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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