

Pathophysiology of the Spreading of Complex Regional Pain Syndrome Revisited: A Case Report

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Objective: To determine if there is a relationship in our patient developing complex regional pain syndrome from a jellyfish and its subsequent spread to the contralateral side.

Methods: Data bases were searched using PubMed and Ovid. Keywords searched include “complex regional pain syndrome,” “jelly fish,” and “pathophysiology.”

Results: This patient was successfully treated with a spinal cord stimulator implantation with bilateral lead placement at thoracic spine (T9) stimulating her lower extremities in addition to the leads that had already been placed in her cervical spine for her upper extremities.

Conclusion: Definite knowledge of the pathophysiology of complex regional pain syndrome would allow better identification of risk factors for the development of this condition after trauma. This patient is at higher risk of developing complex regional pain syndrome and should avoid surgeries (such as knee and wrist surgeries) and high risk physical activities.

Keywords: Complex regional pain syndrome, jellyfish sting, pathophysiology

Conflict of Interest: Billy Huh is a paid consultant for St. Jude Medical. He also has had grant support from St. Jude Medical for clinical trials in the last three years. The patient included in this case report was not part of the clinical trial. The other authors reported no conflicts of interest.

Our patient is a 49-year-old woman with past medical history (greater than three years) of resolving complex regional pain syndrome (CRPS) in her right upper extremity after a spinal cord stimulator implantation in the cervical spine. This previous diagnosis was related to intravenous phenergan infiltration. She presents with a three-week history of pain in bilateral lower extremities after being stung by an unidentified species of jellyfish on her right foot during a visit to the North Carolina coast. After the sting, the patient developed allodynia, hyperalgesia, and swelling without a specific dermatomal pattern in her right foot. Within eight hours after being stung she started to develop the exact symptoms on her left foot and developed skin changes that mirrored her right foot (Figure 1). The next day she started to develop stinging, swelling, skin changes, hyperalgesia, numbness, and tingling in bilateral upper extremities which mirrored the lower extremities. Patient had tried over-the-counter antihistamines and anti-inflammatories after the initial sting with no success. She also had seen her primary care doctor who had tried her on a clonidine patch, gabapentin, and she was then placed on a Fentanyl patch prior to coming to the clinic for treatment.

Past Medical History: Right upper extremity CRPS with spinal cord stimulator placement in 2006, depression, endometriosis, and bilateral carpal tunnel surgery in 2004.

Family History: No history of CRPS.

Social History: Negative for tobacco, alcohol, or illicit substances.

Medications: Prozac 40 mg QDaily, Fentanyl patch 50 µg/hour q72 hours.

Exam: Patient is alert and oriented ×3, in no acute distress. The numbness, hyperalgesia and allodynia, and discoloration were isolated on the ventral and dorsal side of her feet bilaterally, and distal to her wrists bilaterally. She had skin discolorations of the bilateral hands that mirrored the discolorations seen on her feet. On the right she had 3/5 manual muscle strength with right extensor hallucis longus secondary to discomfort but otherwise she had 5/5 on her manual muscle strength throughout bilateral upper and lower extremities.

Treatment: After the patient had tried more conservative medical management, one month later she was then scheduled for and underwent a successful spinal cord stimulator trial over a five-day period; a permanent implant was then placed for her lower

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Figure 1. Picture after jellyfish sting to the right lower extremity. Note the mirror image seen on the left foot.



Figure 2. Picture after spinal cord stimulator implantation for pain in the lower extremities.

extremities after successful results of the trial. The settings of the stimulator were: continuous mode, 90–300 Hz, 250–350 μ sec pulse width, and amplitude range of 2.3–10 mA (Figure 2).

BACKGROUND

Complex regional pain syndrome is a devastating disease process that is difficult to treat and presents with pain disproportionate to the extent of the injury. Characteristics of CRPS include burning, deep pain, allodynia, hyperalgesia, and hyperpathia. Swelling, autonomic dysregulation, movement disorders, atrophy, and dystrophy also are associated with this syndrome.

The pathophysiology of CRPS has been extensively explored in the literature and there have been many theories presented which help explain why certain symptoms occur. In large part, however, CRPS remains a puzzle, and the goal of this paper is not to conclude with certainty the mechanisms which caused our patient to have a “spreading” of her complex regional pain but rather explore the best studied theories and apply them to our case patient. This paper will not reduce the complexity of CRPS to a single pathophysiologic

mechanism, but it will attempt to explain the pathology seen in our patient. A review done by Dr. Breuhl will guide the structure of this discussion (1).

OBJECTIVE

To determine if there is a relationship in our patient developing CRPS from a jellyfish and its subsequent spread to the contralateral side.

