PAIN

Pain 120 (2006) 227–229

www.elsevier.com/locate/pain

Editorial

Is CRPS I a neuropathic pain syndrome?

There is still considerable disagreement as to the mechanisms underlying complex regional pain syndrome (CRPS). This is probably related to the lack of quantitative clinical data, which would allow the formulation of precise testable hypotheses, and to the lack of animal models and experimental approaches using the human patient as the model (Baron et al., 2002; Jänig and Baron, 2002, 2003, 2004). Observations on CRPS patients clearly show that sympathetic, somatomotor, and somatosensory systems contribute to this pain syndrome and we can distinguish peripheral and central nervous systems factors. There are two types of CRPS. CRPS type I may develop after trauma, without nerve lesion (although some damage of nerve fibers usually occurs). CRPS type II develops after trauma with nerve lesion. It is important to emphasize that the severity of symptoms of CRPS type I, which is much more common than CRPS type II, is disproportionate to the severity of the trauma. Moreover, the patterns of symptoms, as variable as they may be, are not related to the type and degree of trauma. In fact, in rare cases, remote trauma in the viscera or in the CNS can trigger CRPS I in an extremity.

Based on this seemingly confusing and complex clinical situation and on preferences of different groups of investigators, primary mechanisms underlying CRPS include:

- Peripheral mechanisms, e.g., CRPS is considered to be primarily an inflammatory disease in the periphery or a consequence of nerve damage, including all other changes observed in the CRPS patients.
- Central mechanisms, e.g., reorganization of somatosensory, somatomotor, and autonomic systems triggered by a peripheral input (McCabe et al., 2003; Moseley, 2004; Pleger et al., 2005). An extreme view is that CRPS I is a pseudoneurological disease, i.e., that many features of CRPS are manifestations of somatoform disorders, malingering, and psychiatric pathology (Ochoa, 1995). This view is now generally disregarded.

We prefer the hypothesis that CRPS I is a syndrome in which the CNS representations of the somatosensory, somatomotor, and sympathetic systems are altered and that this occurs concomitantly with important peripheral changes (such as edema, signs of inflammation, sympathetic-afferent coupling, trophic changes, etc.). The manner in which the peripheral and central changes interact is only partly understood. However, we are not convinced that there is a unitary mechanism that can explain CRPS. For example, we do not believe that it can be reduced to a peripheral inflammatory disease, to a peripheral adrenoceptor disease or to a psychoneural disease (Jänig and Baron, 2002, 2003).

The present issue of PAIN contains two papers in which it is hypothesized that the primary underlying mechanism of CRPS type I is a persistent, minimal distal nerve injury (Oaklander et al., 2006) or that it involves widespread changes of the cutaneous innervation by small-diameter afferent and postganglionic sympathetic efferent fibers (Albrecht et al., 2006).

In 18 CRPS patients, Oaklander and coworkers studied the innervation density of the epidermis of the CRPS-affected site (location of maximum pain), of a nearby (pain-free) control site, and of a mirror-image, contralateral control site. They immunolabeled the nerve fibers in sections of skin biopsies with a polyclonal antibody that recognizes the pan-axonal enzyme, ubiquitin hydrolase (PGP9.5, protein–gene product 9.5). They found on average, a reduction of the axonal density by 29% in the CRPS-affected skin sites compared to the control skin sites, with a huge interindividual variance. They propose that CRPS type I is triggered by nerve injuries predominantly affecting small diameter axons. They further propose that CRPS type I is maintained by ectopic activity generated in these injured afferent fibers, together with other (transcriptional) changes that occur in these afferent neurons. Thus, they clearly take the position that CRPS type I is a neuropathic pain syndrome.

0304-3959/$20.00
doi:10.1016/j.pain.2005.11.015

Albrecht et al. (2006) studied the innervation of CRPS-affected glabrous and hairy skin and in corresponding skin samples not affected by CRPS (as defined by the relatively normal sensations). Their studies were performed in two surgically amputated extremities (upper and lower extremity) from two patients with CRPS type I. They labeled the innervation of epidermis and dermis, including blood vessels, sweat glands, and hair follicles, using double immunostaining with antibodies directed against neuron-related proteins and transmitters. In CRPS-affected skin areas, they found impressive changes of the innervation of the different target tissues, as well as changes of the target tissue itself (e.g., blood vessels). These authors also concluded that CRPS type I can be associated with peripheral pathological changes of the innervation of skin, i.e., that CRPS type I may indeed be a neuropathic pain syndrome.

