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## CASE REVIEWS IN PAIN

# Complex Regional Pain Syndrome—A Multifaceted Disorder Requiring Multidimensional Care: Case Study

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*Editor's Note: This article is one in a series of "Case Reviews in Pain" to be presented by The Journal, designed to share scientific and clinical knowledge in a case review format. This report presents a discussion of Complex Regional Pain Syndrome in a 39-year-old male.*

### Case Review

**A** 39-year-old man sustained a distal tibio-fibular fracture while vacationing in Mexico. The patient was taken emergently to the nearby hospital where he underwent an open reduction internal fixation of his left tibia and fibula. The surgery was uneventful, and the patient was released 5 days later. After returning home, he saw an orthopedic surgeon for follow-up. The surgical site was found to be well-healed, and the patient was referred to physical therapy for mobility and strengthening exercises of his left lower extremity.

After several weeks of physical therapy, the patient began complaining of "severe" pain in his ankle and toes during therapy. He tended to keep his left leg flexed at the knee while standing or lying. A surgical consult was promptly obtained, and a new series of radiographs was unremarkable with changes consistent with successful bone healing. A workup for an infection was performed and was found to be negative. To improve the patient's pain and exercise tolerance, he was switched from acetaminophen to hydrocodone/acetaminophen. The patient, however, continued to complain of pain and increased sensation in his ankle and toes. On close examination, he was found to have a warm, edematous, and erythematous ankle and foot with taut, shiny skin. The ankle and foot were extremely sensitive to touch. Gabapentin, 300 mg every 8 hours, was added and provided some pain relief initially but was discontinued due

to sedation. He started controlled-release oxycodone, and his dose was rapidly increased but without any real decrease in pain or improvement in function. Over the next 6 months, he grew increasingly irritable and "withdrawn." His family and financial situation were strained. To help him cope with his disability, he was offered a psychiatric consult, which he refused, stating that he was not "crazy." A year after the surgery, he remained nonambulatory and unemployed. His leg was held in a fixed, flexed-at-the-knee posture and showed atrophy of the proximal muscles with edema distally. The limb was allodynic to mechanical and cold stimuli and was cold, blue, and sweaty, with dense hair growth, shiny, thin skin, and thick-ridged nails.

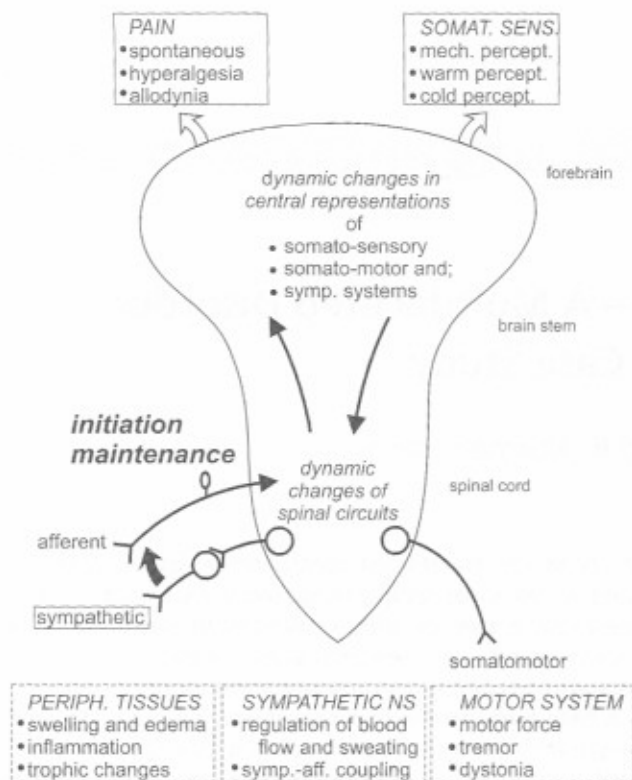
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### Is CRPS I a Disease of the Central Nervous System?

