Spinal Cord Stimulation: “Neural Switch” in Complex Regional Pain Syndrome Type I

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ABSTRACT

Introduction. Complex regional pain syndrome type I (CRPS I) is a neuropathic pain disorder of unclear etiology. It commonly follows a trivial injury and is characterized by spontaneous pain manifesting regionally that is disproportionate to the inciting event. Associated signs and symptoms include allodynia, hyperalgesia, edema, sudomotor, vasomotor abnormalities, and trophic changes. Although multiple modalities exist to treat CRPS I, significant disability, diminution in quality of life, and reduction in overall health often accompany the syndrome.

Case. A case of a 57-year-old man with CRPS I who was treated with spinal cord stimulation (SCS) after failing conservative therapy is presented. One month following treatment, he experienced complete symptom resolution such that stimulation was subsequently discontinued without recurrence over the 1-year follow-up period.

Conclusions. To date there is currently no reliably validated “cure” for CRPS. There has only been one recent report where SCS resulted in the complete eradication of the signs and symptoms associated with CRPS. This series involved adolescent girls aged 11–14 years of age, who tend to have a more benign and self-limited treatment course than that seen in adults. This raises the question as to whether a “neural switch” exists, and if so, where it is located. We postulate that the inter-neuronal connections between the central and peripheral nervous systems implicated by the current pathophysiological model is the most plausible site of this “neural switch,” and that reorganization of this interface can account for the ability of SCS to effect a complete “cure” in CRPS.

Key Words. Spinal Cord Stimulation; Complex Regional Pain Syndrome

Introduction

Complex regional pain syndrome type I (CRPS I; also known as reflex sympathetic dystrophy), is a neuropathic pain disorder of unclear etiology [1,2]. It commonly follows a trivial injury and is characterized by spontaneous regional pain disproportionate to the inciting event [3]. Associated signs and symptoms include allodynia, hyperalgesia, edema, sudomotor, vasomotor abnormalities, and trophic changes [4]. CRPS Type I signs and symptoms tend to have a distal preponderance, and are exacerbated by conditions known to stimulate the sympathetic nervous system (e.g., cold weather and emotional stress). In the absence of effective treatment, CRPS I results in significant disability.

Spinal cord stimulation (SCS) is an important treatment modality to address refractory cases of CRPS. Since its introduction in 1967, considerable efforts have been made to elucidate its mechanism of action. Although the theory in its original form remains somewhat controversial and has been revised several times [5], the rationale
behind SCS stems from a clinical outgrowth of Melzak and Wall’s “gate control theory of pain,” first espoused in 1965 [6]. Pain conditions associated with dysautonomia such as CRPS may either be sympathetically maintained or sympathetically independent. The ability of SCS to attenuate sympathetic outflow may not be relevant to its analgesic effect. For instance, Kemler et al. [7] demonstrated that patients with chronic CRPS who underwent prior surgical sympathectomy experienced pain relief with SCS despite the absence of vasodilation. The current conceptual model for SCS supports segmental inhibition as a tenet for analgesia. Data obtained from animal studies indicate that second-order neurons and interneurons can be affected by SCS, and that spinal and supraspinal inhibitory loops may account for the major effects of SCS in neuropathic pain [8,9]. Although there is evidence supporting SCS in patients with CRPS I, there are few reports documenting functional improvement or the complete resolution of symptoms associated with SCS in this population [10]. We report a case of refractory CRPS whereby SCS resulted in complete amelioration of the patient’s symptoms within 2 months of implantation. The stimulator was switched off 1 month later, yet the patient remained symptom-free through his most recent 1-year follow-up appointment at our tertiary care pain clinic.

**Case Report**

A 57-year-old man with a past medical history significant for well-controlled hypertension and depression developed sudden-onset right foot pain with no inciting event. His primary care physician diagnosed cellulitis and recommended a 10-day course of oral antibiotics. His symptoms resolved approximately 10 days after completing the antibiotics. Shortly thereafter he developed a recurrence of his symptoms and an x-ray of his right foot revealed healing second and third metatarsal fractures as shown in Figures 1 and 2. He was referred to the Department of Orthopedic Surgery and subsequently to the Pain clinic for conservative management. On initial evaluation he was found to have clinical features consistent with complex regional pain syndrome type I, based on the revised International Association for the Study of Pain/CRPS criteria proposed by the Budapest consensus group [11]. These included spontaneous pain disproportionate to the inciting event, and involving the distal lower extremity; hyperesthesia, and allodynia in the affected area; edema below the knee; trophic/motor changes including skin and nail bed changes, with evidence of kinesiophobia; and absence of any other condition or diagnosis that could reasonably explain the signs and symptoms. Consistent with this diagnosis, a multidisciplinary approach was instituted that consisted of physical therapy with desensitization techniques, psychotherapy emphasizing cognitive behavioral techniques to enhance coping strategies, and pharmacotherapy consisting of gabapentin 600 mg p.o. three times a day, nortryptiline...
Discussion

CRPS is a poorly understood condition that can have devastating consequences if left untreated. Though the pathophysiology remains elusive, animal and human studies have generated several postulates. First, CRPS is a neurological disease of the nervous system involving the sympathetic, somatic afferent and motor systems whereby the central nervous system (CNS) potentially orchestrates the myriad changes reflected in the condition [12,13]. Second, signs of inflammation may represent a peripheral inflammatory process [14]. Third, there is a poorly understood interaction between the central and peripheral mechanisms mediated by chemical mediators such as cytokines, neuroendocrine channels or antidromic activation of peptidergic primary afferents [15]. Nonetheless, the search for the specific mechanism or mechanisms by which CRPS I manifests continues to unravel.

