Complex regional pain syndrome related movement disorders : studies on pathophysiology and therapy.

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Chapter 1

General introduction and aims

Trauma to a limb (often minor) is occasionally followed by severe pain and trophic changes characteristic of sympathetic algodystrophy (Sudeck's atrophy). The pathophysiology of the condition is unknown. Even more rarely minor trauma may provoke not only Sudeck's atrophy but also involuntary movements. The clinical picture is so unusual that such patients may be labeled as "hysterical," particularly when compensation is being considered. We, however, have seen four similar cases of muscle spasms associated with Sudeck's atrophy after mild trauma in three different countries. We believe this to be a distinct clinical syndrome, although of unknown pathophysiology.[1]

These words date back to 1984. Since this recognition by professor C. David Marsden and colleagues, a number of case series[2-7] were reported on what is nowadays called 'complex regional pain syndrome (CRPS) related dystonia'.

Dystonia

In general, dystonia is characterized by an abnormal control of movement, with involuntary muscle contractions causing twisting movements and abnormal postures.[8] In CRPS, dystonia typically presents with predominant flexor postures of the fingers (in less severe cases only the third to fifth finger), wrists, and feet. Progression to the proximal part of the extremity as well as spread to muscles outside the affected limb may occur. Because of the presence of postures, which are typically not mobile, this dystonia is called 'fixed'.

What is CRPS?

In 1994, the International Association for the Study of Pain (IASP) introduced the term CRPS, which was the new name for sympathetic algodystrophy (or Sudeck's atrophy or reflex sympathetic dystrophy).[9] It was defined by a combination of sensory and autonomic disturbances which are often preceded by a limb trauma (Table 1.1). It is noteworthy that the presence of a preceding trauma is not a necessary requirement. The IASP made a distinction between two types of CRPS: without nerve injury (type 1) and with nerve injury (type 2). In 2003, new diagnostic criteria for CRPS were proposed by an international consensus group (Table 1.2).[10,11] The validity of these criteria were reconfirmed in a recent study,[11] however, until now these were not formally approved by the IASP.

Table 1.1. IASP diagnostic criteria for CRPS, type 1[9]

Criterium	
1	The presence of an initiating noxious event, or a cause of immobilization
2	Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event
3	Evidence at some time of oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain
4	This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction

Note: criteria 2-4 must be satisfied.

Table 1.2. Proposed clinical diagnostic criteria for CRPS[11]

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

The pathophysiology of CRPS-related dystonia

The pathophysiology of both CRPS and its dystonia is only partly understood. Each (micro-) trauma that leads to activation of local nociceptors results in neurogenic inflammation, i.e. the release of inflammatory mediators. This process causes inflammatory signs, induces

sensitisation of the nociceptors as well as sensitisation at the spinal cord level.[12] It is supposed that this process is out of balance in both type 1 and 2 CRPS. Against this background, it was suggested that inflammatory mediators are involved in the pathophysiology of CRPS. Indeed, increased levels of the pro-inflammatory interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were found in artificially obtained blister fluid of CRPS patients with a mean disease duration of 8 months (range 4-12 months).[13] At three years follow-up,[14] but not at six years follow-up,[15] these levels remained elevated. Neurogenic inflammation induces functional changes at the spinal cord level which play a key role in the maintenance of the pain (central sensitisation).[16]

Dystonia is considered to be a consequence of perturbed sensorimotor processing.[8] Lack of central inhibition plays a key role in the pathophysiology of dystonia in general.[17] In CRPS, the altered processing of noxious, tactile and thermal input has been suggested to be an important factor in the development of fixed dystonia.[18] Central sensitisation is associated with disinhibition of sensory circuits leading to spontaneous pain, allodynia and hyperalgesia. In CRPS patients with and without dystonia, pathophysiological studies have provided evidence of central disinhibition on different levels of the nervous system, ranging from the spinal cord[19] to cerebral cortex[20,21]. The role of central disinhibition in CRPS-related dystonia is further supported by a small placebo-controlled study in which about half of the patients had a marked and sustained reduction of the dystonia severity after administration of intrathecal baclofen, a specific gamma aminobutyric acid (GABA) B agonist. This drug enhances the presynaptic and postsynaptic inhibition of afferent input on neurons in the spinal cord.[22]

CRPS-related tremor and myoclonic jerks

In CRPS, tremor and myoclonic jerks have also been reported, however, information on these movement disorders is scarce.[18]

A hysterical label?