Recently, we have put forward the hypothesis that complex regional pain syndrome (CRPS) is primarily a disease of the central nervous system. The multiple arguments in favor of this idea are based on clinical observations as well as animal and human experimentation. CRPS patients exhibit changes that are related to the sympathetic nervous system innervating skin (blood vessels, sweat glands) and possibly deep somatic tissues, the somatosensory system processing noxious, tactile and thermal information, and the somatomotor system. In addition, it is believed that trophic changes, endothelial damage, and edema, possibly signs or consequences of tissue inflammation, are also dependent on the innervation of the affected extremity by the sympathetic nervous system, although clear-cut experimental evidence supporting this is still missing.<sup>1,7-9</sup> The central changes are reflected in alterations of the efferent autonomic and somatomotor output systems to the affected ex-

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**Figure 1.** Schematic diagram summarizing the sensory, autonomic, and somatomotor changes in CRPS I patients. The figure symbolizes the central nervous system (forebrain, brain stem, and spinal cord). Changes occur in the central representations of the somatosensory, somatomotor, and sympathetic nervous system (which include the spinal circuits) and are reflected in the changes of the sensory painful and nonpainful perceptions, of cutaneous blood flow and sweating, and of motor performances. They are triggered and possibly maintained by nociceptive afferent inputs from the somatic and visceral body domains. It is unclear whether these central changes are reversible in chronic CRPS I patients. These central changes possibly affect the endogenous control system of nociceptive impulse transmission as well. Coupling between the sympathetic neurons and the afferent neurons in the periphery (bold closed arrow) is 1 component of the pain in CRPS I patients with SMP (sympathetically maintained pain). However, it seems to be unimportant in CRPS I patients without sympathetically maintained pain. Modified from Jänig and Baron.<sup>7,8</sup>

tremity and in multiple somatosensory changes (including those leading to pain) (see dots in Fig 1). These changes have been measured quantitatively in CRPS patients under quasi-experimental conditions.<sup>1,4,12-15,17,18</sup>

The results clearly argue that CRPS is a systemic disease involving these neuronal systems and their central representations in spinal cord, brain stem, diencephalon, and forebrain. The peripheral changes (sympathetic-afferent coupling, vascular changes, inflammatory changes, edema, and trophic changes) cannot be seen independent of the central ones. Both the central and peripheral nervous systems interact with each other via afferent and efferent (autonomic and somatomotor) signals. However, the nature of this interaction is still a puzzle. We argue that this way of looking at CRPS shifts the attention away from interpreting this syndrome conceptually in a narrow manner and prevents reducing its

underlying mechanism to 1 system, either in the periphery or in the central nervous system (eg, the nociceptive system, the sympathetic nervous system, a peripheral inflammatory process, or mechanisms underlying sympathetically maintained pain).

This less narrow view should further our understanding as to why CRPS type I may develop after a trivial trauma, after a trauma that is remote from the affected extremity exhibiting CRPS, or possibly, after immobilization of an extremity. The clinical signs and symptoms in CRPS I are disproportionate to the traumatic events initiating or triggering this syndrome. The local changes generated by the trauma may entirely disappear, yet the syndrome persists or develops after healing. It has even been proposed that processes in the prefrontal, frontal, and parietal cortices that are related to psycho-social changes enhance the clinical signs and symptoms in CRPS or even may initiate them. Finally, in CRPS patients with sympathetically maintained pain, a few temporary blocks (and sometimes only 1 block) of the sympathetic supply to the affected extremity may lead to long-lasting (even permanent) pain relief as well as resolution of the other changes present in CRPS. This clinical observation clearly supports the notion that the mechanisms underlying CRPS are related to the central nervous system.

The case reported here fits our general explanatory hypothesis:

1. The "initiating" event (tibio-fibular fracture) is deep somatic. The surgical treatment, subsequent physiotherapy, and healing were successful and uneventful. Thus, the deep somatic tissues are primarily involved.
2. Weeks after surgery and physiotherapy, severe pain developed with mechanical allodynia, warm skin, edema, trophic changes, and possibly motor disorders.
3. Six months to 1 year later, this situation worsened with cold allodynia, cold and sweaty skin, severe trophic changes of the skin, and dystonia (movement disorders). Thus the nociceptive systems of deep somatic tissues and skin, the sympathetic systems supplying skin (vasoconstrictor neurons, sudomotor neurons) and deep somatic tissues, and the somatomotor system are involved in this chronic condition.

