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Case Report

Pruritus and urticaria induced by neurostimulation: A case report and review of literature

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ABSTRACT

Background: Spinal cord stimulation (SCS) consists of the implantation of neuromodulatory devices in the spinal cord to treat refractory neuropathic pain. Although SCS technology has been proven of immense clinical benefit, complications remain including refractory pain, infection risk, and electrode migration or displacement. Till date, there are minimal reports of allergic side effects following SCS implantation.

Case Description: In the first case, a 36-year-old male with chronic axial and radicular neuropathic pain in underwent implantation of an open paddle lead and generator. Within 1–3 h of activating the SCS, he developed diffuse raised erythematous hives. Over time, the SCS had immense clinical benefit for his pain reduction; however, he continued to experience recurrent hives and various other allergic reactions including facial flushing and photosensitivity. Four years later, he ultimately opted to retain the device for its clinical pain benefits. In the second case, a 35-year-old female with acute, intractable bilateral occipital neuralgia and a past medical history of Type 1 Chiari Malformation status-post-posterior fossa decompression underwent implantation of an occipital nerve stimulator (ONS). At 1-month follow-up, she began to experience pruritus across the back of her head and along the subcutaneous course of the lead. At 8 months, she continued to experience persistent symptoms, ultimately opting for device removal.

Conclusion: Although allergic reactions to implanted neurostimulation systems are rare, and mechanisms not completely understood, existing studies posit multiple theories surrounding the pathophysiology of allergic reactions to these devices, such as delayed hypersensitivity reactions or contact dermatitis. Further research is needed to elucidate the cutaneous and immunologic side effects of SCS and ONS devices.

Keywords: Functional neurosurgery, Neuromodulation, Occipital nerve stimulation, Spinal cord stimulation, Stereotactic neurosurgery

INTRODUCTION

Neuromodulation is widely used in the treatment of patients with chronic refractory neuropathic pain. Two commonly used forms of neuromodulation include spinal cord stimulation (SCS) and peripheral nerve stimulation (PNS). These therapies involve the implantation of patient-controlled neurostimulation devices with implanted electrodes and often with an implanted pulse

generator as well.[4,14] Tens of thousands of neurostimulation devices are surgically implanted annually for the treatment of refractory pain.[9] The first uses of SCS and PNS were in the 1960s, and the therapy has proven useful in managing conditions such as persistent spinal pain, chronic regional pain syndrome, post-herpetic neuralgia, occipital neuralgia, and neuropathic visceral pain.[4]

The most common risks of neurostimulation stimulation therapy for pain include wound infection, lead migration, hardware failure, and reduced clinical benefit.[16] Less commonly, hypersensitivity and allergic inflammatory reactions to the implanted components have been reported.[4] These reactions have also occurred with other devices including cardiac defibrillators, pacemakers, and intrathecal drug pumps.[4,7]

Reported inflammatory reactions include pruritus, contact dermatitis, granuloma formation, and foreign body reactions (type IV hypersensitivity reactions) accompanied by giant cell formation.[4] In addition, these complications can be associated with lead migration, breakage, or unwanted stimulation.[2,4] Many times, allergic reactions as a result of neuromodulation systems go unreported as an effect of neuromodulation therapy either because they are not recognized or because these issues are thought to be extremely rare. While reactions to the material of implanted neurostimulation devices have been reported, very little literature exists regarding evoked cutaneous reactions to the actual electrical stimulation. Here, we report two cases of individuals with implanted neurostimulation systems for the treatment of chronic pain who experienced inflammatory reactions to the stimulation itself, one case due to PNS (occipital nerve stimulation, ONS) and one due to SCS.

CASE 1

This is a 36-year-old male who presented with a history of chronic axial and radicular lumbar pain. He had previously undergone implantation of a neurostimulation system (a combination of percutaneous epidural electrodes and subcutaneous electrodes), but this was removed 2 years earlier due to chronic infection.

The patient underwent SCS system reimplantation through an open approach with a paddle lead and generator both implanted at different sites as compared to his previous system. Soon after implantation, he noted that he would develop diffuse raised erythematous hives within 1–3 h of activating the SCS. The SCS system significantly decreased his pain and improved his daily functioning while allowing him to reduce his pain medications by half. However, the patient continued to have intermittent hives and other allergic reactions in various places on his body only when the SCS system was turned on. The skin manifestations would resolve several hours after deactivating the system. The patient used oral antihistamines with mild benefits. In addition, he saw an allergy specialist with neither significant resolution of symptoms nor being given a specific diagnosis.