To date, there are a number of neurologists who consider CRPS-related dystonia a psychogenic movement disorder.[23,24] Though these are expert opinions, and as such meaningful, a scientific approach would be more appropriate. In a study with 27 CRPS-related dystonia patients, no psychological abnormalities were found in comparison with a control population.[25] In a recent study, that was performed at the Leiden University Medical Centre, no unique disturbed psychological profile was found in 46 CRPS patients with dystonia.[26] Nevertheless, in comparison to patients with affective disorders, the level

of somatoform dissociative experiences (medically unexplained analgesia, anesthesia, motor disturbance, alternating preferences for tastes and smells, pain, and loss of consciousness) was elevated. Early traumatic experiences were found to be moderately related to somatoform dissociative experiences which may indicate that early traumatic experiences are a predisposing factor for the development of CRPS-related dystonia.[26] Of course, if psychological or psychiatric abnormalities are present, they also might be part of the syndrome instead of the cause.

Epidemiology

A recent Dutch population-based study[27] found an estimated overall incidence rate of CRPS of 26.2 per 100,000 person years (95% CI 23.0-29.7). Women are affected 3.4 times more often than men. The highest incidence occurred in women in the age category of 61-70 years. Considering a life expectancy at birth of 77.6 years for men and 81.9 years for women (Statistics Netherlands, 2006), the life time risk for CRPS is 0.9% for men and 3.3% for women.

Generally, it is assumed that 14-30% of the CRPS patients may develop dystonia.[28] In comparison with CRPS, the female to male ratio is further increased in patients with CRPS-related dystonia: the ratio was 6.2 in a study that was performed at the Leiden University Medical Centre.[6]

Course

Of 74 CRPS patients that were identified in a population study in the United States, 55 patients (74%) underwent resolution, often spontaneously.[29] In a more recent Dutch study, it was shown that at a minimum of 2 years since onset 65 of 102 CRPS patients (64%) still fulfilled the IASP criteria for CRPS.[30] The course of CRPS-related dystonia was studied in the 185 patients who visited the Department of Neurology of the Leiden University Medical Centre between 1998 and 2004.[6] It was found that the presence of dystonia in the affected limb increased the hazard of developing dystonia in a second limb with 2.29 (95% CI 1.67-3.14). Furthermore, dystonia in two extremities increased the hazard of developing dystonia in the third to 2.15 (95% CI 1.33-3.48), and dystonia in three extremities increased the hazard of developing dystonia in the fourth to 7.4 (95% CI 3.74-14.65). In contrast, as the number of extremities with only non-motor CRPS symptoms increased, which occurred in 21 patients (11.4%), the hazard of developing dystonia decreased. However, this study investigated a highly selected population, and these findings may not be generalised.

Treatment

The Dutch Institute for Healthcare Improvement (CBO) developed the evidence-based 'Guideline Complex Regional Pain Syndrome type I'.[31] The scientific support for most treatments in CRPS is limited. Figure 2.1 shows the proposed treatment algorithm which includes the treatment of dystonia. Clearly, the treatment of CRPS-related dystonia is still in its infancy. Intrathecal baclofen is considered a promising therapy for severe dystonia.[22] However, until now, treatment was restricted to the experimental setting.

Aims of this thesis

First aim was to study the pathophysiology of CRPS-related movement disorders. Neurologists differ in their opinions on whether CPRS-related dystonia is psychogenic or not. *Chapter 2* describes, from a historical point of view, the sway between organic and psychogenic explanations for dystonia including CRPS-related dystonia. The sensory system in CRPS-related dystonia patients was evaluated by means of quantitative somatosensory thermotesting, which is described in *chapter 3*. *Chapter 4* describes the clinical characteristics of CRPS-related dystonia. These findings were used in a neuromuscular model of the wrist to investigate a possible role of disrupted proprioceptive reflexes. The results from cerebrospinal fluid analysis are described in *chapter 5*. We used coherence analysis to investigate myoclonic jerks that occurred in CRPS patients with or without dystonia. The findings are described in *chapter 6*.

