Archives of Epilepsy

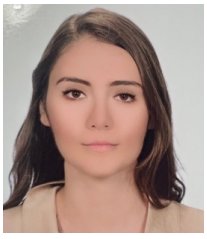
Case Report

Trigeminal Neuralgia Associated with Vagus Nerve Stimulation: A Case Presentation and Literature Review

Gülşah Zorgör[1,2], Günay Gül[1], Fulya Eren[1], Zeynep Baştuğ Gül[1], Alperen Çapan[1], Aysun Soysal[1]

[1]University of Health Sciences Turkey, İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Psychiatric and Neurological Diseases, İstanbul, Turkey

[2]University of Health Sciences Turkey, Başakşehir Çam ve Sakura City Hospital, Clinic of Neurology, İstanbul, Turkey



Gülşah Zorgör MD

Cite this article as: Zorgör G, Gül G, Eren F, Baştuğ Gül Z, Çapan A, Soysal A. Trigeminal Neuralgia Associated with Vagus Nerve Stimulation: A Case Presentation and Literature Review. *Arch Epilepsy.* 2023;29(4):126-131.

Corresponding Author: Gülşah Zorgör MD, E-mail: gulsah.zrgr@gmail.com

Received: 06.09.2023 **Accepted:** 12.09.2023 **Publication Date:** 22.11.2023

DOI: 10.4274/ArchEpilepsy.2023.23101

Abstract

Vagus nerve stimulation (VNS) is an effective therapeutic option that is widely used worldwide in drug-resistant epilepsy cases. Because it is a surgical procedure, some complications may develop with VNS implantation. Although VNS-related pain symptoms have been reported, VNS-related trigeminal neuralgia is an unexpected and rather rare side effect. This report presents a case of trigeminal pain as an adverse effect of VNS. A patient with drug-resistant epilepsy undergoing VNS treatment developed pain synchronously with stimulation in his left upper and lower jaw and teeth. Pain occurred on the day of stimulation's current intensity (SCI) increase. The sudden disappearance of pain with decreasing SCI suggested that trigeminal pain was related to VNS. Because it is a rare side effect, trigeminal pain may not be regarded as a VNS-related side effect and may lead to unnecessary examinations. Being a rapidly reversible side effect, recognizing it and reducing SCI is crucial. VNS stimulation paradigms on nociception are still largely unknown, and it will be an important step to elucidate the important impact of VNS in pain modulation.

Keywords: Epilepsy, nociception, side effects, trigeminal pain, vagus nerve stimulation

INTRODUCTION

Approximately 35% of patients with epilepsy have seizures refractory to antiseizure drugs.[1] For patients who are not candidates for epilepsy surgery, vagus nerve stimulation (VNS) is indicated. VNS is widely used worldwide as an approved add-on therapy in drug-resistant epilepsy cases. Previous reports have shown that 50% of patients responded to VNS with a reduction in epileptic seizures.[2,3] Being a surgical procedure, some complications that involved surgical and technical procedures may develop with VNS implantation. Lead fracture or disconnection and stimulator malfunction are hardware difficulties that lead to VNS complications. Wound infections, wound hematoma, transient bradycardia, lower facial weakness, and vocal cord palsy are surgery-related adverse events of VNS. The most reported stimulation-related side effects were voice alteration/hoarseness, dyspnea, cough, neck pain, headache, pharyngeal paresthesia or pain, and dysphagia. These side effects develop after an increase in stimulation and disappear spontaneously over some time or after a reduction in stimulation.

Here we report a patient treated with VNS who developed trigeminal pain associated with an increase in stimulation current intensity (SCI), which is an extremely rare condition.

