Late-onset asystolic episodes in a patient with a vagal nerve stimulator

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Introduction

Insertion of a vagal nerve stimulator is an option to control partial complex seizures in patients with refractory epilepsy. The therapy is reported to be safe and is generally well tolerated by patients. We present a patient with periodic asystolic episodes causing syncopal events, thought to be caused by a previously placed vagal nerve stimulator. The patient was successfully treated with a pacemaker implantation.

Case report

A 46-year-old woman with a past medical history significant for intractable complex partial seizures underwent implantation of a LINQ rhythm recorder (Medtronic, Minneapolis, MN) for suspicion of cardiac syncope. The patient had established care with our neurology clinic 4 years prior and had an extensive history of epilepsy, having been diagnosed at the age of 21. She experienced breakthrough seizures at least once a month despite being on optimal antiepileptic medical therapy. Medications consisted of maximally tolerated doses of levetiracetam 1000 mg in the morning and 1500 mg in the afternoon, topiramate 200 mg twice daily, and carbamazepine 400 mg 3 times a day. A vagus nerve stimulator (Cyberonics, Houston, TX) was placed in 2004 as she was not considered to be a surgical candidate. A generator change was performed in 2012.

The patient described her seizures as a tonic-clonic activity but also experienced episodes of feeling weak with blanking and staring. In the past 2 years, the patient noted a change in her seizure pattern. She began to experience significant falls with injuries requiring sutures and staples, resulting in multiple admissions to the hospital for further monitoring. No changes to her medications were made. She reported increased frequency of spells, which occurred randomly, were not related to changes in position, and were without a prodromal or postictal period. There was no associated urinary or bowel incontinence. She experienced loss of consciousness for a brief period of time with an average of 2 falls a month. This was different from her prior episodes of staring and unresponsiveness, with gradual automatic behaviors.

On physical examination, the patient had a normal pulse rate and was normotensive. Cardiopulmonary auscultation was unremarkable. There were no symptoms of heart failure. Magnetic resonance imaging of the brain revealed left mesial temporal sclerosis as well as increased signal in the posterior right frontal region near the central sulcus. Three separate prolonged electroencephalogram evaluations consistently revealed a spike in the sharp waves in the F7–T3 distribution, suggestive of hemispheric epileptiform activity. A Ziopatch (iRhythm, San Francisco, CA) monitor was performed and did not reveal any abnormal rhythm. An electrocardiogram demonstrated normal sinus rhythm. An echocardiogram was performed, which was unrevealing. A myocardial perfusion stress test was also performed to rule out ischemia and was normal. No specific cause could be found to explain the appearance of these episodes.

Review of the vagal nerve stimulator settings showed that the output current strength on the stimulator was gradually increased over the past 2 years in order to control the patient’s frequent seizures. She initially showed improvement with these changes; however, she then started falling and experiencing this new seizure pattern. The description of her spells was felt to be most consistent with cardiac syncope; however, differential diagnosis included drop attacks and complex partial seizures. The vagal nerve stimulator settings were changed in order to decrease the vagal stimulation with reduction of current strength and increasing current time off.

Owing to the infrequent nature of events, a LINQ recorder was implanted with periodic interrogation performed in the cardiology clinic. During interrogation it was noted that the patient had several sinus pauses of 10 to 12 seconds in duration. Review of medical records showed that these episodes correlated with date and time of recent falls and injuries as

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reported in her primary care provider’s note (Figures 1 and 2). The leading diagnosis was that the excessive vagal nerve stimulation caused depression of the sinus node and led to profound bradycardia and asystole. The diagnosis of ictal bradycardia syndrome was also considered, as it can cause epileptic discharges that slow the cardiac function and lead to asystole in patients with temporal lobe epilepsy. The close relationship of worsening episodes and change of seizure pattern with increasing vagal nerve stimulation was more suggestive of syncope.

