Complex Regional Pain Syndrome *An unrecognized presentation* confined to the Knee

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Complex Regional Pain Syndrome confined to the Knee, an unrecognized presentation

Complex regionaal pijn syndroom van de knie, een onbekendheid

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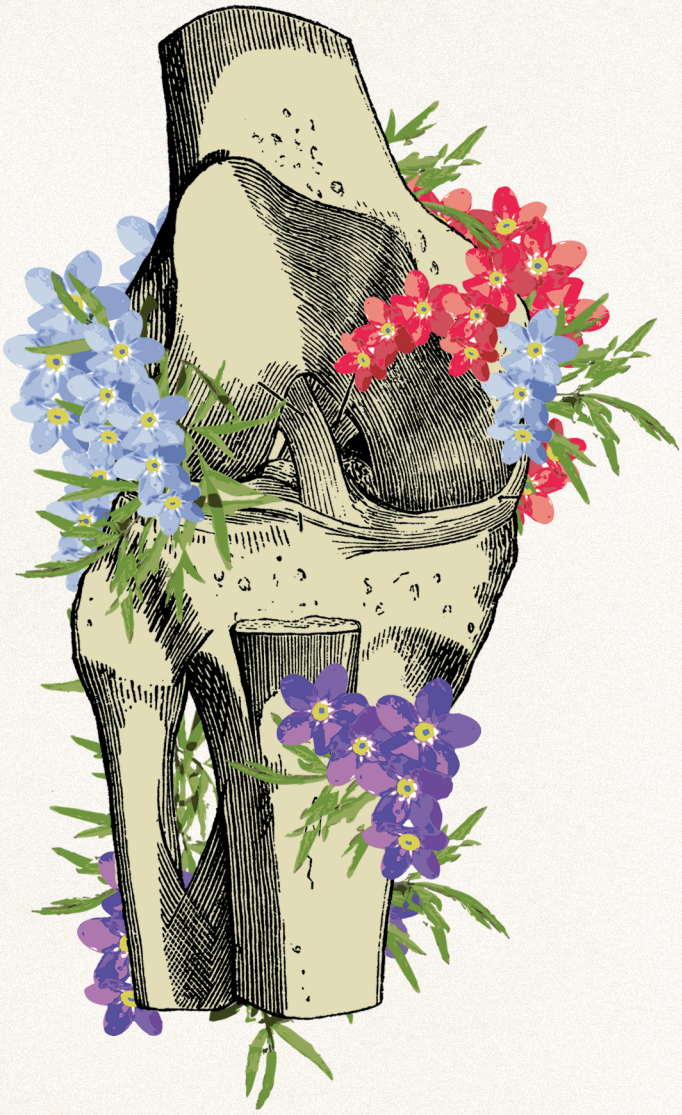

CHAPTER 1

General introduction

THE HISTORY OF COMPLEX REGIONAL PAIN SYNDROME (CRPS)

Sudeck was one of the first to describe complex regional pain syndrome (CRPS), in 1900 (1). One of his students called the clinical picture *Sudeck's atrophy* and integrated a classification of it that described five forms of the disease: 1) nutritional atrophy, 2) disuse atrophy, 3) senile atrophy, 4) acute inflammatory reflex atrophy and 5) neuropathic atrophy (2). The next (and most-used) term for this disease became *reflex sympathetic dystrophy (RSD)* which was introduced in 1946 by Evans after he successfully treated several patients with pain using sympathetic blocks (3). Eventually, after a consensus meeting in 1993, the term *complex regional pain syndrome (CRPS)* replaced the concept of RSD and is now in general use (4). CRPS can be divided into two subtypes: i.e., CRPS type I for cases in which no nerve injury is detected and CRPS type II for cases in which nerve injury is confirmed. CRPS types I and II do not differ in clinical presentation. CRPS manifests itself often after fractures, sprains, contusions and/or crush injuries and exceeds, in both intensity and duration, the expected course of the original trauma (5). The diagnosis is even now purely based on the signs and symptoms, since there are no standard laboratory or imaging tests (6). Through the years, several diagnostic criteria sets have been formulated and used to diagnose CRPS: i.e., the Veldman criteria, the 'old IASP (International Association for the Study of Pain) criteria', the Bruehl and Harden criteria and the currently used Budapest criteria, which were accepted by the Committee for Classification of Chronic Pain of the IASP in 2012 as the 'new IASP diagnostic criteria for CRPS' (7-10). Since 1994, the IASP divides pain mechanisms into nociceptive and neuropathic pain. In 2011, the definition neuropathic changed from 'pain due to lesion or dysfunction of the nervous system' to 'pain caused by a lesion or disease of the somatosensory nervous system'. This change made it difficult to categorise CRPS patients, so in 2017 the IASP introduced a new mechanistic descriptor for 'pain characterized by evidence of altered nociceptive processing', such as CRPS. This new term is *nociplastic pain*, to reflect changes in function of nociceptive pathways (11).

PATHOPHYSIOLOGY

The exact pathophysiology of CRPS remains unknown, but there are several ideas about mechanisms proposed to play a role (12). Although spontaneous development is described, tissue damage typically seems to be the initial trigger for development of CRPS. It is a condition affecting the extremities and has a presentation during the acute phase with oedema, erythema, increase in temperature, impaired function and pain as a result of an inflammatory response to the initiating trauma (13, 14). Alternatively, neurogenic inflammation can also explain the presentation with oedema, erythema and increased sweating (15). Another mechanism that has been described is deep-tissue microvascular

ischaemia-reperfusion injury, which proposes that this injury is the cause of the abnormal pain sensations patients describe and experience in CRPS, such as allodynia (16). Furthermore, a decrease in sweat glands and vascular innervation combined with a decrease in epidermal nerve fibres caused by neuropeptides, could explain the trophic and vasomotor symptoms of CRPS (13). Physicians claim that CRPS patients have a specific, or even a special way of presenting themselves. This could imply a psychological factor in the development of CRPS. Several studies have failed to confirm this, but some evidence has been found of a role for stress, depression or anxiety in the maintenance of CRPS (17). In a prospective study, the researchers concluded that there is no association between psychological factors and the development of CRPS. In addition, it appears that psychological problems of CRPS patients are comparable to those of the normal population, and thus psychological changes may be a result of the chronic pain and disability (18). It is widely accepted that early diagnosis and multidisciplinary treatment are needed to prevent permanent disability (19). Patients diagnosed with CRPS are treated in the Netherlands according to the Dutch CRPS treatment guidelines (last updated in 2014) (20). Previous research suggests possible subtypes, phenotypes and/or stages of the syndrome, which can influence the outcome of the chosen therapy (4, 21). This may suggest the strategy for CRPS treatment should be changed to therapy based on the underlying mechanism (22).

NEUROSTIMULATION

Spinal cord stimulation (SCS) is a proven, effective treatment for CRPS pain, and is a direct clinical application of the gate theory by Melzack and Wall. In 1965, they described a new theory concerning pain, based on a thesis by Noordenbosch. Thin- (pain) and large-diameter (touch, pressure) nerve fibres carry information from the site of the injury to the dorsal horn of the spinal cord. From that point transmission cells carry the pain signal up to the brain, resulting in a painful sensation for the patient. Activation of A-beta nerve fibres, which do not transmit pain signals, can inhibit pain by interfering with these pain signals. This is a simplified model of a probably much more complex reality (23). In 1965, Shealy et al. were the first ones to introduce SCS to reduce pain by activating these A-beta nerve fibres (24, 25). SCS is a common treatment internationally for CRPS when other therapies fail to provide relief. In 2000, a study by Kemler et al. described the results of treatment with SCS stimulation combined with physical therapy versus physical therapy alone for patients with CRPS. A total of 36 patients received test stimulation, of whom 24 received a definitive implantation of SCS, versus 18 patients who received only physical therapy. At 6 months follow-up, a statistically significant difference ($P < 0.001$) was found for the pain score on a visual-analogue scale in favour of the patients who received SCS combined with physical therapy (26). At 2-year follow-up, a clinically significant decrease in pain intensity

was found ($P < 0.001$), and patients stated that they were 'much improved', based on the global perceived effect scale (27). The same group published a 5-year follow-up in 2008 which revealed a diminished effect on pain relief over the years, but still 95% of the patients would undergo the treatment again if necessary (28). This is an interesting finding, but the criteria they used at baseline to diagnose CRPS were not completely in accord with the new IASP diagnostic criteria for CRPS, and some patients diagnosed with CRPS back in 2000 would probably not receive the diagnosis today. Also, CRPS is a dynamic disease that changes over time and has a natural course. Thus, the diminishing effect of SCS could be related to the change of the disease. A new neurostimulation system to treat chronic pain by stimulating the dorsal root ganglion (DRG) has been used commercially since 2012. The organisation of the DRG at each level of the spinal cord offers the possibility of stimulating specific dermatomes. SCS stimulation is more broadly applied, which can result in stimulation of an area much larger than the painful area (29). Van Buyten et al. used DRG stimulation in a group of 8 CRPS patients who experienced some degree of pain relief, persistent at 12-month follow-up. The researchers concluded DRG stimulation to be a promising option as a treatment for CRPS (30). The ACCURATE study, published in 2017, evaluated the efficacy of DRG stimulation compared to SCS for patients diagnosed with CRPS or causalgia (pain following peripheral nerve injury (31)) of the lower extremities. A total of 152 patients were included at baseline and received either DRG stimulation or SCS implantation after a successful trial phase. After 3 months of follow-up, the treatment success (≥50% pain relief compared to baseline) was greater in the group who received DRG stimulation (81.2%) than the SCS group (55.7%). Furthermore, at 12-month follow-up, the pain remained significantly lower for patients treated with DRG stimulation compared to patients with SCS. The authors conclude that DRG stimulation provides precisely targeted stimulation which is beneficial compared to SCS as a therapy for patients with CRPS or causalgia of the lower extremities (32). Although these results are encouraging in favour of DRG stimulation, more than 10% of the included patients suffered from groin pain, which is nearly impossible to treat with SCS, and groin pain is certainly not CRPS. In addition, not all included CRPS patients were diagnosed according to the new IASP diagnostic criteria for CRPS. Nevertheless, DRG stimulation seems to offer more-targeted stimulation than SCS, which has potential clinical implications. It may be possible to use DRG stimulation to treat patients with foot or knee pain, which are more difficult locations to target with SCS.

CRPS CONFINED TO THE KNEE?

In the last few years, we have seen a group of patients in our Center for Pain Medicine with pain and other symptoms and signs normally seen in CRPS but without a distal spread in the extremity, confined instead to just the knee(s). A specific diagnosis was not made

in most of these cases, and the complaints were symptomatically treated with several medications and/or invasive procedures. Over time, the thought arose that perhaps these complaints were due to CRPS, because the clinical picture of the patients had several similarities with this diagnosis, and that perhaps CRPS confined to the knee would be a clinical entity in its own right.

Ernst Baur appears to have been the first to describe patients with possible CRPS confined to the knee, reporting on three such patients in 1954, at least one of whom retrospectively would fulfil the Budapest criteria set based on the signs and symptoms described (33). Over the years, many different strategies have been used to confirm and/or diagnose CRPS confined to the knee in addition to the standard diagnostic criteria set. In line with Evans, pain relief from a lumbar sympathetic block was considered a confirmation of or an additional criterion for the diagnosis (34, 35). A retrospective study of 60 patients diagnosed with CRPS confined to the knee revealed that a surgical procedure (arthroscopic) was the most common event in developing CRPS (36). Several authors have concluded that CRPS is in fact an uncommon and unrecognized cause of knee pain that can follow some sort of trauma (37-39). This fact results in a delay in diagnosing and starting the appropriate treatment (40). Unfortunately, as earlier literature showed, patients with CRPS confined to the knee have responded poorly to any sort of treatment (34, 41, 42). Our own experience confirms the difficulty of treating these patients, because they have a temporary response or no response at all. Even with SCS we have seen mixed results. But as seen in other studies, DRG stimulation has the potential to treat difficult locations, so perhaps this therapy can be successful for patients with CRPS confined to the knee.

THIS THESIS

The aim of this thesis is to find the answers to our following research questions;

1. Is CRPS of the knee an existing clinical entity?
2. Is there a difference between the development of CRPS confined to the knee and that of CRPS of more distal locations (e.g., the ankle/foot or the wrist/hand)?
3. Is there a difference between the clinical course of CRPS confined to the knee and that of CRPS of more distal locations (e.g., the ankle/foot or the wrist/hand)?
4. Does DRG stimulation have a value in the treatment of CRPS confined to the knee?

In summary, we aim to confirm the location of, increase the knowledge of, facilitate the recognition of and provide a potential treatment for CRPS confined to the knee.

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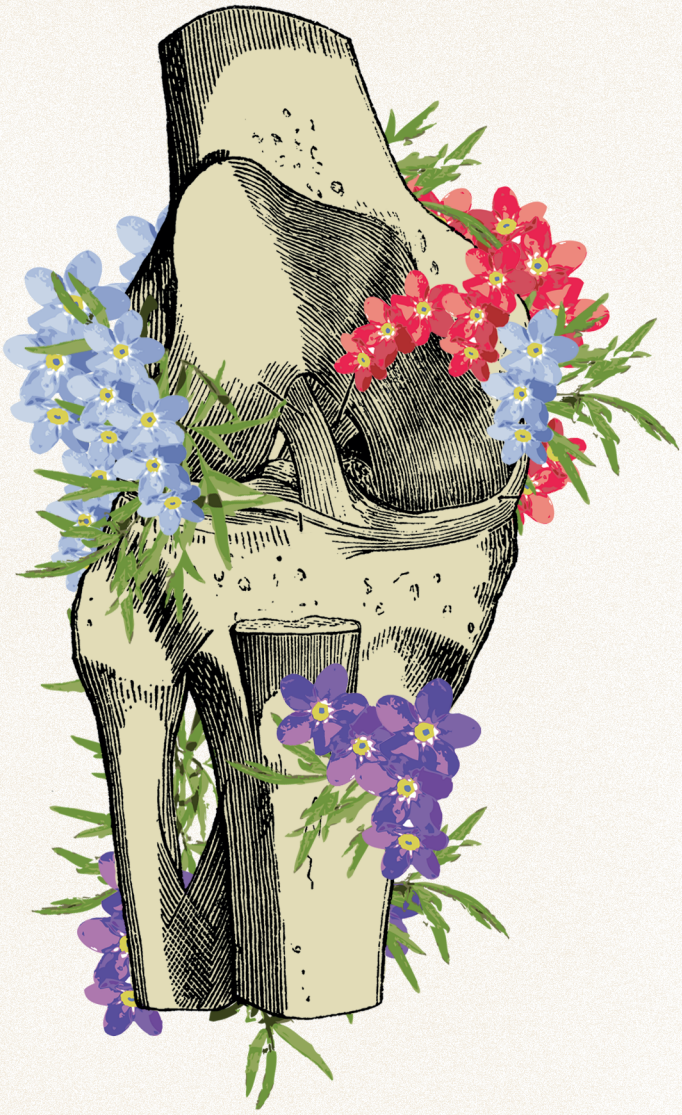

CHAPTER II

Complex regional pain syndrome type I of the knee: A systematic literature review

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ABSTRACT

Background and Objective: In our Center for Pain Medicine, a group of patients reported to have symptoms possibly attributable to complex regional pain syndrome (CRPS) of only the knee(s). Therefore, this study aimed to investigate whether the literature reports on patients with CRPS type I in the knee(s) alone and, if so, to summarize the reported diagnostics, aetiology and treatment strategies of CRPS of the knee(s).

Databases and Data treatment: Medline, Embase, Cochrane Library, PubMed and Web of Science were searched for articles focusing on a painful disorder of the knee, most likely CRPS type I. Screening on title and abstract was followed by full-text reading and searching of reference lists to determine the final set of relevant articles.

Results: Of the 513 articles identified, 31 met the inclusion criteria. These articles reported on a total of 368 patients diagnosed with CRPS of the knee(s) based on the diagnostic criteria used at the time of publication. Knee surgery, especially arthroscopic surgery, was the most common inciting event in developing CRPS of the knee(s). Various treatment strategies were applied with variable outcomes.

Conclusions: The scientific literature does report cases of CRPS type I of only the knee(s). This applies when using the diagnostic criteria prevailing at the time of publication and, obviously for a smaller number of cases, also when using the current Budapest criteria set. Arthroscopic knee surgery is described multiple times as the inciting event. We recommend to include CRPS of the knee in future research on the aetiological mechanisms of and optimal treatment for CRPS.

1. INTRODUCTION

Complex regional pain syndrome (CRPS) type I, formerly known as reflex sympathetic dystrophy (RSD) or algodystrophy, is a collection of locally appearing painful conditions following a trauma, which mainly occur distally in the affected limb and exceed in both intensity and duration the expected clinical course of the original trauma. The symptoms are not confined to the innervation zone of an individual nerve (1). Involvement of the whole extremity can occur. The main clinical features of CRPS are continuing pain, and sensory, vasomotor, sudomotor and motor trophic disturbances (2). CRPS is a clinical diagnosis based on signs and symptoms described in criteria sets and, over the years, different diagnostic criteria sets have been developed. Currently, the use of the Budapest criteria set is recommended (3). Laboratory tests and radiology have only limited additional value in the diagnostic process and are mainly used to exclude another diagnosis. The natural history of CRPS is not always positive and can result in permanent disability. Treatment remains a challenge because the underlying pathophysiologic mechanisms are only partly understood (4).

In our expert center for CRPS, we receive referrals from throughout the Netherlands and see many patients for a second opinion. Our interest was drawn by a group of patients with CRPS-like symptoms confined only to the knee(s); this was the rationale to perform this systematic review.

The following research questions were addressed: 'Are there any descriptions in the medical literature of complex regional pain syndrome type I only affecting the knee(s), and diagnosed with the criteria used at the moment of publication?' and 'If so, what does the literature report on diagnostics, etiology and treatment of complex regional pain syndrome type I affecting only the knee(s)?'

2. LITERATURE SEARCH METHODS

2.1 Search strategy

To find relevant articles, searches were made in Embase, OVID-SP, Cochrane Central, PubMed and Web of Science covering the period 21 December 2012 to 4 January 2013.

The search strategy was divided into elements for CRPS and those for the knee. For optimal results from all five databases, elements from both groups were applied in the correct format for the search in each database. Details on the strategies and results are given in Appendix 1.

2.2 Inclusion/exclusion criteria

Articles were not excluded on the basis of study design. After the search, the title and abstract of each article were checked for relevance. Because the search was made in different databases, Endnote X5 for Windows (Thomson Reuters, New York, NY, USA) was used to ensure that no article was included more than once. The main topic of the article had to be a painful disorder of the knee, most likely diagnosed as CRPS type I. The reference lists of the identified articles were checked for additional studies possibly missed by the search strategies.

Excluded articles had either the wrong main topic, e.g., patients suffered from CRPS type I in a location other than the knee, or patients were suffering from a partial CRPS type I. Partial CRPS type I was considered by authors of some articles as being a CRPS-like syndrome, not completely matching the criteria used at the time of publication. Other excluded articles described patients with CRPS of the knee attributable to verifiable nerve damage (this disorder was most likely CRPS type II). Also excluded were articles written in languages other than Dutch, English or German, because none of the authors mastered these languages, as well as studies involving children with CRPS aged ≤ 18 years.

