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Significant vomiting and weight loss in a pediatric epilepsy patient secondary to vagus nerve stimulation: A case report and review of the literature

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ABSTRACT

Vagus nerve stimulation is a neuromodulatory treatment option for individuals with drug resistant epilepsy who are not resective surgical candidates. As the vagus nerve has widespread neural connections, stimulation can lead to an array of adverse effects. While vomiting and weight loss are known side effects of vagus nerve stimulation, these are typically transient, mild, and do not limit the ability to continue treatment. We describe a 17-year-old female with drug resistant focal epilepsy secondary to tuberous sclerosis complex, who began to experience daily emesis and significant weight loss approximately 2.5 years after VNS device insertion. Her body mass index progressively fell from between the 75th–85th percentiles to less than the first percentile. She underwent extensive workup by neurology, gastroenterology, and adolescent medicine services with no obvious cause identified. Prior to the insertion of an enteral tube for feeding support and urgent weight restoration, her vagus nerve stimulator was switched off, resulting in immediate cessation of her vomiting and a dramatically rapid recovery of weight over the ensuing few months. This case emphasizes the need to consider adverse effects of vagus nerve stimulation in the differential diagnosis of patients with otherwise unexplained new medical sequelae, and provides evidence potentially linking vagal stimulation to significant malnutrition-related complications. Outside of GI-related effects, few studies have shown late-onset adverse effects from VNS, including laryngeal and facial pain as well as bradyarrhythmia. Further research is needed to elucidate the exact mechanisms of vagus nerve stimulation to better anticipate and mitigate adverse effects, and to understand the pathophysiology of late-onset adverse effects in previously tolerant VNS patients.

1. Introduction

The International League Against Epilepsy (ILAE) defines drug-resistant epilepsy (DRE) as the failure to achieve seizure freedom despite trials of two well-tolerated and appropriately chosen antiseizure medication (ASM) regimens [1] This criterion applies to 19.6 % of epilepsy patients according to a recent *meta*-analysis [2]. Potential treatment options for individuals with DRE include continuation of medical management, epilepsy surgery, or neuromodulation techniques such as vagus nerve stimulation (VNS) and deep brain stimulation [3]. Neuromodulatory techniques are particularly useful in patients who may not be candidates for curative resections, including those with multiple epileptogenic foci or foci involving the eloquent cortex. The exact pathophysiological mechanism of VNS's antiepileptic properties continues to be investigated; however, studies have proposed that the activation of neural projections from the nucleus tractus solitarius (NTS) to the noradrenergic locus coeruleus, serotonergic raphe nuclei, and more broadly throughout the cortex, ultimately leads to desynchronization of cortical activity and a decrease in the number of interictal events [4,5]. While few VNS patients achieve complete seizure freedom,

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approximately 50 % of individuals obtain greater than 50 % reduction in seizure burden, with response rates increasing over time of therapy [6].

Considering the widespread efferent projections activated via the vagus nerve, it is not surprising that an array of potential side effects has been observed with VNS therapy. The most common adverse effects include: voice hoarseness, cough, paresthesias, pain, dyspnea, and headache, as well as post-surgical infection [5]. Here, we present the case of an adolescent girl on long-term VNS therapy for DRE presenting with significant vomiting and weight loss, ultimately leading to the patient experiencing growth failure and dramatically falling off her growth curve. Both symptoms showed rapid resolution once her VNS device was turned off. Vagal neurocircuitry has a well-described role in gastric motility, and its associated symptoms of nausea and vomiting. While these symptoms are typically mild, both have been described as significant adverse events of VNS in clinical trials [7,8]. There are previous studies describing weight loss, independent of vomiting, as an adverse effect of VNS therapy in both children and adults [9–11]. However, to our knowledge, this is the first case report of a pediatric patient experiencing such profound weight postulated to be secondary to VNS-induced vomiting that she ultimately required deactivation of her VNS device to support long-term health.