Several questions came to us while reading about this case: (1) The patient underwent physical therapy for mobility and strengthening exercises of his affected extremity. Is it possible that the "severe pain" and other associated changes developed as a consequence of the physical therapy? Did the pain and mechanical allodynia (reported several weeks after physical therapy) initially located in deep somatic tissues (bone, skeletal muscle, joints) of the left leg project into the entire leg over time? (2) Did the movement disorder (keeping the left leg flexed at the knee while standing) worsen in the year after surgery? (3) Did the changes in skin and subcutaneous tissues (edema, taut shiny skin) and pain (spontaneous, mechanical and cold allodynia) deteriorate over 6 months to 1 year and spread over this time from the ankle to the knee and hip? (4) How did the patient perceive his limb (1 year after the surgery)? Were referred

sensations present? What exacerbated or improved the sensory symptoms? Did the patient exhibit any other somatosensory abnormality (eg, hypoesthesias to warm, cool or non-noxious mechanical stimuli)?<sup>13,14</sup> (5) Did the patient exhibit any form of neglect of the limb or annoying feelings that his limb was foreign to him (ie, not belonging to his body) or a desire to "get rid of the limb"? Did the patient's inability to cope with his situation, as evidenced by his becoming withdrawn and irritable, support this possibility? [Lewis JS, Kersten P, McCabe CS, McPherson KM, Blake DR: Body perception disturbance: A contribution to pain in complex regional pain syndrome (CRPS). *Pain* (in press) May 15, 2007]

What do we conclude from this case study as scientists? Although we can describe quantitatively (1) the different clinical phenomena of CRPS type I in detail and (2) the mechanisms underlying some phenomena (eg, increase or decrease of skin temperature, some types of sympathetically maintained pain, lack of thermoregulation of the affected extremity), we are far from understanding the organizing principle that is behind this puzzling syndrome. As formulated in our explanatory hypothesis, we believe that the solution is to be found in the brain. To unravel this mystery, basic research on the mechanisms underlying CRPS must be better integrated with clinical observations of human patients. The design of animal models, including human models, must be more closely integrated with the clinic to focus the scientific questions, to formulate testable hypotheses, and to develop appropriate experimental methods. Only such an interdisciplinary and multidisciplinary approach has a realistic chance of uncovering the pathophysiology, leading to a more mechanism-based therapy of CRPS.

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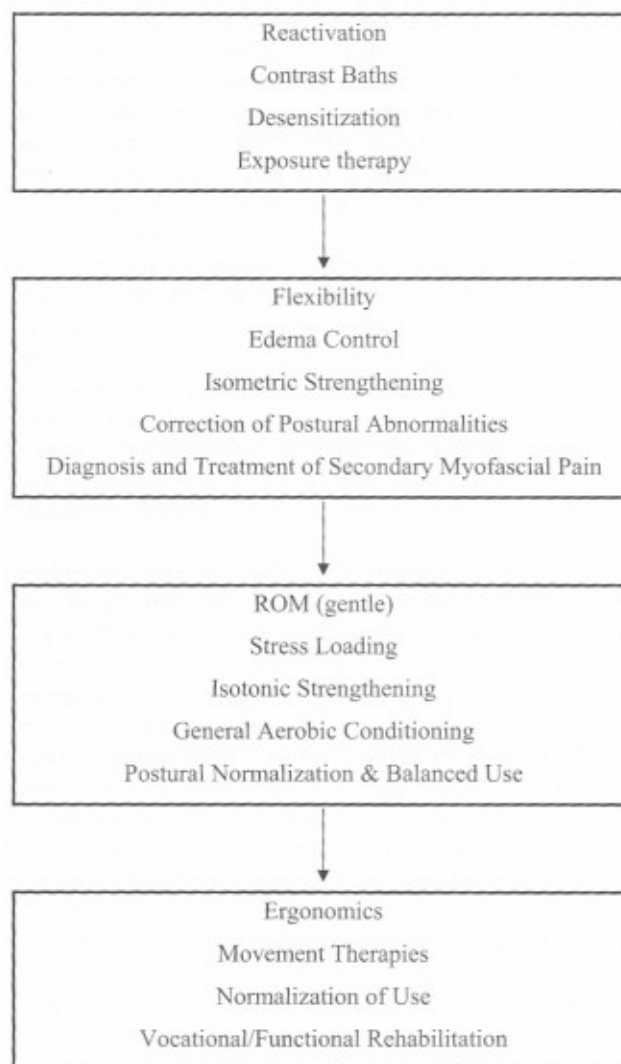
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## Multidimensional Approach to CRPS

