dysfunction is suspected in the light of neurological tests. If the results are abnormal, further investigation is necessary (MRI of the cerebrum) (see *background document, Evidence table Diagnosis: Neurophysiology, nerve conduction on www.cbo.nl*).

1.3.6.3 Electromyography

Electromyography (EMG) offers hardly any additional diagnostic value to practitioners attempting to diagnose CRPS; it is also associated with the risk that the CRPS-I may worsen as the test is invasive.

EMG is normally used in trials as part of the evaluation of motor function disorders where no neurogenic abnormalities have been found^{126,128,130,131}.

Spontaneous EMG activity is observed in patients with CRPS-I only after a CVA and is probably the consequence of a condition affecting the second neuron (see *background document, Evidence table Diagnosis: Neurophysiology, nerve conduction on www.cbo.nl*)¹³².

Other investigation techniques, such as transcranial magnetic stimulation^{128,133}, H-reflex¹²⁸, polysomnography¹²⁸, and magnetic encephalography¹³⁴, have as yet no place in routine diagnosis of CRPS-I in view of the very small number of studies that have been carried out.

Conclusion

Level 4

Electromyography, nerve conduction tests and SomatoSensory Evoked Response are essential to identify a nerve lesion or dysfunction of the central nervous system; the key figure for nerve conduction is a result of more than 20% above the norm. The value of routine application of these techniques to the diagnosis of CRPS-I has not yet been demonstrated.

D Bruehl 1999⁵⁸; Cheng 1995¹³²; Drory 1995³⁵; Hyman 1991¹²⁹; Juottonen 2002⁵⁵; Maihofner 2003¹³⁴; Marsden 1984¹³⁰; Navani 2003¹³¹; Rommel 2001¹²⁵; Verdugo 2000¹²⁶; Rommel 2005¹²⁷; Schwenkreis 2003¹³³; Van de Beek 2000¹²⁸

Recommendation

The project group is of the opinion that nerve conduction, electromyography and SomatoSensory Evoked Response need not be routinely used to diagnose patients with suspected CRPS-I.

1.3.7 Additional diagnosis for CRPS-I: quantitative sensory tests (QST)

Quantitative sensory tests (QST) are used to give an objective clinical description of sensory abnormalities observed. We draw a distinction between stimulus thresholds and stimulus-dependent pain thresholds.

Touch thresholds or pressure thresholds using Semmes-Weinstein Pressure¹³⁵ or Von Frey monofilaments⁵² were determined in CRPS-I patients and healthy individuals; the CRPS-I patients were found to have elevated pressure on both the affected and

unaffected sides. In CRPS-I patients with hemisensory disorders on the side of the dystrophic limb, higher touch or pressure thresholds were found on the ipsilateral side outside the area of the affected limb than on the contralateral side (see *background document, Evidence table Diagnosis: QST sensory thresholds* on www.cbo.nl)¹²⁵.

The same applied to heat and cold thresholds^{52,125,136}. However, other studies in which the sensory disorders were limited to the affected limb found no difference between the affected and unaffected sides in respect of heat and cold thresholds (see *background document, Evidence table Diagnosis: Neurophysiology, nerve conduction* on www.cbo.nl)^{135,137}.

Pain thresholds in response to various types of stimuli, such as mechanical stimuli,^{52,54,138} heat^{54,135,137,138} and cold stimuli, are lower than on the unaffected side (see *background document, Evidence table Diagnosis: Neurophysiology, nerve conduction* on www.cbo.nl)^{135,137}.

Most of these studies used a single (phasic) stimulus application. Two studies used repeated stimuli (summation), evaluating wind-up-related hyperalgesia, and also reported diminished thresholds^{54,138}. If summation occurs, CRPS-I patients display more pain (see *background document, Evidence table Diagnosis: Neurophysiology, nerve conduction* on www.cbo.nl)¹³⁸.

It is not yet clear whether repetitive stimuli in QST has any additional diagnostic value. In the case of CRPS-I patients in whom various sensory and pain-related thresholds can be determined, this would appear to be a good way of producing an objective clinical description of the sensory disorders found. It must be pointed out in this context that the findings are not in themselves specific to CRPS-I. This fact, together with the absence of any sensitivity or specificity tests for QST, mean that the additional diagnostic value of QST has not yet been demonstrated.

Conclusion

Level 4

The additional diagnostic value of quantitative sensory tests in CRPS-I patients has not been demonstrated. However, this technique may be important in quantifying sensory abnormalities in the context of CRPS criteria.

D Freeman 2003¹³⁶; Kemler 2000¹³⁵; Price 1992¹³⁸; Rommel 2001¹²⁵; Sieweke 1999⁵⁴; Tahmouh 2000¹³⁷; Thimineur 1998⁵²

Recommendation

The project group is of the opinion that quantitative sensory tests need not be used to diagnose patients with suspected CRPS-I.

1.3.8 Quantifying clinical symptomatology and the course of CRPS-I

1.3.8.1 Oedema

Oedema is a very common feature of CRPS-I (88-90%)^{66,139}. One study found very low inter-observer concurrence of clinically determined oedema in CRPS-I patients, with a kappa value of 0.40⁶³. However, this study found both overall concurrence and prevalence to be low (0.75 and 0.72 respectively), which may partly explain the low kappa value.

Various methods are used to indirectly quantify oedema in CRPS-I patients. Determination of finger diameter¹⁴⁰⁻¹⁴², skin fold thickness¹⁴⁰ and a volumetric method^{66,140} are applied mainly to the hand. An alternative method, bioelectric impedance analysis (BIA) is used in cases of lymphoedema but is not applied to CRPS-I patients¹⁴³.

Volumetry, comparing the difference in volume between the affected side and the unaffected side, is a valid way of measuring oedema of the hand¹⁴⁴⁻¹⁴⁶. A left/right difference in excess of 3.55% is regarded as abnormal⁶⁶ and correlates well with physical diagnostic tests⁶⁶, although considerable systematic variation is observed¹⁴⁷.

Only one prognostic study of wrist fractures reported data on sensitivity (14%) and specificity (100%). However, this study used unclear CRPS-I criteria and did not include a control group or a reference test¹⁴⁰.

Volumetry in ankle oedema (never applied to CRPS-I patients) is a reproducible method and correlates well to measurement of the ankle circumference¹⁴⁸.

The reproducibility of finger diameter measurement as a way of assessing oedema of the hand has only been assessed for the manual method, and was found to have a good intra-observer and inter-observer coefficient (0.98 and 0.96 respectively)¹⁴¹.

One prognostic study of wrist fractures used an arthrocircometer¹⁴⁹ and reported data on sensitivity (32%) and specificity (94%)¹⁴⁰. These studies used unclear CRPS-I criteria and did not include a control group or reference test¹⁴⁰. A significant correlation was found between volumetry on the one hand and finger diameter ($r = 0.57$) and skin fold measurement ($r = 0.36$) on the other hand, but not between skin fold measurement and finger diameter (0.01)¹⁴⁰.

Conclusion

Level 4

Volumetry and measurement of finger diameter as indirect indicators of hand and ankle oedema can be used to objectify CRPS-I criteria.

D Atkins 1990¹⁴⁰; Iwata 2002¹⁴¹; Mawdsley 2000¹⁴⁸; Oerlemans 1999⁶⁶

Recommendation

The project group is of the opinion that measurement of limb oedema using volumetry and finger diameter need not be routinely used in the day-to-day treatment of CRPS-I patients.

1.3.8.2 Limb motor function impairment

The only aspects of motor function impairment in patients with CRPS-I that we are addressing here are impaired movement and loss of strength in the affected limb. Loss of strength in the affected limb is a common feature of CRPS-I, occurring in 75 to 99% of cases^{1,60,63,140,142,150,153}. A sphygmomanometer¹⁴⁰ or a dynamometer^{1,151,153} is normally used to quantify the physical-diagnostic parameters. The reproducibility of this method is unclear. The benefit of objectifying loss of strength in patients with CRPS-I is open to question, as it can be affected by the presence of pain, oedema or arthrotic symptoms¹⁵⁴. The use of a goniometer to objectify an active and passive movement impairment that has been clinically observed is regarded as a reliable method for the wrist and hand¹⁵⁵, although some studies cast doubt on this¹⁴⁷. The wrist and little finger appear to be worst affected in patients with early-stage CRPS-I⁶⁶.

Conclusion

Level 4

It is doubtful whether any benefit accrues from measuring loss of strength by means of a sphygmomanometer or dynamometer in patients with CRPS-I. This method is therefore as yet unsuitable for quantifying loss of strength in CRPS-I patients that has been observed from physical diagnosis.

D Atkins 1990¹⁴⁰; Oerlemans 2000¹⁵¹; Schasfoort 2003¹⁵²; Schasfoort 2004¹⁵³; Veldman 1993¹

Recommendation

The project group is of the opinion that the day-to-day treatment of CRPS-I patients does not need to involve routinely measuring loss of strength by means of a sphygmomanometer or dynamometer.

Conclusion

Level 4

The lack of clear data as to the reproducibility of movement impairment using a goniometer means that this method is as yet unsuitable for quantifying impaired movement in CRPS-I patients that has been observed from physical diagnosis.

D Dijkstra 2001¹⁴⁷; Horger 1990¹⁵⁵; Oerlemans 1999⁶⁶

Recommendation

The project group is of the opinion that the day-to-day treatment of CRPS-I patients does not need to involve routinely measuring impaired movement by means of a goniometer.

1.3.8.3 Pain measurement

Various published articles report the use of pain measurement instruments to describe the degree of pain. The visual analogue scale (pain VAS) is widely used. The reliability of the pain VAS has been demonstrated in various studies. With regard to the diagnostic value of the pain VAS, maximum sensitivity and specificity figures of 0.83 and 0.73 respectively have been found (for a cut-off point of 3 cm on the pain VAS)¹⁵⁶. However, this study used determination of CRPS-I according to the criteria drawn up by Veldman et al. as a benchmark¹. No information is given on the responsiveness to repeated measurements when this method is used with CRPS-I patients.

There is a high correlation ($r = 0.81-0.95$) between thrice-daily measurements of pain by the VAS for one week and a single measurement of pain by the VAS during the preceding week¹⁵⁷. The McGill Pain Questionnaire is a list of words describing the sensory, affective components and the severity of pain. Both the number of words chosen (NWC-t; 0-20) and the value of the ordinal numbers (PRI; 0-63) are used as an indicator of the severity of the pain. One study reports a combination of maximum sensitivity (0.76) and specificity (0.65) with a cut-off point of six words (NWC-t)¹⁵⁶. This study also contains no data on responsiveness and uses the criteria drawn up by Veldman et al. as a reference.

The neuropathic pain scale (NPS) is a list of pain-related words comprising ten items that describe sensory components of pain. The NPS was investigated with a group of patients suffering from neuropathic pain, including 69 patients with CRPS¹⁵⁸. The NPS seemed able to detect effects of treatment, and the four items ('sharp', 'cold', 'sensitive' and 'itching') discriminated between diagnosis groups.

Conclusion

Level 4

Some evidence has been found for the benefits of using the VAS (severity), the McGill and the NPS (nature).

D Forouzanfar 2002¹⁵⁹; Galer 1997¹⁵⁸; Perez 2005¹⁵⁶

Recommendation

The project group is of the opinion that the McGill Pain Questionnaire, the Neuropathic Pain Scale (NPS) (nature of the pain) and the visual analogue scale (VAS) can all be used to determine the severity of pain experience by CRPS-I patients.

1.3.8.4 Compound scores

As CRPS-I is characterised by a combination of symptoms, a variety of measurement instruments are often used to assess patients taking part in trials. The Impairment level SumScore (ISS) has been developed to measure the severity of an impairment^{160,161}. This indicator combines measurement of pain (VAS and McGill), temperature (infrared thermography), volume difference (water displacement volumeters) and active movement outcome (universal goniometers) to produce a single score. One study using the Veldman criteria as benchmark values found low sensitivity (0.35) and high specificity (0.98) for the ISS¹⁵⁶. Eighteen CRPS-I patients diagnosed using the criteria drawn up by Veldman et al. took part in a study in which the relationship between ISS and the severity of the condition in the lower limb was assessed by the doctor and the progress of the condition was assessed by the patient¹⁶¹. A correlation was found between the severity of the condition and the ISS score. The ISS was also seen to shift in line with changes reported by the patient. Comparable responsivity findings were observed with patients diagnosed as having upper-limb CRPS-I using the criteria drawn up by Veldman et al¹⁶⁰.

Conclusion

Level 4

Little research has been carried out to date on the value of the Impairment level SumScore (ISS) as an indicator of the severity of impairment. The ISS can be used to describe impairments related to CRPS-I in the context of research.

D Oerlemans 1998¹⁶⁰; Perez 2003¹⁶¹

Recommendation

The project group is of the opinion that the day-to-day treatment of CRPS-I patients does not need to involve objectifying the severity of impairment by means of the Impairment level SumScore (ISS).

1.3.8.5. Activity level measuring instruments

Five instruments have been developed to determine impaired activity in CRPS patients, three for the upper limbs and two for the lower limbs. The Radboud skills questionnaire¹⁶² tested on CRPS-I patients (criteria drawn up by Veldman et al.) was found to be reliable, with low variant coefficients for inter-investigator and test-retest reliability (2.3-4.4% and 6.6% respectively (median values)). Moderate to good correlation was found between this and other questionnaires (disabilities of arm, shoulder and hand (DASH) ($r = 0.74$); sickness impact profile (SIP) ($r = 0.48-0.53$)¹⁶³.

The upper limb activity monitor (ULAM)¹⁶⁴, an accelerometer used to measure the level of (movement-related) activity, was found to concur well with activities performed by patients (criteria drawn up by Veldman et al.) in response to video images. Activity profiles measured using the ULAM on ten patients with chronic CRPS-I were different from those of healthy subjects ($n = 10$), although this difference was less evident when the subjects were sitting or standing. Correlations between the ULAM and other activity questionnaires were moderate ($r =$ skills questionnaire: 0.41-0.48; DASH: 0.53-0.57).

The Radboud skills test (RST) is a test of activities of daily life (ADL test) for CRPS-I in one upper limb. The inter (kappa = 0.47-0.96) and intra-observer reliability (kappa = 0.61-1.00) values were found to be good to excellent in a study of 22 CRPS-I patients (according to the criteria of Veldman et al.)¹⁶⁵.

With regard to the lower limb, studies have been performed into the reliability of the walking stairs questionnaire (WSQ) and the questionnaire rising and sitting down (QRSD) on 21 CRPS-I patients (criteria drawn up by Veldman et al.). Test-retest reliability was found to be good to very good for both questionnaires ($r =$ WSQ: 0.79-0.90; QRSD: 0.85-0.89; ICC = WSQ: 0.78-0.87; QRSD: 0.84-0.87). Indications of adequate responsiveness were also found for both questionnaires. The WSQ and QRSD have been studied in a larger-scale trial ($n = 795$; including 70 CRPS-I patients according to the criteria of Veldman et al.) and found to be valid and reliable for other patient groups¹⁶⁶.

The foot function test (FFT) is an instrument which can be used to measure movement-related activity in the lower limb¹⁶⁷. Inter and intra-observer reliability was found to be good to very good in healthy subjects ($r = 0.84-0.99$) respectively. Comparison with 21 CRPS-I patients showed that the FFT was able to discriminate between healthy individuals and CRPS-I patients and between patients needing to use a stick to walk and those who did not need to use a stick to walk. However, correlations with other function

tests (such as the three-minute walk) and questionnaires (such as the sickness impact profile) were limited ($r = 0.02-0.30$), except for the more impairment-related measurement carried out using myometers ($r = 0.73-0.77$).

All the tests referred to above (apart from the RSQ and QRSD) need further validation and reliability examination. The only test which has been adequately investigated for responsivity in measuring change is the RST, which was developed as a clinical test for an occupational therapy setting. As yet no conclusions can be drawn on the possible benefit of this test in monitoring individual patients in a clinical setting. However, these tests do seem suitable for research purposes.

Conclusion

Level 4

Further research is needed into the benefits of the Skills Questionnaire, the Upper Limb Activity Monitor, the Radboud Skills Test, the Radboud Skills Questionnaire, the Walking Stairs Questionnaire, the Questionnaire Rising and Sitting Down and the Foot Function Test as clinical indicators for the severity and progress of activity impairment. These measurement instruments can be used to describe activity levels related to CRPS-I in the context of research.

D De Boer 2001¹⁶⁵; Kemler 2000¹⁶⁷; Oerlemans 2000¹⁶²; Perez 2002¹⁶⁶; Schasfoort 2002¹⁶⁴; Schasfoort 2005¹⁶³

Recommendation

The project group is of the opinion that the Skills Questionnaire, the Upper Limb Activity Monitor, the Radboud Skills Test, the Radboud Skills Questionnaire, the Walking Stairs Questionnaire, the Questionnaire Rising and Sitting Down and the Foot Function Test need not be used in the day-to-day treatment of CRPS-I patients.

