Clinical note

Complex regional pain syndrome as a stress response

Lucinda A. Grande¹,c, John D. Loeser⁴, Judy Ozuna⁴, Alexandra Ashleigh⁵, Ali Samii¹,c,*

¹Department of Neurology, Veterans Affairs Puget Sound Health Care System, Mailstop 127, 1660 S. Columbian Way, Seattle, WA 98108, USA
²Department of Psychiatry, Veterans Affairs Puget Sound Health Care System, Mailstop 127, 1660 S. Columbian Way, Seattle, WA 98108, USA
³Department of Neurology, University of Washington School of Medicine, Seattle, WA 98195, USA
⁴Department of Neurological Surgery, University of Washington School of Medicine, Seattle, WA 98195, USA

Abstract

A man in his 50’s with a prior traumatic brain injury and multiple psychiatric disorders developed acute pain and swelling in his left leg distal to the mid shin. These symptoms arose during an exacerbation of his post-traumatic stress disorder (PTSD). Among his traumatic memories, he reported having witnessed the combat injury and death of a friend who had lost his left leg distal to the mid shin. A diagnosis of conversion disorder was technically excluded because the findings met criteria for Complex Regional Pain Syndrome (CRPS) type I. Based on recent research into the neurobiology of CRPS, PTSD and conversion disorder, we propose a supraspinal mechanism which could explain how emotional stress can produce both symptoms and signs.

Keywords: Complex regional pain syndrome; Reflex sympathetic dystrophy; Conversion disorder; Post-traumatic stress disorder; Encephalomalacia; Traumatic brain injury

1. Introduction

Complex regional pain syndrome (CRPS) is a disorder of the extremities characterized by pain and sensory changes accompanied by observable findings such as swelling and autonomic, motor and/or trophic abnormalities (Merskey and Bogduk, 1994). The pathophysiology of CRPS remains poorly understood. Peripheral, autonomic and central nervous systems and the inflammatory response may all be involved, and there is likely a genetic contribution (Wasner et al., 2003). Emotional stress is often an important precipitating factor (Geertzen et al., 1998).

In this report we describe a patient with highly symbolic, acute onset CRPS symptoms and signs, which arose in the context of a post-traumatic stress disorder (PTSD) exacerbation. We outline a novel psychophysiological mechanism to explain his condition.

2. Case report

2.1. History

A male veteran in his 50’s was admitted to the psychiatric unit of a veterans’ hospital for exacerbation of PTSD symptoms. He had been followed for years in the neurology clinic of that hospital for complex partial seizures, poorly controlled with medication, with no significant recent medication changes. The seizures arose following a remote traumatic brain injury. Brain magnetic resonance imaging (MRI) showed extensive bifrontal encephalomalacia, left greater than right. An electroencephalogram (EEG) showed bilateral frontal slowing, and right frontal epileptiform discharges.

The patient’s psychiatric history included schizoaffective disorder, dissociative episodes and PTSD. One of the psychological traumas precipitating his PTSD involved a combat incident in which a fellow soldier lost his left leg distal to the mid-shin and subsequently died.

Three years prior to admission a minor injury resulted in low back pain and bilateral radiating leg pain. An MRI of his lumbar spine showed minimal degenerative changes.
Shortly afterwards he developed involuntary bilateral leg movements and a stiff gait. One year prior to admission a clinic note mentioned that the dorsal aspect of his left foot was warm and erythematous, without reported injury, and he was supplied with lamb’s wool padding. During the month prior to admission he developed pain and numbness on the plantar aspect of his left foot, progressing slowly to include the dorsum of the foot. He also reported that during that same month, prominent televised war news exacerbated his PTSD.

The patient was admitted to the psychiatric unit for PTSD-related depression with suicidal ideation. During the first night of hospitalization, he awoke and reported severe pain in his entire left foot and the anterior aspect of the leg distal to the mid-shin. The pain was described as sharp, constant and deep without radiation, with an occasional electrical sensation. It was worse with weight-bearing, not relieved by positional change, and only minimally relieved with opioid medication. The following morning his left foot had become swollen, and he additionally noted numbness on the plantar aspect of his right foot. He denied recent trauma to either foot, or recent exacerbation of his low back pain.