CASE PRESENTATION

A 21-year-old mild mentally retarded man with drug-resistant epilepsy has been following in our clinic since 2015. He had seizures since he was 1 year old. He had been diagnosed with hemimegalencephaly with typical MRI features, such as gray matter heterotopia, causing volume increase in the left hemisphere and shifting from left to right. His parents had refused epilepsy surgery at his younger age. He had focal onset seizures with impaired awareness and a motor component that involved oral automatism, ipsilateral head and eye version to the right, and asymmetric tonic limb posturing that could sometimes progress to bilateral tonic-clonic seizures. He was implanted with a VNS in 2016. He did not show a good response with the 1.25 mA SCI reached in the 6th month after implantation. More than 80% reduction in seizure frequency was achieved with 2 mA SCI reached at 1 year after implantation. Four years after VNS implantation, the patient was admitted to the intensive care unit (ICU) with status epilepticus. At that time, he was treated with levetiracetam on 4000 mg/day,

topiramate on 600 mg/day, and clobazam on 30 mg/day. Thiopental infusion was administered until his seizures stopped. Due to not stopping his focal seizures after the initiation of lacosamide at 200 mg/day, phenobarbital was added to his treatment, and the dose was gradually increased to 400 mg/day. His seizures became infrequent, and he recovered consciousness 10 days after the thiopental infusion was stopped. On the last day of his stay in the ICU, the SCI was increased from 2.0 mA to 2.5 mA, and he was transferred from the ICU to the neurology unit. Within the same day, he began to complain of intense shooting pain in his left upper and lower jaw and teeth. The pain recurred many times throughout the day and lasted for seconds. At first, it was suspected that it could be a dental cause of the pain, but a dental examination did not reveal any pathological findings. His mother noticed that the pain appeared with the stimulation on and disappeared with the stimulation off. Because the pain is synchronized with the impulses, it was understood that the pain was related to stimulation. SCI was decreased from 2.5 mA to 2 mA, and his pain was relieved immediately.

DISCUSSION

Dysesthesias such as pain and tingling in the throat and neck region, which are known to be directly related to VNS stimulation, have been reported.[4,5] There has even been a report of VNS-related chest pain thought to be caused by activating the cardiac visceral nociceptive component of the vagus nerve.[6] In addition to the pain referred to regions innervated by the vagus nerve, there have been a small number of cases[7-9] who suffered from trigeminal pain as an adverse effect of VNS. Besides being a rare condition, it is underdiagnosed because of reasons such as the inability of some patients to mention their discomforts, adaptation of mild pain, and trigeminal pain not occurring immediately after SCI increase.[9]

The important role of VNS in the modulation of pain has been demonstrated in many studies over several years. The nucleus of the solitary tract, which is the first relay station for most sensory fibers of the vagal nerve, and the spinal trigeminal nucleus, the second-order nociceptive neuron that receives ipsilateral projections from the vagal nerve, play a prominent role in the pathophysiology of headache. Vagal afferent stimulation modifies pain-modulating brain structures through these pathways. Several non-human studies have demonstrated that low-intensity VNS induces a pronociceptive effect, whereas high-intensity VNS induces an antinociceptive effect.[10] There have been human studies with controversial results showing that patients implanted with a VNS device respond to vagal stimulation with both a decrease[11,12] and an increase[13] in the pain threshold during experimentally induced pain. Moreover, the VNS intensities used in humans (0.25-2.75 mA) were much higher than those used in animals. Similar to the published cases of VNS-related trigeminal pain, the VNS intensity that caused the development of pain in our case (2.5 mA) was within the range of the intensities used in the above-mentioned studies. Although stimulation paradigms favoring pro-or antinociceptive effects of VNS in humans are yet to be clarified[14], individual differences in pain perception change in response to various VNS device parameters should be another consideration to be assessed.[12]

MAIN POINTS

- Trigeminal pain is a rare side effect after vagus nerve stimulation (VNS) implantation.
- VNS-associated trigeminal neuralgia is a reversible side effect associated with a reduction in stimulation current intensity.

The pain in the jaw and tooth region of our patient developed after the increase in SCI, similar to previous cases.[7-9] However, the occurrence of pain differed from these previous cases in that it occurred on the day of SCI augmentation. Time to pain onset from the last augmentation was 2 months in the case reported by Shih[7] and 2 weeks and 2 months in two cases reported by Timarova and Šteňo.[8] Only one of the 3 cases reported by Carius and Schulze-Bonhage[9] developed trigeminal pain symptoms a few days after the last augmentation, and the rest developed after 2 weeks and 1 month. We can associate the early onset of pain in this study with the barbiturates added to his antiseizure medication during his ICU admission. In addition to controlling seizures, barbiturates are involved in pain modulation at the central nervous system (CNS) level by activating the GABA-A receptor. It has been suggested that with the stimulation of GABAergic (inhibitory) neurons associated with the pain-modulating structures that constitute the descending inhibitory system at the upper levels of the CNS, painful inputs from the periphery may increase, and thus phenobarbital-related hyperalgesia may occur.[15]

CONCLUSION

Although it is a rare side effect, both patients with VNS and their relatives should be informed about VNS-related trigeminal pain. Because trigeminal pain under VNS stimulation is a rapidly reversible adverse effect, treating physicians must recognize and reduce the stimulation current.