We suggest that considerable caution must be taken in evaluating these conclusions, as they are based only on the changes of the innervation of CRPS-affected skin areas. The following factors must also be taken into account:

- Almost all patients diagnosed as having CRPS type I were very chronic and went through many medical, and most importantly interventional, procedures. Thus, the conclusions drawn by the authors can only apply to potential mechanisms that maintain chronic CRPS, not to those that operate at the beginning of acute CRPS, i.e., in the first 1–6 months.
- There is increasing evidence that secondary tissue changes occur in the course of the disease, i.e., severe vasoconstriction, blood supply redistribution due to abnormal blood flow shunting with hypoperfusion in nutritive vessels, hypoxia, lactate increase, and acidosis (Birklein et al., 2000; Koban et al., 2003; Schattschneider et al., 2006). All of these could contribute to the small fiber damage that is observed.
- A reduction of the innervation density of the epidermis of CRPS-affected skin by about 30% does normally not lead to clinically detectable changes of sensation, e.g., in patients with diabetic and other neuropathies.
- Most patients with CRPS type I have had trauma in the deep somatic tissues, a few in the viscera, and a few in the CNS. In these patients, the innervation of the skin is not primarily affected. Of course, the patients may have cutaneous allodynia and hyperalgesia as well as other changes, possibly associated with sympathetic vasoconstrictor and sudomotor innervation. In fact, most CRPS type I patients locate the spontaneous pain in deep somatic tissues.
- As noted above: The initiating events leading to CRPS type I are typically out of proportion with the pain (disease) that is experienced. One of the cardinal clinical features of CRPS I is the generalized distribution of all signs at the distal extremity. The patients described by Oaklander obviously had a more territorial distribution, with nearly normal skin areas (as assessed by counts of nerve fibers in the epidermis, quantitative sensory testing, and absence of pain evoked by non-pain stimuli) in close proximity to the painful-affected area. This observation makes one question whether there was an undetected nerve lesion leading to the fiber loss in the affected area.

In our opinion, therefore, it is premature to conclude, based on the data described in these two papers, (1) that the development of CRPS type I can be reduced to persistent minimal nerve injuries and their functional consequences and (2) that CRPS type I is a typical neuropathic pain syndrome, i.e., that nerve injury and the pathophysiological changes in the injured afferent neurons are the important events that initiate and maintain CRPS type I.

We do not deny that pathological changes (and their pathophysiological consequences) as described here may contribute to the maintenance of chronic CRPS type I. Furthermore, pathological changes as described here in special subgroups of CRPS type I patients are not at all at variance with our hypothesis that CRPS type I is a disease of the CNS, with peripheral features contributing. However, we question whether the results presented in these two papers can explain the initiation and maintenance of CRPS type 1 and their underlying mechanisms.

Acknowledgements

Supported by the Deutsche Forschungsgemeinschaft, the Bundesministerium für Bildung und Forschung (BMBF), DFNS (grant 01 EM 0504) and an unrestricted grant from Pfizer Germany (R.B.).

References

Albrecht PJ, Hines S, Eisenberg E, Pud D, Finlay DR, Connolly MK, et al. Pathological alterations of cutaneous innervation and vasculature in affected limbs from patients with complex regional pain syndrome. Pain 2006;120:244–66.

Baron R, Schattschneider J, Binder A, Siebrecht D, Wasner G. Relation between sympathetic vasoconstrictor activity and pain and hyperalgesia in complex regional pain syndromes: a case-control study. Lancet 2002;359:1655–60.

Birklein F, Weber M, Ernst M, Riedl B, Neundörfer B, Handwerker HO. Experimental tissue acidosis leads to increased pain in complex regional pain syndrome (CRPS). Pain 2000;87:227–34.

Jänig W, Baron R. Complex regional pain syndrome is a disease of the central nervous system. Clin Auton Res 2002;12:150–64.

Jänig W, Baron R. Complex regional pain syndrome: mystery explained? Lancet Neurol 2003;2:687–97.

Jänig W, Baron R. Experimental approach to CRPS. Pain 2004;108:3–7.

Koban M, Leis S, Schultze-Mosgau S, Birklein F. Tissue hypoxia in complex regional pain syndrome. Pain 2003;104:149–57.

McCabe CS, Haigh RC, Halligan PW, Blake DR. Referred sensations in patients with complex regional pain syndrome type 1. Rheumatology 2003;42:1067–73.

Moseley GL. Graded motor imagery is effective for long-standing complex regional pain syndrome – a randomized controlled trial. Pain 2004;108:192–8.

Ochoa JL. Reflex sympathetic dystrophy: a common clinical avenue for somatoform expression. Neurol Clin 1995;13:533–6.

Oaklander AL, Rissmiller JG, Gelman LB, Zheng L, Chang Y, Gott R. Evidence of focal small-fiber axonal degeneration in complex regional pain syndrome-I (reflex sympathetic dystrophy). Pain 2006;120:235–43.

Pleger B, Tegenthoff M, Ragert P, Forster AF, Dinse HR, Schwenkreis P, Nicolas V, Maier C. Sensorimotor retuning in complex regional pain syndrome parallels pain reduction. Ann Neurol 2005;57:425–9.

Schattschneider J, Wasner G, Binder A, Baron R. Complex regional pain syndromes: the influence of cutaneous and deep somatic sympathetic innervation on pain. Clin J Pain; 2006 [in press].

Wilfrid Jänig *
Department of Physiology,
Christian-Albrechts-Universität zu Kiel,
Kiel, Germany
E-mail address: w.janig@physiologie.uni-kiel.de

Ralf Baron
Division of Neurological Pain Research and Therapy,
Department of Neurology,
Christian-Albrechts-Universität zu Kiel,
Kiel, Germany

*Corresponding author. Tel.: +431 8802036; fax: +431 8805256.