

Case Report

Desensitization of stimulation-induced weight loss: A secondary finding in a patient with vagal nerve stimulator for drug-resistant epilepsy☆☆☆



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1. Introduction

Vagus nerve stimulation (VNS)¹ is an adjunctive non-pharmacological approach to the treatment of patients with drug-resistant epilepsy. VNS devices direct short bursts of electrical energy into the brain indirectly via the vagus nerve. The process is based primarily on the principle that high-frequency stimulation of the afferent vagus nerve produces neuronal desynchronization, thereby interrupting the synchronized electrical activity seen in seizures [1]. Other proposed mechanisms for seizure inhibition through VNS include intensity-dependent changes in regional cerebral blood flow, an increase in gamma-aminobutyric acid (GABA) with a decrease in glutamate levels, up-regulation of GABA_A receptors, an increase in noradrenergic secretion via the locus coeruleus, and serotonergic transmission via the raphe nucleus [2]. The use of VNS has progressively increased because of its promising results: a greater than 50% reduction in seizure frequency in more than 50% of patients following implantation in both adults and children who have focal as well as generalized seizures [3,4].

VNS has also been suggested to cause significant weight loss (>5% of body weight) within 6–12 months of implantation and initiation

of stimulation. The pathway for the cascade of metabolic and behavioral changes resulting in weight loss is through vagus nerve modulation from the gut to the brain, inducing hypometabolism of the hypothalamus and the consequent involvement of the satiety centers [5,6]. Although VNS has been shown experimentally to affect eating behaviors, food cravings, and weight, these findings are inconsistent in humans using VNS therapy for either treatment-resistant epilepsy or depression. In a few studies, patients who received VNS therapy experienced significant weight loss, whereas in others, the treatment had no effect on weight [7–9].

Our case report describes a middle-aged male patient who experienced substantial appetite suppression and subsequent weight loss with initiation of stimulation that resolved when stimulation was discontinued. With reintroduction of stimulation, the patient had no change in appetite, but seizure control continued.

2. Case report

A 45-year-old male presented with focal onset seizures with dyscognitive symptoms and focal to bilateral convulsions during his first visit to our institution in August 2013. Diagnosed with epilepsy at the age of 6 years, he had been on several antiseizure agents for more than 20 years, with levetiracetam, rufinamide, valproic acid, and clonazepam as his recent medications. Despite his medical management, he experienced seizures occurring in clusters, with a maximum of up to 25 per day. His semiology included motionless staring followed by body shaking lasting for 30 s without any preceding aura. The postictal period lasted for hours during which he remained groggy and had mood changes. His baseline mental functioning included intellectual disability, non-verbal status with limited sign language skills, stable mood with no behavioral outbursts, obsession for American football and normal sleep-wake cycle. He received 24-hour care from well-educated and engaged parents, with reliable adherence to medication. His past medical history also included hypothyroidism, pulmonary valve anomaly, deafness, Hodgkin lymphoma, bladder carcinoma with urostomy, and right kidney transplant. The patient's most recent EEG (electroencephalogram) (performed in October 2010 while the patient was on antiseizure medications) was within normal limits. We found no significant, pertinent abnormal findings on physical examination during his first visit. His follow-up laboratory values were within normal limits, including the anti-seizure drug levels (levetiracetam 39.9 mcg/ml) and TSH (2.2 mIU/L). His brain magnetic resonance imaging was abnormal,

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¹ VNS, vagus nerve stimulation; GABA, gamma-aminobutyric acid

showing mild to moderate age-advanced cerebral and cerebellar atrophy, most likely to be an insult from hypoxic-ischemic encephalopathy at birth. During the patient's follow-up period after his initial visit, he failed adjustments of levetiracetam (increased to 1500 mg BID). Hence, we decided to proceed with VNS implantation for his drug-resistant epilepsy.

