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Botulinum Toxin Chemodenervation for Treating Chronic Sunburn-Induced Painful Peripheral Neuropathy: A Case Report

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Background: We present a rare case of sunburn-induced chronic neuropathic pain that was successfully treated with onabotulinumtoxinA (Ona A).

Case Report: Due to a sunburn, a 21-year-old man developed painful dysesthesias and allodynia lasting more than 2 years on a 15 cm x 12 cm area of his chest. He was treated with 100 units of Ona A which was repeated at 12 weeks and then 200 units at 24 weeks. His pain reduced from 6/10 to 4/10 after the first 2 injections and to 3/10 aftaer the third. He continued to improve to near resolution.

Conclusion: Ona A's effect may be primarily peripheral, due to a decrease in the local release of nociceptive neurotransmitters. However, Ona A can be taken up by the neuron and pass multiple synapses; this may have led to a reduction in pain at the dorsal root ganglion, or more proximally. Lastly, a toxin-induced decrease of afferent mechanical and nociceptive input may have led to a central "wind-down" phenomenon.

Key words: Onabotulinumtoxin, botox, sunburn-induced neuropathic pain, peripheral sensitization, central sensitization, case report

BACKGROUND

Sunburn, the most common type of radiation burn, is caused by an acute overexposure to ultraviolet radiation (UVR) and is typically short lasting. In very rare cases, sunburn can lead to chronic pain. There are 3 different types of UVR:UV-A, UV-B, and UV-C. UV-A has wavelengths between 315 nm–400 nm and affects both the epidermis and dermis in acute exposure. UV-B has shorter wavelengths (280 nm–315 nm) and mainly affects the epidermis. UV-C has even shorter wavelengths (100 nm–280 nm) and is less of a concern due to its rays being blocked by the ozone layer (1). Overexposure to UV-B is the primary cause of sunburn, which is characterized by inflammation, hyperemia, and hyperalgesia often described as a burning, neuropathic-type pain (2).

As the epidermis absorbs UV-B, molecular and cellular changes occur in the overexposed region. The resulting inflammatory response manifests as erythema within hours, typically resolving within 3 to 7 days, with blister healing occurring within 7 to 10 days (3). Histologically, UV-B exposure induces a mixed neutrophilic and lymphocytic infiltration, accompanied by elevated expression of cyclooxygenase-2 at 24 hours and sustained increases in 5-lipoxygenase activity at 72 hours (4,5). These enzymes play critical roles in the synthesis of prostanoids and leukotrienes, which lead to inflammation and propagation of pain (6,7). This inflamed environment amplifies nociceptive signaling via sodium ion and other channels. One epidermal channel, transient receptor potential vanilloid 4 (TRPV4), is a nonselective cation channel that is highly expressed in epithelial skin cells and functions in sensory transduction. It has been

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shown to cause UV-B–evoked skin tissue damage and increase proalgesic/algogenic effects (8,9).

A proposed model suggests that controlled prostaglandin production following UVR-induced injury facilitates tissue repair through cyclooxygenase-2 induction while inhibiting lipoxygenase activity, creating a self-resolving inflammatory response (5). This model highlights the delicate balance between pro-inflammatory and reparative processes in the skin. However, the precise mechanisms underlying the resolution of sunburn, particularly the transition from acute inflammation to tissue repair, remain incompletely understood (10).

When this delicate balance is disrupted, enzyme release can flood the system with nociceptive input, heightening the likelihood of triggering action potentials that transmit pain signals (11,12). Heightened responsiveness of sensory neurons following sunburn can lead to hyperalgesia, a condition characterized by increased sensitivity to pain. The phenomenon is attributed to hyperactive nociceptors , which is known as peripheral sensitization. In patients who experience prolonged postsunburn pain, maladaptive changes within the central nervous system cause dysfunction in pain processing pathways, thereby amplifying pain signals and intensifying pain perception (13,14). This is known as central sensitization. However, the contributions of peripheral sensitization vs central sensitization in UVR-induced pain remain a topic of ongoing debate (2).

The literature on sunburn pain persisting beyond one week, and its progression to chronic pain, is extremely limited. Few cases have documented chronic pain resulting from sunburn, primarily in patients with photodermatoses, where skin eruptions develop or worsen upon exposure to sunlight. However, no case reports describe chronic neuropathic pain in the absence of skin changes (15).