METHODS

Data bases were searched using PubMed and Ovid. Keywords searched include “complex regional pain syndrome,” “jelly fish,” and “pathophysiology.”

RESULTS

Jellyfish release a neurotoxin as part of their hunting mechanism. In the literature reported jellyfish stings have caused mononeuritis multiplex (isolated nerve injuries) in the single limb that was stung (2–4). On our exam this patient did not have any isolated nerve injuries on exam. It is likely, however, that an initial nerve trauma to the C fiber and the A delta fibers such as a jellyfish sting triggered a cascade of events which led to the development of CRPS in the patient’s ipsilateral limb as has been shown in the literature (5,6).

In a patient with a history of CRPS, the literature supports that the theories of wind up and central sensitization can cause ipsilateral changes as seen in the patient’s limb that was stung by the jellyfish. Patients with a history of complex regional pain, such as our case study, have a predisposition to the formation of CRPS reflected by increased excitability of spinal cord neurons evoked by repeated stimulation. However, central sensitization and wind up do not explain the mirror image of allodynia, skin lesions, and hyperalgesia seen in the patient’s contralateral leg and upper extremities (7–10).

Genetic factors could also have predisposed our patient to the development of CRPS. There have been various human leukocyte antigen (HLA) allele and familial patterns that have been described in the literature which may have contributed to our patient’s susceptibility of developing CRPS (11–14).

A plausible theory which may be applied to our patient is that of a poorly regulated neurohumoral sympathetic nervous system allowing her CRPS to spread. Studies by Schurmann and Ackerman both showed that patients with impaired peripheral vasoconstrictor activity are more prone to developing CRPS (15,16). CRPS alters levels of nitric oxide, nitric oxide synthase, calcitonin gene-related peptide, endothelin-1, tumor necrosis factor alpha, interleukins, and endothelial-dependent vasodilator functions (17–19). Changes in the vasodilator function can either be sympathetically mediated or due to altered amounts of neuropeptides such as substance P, calcitonin gene-related peptide, and bradykinin (17,20–27). The decreased ability to control vasodilation can help explain why our patient developed CRPS in all four extremities (28,29). Harden et al. reported norepinephrine changes on the affected side rather than the unaffected side (30). In this study the decreased levels of norepinephrine were localized to areas where the patients had CRPS. A dysregulated sympathetic response combined with the release of proinflammatory cytokines and neu-

ropeptides from the nociceptive fibers could cause system-wide symptoms of CRPS (30,31). Similarly, psychological factors such as anxiety and depression present in our patient can increase catecholaminergic activity and can contribute to the development of the intensity of pain and vasomotor signs, thereby increasing the central sensitization of CRPS (32–35).

Unknown in the medical literature is the involvement of the brain in its association with neuropathic pain. There are several neuroimaging studies showing that in patients with CRPS, there is an association with the reorganization of somatotopic maps and there also is decreased representation of the CRPS-affected limb in the somatosensory cortex compared to the unaffected side (9,36–39). In the studies, these areas return to normal after successful treatment of the CRPS (9,38). Also, studies involving functional magnetic resonance imaging showed there was greater total brain activation following stimulation of the unaffected limb mirror region than following stimulation of the affected region (40). It is a possibility this patient may have had some sort of a reorganization of her somatotopic maps, thus enabling her to have mirror image-like pain. However, the somatotopic anatomy of the brain is such that the fibers on the right side stay together and the fibers on the left side stay together (9). This theory would be easier to explain if the patient's pain was on the entire ipsilateral side of the body and did not cross the contralateral side.

CONCLUSION

In a patient with possible genetic susceptibility, the jellyfish sting served as an initial trigger which then caused a cascade of events to unfold and led to her development of CRPS in all four extremities. Due to her history of previous CRPS, this patient was already susceptible to central sensitization and wind up. This, in combination with abnormal activity from her sympathetic nervous system, increased adrenergics caused by her psychiatric history, and increased activity in her neurohumoral response, may have led her to develop CRPS in all four extremities. This patient was successfully treated with spinal cord stimulator implantation with bilateral lead placement at the thoracic spine (T9) stimulating her lower extremities in addition to the leads that had already been placed in her cervical spine for her upper extremities.

Improved knowledge of the pathophysiology of CRPS would allow better identification of risk factors for the development of this condition after external injury or trauma. This patient is at higher risk of developing CRPS and should avoid elective surgeries (such as knee and wrist surgeries) and high risk physical activities.

Authorship Statements

Dr. Azari, Dr. Lu, and Dr. Huh examined and followed the patient. Dr. Azari, Dr. Clarke, Dr. Collina, Dr. Huh, and Mr. Briones prepared and conducted the literature searches for the manuscript. All authors approved the final manuscript.

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