Six months after the SCS reimplant, the device was reported to still be relieving his pain symptoms. However, he continued to have facial flushing, hives, and skin photosensitivity when the device was activated. The patient also believed that he was having more generalized loss of body hair since the implant. The hives were primarily noted to be on the underarms, back of upper arms, and groin. The patient underwent patch testing of the SCS components and was deemed not allergic to any of them. He was instructed to keep the device turned off for at least 1–2 weeks to see improvements to the allergic reactions and then turn the device on to see if symptoms return. Turning off the device for 6 weeks caused an increase in his pain but there were no hives or pruritus.

Now over 7-year post-implant, he has continued to describe the SCS improvement as "a lifesaver," further mentioning, "I don't know what I would do without it." He felt that SCS provided him with a significant amount of reduction in pain that allows him to be more active. The stimulation-related skin manifestations persist only when SCS is on. He has undergone IPG replacements due to the end of battery life without change in the phenomenon and with continued normal impedances on all electrode contacts.

CASE 2

This is a 35-year-old female who presented with an acute onset of bilateral occipital neuralgia during the middle of the night. She described the experience as having been "hit in the head with a baseball bat." Her pain was focused on the left side and grew in intensity after activity. Eleven years before the pain onset, she was diagnosed with a Type 1 Chiari malformation, and she subsequently underwent a posterior fossa decompression. Unfortunately, she continued to have intractable cranial neuropathic pain. The patient had undergone trials of numerous medications including topiramate, cyclobenzaprine, tramadol, baclofen, narcotics, as well as intranasal and other oral neuromodulatory medications.

She underwent and passed a successful trial of unilateral ONS and subsequently had implantation of the permanent device 3 months after the initial trial. Coverage was adequate and the patient noted pain relief at her 1-month follow-up visit. However, the patient began to experience pruritus across the back of her head and along the subcutaneous course of the electrode array when the device was on. She denied signs or symptoms of infection. An allergy test kit was ordered, the patient was referred to allergy/immunology. These tests demonstrated no allergy to the device components. She used oral Benadryl with some relief from the itching. There were

no associated cutaneous signs accompanying her itching sensation. Repeated reprogramming did not resolve the issue, despite alterations in contact combinations, stimulation frequency, pulse width, and amplitude. Electrode impedances were consistently normal on all electrode contacts bilaterally.

Eight months after the ONS placement, the patient still noted the itching only with the stimulator on, within 10 s of its activation, but none when the device was turned off. She reported that her average visual analog score pain score was 6/10. However, the stimulation-associated pruritus was disturbing enough to her so as to limit her use of the device.

Eventually, she decided to cease using the device due to the uncomfortable itching over the contact arrays while the device was on. She ultimately had the entire device removed. The PNS device was returned to the manufacturer without evidence of defect.

DISCUSSION

The precise neuronal pathways and signaling leading to the perception of "itch" have been thoroughly studied and analyzed in recent literature, with several suggested theories regarding pathophysiology. Davidson *et al*. identified over one hundred unique neurons within the spinothalamic tract that was considered to be "pruriceptive," with evaluated responses to mechanical stimuli, heat, and intradermal capsaicin.[5] In particular, the relationship between histamine and evoked pruritus has been greatly analyzed, and the current evidence suggests that there is perhaps underlying activation of common neural pathways by histamine, capsaicin, and cowhage.[17] Hypotheses have even been provided suggesting specific gene targets, such as gastrin-releasing peptide, can co-function as itch-specific genes, opening the conversation for future therapeutic applications.[19] Other studies instead argue in favor of a common ion channel, such as Transient receptor potential vanilloid 1 (TRPV1), across somatosensory neurons, with the potential to elicit a pruritic output when stimulated by mechanical force or other agents.[15] Ultimately, the exact therapeutic targets remain muddled. Teams such as Solinski and Rukwied have sought to use electrical stimulation in lieu of chemical stimulants to evoke itch and further characterize pruriceptive pathways. Electrical stimulation can be controlled for duration, frequency, and other parameters, and Solinski and Rukwied also documented how a disturbance to the skin, such as atopic dermatitis in their case, can impact clinical results.[18]