3. RESULTS

After filtering with EndNote, the search resulted in 513 articles. After screening the titles and abstracts, 436 articles were excluded either because the main topic was incorrect, or children aged ≤ 18 years were involved, or the articles described CRPS as a result of nerve damage. This left 77 articles of which 26 were written in French, Italian, Spanish or Portuguese and were therefore excluded. This left 51 articles. After full-text reading of these papers, another 20 were excluded because CRPS was only considered as a differential diagnosis. This left 31 relevant articles to present in this review: 10 case reports, 10 case series, five retrospective studies, five prospective studies and one case-controlled study. Checking the reference lists of these articles yielded no additional relevant publications. A flow chart showing the in- and exclusion of the articles is presented in Appendix 2.

3.1 Diagnostics

3.1.1 Criteria sets

The 31 included articles comprised a total of 368 patients diagnosed with RSD, algodystrophy or CRPS based on criteria sets used at the time of publication. Table 1 shows how many patients (based on the symptoms mentioned in the articles) met the various criteria sets used over time in diagnosing CRPS, i.e., the criteria of Veldman, the International Association for the Study of Pain (IASP) criteria, the Bruehl and Harden criteria, and the Budapest criteria. In 187 patients, based on the symptoms mentioned in the articles, it

was not possible to confirm whether the patients met one or more of the criteria sets. Nevertheless, these patients were diagnosed by the authors as having RSD, algodystrophy or CRPS of the knee(s) (5-17).

Table 1. Multiple-response frequency table of the included patients meeting the criteria sets

	Meeting the criteria set		
Criteria set used:	n	%	**Percentage of cases**
Veldman	4	0.85	1.09
Bruehl and Harden	56	11.87	15.22
Budapest	79	16.67	21.47
IASP	148	31.52	40.22
Not possible to confirm	187	39.09	50.81
Total	474	100.00	128.81

Note: Because some patients met more than one criteria set, the percentage of cases does not sum to 100

3.1.2 Lumbar sympathetic blockade

Six articles were found in which the authors described using the relief of symptoms after a lumbar sympathetic blockade as a confirmation, or as an (additional) criterion, for diagnosing RSD or CRPS in patients with extensive knee pain.

The authors of five publications stated that CRPS can be confirmed by at least partial relief of the symptoms after receiving a lumbar sympathetic blockade, besides clinical appearance suggestive for RSD or CRPS. Of these, Cooper *et al*. and Braverman *et al*. reported on patients who matched the Bruehl and Harden, IASP, and the Budapest criteria set (4, 18). Because the authors of the other three publications did not describe (all) the symptoms patients were suffering from, we were unable to confirm their diagnosis of CRPS or RSD based on the criteria sets (8, 15, 16).

In contrast, Neuschwander *et al*. used (partial) relief of symptoms after a lumbar sympathetic blockade only as confirmation of the diagnosis CRPS or RSD (17).

3.1.3 Radiographs/Bone scans

In 13 articles, the authors used a form of radiology as a diagnostic tool or as a confirmation of the diagnosis of RSD, algodystrophy or CRPS of the knee.

Finsterbush *et al*. used abnormalities on a skyline view of the patellofemoral joint or a bone scan as an additional criterion (besides the clinical appearance of the patients) in diagnosing RSD of the knee (19). Malhotra *et al*. used a three-phase bone scan to substantiate the diagnosis of RSD, when RSD was suspected on the basis of clinical appearance (15).

Radiographic investigation of the knee showed patchy bone atrophy in five studies involving patients already diagnosed with RSD of the knee (5, 7, 9-11).

O'Brien *et al*. reported that 19 of the 60 patients diagnosed with RSD had positive findings on pre-treatment bone scans; they stated that if a patient had asymmetry of uptake in the knee(s) on the bone scan this is a supportive but not necessary finding in diagnosing RSD (16). Loew and Isakov *et al*. stated that pathological findings on a three-phase bone scan can be supportive in the clinical diagnosis of RSD of the knees. The scans revealed increased bone uptake in the patellae, femoral condyles or upper part of the tibia (2, 20).

In all patients who developed RSD or CRPS after renal transplantation, radiographs showed patchy osteopenia and bone scintigraphy showed increased uptake in the affected areas; the authors considered these findings as supportive in diagnosing RSD or CRPS (21-23).

3.2 Aetiology

3.2.1 CRPS after (arthroscopic) knee surgery

The authors of ten articles reported on patients with RSD or CRPS of the knee after undergoing (arthroscopic) surgery of the knee (6, 11-14, 16, 20, 24-26).

Cooper *et al*. reported on a group of 14 patients of whom 11 underwent a patellar operation before the onset of RSD symptoms (18). The authors of three articles reported on 32 patients who developed RSD of the knee after undergoing a total knee replacement (4, 13, 19).

Burns *et al*. compared eight patients with CRPS of the knee after total knee arthroplasty with patients who had no complaints after total knee arthroplasty and with patients with preoperative osteoarthritic knees; they stated that prompt diagnosis and early treatment is most important in treating CRPS of the knee (27). Others stated that CRPS should also be considered when a knee does not recover after knee surgery (8).

3.2.2 CRPS after trauma or injury

In 1954 three cases of RSD of the knee after a distortion or contusion were described by Baur (5). In 1995, Isakov *et al*. presented a case of RSD of the knees that developed after burning both knees (2). Miller reported a case of RSD after injuring the left knee; the patient felt a "twinge" and within two weeks developed intense pain and other symptoms (28). In another case, a left patella fracture and emergency surgery was complicated by developing CRPS (29).

A study of 67 patients with unexplained knee pain revealed (in retrospect) that 14 patients were suffering from RSD; all of these patients had injured one knee and had persistent complaints (9).

Ten studies described patients with RSD or CRPS of the knee after a minor twist, injury or trauma (10-12, 15-19, 26, 30, 31).

3.2.3 Non-traumatic CRPS

Two patients were described as being diagnosed with RSD or algodystrophy of the knee without a known trauma or injury before the symptoms occurred (7, 16).

The authors of three articles reported the occurrence of RSD in the lower extremities in patients after renal transplantation. A total of seven patients had severe pain in one or both of the knees and ankles; clinical examination revealed increased local temperature, trophic changes and periarticular soft tissue swelling (21-23).

Table 2. Number and percentage of reported eliciting factors

Aetiology	Number of cases (n)	Percentage (%)
Trauma or injury	197	53.53
(Artroscopic) knee surgery	162	44.02
Non traumatic	9	2.45
Total	368	100

3.3 Treatment

In the included articles many different strategies are described in the treatment of CRPS of the knee, with variable results.

In 11 articles, the authors mentioned the use of physiotherapy (besides other therapy) in patients with CRPS or RSD of the knee (2, 4, 7, 12, 14, 15, 19, 20, 24, 27, 29).

A lumbar sympathetic blockade was performed in 12 studies; this blockade was sometimes used as a single therapy and sometimes combined with another therapy, e.g., physiotherapy (4, 8, 11-14, 16-20, 25). Seven patients with the diagnosis CRPS of the knee were treated with intravenous regional anaesthesia with clonidine and the authors reported this to be a useful treatment in the management of CRPS of the knee, without significant side-effects (26). A study of 30 patients, all diagnosed with CRPS according to the IASP criteria, examined the efficacy of shockwave therapy in the management of CRPS of the medial femoral condyle; only one patient had persisting pathology signs on MRI at six months follow-up (32).

Ching *et al*. reported on a patient with Behçet's disease and CRPS of her left knee (diagnosed according to the Budapest criteria set). The patient was given thalidomide for the Behçet's disease, which resulted in an unexpected gradual improvement of the pain in her knee (30). Ogilvie-Harris and Roscoe described 19 patients suffering from extensive knee pain and (retrospectively) 11 of these patients met the IASP criteria in diagnosing CRPS; the remaining eight patients did not meet any of the criteria sets. All patients received non-steroidal anti-inflammatory drugs (NSAIDs) and intensive physiotherapy and, if a patient did not respond, he/she received a sympathetic blockade (12).

Burns *et al*. compared eight patients with CRPS of the knee (according to the Bruehl and Harden, IASP and Budapest criteria), which developed after a total knee arthroplasty,

with eight patients with uncomplicated total knee arthroplasty. All patients received NSAIDs and physiotherapy and, if needed, manipulation under anaesthesia. The authors concluded that, when managed early, patients complicated with CRPS after total knee arthroplasty have a similar prognosis to patients with uncomplicated total knee arthroplasty (27).

Mak *et al*. reported on a man with CRPS of the knee (diagnosed according to the Bruehl and Harden criteria set) that developed after a patella fracture; the patient received an infusion of bupivacaine with fentanyl for five days, continuous passive stretching at nighttime and daily physiotherapy, resulting in a pain score of zero and sustained improvement in mobilization and function (29). Another patient with the diagnosis algodystrophy of the knee received NSAIDs, prednisone and physiotherapy, and was considered to be cured after two years of therapy (7). Furthermore, the patient described by Malhotra *et al*. with RSD of the knee had almost complete relief of the symptoms after physiotherapy, microwave diathermy and NSAIDs (15).

Two case reports reported on patients with CRPS or RSD of the knee who, despite various pain medication, physiotherapy, transcutaneous electrical nerve stimulation (TENS) and passive motion, never became symptom-free of CRPS of the knee (24, 28).

The authors of seven studies state that therapy should be started as soon as possible to ensure the best outcome for patients (4, 11, 12, 14, 18, 19, 27). This is in contrast to a study performed by O'Brien *et al*. These authors included 60 patients diagnosed with RSD of the knee who were divided into three groups; early (< 6 months), medium (6-12 months) and late (>12 months) diagnosis. The study showed no difference between the three groups of RSD patients in outcome (knee pain, other knee symptoms and range of motion) after treatment (16).

4. DISCUSSION AND CONCLUSIONS

This review investigated whether the literature describes patients suffering from CRPS type I of only the knee(s) and, if so, what the aetiology, diagnostics and treatment were in those patients.

4.1 Limitations in the inclusion of articles

Our search included descriptions of CRPS, RSD, algodystrophy, and derivatives of these terms and descriptions of the knee. CRPS, RSD and algodystrophy are only three of the many descriptions used over the course of time for (or related to) CRPS. Therefore, we may have missed some publications if the authors used yet another description for the same disorder. In addition, we were unable to examine the studies published in the French,

Italian, Spanish or Portuguese language. Of these 26, only nine studies were potentially valuable. We consider this as a possible shortcoming of this review.

4.2 Diagnosis

All the articles included in this review were studies in which patients are described as having RSD, algodystrophy or CRPS of the knee(s). For the diagnosis of these disorders, some authors used only the clinical appearance, others claimed that abnormalities on radiological investigations are needed (beside clinical appearance), and yet others state that at least partial relief of the symptoms after a lumbar sympathetic blockade is needed to make a diagnosis of CRPS. In addition, some authors did not describe all the symptoms (besides extensive knee pain) a patient was suffering from after minor trauma or surgery; in these cases, we were unable to confirm their diagnosis.

Radiographs and bone scans were used in almost every study included in this review. In seven studies, abnormalities found on radiographs (besides the clinical features) were considered supportive in diagnosing RSD or CRPS. The authors of one article stated that the use of a skyline view of the patella would be helpful because, so they say, in RSD of the knee the patella is always involved (19). Currently, however, the diagnosis of CRPS is clinically based and no further tests are acquired.

Some authors stated that RSD is a condition 'better overtreated than underdiagnosed' (14). Tietjen concluded that if the existence of CRPS of the knee was more widely known in the medical world, this would help in diagnosing patients with extensive knee pain after a trauma, injury or surgery as patients with CRPS. For knee pain, he advises the use of arthroscopic techniques to rule out causes other than RSD, thereby reducing the amount of unnecessary surgery on knees with RSD (9). His study was published in 1986, and after that date several cases of RSD or CRPS have been described (as shown in this review) after arthroscopic knee surgery. Therefore, the question arises whether we should consider arthroscopic knee surgery to be a risk factor for developing CRPS of the knee.

4.3 Treatment

The literature is inconsistent and/or unclear about the best time to start therapy and which therapy should be applied to treat CRPS. Comparison of the studies in this review was difficult because of the differences in study design, and the variable time after diagnosis and start of treatment. Moreover, the authors used different treatment strategies and primary outcome measures. Uncertainty about the best treatment for CRPS of the knee seems to be no different than uncertainty for CRPS on other (more distal) locations.

4.4 Budapest criteria set

The Budapest criteria set is currently recommended for the diagnosis of CRPS. One of the requirements in diagnosing CRPS according to this set is continuing pain, which is dispro-

portionate to the inciting event. The criteria set does not include that the patient must have at least partial relief of the symptoms after a lumbar sympathetic blockade, or that radiographs or bone scans must show abnormalities in the affected area when compared with the unaffected area. This could imply that patients with a diagnosis of RSD/CRPS without any inciting event, or based on their clinical appearance and at least partial relief of the symptoms after a blockade, or based on their clinical appearance and radiographic evidence of abnormalities, would nowadays probably not receive the diagnosis of CRPS.

In conclusion, our review of the literature reporting on CRPS affecting only the knee(s) reveals that at least 79 patients (more than 20% of the reported cases) are described who met the current Budapest diagnostic criteria set. Therefore, we conclude that patients suffering from CRPS of only the knee(s), have been described in the medical literature.

In addition, we summarized the authors' description of the diagnostics, aetiology and treatment of CRPS affecting only the knee(s). On this basis, we recommend to consider CRPS of only the knee(s) as a medical entity, similar to the more frequently described CRPS of the hand or foot. Because CRPS as a medical condition is only partially understood, we recommend that future research on the aetiological mechanisms and optimal treatment of CRPS should also include CRPS of only the knee. That CRPS of the knee often appeared after arthroscopic knee surgery is an important finding; this implies that this procedure is a possible inciting factor for the development of CRPS; the same applies when a knee does not recover adequately after an arthroscopic knee surgery.

APPENDIX 1

Search strategies in detail

Embase: 441 hits

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PubMed as supplied by publisher: 3 hits

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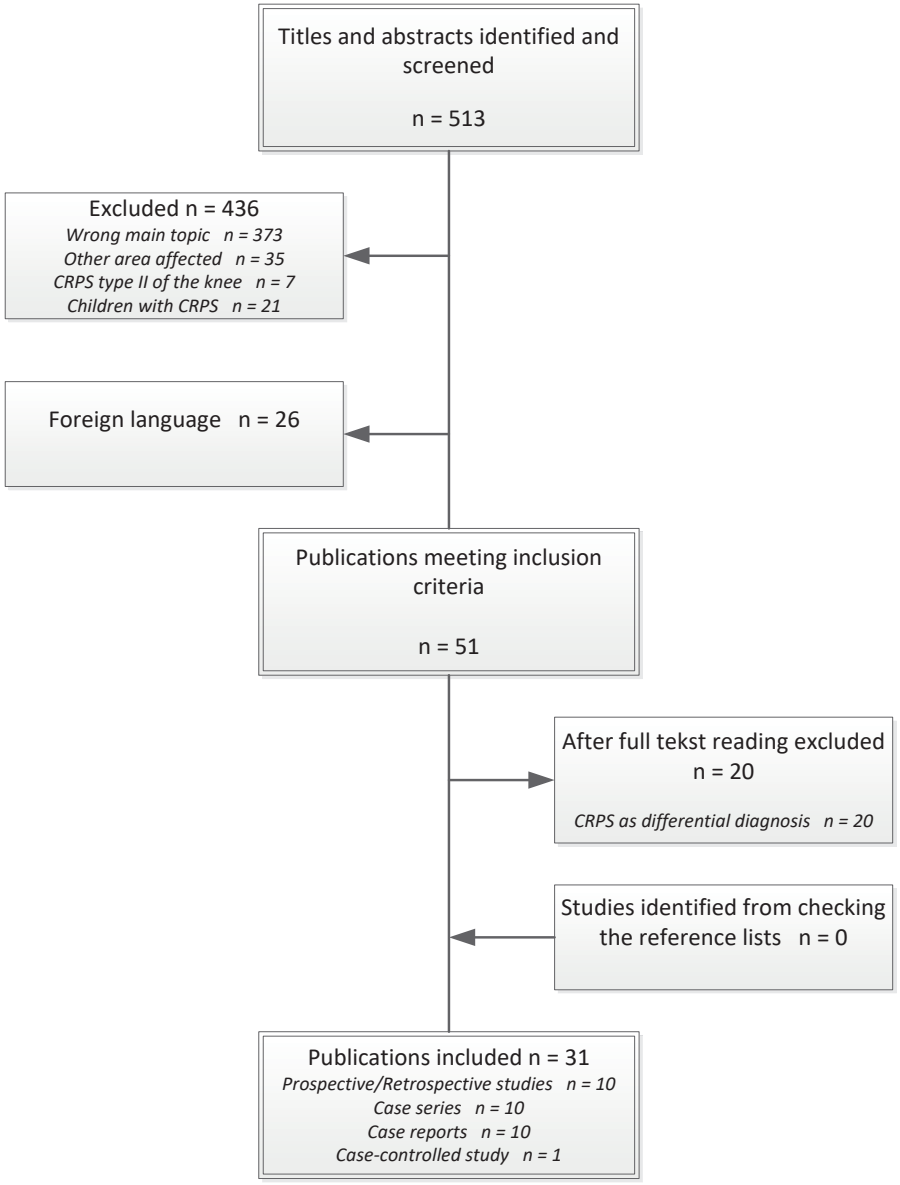
Web of Science: 158 hits

TS=((CRPS OR "complex regional pain" OR Sudeck* OR Sudek* OR Suedeck* OR (RSD* AND (reflex* OR sympathet* OR dystroph*)) OR algodystroph* OR algesidystroph* OR algoneurodystroph* OR ((posttraumatic OR "post traumatic" OR sympathet* OR reflex*) NEAR/3 (osteoporos* OR dystroph*))) AND (knee* OR menisc* OR genu* OR genopath* OR patell* OR femoropatellar* OR (semilun* NEAR/3 (bone* OR cartilage*))))

Total amount of articles: 858. After removing duplicates: 513

APPENDIX 2

Flow Chart



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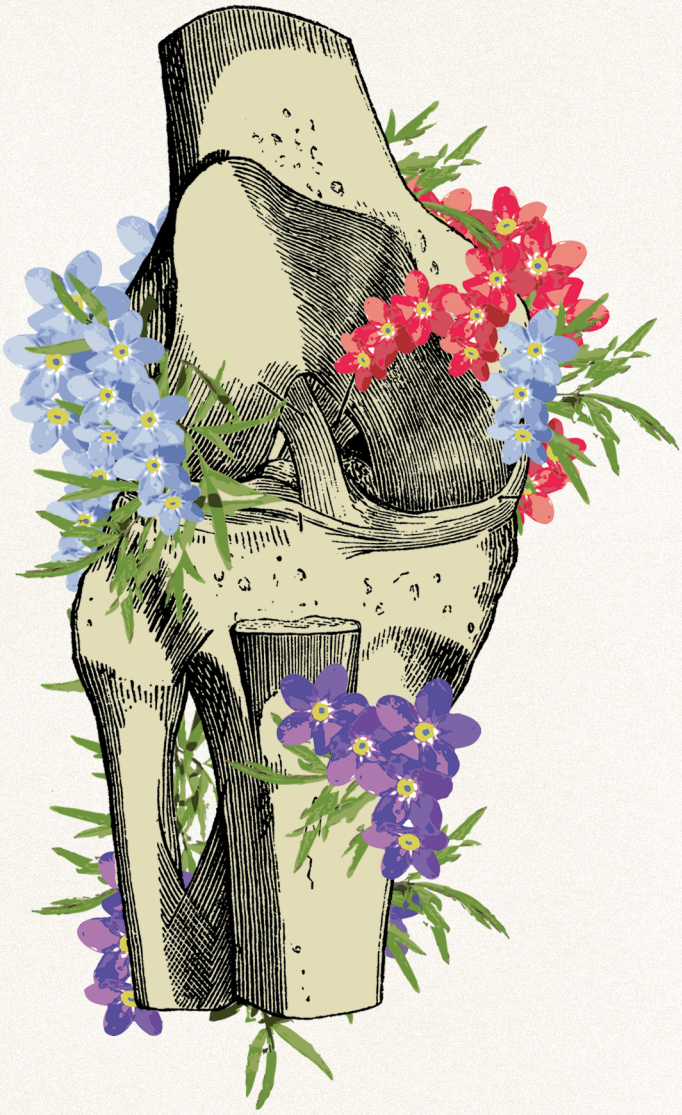

CHAPTER III

Phenotypic Variation in Complex Regional Pain Syndrome: Comparison Between Presentation in Knee Alone or in Ankle/Foot

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Stronks DL,
Huygen FJPM

Pain Medicine. 2016 Dec;17(12):2337-2343

ABSTRACT

Objective: To compare the phenotypes of patients with complex regional pain syndrome (CRPS) of the knee to those with CRPS of the ankle/foot.