2. Case presentation

Our patient is a 17 year-old female with a past medical history of genetically confirmed tuberous sclerosis complex (TSC) with pathogenic TSC2 variant, DRE, moderate intellectual disability, and constipation. She first experienced focal seizures with and without evolution to bilateral tonic-clonic seizures at 1-month-old (main semiology consisting of left upper and lower extremity posturing and rhythmic movements with reduced awareness), and was trialled on multiple scheduled ASMs prior to surgery and VNS insertion including phenobarbital, phenytoin, valproate, topiramate, vigabatrin, carbamazepine, gabapentin, and clobazam, all at appropriate weight-based doses. She ultimately underwent cortical excision of her right superior temporal gyrus and right inferior Rolandic region at 7 years old, but response to surgery was suboptimal and she continued to have multiple seizures per day. Magnetic resonance imaging at 11 years old revealed anticipated post-surgical changes, as well as possible residual cortical dysplasia involving the inferior right precentral gyrus (Fig. 1). She was deemed not to be a candidate for further epilepsy surgery and underwent VNS placement at the age of 12 years (Model 102, LivaNova). She was considered a responder to VNS therapy; at follow-up 16 months after

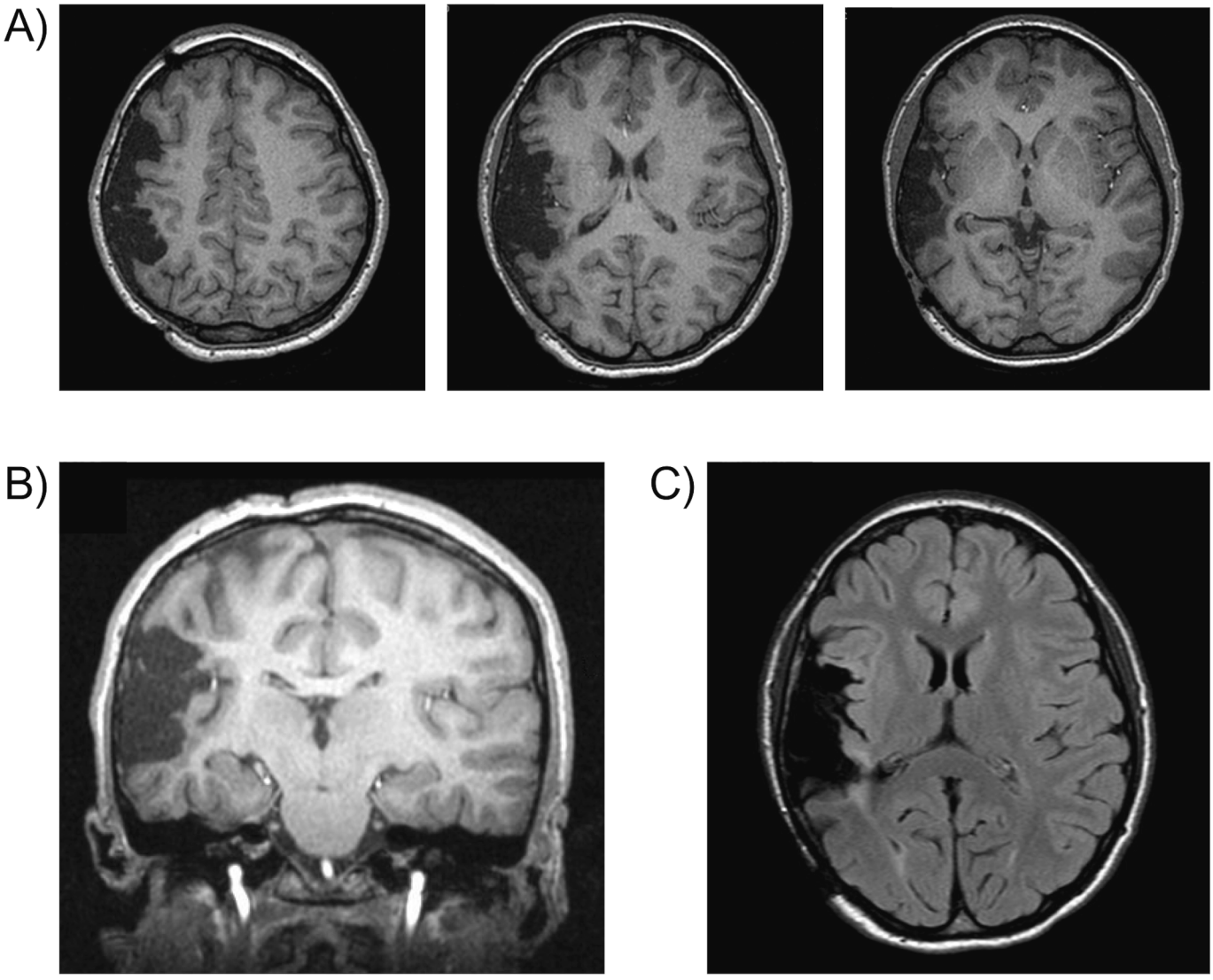

Fig. 1. Magnetic resonance imaging completed at 11 years old revealing anticipated post-surgical changes after cortical excision of the right superior temporal gyrus and right inferior Rolandic region, as well as possible residual cortical dysplasia involving the inferior right precentral gyrus. Area of excised cortex can be seen on (A) serial axial T1 images progressing superiorly to inferiorly, (B) coronal T2 image, and (C) axial FLAIR image.

device placement, her seizure burden had decreased by more than 50 %, from 2 to 3 seizures per day to 1–2 seizures per week, and there were no complaints of adverse effects. At this time, her VNS parameters were as follows: output current 1.5 mA (pulse width 250 microseconds), signal frequency 25 Hz, magnet current 1.75 mA (pulse width 500 microseconds), on-time 30 s, off-time 5 min, and magnet on-time 60 s. She also continued to take oxcarbazepine 600 mg orally twice daily, levetiracetam 500 mg orally twice daily, and phenytoin 400 mg orally as needed for seizure clusters (used on average once per year), with no significant ongoing adjustments to her ASM regimen. While phenytoin is not typically used as an as needed medication, the patient had previously taken this drug on a scheduled basis and it was found to be effective at aborting her rarely-occurring prolonged clusters of seizures, so it was not switched to a more commonly used as needed medication.