1.4 Epidemiology

1.4.1 Epidemiology of CRPS-I

Introduction

Various descriptions of the incidence of CRPS-I are given in the literature. This is partly due to the criteria used to diagnose the condition.

CRPS-I often develops following wrist fractures, though the incidence varies widely from 1%¹⁶⁸ to 37%¹⁶⁹.

Other groups of conditions that can lead to CRPS-I are: other fractures, soft tissue injuries or contusions, CVA (either in isolation or in association with hemiplegia) and myocardial infarction. CRPS-I can also occur as a complication following surgery (CTS, peripheral vascular surgery). CRPS-I in children needs to be considered as a separate issue.

Scientific support

The incidence of CRPS-I in a nationally representative population in the United States is estimated at 5.46 per 100,000 at-risk person-years¹⁷⁰.

CRPS-I is seen most often in individuals who have suffered wrist fractures and other fractures or crush injuries¹⁷⁰.

Incidence of CRPS-I following wrist fractures

In a prospective study of 59 patients with a Colles fracture, CRPS-I was observed in 37% of cases (22 patients)^{140,169}.

In a prospective interventional study¹⁷¹, a placebo group of 65 patients with wrist fractures were given conservative treatment (plaster cast). CRPS-I was diagnosed using modified Veldman criteria in 22% of cases (14 patients).

A higher pressure in the plaster cast was measured in CRPS-I patients given a plaster cast following a distal radius fracture. It is unclear whether the CRPS-I and oedema cause the rise in pressure, or whether the higher pressure leads to CRPS-I¹⁷².

Other authors have also found a link with plaster cast symptoms: early symptoms in plaster are associated with a greater risk of CRPS-I. Zollinger et al. found plaster cast symptoms in 67% of CRPS-I patients following a wrist fracture as against only 18% of patients without CRPS-I¹⁷¹. This difference appeared to be significant.

Various studies have found no link between the number of repositioning procedures, the situation after repositioning and the likelihood of developing CRPS-I^{140,169,171}.

Two studies found a relationship between the severity of the fracture and the likelihood of developing CRPS-I^{171,173}. Zollinger et al. carried out a prospective study of 119 wrist fractures and found CRPS-I in 18 cases. Of these 18 cases, 11 (67%) were AO type B or C (intra-articular). Thirty-three percent of the 101 fractures which occurred in individuals who did not develop CRPS-I were intra-articular. The authors concluded from this that intra-articular comminution in wrist fractures increases the chance of CRPS-I. This link was not seen in other studies^{86,140,174}.

Incidence of CRPS-I following other injuries (table 6)

Table 6 Incidence of CRPS-I following other injuries

	Incidence of CRPS-I	N	
Crush injury to the foot	7%	4/58	Myerson et al. 1994 ¹⁷⁵
Carpal tunnel release	2%	1/47	Sennweld et al. 1995 ¹⁷⁶
Capsulorrhaphy of the shoulder	9%	6/64	Mansat et al. 2000 ¹⁷⁷
Achilles tendon rupture	4%	1/27	Webb et al. 1999 ¹⁷⁸
CVA	35%	24/69	Daviet et al. 2002 ¹⁷⁹
Tibia fracture	30%	18/60	Sarangi et al. 1993 ⁸³

In adults, most cases of CRPS-I occur in the upper limbs^{1,170,180}.

About 20% of patients with upper-limb CRPS-I also have shoulder symptoms indicative of tendinitis of one or both biceps tendons¹⁸¹.

The incidence of CRPS-I in patients who have had a CVA and develop shoulder symptoms can be reduced by performing physiotherapy and rehabilitation at an early stage¹⁸². The term 'shoulder-hand syndrome' is sometimes used to describe these cases or the situation following a myocardial infarction.

1.4.2 Predisposing factors

Ethnic background

CRPS-I is most common in Caucasians: Allen et al.¹⁸³ and Galer et al.¹⁸⁴ state figures of 70 to 90%.

The presence of HLA-DR2¹⁵ and HLA-DQ1^{29,30} antigens is higher in patients with CRPS-I, pointing to a hereditary factor.

One study reported higher seroprevalence of parvovirus B19 in patients with CRPS-I (modified IASP criteria), particularly where it occurs in the lower limbs²⁸.

CRPS-I is twice as likely to occur in women as in men^{1,40}; in one population study the ratio was four to one¹⁷⁰.

Relapse

About 9% of patients experience a relapse, that is a new bout of CRPS-I following an initial complete recovery or a period largely free from symptoms. Most of these cases occur in young patients with primary cold CRPS-I. Relapses usually start spontaneously and with few symptoms¹⁸⁵. Relapse or expansion of CRPS-I can occur either in the same limb or in other limbs^{185,186}.

1.4.3 Natural course and stages

CRPS-I can occur at any age, from children to the very elderly, but is most common between the ages of 20 and 50. The condition is often described as going through three consecutive stages. However, it has not been possible to confirm this in large sets of patients^{1,187}. A population study carried out in the US observed spontaneous improvement and healing of the syndrome in three-quarters of cases¹⁷⁰. The absence of literature means that no conclusions can be drawn as to the prognosis for various sub-groups within CRPS-I.

1.4.4 Children and CRPS-I

CRPS-I has not been frequently monitored or described in children¹⁸⁸. Most cases of CRPS-I in children affect the lower limbs¹⁸⁹. The ratio of girls to boys is 3:1. Trauma features in about half of cases. The progress of symptoms appears to be milder in children than in adults¹⁹⁰. Most children with the condition are completely cured. This is described in the situation with some degree of variation: 58 up to as much as 93% of children¹⁹⁰⁻¹⁹². Treatment takes the form of analgesics and physiotherapy (see also *section 4.2* on physiotherapy for children with CRPS-I). Relapses following apparent healing are frequently observed. Here again the percentages vary, ranging from 10 to 48%^{190,191,193}. Children with a past history of behavioural disorders, eating disorders or some form of psychosocial problem appear to be at greater risk of relapse¹⁹⁴.

Conclusions

Level 3

Most cases of CRPS-I affect Caucasians.
CRPS-I affects two to three times more women than men.

B Birklein 1999¹⁸⁰; Veldman 1993¹
C Allen 1999¹⁸³; Galer 2000⁵⁰; Sandroni 2002¹⁷⁰

Level 3

The incidence of CRPS-I varies depending on the original injury. The incidence following wrist fractures is relatively high.

C Atkins 1990¹⁴⁰; Daviet 2002¹⁷⁹; Mansat 2000¹⁷⁷; Myerson 1994¹⁷⁵; Sarangi 1993⁸³; Sennwald 1995¹⁷⁶; Webb 1999¹⁷⁸; Zollinger 1999¹⁷¹

1.4.5 The use of an external fixator and CRPS-I

Scientific support

Two RCTs have been carried out to compare conservative treatment of distal radius fractures with treatment using an external fixator^{174,195}. Howard et al. describe 50 patients with a severely dislocated Colles fracture allocated at random to two groups: 25 patients underwent repositioning with a Biers block and 25 patients were given an external Hofmann fixator¹⁹⁵. CRPS-I did not occur in either group.

Roumen et al. recruited 126 patients undergoing repositioning under local anaesthetic for a prospective study, with a randomised part including patients with more than 10% angulation. Of this group, 101 were available for follow-up, of which 58 received regular plaster, and 43 were randomised into an external fixation group and a control group (with plaster casts). Reflex symptomatic dystrophy according to Veldman's criteria developed in 14 patients (14%). In total, 10 of these patients (71%) received a plaster

cast, and 4 (28%) an external fixator. Six of these patients participated in the randomised part of the trial, 4 (67%) of whom in the external fixation group, and 2 (33%) in the control group. No correlation was found between development of CRPS-I and the final anatomical outcome.

In a cohort study carried out by Gradl et al., 158 patients with a distal radius fracture were assessed for sensitivity disorders, range of motion (ROM), strength, oedema, temperature and radiological image after eight and sixteen weeks⁸⁶. The diagnosis of CRPS-I was made on the basis of Bruehl's criteria. Treatment consisted of immobilisation in plaster, open reduction and fixing with plates/screws or an external fixator. The 18 patients (11%) who developed CRPS-I were compared with the 140 patients who did not develop the condition. There was no difference in the type of fracture. The anatomical/radiological outcome was poorer in the CRPS-I group; this was attributed to the poorer functional results. There was no difference between the two groups with regard to the type of treatment (conservative versus surgery, including external fixator).

Suso et al. conducted a prospective, non-randomised study of 28 patients treated with an external fixator. Mild to moderate (second to third-degree Bonica) reflex sympathetic dystrophy occurred in 17 cases (60.7%)¹⁹⁶. The symptoms disappeared in four to eight months following treatment with calcitonin and physiotherapy.

Conclusion

Level 2

There is no indication that the use of an external fixator in patients with a severe distal radius fracture increases the likelihood of developing CRPS-I¹.

B Howard 1989¹⁹⁵; Roumen 1991¹⁷⁴

C Gradl 2003⁸⁶; Suso 1993¹⁹⁶

Other considerations

Distal radius fractures, and especially Colles fractures, are responsible for many of the known cases of CRPS-I in adults¹.

External fixators are mainly used in severe forms of shattering (comminution), unstable fractures and/or fractures associated with severe soft tissue damage.

Selection of patients on the basis of fracture type could explain the higher incidence of CRPS-I where an external fixator is used. Zollinger et al.¹⁷¹ and Zuluk et al.¹⁷³ observed that CRPS-I was more likely in fractures with severe comminution and/or movement, but Atkins et al.,¹⁴⁰ Roumen et al.¹⁷⁴ and Gradl⁸⁶ did not make the same observation. Studies have also found that there appears to be no link between (over)distraction,^{196,197} the degree of repositioning of the components of the fracture^{86,174,195} and CRPS-I. The latter studies report better anatomical recovery of the distal radius where an external fixator is used.

Recommendation

There is no need to consider the possibility of a greater risk of CRPS-I when deciding whether to apply an external fixator to a patient who has had a distal radius fracture.

Chapter 2

Drug treatment and invasive treatment

2.1 Drug treatment

2.1.1 Pain medication for patients with CRPS-I

General introduction

Although analgesics are often used in clinical practice when treating patients with CRPS-I, and their use is described in various treatment protocols and guidelines¹⁹⁸⁻²⁰¹, the scientific support for their administration to patients with CRPS-I is very limited. Administration of standard analgesics appears to be based on experience in other fields. The administration sequence in Dutch practices is based on the WHO ladder (see *appendix 3*)²⁰². Oral administration of analgesics^{203,204} is followed by intravenous²⁰⁵ or peripheral blockade techniques^{206,207}. Intravenous administration of the anaesthetic ketamine²⁰⁸ and epidural anaesthesia²⁰⁹ have also been described in the context of pain treatment for CRPS-I patients.

2.1.1.1 Paracetamol

Scientific support

The use of paracetamol is described in the context of an adjuvant pain protocol in a study into the efficacy of free radical scavengers in treating CRPS-I¹¹. No studies have been found looking into paracetamol as a stand-alone treatment for CRPS-I.

Conclusion

Level 4

There is no evidence that paracetamol is effective in treating pain in CRPS-I patients.

D Opinion of project group members

Other considerations

Administration of paracetamol in pain control is generally accepted, partly thanks to the low threshold of administration and the minor side-effects profile.

2.1.1.2 NSAIDs

Scientific support

The efficacy of NSAIDs has been examined in two studies²⁰³. The authors concluded that calcitonin is more effective at reducing bone resorption, but make no comment on the extent of pain reduction.

Sixty-one CRPS-I patients were prospectively monitored during the course of a retrospective study into the effects of 60 mg of ketorolac administered by means of a regional intravenous blockade²⁰⁵. Twenty-six percent of patients had a complete response, 42% had a partial response and 31% had no response. Patients with allodynia had a significantly poorer response to the treatment.

Conclusion

Level 3

There is insufficient evidence of the degree of pain control achieved by NSAIDs in CRPS-I patients.

C Connelly 1995²⁰⁵

Other considerations

NSAIDs are often associated with side-effects. These involve, inter alia, the gastrointestinal system, renal function, blood clotting and blood pressure, the central nervous system and cardiac function²¹⁰. Although the new generation of COX2 inhibitors is thought to cause milder gastrointestinal side-effects, these drugs are associated with a higher incidence of cardiac side-effects²¹¹. Conflicting data has been published with regard to the use of NSAIDs in patients with neuropathic pain²¹².

2.1.1.3 Opioids

Scientific support

One placebo-controlled RCT was found investigating the effects of sustained-release oral morphine on patients who had previously been treated with epidural spinal cord electrical stimulation (ESES)²⁰⁴. No significant differences were found between the extent of pain reduction and the average time for ESES to become effective. On average the morphine group reported 20 side-effects a day, as against 2 a day in the placebo group. A study of nine patients with upper-limb CRPS-I or -II (no control group) looked at the effects of continuous infusion of morphine in the axillary plexus following stellate blockade²⁰⁶. Significant pain reduction at rest and when moving was found, along with greater grip strength. However, the steady-state morphine concentrations measured for these patients was lower than the minimally effective analgesic concentration.

Conclusions

Level 3

There is insufficient evidence of whether pain control is achieved by oral opioids in CRPS-I patients.

B Harke 2001²⁰⁴

Level 3

There is insufficient evidence of whether continuous infusion of morphine to the axillary plexus is an effective method of pain control for CRPS-I patients.

C *Azad 2000*²⁰⁶

Other considerations

Many side-effects have been described for the various weak and strong-acting opioids²¹⁰. Although we have little specific information on weak and strong-acting opioids in patients with CRPS-I, systematic reviews on their use for neuropathic pain have found tramadol to be effective²¹³. Positive short-term effects have also been reported for strong-acting opioids administered for neuropathic and muscular-skeletal pain²¹⁴. No clear statement can as yet be made regarding the long-term effects of opioids or problems associated with tolerance and addiction²¹⁴.

2.1.1.4 Local anaesthetics

Scientific support

We identified three studies in which the effects of local anaesthetics on CRPS-I were examined. The force of the outcomes is limited by the unclear intervention in the retrospective study and the small number of patients in the prospective studies²⁰⁷. An open study with no control group looked at the degree of pain reduction and improvement in grip strength in nine patients with CRPS-I or II following stellate ganglion blockade²⁰⁶. A significant reduction in pain and a significant improvement in pain symptoms were observed.

An open study with no control group investigated the effects of epidural administration to 14 patients with CRPS-I in the knee²⁰⁹. Treatment was continued with continuous administration of a narcotic. No pain control data were described; however, all patients were found to have improved movement outcomes and 11 patients were seen to have a complete improvement of CRPS-I

symptoms at the end of the follow-up. It is difficult to assess this study, however, in view of the limited description of the measuring instruments, baseline data and follow-up.

Conclusions

Level 3

The evidence available is insufficient to allow any conclusions to be drawn on the efficacy of local anaesthetics in the sympathetic ganglia when treating pain in CRPS-I patients.

B Price 1998²⁰⁷
C Azad 2000²⁰⁶

Level 3

There is insufficient evidence to allow any statement to be made as to the efficacy of local epidural anaesthetic administered to CRPS-I patients. Various interventions have been unable to demonstrate the efficacy of epidural administration of local anaesthetics.

C Cooper 1989²⁰⁹

2.1.1.5 Anaesthetics

Scientific support

The effects of a sub-anaesthetic ketamine infusion were assessed in a retrospective study of 33 patients with CRPS-I or -II²⁰⁸. Twelve patients experienced a relapse and had a second course of infusions; three patients had a third course. The pain disappeared completely in 83% of patients. The average duration of pain reduction (data for 20 patients) was 9.4 months. The side-effects mentioned were 'inebriation' (intoxication), hallucinations, dizziness, nausea, light-headedness and blurred vision.

Conclusion

Level 3

There are indications that intravenous administration of a sub-anaesthetic dose of ketamine reduces the pain experienced by CRPS-I patients.

C Correll 2004²⁰⁸

Other considerations

Ketamine should be administered in a clinical setting.

Recommendations

A sub-anaesthetic dose of ketamine should be considered for patients with CRPS-I who are experiencing pain symptoms. The project group considers that pain medication should be administered in accordance with the WHO pain ladder up to and including step 2. Strong opioids should not be administered to this patient group.

The project group also recommends that further research should be carried out into the specific effect of pain medication on CRPS-I.

2.1.2 Gabapentin

General introduction

Anticonvulsants also control pain symptoms. The mechanism of action is not fully understood, but is thought to depend on reducing the hyperexcitability of the central nervous system. Gabapentin is by far the most thoroughly investigated of all anticonvulsants.

Scientific support

Two placebo-controlled, randomised studies have been found that examined the use of gabapentin with CRPS-I patients. The first study of gabapentin in cases of neuropathic pain syndromes was conducted in 2002²¹⁵. This study indicates that gabapentin causes a modest but significant reduction in neuropathic pain symptoms eight weeks after the start of treatment. It is unclear what this means for the CRPS-I patients concerned (according to IASP criteria), who made up 28% of the sample population. We can conclude from the second randomised study that gabapentin has a moderate effect on pain experienced by CRPS-I patients (according to IASP criteria), but that it does lead to a significant reduction in sensory abnormalities in the affected limb²¹⁶.