Setting: A retrospective study.

Subjects: Patients with CRPS of the knee and patients with CRPS of the ankle/foot.

Methods: We used electronic patient databases to identify patients with CRPS of the knee and patients with CRPS of the ankle/foot. The following variables were recorded: age, gender, duration of complaints, initial injury, and symptoms and signs. Frequency distributions and statistical significant differences between the groups were determined.

Results: Included were 50 patients with CRPS of the knee and 64 patients with CRPS of the ankle/foot. These patients were all diagnosed with CRPS according to the criteria used at the time of diagnosis. No significant differences were found in demographic characteristics. A few symptoms and signs appeared to be proportionally more prevalent in patients with CRPS of the ankle/foot. However, patients with CRPS of the knee suffered significantly longer from the disease than patients with CRPS of the ankle/foot.

Conclusions: Some signs and symptoms appeared to be statistically significant more prevalent in CRPS of the ankle/foot than in CRPS confined to the knee. We conclude that the phenotypes of CRPS confined to the knee and CRPS of the ankle/foot are comparable, but not identical. This can be a reason why CRPS in patients with pain of the knee, that is disproportionate to the initial trauma, is sometimes not recognized.

KEYWORDS

Signs, symptoms, phenotype, complex regional pain syndrome, knee, ankle/foot

INTRODUCTION

Complex regional pain syndrome (CRPS) is a painful, potentially disabling disease. The clinical features include pain, sensory, sudomotor/vasomotor disturbances, impaired motor function and trophic changes (1). Diagnosing CRPS is based on the patient history (symptoms) and the physical examination (signs). Symptoms are defined as subjective; that is, what the patient tells the physician during the visit to the outpatient clinic. Signs are defined as objective; that is, what the physician finds during the physical examination. CRPS can appear after a fracture, after surgery, and even spontaneous origination has been described (2, 3). Several diagnostic criteria sets have been used to diagnose CRPS (4-8). In 2012, the Taxonomy Committee of the International Association for the Study of Pain (IASP) validated the clinical Budapest or "new IASP" criteria for diagnosing CRPS (9).

CRPS is seldom considered as a reason of disproportionate pain of the knee. Only sporadic reports involving patients diagnosed with CRPS confined to the knee have been published (10). Nevertheless, our interest focused on a group of patients whose continuing pain of the knee was disproportionate to the initial trauma. Our recent systematic review on CRPS concluded that CRPS confined to the knee is an acknowledged entity and that some of these patients meet the IASP clinical Budapest diagnostic criteria for diagnosing CRPS (11).

Cooper *et al.* have described in their report that patients diagnosed with CRPS of the knee had continuing pain, stiffness and atrophy. In contrast, changes in skin, burning sensations and/or decrease range of motion were variably present (12). Our group of patients had, next to the continuing pain, symptoms and signs (for example changes in skin, decreased range of motion or asymmetry in temperature) which could be part of CRPS. The aim of this study was to compare the phenotype of CRPS of the ankle/foot with that of CRPS confined to the knee. In addition, we want to improve the knowledge of CRPS confined to the knee and to aid in the recognition of this diagnosis, so patients will be recognized as early as possible.

METHODS

Design

A retrospective study to compare the phenotype (in terms of symptoms and signs) of patients diagnosed with CRPS of the knee with that of patients with CRPS of the ankle/foot.

Patient selection

Every patient who was included in this study was referred to the outpatient clinic of our hospital during the period 2000-2013 with symptoms and signs possibly due to CRPS.

Every patient was seen by the same pain specialist (FH) or under direct supervision of this specialist. The diagnosis CRPS was set according to the Bruehl and Harden criteria and the IASP clinical Budapest criteria. For the purpose of future research, the data of the patients diagnosed with CRPS were entered into the database from the Trauma Related Neuronal Dysfunction (TREND) consortium. TREND is a Dutch knowledge consortium that integrates research on epidemiology, assessment technology, pharmacotherapy, biomarkers and genetics on CRPS and serves as a research platform in which the various research lines of CRPS are integrated (www.trendconsortium.nl). The data of the included patients were retrieved from this database. However, because the diagnosis CRPS confined to the knee was not (yet) well recognized, we also made a manual check of all hospital records of patients with the diagnostic code for CRPS, visiting the outpatient clinic of our hospital during the above mentioned period. Most of the patients with CRPS confined to the knee were identified by this procedure.

Measures

Clinical measures included demographic information (age and gender), duration of complaints, precipitating injury, symptoms as reported by the patient and signs as objectified by the physician. Also, we recorded whether or not the patient met the currently recommended IASP clinical Budapest diagnostic criteria set for diagnosing CRPS (see figure 1).

IASP Clinical Budapest Criteria in diagnosing CRPS	
1. Continuing pain that is disproportionate to any inciting event	
2. At least one symptom reported in at least three of the following categories:	
Sensory	Hyperesthesia or allodynia
Vasomotor	Temperature asymmetry, skin color changes, skin color asymmetry
Sudomotor	Edema, sweating changes, sweating asymmetry
Motor/trophic	Decreased range of motion, motor dysfunction (weakness, tremor, dystonia), trophic changes (hair, nail, skin)
3. At least one sign at time of evaluation in at least two of the following categories:	
Sensory	Evidence of hyperalgesia (to pinprick), allodynia (to light touch, temperature sensation, deep somatic pressure or joint movement)
Vasomotor	Evidence of temperature asymmetry (>1 C°), skin color changes or asymmetry
Sudomotor	Evidence of edema, sweating changes or sweating asymmetry
Motor/trophic	Evidence of decreased range of motion, motor dysfunction (weakness, tremor, dystonia), trophic changes (hair, nail, skin)
4. No other diagnosis can better explain the symptoms and signs	

Figure 1. IASP clinical Budapest criteria in diagnosing CRPS.

Statistical analysis

Descriptive statistics were used to determine the frequencies of the demographic and outcome parameters. The Kolmogorov-Smirnov test was used to analyse whether or not parameters were normally distributed. For parameters with a normal distribution, central tendency and dispersion are described in terms of the mean and the standard deviation (SD); parameters with a non-normal distribution are described in terms of the median and the interquartile range (IQR). Differences between the cohorts in the proportions of patients exhibiting a particular sign or symptom were tested using the Fisher's exact test. Differences in continuous variables were evaluated using the independent samples Mann-Whitney U-test or the independent samples T-test dependent on the shape of their distribution. For all statistics, *P* was set at the 0.05 level. The data were analysed using IBM SPSS Statistics version 21.0 (Armonk, NY: IBM Corp).

RESULTS

Patients with CRPS of the ankle/foot

The data of 161 patients diagnosed at our outpatient clinic with CRPS were found in the TREND database. From these, 94 patients were diagnosed with CRPS of the wrist/hand and were therefore excluded. Of the remaining 67 patients, three patients were diagnosed with CRPS confined to the knee and included in the relevant group. All remaining 64 patients were diagnosed with CRPS of the ankle / foot.

Patients with CRPS confined to the knee

The subsequent manual search of all the hospital records resulted in the identification of a total of 1193 patients coded with CRPS. The patients' charts were manually checked and screened on problems with one or both knees. Sixty-eight (5.7%) of them had complaints of the knee(s). After reading the complete charts of these 68 patients, 18 patients were excluded because they were not diagnosed by the specialist with CRPS confined to the knee. This resulted in a cohort of 50 patients with CRPS of the knee based on the diagnostic criteria set used at the time of referral to our hospital (see figure 2).

Analyses of the included patients revealed no significant difference between both cohorts in gender (*P*=0.44) or age (*P*=0.13), whereas there was a significant difference in the duration of symptoms and signs before diagnosing CRPS (*P*=0.02). Patients with CRPS of the knee suffered longer from their complaints than those with CRPS of the ankle/foot before diagnosis (Table 1). The duration of complaints in the knee cohort had a median of 21.50 months (IQR 10.50-48.00) and the duration of complaints in the ankle/foot cohort had a median of 9.50 months (IQR 3.25-40.50). In addition, both cohorts were checked to see whether patients fulfilled the currently recommended IASP clinical Budapest criteria

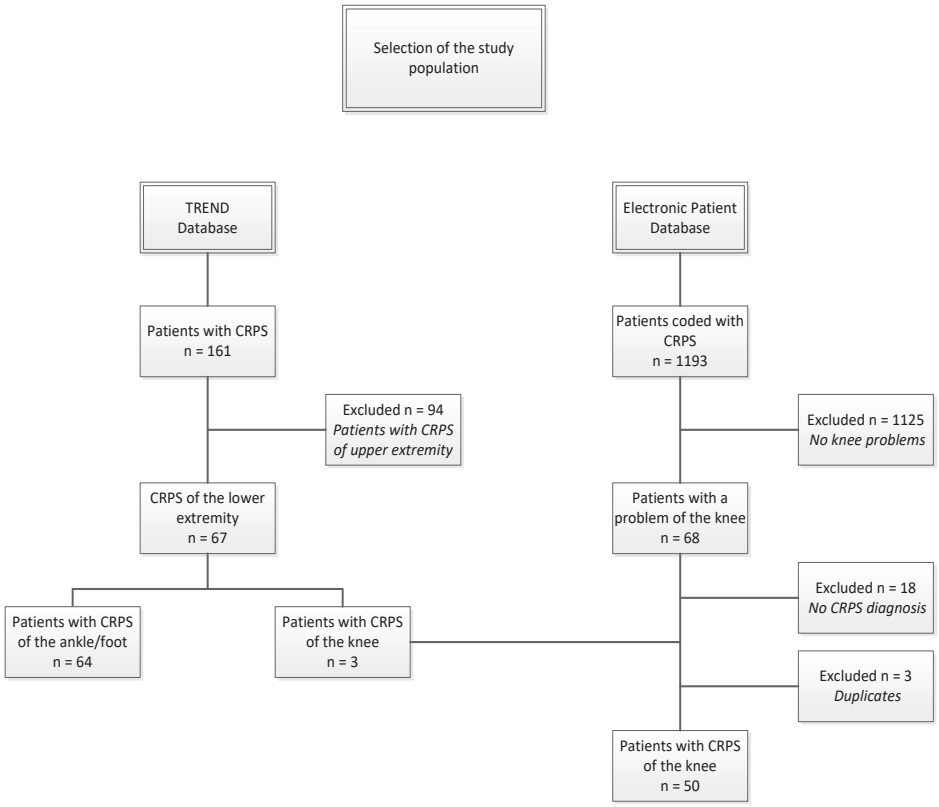

Figure 2. Flow chart of selection of the study population

for diagnosing CRPS. There was no significant difference in the proportion of patients in both groups who met the IASP clinical Budapest criteria (p=0.52): in the knee cohort, 36/50 patients (72%) met these diagnostic criteria and in the ankle/foot cohort 47/64 patients (73%) fulfilled these criteria.

At presentation, all participants mentioned severe, continuing pain, with a pain score of at least 5 on the numeric rating scale (NRS), where 0 = no pain and 10 = worst imaginable pain. Table 2 summarizes the patients' symptoms and signs. In both patient groups allodynia, color asymmetry, temperature asymmetry, edema and decreased range of motion were the most frequently reported symptoms as well as seen signs. Concerning the reported symptoms, a statistically significant difference between the groups in the prevalence of hyperesthesia, hyperalgesia, decreased range of motion and dystonia was found. With regard to the signs, a significant difference was found between the groups in hypoesthesia, hyperalgesia, color asymmetry, and sweating asymmetry. These specific symptoms and signs were more often mentioned and seen in the CRPS of the ankle/foot cohort.

Table 1. Characteristics of the patients by location of CRPS

	Knee cohort n = 50	Ankle/Foot cohort n = 64	P
Female gender n (%)	44 (88%)	52 (81.3%)	0.44
Age/years mean (SD)	41.44 (14.37)	41.05 (16.56)	0.13
Duration/months median (IQR)	21.50 (10.50-48.00)	9.50 (3.25-40.50)	0.02*
Met the Budapest diagnostic criteria set n (%)	36 (72%)	47 (73%)	0.52

CRPS, complex regional pain syndrome; SD, standard deviation; IQR, interquartile range,
* significant difference

Table 2. Symptoms (subjective) and signs (objective) by location of CRPS in 114 patients

	Symptoms			**Signs**		
	Knee cohort	Ankle/Foot cohort		Knee cohort	Ankle/Foot cohort	
	n (%)	*n* (%)	*P*	*n* (%)	*n* (%)	*P*
Sensory						
Allodynia	32 (64)	45 (70)	0.55	30 (60)	45 (70)	0.32
Hyperalgesia	17 (34)	36 (56)	0.02*	6 (12)	32 (50)	<0.001*
Hyperesthesia	7 (14)	44 (69)	<0.001*	11 (22)	24 (38)	0.10
Hypoesthesia	1 (2)	6 (9)	0.13	3 (6)	16 (25)	0.01*
Vasomotor						
Asymmetry in temperature	40 (80)	54 (84)	0.62	34 (68)	41 (64)	0.70
Asymmetry in color	36 (72)	53 (83)	0.18	23 (46)	44 (69)	0.02*
Sudomotor						
Edema	43 (86)	48 (75)	0.16	30 (60)	42 (66)	0.56
Asymmetry in sweating	14 (28)	24 (38)	0.32	0 (0)	12 (19)	0.001*
Motortrophic						
Decreased range of motion	25 (50)	48 (75)	0.01*	29 (58)	46 (72)	0.16
Weakness	21 (42)	36 (56)	0.19	14 (28)	28 (44)	0.12
Trophic disturbances	20 (40)	36 (56)	0.09	19 (38)	29 (45)	0.45
Dystonia	2 (4)	20 (31)	<0.001*	1 (2)	2 (3)	1.00
Tremor	5 (10)	5 (8)	0.75	2 (4)	2 (3)	1.00

CRPS, complex regional pain syndrome, * significant difference

The precipitating events for development of CRPS are presented in table 3. In the knee cohort, surgery and arthroscopy were the most frequently occurring precipitating events: 15 patients (30%) had (arthroscopic) surgery and 14 (28%) had an arthroscopy before the onset of CRPS. In the ankle/foot cohort, a fracture of the lower leg (20 patients, 31.3%) and a trauma, for example, distortion and/or inversion, (16 patients, 25%), were the most frequently reported precipitating events.

Table 3. Precipitating events for development of CRPS in both cohorts

	Knee cohort	Ankle/Foot cohort
	n (%)	*n* (%)
Event		
(Arthroscopic) surgery	15 (30)	14 (21.8)
Arthroscopy	14 (28)	0 (0)
Anterior knee trauma	10 (20)	-
Luxation	4 (8)	1 (1.6)
Burns	1 (2)	0 (0)
Fracture	1 (2)	20 (31.3)
Twisting injury	1 (2)	0 (0)
Trauma (inversion, distortion)	0 (0)	16 (25)
Spontaneous	0 (0)	7 (10.9)
Other	4 (8)	6 (9.4)
Total	50 (100)	64 (100)

CRPS, complex regional pain syndrome

DISCUSSION

The aim of this retrospective study was to compare the phenotype (in terms of symptoms and signs) of CRPS confined to the knee to that of CRPS of the ankle/foot. The results indicate that a limited phenotypical variation exists, but the phenotypes are not identical.

This study included 50 patients with CRPS of the knee and 64 with CRPS of the ankle/foot. For reasons of comparability, we excluded patients diagnosed with CRPS of an upper extremity (i.e. the hand or wrist). All patients were diagnosed with CRPS based on the criteria applied at the time they visited our outpatient department. When applying the IASP clinical Budapest criteria to the included patients, a minority in both cohorts (28% and 27%) did not completely meet these criteria currently recommended. However, as the complaints could not be explained by any other diagnosis, these patients would nowadays probably be diagnosed with CRPS-NOS (not otherwise specified). CRPS-NOS was added as a subtype, next to CRPS type 1 (without nerve damage) and type 2 (with nerve damage), to capture patients who were diagnosed with CRPS previously and who did not fulfill the criteria anymore (8).

Although both cohorts were similar with regard to gender and age, patients with CRPS of the knee had suffered from this condition for a significantly longer time than those with CRPS of the ankle/foot. This fact can probably be attributed to physicians' unfamiliarity with diagnosing CRPS of the knee (13). A delay in diagnosing CRPS confined to the knee is not uncommon. Katz *et al.* described an average delay of 29 months (range: 3 weeks to 11 years) and Cameron *et al.* described a delay of 26 months before receiving the diagnosis CRPS of the knee (10, 14). An average of 11.2 months (range: 3 months to 58.8 months) from

the time of injury to diagnosing CRPS of the knee has been described by Neuschwander *et al* (15). The retrospective design counts as a limitation of this study. Physicians at our outpatient clinic may not have recognized the complaints of the knee as CRPS, so the symptoms reported and the signs found during clinical examination (and written in the patients' charts) may not give a true picture of the patients' actual condition.

Significant differences in symptoms and signs between the two cohorts were found with regard to four symptoms (hyperesthesia, hyperalgesia, decreased range of motion, and dystonia) and four signs (hypoesthesia, hyperalgesia, color asymmetry, and sweating asymmetry). Although these differences might be due to (not having corrected for) multiple testing, (some of) the differences in signs are plausible. Dystonia of the knee is uncommon and difficult to examine, because decreased range of motion in the knee already influence the flexion and extension of the knee (16). Birklein *et al.* concluded that patients with CRPS have hyperhidrosis in the affected limb, but particularly during the acute phase (<2 months) (17). As this retrospective study shows, patients with CRPS of the knee suffered longer from this condition. Therefore, by the time the CRPS was diagnosed it could already be in a chronic phase. So, an asymmetry in sweating between both knees was hard and probably even impossible to objectify.