Although allergic reactions to implanted neurostimulation systems are rare, reactions such as delayed hypersensitivity, contact dermatitis, development of erythematous plaques, and generalized pruritus have been reported.[4,20] Several materials including titanium, nickel, epoxy, metal polyurethane, and silicone rubber of pacemakers have shown to be allergens for patients receiving the device.[4,20] Brown *et al*. conducted a literature review and documented 13 published cases regarding allergic reactions to neuromodulation devices, with local dermatitis, erythema, and pruritus among the most common symptomatologies described.[3] In many cases, a complete replacement of the device to a customized one free of allergen(s) affecting the patient has been necessary to prevent unforeseen inflammatory reactions.[20] Thus, these customized devices can necessitate the use of materials such as gold.[20]

Delayed hypersensitivity is a result of responses to specific antigens or foreign body giant cell granuloma reactions to device materials.[16] Giant cells, formed from macrophages, and T cells contribute to the inflammatory pattern known as a granuloma. This could have been possible given the symptoms that the patient in the first case experienced. Granulomas form as a result of macrophages or monocytes taking up an antigen and then presenting the antigen to T cells.[4] This can lead to pro-inflammatory responses to a given area.[4]

Contact dermatitis on the other hand is a form of delayed hypersensitivity in which the reaction to the antigen is present at the surface of the skin.[20] Such reactions have been shown to present in as little as a week to a month after device implantation.[4,20] Although patch testing has been a popular diagnostic technique for assessing contact dermatitis, false positives and false negatives regarding inflammatory responses on the surface of the skin from a particular substance are inevitable.[4] As such, patch testing is not fully reliable in helping to predict inflammatory responses purely as a result of the implantation of devices like SCS.[4,20]

While an allergic reaction to the stimulation system is a possible explanation for the symptoms our patients experienced, the inflammatory side effects only presented when the stimulation was turned on and patch testing to device component materials did not show hypersensitivity in either patient. With stimulation turned off, the systemic and local inflammatory side effects resolved in both cases. In our review of the literature, only one group previously described a similar side effect to stimulation. Abboud *et al*. reported the case of a patient who had a sacral stimulator placed for a diagnosis of neurogenic bladder.[1] Several years after its placement, the patient presented with chronic vulvar pruritus. An extensive workup was performed to determine an etiology before attempted reprogramming of the stimulator. The reprogramming changed the characteristics of the pruritus, indicating that a neurologic etiology for the pruritus was most likely. Subsequent revision of the stimulator demonstrated lead migration. Replacement with repositioning of the stimulator led to resolution of the pruritus. This along with our case study indicates that pruritus may be a rare side effect of stimulation.

While a current leak from the device could theoretically cause a local sensation of stimulation (such as buzzing or tingling),

our patients both exhibited intense itching. Importantly, if a current leak was the etiology in our SCS patient, the reaction would more likely manifest itself as a local reaction rather than the generalized reaction our patient experiences. When neurostimulation devices experience current leak, impedances are often abnormal or the electrical sensation is experienced locally at the generator site (more often the source of the leak). In both of our patients, the electrode impedances have been consistently normal and there has been no sensation of electrical stimulation at the generator site in either person. The current leak more often manifests as a sensation of paresthesia in our experience and less likely pruritus. The current leak should also become less prominent with lower intensity stimulation settings (lower amplitude, frequency, pulse width) but this has not been the case with our PNS patient.

There have been reports of micturition inhibition[13] and relapse of ulcerative colitis[11] with SCS previously reported in the literature. Further allergic and non-infectious cutaneous reactions to neurostimulation devices have also been reported.[4,6,8] However, stimulation-induced, generalized urticaria, and facial flushing, such as that seen by our SCS patient, have not been previously reported. Some report that electricity can induce pruritus,[10] while others have reported that it may actually reduce pruritus.[12] This indicates that neurostimulation can potentially have effects outside of the targeted pain pathways, producing the systemic symptoms observed in our case study.

CONCLUSION

Neuromodulation has been utilized in clinical practice for decades, and modifications to the technology have helped ensure more positive patient outcomes. Despite negative side effects of neurostimulation, the technology has proven effective for pain reduction in certain conditions. While their mechanism remains uncertain, stimulation devices may help mask pain through modification of electrical pulses; the brain receives from a given area. As with most forms of treatment, side effects are possible and should not be neglected when considering device implantation. Therefore, it is of utmost importance that patients regularly follow-up with physicians regarding the functionality of the device and to determine if side effects, such as allergic reactions, have occurred. Identifying certain allergens within the components of the devices may indicate a need for replacement of the device. However, in our case studies, no allergens were identified and side effects resolved with cessation of stimulation.

Declaration of patient consent

Patients' consent not required as patients' identities were not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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