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.

REFERENCES

1. Sudeck P. Ueber die acute Entzundliche Knochenatrophie. Arch Klin Chir. 1900(62):147-56.
2. Iolascon G, de Sire A, Moretti A, Gimigliano F. Complex regional pain syndrome (CRPS) type I: historical perspective and critical issues. Clin Cases Miner Bone Metab. 2015;12(Suppl 1):4-10.
3. Evans JA. Reflex sympathetic dystrophy. Surg Gynecol Obstet. 1946;82:36-43.
4. Stanton-Hicks M, Janig W, Hassenbusch S, Haddox JD, Boas R, Wilson P. Reflex sympathetic dystrophy: changing concepts and taxonomy. Pain. 1995;63(1):127-33.
5. Allen G, Galer BS, Schwartz L. Epidemiology of complex regional pain syndrome: a retrospective chart review of 134 patients. Pain. 1999;80(3):539-44.
6. Borchers AT, Gershwin ME. The clinical relevance of complex regional pain syndrome type I: The Emperor's New Clothes. Autoimmun Rev. 2017;16(1):22-33.
7. Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. Lancet. 1993;342(8878):1012-6.
8. Reinders MF, Geertzen JH, Dijkstra PU. Complex regional pain syndrome type I: use of the International Association for the Study of Pain diagnostic criteria defined in 1994. Clin J Pain. 2002;18(4):207-15.
9. Bruehl S, Harden RN, Galer BS, Saltz S, Bertram M, Backonja M, et al. External validation of IASP diagnostic criteria for Complex Regional Pain Syndrome and proposed research diagnostic criteria. International Association for the Study of Pain. Pain. 1999;81(1-2):147-54.
10. Harden RN, Oaklander AL, Burton AW, Perez RS, Richardson K, Swan M, et al. Complex regional pain syndrome: practical diagnostic and treatment guidelines, 4th edition. Pain Med. 2013;14(2):180-229.
11. Kosek E, Cohen M, Baron R, Gebhart GF, Mico JA, Rice AS, et al. Do we need a third mechanistic descriptor for chronic pain states? Pain. 2016;157(7):1382-6.
12. Birklein F, Schlereth T. Complex regional pain syndrome-significant progress in understanding. Pain. 2015;156 Suppl 1:S94-103.
13. Birklein F, Schmelz M. Neuropeptides, neurogenic inflammation and complex regional pain syndrome (CRPS). Neurosci Lett. 2008;437(3):199-202.
14. Tan EC, Oyen WJ, Goris RJ. Leukocytes in Complex Regional Pain Syndrome type I. Inflammation. 2005;29(4-6):182-6.
15. Birklein F, Schmelz M, Schifter S, Weber M. The important role of neuropeptides in complex regional pain syndrome. Neurology. 2001;57(12):2179-84.
16. Laferriere A, Millecamps M, Xanthos DN, Xiao WH, Siau C, de Mos M, et al. Cutaneous tactile allodynia associated with microvascular dysfunction in muscle. Mol Pain. 2008;4:49.
17. Beerthuizen A, van 't Spijker A, Huygen FJ, Klein J, de Wit R. Is there an association between psychological factors and the Complex Regional Pain Syndrome type 1 (CRPS1) in adults? A systematic review. Pain. 2009;145(1-2):52-9.
18. Beerthuizen A, Stronks DL, Huygen FJ, Passchier J, Klein J, Spijker AV. The association between psychological factors and the development of complex regional pain syndrome type 1 (CRPS1)--a prospective multicenter study. Eur J Pain. 2011;15(9):971-5.
19. Bussa M, Guttilla D, Lucia M, Mascaro A, Rinaldi S. Complex regional pain syndrome type I: a comprehensive review. Acta Anaesthesiol Scand. 2015;59(6):685-97.
20. Perez RS, Zollinger PE, Dijkstra PU, Thomassen-Hilgersom IL, Zuurmond WW, Rosenbrand KC, et al. Evidence based guidelines