One of the main challenges in elucidating the pathophysiology of CRPS has been difficulty defining the patient population. A preliminary attempt to standardize the diagnostic criteria for CRPS was undertaken at a consensus workshop in Florida in 1994, which was subsequently codified the following year by the International Association for the Study of Pain task force on taxonomy [3]. Although this represented a major advancement in the classification of regional pain disorders associated with autonomic changes, internal, and external validation studies suggested that CRPS was over–diagnosed, with a sensitivity of 0.98 but a specificity of only 0.36 [16,17]. This lack of external validity led to the recent proposal of new diagnostic criteria driven by validation studies that requires at least one symptom in three of four subcategories, and at least two signs in two of four subcategories [5]. Based on these revised criteria, the specificity has considerably improved considerably without a concomitant loss of sensitivity (clinical diagnostic criteria sensitivity 0.85, specificity 0.60, research diagnostic criteria, sensitivity 0.70, specificity 0.96). Based on this updated diagnostic algorithm, our patient met the clinical diagnostic criteria for CRPS by presenting with three symptoms and three signs from each of the four subcategories.

Various diagnostic tests have been advocated to confirm the diagnosis of CRPS including radiological studies, triple-phase bone scans, quantitative sensory testing, and extremity temperature differences recorded with and without sympathetic stimulation. But with the exception of thermography during sympathetic stimulation which has a sensitivity of 0.76 and specificity of 0.96, the utility of all these tests are limited by low specificity. One limitation of our report is the absence of a confirmatory diagnostic test with high specificity (i.e. thermography during sympathetic stimulation). Yet, this test can be cumbersome to perform in a busy clinical practice, has not been shown to improve treatment outcomes, and is not necessary to diagnose CRPS. A second criticism that may be leveled is that we did not use a treatment algorithm to guide therapy. However, there is a paucity of evidence-based treatment algorithms for CRPS, none of which is considered standard of care, and outcome studies provide modest consistency with regards to the pharmacological treatment approach to CRPS [18]. We therefore adopted a multidisciplinary treatment approach consistent with that proposed by Stanton-Hicks et al., which informed our decision to institute SCS when more conservative treatment proved suboptimal [19].

There is evidence suggesting that the possible mechanism responsible for sustaining symptoms in CRPS involves the CNS orchestration of interactions between the sympathetic, sensory afferent and motor systems [20,21]. This evidence may
explain the potential of SCS to provide sustained targeted neuromodulation that ultimately facilitates the reorganization (i.e., “unwinding”) of the central–peripheral dysfunction characterizing the condition. Currently, SCS is the only modality capable of providing sustained interventional pain relief with reversibility at any treatment stage. A recent literature review revealed only one report whereby SCS successfully eradicated all signs and symptoms of CRPS. This occurred in a series in adolescent girls (11–14 years old). In three of seven girls, the stimulator was explanted after complete resolution of symptoms, while two other girls continued to use it intermittently for sporadic pain [22]. However, the natural course of CRPS is qualitatively and quantitatively different in children. In general, children experience less neurological and autonomic symptoms, and tend to have more limited disease progression [23]. To our knowledge, similar cases involving complete symptom resolution without recurrence after deactivation/explantation of SCS have not been reported in adults. This raises the question as to where the “neural switch” is located. In an extensive review of SCS physiology, Linderoth and Foreman concluded the mechanism for suppression of neuropathic pain may differ from the mechanism required to treat ischemic pain. The authors alluded to the effects of SCS in suppressing wide dynamic range dorsal horn neurons and in modulating neurotransmitter release at the spinal cord level as possible mechanisms of action. But they also emphasized the need to more clearly define the role of supraspinal circuits in algnesia [23]. Nihashi et al. [24] assessed the brain response during SCS in seven patients with CRPS using fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET). They found increased uptake in the ipsilateral thalamus in the six patients for whom SCS was effective, in contrast to decreased uptake in the contralateral thalamus in the patient for whom SCS was ineffective. The authors concluded that thalamic metabolism may therefore be a determinant of SCS efficacy. However, less information exists regarding spinal and supraspinal mechanisms involved in the disease process. The pathophysiological model implicating the interaction between the central and peripheral nervous systems as the root cause of CRPS (and the most likely site for the “neural switch”) provides the most plausible explanation for the ability of the SCS to effect a complete “cure” through reorganization, as demonstrated in this case presentation. Clearly, continued research is necessary to clarify both the etiology and provide conclusive evidence for the presence and site of the “neural switch” for CRPS.

In conclusion, this case demonstrates the continued challenge posed by CRPS in terms of the quest for a clearer understanding of the pathophysiology, which may ultimately drive the discovery of more effective treatment modalities. The major advance in the classification and development of clear diagnostic criteria for CRPS has enhanced clinicians’ ability to make a diagnosis in a cohesive manner. This will also help ensure that future research will be directed to a more homogeneous patient population, and thus engender a more uniform response to treatment. Ongoing research into the nature of the neural networks implicated in CRPS may yet hold the key to the explanation of the response to treatment as reported in this case.

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References