Because of the significant difference in duration of the disease, and the possibility that symptoms and signs of CRPS can differ over time (18), we decided to perform post hoc a pairwise matching analysis. We matched the patients based on gender, duration of complaints and age. The range for matching based on duration was within 1 year of complaints and the range for matching on age was within 10 years of age; this resulted in 38 pairs of patients. Re-analysis yielded no significant difference in gender, age or duration ($0.20 \leq p \leq 1.00$). Interestingly, after pairwise matching, the significant differences in symptoms and signs that we found earlier (when comparing the two complete cohorts) were the same. This supports the assumption that CRPS of the knee does differ from CRPS of the ankle/foot in terms of a few symptoms and signs and that the observed phenotypic variation is not due to (possible) inherent changes over time.

The precipitating events differed between both cohorts; patients reported more surgical events before development of CRPS of the knee than before development of CRPS of the ankle/foot. Earlier reports by O'Brien et al., Katz et al. and Burns et al. confirm this surgical cause of CRPS confined to the knee (10, 19, 20).

In conclusion, the phenotypic variation in terms of symptoms and signs of CRPS of the knee compared to CRPS of the ankle/foot is limited, but the phenotypes are not identical. We found some significant differences between the two cohorts, which probably can be explained by the location of the CRPS. The phenotypic variation might be a reason why CRPS in patients with pain of the knee, that is disproportionate to the initial trauma, is sometimes not recognized. We recommend that physicians add CRPS to their differential diagnosis when encountering a patient with pain of the knee that is disproportionate to the precipitating injury.

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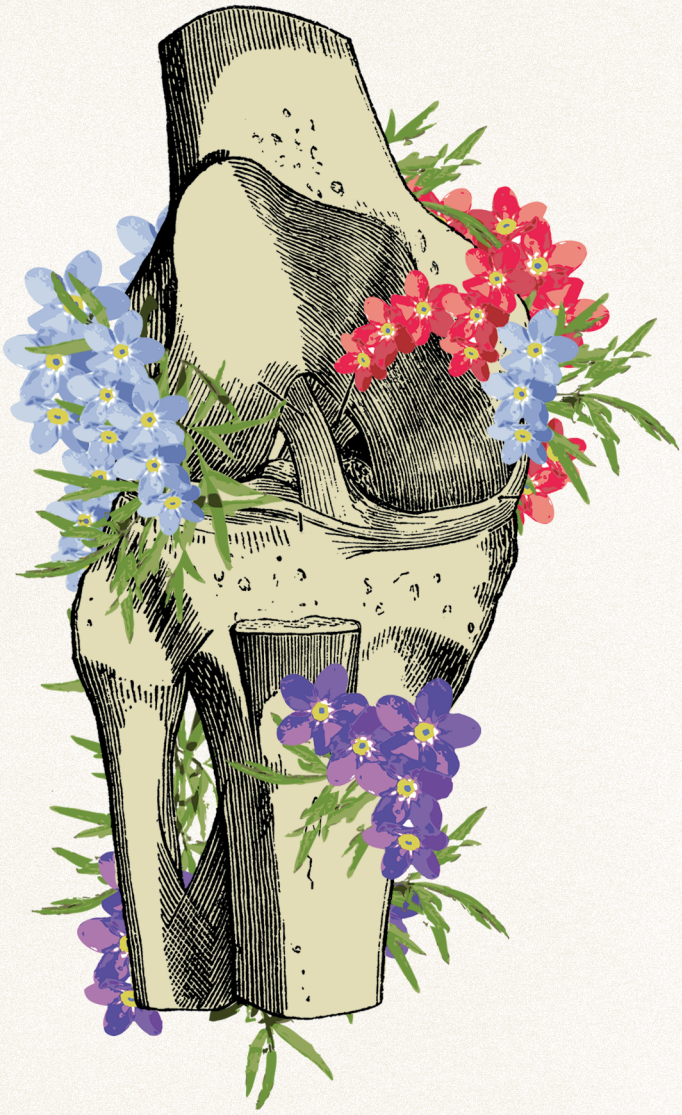

CHAPTER IV

Clinical course and impact of complex regional pain syndrome confined to the knee

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ABSTRACT

Objective: Although complex regional pain syndrome (CRPS) of the knee is comparable to CRPS of the ankle/foot at time of diagnosis, no reports are available concerning the course of knee CRPS. Therefore, this study investigated the clinical course in terms of the symptoms and signs, health-related quality of life (HR-QoL), and work status of patients diagnosed with CRPS of the knee.

Design: Observational, descriptive study.

Setting: Single-center study.

Subjects: Patients with CRPS of the knee.

Methods: Patients self-reported their past and current CRPS symptoms, HR-QoL and work status; all underwent a physical examination. A comparison was made of changes in symptoms over time between patients with CRPS of the knee and those with CRPS of more distal locations.

Results: In total, 32 patients were enrolled. The follow-up time was 11.5±6.29 years since diagnosis, and symptoms and signs showed a significant decrease over time. Twelve patients (37.5%) rated their health as (generally) positive. Patients who were still able to work (31.3%) stated that their physical health gave them at least some problems in the performance of their job. A change in symptoms occurred significantly less often in CRPS of the knee.

Conclusions: CRPS of the knee changes in terms of symptoms over time, but significantly less than CRPS of other locations. A change in work status was reported in 82% of the patients due to their CRPS, and in 91% the pain interfered with their daily life. CRPS of the knee is a painful condition with persistent symptoms causing a diminished HR-QoL.

KEY WORDS

Complex regional pain syndrome, knee, course, quality of life, work status

INTRODUCTION

Chronic pain due to complex regional pain syndrome (CRPS) is known to adversely affect the life of a patient (1). CRPS is a potentially chronic disease; moreover, continuing pain is the most disabling factor for patients and, unfortunately, pain intensity can increase with disease duration (2-4).

CRPS confined to the knee is less well known in the medical world (5). The most commonly reported initiating trauma for developing CRPS confined to the knee is (arthroscopic) surgery, whereas for CRPS of other locations, fracture is the most reported trauma (6, 7). We concluded from a previous study that, at the time of diagnosis, the clinical picture of CRPS of the ankle/foot (lower limb) is comparable but not identical to that of CRPS confined to the knee. In addition, we found a significantly longer duration of disease of CRPS confined to the knee before receiving the diagnosis, compared to CRPS of the ankle/foot (8).

No reports are available on the outcome of CRPS confined to the knee, whereas multiple studies have investigated the outcome of CRPS of other (more distal) locations. For example, Anderson and Fallat investigated a group of 13 patients with CRPS of a lower limb with an average disease duration of 3.5 years after diagnosis; of this group, 12 (92%) still had continuous pain (9). Others have also found significant pain and impairment in patients with CRPS of the lower limb (10); the same applies for patients with CRPS of an affected upper limb (11). De Mos et al. concluded that, in their CRPS group, although a severe disease outcome was rare, incomplete resolution of all symptoms and signs was common (7).

A study on 656 patients with a duration of CRPS of at least one year showed that 81% of these patients were no longer able to do their work due to pain at some point after diagnosis; of the 81% who stopped working, only 27% resumed their job (4). Others reported a diminished health-related quality of life (HR-QoL) due to disability of the affected extremity (2, 12). As no data are available for CRPS confined to the knee, the present study aimed to investigate the course of symptoms and signs, HR-QoL and work status of patients diagnosed with CRPS confined to the knee. In addition, a comparison was made of symptom presentation between patients with CRPS confined to the knee and patients with CRPS of a more distal location.

METHODS

Design

This was a single-center, observational, descriptive study.

Study Population

All patients included in this study were referred to the outpatient pain clinic of our hospital during the period 2000-2013. For the purpose of an earlier study, we had already performed a manual check of all hospital records of patients with the diagnostic code for CRPS to identify patients with CRPS confined to the knee (8). Every patient was seen by the same physician (FH), or under direct supervision of this pain specialist. Our institutional ethics committee approved a trial we performed at our center (MEC-2014-70) to find patients with CRPS confined to the knee, and all patients consented to participate. If a patient was diagnosed according to the International Association for the Study of Pain (IASP) clinical Budapest diagnostic criteria set (13), they were eligible for inclusion. The IASP clinical Budapest diagnostic criteria were adopted in 2010 as the standard for CRPS diagnosis.

To investigate the clinical course of CRPS confined to the knee, a pairwise matched analysis was made to compare the course with CRPS of distal locations. Information on the clinical course of CRPS of distal locations was collected earlier by De Mos et al. (7); all results of this latter study were available at our research center.

Measurements

All patients were asked to visit the department once again to undergo a physical examination to assess the current signs of their CRPS. The physical examination was performed by a physician who has a lot of experience in diagnosing CRPS. Prior to this visit, they were asked to answer questionnaires about: 1) their previous and current symptoms of CRPS, 2) their HR-QoL, 3) their work status, 4) whether they considered their CRPS to be cured or stabilized, and 5) whether they experienced sequelae. The questionnaires were completed by the patients in advance and were discussed during the visit to avoid missing and/or wrong interpretation of their answers. The signs present at the time the patient received the diagnosis of CRPS confined to the knee, were collected by inspection of the hospital records of each patient.

Statistical analysis

Descriptive statistics were used to determine the frequencies and measures of the central tendency of the demographic and outcome parameters. The Kolmogorov-Smirnov test was used to analyze whether parameters were normally distributed. For parameters with a normal distribution, central tendency and dispersion were described in terms of the mean and standard deviation (SD), and parameters with a non-normal distribution in terms of the median and interquartile range (IQR). The McNemar test was applied to investigate changes that occurred in symptoms and signs.

For all statistics, α was set at the 0.05 level. Data were analyzed using SPSS Statistics, version 21 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 50 patients diagnosed with CRPS confined to the knee were found in the digital patient database of our hospital (8). The research physician (CvB) tried to contact every patient by telephone: five patients were not available, and of the remaining patients, 37 were willing to fill in the questionnaires. Eventually, 32 patients returned their questionnaires to the outpatient clinic and were included in this study. Within this group, 29 patients gave permission to perform a physical examination to assess the current CRPS signs.

Demographics

The group of patients diagnosed with CRPS confined to the knee consisted of 28 females (88%). At the time of diagnosis, all patients fulfilled the Bruehl and Harden criteria or the IASP clinical Budapest criteria. The mean age at the time of this study was 51.2 (SD 15.33) years. The mean time since receiving the CRPS diagnosis (SD) was 11.5 (6.29) years. The initiating events of the CRPS, as described by the patients, were surgery (44%), some kind of trauma (38%), a fracture (6%), and unknown (12%).

Course of CRPS confined to the knee

Table 1 shows the current symptoms and those at the time of diagnosis of the CRPS. With the exception of coordination disorder, the relative frequency of all 20 symptoms decreased over time; in nine of these, the decrease was statistically significant. Table 2 shows the CRPS signs at the time of diagnosis and the current signs as measured by physical examination. An increase in relative frequency was found for allodynia, asymmetry in color, hyperalgesia and asymmetry in sweating; however, only the increase in hyperalgesia was significant. The relative frequency of the remaining signs decreased.

Of all 32 patients, 31 (97%) reported temperature asymmetry at the time of diagnosis, and 28 (88%) at follow-up. In 22 (68%) of these patients, the temperature asymmetry remained the same (cold, warm, or alternating hot and cold) and in 10 patients (32%) the temperature asymmetry shifted to another status (Table 3). Furthermore, five patients (16%) considered their CRPS to be cured, six (19%) patients reported their CRPS to be stable, and 27 (84%) experienced sequelae due to CRPS. Of the six patients reporting their CRPS to be stable, all experienced sequelae. Of all patients, 17 (53%) were still on medication and 11 (34%) received physiotherapeutic treatment for the CRPS.

Current Work Status

Of all patients, 22 (69%) had a job at the time they were diagnosed; of those patients, 18 (82%) reported that their work had changed over time due to the CRPS. Of these 18 patients, 10 (56%) had to stop working, of whom eight patients are still receiving benefits, six (33%) changed their job, and the remaining two (11%) adapted their way of performing their job.

Table 1. Symptoms at time of diagnosis and current symptoms in 32 patients with CRPS confined to the knee

Symptom	At diagnosis n = 32	At follow-up n = 32	Change n = 32		
			Yes → No	No → Yes	
	n (%)	n (%)	n	n	p
Continuous pain	32 (100)	21 (66)	11	0	-
Weakness	32 (100)	27 (84)	5	0	-
Increase after exercise	32 (100)	25 (78)	7	0	-
Hyperesthesia	31 (97)	24 (75)	8	1	0.04*
Decreased range of motion	31 (97)	26 (81)	6	1	0.13
Hyperalgesia	30 (94)	28 (88)	2	0	0.50
Asymmetry in temperature	30 (94)	22 (69)	8	0	0.008*
Asymmetry in color	29 (91)	20 (63)	9	0	0.004*
Swelling	28 (88)	22 (69)	6	0	0.03*
Allodynia	27 (84)	17 (53)	12	2	0.01*
Stiffness	27 (84)	20 (63)	7	0	0.02*
Hypoesthesia	22 (69)	18 (56)	5	1	0.22
Cramp	18 (56)	17 (53)	2	1	1.00
Tingling	17 (53)	12 (38)	5	0	0.06
Involuntary movements	17 (53)	11 (34)	6	0	0.03*
Asymmetry in sweating	15 (49)	8 (25)	7	0	0.02*
Tremor	14 (44)	8 (25)	6	0	0.03*
Asymmetry in hair	14 (44)	11 (34)	3	0	0.25
Asymmetry in nails	11 (34)	10 (31)	3	2	1.00
Coordination disorder	10 (31)	10 (31)	2	2	1.00

*, significant proportional decrease; CRPS, complex regional pain syndr

Table 2. Signs at time of diagnosis and current signs in 29 patients with CRPS confined to the knee

	Signs at diagnosis n = 29	Current signs n = 29	Change of signs n = 29		
			Yes → No	No → Yes	
	n (%)	n (%)	n	n	p
Asymmetry in temperature	22 (76)	15 (52)	10	3	0.09
Swelling	19 (66)	17 (59)	8	6	0.79
Decreased range of motion	19 (66)	18 (62)	7	6	1.00
Allodynia	16 (55)	19 (66)	5	8	0.58
Asymmetry in color	10 (34)	13 (45)	4	7	0.55
Motor changes (tremor, dystonia, weakness)	10 (34)	3 (10)	10	3	0.09
Trophic changes (hair, nails)	9 (31)	5 (17)	8	4	0.39
Hyperalgesia	3 (10)	14 (48)	2	13	0.007*
Asymmetry in sweating	0 (0)	1 (3)	0	1	-

*, significant increase; CRPS, complex regional pain syndrome

Table 3. Patients with CRPS confined to the knee (n=32) who did/did not show change in type of temperature asymmetry

	Change in temperature asymmetry over time				
	Warm	Cold	Variable	No difference	Temperature at time of diagnosis
	n (%)	n (%)	n (%)	n (%)	n (%)
Warm	9 (28)	5 (16)	1 (3)	2 (6)	17 (53)
Cold	0	9 (28)	0	1 (3)	10 (31)
Variable	0	1 (3)	3 (9)	0	4 (13)
No difference	0	0	0	1 (3)	1 (3)
Current temperature asymmetry	9 (28)	15 (47)	4 (12.5)	4 (12.5)	32 (100)

CRPS, complex regional pain syndrome

Six patients have filed a claim for a work-related injury with their employer. Of those, one claim has been settled, whereas the others are pending. At the time of this study, the 10 patients that had a job were asked additional questions about their ability to perform their job. Eight reported that their physical health gave some, or major, problems in performing their job due to CRPS. The most frequently reported reason for this was decreased range of motion of the knee.

Current Quality of Life

All 32 patients with CRPS confined to the knee were asked to rate their health; six (19%) rated their health as poor, 14 (44%) as fair, nine (28%) as good, and three (9%) as very good. Of all patients, 28 (88%) reported that their health status caused limitations in performing moderate or more demanding activities (e.g. moving a table) and 29 patients (91%) reported that the pain interfered with their daily life. In addition, almost 50% of the patients stated that, as a result of emotional problems, they experienced difficulties with their work or (other) regular daily activities (Table 4).

Comparison of knee CRPS and other CRPS

Patients with CRPS confined to the knee were pairwise matched (based on disease duration) with patients with CRPS of distal locations (hand/wrist/ankle/foot) to compare changes in the relative frequency of symptoms over time between the groups. For this analysis, we matched 24 patients from each group. The results show that, in terms of the defined symptoms, CRPS confined to the knee showed less change over time compared to CRPS of distal locations: that is, of the 20 symptoms, only four showed a significant change in patients with CRPS confined to the knee, compared with 11 in patients with CRPS of distal locations (Table 5).

Table 4. Frequency of answers of patients diagnosed with CRPS confined to the knee (n=32) regarding their quality of life (QoL)

Current quality of life (QoL)	**Frequency (n)**				
	Excellent	Very good	Good	Fair	Poor
Health in general	0	3	9	14	6
	Yes, a lot		Yes, a little	No, not at all	
Health limits in:					
Moderate activities	21		7	4	
Climbing flights of stairs	20		9	3	
	Yes			No	
Physical health:					
Accomplished less	26			6	
Limited in activities	27			5	
Emotional problems:					
Accomplished less	15			17	
Limited in activities	13			19	
	Not at all	A little bit	Moderately	Quite a bit	Extremely
How much did pain interfere	3	6	6	8	9
	All of the time	Most of the time	A good bit of the time	Some of the times	A little of the time	None of the time
Felt calm and peaceful	1	7	7	14	3	0
Had a lot of energy	1	4	6	14	6	1
Felt downhearted and blue	0	3	3	10	8	8
Interference with social activities	5	12	0	9	1	5

DISCUSSION

The aim of this study was to investigate the course of CRPS confined to the knee in terms of symptoms and signs, self-reported HR-QoL, and the work status of patients diagnosed with this disorder. This study was performed due to the absence of earlier reports on this specific topic.