for complex regional pain syndrome type 1. BMC Neurol. 2010;10:20.
21. Bruehl S, Harden RN, Galer BS, Saltz S, Backonja M, Stanton-Hicks M. Complex regional pain syndrome: are there distinct subtypes and sequential stages of the syndrome? Pain. 2002;95(1-2):119-24.
22. Bharwani K, Dirckx M, Huygen F. Complex regional pain syndrome: diagnosis and treatment. Bja Educ. 2017;17(8):262-8.
23. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150(3699):971-9.
24. Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. Anesth Analg. 1967;46(4):489-91.
25. Shealy CN, Taslitz N, Mortimer JT, Becker DP. Electrical inhibition of pain: experimental evaluation. Anesth Analg. 1967;46(3):299-305.
26. Kemler MA, Barendse GA, van Kleef M, de Vet HC, Rijks CP, Furnee CA, et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. N Engl J Med. 2000;343(9):618-24.
27. Kemler MA, De Vet HC, Barendse GA, Van Den Wildenberg FA, Van Kleef M. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial. Ann Neurol. 2004;55(1):13-8.
28. Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FA, van Kleef M. Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: five-year final follow-up of patients in a randomized controlled trial. J Neurosurg. 2008;108(2):292-8.
29. Liem L, Russo M, Huygen FJ, Van Buyten JP, Smet I, Verrills P, et al. A multicenter, prospective trial to assess the safety and performance of the spinal modulation dorsal root ganglion neurostimulator system in the treatment of chronic pain. Neuromodulation. 2013;16(5):471-82; discussion 82.
30. Van Buyten JP, Smet I, Liem L, Russo M, Huygen F. Stimulation of dorsal root ganglia for the management of complex regional pain syndrome: a prospective case series. Pain Pract. 2015;15(3):208-16.
31. Schott GD. Mechanisms of causalgia and related clinical conditions. The role of the central and of the sympathetic nervous systems. Brain. 1986;109 (Pt 4):717-38.
32. Deer TR, Levy RM, Kramer J, Poree L, Amirdelfan K, Grigsby E, et al. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. Pain. 2017;158(4):669-81.
33. Baur E. [Post traumatic dystrophy of the knee] Beitrag zur posttraumatischen Dystrophie des Kniegelenkes. Z Unfallmed Berufskr. 1954;47(3):224-32.
34. Cameron HU, Park YS, Krestow M. Reflex sympathetic dystrophy following total knee replacement. Contemp Orthop. 1994;29(4):279-81.
35. Malhotra R, Dhingra SS, Padhy AK, Kumar R, Ravishankar U. Reflex sympathetic dystrophy of the patello-femoral joint. Diagnosis and relevance. Clin Nucl Med. 1995;20(12):1058-60.
36. O'Brien SJ, Ngeow J, Gibney MA, Warren RF, Fealy S. Reflex sympathetic dystrophy of the knee. Causes, diagnosis, and treatment. Am J Sports Med. 1995;23(6):655-9.
37. Tietjen R. Reflex sympathetic dystrophy of the knee. Clin Orthop Relat Res. 1986(209):234-43.
38. Coughlan RJ, Hazleman BL, Thomas DP, Sattelle L, Crisp AJ, Jenner JR, et al. Algodystrophy: a common unrecognized cause of chronic knee pain. Br J Rheumatol. 1987;26(4):270-4.
39. Katz MM, Hungerford DS, Krackow KA, Lennox DW. Reflex sympathetic dystrophy as a cause of poor results after total knee arthroplasty. J Arthroplasty. 1986;1(2):117-24.

40. Reuben SS, Sklar J. Intravenous regional anesthesia with clonidine in the management of complex regional pain syndrome of the knee. J Clin Anesth. 2002;14(2):87-91.
41. Ogilvie-Harris DJ, Roscoe M. Reflex sympathetic dystrophy of the knee. J Bone Joint Surg Br. 1987;69(5):804-6.
42. Miller RL. Reflex sympathetic dystrophy. Orthop Nurs. 2003;22(2):91-9; quiz 100-1.