Patients with photodermatoses are typically managed with conservative treatments, including nonsteroidal anti-inflammatory drugs and gabapentinoids, which are standard treatments for neuropathic pain. However, refractory cases may require more intensive interventions. Recent studies on neuropathic pain models suggest that onabotulinumtoxinA (Ona A) is a promising therapeutic option (16,17).

Despite the well-documented transient nature of sunburn-induced pain, to our knowledge an extensive literature review revealed no reported cases of persistent neuropathic pain secondary to sunburn in the absence of persistent skin changes (2,3,19-21). Sunburn-related pain rarely persists for months or years (10,18). However, when hypersensitivity is prolonged, it can lead to chronic pain, significantly affecting quality of life. We present a rare case of chronic postsunburn neuropathic pain, which had persisted for years and was successfully treated with Ona A injections.

CASE PRESENTATION

Our patient gave informed consent for this case report. Since our report has no identifiable patient information, it is exempt from institutional review board approval.

A 21-year-old man with history of well-controlled obsessive-compulsive disorder and idiopathic scoliosis with a surgical history of T10–L3 posterior spinal fusion surgery was referred to our chronic pain clinic. He reported chronic superficial skin discomfort. The pain began after he experienced a severe diffuse sunburn while kayaking more than 2 years earlier. Since the incident, he reported persistent superficial pain in the lower anterior neck and upper chest at midline in an oval-shaped area roughly 13 cm x 8 cm (Fig. 1A). He described the pain as pins and needles, tingling, sharp, and itchy, with a baseline intensity of 5/10, escalating to 7/10 with certain triggers. His pain worsened with movement, pressure, wearing clothes that touched the painful area, and heat. He reported that the pain significantly interfered with activities of daily living, particularly sleep, as it often awakened him at night, especially when bed sheets touched the painful area.

Our exam was notable for a focal area of paresthesia localized to the anterior lower neck and upper chest. The skin appeared normal, without erythema, rash, or lesions. There was hyperesthesia to pinprick, and allodynia to light touch and cold temperatures in the affected area. There was no specific dermatomal distribution or visual skin abnormalities.

He previously consulted dermatology, where a diagnosis of dermatitis was considered. Topical ointment and detergent changes were recommended, but these measures were ineffective. In addition, he tried multiple medications, including acetaminophen, nonsteroidal antiinflammatory drugs, gabapentin, amitriptyline, sertraline, duloxetine, memantine, topical ointments, lidocaine patch, capsaicin cream, and a short course of oxycodone, all at maximally tolerated doses, but none of them provided meaningful pain relief.

One year after initially presenting to the chronic pain clinic, he underwent lidocaine and ketamine infusions