It can be concluded that a sub-population of CRPS-I patients respond well to gabapentin.

Conclusion

Level 2

There are indications that gabapentin administered at doses of 600 to 1800 mg every 24 hours in the first eight weeks can cause some reduction in pain symptoms suffered by patients with CRPS-I. There is also some evidence that gabapentin reduces sensory abnormalities such as hyperaesthesia and allodynia. The longer-term effect of gabapentin on patients with CRPS-I is not known.

B Serpell 2002²¹⁵; Van de Vusse 2004²¹⁶

Other considerations

Dizziness, sleepiness and fatigue occurred significantly more often in patients taking gabapentin than in patients taking placebo.

Recommendation

Administration of gabapentin should be considered for patients with CRPS-I. Gabapentin should be withdrawn if no clear reduction in pain symptoms, allodynia or hyperaesthesia occurs within an eight-week trial period.

2.1.3 Other anticonvulsants

Scientific support

There are two other anticonvulsive drugs that can be used to treat neuropathic pain in addition to gabapentin.

Carbamazepine is used mainly to combat trigeminal neuralgia. We are not aware of any studies testing carbamazepine in patients with CRPS-I.

We identified only a very small number of studies looking at the use of carbamazepine in cases of neuropathic pain in general. An old study investigated its effect on diabetic neuropathy²¹⁷.

Phenytoin is the other anticonvulsant often given to treat neuropathic pain. This drug has been tested most often in cases of diabetic polyneuropathy^{218,219}.

This trial investigated the long-term effect of the drug and found no long-term improvement of pain symptoms.

Conclusion

Level 4

There is no evidence that anticonvulsants such as carbamazepine, pregabalin and phenytoin are effective in reducing pain in CRPS-I patients.

D Opinion of project group members

Other considerations

Some of the pain associated with CRPS-I is neuropathic in nature. In view of experience from other studies, the use of anticonvulsants to treat neuropathic pain in CRPS-I should be considered.

Recommendation

A trial course of carbamazepine, pregabalin or other anticonvulsants can be considered for patients with CRPS-I suffering significant attacks of neuropathic pain.

2.1. Antidepressants

Scientific support

Tricyclic antidepressants affect noradrenergic neurotransmission and are widely used in patients suffering from constant neuropathic pain. They are currently regarded as the best drugs to treat neuropathic pain. It is thought that tricyclic antidepressants act against neuropathic pain by a variety of mechanisms. The mechanism of action potentiates serotonergic and noradrenergic descending inhibiting pathways, which as a result reduce posterior horn hyperactivity.

Tricyclic antidepressants also affect patients' moods, especially the depression that often accompanies neuropathic pain and CRPS-I. Studies of tricyclic antidepressants (especially amitriptyline) used in cases of diabetic neuropathy show them to be effective²²¹. There is even level 1 and level 2 evidence that the use of tricyclic antidepressants in treating post-herpetic neuralgia produces good results. Two good-quality RCTs^{222,223} and three other RCTs demonstrate efficacy²²⁴⁻²²⁶. Tricyclic antidepressants which raise synaptic concentrations of noradrenaline are much more effective than those which have purely or primarily serotonergic effects. This is why some studies show amitriptyline and nortriptyline in particular to be effective²²⁷. No studies testing tricyclic antidepressants on patients with CRPS-I were available.

Conclusion

Level 4

The efficacy of antidepressants in patients experiencing pain as a result of CRPS-I is not proven.

D Opinion of project group members

Other considerations

Some of the pain associated with CRPS-I is neuropathic in nature. In view of experience from other studies, the use of antidepressants to treat neuropathic pain in CRPS-I should be considered.

Recommendation

A trial course of amitriptyline or nortriptyline can be considered for patients with CRPS-I who are suffering continuous neuropathic pain.

2.1.5. Capsaicin

Scientific support

Capsaicin (8-methyl-N-vanillyl-6-noneamide) is obtained from chilli peppers. This substance has in recent years come to attention as a treatment for neuropathic pain. The mechanism of action is unclear, but it is assumed that capsaicin may have a selective effect on the nociceptors bound to the C fibres.

It is unknown whether this effect is reversible or permanent. Two studies found diminished sensitivity to heat in patients treated with capsaicin^{228,229}. A number of investigators claim that the effect in terms of diminished sensitivity of these C-bound nociceptors is strongly dependent on the dose of capsaicin used.

Only one study has been found in which an extremely high dose of capsaicin (5 to 10%) was administered to ten patients with CRPS-I. Doses of this strength can only be spread onto patients' skin if the painful body part is first numbed by epidural anaesthesia.

The investigators claim to have succeeded in 90% of patients. No scientific conclusions can as yet be drawn from this open-label study.

Conclusion

Level 4

There is no evidence that capsaicin is effective in CRPS-I patients.

D Opinion of project group members

Recommendation

Capsaicin has no place in the treatment of CRPS-I.

2.1.6 Free radical scavengers and CRPS-I

Scientific support

The use of oxygen radical inhibitors or free radical scavengers to treat CRPS-I has only been evaluated scientifically in the Netherlands. The first trial examining the positive effect of dimethyl sulphoxide (DMSO) applied locally to CRPS-I patients was carried out in 1987²³⁰.

This prospective cross-over study on 20 patients found that DMSO had a beneficial effect on the function of the affected limb. Another prospective study on CRPS-I patients (n = 26) also found DMSO to be significantly more effective than the conventional regional ismelin block²³¹. In 1996 Zuurmond was the first investigator to compare DMSO cream with a placebo in a randomised double-blind trial conducted on 32 CRPS-I patients²³². The DMSO (50%) cremor vaselini cetomacrogolis was spread on the affected part of the limb five times a day. This study found the DMSO cream to have a much greater beneficial impact on CRPS-I symptoms than placebo after two months of treatment.

Perez et al. conducted a double-blind randomised study on a large group of CRPS-I patients (n = 146) and found that DMSO cream had a beneficial effect on the symptoms of CRPS-I¹¹. This was the first study to also analyse the effect of N-acetylcysteine (NAC) at a dose of 600 mg three times a day. NAC was found to have a significantly better effect on primary cold CRPS-I than DMSO cream.

Intravenous mannitol is the other treatment often applied in the Netherlands, especially in the acute phase of CRPS-I. The treatment consists of intravenous applications of 10% mannitol for one week. Results of an open study without a control group conducted by Smeets et al. indicate that mannitol administered at home is safe, economical and presents no practical problems²³³. The authors state that 65% of patients had an improvement in their condition. So far, no (placebo-)controlled studies of the effects of mannitol have been carried out.

Conclusions

Level 2

DMSO (dimethyl sulphoxide) cream (50%) reduces the symptoms of CRPS-I patients.

A2 *Perez 2003*¹¹

B *Geertzen 1994*²³¹; *Goris 1987*²³⁰; *Zuurmond 1996*²³²

Level 3

It is likely that 600 mg of N-acetylcysteine administered three times a day reduces the symptoms of CRPS-I.

A2 *Perez 2003*¹¹

Level 3

There are indications that 50% DMSO (dimethyl sulphoxide) cream is more effective on primary hot CRPS-I while N-acetylcysteine is more effective on primary cold CRPS-I.

C *Perez 2003*¹¹

Level 4

There is no evidence that mannitol is effective in treating CRPS-I.

D *Smeets 1999*²³³

Other considerations

In general, DMSO generates lower (direct and indirect) costs than N-acetylcysteine. However, sub-group analysis indicates that N-acetylcysteine generates lower costs and is more effective for patients with a cold form of CRPS-I. DMSO generates lower costs and is more effective for hot forms of CRPS-I²³⁴.

Recommendations

A three-month course of 50% DMSO (dimethylsulphoxide) cream applied daily is recommended for patients who have had CRPS-I for less than a year.

A one-month trial course of DMSO applied locally every day can be considered for patients who have had CRPS-I for more than a year. If the results are favourable, the treatment can be continued for three months.

A three-month course of 600 mg of N-acetylcysteine 3 times a day can be considered for patients with CRPS-I who have a primary cold skin temperature.

Until trials have found mannitol to be effective in reducing oedema, the project group is of the opinion that it should only be administered in the context of a trial.

2.1.7 Muscle relaxants

2.1.7.1 Oral pharmacotherapy

Scientific support

Motor symptoms are a relatively underexplored category of the clinical spectrum of CRPS-I. They can include paresis, dystonia, myoclonias and/or tremor. Some articles refer to spasms, though it is not always clear whether this term also covers intermittent dystonia or myoclonias. No controlled drug trials have been carried out on orally administered muscle relaxants to treat the aforementioned motor symptoms. Five descriptive studies have been conducted into movement disorders in CRPS-I patients^{130,235-238}. Three of them report that a small number of CRPS-I patients with dystonia/spasms benefit from treatment with benzodiazepines and high doses of baclofen. Few of the studies specify the extent of improvement.

Conclusion

Level 3

There is insufficient evidence of the efficacy of muscle relaxants in treating movement disorders associated with CRPS-I, such as dystonia and muscle spasms.

C Bhatia 1993²³⁷; Van Hilten 2001²³⁸; Jankovic 1988²³⁵; Marsden 1984¹³⁰; Schwartzman 1990²³⁶

Other considerations

Although anticholinergics, carbamazepine and magnesium salts are also used in treating dystonia or spasms affecting CRPS-I patients, these forms of medication do not strictly speaking belong to the muscle relaxant group. No controlled studies have been carried out into the treatment of either dystonia or spasms in patients with CRPS-I. Two of the aforementioned descriptive studies report that anticholinergics have never produced (lasting) effects^{237,238}. Prescribers using diazepam or clonazepam must be alert to the possible risk of addiction.

Recommendation

The project group recommends the following initial treatment regimen for CRPS-I patients experiencing dystonia, myoclonias or muscle spasms:

1. oral baclofen according to the standard dose-increase pattern;
2. diazepam or clonazepam, titrated slowly in the light of the effect and side-effects.

2.1.7.2 Botulin toxin

Scientific support

No controlled studies have been carried out into the use of botulin toxin to treat dystonia in CRPS-I patients. A recent study described experience with the use of botulin toxin A to treat 14 patients with very severe tonic dystonia of the hand ('clenched fist')²³⁹. In four of these patients, the dystonia developed in the context of CRPS-I. An 'overall' improvement in pain and muscle relaxation was achieved in four out of five hands, but the extent of improvement was not described. Some publications report that botulin toxin injections never work, or only work for a short period, and rarely lead to improvement in functionality^{235,238}.

Conclusion

Level 3

There is insufficient evidence that botulin toxin A is effective in treating dystonia in CRPS-I patients.

C Cordivari 2001²³⁹; Van Hilten 2001²³⁸; Jancovic 1988²³⁵

Recommendation

The project group considers that botulin toxin has no place in the treatment of CRPS-I-patients with dystonia.

2.1.7.3 Intrathecal baclofen administration

Scientific support

Intrathecal baclofen therapy (ITB) is an invasive technique that has only been investigated in a small number of patients with CRPS-I alone²⁴⁰ or CRPS-I and dystonia²⁴¹ whose condition has failed to respond to previous treatment. Only the latter study was preceded by a double-blind placebo-controlled crossover screening procedure aimed to ascertain whether patients would be suitable for having a programmable pump for ITB fitted. Comparison with a placebo found that baclofen significantly improved outcomes. Six patients underwent the implant procedure and were monitored for 1.7 years as part of an open trial with varying degrees of success. Zuniga et al. also reported an open trial with ITB on two CRPS-I patients with no motor disorder²⁴⁰. Pain, allodynia and autonomic disorders responded well to ITB.

Conclusion

Level 3

There is insufficient evidence that intrathecal baclofen (ITB) is effective in treating dystonia in CRPS-I patients.

C Van Hilten 2000²⁴¹; Zuniga 2002²⁴⁰

Other considerations

The main side-effects of the screening process and continuous administration of ITB are post-puncture headache, diminished consciousness and urine retention²⁴¹.

Recommendation

Intrathecal baclofen (ITB) has no place in the treatment of patients with CRPS-I. Intrathecal baclofen can only be considered for patients with CRPS-I if dystonia is a major problem and conventional therapy has proven ineffective. Treatment must be administered in the context of a trial.

2.1.8 CRPS-I treatment with corticosteroids

Scientific support

Corticosteroids are adrenal hormones that inhibit inflammation. They have been used in open trials^{242,243} and in one controlled trial²⁴⁴ to treat CRPS-I since the 1970s.

In the only placebo-controlled trial (13 patients) of prednisone, the substance was found to have a stronger beneficial effect than placebo²⁴⁴.

All the other studies of prednisone were open trials in which prednisone was applied either orally²⁴² or by intramuscular injection²⁴³. All the studies found corticosteroids to have a very pronounced beneficial effect.

Conclusion

Level 3

Corticosteroids may have an effect on CRPS-I. Little is known as to the duration and dosage.

C Christensen 1982²⁴⁴; Grundberg 1996²⁴³; Kozin 1981²⁴²

Other considerations

Some studies of limited quality indicate that corticosteroids have a beneficial effect. The project group recommends that corticosteroids should not be routinely used in view of the side-effects.

Recommendation

Routine administration of corticosteroids has no place in the treatment of CRPS-I patients.

2.1.9 Treating CRPS-I with calcitonin (subcutaneous and intranasal administration)

Scientific support

Calcitonin, a hormone produced by the C cells in the thyroid gland, inhibits osteoclasts in the bone, thereby reducing bone resorption. It also has an analgesic effect and increases calcium secretion via the kidneys.

Calcitonin can be administered subcutaneously or via a nasal spray. There are various sorts of calcitonin; salmon calcitonin is the most effective. Two placebo-controlled studies have been carried out with intranasal calcitonin^{245,246} and with subcutaneous calcitonin^{247,248}.

Two meta-analyses and two systematic reviews have evaluated the effects of calcitonin. The meta-analysis carried out by Kingery et al.²⁴⁹ reports conflicting findings as to the effects of calcitonin. The systematic review conducted by Van den Berg et al. finds no evidence that calcitonin is effective in cases of CRPS-I²⁵⁰. In contrast, the meta-analysis carried out by Perez et al. points to calcitonin having a positive effect on pain on average²⁵¹, and the review carried out by Forouzanfar et al. also describes positive results for calcium-regulating drugs (including calcitonin) administered to CRPS-I patients²⁵².

Conclusion

Level 1

The evidence relating to calcitonin (both intranasal and subcutaneous) is conflicting.

A1 *Van den Berg 2002²⁵⁰; Forouzanfar 2002²⁵²; Kingery 1999²⁴⁹; Perez 2001²⁵¹*

Other considerations

There is only limited experience with the administration of calcitonin to patients with CRPS-I in the Netherlands.

Recommendation

The project group is of the opinion that in view of the conflicting results of research, it is impossible to give any clear advice as to the use of calcitonin in patients with CRPS-I.

2.1.10 Treating CRPS-I with bisphosphonates

Scientific support

Bisphosphonates inhibit osteoclasts in the bone marrow and are used in bone conditions such as Paget's disease and in the treatment of osteoporosis. There are a number of structural analogues of bisphosphonates, such as etidronate, clodronate, pamidronate, risedronate and alendronate. Resorption from the stomach is often relatively poor, which is why intravenous administration is preferred.

Patients with CRPS-I can have elevated bone turnover (three-phase bone scan), and spotty bone decalcification can sometimes be seen on X-ray images. Various articles on the effects of intravenous bisphosphonate to treat CRPS-I have been published since 1992²⁵³⁻²⁵⁶, and a more recent article looked at oral bisphosphonate²⁵⁷. Three placebo-controlled studies have been carried out to date^{253,255,257}.

One study involved administration of alendronate three days in a row²⁵³. Another study looked at clodronate²⁵⁷. Both are described in the systematic review conducted by Fourouzanfar et al²⁵². In a third study, treatment comprised alendronate (40 mg: the dose is four times as high as that given for osteoporosis)²⁵⁵. In the three studies, the parameters in the group of patients treated with bisphosphonates improved significantly more than in the placebo group.

Conclusion

Level 1

Bisphosphonates have a beneficial effect on the signs of inflammation in patients with CRPS-I. At present little is known as to the optimum dosage, frequency and duration of treatment.

A1 *Forouzanfar 2002*²⁵²

A2 *Manicourt 2004*²⁵⁵

Other considerations

There is little experience in the Netherlands with the use of bisphosphonates to treat CRPS-I. Intravenous bisphosphonates cause relatively few side-effects, but the dosage, frequency and duration are unclear. Consideration can be given to 40 mg of alendronate a day for eight weeks, especially for patients with elevated bone metabolism.

Recommendation

As there is little experience with the use of bisphosphonates in patients with CRPS-I, it is currently advised that these drugs should only be considered in the context of a trial.

2.1.11 Calcium-channel blockers

Introduction

The reasoning behind the use of calcium-channel blockers to treat CRPS-I lies in the theory that these drugs should improve peripheral blood circulation in cold CRPS-I²⁵⁸.