In our patients, a self-reported recovery rate of 16% was found after a mean follow-up of 11.5 years, compared with the 29% reported by de Mos et al. (7). However, in the latter study, follow-up was only 5.8 years and, in contrast to our sample, their 102 patients were diagnosed with lower/upper limb CRPS. Although spontaneous resolution did not occur in our patients with knee CRPS, this has been described previously (14-16); however, in these latter studies, most patients had CRPS of the upper extremity. In our group, only one patient was free of symptoms and signs, but this was after extensive treatment. Some significant changes in symptoms were found in our patients at follow-up, mostly based on a decrease in presentation. Regarding possible changes in signs, we found a significant increase in presentation only for hyperalgesia. Therefore, although our patients experi-

Table 5. Changes in symptom presentation in both groups after matching duration of disease

	Change in Knee CRPS group n = 24	p	Change in Distal CRPS group n = 24	p
Symptom	n (%)		n (%)	
Continuous pain	9 (38)	-	15 (63)	<0.001*
Allodynia	8 (33)	0.02*	14 (58)	<0.001*
Asymmetry in color	7 (29)	0.02*	15 (63)	<0.001*
Hyperesthesia	7 (29)	-	6 (25)	0.07
Asymmetry in temperature	6 (25)	0.03*	11 (46)	0.001*
Asymmetry in sweating	5 (21)	0.06*	7 (29)	0.02*
Increase after exercise	5 (21)	-	4 (17)	0.22
Stiffness	5 (21)	0.06	3 (13)	0.38
Decreased range of motion	4 (17)	0.22	9 (38)	0.004*
Swelling	4 (17)	0.25	15 (63)	<0.001*
Tremor	4 (17)	0.13	1 (4)	1.00
Weakness	4 (17)	-	6 (25)	0.07*
Hypoesthesia	3 (13)	0.25	4 (17)	0.22
Tingling	3 (13)	0.25	4 (17)	0.13
Involuntary movements	3 (13)	0.25	1 (4)	1.00
Asymmetry in hair	1 (4)	1.00	7 (29)	0.02*
Asymmetry in nails	1 (4)	1.00	7 (29)	0.02*
Hyperalgesia	1 (4)	1.00	8 (33)	0.01*
Cramp	0 (0)	1.00	3 (13)	0.25
Coordination disorder	0 (0)	1.00	2 (8)	0.50

*, significant difference; CRPS, complex regional pain syndrome

enced a subjective recovery of CRPS or a reduction in symptoms, the objective signs did not show a significant decrease, that is, the subjectively experienced improvement could not be objectified. As there are no earlier reports on the clinical course of CRPS confined to the knee in terms of symptoms and signs, no comparison could be made between our results and other studies.

Currently, the diagnosis of CRPS is still based on symptoms and clinical signs, and no additional measurements are needed. So, a physician needs a significant amount of experience in diagnosing CRPS. The clinical examination in our patients was done by an experienced physician. Still, we figure this to be a limitation of diagnosing patients with CRPS and also a limitation of this study. The CRPS Severity Score (CSS) may be a helpful tool for monitoring the course of CRPS and outcomes research (17). We did use the CSS at the time of the study, but unfortunately, it was not used at the time the patients received their diagnosis of CRPS. We would like to add the CSS in future research at our center.

Based on the pairwise matched analysis, the symptoms of CRPS confined to the knee were more stable over time compared to CRPS of more distal locations, and recovery was less common. However, due to multiple testing, our study may have been at increased risk of a type 2 error; this implies that some statistical tests may have incorrectly resulted in significance. Nevertheless, as reported earlier, the diagnosis of CRPS confined to the knee seems problematic; for example, it took longer (possibly due to phenotypic variation) before a diagnosis of CRPS was made (8). This can lead to a potential delay in starting the appropriate treatment and, subsequently, to a more stable course in terms of symptoms (i.e. a significantly reduced decrease in reported symptoms). This corresponds to earlier reports stating that earlier recognition and treatment result in potentially better outcome in patients with CRPS (18).

Patients with cold CRPS at the time of diagnosis are reported to have a poorer clinical pain outcome (19). In our patients diagnosed with CRPS confined to the knee, 11 (34%) started with cold CRPS, of whom five reported that their continuous pain resolved over time. On the other hand, 17 patients (53%) started with warm CRPS, and at the time of this study, five reported that they no longer had continuous pain. Therefore, for this patient group, we cannot confirm the poorer clinical pain outcome based on the temperature at diagnosis. A possible explanation for this could be that, as shown in this study, CRPS confined to the knee has a limited change in symptoms over time compared to other more distal locations. In 10 of our patients, the temperature asymmetry changed based on the symptoms. This self-reported temperature shift could imply that physicians should change their treatment strategy based on the possible underlying mechanisms, to achieve a better outcome for patients diagnosed with CRPS (20, 21).

Patients with CRPS confined to the knee appear to have reduced HR-QoL, similar to patients with CRPS in more distal locations. For example, van Velzen et al. described patients with lower limb CRPS who reported poor HR-QoL; they also found a negative correlation between disease duration and physical functioning. In line with this finding, they reported that the HR-QoL of patients is best explained by the impact of CRPS on their physical health (12). Kemler and de Vet reported that the HR-QoL of patients with chronic reflex sympathetic dystrophy (RSD, a term earlier used to describe CRPS) of the leg was affected due to CRPS (10). In addition, Galer et al. concluded that persistent CRPS symptoms after a mean disease duration of 3.3 years substantially interfered with patients' health-related quality of life and daily functioning (22).

In the present study, there was a change in the work status of 82% of our patients diagnosed with CRPS confined to the knee. This is in line with Kemler and Furnee, who found that in 72% of their patients, the work status changed due to the CRPS (1). Dumas et al. found that lower limb involvement was significantly negatively correlated with return to work (23). In contrast, Duman et al. reported a return to work ability of 72% (24); surprisingly, this latter group consisted solely of male patients, whilst mostly female patients are

diagnosed with CRPS (15, 25). In our group of patients, 80% reported that their physical health gave them problems in performing their job. This is in line by other reports that CRPS interferes with functional activity and the ability to (resume) work (22). In contrast, two studies reported that 68% and 72% of their patients with CRPS of the upper limb resumed their work (23, 24). Also, CRPS of the lower limb led to difficulties in social activities and work compared with patients with an affected upper limb (10).

Furthermore, Thevenon et al. described that patients with CRPS affecting an upper limb needed longer treatment and had longer work absence than patients with CRPS affecting a lower limb (26). A study on 656 patients (after a duration of CRPS of at least one year) showed that 81% of these patients were no longer able to do their work due to pain at some point after diagnosis; of the 81% who stopped working, only 27% resumed their job (4).

In conclusion, this study was performed to investigate the course of CRPS confined to the knee. Since this is the first study to provide information on the clinical course of this specific CRPS location, no comparison can be made with other studies. Despite a decrease in symptom presentation, most of our patients had persistent symptoms and signs at a mean of 11.5 years after initial diagnosis, and only a minority returned to their original work. Compared to CRPS of more distal locations, CRPS confined to the knee shows significantly less change in terms of symptoms. Most of our patients reported to have sequelae, and only five (16%) considered themselves to be cured. Also, the pain continued to interfere with their daily activities.

In summary, CRPS confined to the knee is a painful condition with a less favorable clinical course than CRPS of more distal locations, including an adverse impact on work status and a diminished HR-QoL, which could potentially lead to high socioeconomic costs.

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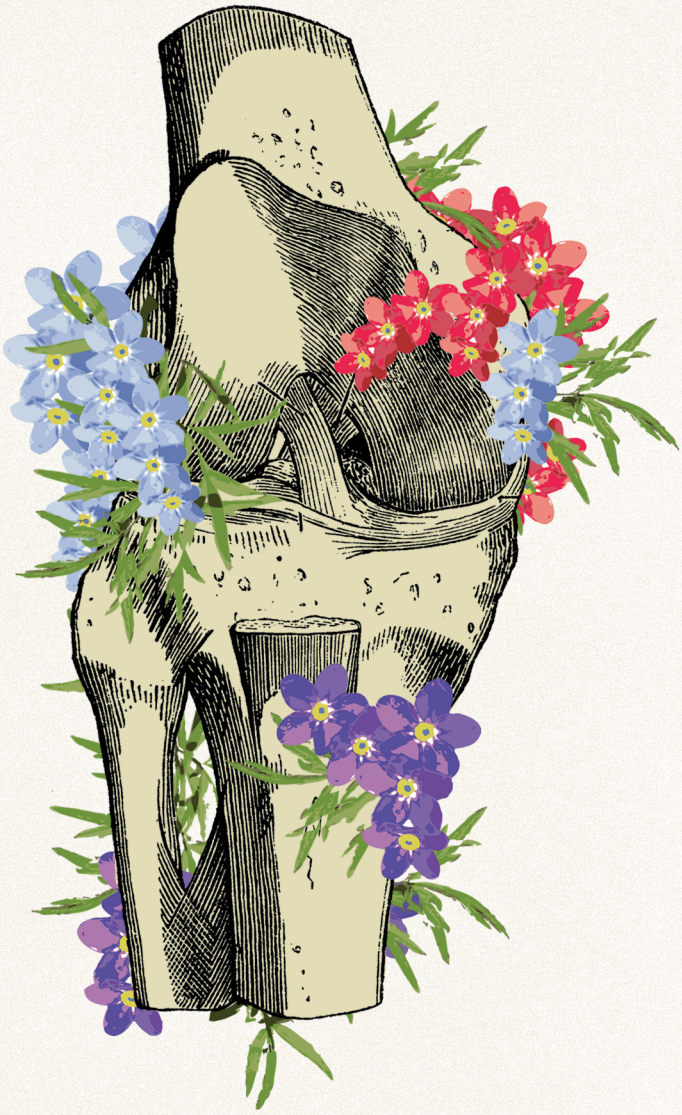

CHAPTER V

Successful treatment of intractable complex regional pain syndrome type I of the knee with dorsal root ganglion stimulation: A case report

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Neuromodulation. 2015 Jan;18(1):58-60

ABSTRACT

Objectives: To report on the efficacy of dorsal root ganglion (DRG) stimulation in a patient with complex regional pain syndrome (CRPS) type I of the knee.

Materials and Methods: A 48-year-old woman with CRPS type I of the right knee, diagnosed according to the Budapest criteria set, received DRG stimulation for intractable CRPS type I of the knee.

Results: After a successful trial period with three DRG stimulation leads on spinal levels L2, L3 and L4 (covering 90% of the painful area of her knee), a definitive pulse generator was implanted. Three months after implantation, the entire painful was area covered and the patient reported a numeric rating scale score of 1-2.

Conclusion: Placement of three DRG stimulation leads at levels L2, L3 and L4 in a patient with intractable CRPS type I of the knee resulted in major pain relief. We recommend further investigation of the effect of DRG stimulation on pain due to CRPS of the knee.

KEYWORDS

Complex regional pain syndrome type I, dorsal root ganglion stimulation, knee, numeric rating scale, numeric rating scale, treatment

INTRODUCTION

Complex regional pain syndrome (CRPS) is a collection of locally appearing painful conditions that mainly occur distally and exceed in both intensity and duration the expected clinical course of the original trauma. In a minority of patients, the condition is restricted to the knee. Recently, a systematic review was performed to find evidence for the diagnosis of CRPS of the knee. The authors concluded that this diagnosis has been described before and the best therapy is yet to be found (1).

Dorsal root ganglion (DRG) stimulation is an effective and safe stimulation technique, and previous reports have implicated the DRG in the development and persistence of chronic pain. The ganglion houses cell bodies of primary sensory neurons, including cells that transmit pain information to the central nervous system (2). Deer *et al*. reported the successful use of DRG stimulation in 10 patients with chronic, intractable neuropathic pain of the trunk and/or limbs. These patients received DRG stimulation for 3-7 days. All patients experienced pain relief in the targeted anatomical regions, with reported improvement ranging from 17% to 100%(3). Liem *et al*. reported on 32 patients with pain of the back, leg, and foot treated with DRG stimulation; at 6 months after implantation, ≥ 50% of the patients had 50% or more pain relief (4).

The above-mentioned favorable results of DRG stimulation of body parts other than the extremities led us to stimulate the DRG in a patient with CRPS type I of the knee that appeared to be intractable.

CASE REPORT

History

We retrospectively present a case of CRPS in a 48-year-old woman who suffered complaints of the right knee for five years. One week after a diagnostic arthroscopy to rule out any meniscal problem, she developed CRPS type I of the knee. This patient was referred to our department for a second opinion. She had already been extensively treated with different types of oral medication. In addition, a lumbar sympathetic block resulted in no clinically significant relief of symptoms, and physical therapy also failed. In particular, the patient's pain (reported to be the most disabling factor) did not decrease.

Examination

When the patient visited our department, the pain on the lateral side and within the knee was described as "irritable and aching" with a score of 6-9 on a numeric rating scale (NRS) ranging from 0 ("no pain") to 10 ("extremely painful"). In addition, she experienced allodynia, hyperalgesia, and tingling around her right knee. The sensory symptoms were not

limited to the innervation area of a single nerve. She also mentioned discoloration of the whole knee, a colder temperature compared to the left knee, trophic changes in leg hair, and motoric dysfunction, but no sweating changes or edema.

Physical examination revealed a swollen, cold, and dark-colored right knee. Palpation was very painful, especially around the patella and the medial tibia head. Allodynia and hyperalgesia around the whole knee and movement restriction also were present. Exploratory neurological examination revealed no other signs as the earlier-mentioned sensory disturbances. The area of the sensory disturbances could not be explained by a mono neuropathy or other neurological etiology. We confirmed the diagnosis CRPS type I of the knee, based on the Budapest criteria set. In addition, thermography revealed the right knee to be colder compared to the left knee.

Treatment

Our treatment started with different types of oral medication, followed by ketanserin/carnitine intravenously. None of these provided any relief of her symptoms; the allodynia even became worse and edema developed. Therefore, we considered neurostimulation as a treatment. In view of the limited area involved and of earlier experience in our department of disappointing results with dorsal column stimulation in patients with comparable localized CRPS, we decided to apply DRG stimulation and included her in a medical ethical committee-approved observational study in our department for the use of DRG stimulation. The patient was informed and gave written consent.

DRG stimulation

The DRG was approached in the same way as described by Liem *et al*. (4) We implanted three DRG stimulation leads at spinal levels L2, L3, and L4, at the right side of the spine (Fig. 1).

The treatment started by implanting one DRG stimulation lead at spinal level L3. The patient reported stimulation vibes within her knee, but these did not cover the entire area. A second DRG stimulation lead was implanted at level L4. The stimulation now covered more of the painful area, but still not everything. So we tried a third DRG stimulation lead on level L2. This level was chosen because of earlier experience with DRG stimulation in our department: sometimes the best level for DRG stimulation is above or below the level one would expect based on the dermatome map. After implantation of this third lead, the stimulation covered almost the entire area; only one spot on the lateral knee side was not covered.

When one lead was in place, it was connected to an external neurostimulator. The neurostimulator was programmed to ensure that the paresthesias were directed to the correct location; the same procedure applies to the other two leads. The parameters of stimulation are presented in table 1.

After eight days of stimulation coverage, the patient reported a substantial decrease in pain intensity. One spot on the lateral knee side was still not covered, but she was very pleased with the results and requested to proceed with permanent implantation. Before, she scored the pain as NRS 6-9, whereas now she scored it as 1. One week later, the implantable pulse generator was placed in the patient's left buttock (Fig. 2).

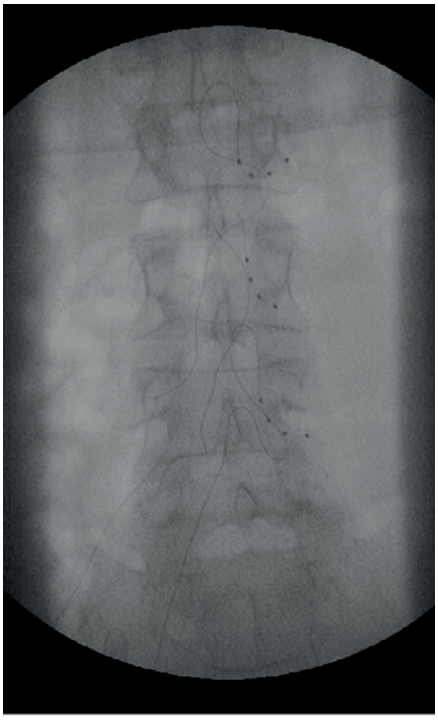

Figure 1. Dorsal root ganglion stimulation leads with four electrical contacts at levels L2, L3, and L4

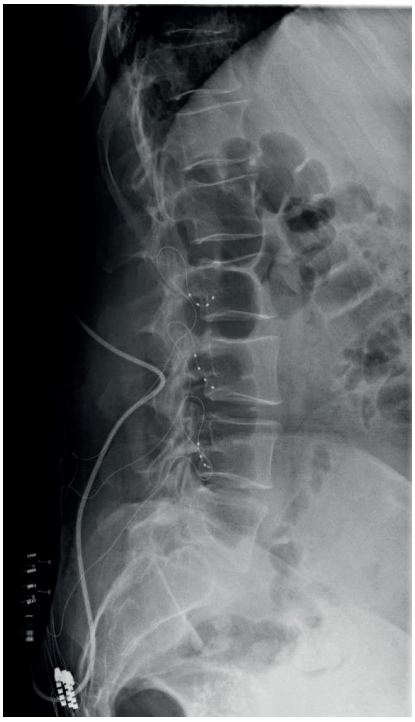

Figure 2. Implantable pulse generator placed in the left buttock

Table 1. Parameters of dorsal root ganglion stimulation in a 48-year-old female patient

		Lead 1 (Spinal level L2)	Lead 2 (Spinal level L3)	Lead 3 (Spinal level L4)
Electrode configuration	1	N	-	N
(+, - or N)	2	N	N	N
	3	+	+	+
	4	-	N	-
Pulse width (μsec)		170	170	160
Frequency (Hz)		20	20	20
Amplitude (μA)		700	1030	500

+, positive; -, negative; N, neutral

One month post-implant, she stated that the entire painful area was covered and graded her pain as 1-2 during stimulation. In addition, movement of the right knee had improved. The device was used 24 hours a day. At 3-months follow-up the NRS score was still 1-2 during stimulation. She did not feel the stimulation vibes anymore, but she certainly could tell when the device was switched off, as her pain returned within minutes. On the other hand, when it was switched on, the effect kicked in within one minute. The patient will further be periodically monitored over one year.

DISCUSSION

This patient with CRPS type I of the knee failed to respond to multidisciplinary pain management. The symptoms fit the Budapest criteria set, but infrapatellar nerve injury should be considered as differential diagnosis (5). An electromyography was not performed, so we cannot be 100% sure that there was no demonstrable nerve damage. In case of nerve damage, the diagnosis should be CRPS type II. The DRG stimulation therapy resulted in a clinically significant result: the pain level dropped from an initial NRS score of 9 to 1-2 and the movement of the knee became better. We chose DRG stimulation due to earlier experience in our department with CRPS of the knee: most patients barely respond to conservative treatment and dorsal column stimulation. Our first results with DRG stimulation therapy for CRPS of the knee are promising and in line with others (3, 4). However, none included a patient with CRPS of the knee. In addition, our follow-up was three months whereas that of Liem *et al*. (4) was six months, making it difficult to extrapolate their results to ours. We realize that this is a case report and therefore had limitations concerning the generalizability across patients; nevertheless, we consider the present results to be encouraging and the DRG to be a potential new neural target for reducing chronic neuropathic pain due to CRPS of the knee.

CONCLUSION

This report indicates DRG stimulation to be an effective therapy for reducing chronic neuropathic pain due to CRPS of the knee. Stimulating the DRG covered the entire painful area, and up to three months post-implant the initial NRS score of 9 had decreased to 1-2. Long-term results are not yet available, and more patients with similar complaints need to be investigated. If such studies replicate the present findings, a controlled study should be performed in order to draw more definite conclusions.