VNS device implantation (Model Demipulse 103, Liva Nova, Houston, TX) was performed on October 21, 2013. The electrodes were placed over the left vagus nerve following standard procedure. Two weeks later, stimulation was initiated with the following parameters: amplitude of 0.25 mA, frequency of 30 Hz, and pulse width of 500 μ s with a stimulation period of 30 s followed by a 5-minute off-time. The patient's baseline height, weight, and basal metabolic index were 4 ft. 6 in, 47.6 kg, and 25.3 kg/m², respectively. The weight measured was 22% greater than the ideal body weight (39 kg). On follow-up, the patient's parents reported improvement in seizure frequency with only 4 episodes occurring during the 3-month period and improved quality of life with no side effects from VNS such as a change in his voice or neck pain. Follow-up repeat EEG was also normal. Hence, VNS was continued with medication adjustments, including a decrease in the dose of levetiracetam to 1000 mg BID and initiation of ezogabine at 100 mg TID, after ophthalmology screening for pigment retinopathy. In addition, he was continued on his previous regimen of rufinamide, valproic acid, and clonazepam. At his follow-up visit in December 2013, the patient had complaints of throat irritation and poor oral intake. His weight was 45.8 kg, and he was advised to take Cepacol lozenges twice daily for the next 3 months. In March 2014, his weight was 41.7 kg. Because of his significant weight loss, we adjusted the stimulation parameters to a reduced setting as shown in Fig. 1. During the next 6 months, the patient's appetite remained suppressed, and VNS was eventually discontinued in August 2014. Anti-seizure drug levels were within acceptable limits (levetiracetam: 73.8 mcg/ml; valproic acid: 43.1 mcg/ml). However, during his visit in December 2014, the patient reported 4 seizures, so VNS was restarted in January 2015. By October 2015, the patient's seizure frequency improved, and stimulation parameters were increased. However, this time the patient's weight and appetite improved, and he gained a total of 3.6 kg. By April 2016 his body weight exceeded his baseline weight at the time of implantation of the VNS device. Furthermore, his seizure burden continued to improve. He remained seizure free from April 2016 till his recent visit in January 2017. No changes to his antiseizure medications were made from November 2013 till January 2017.

3. Discussion

The efficacy of VNS therapy in the treatment of intractable epilepsy is well established, showing improvement both in seizure inhibition and quality of life [1–3]. In addition to seizure control, chronic VNS

has become a valuable, modern option in the therapeutic armamentarium for obesity, despite the reported inconsistencies about the effects of VNS on appetite and weight change in humans. Recently, following the analysis of EMPOWER and ReCharge studies, the US Food and Drug Administration approved its use to treat patients greater than 18 years with a BMI range of 35–45 kg/m² and at least one other obesity-related condition [10,11]. The EMPOWER and ReCharge studies were randomized, prospective, double-blind, multicenter trials assessing the effect of reversible intermittent intra-abdominal vagus nerve blockade (VBLOC® Therapy) on morbid obesity that confirmed its safe use with considerable level of reliability on inducing weight loss related to hours of device usage.

The precise mechanisms for VNS-induced weight loss are largely unknown. The vagus nerve forms the integral link between receptors in the proximal stomach, pylorus, and duodenum (e.g. mechano-, chemo-, osmo-, and thermo-receptors) and the satiety and feeding centers of the brain, located in the ventromedial hypothalamus and lateral hypothalamus, generating appropriate endocrine, metabolic, autonomic, and behavioral response to peripheral gastrointestinal events [12]. Hence, it is hypothesized that the disruption of this brain-gut axis would result in changes in metabolism, attenuation of the effects of cholecystokinin and leptin (satiety hormones), changes in hunger and/or satiety signaling in the brain, or changes in food cravings [13,14].

Studies of patients who received VNS therapy for the treatment of epilepsy have shown significant weight loss within 6–12 months of device implantation and with increasing stimulation parameters for seizure inhibition [9,15,16]. Our patient experienced a similar weight loss of 12% of his body weight (approximately 6 kg) within 6 months of VNS initiation, with standard stimulation parameters for seizure control of amplitude 0.25 mA, frequency 30 Hz, pulse width 500 μ s, on-time 30 s, and off-time 5 min. His lowest weight while on VNS therapy was 41.6 kg, which was 7% above the ideal body weight for height (39 kg). Furthermore, studies have outlined a relationship between baseline BMI and VNS-related weight loss in which a tendency toward greater weight loss was observed in patients with higher BMIs [17]. We observed similar findings of weight loss proportional to initial BMI in our patient who had a relatively higher BMI based on height.

However, inconsistencies exist among studies, questioning the effects of VNS on weight loss and associations of baseline BMI with weight loss. Few studies showed that VNS did not lead to significant changes in body weight in patients with epilepsy [7,18]. A study of the effects of chronic VNS on caloric intake showed that lean individuals consumed fewer calories than those who were overweight or obese, affecting the BMI–VNS relationship [14]. The possible explanations for this scenario included development of a decreased craving for palatable foods, resistance to the satiating effects of leptin, and the alteration of vagal afferent pathways in patients with a history of over-eating higher fat and caloric foods who are less likely to have food intake altered after VNS. Also, the