This case is characteristic of CRPS. The history (pain persisting and disproportionate to the expected course of the inciting trauma) as well as signs and symptoms (allodynia, hyperalgesia, autonomic dysregulation with vasomotor and sudomotor abnormalities, edema, trophic changes, and motor abnormalities) are consistent with the IASP diagnostic criteria<sup>11</sup> and newer statistically derived criteria (the Budapest criteria<sup>5</sup>). CRPS is biomedically multifaceted and is frequently associated with psychosocial components that are additional pivotal diagnostic features (and thus, treatment targets). As such, any unimodal approach usually fails, and multiple modalities/disciplines are required to optimize pain management, functional rehabilitation, and quality of life.<sup>2</sup> There is very little detail as to the modalities or therapies tried in this case, but clearly "several weeks of physical therapy" early on does not meet the standard of care,



**Figure 2.** Functional restoration algorithm for CRPS. The CRPS patient should have early access to medications and/or psychotherapy and/or injections. If the patient cannot begin or fails to progress at any step in this algorithm, the interdisciplinary team should consider starting (or adding) more or stronger medications and/or more intensive psychotherapies and/or different interventions (extrapolated and modified from 2 clinical consensus meetings: Malibu,<sup>4</sup> Budapest<sup>5</sup>).

which ideally should be a systematic and coordinated interdisciplinary approach with a primary goal of functional restoration<sup>3,6,16</sup> (Fig 2). Interdisciplinary treatment is defined as a dedicated, coherent, synchronized, specially trained group of relevant professionals that meet regularly to plan, coordinate care, and adapt to treatment eventualities. It is critical to identify and methodically treat all spheres of the pain experience, particularly the often neglected psychosocial targets. CRPS is not specifically a psychological disorder, however, and it is therefore equally naive to conclude psychotherapy alone will succeed.

Functional restoration has empirically been considered a critical and necessary component of interdisciplinary pain management programs for CRPS and this contention has been codified by 2 large international consen-

sus-building conferences,<sup>6,16</sup> yet there is little solid evidence concerning this intuitive and traditional approach.<sup>10</sup> A functional restoration protocol should emphasize physical activity ("reanimation"), desensitization of the affected body part, and normalization of sympathetic tone in the affected limb. Functional restoration involves a steady progression from the most gentle, least invasive interventions to the ideal of optimal rehabilitation in all aspects of the patient's life (Fig 2). The most efficient team for delivering this standard includes pharmacotherapy, psychotherapy, physical therapy, occupational therapy, recreational therapy, and, if necessary, interventional therapies.<sup>3,6,16</sup> The core principles of treatment include patient motivation, desensitization, and reactivation facilitated by pain relief; the use of pharmacologic and/or interventional procedures to treat specific signs and symptoms; and cognitive behavioral psychotherapeutic techniques.<sup>3,6,16</sup>

The traumas usually identified in the underlying cause of CRPS most likely begin with peripheral nociceptive overstimulation, and this "nociceptive barrage" and disuse of the affected part can initiate and sustain peripheral and central sensitization/augmentation that is suggested by the sensory features of the syndrome. It is hypothesized that restoration of regular use of affected part will normalize afferent input and its processing, thus resetting the sensitization. Pain is often a limiting factor to achieving this and provides the rationale for medications, blocks, and psychological support early in the course (and not to "reserve" these interventions until after a patient has "failed to progress"). Pain drives the type, quality, intensity, and pace of other interventions; however, function must be the outcome to ultimately measure success.

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In our experience, multiple interventions often are required to get a patient started in a functional restoration process.<sup>3,6,16</sup> As immobilization, disuse, and fear of movement are common features of CRPS, the reversal of this operant movement phobia ("kinesiophobia") provides an example of the need for coordinated cotreatment of modalities; in this example, physical and psychological therapies. Primary goals of physiotherapy are to normalize sensation and power, promote normal positioning range of motion and flexibility, decrease muscle guarding, minimize edema, and increase functional use of the extremity in order to increase independence in all areas—work, leisure, and activities of daily living. Blood flow and nutrition to the area may be improved by local activity in the affected part, and processes such as osteopenia (ie, "Sudeck's atrophy") may also be reversed. On the other hand, inappropriately aggressive therapy can trigger extreme pain, edema, distress, and fatigue and may in turn exacerbate inflammation and sympathetic symptoms of CRPS and should be avoided. The cognitive behavioral approaches commonly used in chronic pain in general, including biofeedback, are usually necessary to effectively restore healthy behavior and function in the face of potent operant contingencies. The interdisciplinary approach for treating patients with CRPS remains the most pragmatic, helpful, and cost-effective therapeutic approach available today.

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