Ethics

Informed Consent: Consent form was filled out by a participant.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.Z., A.Ç., Concept: G.Z., G.G., F.E., Design: G.Z., G.G., F.E., A.S., Data Collection or Processing: G.Z., F.E., Analysis or Interpretation: G.Z., G.G., F.E., Z.B.G., A.Ç., A.S., Literature Search: G.Z., G.G., Z.B.G., A.Ç., A.S., Writing: G.Z., Z.B.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Behr C, Goltzene MA, Kosmalski G, Hirsch E, Ryvlin P. Epidemiology of epilepsy. *Rev Neurol (Paris)*. 2016;172(1):27-36. [Crossref]
2. Englot DJ, Chang EF, Auguste KI. Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response. *J Neurosurg*. 2011;115(6):1248-1255. [Crossref]
3. Casazza M, Avanzini G, Ferroli P, Villani F, Broggi G. Vagal nerve stimulation: relationship between outcome and electroclinical seizure pattern. *Seizure*. 2006;15(3):198-207. [Crossref]
4. Ergene E, Behr PK, Shih JJ. Quality-of-Life Assessment in Patients Treated with Vagus Nerve Stimulation. *Epilepsy Behav*. 2001;2(3):284-287. [Crossref]

5. Galbarriatu L, Pomposo I, Aurrecoechea J, et al. Vagus nerve stimulation therapy for treatment-resistant epilepsy: a 15-year experience at a single institution. *Clin Neurol Neurosurg.* 2015;137:89-93. **[Crossref]**
6. Nichols JB, McCallum AP, Khattar NK, et al. Pseudoanginal chest pain associated with vagal nerve stimulation: A case report. *BMC Neurol.* 2020;20(1):144. **[Crossref]**
7. Shih JJ, Devier D, Behr A. Late onset laryngeal and facial pain in previously asymptomatic vagus nerve stimulation patients. *Neurology.* 2003;60(7):1214. **[Crossref]**
8. Timarova G, Šteňo A. Late-onset jaw and teeth pain mimicking trigeminal neuralgia associated with chronic vagal nerve stimulation: Case series and review of the literature. *BMC Neurol.* 2017;17(1):113. **[Crossref]**
9. Carius A, Schulze-Bonhage A. Trigeminal pain under vagus nerve stimulation. *Pain.* 2005;118(1-2):271-273. **[Crossref]**
10. Ren K, Randich A, Gebhart GF. Vagal afferent modulation of a nociceptive reflex in rats: involvement of spinal opioid and monoamine receptors. *Brain Res.* 1988;446(2):285-294. **[Crossref]**
11. Ness TJ, Fillingim RB, Randich A, Backensto EM, Faught E. Low intensity vagal nerve stimulation lowers human thermal pain thresholds. *Pain.* 2000;86(1-2):81-85. **[Crossref]**
12. Borckardt JJ, Kozel FA, Anderson B, Walker A, George MS. Vagus nerve stimulation affects pain perception in depressed adults. *Pain Res Manag.* 2005;10(1):9-14. **[Crossref]**
13. Ness TJ, Randich A, Fillingim R, Faught RE, Backensto EM. Left vagus nerve stimulation suppresses experimentally induced pain. *Neurology.* 2001;56(7):985-986. **[Crossref]**
14. Latremoliere A, Woolf CJ. Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity. *J Pain.* 2009;10(9):895-926. **[Crossref]**
15. Yokoro CM, Pesquero SM, Turchetti-Maia RM, Francischi JN, Tatsuo MA. Acute phenobarbital administration induces hyperalgesia: pharmacological evidence for the involvement of supraspinal GABA-A receptors. *Brazilian J Med Biol Res.* 2001;34(3):397-405. **[Crossref]**