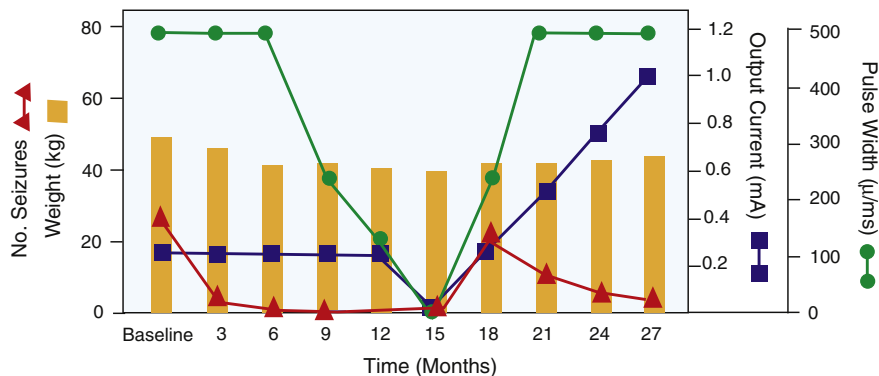


Fig. 1. Weight trend with relation to number of seizures and vagus nerve stimulation parameters. The weight trend in our patient during 27 months of follow-up with relation to vagus nerve stimulation parameters, including pulse width (in microseconds) and output current (in milliamperes).

location of stimulation along the vagal nerve course can differentially affect eating habits and weight loss. Studies propose that electrical blockade of vagal trunks at the level of the gastric cardia has a more pronounced impact on eating behavior and weight loss and is comparatively less diluted than stimulation of the vagus nerve in the cervical area [19–21].

In our patient, we hypothesize two distinct potential mechanisms to be responsible for the weight loss. The first being a central mediated process effecting appetite as reported in the literature. The second being a peripheral effect of VNS on the throat leading to irritation and reduced oral intake in a patient with limited language skills (indirect mechanism). After the VNS-induced weight loss, very interestingly our patient developed desensitization to this effect on body weight. The later stimulation parameters were, in fact, higher than the initial parameters with no effect on weight. Our patient steadily regained the weight he had lost throughout the stimulation break period and through the period of reintroduction of stimulation. The cessation of stimulation for a period of 3 months may have reset the vagal tone. We postulate that vagal remodeling after initial stimulation and discontinuation may explain the diminishing effect of vagal stimulation on weight loss over time. This phenomenon may have affected both the centrally mediated appetite suppression and the peripherally mediated throat irritation. Our findings and findings from prior reports where the weight loss was not sustained 1 year after implantation may be explained by the theory that surgical interruption of the vagus nerve is usually associated with some degree of remodeling that can result in reformation of afferent but not efferent pathways, contributing to the observed effect [22]. However, the exact physiological basis remains elusive. Interestingly, the effect on seizure control remained positive following the reintroduction of stimulation.

We attempted to provide potential explanations for the observed weight loss. We carefully analyzed potential confounding factors for the observed weight trends. Our patient experienced a significant adverse effect of throat irritation within 3 months of VNS implantation. The initial period of throat irritation coincided with the period of weight loss. The mechanism for the commonly reported side effects such as coughing, voice alteration, and throat irritation is related to adduction of the left vocal fold induced by the stimulation of the left vagus nerve. These side effects are typically transient, occurring during the initial calibrating period and tend to decrease with adjustments of device parameters or patient acclimation [23,24]. Besides the throat irritation, no gastrointestinal tract dysfunction like nausea or vomiting was observed. The patient's diligent caregivers reported no change in diet, eating patterns, and life style during the time period of VNS implication. No dietary supplements were involved.

Considerations for any significant medication changes related to weight impact were studied. Initiation of ezogabine and lowering of levetiracetam dose were done at the initiation of VNS. However, post stimulation period no changes were made in dosing and no concerns about compliance were noted. Prior history of depression, hypothyroidism, bladder cancer, kidney transplant and Hodgkin's lymphoma were also considered. Though it cannot be definitively ruled out as a contributing factor, the patient's clinical profile remained stable with regard to this aspect, with chronic immunosuppression on low dose steroids and unchanged levothyroxine supplementation, during the time period of VNS implementation.

4. Conclusions

VNS for drug-resistant epilepsy has been associated with weight loss and decreased appetite. The stimulation parameters may moderate the effect on weight loss. To our knowledge, our case is a unique report of the development of desensitization to the initial effect on appetite and throat irritation ultimately leading to weight loss from VNS, after a period of cessation of stimulation and subsequent reintroduction, with no effect on seizure control. We hypothesize that short-term cessation of

VNS may allow remodeling of the vagus nerve and development of desensitization to electrical stimulation possibly limited to selective effects of VNS on the brain. This plasticity of the vagus nerve may be important in the long-term successful management of epilepsy through VNS and may impact the potential use of VNS in other neurologic conditions such as cluster headaches, stroke rehabilitation, and tinnitus [25].

Because of the significant variability in VNS-reported changes in appetite, food cravings, and weight loss, systematic research is needed to elucidate this relationship. Despite inconsistencies in reporting and the unknown reasons for these inconsistencies, the use of neuromodulation via the vagus nerve for obesity management is currently being reinvestigated and appears to be promising in specific individuals [26].

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