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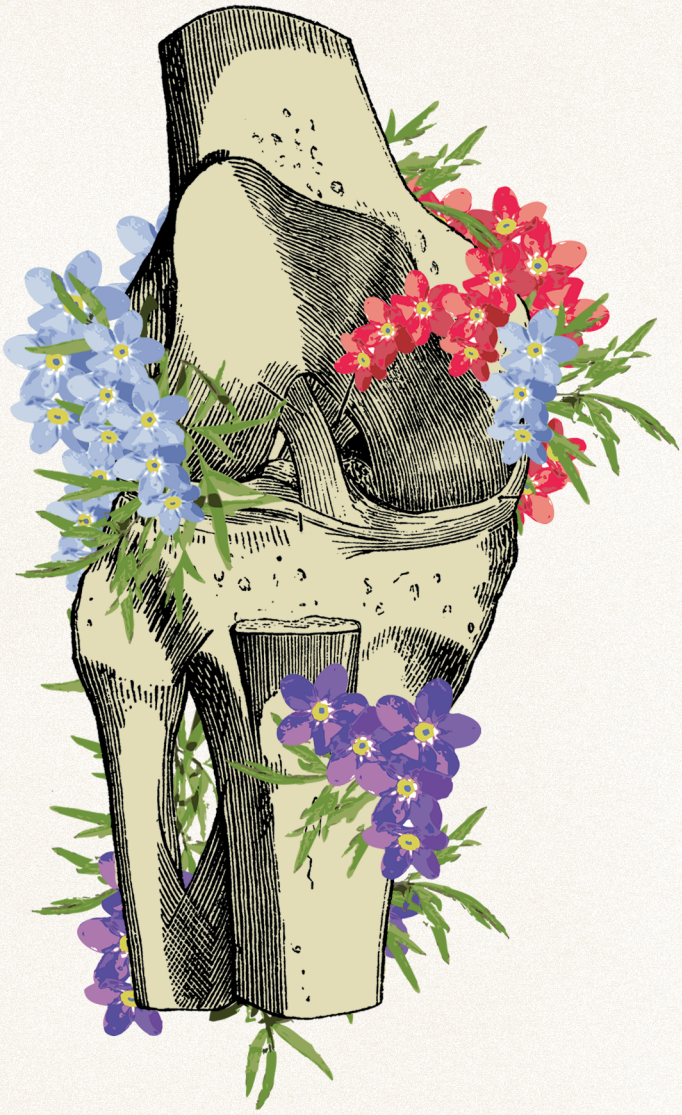

CHAPTER VI

Dorsal Column Stimulation vs. Dorsal Root Ganglion Stimulation for Complex Regional Pain Syndrome Confined to the Knee: Patients' Preference following the Trial Period

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ABSTRACT

Background and Objectives: Patients with complex regional pain syndrome (CRPS) confined to the knee are often therapy resistant. Neurostimulation is an accepted treatment for CRPS. Although results with dorsal column (DC) stimulation in patients with CRPS confined to the knee are often disappointing, the availability of dorsal root ganglion (DRG) stimulation may provide new opportunities for this complaint. Therefore, this study explores patients' preference for DC stimulation versus DRG stimulation in treating chronic pain due to CRPS confined to the knee.

Methods: A prospective, observational crossover cohort study was conducted comparing 2 methods of neurostimulation, in randomized order, in patients with CRPS confined to the knee. After receiving DC and DRG stimulation during a trial period of 16 days, patients were asked which of the 2 methods they preferred. Patients with a successful trial period with one or both stimulation methods received a fully implantable system.

Results: Twelve patients were included. After finishing the trial period, 10 patients (83.3%) preferred DRG stimulation and 2 (16.7%) preferred DC stimulation (P = 0.04).

Conclusion: To our knowledge, this is the first study to compare these 2 neurostimulation methods in patients with CRPS confined to the knee. Results show that the probability of the preference for either neurostimulation treatment significantly deviates from chance in favor of DRG stimulation.

KEYWORDS

Complex regional pain syndrome, knee, patients' preference, dorsal Column stimulation, dorsal root ganglion stimulation

INTRODUCTION

Complex Regional Pain Syndrome (CRPS), formerly known as reflex sympathetic dystrophy (RSD) or algodystrophy, is a collection of locally appearing painful conditions following a trauma. Although CRPS mainly occurs in the feet or hands, other locations are also reported (1). CRPS exceeds in both intensity and duration the expected course of the original trauma. The main clinical features are continuing pain and sensory, vasomotor, sudomotor, and motor trophic disturbances (2). CRPS is a clinical diagnosis based on signs and symptoms described in criteria sets. Currently, the use of the International Association for the Study of Pain (IASP) clinical Budapest diagnostic criteria is recommended (3). The natural history of CRPS is not always positive and can result in permanent disability.

Until now, little has been known about patients with CRPS confined to the knee. In a systematic review, we concluded that CRPS confined to the knee should be considered as a separate phenotype, distinct from CRPS of more distal locations (4). In addition, uncertainty remains regarding the best treatment for CRPS confined to the knee (4). In the Netherlands, all patients with CRPS are treated according to the Dutch Guidelines (5) (updated in 2014). However, as earlier literature shows, patients diagnosed with CRPS confined to the knee are difficult to treat (6-8).

Dorsal column (DC) stimulation is an accepted, effective and safe way of treating specific types of neuropathic chronic pain. In the Netherlands, driven by reimbursement policies, this therapy is used as a last resort for patients in whom the more conservative treatment (eg, oral pain medication) has failed. The presumed mechanism of action is based on electrical stimulation of the large ascending fibers located in the dorsal columns (A beta-fibers), which leads to inhibition of the nociceptive signal entering the spinal cord through the dorsal root (A delta- and C-fibers). CRPS is the second most common indication for DC stimulation, failed back surgery syndrome being the first (9). DC stimulation can provide evident and clinically relevant pain reduction in patients with CRPS (10-14).

The dorsal root ganglion (DRG) is a different target for neurostimulation. The DRG plays a pivotal role in the development and maintenance of chronic pain (15). The ganglion houses the cell bodies of primary sensory neurons, including those cells that transmit pain information to the central nervous system (15). In 2011, the first patients received DRG stimulation for their chronic neuropathic pain. After 12-month follow-up, patients experienced improvement in pain symptoms, health-related quality of life, and their mood (16). In a prospective case series by van Buyten et al., 8 patients with CRPS of the lower extremities received DRG stimulation after a successful trial period. Follow-up of 12 months showed improvement in quality of life in all patients and a reduction in pain ≥50% compared to baseline in 6 of the 8 patients ($P < 0.05$) (17).

Our department has experienced both the failures and successes of DC stimulation in several patients diagnosed with CRPS confined to the knee. When DRG stimulation be-

came available, 1 patient with CRPS confined to the knee was successfully treated using this method (18); this result gave rise to the present study. Based on our hypothesis that DRG stimulation would be more specific than DC stimulation, we compared both methods of neurostimulation in patients with CRPS confined to the knee.

The aim of this trial was to explore patients' preferences in treatment by neurostimulation of their chronic neuropathic-like pain due to CRPS confined to the knee.

METHODS

The institutional research ethics committee approved this study (MEC-2014-170).

Design

This was a prospective, observational, crossover, cohort study comparing 2 methods of neurostimulation, that is, DC and DRG stimulation in randomized order. All patients were diagnosed with CRPS confined to the knee according to the IASP clinical Budapest diagnostic criteria (3) and received (in randomized order) both methods of neurostimulation in succession during a trial period of 16 days in total. During this period, all patients were asked to keep a diary in which they registered their pain intensity on a visual analog scale (VAS) 3 times a day (19). After the trial period, all patients were asked to state which stimulation method they preferred as treatment. The study was registered at www.trialregister.nl (NTR5662).

Study population

Patients diagnosed with CRPS confined to the knee who visited the outpatient pain clinic were invited to participate. To be included, a patient had to meet all the following inclusion criteria: ≥1 year of CRPS confined to the knee; diagnosed according to the IASP clinical Budapest diagnostic criteria; minimum age of 18 years; no improvement in symptoms after ≥1 year of treatment according to the Dutch guidelines for CRPS (updated in 2014) (5); and a pain intensity of ≥50 mm measured on a VAS of 0 to 100 mm. Table 1 presents the inclusion/exclusion criteria.

Intervention

Neurostimulation methods are fully implantable medical devices which are placed epidurally and produce controlled electrical stimulation to spinal neural tissue. For this study, in randomized order, using a crossover design, we applied DC stimulation (Medtronic Inc.®; Fridley; MN, USA) with one 8-contact lead, and DRG stimulation (St. Jude Medical Inc.®; Little Canada; MN, USA) with two 4-contact leads.

Table 1. Inclusion and exclusion criteria for participation in the study

Inclusion criteria	Exclusion criteria
Over 1 year CRPS confined to the knee, diagnosed according to the IASP clinical Budapest diagnostic criteria	Previous neurostimulation
	Depression or anxiety disorder measured with the Hospital Anxiety and Depression Scale (HADS)
	Pregnancy, or pregnancy desire within 1 year
Minimum age 18 years	Patients unable to complete the questionnaires
No improvement of symptoms after at least 1 year of treatment according to the Dutch guidelines for CRPS in primary care	Body Mass Index > 35
	Life expectancy < 1 year
	Implantable cardioverter defibrillator, pacemaker
Pain intensity of at least 50 mm measured on a visual analog scale 0-100 mm	Anticoagulant drug therapy or disturbed coagulation
	Immunocompromised patients
	Drugs/medication/alcohol addiction

CRPS, complex regional pain syndrome; IASP, international association for the study of pain

Following patient consent and study entry, baseline measurements were made (T0). Patients used the 2 neurostimulation methods during the trial period, which lasted 16 days in total. On day 1, implantation of the stimulation leads of both methods took place. A qualified physician with extensive experience in implantation of DC and DRG stimulation systems (F.J.P.M.H.) implanted (under local anesthesia) one 8-contact lead for DC stimulation and two 4-contact leads for DRG stimulation at the same time, during the same procedure. All leads were sutured to the fascia with soft tissue anchors, and the external lead exit point was protected with a bandage.

During the first week, patients received stimulation method 1 (T1); between the 2 stimulation methods, a washout period of 2 days was included (ie, a period without any stimulation, T2); during the second week, patients received stimulation method 2 (T3). A randomization based on a computer program decided the order of stimulation. A qualified nurse took care of turning on the stimulation method, of securing the right settings (DC stimulation was set between 30 and 60 Hz), and of the evaluations during the trial period based on the patients' report and diaries.

The effect of either stimulation method was considered successful if the patient reported at least 50% reduction of pain compared to the situation just prior to that method of stimulation and/or at least a slight improvement on the global perceived effect (GPE) scale (20) after that stimulation. When one of the stimulation methods was considered successful, the patient was eligible to continue treatment with that stimulation method. In case both of the stimulation methods were considered successful, the patient was allowed to choose the stimulation method he or she preferred.

A second surgical procedure, under general anesthesia, took place on day 16 of the trial period. A qualified physician (F.J.P.M.H.) implanted an implantable pulse generator (IPG)

in the abdomen or buttock of the patient for the lasting stimulation and removed the leads of the other system. Patients then entered the long-term follow-up period of 12 months. In case both stimulation methods failed, both were explanted during the second surgical procedure. During the 12-month follow-up period, patients visited the pain department at 1, 3, 6 and 12 months after the second surgery.

Statistical analysis

The primary outcome parameter was the patient's preference for one stimulation method over the other, being a binomial variable. As this was an explorative study, the aim of the statistical analysis was primarily descriptive, not inferential. The proportion of patients preferring one stimulation method over the other will be reported, including the 95% confidence interval (CI) of that proportion (Clopper-Pearson Exact method). Analyses were performed using IBM SPSS Statistics 21 (IBM Corp. Armonk. NY, U.S.A).

RESULTS

Of the 74 patients considered for inclusion, 60 were excluded because 1) the diagnosis CRPS of the knee could no longer/not be confirmed, 2) they had already received treatment with neurostimulation, or 3) they were unwilling to participate. Of the remaining 14, 1 patient dropped out during the first operational procedure. In this patient, it proved impossible to implant the two 4-contact leads of the DRG stimulation, possibly due to degenerative deviations in the lumbar spine. Another patient dropped out during the trial period because he experienced sensory complaints in both legs the day after the first operational procedure. The sensory complaints were not objectivized by a neurologist, and an infection or epidural bleeding was ruled out. However, to reduce any potential risk of damage, the leads of both systems were removed shortly thereafter; the complaints disappeared immediately after removal and no permanent injury occurred.

This left 12 patients who finished the entire trial period: 11 females, 1 male; mean age 38.7 (range 22 to 57) years. In this group, mean VAS score at baseline was 68 on a scale of 0 to 100 (0 representing no pain, 100 representing worst imaginable pain). None of the included patients had demonstrable nerve injury in the affected knee (as measured by an electromyogram). Coverage of the painful area during implantation, was achieved in every patient with placement of the DC stimulation lead at the 8^{th}, 9^{th} or 10^{th} thoracic vertebra (Th-8, Th-9 or Th-10) and placing the DRG stimulation leads at the 3^{rd} and 4^{th} lumbar vertebrae (L-3 and L-4). Figure 1 shows the lead placement in a representative patient: the DC stimulation lead tip was positioned at Th-10 and the DRG stimulation leads were positioned at L-3 and L-4.

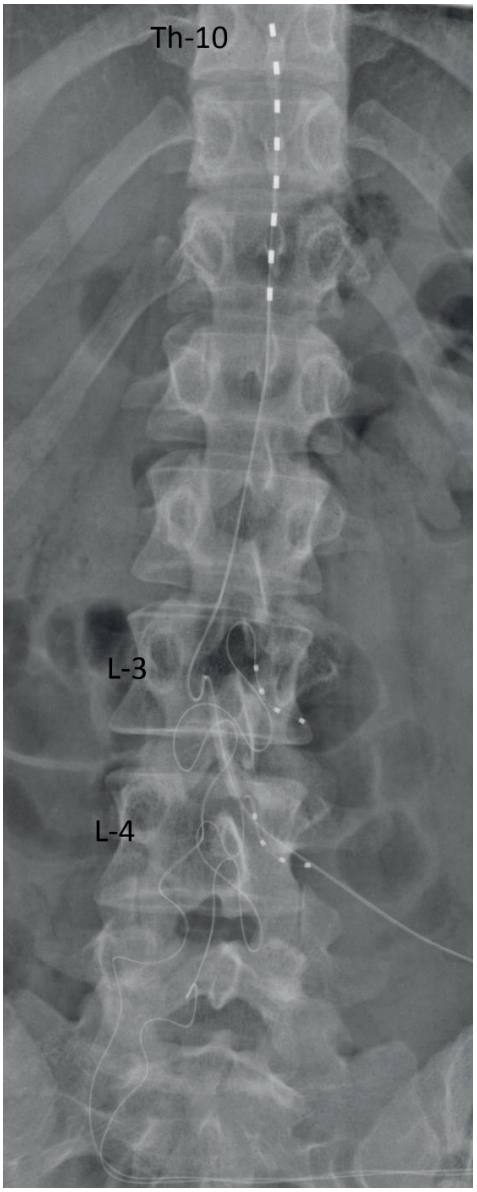

Figure 1. Lead placement during trial period
Th-10, 10th thoracic vertebra; L-3/L-4, 3rd and 4th lumbar vertebrae

Patients' Preference

Ten patients (83.3%) preferred DRG stimulation and 2 [16.7%; (95% CI: 0.02 to 0.48)] preferred DC stimulation (P = 0.04, one-sample binomial test).

In 5 patients, both stimulation methods were considered successful (patients 2, 4, 10, 11, and 13). These patients were allowed to decide which stimulation method they would have implanted permanently. Four patients (2, 4, 10 and 13) chose the DRG stimulation. Their main reason for this was that (in contrast to DC stimulation) they felt no stimulation vibrations. Moreover, during the evaluation of DC stimulation, all mentioned that they had to adjust the stimulation intensity multiple times a day. One of these patients also chose DRG stimulation because DC stimulation did not cover the whole painful area. In contrast, patient 11 chose DC stimulation because she liked the fact that she felt the stimulation vibrations and found that her walking ability had improved more with DC stimulation.

For all 12 patients, the stimulation method they preferred was implanted during the second surgical procedure.

The implanted method

In 7 of the 12 patients, the decision regarding which stimulation method was to be implanted was based on the fact that only one stimulation method proved successful after completing the trial period (patients 1, 3, 6, 7, 9, 12, and 14). The 4 patients who had success with only DRG stimulation stated that the vibrations of DC stimulation were intermittent to intensive and rather nonspecific (ie, the area covered by stimulation was larger than the painful area alone) or did not stimulate the actual painful area. The patient in whom only DC stimulation worked stated that DRG stimulation provided no pain relief, and no improvement was experienced in relative to the baseline GPE score.

Measurements during the trial

During the trial period, patients returned to our department 3 times. At each visit, the nurse turned on/off the stimulation method and made an evaluation based on the patient's self-report and diary. Mean VAS scores were calculated for each stimulation method based on the 3 scores in the patient's diary on the last day of stimulation with that method. Using the GPE scale, patients were asked at T1 and T3 to rate how much their condition had changed in comparison with T0 and T2, respectively. All patients responded that their condition had (much) improved and that they were (absolutely) satisfied with the result based on their preferred stimulation method. Table 2 presents these data.

Adverse Events

During the trial period, 3 adverse events were experienced by 2 patients; these were judged by the investigators to be related to the device or to the surgical procedures. One patient had cerebrospinal fluid leak with associated headache after the first surgical procedure; in this patient, all leads were removed during the second surgery, due to possible infection, and 3 months later, the device of choice (ie, DRG stimulation) was implanted. Another patient was admitted to hospital for a few days because of elevated temperature; however,

no active infection was demonstrated on blood tests. The patient with sensory complaints in both legs 1 day after the first procedure was excluded from the study; nevertheless, this patient was reported as experiencing an adverse event, possibly related to the device. The sensory complaints were not objectivized by a neurologist, and an infection or epidural bleeding was ruled out.

Table 2. Scores on the VAS and GPE, and patients' preference during the trial period

Patient ID no.	VAS score T0	Stimulation 1	VAS score T1	GPE T1	VAS score T2	Stimulation 2	VAS score T3	GPE T3	Patients' preference
1	82	DRG	71	No change	83	DC	32*	Much improved*	DC
2	76	DRG	10*	Much improved*	78	DC	0*	Much improved*	DRG
3	85	DC	54	Slightly improved*	70	DRG	33*	Slightly improved*	DRG
4	70	DC	0*	Completely recovered*	35	DRG	0*	Completely recovered*	DRG
6	74	DRG	49	Slightly improved*	82	DC	78	No change	DRG
7	50	DC	24*	No change	31	DRG	11*	Slightly improved*	DRG
9	70	DRG	21*	Slightly improved*	65	DC	51	Slightly improved*	DRG
10	85	DRG	36*	Slightly improved*	90	DC	51	Slightly improved*	DRG
11	71	DC	3*	Much improved*	80	DRG	16*	Much improved*	DC
12	75	DC	49	No change	46	DRG	67	Slightly improved*	DRG
13	80	DC	43	Slightly improved*	67	DRG	35	Much improved*	DRG
14	63	DC	67	No change	61	DRG	30*	Much improved*	DRG

VAS, visual analog scale; GPE, global perceived effect scale; DRG, dorsal root ganglion; DC, dorsal column.
*Trial success
T0, baseline; T1, after stimulation 1; T2, after washout period; T3, after stimulation 2

DISCUSSION

The aim of this prospective trial was to explore patients' preference in treatment by neurostimulation of their chronic neuropathic-like pain due to CRPS confined to the knee. In a crossover design, DC stimulation was compared with DRG stimulation. The results show that, in these patients, the probability of the preference for either neurostimulation treatment significantly deviates from chance in favor of DRG stimulation.