Scientific support

Two studies of moderate quality and size investigated the effect of calcium-channel blockers in treating CRPS-I^{259,260}. Muizelaar et al. report that they are most effective on CRPS-I in the acute phase²⁵⁹. Both studies are primarily descriptive and the outcomes are subjective, failing to describe the nature of the improvement in patients' conditions.

Conclusion

Level 3

There are indications that calcium-channel blockers have some effect in the acute phase of CRPS-I. While they improve blood circulation, they also cause side-effects such as a drop in blood pressure and headache.

C Muizelaar 1997²⁵⁹; Prough 1985²⁶⁰

Recommendation

A calcium channel blocker can be prescribed for patients with a cold CRPS-I. The effect must be assessed a week after administration. The drug must be withdrawn if it is having no effect.

2.2 Invasive treatment

2.2.1 Sympathetic blockade

Introduction

It is not yet clear to what extent the sympathetic system is involved in the pathophysiology of CRPS-I. Hyperactivity of the sympathetic system is suspected in some cases. This hyperactivity ought to be associated with an elevated concentration of adrenaline or noradrenaline in the venous outflow of the affected limb, but this phenomenon has never been observed in practice⁶.

Lower levels of adrenaline and noradrenaline have been measured in the limbs, suggesting that the sympathetic receptors in the affected limbs might be hypersensitive⁴.

The role of the sympathetic nervous system in CRPS-I seems unclear at the moment. Various studies have been carried out into the effects of intravenous sympathetic blockade and percutaneous anaesthesiological sympathetic blockade of the upper and lower limbs; these procedures were found to have no effect, or an unclear effect at most.

2.2.1.1 Intravenous sympathetic nerve blockade

Scientific support

Eight studies have been carried out into the effects of intravenous guanethidine on a group of CRPS-I patients^{231,261-267}. The doses administered ranged from 10 to 30 mg. Four of these studies were randomised, comparing guanethidine to a placebo (in most cases 0.9% NaCl)^{261,263,265,267}. The other studies examining the effect of guanethidine found it to have a temporary effect on only around one-third of patients.

Three of the studies were very small patient studies from which it would be difficult to draw any conclusions²⁶⁸⁻²⁷⁰. One study described only the temporary effect of intravenous lidocaine on mechanical and thermal allodynia²⁷¹. Intravenous blockades brought about by guanethidine, lidocaine, bretylium, clonidine, droperidol and reserpine have been investigated in three review articles^{249,251,252}.

One review described 11 acceptable articles on sympatholytic drugs administered by intravenous injection²⁵¹. The review concluded that there was no evidence for intravenous sympathetic blockade being effective. The reviews conducted by Kingery et al.²⁴⁹ and Forouzanfar et al.²⁵² point in the same direction.

Conclusion

Level 1

Intravenous sympathetic blockade produces no added value (pain reduction) compared to placebo in CRPS-I patients.

A1 Kingery 1999²⁴⁹; Forouzanfar 2003²⁵²; Perez 2001²⁵¹

Recommendation

Intravenous sympathetic blockade has no place in the treatment of patients with CRPS-I.

2.2.1.2 Other intravenous treatment

Scientific support

A number of intravenous drugs have been tested for efficacy. Intravenous regional blockades produced by bretylium and ketanserine were found to achieve a significant reduction in pain in the treatment group^{272,273}. Ketanserine (10 mg for arms and 20 mg for legs), and two intravenous applications of bretylium at 1.5 mg/kg with lidocaine achieved slight pain relief. Intravenous administration of reserpine, droperidol and atropine had no effect²⁴⁹.

Conclusion

Level 1

There are indications that 10-20 mg of ketanserine administered by intravenous injection reduces pain in CRPS-I patients. Reserpine, droperidol and atropine do not relieve pain in CRPS-I patients.

A1 Kingery 1999²⁴⁹

B Hanna 1989²⁷²; Hord 1992²⁷³

Other considerations

The positive findings in relation to the effects of bretylium cannot be confirmed as the study was of mediocre quality and small in size. Bretylium is not registered in the Netherlands.

Recommendations

Intravenous administration of 10-20 mg of ketanserine can be considered for the treatment of CRPS-I patients.

Routine administration of reserpine, droperidol and atropine is not recommended for CRPS-I patients.

2.2.1.3 Percutaneous sympathetic blockade

Scientific support

Sympathetic nerve blockade is a traditional treatment for CRPS-I patients. For the upper limbs, this could be a blockade of the stellate ganglion or the thoracic sympathetic nerves, and for the lower limbs it could be a blockade of the lumbar sympathetic nerves, usually carried out at L2 and L3. The literature contains surprisingly few studies into the effect of these blockades. It is striking to find that no randomised studies have been carried out on CRPS-I patients comparing the effect of sympathetic blockades performed under local anaesthetic with placebo blockades. The literature contains one systematic review of the therapeutic role of local anaesthetic sympathetic blockades in patients with CRPS-I²⁷⁴. That review assessed 29 studies performed on 1,144 patients with CRPS-I, and concludes that critical examination of the studies raises the question of whether sympathetic blockade is of any benefit at all in CRPS-I. Less than a third of patients reported temporary relief of pain symptoms following a sympathetic blockade. However, it is unclear whether this is due to a placebo effect. After all, the outcome of studies carried out with no control groups overestimates the therapy effect. Our evaluation considered nine articles. All of them were class B or C in terms of evidential strength. Two were randomised studies, one of which was carried out by Bonelli et al.²⁷⁵ comparing the effect of a stellate block with 20 mg of intravenous guanethidine. There was no difference in efficacy between the two methods after three months. In the other randomised study, carried out by Price et al.²⁰⁷, the effect of a local anaesthetic was compared with salt in a very small group of patients⁷. The study was too small to allow any conclusions to be drawn. Two retrospective studies looked at the effect of a radiofrequent (RF) lesion at the lumbar level. In the study carried out by Rocco et al. on 20 patients who underwent an RF lesion at L2-L3, and sometimes also L4, it was concluded that many patients experienced a rise in temperature in the treated limb, but that the reduction in pain did not last long²⁷⁶. We found one retrospective study looking at treatment at the cervical level²⁷⁷. A small number of patients underwent RF lesion of the stellate ganglion. Thirty-seven of patients reported a reduction in pain symptoms. In a non-randomised study, DelleMijn et al. examined the effect of a stellate ganglion blockade using 0.25 0,25% of bupivacaine and

compared it with the effect of 35 mg of intravenous phentolamine²⁷⁸. The study only assessed the short-term effect and the impact on sensory changes after treatment. Wang et al. conducted a retrospective study into the effects of lumbar sympathetic blockade comparing it with conservative treatment²⁷⁹. This poorly conducted retrospective study concluded that 65% of patients improved after sympathetic blockade as against 41% after conservative treatment. No conclusions can be drawn from this study due to its mediocre quality.

Glynn et al. conducted a study involving injections of bupivacaine around the stellate ganglion, but it is unclear whether the patients had CRPS-I²⁸⁰.

Conclusion

Level 2

Routine administration of percutaneous sympathetic blockade in patients with CRPS-I is not useful.

A2 Cepeda 2002²⁷⁴

B Bonelli 1983²⁷⁵; DelleMijn 1994²⁷⁸; Price 1989²⁰⁷

C Forouzanfar 2000²⁷⁷; Glynn 1993²⁸⁰; Rocco 1995²⁷⁶; Wang 1985²⁷⁹

Other considerations

The project group considers that percutaneous sympathetic blockade may be a good way of improving the circulation in patients with cold CRPS-I.

Recommendation

Patients with cold CRPS-I who do not respond adequately to vasodilating medication can be considered for percutaneous sympathetic blockade using local anaesthetics. If a trial blockade has proved successful, definitive sympathetic blockade using radiofrequent lesions, phenol or alcohol can be considered in the context of a trial.

2.2.2 Spinal cord stimulation for patients with CRPS-I

Scientific support

Spinal cord stimulation is a treatment in which an electrode is placed in the epidural space behind the spinal cord at the level of the nerve roots which innervate the painful area. The electrode produces an electrical current that causes tingling, a sensation that suppresses the pain. The precise mechanism of action is not known. The treatment is uncomfortable and very expensive, and so is reserved for candidates meeting strict inclusion criteria, in whom psychopathology has been ruled out, in whom trial stimulation has produced clear pain relief, and where it has been established that the entire painful region can be covered by tingling²⁸¹.

Only one RCT has been conducted for this technique: patients with chronic CRPS-I for whom all possible treatments have been tried without success were allocated at random to spinal cord stimulation plus physiotherapy (n = 36) or physiotherapy alone (n = 18). Trial stimulation proved successful in 24 of the 36 patients; only these patients underwent a procedure to implant a permanent system. The intention to treat analysis found that pain intensity fell by 2.4 cm more (VAS) after six months in the group receiving spinal cord stimulation plus physiotherapy and by 2.1 cm more after two years when compared with the group undergoing physiotherapy alone. Quality of life improved only in the 24 patients with an implanted system; function remained unchanged. Nine of the 24 patients with an implanted system (38%) experienced complications requiring further surgery within two years^{282,283}.

The value of the systematic review is limited as only one RCT is included²⁸⁴. A number of retrospective cohort studies have investigated pain relief brought about by spinal cord stimulation²⁸⁵⁻²⁸⁷.

Conclusion

Level 3

Spinal cord stimulation administered to CRPS-I patients who are carefully selected and undergo successful trial stimulation causes long-term pain reduction and improves quality of life, but does not improve function.

A2 *Kemler 2000*²⁸²

C *Bennett 1999*²⁸⁷; *Calvillo 1999*²⁸⁶; *Kemler 1999*²⁸⁵; *Kemler 2004*²⁸³

Other considerations

All the studies relate to carefully selected patients whose CRPS-I has been treated with all possible therapies without success; there is no scientific evidence for spinal cord stimulation being effective in non-chronic CRPS-I.

A cost-effectiveness analysis has found that treatment of chronic CRPS-I by spinal cord stimulation is cheaper than standard therapy²⁸⁸.

Though life-threatening complications associated with spinal cord stimulation are rare, complications requiring further surgery do occur in 25-50% of patients²⁸⁹.

Recommendation

Pain control with spinal cord stimulation is a responsible choice for carefully selected CRPS-I patients who have not responded to other treatments. Spinal cord stimulation should ideally only be administered to other CRPS-I patients in the context of a trial.

2.2.3 Amputation and CRPS-I

Introduction

Amputation generally represents a new approach to possible recovery. The aim is to improve quality of life. It can save lives (severe, untreatable inflammation with the threat of sepsis or in the case of oncological processes). CRPS-I patients who are in despair sometimes request amputation as a last resort.

Scientific support

Several case histories appear in the scientific literature. We found two retrospective studies^{290,291}. One was carried out on seven patients with upper-limb CRPS-I²⁹¹. Three patients were happy with the results of the amputation, two were undecided and two were unhappy.

In another study, 34 amputations were carried out on 28 patients²⁹⁰. The reasons were: pain (n = 5), recurrent infections (n = 14) and in order to encourage functional recovery (n = 15). Two patients were pain-free; ten infections were adequately controlled, and functional improvement was achieved in nine cases. CRPS-I relapse occurred in 28 cases, but 24 patients were in the end satisfied with their amputation.

Conclusion

Level 3

There is insufficient evidence that amputation makes a positive contribution to the treatment of CRPS-I.

C *Dielissen 1995*²⁹⁰; *Stam 1994*²⁹¹

Other considerations

Amputation of the affected limb cannot always be prevented in cases of potentially life-threatening, untreatable or recurrent infections.

Recommendation

Amputation for CRPS-I patients can only be considered in order to improve quality of life in the case of severe, recurrent infections and severe functional disorders. It would have to be performed at a specialist centre.

2.2. Surgical sympathectomy in cases of CRPS-I

Scientific support

The efficacy of surgical sympathectomy is summarised in a systematic review²⁹²; however, this review is of limited value as it is based only on a number of retrospective studies²⁹³⁻²⁹⁷. The cohort studies describe groups of between 7 and 73 patients. All the studies measure a clear reduction in pain due to sympathectomy, but the extent of pain relief declines over time. A number of studies including a follow-up carried out at least a year later indicate that the chance of success is greatest if treatment is given soon (less than three months) after the initial trauma²⁹⁵⁻²⁹⁷.

Conclusion

Level 3

There are indications that surgical sympathectomy can relieve pain in CRPS-I.

C AbuRahma 1994²⁹⁷; Bandyk 2002²⁹⁴; Bosco Vieira Duarte 2003²⁹³; Mailis 2003²⁹²; Schwartzman 1997²⁹⁵; Singh 2003²⁹⁶

Other considerations

Surgical sympathectomy is carried out on the basis of poor quality evidence, studies without control groups, and personal experience. Though it would appear logical (and has been suggested) that surgical sympathectomy is indicated primarily for patients with confirmed 'sympathetic-dependent pain'²⁹⁴, other authors take the view that the treatment results are not correlated to this²⁹⁶. Eighteen percent of patients undergoing sympathectomy for neuropathic pain experience compensatory hyperhidrosis and 25% experience neuropathic complications²⁹⁸.

Recommendation

Extreme caution is called for when considering surgical sympathectomy for pain control in CRPS-I. The procedure should be conducted in the context of a trial in order to ascertain the efficacy and potential risks.

Chapter 3

Treatment by paramedical, rehabilitation and psychological methods

Introduction to paramedical care for patients with CRPS-I

Patients with CRPS-I experience a reduction in the amount of strain the affected limb can bear and also suffer pain. The limb often reacts excessively to the slightest effort or strain: the patient often experiences an extreme increase in pain following the slightest activity.

Patients generally react to this increase in pain in one of two ways: 1. They may decide to immobilise the affected limb, for instance by resting the leg on a cushion or placing the arm in a sling, and keep it as still as possible. If they do have to move the limb, then the pain is so intense that the patient immobilises it further.

2. The other reaction is for the patient to exert the limb (much) more than usual, to 'get it fit'. Here again a excessive pain reaction occurs, but the patient interprets this as a sign that the limb is not fit enough and continues intensive exercise.

The key to recovery in CRPS-I seems to lie in properly adjusted movement and in learning to reintegrate the affected limb into everyday activity. Treatment focusing on pain seems to be more important for patients who have recently developed CRPS-I, while a time-contingent approach seems more important for longer-established cases of CRPS-I (the chronic pain stage).

In the case of treatment focused on pain, the level and progression of exercises and strain are determined primarily by the intensity of the pain. The intensity of treatment should be low in cases of highly intense pain, and vice versa.

High-intensity treatment leading to an increase in the intensity of pain must be avoided in cases of recently developed CRPS-I. A short increase in pain brought about by this form of treatment (one to two hours) is not considered harmful.

Stimuli can be offered and the patient can exercise within these boundaries. The patient is taught to observe his or her body's reactions to activity and other stimuli, and to adjust his or her movements accordingly. Pain-focused treatment has led to a considerable reduction in symptoms in cases of CRPS-I of recent onset^{299,300}. This approach also fits in well with the patient's wish to protect the limb, increasing his or her confidence in the therapy.

In the case of time-focused treatment, the level of exercises and strain is gradually built up over time irrespective of pain.

It is impossible to pinpoint a time when pain-focused treatment gives way to time-focused treatment. Clinically, both forms of treatment can gradually give way to each other. Practitioners should opt for a time-focused treatment if signs of chronic pain

behaviour are observed. No information on scientific outcomes of time-focused treatment for CRPS-I is yet available. The working group considers that absolute immobilisation is not indicated because properly adjusted movement is the key to recovery from CRPS-I.

In very broad terms, physiotherapy primarily addresses the impairments of the affected limb, while occupational therapy focuses on activities of daily living. Psychological treatment concentrates mainly on the emotional and/or mental consequences of the condition. The indications for physiotherapy, occupational therapy, psychological and multidisciplinary treatment are set out below.

Patients should be referred to a physiotherapist if they are suffering from:

- pain
- violent reaction to exertion
- mobility disorders
- strength disorders
- sensitivity disorders
- coordination disorders
- inability to cope with the condition.

Patients should be referred to an occupational therapist if they are suffering from:

- pain, swelling and mobility disorders
- sensitivity disorders
- reduced ability of the affected limb to bear strain
- problems in self-care, productivity and relaxation
- inability to cope with the condition.

Patients should be referred to a psychologist if they are suffering from:

- discrepancy between symptoms that can be objectively described and the patient's (pain-related) behaviour
- stagnation in recovery despite adequate somatic treatment
- extreme suffering as a consequence of the symptoms.

Patients should be referred for multidisciplinary treatment if they are suffering from:

- long-standing CRPS-I with signs of chronic pain behaviour
- stagnating functional recovery
- indications of psychosocial problems
- inability to cope with the condition.

If multidisciplinary treatment is given, it is important for one practitioner to act as case manager and coordinate the work of the various practitioners and be a point of contact for the patient.