Second aim was to find new treatments for CRPS-related movement disorders. Two chapters describe studies that evaluated continuous administration of intrathecal baclofen (*chapter 7*) and glycine (*chapter 8*). Both these agents have the potential to reverse the lack of inhibition in the central nervous system. A study that evaluated intrathecal methylprednisolone in CRPS is described in *chapter 9*. We found a high incidence and prolonged course of post-dural puncture headache after implantation of the pump for intrathecal administration. This observation and, moreover, its implications, are described in *chapter 10*.

Figure 2.1 (next page). CBO treatment algorithm for CRPS in adults (printed with permission from Van Zuiden Communications).[31]

Primary prevention:
• in the case of wrist fractures, vitamin C

Secondary prevention (for existing or past CRPS-I):
• postpone surgery until CRPS-I symptoms have almost disappeared
• keep the operation as short as possible and try to prevent to operate without removing blood from the operated extremity
• adequate pre- and perioperative pain control
Consider:
• perioperative stellate ganglion block or administer regional i.v. anaesthesia (clonidine)
• anaesthesia with sympathicolytic effect
• perioperative calcitonin

Treatment:
Paramedical:
• physiotherapy according to a protocol
• occupational therapy according to a protocol

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

Treatment of children with CRPS-I:
• In addition to drug treatment, physiotherapy and/or occupational therapy
• if necessary, psychological support from a paediatric/adolescent psychologist

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

In the case of allodynia/hyperalgesia:
• gabapentin
• carbamazepine
• amitriptyline/nortriptyline

In the case of dystonia, myoclonia or muscle spasms:
• oral baclofen, diazepam or clonazepam

If ineffective:
• intrathecal baclofen at a specialised clinic

In the case of cold CRPS-I:
• vasodilating medication

If ineffective:
• percutaneous sympathetic block

Communication and information:
• verbal and written
• involve relatives
• put patients in touch with patient association for CRPS-I
CRPS-I and work:
• have the patient's working conditions assessed by the company doctor
• consult the patient's company doctor / doctor treating him or her to establish how much strain he or she can bear

Other therapies:
If other therapies prove ineffective, you may consider:
• spinal cord stimulation at a specialised clinic
If recurrent infections occur, you may consider:
• amputation at a specialised clinic