2.2. Examination and studies

Examinations demonstrated 1–2+ pitting edema initially in the left foot, extending to the left ankle within 2 days, and to the right foot within 6 days. There was no discoloration, no abnormal warmth or temperature difference between the feet, no notable change in sweating, skin thickness, hair pattern or nail growth. Active and passive ankle and toe movements were limited by pain and possibly by weakness and stiffness, but no muscle atrophy was noted. Sensation was abnormal with hypoaesthesia, allodynia and hyperalgesia up to 10 cm circumferentially above the ankle, with some sparing on the posterior leg.

Laboratory studies, plain films, venous duplex, ankle brachial indices, and nerve conduction studies were all normal. A three phase technetium-99 bone scan showed decreased perfusion of the left lower leg and foot, and in delayed images, decreased radiotracer uptake in the left tibia, foot bones and toes.

2.3. Treatment

He was provisionally diagnosed with CRPS type I, although the bone scan was considered atypical. He refused a diagnostic lumbar sympathetic block. His pain was partially relieved by capsaicin cream, acetaminophen with codeine, indomethacin, and amitriptyline. He received four sessions of physical therapy in which he did foot exercises and progressively increased his walking distance using a rolling walker. On the ninth day he could tolerate pressure stockings and two days later was fitted with a walking brace. His psychiatric care included antipsychotic and antidepressant medications and goal-oriented cognitive therapy. He reported temporary pain relief while attending a social dinner at a local veterans’ hall about one week into his hospitalization. By the time of discharge at two weeks, his bilateral lower extremity pain and edema were improved. On outpatient followup two weeks later, his mental state showed marked improvement, and his pain and swelling had largely resolved. He continued to receive regular outpatient psychiatric and neurological care.

3. Discussion

The clinical diagnosis of CRPS, while fraught with pitfalls (Ochoa, 1999), was based on a constellation of sensory changes (spontaneous pain, allodynia, etc.) and other findings (pitting edema, joint stiffness, and abnormal bone scintigraphy), together with a negative workup for other conditions. The progressive involvement of both lower extremities was consistent with this diagnosis (Maleki et al., 2000). The inciting event may have been his minor back injury three years earlier. His condition was likely an exacerbation of a mild chronic CRPS, evidenced by the left foot warmth and erythema observed one year prior to admission. The bone scan hypoperfusion, in contrast to hyperperfusion typical of early CRPS, would be consistent with a chronic condition (Lee and Weeks, 1995). Because of his psychiatric history and the symbolic location of the symptoms, the differential diagnosis included pseudodystrophy, a recently described complication of conversion disorder resulting from disuse of the extremity (Driessen et al., 2002). However, ambulation prior to admission would preclude a disuse syndrome.

Psychological factors were integral to the timing and manifestation of the disease process. Symptom onset was associated with emotional stress, and symptoms were relieved cognitively, with temporary distraction at the social dinner and perhaps with psychotherapy (in conjunction with other treatment modalities). The striking symbolism of the symptom location suggests secondary gain, that is, an unconscious attempt to resolve the conflict of his survivor’s guilt by experiencing his comrade’s leg pain. His psychiatric profile was remarkably characteristic of conversion disorder patients (Andreski et al., 1998; Ettinger et al., 1999). However, conversion disorder was excluded due to objective physical findings.

We hypothesize that our patient’s CRPS exacerbation resulted from a dysfunctional relationship between the anterior cingulate cortex (ACC) and the periaqueductal gray (PAG). PAG is a midbrain structure, which coordinates defensive responses such as fight, flight, and passive immobilization (Bandler et al., 2000). Stimulation of PAG inhibits nociception via secondary noradrenergic projections to dorsal horn (Bajic and Proudfoot, 1999). PAG dysfunction has been identified as a possible component of CRPS because of its co-localization of autonomic, motor
and anti-nociceptive functions (Drummond, 2001). It receives forebrain input, and can trigger active coping responses to psychological stressors (Canteras and Goto, 1999). Its output has functional and regional specificity, as demonstrated by arching of the back, ear retraction and vocalization elicited by its stimulation in decerebrate cats (Bandler, 1982).