3.1 Physiotherapeutic treatment

Introduction

Published articles often recommend 'physiotherapy' as adjuvant treatment, without specifying exactly what this physiotherapy involves. In general, it is emphasised that functional recovery is essential and forms the key to recovery. Recommendations on what therapy should consist of are usually based on 'expert' opinion. It is interesting to note that no research seems to have been done into the question of whether physiotherapy offers any added benefits in the treatment of CRPS-I; it seems to have simply been assumed that this is the case. One study investigated the efficacy of two forms of physiotherapeutic treatment on patients with CRPS-I³⁰¹, and another study investigated the effect of the frequency of physiotherapy (once a week versus three times a week) on children with CRPS-I also receiving cognitive behavioural therapy¹⁹³. Although both studies put forward the argument that physiotherapy is an effective form of treatment for CRPS-I, the lack of a control group not receiving physiotherapy makes it impossible to back up these conclusions.

Scientific support

Randomised controlled studies show that physiotherapy given in addition to medical treatment has a clinically relevant effect on the severity of functional disorders^{299,300}. Physiotherapy contributes primarily to quicker recovery from pain, skin temperature, active mobility and limb volume. In view of the rapid improvement of disorders it is recommended that physiotherapy should be started at an early stage, or soon after the diagnosis is made^{299,300,302}. Mirror therapy is a new treatment method for reducing experienced pain^{303,304}. There is little scientific literature on the content of physiotherapeutic treatment. Most of the publications are inventories of experts' views^{8,305,306}. The only protocol demonstrated as being effective is a pain-focused physiotherapy protocol aimed at

improving patients' ability to cope with the condition (see *Other considerations*)^{299,300,307}. A time-focused physiotherapy treatment for longer-standing CRPS-I has been described but not yet evaluated³⁰⁸.

Conclusions

Level 2

Physiotherapy for upper-limb CRPS-I is likely to have a beneficial impact on the disorders and on how patients cope with the condition.

A2 *Oerlemans 1999*²⁹⁹, *2000*³⁰⁰
B *McCabe 2003*³⁰³
C *Fialka 1992*³⁰¹

Level 3

There are indications that physiotherapy treatment is also a good idea for later-stage CRPS-I.

B *Moseley 2004*³⁰⁴
D *Wilgen 2002*³⁰⁸

Level 2

Physiotherapy treatment has a role in the standard treatment of patients with CRPS-I.

D Opinion of working group members

Other considerations

As far as we know, there are no contraindications for physiotherapy treatment. The patient's ability to exert control is a key part of the pain-focused treatment protocol. He or she is helped to gain control over the syndrome. This is done by means of advice, information and emotional support, and to a lesser extent by means of physical support. Exercise therapy is accompanied by activities carried out at home, including self-massage. Massage administered by the therapist does not form part of the protocol, and nor do almost all physical applications. TENS can be administered if this is indicated following a successful trial treatment. See also *appendix 4*.

Recommendation

It is recommended that physiotherapy aimed at restoration of function be started as soon after the onset of CRPS-I as possible.

TENS and CRPS-I

Scientific support

TENS (Transcutaneous Electrical Nerve Stimulation) is a process whereby a low-amp electrical current is applied to the painful area. Skin electrodes are placed on the painful area; these are connected by a wire to a current-generating box the size of a Walkman. The tingling sensation produced suppresses the pain. The precise mechanism of action is not known. The therapy has been and continues to be used in 'conservative' CRPS-I treatment protocols despite the lack of firm evidence of its efficacy. Some articles have been published describing small groups of CRPS-I patients being treated with TENS and other techniques^{309,310}. These articles have no scientific value. Randomised studies into the efficacy of TENS have been carried out only for chronic lower back pain; the findings are not conclusive³¹¹.

Conclusion

Level 4

There is no evidence that TENS (Transcutaneous Electrical Nerve Stimulation) is effective in the treatment of CRPS-I.

D Opinion of working group members

Other considerations

Apart from allergic reactions to the adhesive used to fix the skin electrodes, there are no known contraindications for TENS. The value of the various TENS application programmes has not been demonstrated either.

Recommendation

TENS can be tried out without risk in CRPS-I patients as an additional treatment. It is only sensible to continue with the treatment if it is found to be effective.

3.2 Occupational treatment

Introduction

Occupational therapy is sometimes briefly mentioned and/or recommended as an adjuvant treatment in articles on CRPS-I. However, little scientific research has been done into its effect on CRPS-I. It is also difficult to track down information as CRPS-I literature sometimes mentions forms of occupational therapy without actually using the term 'occupational therapy'. Occupational therapy used in the context of CRPS-I has two objectives: one is to help patients cope with symptoms and provide advice on how to prevent the symptoms getting worse. The other is to maintain and/or increase the limb's function while reducing impairments to levels of activity and participation.

Scientific support

We found one RCT on the efficacy of occupational therapy in CRPS-I. This study looked at the effect of the entire occupational treatment rather than its individual components³¹². Occupational therapy provided in addition to medical treatment had a positive effect on the severity of the functional disorders^{299,300}. It also appeared to have a positive impact on activity levels^{299,300}. However, as most of the outcome measures related to function, it was not possible to adequately demonstrate effects on activity. Most of the other scientific research carried out in respect of CRPS-I does not use activity measurements either³¹³.

Conclusion

Level 3

Occupational treatment has a positive effect on functional disorders, and it is likely that occupational therapy has a positive effect on the activity level of patients with upper-limb CRPS-I.

A2 *Oerlemans 1999²⁹⁹, 2000³⁰⁰*

D *Cup 1999³¹²; Hardy 1997³¹⁴; Hareau 1996³¹⁵; Schasfoort 2000³¹³; Stanton-Hicks 1998¹⁹⁸; Vacariu 2002³¹⁶*

Other considerations

There are no known contraindications for occupational therapy.

Splint treatment seems to be indicated if it is part of the total occupational treatment, and is always accompanied by instructions on how to wear the splint. Splints ideally act by giving functional support, but can also offer protection and focus on minimising clinical symptoms. Practitioners try to gradually reduce the duration and frequency of splint use over time³¹². Where possible, splints should not immobilise the patient;^{198,315,316} i.e. they should not be worn continuously and the joints (or joint mobility) should be kept as unrestricted as possible.

Desensitisation programmes as part of occupational treatment are used to 'normalise sensitivity'³¹². These programmes, involving a build-up of stimuli, lead to an increase in tolerance of tactile stimuli^{198,314}.

Promoting functional use of the limb within the boundaries of pain and promoting independence are other important aims of occupational therapy³¹⁶.

This is why it is recommended that occupational therapy should be practiced every day¹⁹⁸.

The Netherlands has developed 'Standard occupational therapy for upper-limb CRPS-I' (see *appendix 5*) based on experience, literature, and consultation with occupational therapists working for various institutions³¹². This standard is followed in various institutions and used to train professional occupational therapists.

As the severity of symptoms can vary, treatment must be adjusted to the individual. Exercise and advice can be sufficient for mild symptoms. Multidisciplinary treatment is desirable for severe symptoms and should be started as early as possible^{299,300,316}.

Recommendation

The working group recommends that patients with upper-limb CRPS-I be referred for occupational therapy.

3.3 Rehabilitation medicine treatment

Introduction

Rehabilitation medicine treatment comprises coordinated cooperation between various practitioners, including a rehabilitation medicine specialist, physiotherapist, occupational therapist, social worker and a psychologist, together with a certified orthotist or shoe technician if appropriate. The rehabilitation team and other medical specialists hold regular case conferences to coordinate the various treatments. This approach can offer added value over and above a single therapy. It is important for one practitioner to take the lead and act as the case manager. He or she will have regular contact with the patient and all practitioners, ensuring that there is no conflict between treatments and providing clear lines of communication with the patient and all practitioners. The ideal person to fill this role is a doctor with experience and knowledge of CRPS-I, as the patient's drug regime also has to be monitored.

Scientific support

Though no studies have been carried out to date into the efficacy of a combination of methods to treat CRPS-I, experts argue for a multidisciplinary approach to CRPS-I patients because of the complex nature of the condition, the possibility of a multifactorial cause, and the varying nature of its progress^{198,317}.

Conclusion

Level 4

There is no evidence that multidisciplinary treatment is beneficial for CRPS-I patients.

D Stanton-Hicks 1998¹⁹⁸; Rho 2002³¹⁷

Other considerations

A number of arguments can be put forward in favour of a multidisciplinary approach to treating patients with chronic CRPS-I:

- The treatment requires the involvement of various disciplines. The treatment needs to address both disorders (pain control, restoration of vegetative irregularities) and limitations experienced by the patient (such as restoration of hand function or walking). The main role of the doctor is in pain control. The physiotherapist concentrates on functional disorders. The occupational therapist's main interest lies in compensating for the patient's limitations so as to help him or her play a more active role in society. The various therapies complement one another.
- Patients with chronic CRPS-I experience problems in various areas. They often suffer psychosocial problems due to the condition in addition to loss of function and the accompanying social and professional problems. Support by a social worker or psychologist can be desirable here.
- Regular consultation between practitioners is desirable so that a clear message can be given to the patient. Patients are often known to various departments of various hospitals, and are sometimes given conflicting advice by different practitioners. This can lead to uncertainty with regard to the nature of the condition, the best treatment, and the prognosis.

Recommendation

Where a number of practitioners are treating a CRPS-I patient at the same time, it is advisable that one of them act as case manager.

Multidisciplinary pain programmes in the Netherlands

A recent inventory of multidisciplinary pain treatment teams in the Netherlands³¹⁸ showed that institutions in the Netherlands (hospitals and rehabilitation centres) offered multidisciplinary pain programmes as part of their regular healthcare provision. Practically all of them have the same aim: helping patients learn to cope with pain and improving their functional capabilities and quality of life. Most of these pain programmes are run by a rehabilitation specialist; less often by an anaesthesiologist or neurologist. Though the literature shows that multidisciplinary pain programmes are effective, some comments need to be made with regard to the situation in the Netherlands. There are considerable differences in the content of these programmes and the way they are carried out, and there is no consensus as to the cognitive methods used. There are also considerable differences in the duration and intensity of the programmes, and some specific aspects, such as CRPS-I, have not yet been subjected to good-quality research.

With a view to increasing transparency for referring physicians and patients, the Maastricht Centre for the Understanding and Treatment of Pain recently joined forces with the Netherlands Working Group for Pain Rehabilitation to start working towards a consensus on the purpose and content of the pain rehabilitation programmes offered in the Netherlands. The aim of this initiative was to create a clear definition and description of pain rehabilitation programmes for use in scientific research, for example.

3.4 Effect of psychological factors on the onset and development of CRPS-I

Introduction

As no clear objective somatic cause has so far been found, it has been suggested that CRPS-I might be caused or worsened and maintained by non-organic factors^{231,319}. In clinical practice, the feeling that something is 'not quite right' with these patients is quite prevalent. A certain premorbid psychological process is thought to be involved. It is not quite clear whether the cause and/or progress of the symptoms is determined by mental factors, or whether the mental factors should be seen as the consequence of CRPS-I, and in particular the pain symptoms. The methodological quality of the studies carried out into psychological diagnosis is generally moderate to poor. We found one RCT carried out on children and no RCTs on adults. Retrospective cohort surveys or

cross-sectional studies with no control group and limited follow-up are common. We did not find any scientific publications of psychological treatments administered to adults.

3.4.1 Scientific support in respect of diagnosis

3.4.1.1 *Psychological malfunction in general*

Psychological malfunction is thought to play a greater role in the onset and maintenance of symptoms in the case of CRPS-I than in other types of chronic pain³²⁰. However, patients with CRPS-I did not achieve significantly different scores to the control group on the Symptom Check List-90 (SCL-90), apart from on the scale measuring somatic symptoms³²⁰. What this means is that this group of patients reported more somatic symptoms than the control group; it does not mean, as is often assumed, that they have a somatisation disorder. No clear profile emerged from the SCL-90 scores or the General Health Questionnaire (GHQ) scores. There is therefore no evidence from these questionnaires that CRPS-I patients form a sub-group within the category of patients experiencing pain. CRPS-I patients reported fewer symptoms on the SCL-90 (general level of psychological and physical malfunction) compared to control groups (mixed headache group and chronic non-specific back symptoms)³²¹⁻³²⁴.

Conclusion

Level 2

There is no specific profile within the SCL-90 (Symptom Check List-90) differentiating patients with CRPS-I from control subjects or other patients with pain.

B Bruehl 1996³²⁰; Ciccone 1997³²²; DeGood 1993³²¹; Field 1997³²³; Van der Laan 1999³²⁴

Other considerations

The SCL-90 is a psychological questionnaire that is not sensitive enough for CRPS-I patients, but it does give an impression of the general level of psychological and physical function.

3.4.1.2 Life events and coping

It is thought that life events and intense mental stress can predispose an individual to develop CRPS-I. Both the number and severity of life events are likely to be higher than in a control group²³¹. However, there is research that fails to demonstrate this link³²⁵. Coping strategies are not thought to be any different for patients with CRPS-I and a group that recovered from CRPS-I³²⁶.

Conclusion

Level 2

The role of life events in the development of CRPS-I is not clear. There seems to be no difference in coping strategies between patients with CRPS-I and a group that recovered from CRPS-I.

B Geertzen 1994²³¹; Monti 1998³²⁵; Rose 1992³²⁶

3.4.1.3 Depression

Little research has been carried out into the influence of depression on the development of CRPS-I. Studies have been conducted into depression as a consequence of CRPS-I.

Measurements taken by the Beck Depression Inventory (BDI) found no difference between CRPS-I and the control group^{231,322,325,327}. But this is contradicted by research finding lower scores for CRPS-I patients on the scale measuring depressive symptoms (fewer/no depressive symptoms) compared to a control group (headache and chronic lower back pain respectively)³²¹.

Conclusion

Level 2

There is insufficient evidence that depression is involved in the onset and/or maintenance of CRPS-I.

B Bruehl 2003³²⁷; Ciccone 1997³²²; DeGood 1993³²¹; Geertzen 1994²³¹; Monti 1998³²⁵

Other considerations

If treatment is indicated for patients with CRPS-I and depression, preference should be given to amitriptyline (no selective serotonin reuptake inhibitors) in combination with psychological treatment. As severe pain causes emotional suffering, it would be remarkable for CRPS-I patients to achieve low scores on scales measuring depression and anxiety.

3.4.1.4 Anxiety

It is assumed that anxiety is an important factor in maintaining symptoms of CRPS-I and other chronic conditions. A number of studies have investigated the effect of anxiety in maintaining CRPS-I, but none were able to demonstrate a clear link^{231,321,322,324}.

Conclusion

Level 2

No link has been found between anxiety and maintenance of CRPS-I symptoms.

B Ciccone 1997³²²; DeGood 1993³²¹; Geertzen 1994²³¹; Van der Laan 1999³²⁴

Other considerations

More attention has been paid to movement anxiety in recent years. The patient is excessively worried that certain activities might lead to tissue damage. We now know that in other chronic pain syndromes this anxiety leads to increased restrictions and pain³²⁸. The working group considers that practitioners must be alert to the presence of movement anxiety. This can be done by asking what activities the patient avoids even though he or she should be able to carry them out reasonably well, or by using the TAMPA

kinesiophobia scale (TSK)^{328,329}. Effective treatment of movement anxiety leads to a reduction in anxiety, pain and restrictions for patients with CRPS-I and other conditions.

3.4.1.5 Personality

Research into personality has focused mainly on the 'neuroticism' factor. It is difficult to compare the various studies carried out, as each one operationalises neuroticism in a different way. Furthermore, various studies use different tests based on separate constructs of neuroticism.

Elevated scores are found on the 'hysteria', 'depression' and 'hypochondria' subscales in the Minnesota Multiphasic Personality Inventory (MMPI); taken together, these could give an impression of neuroticism. However, this research was carried out on small numbers of patients and the findings were not significant^{330,331}. No significant difference was found between patients with CRPS-I and a control group on the Netherlands Personality Questionnaire (NPV) either²³¹. In the structured clinical interview for DSM III-R (SCID), elevated scores were found for the 'obsessive-compulsive' personality and the 'self-undermining' personality in both the CRPS-I group and the control group (chronic lower back pain)³²⁴.

Conclusion

Level 2

There is no indication that CRPS-I patients have a specific personality profile.

B Geertzen 1994²³¹; Monti 1998³²⁵; Subbarao 1981³³⁰; Zucchini 1989³³¹

3.4.1 Scientific support in respect of treatment

We found no articles investigating the effect of psychological treatment of patients with CRPS-I.

Other considerations

Although the questionnaires used do not describe a specific profile for patients with CRPS-I, it would be quite reasonable to carry out further investigation before starting psychological treatment. The SCL-90 is a useful instrument for giving an impression of the general level of mental and physical function. This questionnaire can also serve as an adequate evaluation instrument. It would also appear sensible to make some statement as to the degree of movement anxiety, using the TSK for example³²⁹. In view of the (psychometric) match between patients with CRPS-I and patients with a different chronic pain syndrome, cognitive behavioural therapy could be an appropriate form of treatment focusing on the consequences of the condition.