References

1. Marsden CD, Obeso JA, Traub MM, Rothwell JC, Kranz H, La Cruz F. Muscle spasms associated with Sudeck's atrophy after injury. Br Med J (Clin Res Ed) 1984;288:173-6.
2. Bhatia KP, Bhatt MH, Marsden CD. The causalgia-dystonia syndrome. Brain 1993;116:843-51.
3. Birklein F, Riedl B, Sieweke N, Weber M, Neundorfer B. Neurological findings in complex regional pain syndromes--analysis of 145 cases. Acta Neurol Scand 2000;101:262-9.
4. Harden RN, Bruehl S, Galer BS et al. Complex regional pain syndrome: are the IASP diagnostic criteria valid and sufficiently comprehensive? Pain 1999;83:211-9.
5. Schwartzman RJ, Kerrigan J. The movement disorder of reflex sympathetic dystrophy. Neurology 1990;40:57-61.
6. van Rijn MA, Marinus J, Putter H, van Hilten JJ. Onset and progression of dystonia in complex regional pain syndrome. Pain 2007;130:287-93.
7. Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. Lancet 1993;342:1012-6.
8. Breakefield XO, Blood AJ, Li Y, Hallett M, Hanson PI, Standaert DG. The pathophysiological basis of dystonias. Nat Rev Neurosci 2008;9:222-34.
9. Merskey H, Bogduk N. Relatively generalized syndromes. In: Merskey H, Bogduk N, eds. Classification of chronic pain. Description of chronic pain syndromes and definitions of pain terms. Seattle: IASP Press, 1994:40-3.
10. Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med 2007;8:326-31.
11. Harden RN, Bruehl S, Perez RS et al. Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome. Pain 2010;150:268-74.
12. Birklein F, Schmelz M. Neuropeptides, neurogenic inflammation and complex regional pain syndrome (CRPS). Neurosci Lett 2008;437:199-202.
13. Huygen FJ, de Bruijn AG, De Bruin MT, Groeneweg JG, Klein J, Zijlstra FJ. Evidence for local inflammation in complex regional pain syndrome type 1. Mediators Inflamm 2002;11:47-51.
14. Munnikes RJ, Muis C, Boersma M, Heijmans-Antonissen C, Zijlstra FJ, Huygen FJ. Intermediate stage complex regional pain syndrome type 1 is unrelated to proinflammatory cytokines. Mediators Inflamm 2005;2005:366-72.
15. Wesseldijk F, Huygen FJ, Heijmans-Antonissen C, Niehof SP, Zijlstra FJ. Six years follow-up of the levels of TNF-alpha and IL-6 in patients with complex regional pain syndrome type 1. Mediators Inflamm 2008;2008:469439.
16. Scholz J, Woolf CJ. The neuropathic pain triad: neurons, immune cells and glia. Nat Neurosci 2007;10:1361-8.
17. Hallett M. The neurophysiology of dystonia. Arch Neurol 1998;55:601-3.
18. van Hilten JJ, Blumberg H, Schwartzman RJ. Factor IV: Movement Disorders and Dystrophy--Pathophysiology and Measurement. In: Wilson P, Stanton-Hicks M, Harden RN, eds. CRPS: Current Diagnosis and Therapy, Progress in Pain Research and Management. Seattle: IASP Press, 2005:119-37.
19. van de Beek WJ, Vein A, Hilgevoord AA, van Dijk JG, van Hilten BJ. Neurophysiologic aspects of patients with generalized or multifocal tonic dystonia of reflex sympathetic dystrophy. J Clin Neurophysiol 2002;19:77-83.
20. Maihofner C, Baron R, DeCol R et al. The motor system shows adaptive changes in complex regional pain syndrome. Brain 2007;130:2671-87.
21. Schwenkreis P, Janssen F, Rommel O et al. Bilateral motor cortex disinhibition in complex regional pain syndrome (CRPS) type I of the hand. Neurology 2003;61:515-9.
22. van Hilten BJ, van de Beek WJ, Hoff JI, Voormolen JH, Delhaas EM. Intrathecal baclofen for the treatment of dystonia in patients with reflex sympathetic dystrophy. N Engl J Med 2000;343:625-30.
23. Lang A, Fahn S. Movement disorder of RSD. Neurology 1990;40:1476-8.
24. Verdugo RJ, Ochoa JL. Abnormal movements in complex regional pain syndrome: assessment of their nature. Muscle Nerve 2000;23:198-205.
25. van der Laan L, van SK, Horstink MW, Goris RJ. The Symptom Checklist-90 Revised questionnaire: no psychological profiles in complex regional pain syndrome-dystonia. J Pain Symptom Manage 1999;17:357-62.

26. Reedijk WB, van Rijn MA, Roelofs K, Tuijl JP, Marinus J, van Hilten JJ. Psychological features of patients with complex regional pain syndrome type I related dystonia. Mov Disord 2008;23:1551-9.
27. de Mos M, de Bruijn AG, Huygen FJ, Dieleman JP, Stricker BH, Sturkenboom MC. The incidence of complex regional pain syndrome: a population-based study. Pain 2007;129:12-20.
28. Marinus J, van Hilten JJ. Clinical expression profiles of complex regional pain syndrome, fibromyalgia and a-specific repetitive strain injury: more common denominators than pain? Disabil Rehabil 2006;28:351-62.
29. Sandroni P, Benrud-Larson LM, McClelland RL, Low PA. Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. Pain 2003;103:199-207.
30. de Mos M, Huygen FJ, Hoeven-Borgman M, Dieleman JP, Ch Stricker BH, Sturkenboom MC. Outcome of the complex regional pain syndrome. Clin J Pain 2009;25:590-7.
31. Complex regional pain syndrome type 1 guidelines. Alphen aan den Rijn: Van Zuiden Communications B.V., 2006.