ACC is a forebrain structure with a complex contribution to emotional behavior (Devinsky et al., 1995). It has pathological activity patterns in conversion disorder, in which emotional conflict is symbolically transformed into neurological dysfunction (Mailis-Gagnon et al., 2003; Marshall et al., 1997). Its additional role in pain processing (Sewards and Seward, 2002) suggests the potential for a pathological transformation of emotional conflict into pain.

There are two ACC subdivisions which have reciprocal inhibitory influences on one another (Drevets and Raichle, 1998). The rostral division connects with PAG. It regulates autonomic functions and emotional motor responses (Devinsky et al., 1995). The caudal division connects with prefrontal cortex. It is involved with cognitive assessment of noxious stimuli. Reduced pain sensitivity during cognitively demanding tasks correlates with suppressed activity in caudal ACC (Bantick et al., 2002).

The patient’s bifrontal slowing and right frontal epileptiform discharges suggest frontal lobe dysfunction with the potential to alter normal processing in ACC. Compromised prefrontal cortex adjacent to ACC might predispose a patient to CRPS as a response to emotional stress. Attention suddenly directed to powerful emotional stressors could strongly excite caudal ACC, overwhelming cognitive compensatory processes in prefrontal cortex, thereby allowing caudal ACC to strongly inhibit rostral ACC. In a predisposed individual, inhibition of rostral ACC in turn could result in reduced stimulation of PAG, resulting in a nociceptive surge. The ensuing increase in afferent pain signals would then further excite caudal ACC. Such an imbalanced pattern, following a minor injury which has presensitized peripheral nociceptive and autonomic pathways, may result in CRPS. Forebrain and midbrain circuitry has not yet been established in sufficient detail to describe how a particular psychological stressor represented in ACC might influence a symbolically related functional subdivision of PAG (Bandler et al., 2000).

The clinical association of PTSD and CRPS in this patient suggests the possibility of shared neural substrate elements. Indeed, the proposed circuit is consistent with functional neuroimaging of PTSD subjects, in which abnormally increased and reduced blood flow, respectively, in caudal and rostral ACC was seen in PTSD subjects during exposure to reminders of traumatic events (Bremner et al., 1999). Abnormal blood flow in PAG was not seen in PTSD subjects.

The clear symbolism of this patient’s CRPS is unusual, but its supraspinal origin may not be. Common CRPS precipitants such as stressful life events (Geertzen et al., 1998), stroke (Petchkrua et al., 2000), and brain injury (Gellman, 1992) could compromise cortical regulation of ACC, particularly in the high proportion of CRPS patients with psychiatric comorbidities (Monti et al., 1998).

This patient’s CRPS exacerbation may be viewed as having a psychophysiological origin (Breuhl, 2001). That is, the physiological correlate of a psychological process (emotional stress) may have activated a latent pathophysiological process (CRPS). Stress could alter the brain’s pain processing network (the ‘neuromatrix’) by activating any of the body’s homeostatic regulation systems (neural, hormonal, immunological, and behavioral) (Melzack, 1999).

We have described a direct neural mechanism, with potentially wide applicability. Imbalanced cortical regulation of ACC, with consequent autonomic dysregulation, could also contribute to well-recognized stress-related medical conditions such as gastric ulcers and angina. The mental processes involved are unconscious, not under the patient’s voluntary control as in malingering.

CRPS is likely a multi-factorial disease process, requiring a multi-disciplinary therapeutic approach. Psychological treatment strategies designed to relieve stress and strengthen cognitive coping skills might favorably influence supraspinal activity patterns. For CRPS patients with emotional stress as a precipitating factor, these approaches should be more vigorously explored.

Acknowledgements

Carl Jensen, MD (Psychiatry), John Oakley, MD, PhD (Neurology) and multiple other specialists provided inpatient care. Janet Ploss, MD provided helpful comments.

References


Breuhl S. In: Harden RN, Baron R, Janig W, editors. Do psychological factors play a role in the onset and maintenance of CRPS-I? Complex