In short, a number of questions can be put to the psychologist:

1. Are there any psychological factors that are maintaining and/or aggravating the syndrome, and if so what are they?
2. Is psychological treatment indicated? If so, by whom should it be provided? Is the patient motivated, do you think that the psychological factors that have been determined are susceptible to change?
3. Is there any psychological contraindication against medical and/or psychological treatment? Psychological treatment is contraindicated for patients who are not thought to be capable of self-reflection or behavioural change, or who are not motivated. Another factor that may lead to treatment being withheld is if the patient is involved in legal proceedings.

The psychologist is not concerned with whether the symptoms are caused by psychological factors, but looks at the consequences of the syndrome.

Recommendation

The working group advises that CRPS-I patients should consult a psychologist if the practitioner observes a discrepancy between symptoms that can be clinically described and the patient's (pain-related) behaviour, if stagnation in (somatic) treatment occurs, if the burden of suffering in response to the symptoms is great, or if the patient requests this.

Chapter 4

Treatment of children with CRPS-I

4.1 Drug and invasive treatment in children

Scientific support

Little research has been published on specific drug or invasive treatments for children with CRPS-I. Most of the information is limited to descriptions from a multidisciplinary context^{190,192}, with the use of analgesics only mentioned in passing.

Two sets of case descriptions of moderate quality were identified, describing home administration of continuous peripheral nerve blockade (ropivacaine)³³² and continuous intravenous infusion of a carbacyclin derivative in children with untreatable CRPS-I³³³.

Dadure et al. describe a group of 13 children with CRPS-I (9-16 years old; criteria not reported)³³². A peripheral nerve blockade consisting of 0.5ml/kg 1% lidocaine, epinephrine and 0.5% ropivacaine was administered under general anaesthetic via a peripheral nerve catheter, followed by an intravenous (Biers) block comprising 0.2 ml/kg 1% lidocaine, 3 ml/kg hydroxyethyl, and 5 mg/kg buflomedil. Continuous infusion of 1.1 ml/kg/hour of 2% ropivacaine was administered until 96 hours after the catheter had been inserted. All patients then underwent intensive physiotherapy. The continuous analgesia was assessed as excellent, with the motor block lasting for a limited time (12 hours). The children were able to walk within 24 hours, and none of them showed signs of CRPS-I two months later. It is impossible to assess the effects described in this research individually because of the lack of baseline data, the summary nature of the description of the results, and the combination of various treatment options.

The case series described by Petje et al.³³³ also examined continuous intravenous infusions of carbacyclin derivatives administered over three days, physiotherapy, and psychological consultation. The study was conducted on 7 children with CRPS-I (aged between 6 and 11, diagnosed with CRPS-I according to the IASP criteria). The patients were symptom-free after a follow-up period lasting 30 months on average (range: 25 to 37 months). Repeated infusion was necessary in two cases. Here again the data is presented in a summary form and the study used a variety of methods, so that it is impossible to assess the drug interventions individually.

Conclusion

Level 3

There is insufficient data to allow any conclusions to be drawn as to the effects of continuous peripheral nerve blockade by means of ropivacaine or continuous intravenous infusion with a carbacyclin derivative in children with CRPS-I.

C *Dadure 2005*³³²; *Petje 2005*³³³

Other considerations

To sum up, we can say that too little data is available to allow a balanced conclusion to be drawn on the effects of the (aforementioned) drug and invasive interventions on children with CRPS-I. This also applies to other interventions described in these guidelines, as they have not been investigated for this target group. Further research is necessary to chart the effects of interventions aimed at CRPS-I on children.

The foregoing comments should be borne in mind by practitioners applying drug and invasive treatments described in these guidelines to children. It is essential to remember the specific features of treating children; particular attention must be paid to dosage and to supporting the child through the disease process. Close cooperation with a paediatrician appears justified in this context.

Recommendation

The working group considers that further research is needed to determine the effects of drug treatment and invasive treatment on children with CRPS-I.

Caution is advised when applying the treatments described in these guidelines to children. Particular attention must be paid to setting the dose and giving (medical) support to the child.

4.2 Paramedical and psychological treatment of children

4.2.1 Physiotherapy treatment of children

Scientific support

Physiotherapists are often involved in the treatment of CRPS-I in children. It is generally accepted that the objectives of treating children with CRPS-I are the same as those of treating adults with the condition: reducing pain and increasing the function of the affected limb. The tools available are almost exactly the same as those used with adults: active and passive exercise, massage, and physical applications.

The difficulty in interpreting the outcomes of research into the effects of physiotherapy on children with CRPS-I is that many different criteria for CRPS-I are used. Some authors do not describe the criteria at all,¹⁹¹ or use their own^{189,334,335}. Other authors apply the criteria drawn up by Kozin et al.^{142,242} or Bernstein et al.^{336,192,309} The IASP criteria, or criteria derived from them^{7,8,60}, are used sometimes in isolation and sometimes in combination with other criteria^{190,192-194}.

It is impossible to draw any conclusions from the existing literature as to the efficacy of one type of physiotherapy treatment, to compare different types of physiotherapy treatment, or to compare the efficacy of physiotherapy treatment with other forms of treatment. No well-designed trials have been carried out.

Between 47 and 93% of patients recovered.

Physiotherapy given once a week for six weeks had the same effect as physiotherapy given three times a week for six weeks¹⁹³. The number of children experiencing one or more relapses during treatment ranges from 10 to 48%.^{189,194,309,334}

Conclusions

Level 3

There are indications that physiotherapy is helpful for children with CRPS-I. It is not clear what elements of physiotherapy are effective, as different forms of treatment are combined.

B Lee 2002¹⁹³
C Barbier 1999¹⁹¹; Kesler 1988³⁰⁹; Maillard 2004¹⁹²; Murray 2000¹⁹⁰; Sherry 1999¹⁹⁴; Wesdock 1999³³⁴; Wilder 1992¹⁸⁹

Level 3

There are indications that children with CRPS-I may relapse after receiving physiotherapy (10-48%).

B Lee 2002¹⁹³
C Barbier 1999¹⁹¹; Kesler 1988³⁰⁹; Maillard 2004¹⁹²; Murray 2000¹⁹⁰; Sherry 1999¹⁹⁴; Wesdock 1999³³⁴; Wilder 1992¹⁸⁹

Other considerations

Various different interventions are usually applied at the same time or in sequence: these include exercise therapy, massage, contrast baths and TENS^{189,194,309,334,337}. Psychologists are very often involved (in diagnosis and therapy) in the treatment of children with CRPS-I¹⁸⁹⁻¹⁹⁴.

Recommendation

The working group recommends that children with CRPS-I should receive physiotherapy treatment.

4.2.1 Occupational treatment of children

Introduction

Occupational therapists are often involved in the treatment of children with CRPS-I. However, little has been published on the occupational treatment of children with CRPS-I. Hardly any scientific research has been conducted into the effect of occupational therapy in children with CRPS-I and/or very few publications on this topic can be found.

Scientific support

Overall, the objectives of treating children with CRPS-I can be the same as those of treating adults.

An intensive treatment programme, comprising occupational therapy, physiotherapy and hydrotherapy, has appeared to be effective¹⁹⁴. We recommend multidisciplinary treatment, including occupational therapy¹⁹².

No conclusions can be drawn from the existing literature on occupational therapy in children with CRPS-I as to the comparative efficacy of this and other treatments.

Conclusion

Level 3

There are indications that occupational therapy can be beneficial as part of a multidisciplinary approach to treating children with CRPS-I.

C Maillard 2004¹⁹²; Sherry 1999¹⁹⁴

Recommendation

The working group advises that occupational therapy should be a component of multidisciplinary treatment for children with CRPS-I.

4.2.3 Psychological aspects of CRPS-I in children

4.2.3.1 *Diagnosis*

There are some indications that psychological factors may be involved in the aetiology of children with CRPS-I, though the evidence is weak. Psychological investigation found emotional problems in around 83% of children with CRPS-I¹⁹¹. However,

another study using the Brief Symptom Inventory (BSI, an abbreviated form of the SCL-90)¹⁹⁴ found no serious psychopathology, though this study did find a strong mother-daughter relationship (parentification) in almost all cases during the course of the clinical interview.

4.2.3.2 Treatment

Advice on treatment is based on findings in studies of CRPS-I in adults. Hardly any scientific research has been carried out into the psychological treatment of children with CRPS-I.

Cognitive behavioural therapy has been studied in combination with physiotherapy as a method of treating children with CRPS-I¹⁹³. However, the cognitive behavioural therapy applied in this study consisted of relaxation therapy and biofeedback, which is not specifically cognitive behavioural therapy. It is unclear what exact cognitive behavioural therapy techniques were used. Comparison of 'cognitive behavioural therapy', physiotherapy and TENS shows that all three treatments have a variety of effects. It is not possible to ascertain from this study which of these three treatments is most effective. Cognitive behavioural therapy (in this case relaxation therapy and biofeedback) improved both pain symptoms and physical function in 57% of cases¹⁸⁹.

Conclusion

Level 2

No conclusions can be drawn as to the effect of cognitive behavioural therapy on children with CRPS-I.

B Lee 2002¹⁹³; Wilder 1992¹⁸⁹
C Sherry 1988¹⁹⁴

Other considerations

No psychological questionnaires devised specifically for children with CRPS-I have been investigated. In general, there are hardly any questionnaires validated for children. Practitioners considering treatment could use clinical interviews, drawings of the body

and visual analogue scales (VAS). Sometimes, consideration could be given to using the Netherlands Personality Questionnaire for children (NPV-J) and/or the Child Behaviour Check List (CBCL). Treatment for children with CRPS-I focuses mainly on the consequences of the symptoms, as does treatment for adults. Research carried out in the United States indicates that cognitive behavioural therapy, which can include relaxation methods, is effective. It is important to realise that the term 'cognitive behavioural therapy' has become somewhat muddled: in the US it often comes down to relaxation therapy and biofeedback, while in the Netherlands it involves learning to cope with the disease. When treating children it is advisable to include the parents or the entire family in the therapy. Contraindications in children are age-dependent. If direct contact with the child is necessary to carry out a procedure, it is important that the child has the necessary intellectual maturity to reflect on how his or her body functions and to control his or her own behaviour. Some children are able to do this before the age of ten. Play or mediation therapy could be appropriate for young children. In the case of mediation therapy, the parents would be the 'behaviour-influencing agents'.

Recommendation

Psychological diagnosis and treatment of children with CRPS-I should ideally be carried out by a psychologist specialising in children or adolescents.

Chapter 5

Communication, information and prevention

5.1 Communication and information

Introduction

Patient information covers the provision of information to patients, may influence their emotions and attitudes, and change their behaviour. Patient information should relate to the problems experienced by the patient and the strategies he or she uses to deal with them. Patient information, psychosocial support and help with altering behaviour are all closely interconnected.

Patients with CRPS-I often feel very insecure. The pathophysiology and course of their condition are unknown, and it is impossible to predict how patients will respond to treatments. That is why good communication between practitioners and patients about the syndrome is so important. One of the other reasons for this is that the condition can be very disabling, having a strong impact on the physical, mental and social well-being of the patient and his or her family. Good support seems to be essential in helping them deal with both psychosocial and physical problems.

5.1.1 Provision of information to patients and their relatives

Scientific support

We did not find any research into the effects of providing information to patients with CRPS-I.

Conclusion

Level 4

There is probably no scientific research into the effects of providing information to patients with CRPS-I.

Other considerations

Information is not unidirectional. A style of communication in which the doctor gives information not just about physical symptoms but also about emotional aspects and consequences for quality of life is connected to greater patient satisfaction and even to improved health³³⁸.

Practitioners must be aware of their own attitude and role when communicating with patients. The practitioner's views on the syndrome and the behaviour that results from it do have an impact on the patient. Prognostic statements must of course be accurate. Taking the condition too lightly, using phrases such as 'not that serious', or 'to be expected', should be avoided, as should excessively gloomy statements such as 'very serious' or 'highly disabling', because these can cause patients to adopt a defeatist and unnecessarily anxious attitude.

Active listening is just as important a part of diagnosis as are looking, feeling and measuring. Information is an integral part of treatment, and must be just as obvious a part of medical care as drugs and invasive treatment.

Giving information is more than just reading out a text from an information brochure. Information that makes a connection with the patient's feelings and expectations is taken on board more readily by the patient. People have a need to know and understand things, and to feel that they have been heard and understood as well. As with all other patients, talking with and listening to patients (and their families) is an important part of the diagnosis, treatment and support of patients with CRPS-I.

Practitioners are advised to involve relatives in the process of giving information, as it often seems that the information given is not (fully) heard or remembered by the patient. In addition, chronic disabling conditions such as CRPS-I have a significant impact on relatives,^{231,339-341} and so involving them in the information process often leads to greater understanding and better support.

Written information is a vital complement to verbal information.

Recommendation

The project group is of the opinion that all doctors and other medical professionals engaged in consultation with CRPS-I patients should actively inform and listen for physical symptoms, behaviour and social factors, and offer targeted and appropriate information.

Written information should be given as a back-up to verbal information provided by the medical professional, and must not be used as a substitute for such verbal information.

5.2 CRPS-I and work

5.2.1 Employment limitations and job losses due to CRPS-I

It is estimated that 5,000 to 8,000 new cases of CRPS-I appear in the Netherlands each year. Five percent of these cause long-term, severe symptoms³⁴². The Netherlands Association of Post-traumatic Dystrophy Patients has around 4,000 members, most of whom are facing moderate to severe limitations. Young adults and women are over-represented in the CRPS-I patient population. CRPS-I is associated with limitations such as muscle weakness, mobility impairment and coordination problems that can make it difficult for sufferers to function effectively in everyday life and at work. Tests measuring the mobility of shoulder, wrist and hand joints and pinching strength in patients five to nine years after the onset of CRPS-I show significantly worse results on the affected side than on the unaffected side³⁴³. Furthermore, many patients continue to experience pain at low and/or high temperatures, lack of muscle strength and loss of dexterity long after developing CRPS-I. Only 35% of patients reported no limitations at all in activities of daily living³⁴³.

In another study, three-quarters of patients reported limitations in carrying out activities of daily living, while three-quarters said that they experienced problems with work and leisure activities¹⁸⁴.

These limitations and symptoms mean that patients with CRPS-I are less able to carry out strenuous tasks at work and can find it difficult to hold down a job.

Conclusion

Level 3

CRPS-I is a condition that can be objectively described and is often associated with significant limitations that can impact on patients' ability to work.

C *Galer 2000¹⁸⁴; Geertzen 1998³⁴³; Veldman 1993³¹*

5.2.2 Social consequences of CRPS-I

Data from the Dutch Employers' Insurance Board indicate that in 2002 disability benefits of various kinds were paid to 2,443 individuals suffering from CRPS-I³⁴⁴. This accounted for 2.5% of all disability benefit payments. Seventy-seven percent of people with CRPS-I are women, and women account for 45% of all people in receipt of disability benefits. Eighty-one percent of people in receipt of disability benefit for CRPS-I were on the full rate of benefit (as opposed to 73% of the total population of disability benefit recipients). 396 new claims for disability benefit due to CRPS-I were accepted in 2002, and 150 people came off benefit. About 6% of patients with CRPS-I who were in paid employment were off work for over a year (at the time, this was the maximum period for which invalidity benefit could be paid) and half of all patients in paid employment did not seem to be working after five years³⁴⁵. Research carried out in the United States showed that 30% of patients who were initially in work returned to their old job after approximately one year, and about half still seemed to be in paid employment of some kind.³³⁰ As the duration and severity of CRPS-I varies, it is not possible to predict how long someone with CRPS-I will be completely or partly unable to work.

5.2.3 Workplace factors causing CRPS-I

A status survey of 13 patients being treated in a third-line pain centre in the United States found that 6% of them had suffered an injury at work¹⁸³. Groups at high risk of developing CRPS-I included police officers, construction workers and farmers. In the Netherlands around 110,000 people a year attend the casualty department of hospitals as a result of accidents at work. At least a quarter of these accidents, which include sprains, dislocations, fractures and crush injuries, can lead to CRPS-I³⁴⁶. In 2003 4.5% of Dutch workers suffered an accident at work involving physical injury³⁴⁷. This figure rises to around 15% for workers who are often required to work under pressure. The most risky sectors of employment (accident percentages > 10%) are construction, police, agriculture, engineering, the food industry, and culture, sports and recreation. The main causes of accidents for all categories of workers are: trips and slips (11.5 %), cuts and stabs (8.5 %), falls from heights (8%), collisions (5.5 %) and getting trapped (5.2%). This is sufficient reason to prevent accidents at work and thereby avoid an unknown number of cases of CRPS-I. This could be achieved by, for example, improving working conditions and reducing excessive pressure on workers. CRPS-I can be caused by work-related carpal tunnel syndrome (CTS), or as a result of surgery to treat this condition, as well as by an accident at work. However, the reported incidence of CRPS-I following carpal tunnel release is low (2%). The project group has therefore decided to ignore these indirect work-related effects, and refers readers to the CTS EBGD guidelines for more information on 'CTS and work'³⁴⁸.