DC vs. DRG stimulation

Reduction in pain due to DC or DRG stimulation turned out to be comparable between the patients, as shown in table 2. So, apparently, patients have other, probably individual, reasons to prefer a stimulation method, and this is not solely based on obtained pain

relief. This finding is in line with the results found by others (21). DC stimulation is known to be somewhat nonspecific and to have more positional side-effects (22). In this study, both these items were often mentioned by patients as reasons for their preference for DRG stimulation over DC stimulation. Three patients stated that DC stimulation did not cover the entire painful area. In contrast, 4 patients reported that DC stimulation covered an area that was actually larger than their painful area. During evaluation of DC stimulation, 6 patients said that they thought the stimulation vibrations were too strong, even after lowering the intensity themselves. They also mentioned they found it bothersome to have to adjust the stimulation level several times a day, as well as experiencing different stimulation intensities during walking, sitting, or lying down. Therefore, the present study confirms that DC stimulation can be rather nonspecific and has more positional side effects. None of these limitations were mentioned in relation to DRG stimulation and were reasons for patients to prefer that form of stimulation.

In one patient, it was impossible to implant the DRG leads, whereas the DC stimulation lead was placed in the right position without any problem. A computerized axial tomographic scan showed a degenerative lumbar spine, but no neuroforaminal stenosis. Thus, even when the neuroforamina appear to have a normal entry, it can be difficult to place DRG leads, in our case possibly due to degeneration of the lumbar spine. This can be an important item when considering the feasibility of applying DRG stimulation. Also, in 2 of the patients, motor stimulation occurred when stimulating one of the DRG leads. Adjusting the settings turned out to be the solution to remove the motor stimulation. This motor stimulation did not occur with DC stimulation.

Methodological Remarks

The trial period included a washout period of 2 days; there are no earlier reports concerning the appropriate duration of a washout period. At T2 (after the washout period), all patients reported that the pain relief ceased within minutes to hours after stopping the first stimulation method; this applied to both DC and DRG stimulation. However, when comparing the T0 VAS scores with the T2 VAS scores, different VAS scores emerged in 7 of the 12 patients. This could imply that patients need a longer recovery time to prevent a carryover effect or that a response shift occurred during the first stimulation. As the VAS scores were compared before the start of a stimulation method and at the end of that specific stimulation method, the ascertainment of success cannot have been influenced by (events in) the washout period.

Regarding adverse events, as 2 different stimulation methods were implanted simultaneously, it was impossible to relate these events to either stimulation method. Of the 2 patients with a possible infection, in one patient this necessitated removal of all the leads during the second surgical procedure. No wound complications were seen in the patient

group. As infection and wound complications are reported with either neurostimulation treatment (23), this did not differ in the present patient group.

All surgical procedures were performed by the same qualified physician (F.J.P.M.H.). The first surgical procedure was undoubtedly intense for patients, because 2 different stimulation methods were implanted simultaneously. Patients later reported that especially placement of the 2 DRG leads was more painful than placement of the single DC lead, which always took place first during the procedure. Also, for the physician, these procedures took longer, implying a potentially higher risk of infection and/or contamination (24).

A possible limitation of the present study was the lack of blinding; future studies should aim to find a more controlled, blinded way of comparing the 2 neurostimulation methods using a crossover design. Monitoring patients' preference of stimulation method only immediately after the trial period can also be considered as a limitation of the present study. After all, patients can change their mind over time. So the results at trial end cannot be generalized to the long term.

CONCLUSION

To our knowledge, this is the first study to explore preferences for DC or DRG stimulation in patients with CRPS confined to the knee. The results show a preference for DRG stimulation over DC stimulation, because DRG stimulation can be more specific for the painful area and is independent of the body position, and patients appreciated the absence of stimulation vibrations. It is not possible to generalize the results of this study to other CRPS locations (the foot or the hand). Nevertheless, we recommend that physicians consider DRG stimulation, rather than DC stimulation, in case of intractable CRPS confined to the knee. Follow-up data from this study are currently being processed.

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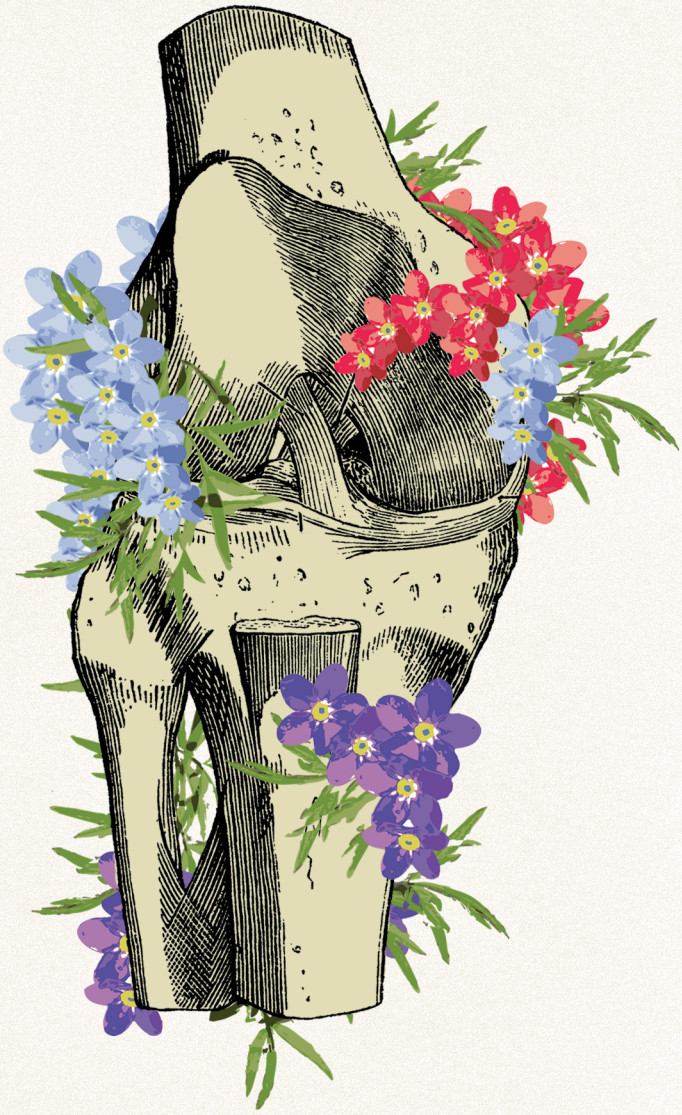

CHAPTER VII

Letter to the editor

CRPS knee: how frequently encountered in differential diagnosis of knee pain?

Aggarwal A,
Agarwal A

Response to the letter to the editor

Bussel, CM van
Stronks DL,
Huygen FJPM

Pain Practice. 2019 Jan;19(1):131

LETTER TO THE EDITOR

CRPS knee: how frequently encountered in differential diagnosis of knee pain?

To the Editor:

We have read with great interest the paper by van Bussel et al. recently published in Pain Practice (1). I wish to congratulate the authors for their valuable contributions.

In the article, 12 patients who had complex regional pain syndrome (CRPS) confined to the knee were included. Although reports have been published involving primarily the knee after total knee arthroplasty, the incidence of CRPS of the knee following trauma or otherwise is not well appreciated (2, 3). We would have appreciated the authors mentioning the presence or absence of any inciting event for the development CRPS of the knee in these 12 patients, which could help better diagnose and manage patients with CRPS of the knee.

Further, conditions affecting the knee frequently do not present with the classic combination of signs and symptoms seen in the upper extremity (4, 5). Did all 12 of the patients fully meet Budapest diagnostic criteria or was any working hypothesis of CRPS made in any patient on clinical grounds after ruling out other conditions? Commentary on this by the authors might have helped in reducing the wide discrepancy in interpretation of the signs and symptoms necessary to make the diagnosis of CRPS.

Also, since CRPS confined to the knee is infrequently encountered in the differential diagnosis of knee pain (6), we would have preferred that the authors share the time frame during which this particular study was conducted.

Thank you.

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RESPONSE TO THE LETTER TO THE EDITOR

Dear Editor,

We totally agree with the statement of the authors of the letter to the editor that "the incidence of CRPS knee following trauma or otherwise is not well appreciated." We would like to refer to our earlier published paper in which we concluded that the scientific literature does report cases of complex regional pain syndrome (CRPS) type I of only the knee(s). Our recommendation was to consider CRPS confined to the knee as a medical entity and therefore to include CRPS of only the knee(s) in future research on the etiological mechanisms of and optimal treatment for CRPS (7).

The authors of the letter to the editor stated that "we would have appreciated if presence or absence of any inciting event for the development CRPS knee in these 12 patients could be mentioned, which could be helpful in a better diagnosis and management...." This is a good addition, and we certainly want to provide this information. Within the group of 12 patients who all finished the trial period, the following causes of the knee CRPS were given: 7 patients had undergone (arthroscopic) surgery or an arthroscopy, 4 patients had a trauma of the knee (2 had a luxation of the patella and 2 patients had fallen on the specific knee), and 1 patient had a fracture of the tibia plateau. The surgical causes of CRPS confined to the knee are in line with one of our earlier reports concerning CRPS confined to the knee (7).

Another thing stated by the authors of the letter to the editor was "further, conditions affecting the knee frequently do not present with the classic combination of signs and symptoms seen in the upper extremity (3, 4)." We have studied presentation of CRPS confined to the knee in an earlier study (8). Our conclusion was that the variation in terms of symptoms and signs of CRPS confined to the knee compared to CRPS of the ankle/foot is limited. And the phenotypes of CRPS confined to the knee and CRPS of the ankle/foot seem to be comparable, but not identical. This can be a reason why CRPS in patients with pain of the knee that is disproportionate to the initial trauma is sometimes not recognized. Nevertheless, the International Association for the Study of Pain (IASP) clinical Budapest diagnostic criteria can and should be used to diagnose CRPS confined to the knee.

A further question raised by the authors of the letter to the editor was "... did all of the 12 patients fully meet Budapest diagnostic criteria or any working hypothesis of CRPS...?" We can answer this question with "yes." All of the patients included in this study fully met the IASP clinical Budapest diagnostic criteria, as this was one criterion for participation

in the study. All inclusion and exclusion criteria were described in Table 1 of the original manuscript.

The last question of the authors was "... could share with us the time frame during which this particular study was conducted?" Patients who were included in the study had a diagnosis of CRPS for over 1 year, as this was one of the inclusion criteria for participation. The total length of the study was 1 year per patient; this includes the follow up of 12 months after neurostimulation implantation. The time between the first patients being included and the last patient scheduled for 12 months' follow-up was approximately 3 years.

We agree with the authors of the letter to the editor that "CRPS confined to the knee is infrequently encountered in differential diagnosis of knee pain (6)." We hope that our previous and current work, the letter to the editor, and our answers will change this and be of help for those patients with a serious, invalidating problem that is denied too often.

On behalf of all the authors, I thank the editor for the opportunity to comment on the questions raised and the notes made by the authors of this manuscript. We hope we have added more understanding of our paper with these answers.

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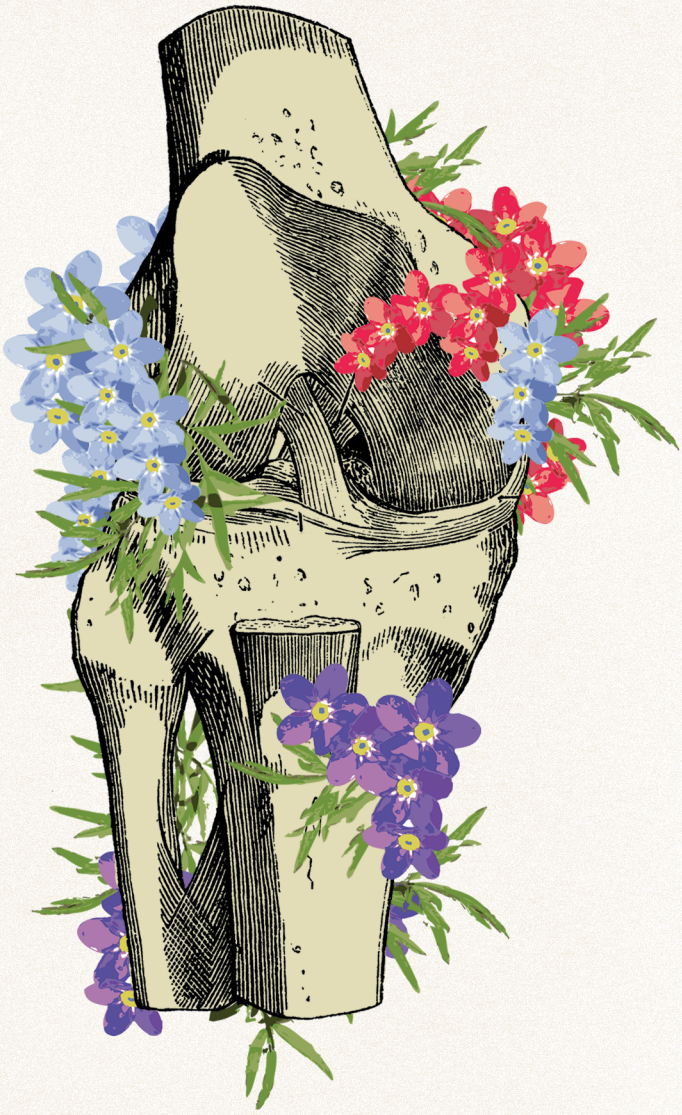

CHAPTER VIII

General discussion

COMPLEX REGIONAL PAIN SYNDROME (CRPS) CONFINED TO THE KNEE: TO BE OR NOT TO BE?

Over the years, complex regional pain syndrome (CRPS) has been relabelled several times. Before the term CRPS was adapted for this disease, *algodystrophy* and *reflex sympathetic dystrophy (RSD)* were most commonly used. 'Complex' refers to the clinical symptoms such as pain and sensory and motor abnormalities, and 'regional' to the distribution of the signs and symptoms. This distribution is often glove or stocking shaped and not within a specific nerve distribution or a dermatome. 'Pain' is the main symptom of the disease and is disproportionate to the intensity of the initial trauma (1). CRPS affecting a hand or a foot has been widely accepted and discussed.

A group of patients was seen in the Center for Pain Medicine, Erasmus University Medical Center, with painful complaints confined to the knee. Our motivation to perform the studies mentioned below and to write this thesis is to determine whether these complaints meet the diagnostic criteria for CRPS. The main objective is to establish whether CRPS confined to the knee is a legitimate diagnosis and, if so, to increase the knowledge of its development. We hope to disseminate the knowledge of this diagnosis among physicians and thus to facilitate the recognition of patients' complaints as CRPS confined to the knee. We also want to offer patients a treatment for this very disabling and painful condition. In this chapter, we discuss the results of our studies and make a recommendation for future research.

DISCUSSION OF THE RESULTS

Regarding the legitimacy of the diagnosis CRPS confined to the knee, we performed a systematic review to answer this question: Are there descriptions in the medical literature of CRPS affecting the knee(s) that is diagnosed according to the criteria used at the time of publication (see Chapter 2)? We concluded that CRPS affecting solely the knee(s) has actually been described before, and more than 20% of the reported cases would meet the current Budapest diagnostic criteria set. In addition, we summarised the aetiology and possible treatment of CRPS confined to the knee. A total of 44% of the cases had (arthroscopic) knee surgery as the inciting event (2-4). When considering the differential diagnosis of CRPS confined to the knee, however, inflammatory arthritis, cellulitis, osteomyelitis, deep vein thrombosis, vascular disorders, entrapment neuropathies and malignancy should always be considered (5). Furthermore, post-surgical pain (if development started after a surgical procedure) and infrapatellar saphenous neuralgia (which causes characteristically neuropathic pain) should also be considered as a differential diagnosis (6).

Having assumed that CRPS confined to the knee is a legitimate diagnosis, we compared the phenotypes at the time of diagnosis of patients with CRPS of the knee to those of patients diagnosed with CRPS of the ankle/foot. In this retrospective study, which is described in Chapter 3, we found a significant difference in the duration of complaints before patients received a diagnosis of CRPS ($P = 0.02$). Patients with CRPS of the knee suffered longer than patients with CRPS of the ankle/foot before being correctly diagnosed. This delay in diagnosing CRPS confined to the knee was not a new finding. Earlier reports had described averages delay of 29 months, 26 months and 11.2 months (3, 5, 8). All patients in our study mentioned severe, continuing pain at the time of diagnosis. At diagnosis, patient reports of hyperesthesia, hyperalgesia, decreased range of motion and dystonia were statistically significantly more common in the ankle/foot group than in the knee group. In terms of signs, hypoesthesia, hyperalgesia, color asymmetry and sweating asymmetry were observed statistically significantly more often in the ankle/foot group. Because of the longer duration before diagnosing CRPS confined to the knee, and the fact that CRPS changes over time, we performed a post hoc pairwise matching analysis excluding this difference in duration. This factor could, after all, have impaired internal validity of our research. When the difference in time to diagnosis was controlled for, however, the differences in the proportions of patients suffering from the symptoms and signs listed above were unchanged. These differences might be due to (not having corrected for) multiple testing, but for example, dystonia of the knee is uncommon and difficult to examine, because decreased range of motion in the knee will already influence flexion and extension. For the knee CRPS group, surgery or arthroscopy turned out to be the most common initiating event. In contrast, for the ankle/foot group, a fracture of the lower leg was the most frequently reported precipitating event. Based on our results, we concluded that although the variation between the phenotypes of knee CRPS and ankle/foot CRPS is small, the two conditions are not identical.

Having found phenotypical variation at the time of diagnosis between these two conditions, we investigated the clinical course of CRPS confined to the knee. In addition, we compared the clinical course between pairwise-matched patients in the two groups. This work is described in Chapter 4. Spontaneous resolution (without having received any kind of treatment) did not occur in the group of patients with CRPS of the knee, although such resolution has been described for CRPS of more distal locations (7, 8). The self-reported recovery rate (among those having received treatment) was 16% in our CRPS confined to the knee group, which contrasts with a recovery rate of 29% in a CRPS of the ankle/foot group in an earlier study reported by de Mos et al (9). Based on the pairwise matching analysis across the groups, we concluded that symptoms in the group with CRPS confined to the knee were more stable over time, although recovery was less common. Both of these differences may be because the delay in recognition of CRPS in this group may result in aggravation or stabilization of the signs and symptoms before correct treatment is started

(10). The health-related quality of life experienced by patients with CRPS confined to the knee turned out to be comparable to that of patients with CRPS in more distal locations. Also, we found a work status change due to CRPS of 82% in the CRPS of the knee patient group, which is in line with the 72% work status change due to CRPS of other locations described by Kemler et al (11). Thus, the adverse impact on working status and health-related quality of life of CRPS confined to the knee seems to be comparable to that of CRPS of more distal locations. This despite the fact that CRPS of the knee seems to have a less favorable clinical course than CRPS of more distal locations in terms of presentation of symptoms and signs over time.