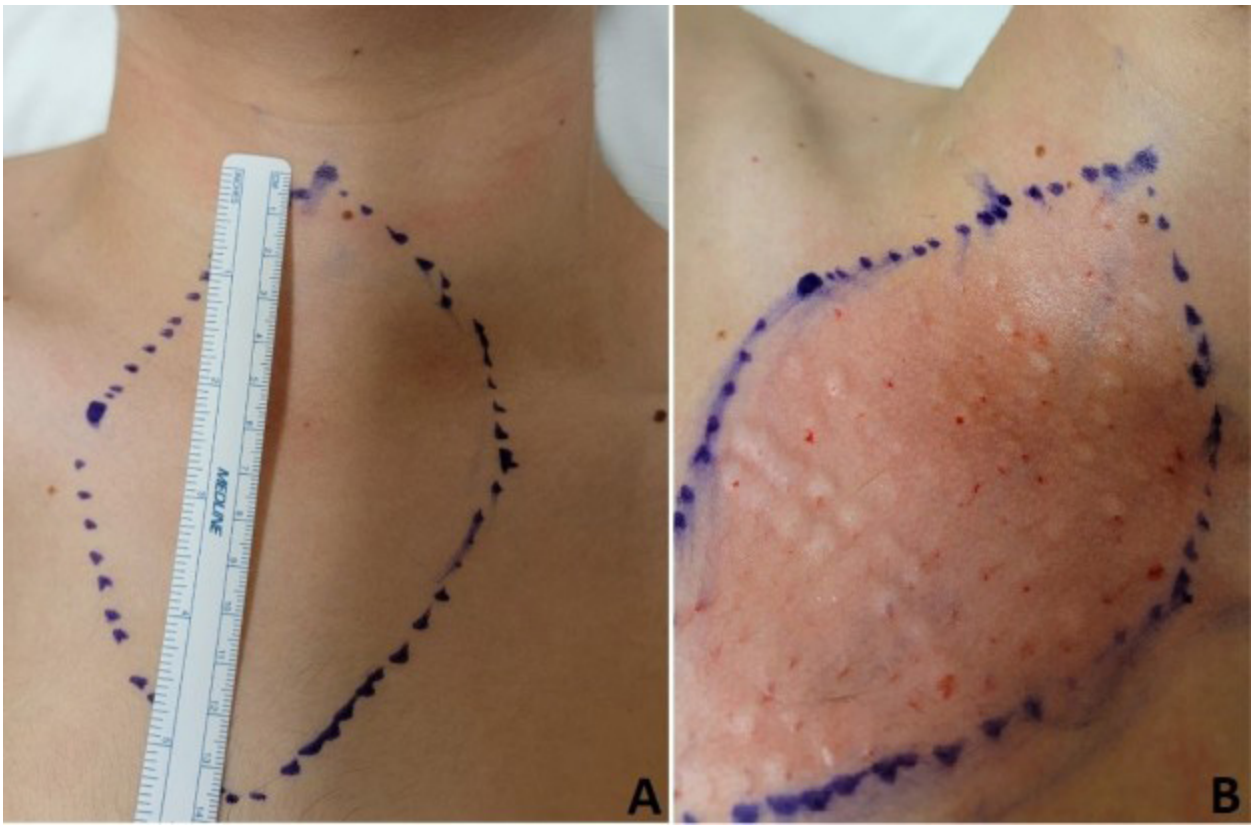

Fig. 1. A. Area of neuropathic pain and allodynia measuring 13 cm x 8 cm. B. Skin surface after subcutaneous injections of onabotulinumtoxinA in a mesh-like pattern, roughly 2 to 3 units per injection site.

after posterior spinal fusion surgery, which offered one day of temporary relief. He also tried medical acupuncture and desensitization therapy without relief.

Due to the neuropathic nature of his pain, we ultimately offered chemodenervation with Ona A. For the Ona A procedure, the patient's anterior lower neck and upper chest were prepped in a sterile fashion using alcohol. The painful area was marked with a blue skin marker. Using a 32G 0.5-inch needle, we injected approximately 2 to 3 units of Ona A subcutaneously at about 45 different spots within a 13 x 8 cm oval area (Fig. 1B). He received a total of 100 units of Ona A at the initial procedure, with a subsequent injection of 100 units of Ona A at 12 weeks, followed by an injection of 200 units of Ona A injection after another 12 weeks.

Our patient reported notable improvement following the 3 rounds of injections. The Ona A injections at 3-month intervals decreased his pain progressively from 6/10 to 4/10 after the first 2 sessions, and to 3/10 after the third session. At a follow-up visit more than a year after the last injection, he reported significant and sustained benefits, stating that his pain had "essentially gone away."

He is now able to wear different shirts without discomfort and experiences improved sleep quality. The combination of pain psychology interventions, cognitive behavioral therapy and mindfulness, along with Ona A injections achieved near complete pain relief. Due to his excellent progress, he was discharged from pain psychology and no longer requires pain clinic visits.

DISCUSSION

We present a rare case of UVR-induced injury resulting in chronic neuropathic pain that responded favorably to Ona A therapy. This case also highlights the potential for sunburn, typically a transient and self-limiting condition, to cause long lasting neuropathic pain.

Sunburn-induced injury is a dose-response injury to UVR exposure (8,19). Unfortunately, given the time lapse

between his initial injury and clinical presentation, our patient was unable to recall his exposure duration, but it was likely at least more than 4 hours.