The project group considers that CRPS-I is not a major problem in terms of occupational disease.

5.2.4 Work factors that cause problems

Research carried out by the American CRPS-I patient organisation indicates that 38% of them were unemployed as a consequence of the syndrome, 21% had given up paid employment, 79% said that they suffered an increase in pain symptoms as a result of work and movement, and 63% reported continuous problems due to pain while working (18% reported occasional problems due to pain)³⁴⁹.

The project group believes that a number of general principles apply to people who continue working while suffering from CRPS-I. A supportive attitude on the part of colleagues and especially direct superiors is important; the organisation should also ensure that the employee's working conditions are suitable and that the tasks he or she is asked to undertake are adjusted to take account of the condition.³⁵⁰ Adequate climate control (not hot or cold),^{342,343} a reduced workload for employees required to adopt postures and undertake movements that impose physical strain,^{1,343} greater flexibility with regard to working hours and travel to work, among other things, are important factors to workers with CRPS-I. Implementing these measures is often quite straightforward.

Conclusion

Level 4

Patients with CRPS-I who are in employment often recover more quickly and are more successfully reintegrated into the workplace if their direct superior is supportive, they receive help from medical practitioners focusing on their job, and if their working conditions and role are adjusted to take account of their condition.

D Detaille 2003³⁵⁰; Geertzen 1998³⁴³; Goris 2003³⁴²; Veldman 1993¹;

Opinion of project group members

5.2.5 Improving diagnosis, treatment and support

Recognition of the clinical syndrome of CRPS-I by first-line practitioners (GPs, (workplace) physiotherapists and company doctors) improves the prognosis as intervention can start at an early stage. The project group is strongly in favour of promoting awareness of CRPS-I so that it can be detected at an early stage. The Netherlands Association of Post-traumatic Dystrophy Patients points out that its members often encounter little understanding of their chronic pain symptoms on the part of doctors working for insurance companies. Officers working for the Dutch Employers' Insurance Board assess the claims of a small number of CRPS-I patients. Over the past few years, company doctors and doctors working for insurance firms have concentrated on what kind of work a patient could still undertake rather than on his or her (actual) limitations. They are increasingly reluctant to accept pain symptoms as a legitimate reason for not working.

Company doctors, and doctors working for insurance firms, apply a time-focused rather than a symptom-focused approach in terms of their sociomedical support. This approach can conflict with the advice of practitioners, who follow the adage 'with pain, no gain'. Patients with CRPS-I must not pass the pain threshold when placing stress on the affected limb. Both absolute rest and any perception of pain are to be avoided. Many patients will consider that working is completely out of the question if they must not pass the pain threshold. CRPS-I patients are less able to bear strain in the early stages of their condition as a result of sensitivity disorders, movement limitations or muscle weakness. As the duration of the condition extends, the kind of treatment suitable for CRPS-I patients becomes more similar to that suitable for patients with a chronic pain syndrome.

Different categories of doctors have different tasks and responsibilities when a patient is medically unfit for work.

Doctors treating the patient concentrate mainly on treating the symptoms. Company doctors look at how the amount of stress to which the patient can be exposed at the workplace can be adjusted in the light of the company's needs, and offer support. Doctors working for insurance firms assess the disability insurance claim (compensation for loss of ability to work).

The worker has a key role in reintegration into work, and must actively contribute by cooperating with treatment and accepting suitable work. The introduction of the Netherlands Gatekeeper Improvement Act in 2002 made employees and employers jointly responsible for reintegration. Employers have a duty to assist in reintegration by offering suitable work, even in another company if necessary. Company doctors, GPs and medical specialists can guide patient treatment with a view to restoring activity. It is important to ease the patient back into work at an early stage, rather than waiting until all the symptoms have disappeared, as it becomes increasingly difficult for patients to return to their (old) job the longer they have been off sick. Resumption of work, in an adapted role if necessary, can also help the worker with CRPS-I bear more strain and become more self-confident. (Partial) resumption of work is in the patient's interest in these cases.

Conclusion

Level 4

Sociomedical support aimed at increasing the patient's level of activity, and a time-focused rather than symptom-focused approach, are advisable with a view to promoting functional recovery and resumption of work by CRPS-I patients.

D Opinion of project group members

It is essential that the various (para)medical disciplines cooperate. This avoids duplication of tests, time-wasting and confusion, for example if conflicting advice is given. Consultation offers the chance to draw on the experience of other practitioners and to streamline treatment and support. However, this cooperative approach can make the patient/worker vulnerable, as health is an important factor for his or her position on the labour market. Careless exchange of information about a patient's health can undermine this position. Great care is essential in order to protect the patient's privacy and maintain medical confidentiality. The patient's consent (ideally in writing) must be obtained before any information is exchanged between a doctor treating the patient and his or her company doctor³⁵¹.

Recommendations

Company doctors should assess whether workplace adjustments or organisational measures are needed to allow a patient with CRPS-I to work without damaging his or her health and, if such adjustments or measures are needed, what form they should take. This process involves weighing up the stress involved in a job and the patient's ability to bear such stress.

The project group recommends that the diagnosis of Complex Regional Pain Syndrome Type I (with the secondary terms 'Sudeck's atrophy' and 'post-traumatic dystrophy') should be added to the health and safety and social insurance scheme's classification system under 'Disorders of the nervous system'.

If it appears that a time-focused approach is not feasible for CRPS-I patients, or if insufficient information is available for an assessment of the amount of stress that the patient can bear, then the company doctor should consult the treating physician.

5.3 Prevention of CRPS-I

Introduction

Prevention of CRPS-I can be subdivided into primary and secondary prevention. Primary prevention is understood as the prevention of CRPS-I in patients who have never had CRPS-I before and who need to have surgery on a limb, or who have recently suffered trauma to a limb. Secondary prevention (prevention of relapse) is the prevention of CRPS-I in patients who have had CRPS-I in the past.

5.3.1 Primary prevention

5.3.1.1 Vitamin C

Scientific support

In a randomised double-blind trial, patients with a wrist fracture treated with a plaster cast were referred for treatment with vitamin C (500 mg/day for 50 days) or a placebo. They had been diagnosed with CRPS-I on the basis of Veldman's criteria (slightly modified). Seven percent of patients in the group taking vitamin C developed CRPS-I, as against 22% of patients in the control group (absolute risk reduction 15%, and number needed to treat 7).¹⁷¹

In a cohort study, patients with wrist fractures treated by surgery were given vitamin C (1.000 mg/day for 45 days). The percentage of patients developing CRPS-I was compared with the percentage of a historic cohort that had not been treated with vitamin C. Two percent of patients in the group treated with vitamin C developed CRPS-I, compared with 10% in the control group³⁵².

Conclusion

Level 2

It is likely that oral administration of 500 mg of vitamin C per day for 50 days from the date of the injury reduces the incidence of CRPS-I in patients with wrist fractures.

A2 *Zollinger 1999*¹⁷¹
B *Cazeneuve 2002*³⁵²

Recommendation

In order to reduce the risk of CRPS-I in adults who have had a wrist fracture, the prescription of 500 mg of vitamin C to be taken orally for 50 days should be considered.

5.3.1.2 Guanethidine

Scientific support

In a randomised study, patients scheduled for surgery for Dupuytren's disease were referred for preventive intravenous guanethidine blockade or a placebo blockade. Patients were diagnosed with CRPS-I if they were suffering pain and two other symptoms which were worsening over time, such as temperature change, colour change, swelling, and excess sweating. After eight weeks 13% of the patients taking guanethidine were found to have developed CRPS-I, as against 6% in the control group.³⁵³

Conclusion

Level 3

There are no indications that perioperative intravenous guanethidine in patients undergoing fasciectomy for Dupuytren's disease has any effect on the incidence of CRPS-I.

A2 *Gschwind 1995*³⁵³

Other consideration

Guanethidine is no longer available in the Netherlands.

Recommendation

Perioperative administration of intravenous guanethidine is not advised for primary prevention of CRPS-I.

5.3.1.3 Calcitonin

Scientific support

In a double-blind randomised study, patients undergoing wrist, knee or foot surgery were referred for 100 IU of thyrocalcitonin administered subcutaneously (from the day of the operation or the trauma once a day for one week and three times a week for three weeks thereafter) or placebo injections. The diagnostic criteria for CRPS-I were pain, edema, trophic disorders and radiological demineralisation. Eight percent of patients in the group treated with calcitonin developed CPRS-I, compared with 13% in the control group. However, this difference was not significant³⁵⁴.

Conclusion

Level 3

There are no indications that subcutaneous administration of calcitonin for four weeks from the onset of the trauma or from the date of surgery can prevent patients developing CRPS-I (primary prevention).

*B Riou 1991*³⁵⁴

Recommendation

Perioperative administration of subcutaneous calcitonin is not advised for primary prevention of CRPS-I.

5.3.2 Secondary prevention

Scientific support

Various interventions or combinations of interventions aimed at preventing relapse of CRPS-I have been described, but little adequate research has been carried out.

Despite a combination of interventions aimed at preventing relapse of CRPS-I (waiting until the symptoms of CRPS-I had abated, minimising the amount of blood removed from the patient's body during surgery, administering vasodilators to encourage circulation, sympathetic blockades and mannitol), relapse appeared to occur in 13% of patients³⁵⁵. Six percent of patients who had had CRPS-I in the past and were being treated with calcitonin (100 IU a day s.c. for four weeks) underwent a relapse of CRPS-I, as against 28% of patients in the historic control group. The criteria for CRPS-I were not stated³⁵⁶. A retrospective study found that perioperative stellate ganglion blockade carried out to prevent a relapse of CRPS-I was unsuccessful in 10% of cases. The relapse rate in an untreated control group was 72%³⁵⁷.

Theoretically, optimal pre, per and post-operative analgesia should prevent sensitisation of the central nervous system and also reduce the incidence of CRPS-I. A retrospective study found that 1% of patients undergoing pre-emptive analgesia (comprising administration of paracetamol and NSAIDs starting before surgery) combined with a regional anaesthesia technique and a fixed post-operative drug regime consisting of paracetamol, NSAIDs and oxycodone (multimodal analgesia) experienced a relapse of CRPS-I. The CRPS-I relapse rate for a control group, taking painkillers only as required after surgery, was 4%³⁵⁸.

In a randomised double-blind study, patients with a prior history of CRPS-I in the hand or arm scheduled for hand or arm surgery were referred for intravenous regional blockade in the form of lidocaine and clonidine (1 µg/kg) or lidocaine alone. The CRPS-I relapse rate for patients treated with clonidine was 10% as against 74% in the control group³⁵⁷.

Experts consider that it is best to wait until the symptoms of CRPS-I have disappeared before performing surgery. Patients should ideally be given regional anaesthetic, such as brachial plexus block and epidural anaesthesia. This preference is based on a number of case descriptions in view of the importance of optimally protecting the central nervous system against damaging painful peripheral impulses and in the light of the sympathetic blockade which accompanies regional anaesthesia³⁵⁸.

Conclusions

Level 3-4

Despite the lack of evidence, the project group is of the opinion that:

- it is best to wait until the signs and symptoms of CRPS-I have abated before conducting surgery on patients with CRPS-I;
- patients should ideally be given regional anaesthetic, such as brachial plexus block and epidural anaesthesia.

There are indications that stellate blocks and intravenous regional anaesthesia using clonidine (not guanethidine) offer protection.

There are indications that the use of multimodal analgesia offers protection.

There are indications that daily administration of 100 IU of salmon calcitonin s.c. (perioperatively for four weeks) can prevent a relapse of CRPS-I.

Mannitol has not been shown to offer any protection against relapse of CRPS-I.

A2 *Reuben 2004*³⁵⁸

B *Kissling 1991*³⁵⁶

C *Veldman 1995*³⁵⁵

Other considerations

In general it seems sensible to wait until the signs and symptoms of CRPS-I have abated before performing surgery on an individual with CRPS-I³⁵⁵⁻³⁵⁹. However, it may be that one factor is maintaining the CRPS-I (trigger point) and the surgery is intended to deal with this factor. Under these circumstances surgery should not be postponed³⁵⁵. Surgery on cold, oedematous limbs is probably contraindicated³⁵⁵.

There is no experience with the use of calcitonin in the Netherlands.

Recommendations

Timing of surgery: It is recommended that surgery of the (previously) affected limb be postponed until the signs and symptoms of CRPS-I have almost disappeared. This does not apply to operations intended to eliminate an underlying factor that may be responsible for CRPS-I.

It is recommended that the duration of the operation and blood content be minimised.

Adequate pre-, per- and postoperative pain control is recommended.

Perioperative blockades of the stellate ganglion or *i.v.* regional blockades using clonidine 1 µg/kg (not guanethidine) can be considered in the case of upper-limb surgery in patients who previously suffered from CRPS-I.

The use of regional anaesthesia with a sympathicolytic effect (epidural/spinal analgesia, plexus brachialis blockade), either alone or in combination with general anaesthesia, can be considered in the case of surgery on patients who previously suffered from CRPS-I.

The perioperative use of calcitonin can be considered.

The perioperative use of mannitol to prevent CRPS-I is not recommended.

Summary of guidelines on Complex Regional Pain Syndrome type I

DEFINITION

The most recent definition produced by the IASP, the International Association for the Study of Pain, reads as follows:

Complex Regional Pain Syndrome is a term describing a variety of painful conditions following injury which appears regionally having a distal predominance of abnormal findings, exceeding in both magnitude and duration the expected clinical course of the inciting event, often resulting in significant impairment of motor function, and showing a variable progression in the course of time.

Complex regional pain syndrome type I (CRPS-I) is a condition that causes multiple problems for both patients and practitioners. The condition often starts in an arm or leg, usually following a trauma of some kind, and is characterised by a combination of autonomic, sensory and vasomotor symptoms.

DIAGNOSTIC CRITERIA

Recommendation

The clinical diagnosis of CRPS-I can be established using the criteria drawn up by Veldman et al. and the IASP. The working group prefers to use Veldman et al's criteria for the situation in the Netherlands. For scientific research it is recommended that patient groups be described using the criteria drawn up by Veldman et al. and/or the IASP and/or Bruehl et al.

Diagnostic criteria according to Veldman et al. (Veldman et al. 1993)

1. 4 or 5 of:

- Unexplained diffuse pain
- Difference in skin colour relative to other limb
- Diffuse edema
- Difference in skin temperature relative to other limb
- Limited active range of motion

2. Occurrence or increase of above signs and symptom after use
3. Above signs and symptoms present in an area larger than the area of primary injury or operation and including the area distal to the primary injury

Diagnostic criteria according to the IASP (Merskey et al. 1994)

1. Develops after an initiating noxious event (type I) or after a nerve injury (type II)
2. Spontaneous pain or allodynia/hyperalgesia that is not limited to the territory of a single peripheral nerve and is disproportionate to the inciting event
3. There is or has been evidence of edema, skin blood flow abnormality, or abnormal sudomotor activity in the region of the pain since the inciting event
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

Establishment of clinical symptoms:

If a diagnosis other than CRPS-I is suspected, blood tests and neurophysiological examinations must also be carried out

Diagnosis:

CRPS-I if:

1 four or five of:

- unexplained diffuse pain
- difference in skin colour
- diffuse oedema
- difference in skin temperature
- active movement impairment

2 symptoms develop or worsen on exertion

3 symptoms in an area larger than the area of the primary injury or surgery, and always distal to the primary injury.

Primary prevention:

- in the case of wrist fractures, vitamin C

Treatment:

Paramedical:

- physiotherapy according to a protocol
- occupational therapy according to a protocol

Drug treatment:

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

Secondary prevention (for existing or past CRPS-I):

- postpone surgery until CRPS-I symptoms have almost disappeared
- keep the operation as short as possible and try to prevent to operate without removing blood from the operated extremity
- adequate pre- and perioperative pain control

Consider:

- perioperative stellate ganglion block or administer regional *i.v.* anaesthesia (clonidine)
- anaesthesia with sympatholytic effect
- perioperative calcitonin

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

- consult a psychologist

In the case of allodynia/hyperalgesia:

- gabapentin

- carbamazepine
- amitriptyline/nortriptyline

In the case of dystonia, myoclonia or muscle spasms:

- oral baclofen, diazepam or clonazepam

In the case of cold CRPS-I:

- vasodilating medication

Communication and information:

- verbal and written
- involve relatives
- put patients in touch with patient association for CRPS-I

CRPS-I and work:

- have the patient's working conditions assessed by the company doctor
- consult the patient's company doctor / doctor treating him or her to establish how much strain he or she can bear

Treatment of children with CRPS-I:

- In addition to drug treatment, physiotherapy and/or occupational therapy
- if necessary, psychological support from a paediatric/adolescent psychologist

If ineffective:

- intrathecal baclofen at a specialised clinic

If ineffective:

- percutaneous sympathetic block

Other therapies:

If other therapies prove ineffective, you may consider:

- spinal cord stimulation at a specialised clinic

If recurrent infections occur, you may consider:

- amputation at a specialised clinic

Proposed modified research diagnostic criteria for CRPS-I (Bruehl et al. 1999)

1. Continuing pain which is disproportionate to any inciting event
2. Must report at least one symptom in each of four following categories
 - Sensory: reports of hyperesthesia
 - Vasomotor: reports of temperature asymmetry and/or skin colour change and/or skin colour asymmetry
 - Sudomotor/edema: reports of edema and/or sweating changes and/or sweating asymmetry
 - Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign 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/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)

Chapter 7

Future research and CRPS-I

Based on the literature identified and the extent of evidence found therein for the fundamental, epidemiological and therapeutic understanding of CRPS-I, we can conclude that further research is needed into each of the aspects discussed in these guidelines. Our understanding of the pathophysiology, diagnostics, epidemiology, prevention and medical, paramedical and psychological treatment of this condition is patchy, and the foundations for what knowledge we do have are limited. Scientific data is also lacking in respect of treatment-related aspects, such as the role of the multidisciplinary approach, problems relating to work and communication with the patient and his or her family and close friends.