The literature describes various treatment strategies, with various outcomes (12, 13). In our department, we have seen patients with CRPS confined to the knee who failed to respond to all treatments. The failure to respond to treatment in this patient group has also been described by Miller (14). So, the challenges of finding a successful therapy for CRPS confined to the knee seem to match those encountered in the search for a successful therapy for CRPS of more distal locations. This gave rise to our next studies. Spinal cord stimulation (SCS) is an accepted and effective treatment for specific types of chronic pain, and CRPS is the second most common indication (15). Because dorsal root ganglion (DRG) stimulation became available, and provided positive results in patients with CRPS of the lower extremities (16), we hypothesized that this type of stimulation could be an option for patients with CRPS confined to the knee. In Chapter 5, we described a patient diagnosed with CRPS confined to the knee that we successfully treated with DRG stimulation. After the implantation of three DRG leads at the lumbar spinal level, the entire painful area at the knee was covered with stimulation vibrations and the patient reported a substantial decrease in pain intensity. We considered these results to be encouraging and the DRG to be a potential new target for reducing neuroplastic pain due to CRPS confined to the knee.

Because we have seen both the successes and the failures of SCS in patients with CRPS confined to the knee, we performed a prospective study comparing the two methods of neurostimulation, that is, SCS and DRG stimulation, to determine patients' preference. This study is reported in Chapter 6. A total of 14 patients were included, of whom 12 finished the trial period, and all received an implantable pulse generator (IPG) because of a successful trial. Ten patients (83.3%) preferred DRG stimulation, and two preferred SCS ($P = 0.04$). The pain reduction, assessed on a visual analogue scale (VAS), turned out to be comparable between SCS and DRG stimulation, so patient preferences were not solely based on pain relief experienced. This is in line with results presented by others (17). Our study confirms that SCS tends to be nonspecific and has more positional side effects (18). These nonspecific stimulation vibrations (covering an area bigger than solely the painful area) and positional side effects were reasons patients cited in expressing a preference for DRG stimulation over SCS. Pain not restricted to a specific dermatome could be targeted by DRG stimulation, as we saw in the first patient we treated. DRG stimulation can relieve

pain in the affected area without the patient's experiencing stimulation vibrations, which was one of the main reasons patients in our group preferred DRG over SCS. In addition, DRG stimulation turned out to be more user-friendly than SCS, as patients had to adjust the SCS intensity multiple times a day. Also, DRG stimulation could be superior to SCS in treating the dystonia component of CRPS. This is an interesting finding for patients with CRPS confined to the knee, as dystonia of the knee results in a completely non-usable limb.

All included patients mentioned the fact that the implantation of the DRG leads was much more painful than the implantation of the SCS lead. Also, we found it impossible to implant the DRG leads in one patient, possibly due to degeneration of the spine, which is something the physician should be aware of when choosing DRG stimulation as a potential treatment. Overall, DRG stimulation was preferred over SCS by the majority of the patients with CRPS confined to the knee. We recommend that physicians consider DRG stimulation, rather than SCS, as a potential treatment for patients with chronic neuroplastic pain due to CRPS confined to the knee. A letter to the editor concerning this prospective study and our response to the letter are presented in Chapter 7. The authors of the letter posed pertinent questions and provided relevant comments, to which we replied.

IN CONCLUSION

Having applied the currently recommended IASP clinical Budapest diagnostic criteria to patients with signs and symptoms of CRPS at the knee, we can state that CRPS confined to the knee is a legitimate diagnosis. This means that the knee should be considered a location in which CRPS can develop. Surgery is the most common preceding event related to this type of CRPS.

We hope the research described in this thesis will aid physicians in recognising CRPS of the knee(s) as a legitimate diagnosis, so that these patients will be better understood by their physicians.

The phenotypes of symptoms and signs of CRPS confined to the knee and those of CRPS of the ankle/foot at the time of diagnosis are not identical, although their variation is limited. Considering the location of the CRPS, some significant differences are understandable, although some of the variation may be due to a delay in diagnosing.

The clinical picture of CRPS confined to the knee is more stable over time, and thus has a less favourable clinical course than CRPS of other, more distal locations. The effects of this include an adverse impact on work status and health-related quality of life for these patients.

Neurostimulation should be considered as a potential treatment for patients with CRPS confined to the knee. We have found a patient preference for DRG stimulation over SCS,

although both neurostimulation methods gave equal pain reduction. Thus, physicians should not measure their treatment success only in terms of pain reduction.

RECOMMENDATIONS FOR FUTURE RESEARCH

CRPS confined to the knee should be included among CRPS locations in all research into the condition. Much research has been conducted on the use of vitamin C as a preventative to the development of CRPS after wrist, hand, ankle and foot surgery. High-level evidence has been found supporting perioperative supplementation of vitamin C of 1g/d for 50 days for prevention of CRPS (19). As this thesis has shown, most cases of CRPS confined to the knee developed after (arthroscopic) knee surgery. This suggests we should consider the use of vitamin C supplementation during the perioperative period in patients who will undergo knee surgery.

Because the development of CRPS confined to the knee primarily occurs after surgery, there is a need to distinguish patients with post-surgical pain from patients with CRPS. Post-surgical pain is labelled as pain for at least 3–6 months after surgery that normally stabilises within these months and is regularly described in patients who underwent a total knee arthroplasty (20). CRPS is characterized by a continuing pain that is disproportionate in time or degree to the usual course of pain after trauma or another lesion. The pain is regional (i.e., not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor/edema and/or trophic findings. The syndrome shows variable progression over time. The difference between post-surgical pain and CRPS is the ongoing autoinflammation, which is not seen in post-surgical pain, but actually is the distinguishing pathophysiologic characteristic phenomenon of especially acute CRPS. Also, patients with post-surgical pain of the knee describe primarily sensory and/or sudomotor complaints and, thus, do not meet the Budapest criteria to be diagnosed with CRPS (21). If the autoinflammation diminishes over time in CRPS, and the clinical picture is mainly based on what was damaged during the active inflammatory stage, it can become very challenging to distinguish between post-surgical pain and CRPS. Whenever an orthopaedic or trauma surgeon has doubts concerning the diagnosis and/or treatment in these cases, it is advisable that patients be referred to a pain specialist, given the necessity for a different therapeutic strategy.

The inter-individual variations in presentation of CRPS represent the heterogeneity of the underlying mechanisms, and an increasing amount of evidence is being collected towards a mechanism-based treatment for CRPS (1, 22). We recommend continuing research into understanding the pathophysiology of CRPS and identifying the best therapy for patients, preferably mechanism-based therapy.

Recently Bharwani et al. have shown that plasma levels of the soluble interleukin-2 receptor (sIL-2R) are elevated in CRPS. The receptor reflects the activity of T-cells and, hence, the presence of an inflammatory process (23). This finding can guide physicians in distinguishing post-surgical pain from CRPS and in their treatment algorithm.

As shown in this thesis, neurostimulation should be considered as a treatment option for CRPS confined to the knee. Due to reimbursement policies, neurostimulation is used as a last resort for patients in whom more conservative treatment has failed. Using this treatment as a last resort is a disputable approach. First, we know by experience that these patients in particular are quite therapy-resistant to more conventional treatments. This calls into question the wisdom of having to exhaust more conservative treatments before moving to neurostimulation. Second, Gravius et al. recently performed a preliminary study to evaluate the impact of DRG stimulation on inflammatory markers in serum and saliva in patients with CRPS and matched controls. They found a significant decrease in serum anti-inflammatory interleukine-10 (IL-10), which had been elevated at baseline, 3 months after DRG stimulation in the CRPS group. This suggests a diminution of the ongoing inflammatory process known to occur in CRPS (24). This finding supports the consideration of applying neurostimulation therapy earlier in the treatment algorithm for CRPS confined to the knee.

We are aware of the fact that the diagnosis of CRPS confined to the knee is rare, but it has great consequences for the patients who develop it, and they should be diagnosed correctly and treated as quickly as possible. CRPS should be considered as a multidimensional disease requiring an interdisciplinary approach, including psychological care (25). Thus, the answer to our ‘to be or not to be?’ question at the start of this chapter about CRPS confined to the knee must be ‘to be!’

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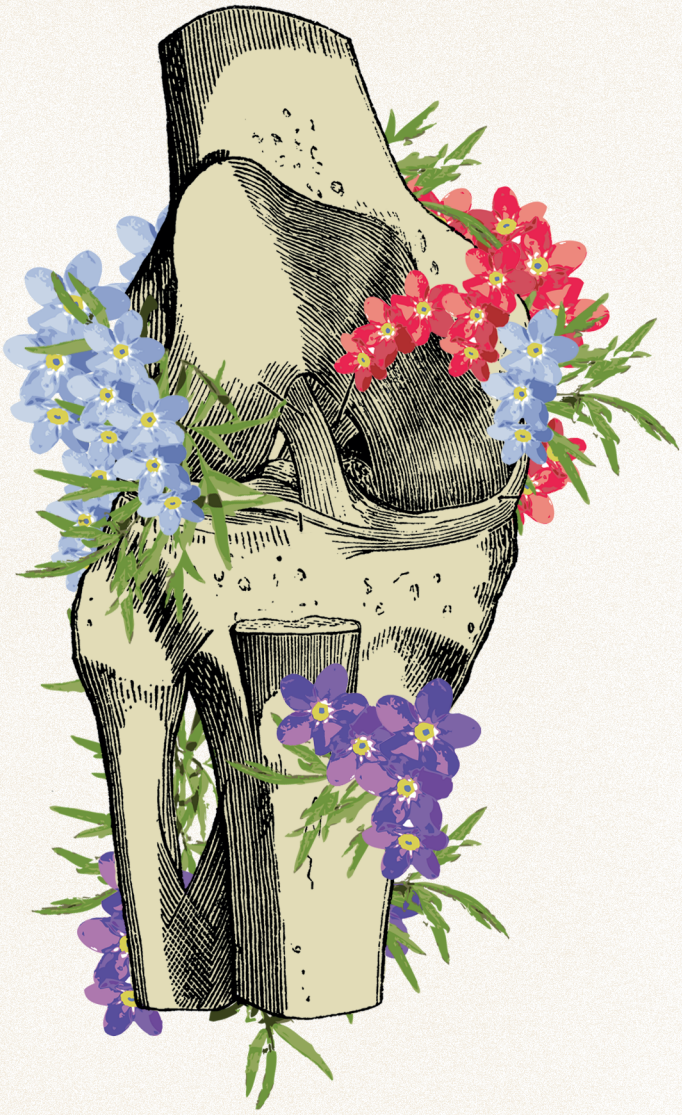

CHAPTER IX

Summary

Nederlandse samenvatting

SUMMARY

Chapter 1

The general introduction describes the rationale for this thesis. CRPS confined to the knee is an unrecognized location for CRPS. Due to this unfamiliarity, it typically takes considerable time before patients with this condition receive the right treatment for their complaints. In gathering more information about this specific location of CRPS, we hope to minimize this delay. Therefore, we explored the literature, performed several studies to investigate the clinical picture and the course of the disease, and conducted a clinical trial concerning the possibility of neuromodulation treatment.

Chapter 2

A systematic literature research revealed 31 articles concerning CRPS of only the knee(s) compromising a total of 368 patients. Most of these patients were diagnosed based on their clinical picture, and we determined that more than 20% of them would meet the currently recommended Budapest criteria. Several authors used lumbar sympathetic blockades and radiographs/bone scans to confirm whether a patient should be diagnosed with CRPS. This is in contrast to the currently used method of diagnosing CRPS purely based on the clinical picture. An (arthroscopic) surgery or arthroscopy of the knee appeared to be the main inciting factor for development of CRPS, and the ideal treatment is yet to be found.

Chapter 3

To gain more information about the clinical features of CRPS confined to the knee, a retrospective comparison was made between CRPS of the knee and CRPS of the ankle/foot at the time of diagnosis. We discovered that patients with CRPS confined to the knee had a significantly longer duration of their complaints before diagnosis than did patients with CRPS of the ankle/foot. Additionally, we found some significant differences regarding four symptoms and four signs, which probably can be explained by the difference in location of the CRPS. These findings indicate that the phenotypic variation in terms of symptoms and signs of CRPS confined to the knee compared to CRPS of the ankle/foot is limited, but the phenotypes are not identical.

Chapter 4

No earlier reports are known of the clinical course and impact of CRPS confined to the knee.We asked a total of 32 patients diagnosed with CRPS confined to the knee to report their past and current CRPS symptoms, work status and quality of life. Their mean follow-up time since having received a CRPS diagnosis was 11.5 years, and their recovery rate was only 16%. The work status of most of the patients changed due to the diagnosis, and 91%

of the patients implied that pain in some way interfered in their lives. We also compared the clinical picture in terms of symptoms and signs of this group of patients with that of a group of patients with CRPS of more distal locations; patients with CRPS confined to the knee exhibited less change over the course of time.

Chapter 5

The dorsal root ganglion plays a pivotal role in the development and persistence of chronic pain and stimulation of this structure can be an effective and safe treatment for pain. Here, we describe the first patient diagnosed with intractable pain due to CRPS confined to the knee to be successfully treated with dorsal root ganglion stimulation.

Chapter 6

In this chapter, we present the results of our prospective, crossover, cohort study comparing two methods of neurostimulation (dorsal root ganglion and spinal cord stimulation). The aim of the study was to explore patients' preference in neurostimulation treatment of their chronic pain due to CRPS confined to the knee. A total of 12 patients finished the trial period, and the results show that the probability of a preference for one of the neurostimulation treatments significantly deviates from chance in favor of DRG stimulation. Therefore, we recommend that physicians consider DRG stimulation in cases of intractable CRPS confined to the knee.

Chapter 7

Relevant questions and notes were made by two authors concerning our prospective study. They wrote a letter to the editor of the journal in which our study was published, and we had the opportunity to respond to this letter. The letter and our response are included in this chapter.

Chapter 8

Our general discussion in this chapter describes the current knowledge of CRPS confined to the knee and we summarize and comment on the findings of the several studies we conducted.. CRPS confined to the knee is a little known condition, but physicians should consider this diagnosis for patients with chronic pain of the knee, disproportionate to the event, that does not respond to treatment. CRPS is still a medical condition that is only partially understood, and future research on the etiological mechanisms should include CRPS confined to the knee.

NEDERLANDSE SAMENVATTING

Hoofdstuk 1

Het ontwikkelen van CRPS in de knie komt niet vaak voor. Mogelijk doordat deze locatie onbekend is onder artsen, lopen de patiënten een vertraging op met het krijgen van hun diagnose en daar aan gekoppelde behandelingen. Door meer kennis over het ontwikkelen van CRPS in de knie te verkrijgen, hopen we dat deze vertraging in de toekomst minder voor zal komen. Om dit voor elkaar te krijgen hebben we de huidige literatuur onderzocht, onderzoeken uitgezet naar het klinisch beeld van CRPS van de knie (ten tijde van de diagnose en na verloop van tijd) en hebben we een onderzoek gestart naar een mogelijke behandeling met neurostimulatie.

Hoofdstuk 2

Voor het verzamelen van al bekende literatuur over CRPS van de knie hebben we op systematische wijze gezocht, en vonden we 31 artikelen die een totaal van 368 patiënten beschrijven. De meeste van deze patiënten waren gediagnosticeerd met CRPS van de knie op basis van het klinisch beeld, en retrospectief blijkt 20% te voldoen aan de Budapest criteria set. Ook blijken in het verleden invasieve methoden en radiologische bevestiging te zijn gebruikt voor het stellen van de diagnose CRPS, dit in tegenstelling tot de huidige manier van diagnose stellen. Artroscopische chirurgie of een artroscopie van de knie bleek de meest genoemde oorzaak van de CRPS. Meerdere vormen van behandelingen zijn gebruikt, maar de juiste/beste behandeling moet nog gevonden worden.

Hoofdstuk 3

Om meer informatie te verkrijgen over het klinische beeld van CRPS van de knie ten tijde van de diagnose hebben we een retrospectieve vergelijking gemaakt tussen deze locatie en CRPS van de voet/enkel. Patiënten gediagnosticeerd met CRPS van de knie bleken significant langer klachten te hebben voor het krijgen van de diagnose in vergelijking met patiënten met CRPS van de voet/enkel. Hiernaast vonden we ook een significant verschil bij een aantal klachten dat mogelijk verklaard kan worden door de desbetreffende locatie van de CRPS. Deze bevindingen indiceren dat de fenotypische variatie van klinische kenmerken van CRPS van de knie en CRPS van de voet/enkel ten tijde van de diagnose beperkt is, maar dat de fenotypes niet identiek zijn.

Hoofdstuk 4

Er is nog niets bekend in de literatuur over het klinische beeld en de impact van CRPS van de knie over het verloop van tijd. We vroegen aan 32 patiënten of ze een aantal vragen wilden beantwoorden over de klachten ten tijde van de diagnose en de huidige klachten, over hun werkstatus en over de kwaliteit van leven. Het bleek dat maar 16% volledig

hersteld was na een gemiddelde CRPS duur van 11.5 jaar. Hiernaast was de werkstatus van de meeste patiënten veranderd door de diagnose en 91% van de patiënten gaf aan dat de pijn die ze ervaarden voor last zorgde in hun leven. Een vergelijking van het klinische beeld tussen CRPS van de knie en CRPS van andere locaties liet zien dat CRPS van de knie significant minder verandering doormaakt in het verloop van de tijd.

Hoofdstuk 5

Van het spinale ganglion is inmiddels bekend dat het een zeer belangrijke rol speelt bij de ontwikkeling van en het behouden van chronische pijn. Stimulatie van het spinale ganglion middels neurostimulatie blijkt een veilige en effectieve manier van behandelen van de pijnklachten. In dit hoofdstuk beschrijven we een patiënt met CRPS van de knie, die succesvol behandeld is met behulp van neurostimulatie op het spinale ganglion.

Hoofdstuk 6

Dit hoofdstuk beschrijft de resultaten van de proefperiode van ons prospectieve onderzoek naar twee manieren van neurostimulatie bij patiënten gediagnosticeerd met CRPS van de knie. We vergeleken de stimulatie van het spinale ganglion met de stimulatie van de dorsale hoorn. Het doel van het onderzoek was om achter de voorkeur van manier van stimuleren bij deze patiënten te komen. Twaalf patiënten hebben uiteindelijk de proefperiode volledig doorlopen en het bleek dat stimulatie van het spinale ganglion de voorkeur had over stimulatie van de dorsale hoorn. Daarom raden we artsen dan ook aan om spinale ganglion stimulatie te overwegen voor een patiënt met onbehandelbare CRPS van de knie.

Hoofdstuk 7

Terechte vragen en opmerkingen over het prospectieve onderzoek zijn geplaatst door twee lezers in een brief aan de editor. In dit hoofdstuk zijn de brief aan de editor en de reactie die we hierop schreven te vinden.

Hoofdstuk 8

In de discussie wordt de huidige kennis over CRPS van de knie besproken. Hiernaast worden alle resultaten van de onderzoeken die uitgevoerd zijn in het kader van dit proefschrift samengevat en becommentarieerd. CRPS van de knie is een diagnose die nog niet vaak gesteld wordt, en mogelijk weinig voorkomt, maar heeft wel een potentieel lange ziektelast. Zodoende raden we artsen aan om differentiaal diagnostisch te denken aan CRPS bij een patiënt met onbehandelbare pijnklachten van de knie. Tot op heden is CRPS nog maar deels verklaard en in toekomstig onderzoek naar de etiologie van CRPS zou de knie als mogelijke locatie ook moeten worden opgenomen.