Around 2.5 years after VNS placement, at 15 years of age, our patient developed an acute onset of 4–6 episodes of daily emesis, occurring postprandially and exclusively in the mornings. She was trialled on ranitidine, dimenhydrinate, and lansoprazole by her primary care provider with no improvement of her symptoms; she also experienced a concomitant slight increase in seizure frequency, which was postulated to be secondary to emesis of her morning ASM doses. Review of systems also noted sporadic dysphagia (patient had a past history of normal videofluoroscopic swallowing study), coughing, and weight loss. She was urgently referred to gastroenterology and, at time of assessment, had lost 8.7 kg over the last year with body mass index decreasing from greater than 75th percentile to the 1st percentile (Fig. 2). Her emesis was now occurring typically once daily in the mornings, a decrease which her parent attributed to reduced intake. Routine bloodwork was normal (including complete blood count, liver function tests, C-reactive protein, thyroid studies, iron studies, TTG and immunoglobulins), abdominal X-ray revealed some fecal loading, and the patient was trialled on a sodium picosulfate cleanout for constipation as well as domperidone 10 mg orally twice daily as a prokinetic agent. Our patient had no improvement and was continuing to lose weight at 6-month follow-up. Around this time, she had an upper gastrointestinal (GI) series with small bowel follow-through which did not show any intraluminal filling defects secondary to her TSC. She reached a weight of 40.5 kg three months later (maximum previous weight 51.6 kg) and was trialled on cyproheptadine 4 mg orally twice daily, an appetite stimulant in the antihistamine class of medications. She was also referred to adolescent medicine urgently for assessment of a potential underlying eating disorder, given that she had lost over 20 % of her total body weight and was at risk of associated adverse health effects; after thorough review, she was not felt to have a primary eating disorder. Her VNS output current and magnet current were reduced to 1.25 mA and 1.5 mA, respectively, due to her coughing and dysphagia, but there was no improvement in her emesis with this adjustment. The patient's parents and healthcare providers were initially reluctant to turn the VNS off completely or lower the settings by a more significant proportion because of her good seizure control with device use, as well as atypical presentation thought less likely related to her VNS device (i.e. emesis in mornings only, delayed presentation of vomiting following insertion of VNS, and no previous reports of severe emesis in the literature). A chest X-ray was also performed which ruled out recurrent aspirations, and assessment by occupational therapy revealed no concerns with swallowing.