He also had an obsessive-compulsive disorder diagnosis as well as scoliosis requiring spinal fusion surgery; both diagnoses may have affected his clinical presentation and treatment response. However, his obsessive-compulsive disorder was very well controlled without and did not interfere with his activities of daily living or his employment. Also, his scoliosis surgery was uneventful. He did not require pain management outside of the usual perioperative period of his scoliosis surgery; in general, he did not have any other pain outside of the area from his sunburn. suggesting a lower likelihood of a somatization component to his pain perception and pain experience. Nevertheless, the persistence of his sunburn symptoms for more than 2 years is highly unusual.

While the literature extensively documents neuropathic pain following thermal burns, which can persist for years, there is a notable lack of scientific literature describing neuropathic pain secondary to radiation burns outside the context of radiotherapy for malignancy (20). The mechanisms underlying such a rare case remain poorly understood, highlighting the need for further research into the long-term effects of UVR exposure on nociceptive pathways.

The pathophysiology of sunburn-induced pain remains a topic of debate, particularly the relative contributions of peripheral and central mechanisms (2). It has been postulated that UV-B exposure elevates chemokines levels and activates peripheral nociceptors that lead to exaggerated pain receptor activity in the skin (21). As mentioned, hyperexcitability of peripheral nerve endings can result from pro-inflammatory enzymes overwhelming the system with nociceptive input, increasing the likelihood of action potential generation via sodium channels. Persistent pain signals can then alter the ascending and descending pain pathways, which can intensify pain impulses and amplify pain perception (11-14,22). In our patient's case, his symptoms' chronicity suggests the involvement of both peripheral and central sensitization.

Fortunately, our patient was initially able to achieve about 50% reduction in refractory neuropathic pain with the first and second Ona A injections and a greater pain reduction after the third injection along with a significant decrease in allodynia. This improvement may be attributed to Ona A's peripheral effects, particularly its ability to inhibit the local release of nociceptive neurotransmitters such as glutamate, substance P, and calcitonin gene-related peptide (17,23). Experimental animal studies on neuropathic pain have proposed Ona A inhibits the secretion of pain mediators at multiple locations including peripheral nerve terminals, dorsal root ganglions, and spinal cord neurons (17,24). This mitigation of pain mediators reduces local inflammation around nerve endings, which can prevent peripheral and central sensitization from developing. Ona A can deactivate sodium channels, which also reduces spontaneous action potentials and hyperexcitability (17). Furthermore, Ona A may promote Schwann cell proliferation that could lead to a regenerative effect after nerve injury (25). By modulating these neurotransmitters, Ona A may reduce peripheral sensitization and alleviate pain at site of injury.

Our patient's concurrent use of oral and topical pain medications, which provided partial relief, may complicate the interpretation of whether the observed improvement was due to peripheral or central mechanisms. However, he had been on these medications for multiple months before Ona A was administered; there were no significant dose changes or new medications prescribed during the Ona A treatment period.

Furthermore, the chronicity of the patient's pain suggests that central mechanisms may also play a significant role. UV-induced skin injury may involve centrally localized processes, since intradermal local anesthetic injections do not consistently alleviate UV-induced pain (26). The prolonged duration of our patient's symptoms likely contributed to maladaptive changes within the central nervous system, where dysfunction in pain processing pathways amplifies pain signal and intensifies pain perception (i.e., central sensitization).

Ona A's ability to undergo retrograde axonal transport and affect multiple synapses within the central nervous system may underlie its therapeutic efficacy by targeting the central mechanism of pain, as observed in this case. Studies have demonstrated Ona A can act at the dorsal root ganglion and even more proximally within the central nervous system, modulating pain pathways and reducing central sensitization (27-30).

Nonetheless, our patient's significant clinical improvement following serial Ona A injections underscores its potential as a therapeutic option for neuropathic pain. This case aligns with emerging evidence supporting the use of Ona A for various chronic pain conditions, especially neuropathic pain (29,30). However, further

research is needed to understand the precise mechanisms by which Ona A exerts its effects on UVR-induced neuropathic pain and to establish standardized treatment protocols.

CONCLUSION

This case report highlights a rare instance of chronic sunburn-induced neuropathic pain that was successfully treated with Ona A injections. Our patient's significant pain reduction after serial Ona A injections illustrates the potential efficacy of this treatment for refractory neuropathic pain. Additionally, this case contributes to the understanding of sunburn-induced pain and clinically supports the reduction of peripheral and central sensitization via Ona A.

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