The project group considers that particular attention needs to be paid to further development of the diagnostic process. This development must be accompanied by research into possible underlying pathophysiological mechanisms (such as genetic factors) associated with CRPS-I, with particular attention being paid to possible sub-groups of the condition related to these underlying mechanisms.

With regard to drug treatment, further investigation is needed into the efficacy of pain medication and the percutaneous sympathetic blockade. More research is also needed into the use of drugs and invasive treatment with children suffering from CRPS-I.

In terms of paramedical treatment, the emphasis must be placed on the difference between symptom-focused and time-focused approaches.

Research is needed into the effects of various interventions on more long-standing (chronic) CRPS-I and into a multidisciplinary approach to CRPS-I.

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Appendix 1

Diagnostic criteria

Kozin (1981): clinical diagnostic criteria for Reflex Sympathetic Dystrophy Syndrome (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 skin changes often present)

Possible RSDS

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

Doubtful RSDS

- Unexplained pain and tenderness in an extremity

Bonica (1990)

History of recent or remote accidental iatrogenic trauma or disease

Presence of a persistent pain that is burning, aching an/or throbbing in character

One or more of the following:

- Vasomotor and sudomotor disturbances

- Trophic changes, oedema of the limb, sensitivity to cold, muscle weakness or atrophy, or trophic changes. Relief of pain and modification of signs after regional sympathetic blockade

AAHS (1990)

Diffuse pain

- Hyperalgesia, hyperpathia or allodynia
- Loss of hand/foot function
- Any activity or motion impairment associated with the pain
- 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, atrophy of skin or subcutaneous tissue, oedema, blood flow increase, Sudeck's osteoporosis or characteristic bone scan.

Gibbons (1992)

- Allodynia or hyperpathia
- Burning pain
- Oedema
- Colour and hair growth changes
- Sweating changes
- Temperature changes
- Radiographic changes (demineralization)
- Quantitative measurement of vasomotor/sudomotor disturbance
- Bone scan consistent with RSD
- Response to sympathetic block

Score < 3: no RSD

Score 3 – : possible RSD

Score \geq : probable RSD

Veldman diagnostic criteria for RSD (Veldman et al. 1993)

1. 4 or 5 of:

- Unexplained diffuse pain
- Difference in skin colour relative to other limb
- Diffuse oedema
- Difference in skin temperature relative to other limb
- Limited active range of motion

2. Occurrence or increase of above signs and symptom after use

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

IASP-criteria for CRPS-I (Merskey et al. 1994)

1. Develops after an initiating noxious event (type I) or after a nerve injury (type II)

2. Spontaneous pain or allodynia/hyperalgesia that is not limited to the territory of a single peripheral nerve and is disproportionate to the inciting event

3. There is or has been evidence of oedema, skin blood flow abnormality, or abnormal sudomotor activity in the region of the pain since the inciting event

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

Wilson (1996)

- History of pain
- Allodynia, hyperalgesia or hyperesthesia

Two signs:

- Oedema
- Vasomotor changes: colour, temperature instability, asymmetry
- Sudomotor changes
- Trophic changes in skin, joint, nail, hair

- Impaired motor function (may include components of dystonia and tremor)

Proposed modified research diagnostic criteria for CRPS-I (Bruehl et al. 1999)

1. Continuing pain which is disproportionate to any inciting event
2. Must report at least one symptom in each of four following categories
 - Sensory: reports of hyperesthesia
 - Vasomotor: reports of temperature asymmetry and/or skin colour change and/or skin colour asymmetry
 - Sudomotor/oedema: reports of oedema and/or sweating changes and/or sweating asymmetry
 - Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign 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)

New criteria according the Budapest Task Force (Baron et al. 2005)

Categories of clinical signs or symptoms

1. Positive sensory abnormalities:
 - Spontaneous pain, Mechanical hyperalgesia, Thermal hyperalgesia, Deep somatic hyperalgesia, Vascular abnormalities, Vasodilation, Vasoconstriction, Skin-temperature asymmetries, Skin-colour changes, Oedema/sweating abnormalities, Swelling, Hyperhidrosis, Hypohidrosis
 2. Motor (M) or trophic (T) changes:
 - Motor weakness (M), Tremor (M), Dystonia (M), Coordination deficits (M), Nail or hair changes (T), Skin atrophy (T), Joint stiffness (T), Soft-tissue changes (T)
- Interpretation* Clinical use ≥ 1 symptoms of ≥ 3 categories each AND ≥ 1 signs of ≥ 2 categories each Sensitivity 0.8 , specificity 0.60 Research use ≥ 1 symptoms in each of the categories AND ≥ 1 signs of ≥ 2 categories each

Appendix 2

Pain ladder

Step 2.

Step 1 + weak opioid

Persistent or worsening pain

Step 1.

Paracetamol + NSAIDs ± adjuvant medication (gabapentin, carbamazepine, nortriptyline)

Figure 1 Graphic representation of the pain ladder

Modified WHO pain ladder

Step 1: Paracetamol + NSAIDs + adjuvant medication

Step 2: Step 1 + weak opioid

Appendix 3

Physiotherapeutic treatment protocol for upper-limb CRPS-I

The principal objective of the physiotherapeutic treatment protocol as developed by the physiotherapy department of St. Radboud University Medical Centre (Nijmegen, the Netherlands) is to enable the patient to gain the greatest possible degree of control over his or her symptoms.

A specific set of questions, VAS scales and tests carried out during inspections and physical examinations are used to gain an impression of the degree of segmental dysregulation and the extent to which pain can be managed. The treatment programme is set up on the basis of the information obtained. It comprises a number of physiotherapy instruments such as support, exercise therapy, improving skills and relaxation therapy.

The key components of this protocol are:

- Increasing the degree of control over the pain and improving the way the patient copes with the syndrome, for instance by giving him or her information and support (recording and discussing a programme of daily activities) or relaxation exercises.
- Extinguishing the source of pain and treating any dysregulation, for example by performing exercises to attenuate pain, desensitisation, or the use of a sling or splint.
- Improving skills, for example by practising compensatory skills, training skills, and posture and movement instruction. The patient's need for (and interest in) help will determine the specific exercises carried out at a later stage.

Efforts to improve mobility can start as soon as the pain is 'under control'. The emphasis here will be on active and functional movement. Attention needs to be paid throughout the entire course of treatment to maintaining as normal a posture and movement pattern as possible and to preventing changes to adjacent joints and muscles (for example, changes brought about by contraction).

Appendix 4

Standard occupational therapy for upper-limb Complex Regional Pain Syndrome type I

The 'Standard occupational therapy for upper-limb Complex Regional Pain Syndrome type I' describes the occupational therapeutic diagnosis and treatment of the condition.

This Standard describes the instruments used to establish the occupational therapeutic diagnosis: the intake interview, visual analogue scale (VAS), video recording, Radboud Sensitivity Assessment (RSA), Radboud Skills Test (RST), Canadian Occupational Performance Measure (COPM) and optional instruments such as the activities registration list, the goniometer and the Jamar pinch tester.

The occupational therapeutic treatment section describes interventions in the light of four treatment objectives. According to this Standard, the general occupational therapeutic objectives when treating patients with upper-limb CRPS-I are:

1. to reduce clinical symptoms, and protect and support the affected limb in the most functional and comfortable position by means of a splint, and explanation and advice (see above). The practitioner will decide whether the patient should be measured for a supportive splint. This could be a resting splint for the entire hand and forearm, or for part thereof (wrist or thumb, for instance). Patients are instructed individually on how to wear the splint. The aim of wearing an orthotic device is to minimise symptoms and prevent overstrain;
2. to normalise sensitivity by carrying out an extensive desensitisation programme;
3. to encourage the functional use of the limb within the pain threshold. Various play activities, dexterity techniques and/or everyday activities are carried out for this purpose;
4. to encourage independence, particularly with regard to self-care, productivity and relaxation. The strategies can be targeted at restoring the necessary skills, at learning to do things in another way (with one hand, for instance), or at advising the patient on devices he or she could use or sources of additional support and care that are available.

A decision is made as to which treatment objective is most urgent or most important after consulting the patient and the other practitioners involved.

Treatment is assessed regularly by means of measurement and observation instruments in order to ascertain whether treatment should continue or can be stopped.

Appendix 5

Nomenclature

Anaesthesia	complete loss of sensitivity (painless)
Hypaesthesia	diminished non-painful sensitivity
Dysaesthesia	abnormal sensation, described as 'pins and needles'; unpleasant and nagging sensation, but not really painful (synonymous with paresthesia)
Hyperalgesia	painful sensation; slight contact with the skin causes obvious pain; characterised as lowered pain threshold with elevated pain response to normal stimulus
Hyperpathy	prolonged pain in response to stimulus
Allodynia	evident pain in response to a non-painful stimulus
Neuromatous pain	sensitive area following local peripheral nerve condition; percussion of the neuroma causes paresthesia in the area of the affected nerve
Causalgia	burning pain and hyperalgesia in the course of an affected peripheral nerve
Sudomotor activity	sweat secretion; caused by changes to sweat secretion and/or asymmetry in sweat secretion
RSD	Reflex Sympathetic Dystrophy
SRD	Sympathetic Reflex Dystrophy

CRPS-I

Complex Regional Pain Syndrome type I: the classic dystrophy, formerly known as RSD

CRPS-II

Complex Regional Pain Syndrome type II: caused by nerve injury, formerly known as causalgia

Appendix 6

Details of the Netherlands Association of Posttraumatic Dystrophy Patients

Office of the Netherlands Association of Posttraumatic Dystrophy Patients

PO Box 31157

6503 CD Nijmegen (The Netherlands)

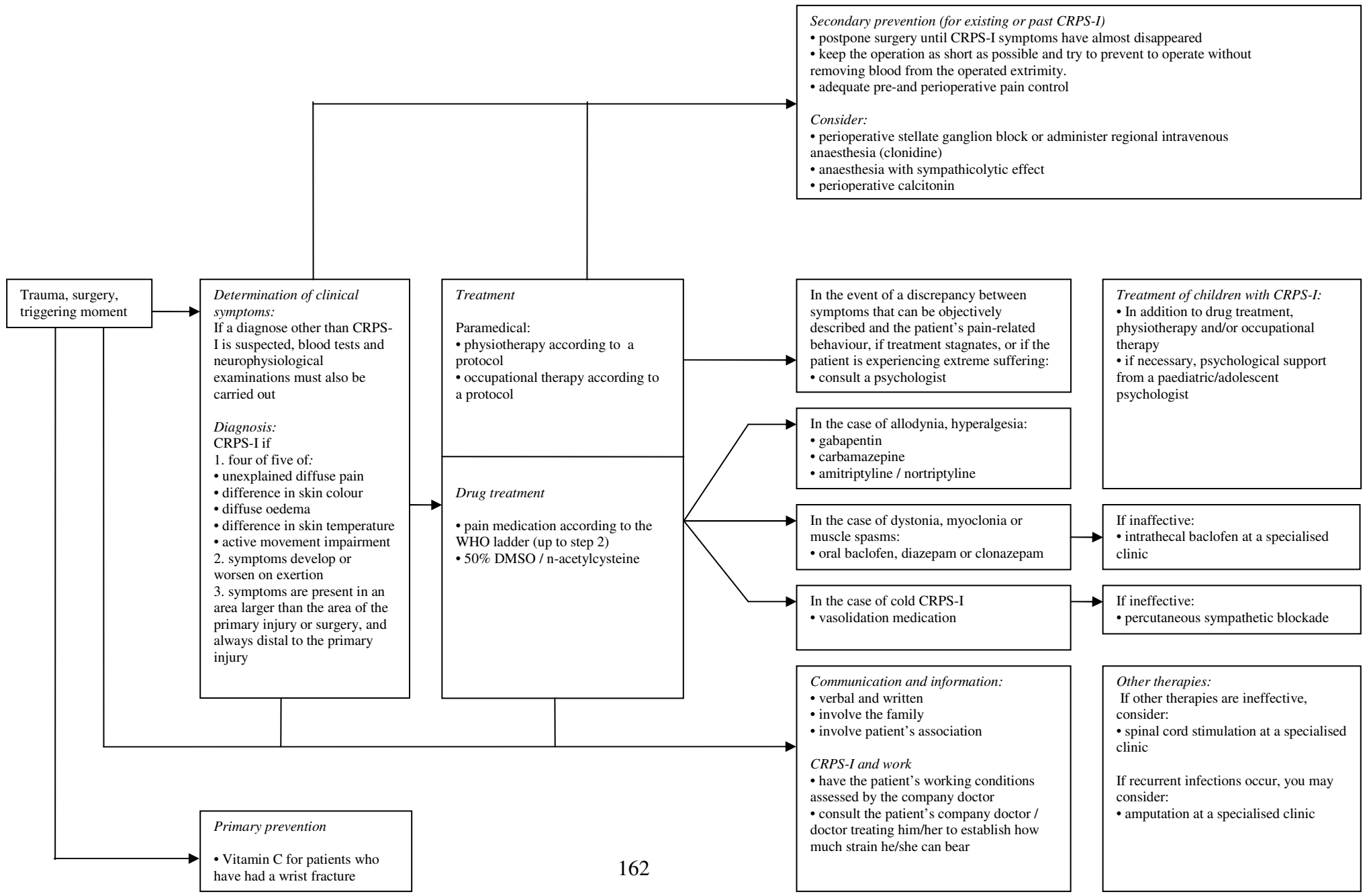
Website: www.posttraumatischedystrofie.nl

On the website you can find the English version of the guidelines for professionals, as well as the English version for patients.

Please contact the national telephone helpline or write to the office to obtain information about CRPS-I (known as posttraumatic dystrophy in the Netherlands) or the Association.

National telephone helpline: 0031 - 13 4554951. The helpline operates from 9.30 a.m. to midday and from 2.00 p.m. to 4.30 p.m. Mondays to Fridays.

The Netherlands Association of posttraumatic Dystrophy has 4,000 registered members and a network of 80 volunteers.



Trauma, surgery, triggering moment

Determination of clinical symptoms:
 If a diagnose other than CRPS-I is suspected, blood tests and neurophysiological examinations must also be carried out

Diagnosis:
 CRPS-I if

- four of five of:
 - unexplained diffuse pain
 - difference in skin colour
 - diffuse oedema
 - difference in skin temperature
 - active movement impairment
- symptoms develop or worsen on exertion
- symptoms are present in an area larger than the area of the primary injury or surgery, and always distal to the primary injury

Primary prevention

- Vitamin C for patients who have had a wrist fracture

Treatment

Paramedical:

- physiotherapy according to a protocol
- occupational therapy according to a protocol

Drug treatment

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

Secondary prevention (for existing or past CRPS-I)

- postpone surgery until CRPS-I symptoms have almost disappeared
- keep the operation as short as possible and try to prevent to operate without removing blood from the operated extremity.
- adequate pre-and perioperative pain control

Consider:

- perioperative stellate ganglion block or administer regional intravenous anaesthesia (clonidine)
- anaesthesia with sympathicolytic effect
- perioperative calcitonin

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

- consult a psychologist

Treatment of children with CRPS-I:

- In addition to drug treatment, physiotherapy and/or occupational therapy
- if necessary, psychological support from a paediatric/adolescent psychologist

In the case of allodynia, hyperalgesia:

- gabapentin
- carbamazepine
- amitriptyline / nortriptyline

If ineffective:

- intrathecal baclofen at a specialised clinic

In the case of dystonia, myoclonia or muscle spasms:

- oral baclofen, diazepam or clonazepam

If ineffective:

- percutaneous sympathetic blockade

In the case of cold CRPS-I

- vasodilation medication

Communication and information:

- verbal and written
- involve the family
- involve patient's association

CRPS-I and work

- have the patient's working conditions assessed by the company doctor
- consult the patient's company doctor / doctor treating him/her to establish how much strain he/she can bear

Other therapies:

If other therapies are ineffective, consider:

- spinal cord stimulation at a specialised clinic

If recurrent infections occur, you may consider:

- amputation at a specialised clinic

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Summary of Complex Regional Pain Syndrome type 1 Guidelines
The full text of these guidelines is available on www.cbo.nl