At this point, after more than two years had passed since her vomiting onset with no clinical improvement, domperidone and cyproheptadine were discontinued as they were ineffective. Discussions with family about enteral tube feeding support commenced given her lack of improvement and persistent weight loss. Esophagogastroduodenoscopy with esophageal manometry was arranged to obtain mucosal biopsies, as well as to assess for any VNS contribution to her dysphagia and

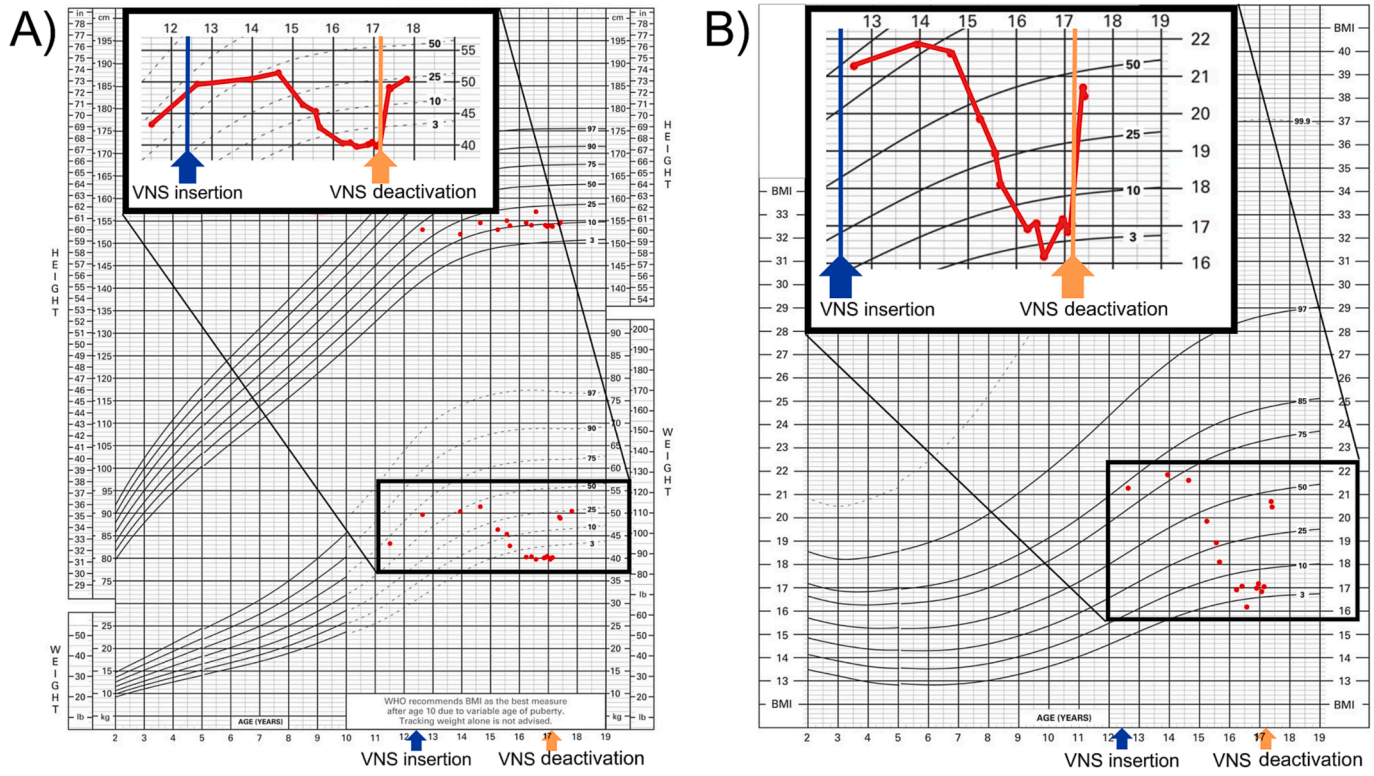

Fig. 2. WHO growth charts showing significant weight loss. WHO height-for-age and weight-for-age chart for girls 2- to 19-years old (A) demonstrates decrease in weight from 51.6 kg (50–75 %weight-for-age) at 14-years-old to a nadir of 39.9 kg (<1% weight-for-age) at 17-years-old, priorto vagus nerve stimulator deactivation. WHO body mass index-for-age chart for girls 2- to 19-years-old (B) shows a similar pattern of significant decrease from 75 to 85 % BMI-for-age to < 1 % BMI-for-age. Both weight and body mass index showed significant recovery following VNS deactivation. Time of VNS insertion indicated by blue arrow and time of VNS deactivation indicated by orange arrow.

coughing, potential neuromuscular spasms causing inappropriate peristalsis, or abnormal lower esophageal sphincter tone predisposing to reflux. This study revealed a borderline hypotensive lower esophageal sphincter and small hiatal hernia, with normal peristalsis. After a detailed case discussion and consideration of more invasive treatment options, the decision was made to trial a deactivation of the VNS device as all other potential contributing factors were felt to have been adequately explored. Following VNS deactivation, her emesis immediately and entirely ceased, and she experienced a 9 kg weight gain over the course of the next 3 months. While she did experience a transient increase in seizure frequency, this settled to her baseline seizure burden over the ensuing months with minor adjustments to her ASM regimen. She also experienced occasional non-functionally impairing coughing episodes, which had a strong contextual association and that her parents attributed to stress. She was able to successfully transition to adult care and continues with routine follow-up of her DRE; her stimulator remains in situ and deactivated.

3. Discussion

The precise mechanism for VNS's antiepileptic properties continues to be an active area of research, but it is thought that the vagus nerve's widespread projections ultimately leads to cortical desynchronization and disruption of interictal events [4,5]. The widespread nature of these projections may also predispose to a vast array of adverse effects. For instance, the relationship between vagal neurocircuitry and vomiting has been extensively studied [7]. Gastrointestinally, stimulation of vagus nerve afferent fibers leads to activation of the NTS located within the brainstem's medulla. Subsequently, neurons within the NTS activate the nearby dorsal motor nucleus of the vagus nerve, from which preganglionic parasympathetic motor efferents originate. These efferent fibers activate postganglionic parasympathetic fibers which, depending on their inherent neurotransmitter, either facilitate contraction or relaxation of key organs within the upper GI tract. In the case of vomiting, this response includes relaxation of the lower esophageal sphincter, contraction of the stomach, and contraction of the esophagus; in addition to the emetic reflex, vagal activation causes gastric dysmotility which can lead to impaired gastric emptying and resultant nausea. In reality, the role of vagal neurocircuitry in vomiting is significantly more complex, as the NTS also receives relevant connections from numerous other regions including cranial nerves, the spinal cord, the area postrema, the hypothalamus, cerebellovestibular pathways, and the cerebral cortex.

Vomiting was first noted as a statistically significant adverse effect in the clinical trial which facilitated VNS device approval by the Food and Drug Administration; however, no individuals required discontinuation of therapy because of this symptom [14]. To our knowledge, there are no published cases of such severe vomiting from VNS as to require deactivation of the device, and our patient's case emphasizes the significant morbidity and unique diagnostic consideration in this population. In prior studies that have examined adverse effects related to VNS, these are typically transient and improve or resolve with continued therapy; in our patient's case, she was initially a VNS responder who tolerated therapy with minimal side effects for over 2 years before developing intractable emesis [15]. Outside of the scope of GI-related side effects, there are limited previous reports of late-onset adverse effects experienced by VNS patients who previously tolerated stimulation well; these include bradyarrhythmia starting 2 years and 4 months after device implantation in one patient, as well as laryngeal and facial pain commencing 2 and 8 months post-current adjustment in two other patients [16,17]. To date, there is no evidence-based hypothesis explaining a potential pathophysiological mechanism of late-onset adverse effects of VNS. Another unique feature of our patient's presentation was her regularly occurring emesis in the mornings only. While further research needs to be completed, one possible explanation for this presentation is circadian variation in sensitivity of vagal afferents. Gastrin hormone, which regulates gastric motility and secretion of hydrochloric acid in the stomach, is subject to circadian variability, and may have exacerbated baseline changes in gastric dysmotility and lower esophageal sphincter tone caused by VNS activation [18]. This phenomenon of cirdacian variation in the GI tract has also been studied in animal models; for instance, Kentish et al. revealed that gastric mechanoreceptors in a mice model displayed a circadian rhythm independent from the light/dark cycle or food intake [19].

As a critical integrator of the gastrointestinal system and central satiety centres, activation of the vagus nerve can lead to weight loss through a number of mechanisms independent of vomiting, including modulation of metabolism and hunger signalling [12,13]. Multiple previous studies have shown that individuals undergoing VNS for DRE have experienced unintentional weight loss. This was initially investigated after the incidental finding of an adult patient who lost over 80 lb after initiation of therapy. Most DRE patients experience mild weight loss that does not limit their ability to continue treatment; however, it is worth noting that even less significant weight loss, or failure to make expected gains, can lead to serious adverse effects in the pediatric population [9–11]. More recently, intermittent vagal nerve blockade has been proven to be effective for primary treatment of obesity [20]. While our patient's concomitant reduced food intake was initially attributed as secondary to her vomiting, it is possible that increased satiety was an independent adverse effect from VNS exacerbating her clinical presentation. While cyproheptadine was trialled in this patient to improve appetite, its anti-histaminergic and anti-serotonergic mechanism of action may not have been sufficient to overcome the central effects of VNS.

When investigating potential causes of nausea and vomiting in our patient, it was also important to consider the potential GI sequelae resulting from TSC itself. Pathogenic variants in TSC1 and TSC2 lead to the deactivation of tumour suppressor genes and a resultant predisposition towards the development of multiorgan tumours [21]. Individuals with TSC exhibit a wide range of phenotypes, and potential GI sequelae of TSC include rare findings such as gastrointestinal polyposis, pancreatic neuroendocrine tumours, and hepatic angiomyolipomas [21,22]. In our patient, an upper gastrointestinal (GI) series with small bowel follow-through was completed to help rule out vomiting secondary to an intraluminal filling defect from polyposis, and additional imaging also did not reveal any GI pathologies related to TSC.

The relationship between our patient's weight loss and VNS treatment may only be described as correlational since, aside from a borderline hypotensive lower esophageal sphincter, there is limited direct objective evidence of her stimulator's effect on her upper GI function, and the start of her symptoms was temporally separated from VNS insertion. Supporting evidence which favours this etiology including her extensive negative workup (including bloodwork, imaging, empiric medication trials, and diagnostic endoscopy) by multiple services including gastroenterology and adolescent medicine, her rapid and complete symptom resolution upon VNS device deactivation with no other management changes at that time, and the known physiologic association between VNS and vomiting. A limitation of this case study is that the patient's VNS device was never re-trialled given her adequate seizure control and resolution of adverse effects following device inactivation; notably, however, there were no concomitant changes to her management at time of device deactivation.

4. Conclusions

VNS is a prevalent adjunctive therapy for individuals with DRE and, due to the broad role of the vagus nerve, there are many potential side effects. We describe a case of an adolescent female with acute onset of daily emesis arising two years after VNS insertion, ultimately leading to loss of 22.7 % of her baseline body weight down to $<$ 1st percentile weight-for-age. After thorough GI workup, evaluation for possible eating disorder, and multiple empirically trialed therapies, her vomiting dramatically ceased with complete reversal of her weight loss following

VNS deactivation, with no other concomitant management changes. This case emphasizes the need to consider adverse effects of VNS as a differential diagnosis in patients presenting with otherwise unexplained new medical sequelae, even after the typical timeframe of transient VNS-related adverse effects has passed. More specifically, our patient's presentation provides evidence that VNS may cause severe weight loss with concern for increased morbidity from malnutrition and low body mass index, a previously unreported complication. Further research is needed to elucidate the exact mechanisms of VNS to better anticipate potential adverse effects, understand the pathophysiological mechanism of late-onset adverse effects, and identify effective strategies to help mitigate these.

Declarations

Consent for publication.

Written informed consent for publication was obtained and is available upon request.

Availability of data and materials.

The authors declare that all the data are contained within the manuscript.

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CRediT authorship contribution statement

Hannah E. Snyder: Data curation, Writing – original draft, Writing – review & editing. **Nikhil Pai:** Conceptualization, Data curation, Writing – review & editing. **Brandon Meaney:** Data curation, Writing – review & editing. **Cynthia Sloan Birbeck:** Data curation, Writing – review & editing. **Robyn Whitney:** Writing – review & editing. **Natasha Johnson:** Data curation, Writing – review & editing. **Laura Rosato:** Data curation, Writing – review & editing. **Kevin Jones:** Data curation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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