A collaborative risk-and-benefit discussion took place with the patient and Neurology and Cardiology teams. Deactivation and removal of the vagal nerve stimulator was entertained; however, the patient’s epilepsy was very hard to control with just the use of antiepileptic medications. A permanent pacemaker was recommended and implanted via a right subclavian vein approach (Figure 3). There was consideration of a leadless pacemaker placement; however, the device was relatively new at the time and not available in our institution. The implantable loop recorder was removed prior to the procedure. The device representatives for the pacemaker and the vagal nerve stimulator were both present onsite during implantation. No interference between the vagal nerve stimulator and the pacemaker was noted. The patient has been seen in follow-up several times and has been doing well, without any further syncopal episodes. She has been followed every 3 months for the past year.

Discussion
The vagus nerve is a parasympathetic nerve with efferent and afferent function. Through its motor efferent fibers, it regulates the autonomic tone of various organs such as the heart. Through its afferent sensory fibers, it transmits information to the brain from the head, neck, thorax, and abdomen.1 Autonomic neural input to the heart exhibits a degree of “sidedness,” with studies suggesting that this is perhaps owing to rotation of the body during embryonic development.1 The right sympathetic and vagal nerves affect the sinus node more than the atrioventricular (AV) node. The left sympathetic and vagal nerves have more influence on the AV node, with the left vagal nerve having more influence on the atrioventricular node and right vagal nerve having more influence on the sinus node, which is why the stimulator is placed on the left side of the chest. This is thought to be secondary to the embryonic rotation of the body during development. However, it is important to know that there is some degree of overlap between the left and right vagal nerve innervation.

Figure 1  Severe symptomatic bradycardia with heart rate of 46 beats per minute, which coincided with a syncopal episode as stated in patient’s primary care note. A: LINQ report of severe bradycardia. B: LINQ tracing of severe bradycardia.
However, significant overlap exists in the distribution of the neural input to the sinoatrial node and AV node. Vagal nerve stimulation was approved in 1997 to prevent or reduce seizures in patients with partial epilepsy who do not respond to medical therapy. To date, more than 85,000 people worldwide have used this therapy. Vagal nerve stimulation is delivered through a bipolar pulse generator that is implanted in the left chest wall. It delivers electrical signals to the left vagus nerve in the neck through a bipolar lead wrapped near the carotid artery. It prevents seizures by providing high-frequency electrical stimulation of the left vagal nerve afferent fibers that carry information to the brain and reduce seizure activity.

The device can be adjusted using a programming wand. It is usually set to give stimulation at regular intervals throughout the day, usually with 30 seconds of stimulation alternating with 5 minutes of no stimulation. Settings also include a stimulation amplitude of 1.0 to 3.0 mA, a stimulation frequency between 20 and 30 Hz, and a pulse width between 130 and 500 microseconds. When a magnet is applied over the device, it causes increased output current and stimulation of the vagal nerve. For people with warnings before their seizures, activating the stimulator with the magnet when auras occur may help abort the seizure.

Owing to the known effects of the vagus nerve on cardiac and gastrointestinal function, cardiac evaluation of the device was performed during clinical trials of the device. Holter monitors were worn by patients and showed no change of cardiac function from baseline. However, cardiac arrhythmias have been reported. Six cases of 10 to 20 seconds of asystole were reported during diagnostic testing, called lead testing, in the operating room during the implantation of device. This test consists of 15 seconds of vagal nerve stimulation at 1.0 mA at 500 microseconds and 20 Hz of frequency. Three of the patients had the vagal nerve stimulator implanted with no long-term sequelae reported. There have been very few cases—to our knowledge, 5 in total—of late-onset syncopal events associated with vagal nerve stimulation therapy. These patients were treated with removal or deactivation of the device.

![Figure 2](image1.png) **Figure 2** Sinus pause of 10 seconds that coincided with a syncopal event as stated in patient’s medical record. A: LINQ report of sinus pause. B: LINQ tracing of sinus pause.

![Figure 3](image2.png) **Figure 3** A: Radiograph showing patient’s vagal nerve stimulator (VNS) on the left side of chest and pacemaker on the right side of chest. B: Radiograph showing patient’s VNS prior to the procedure.
Suggested mechanisms for the asystolic episodes include long-term changes that occur within the central nervous system or the cardiac mechanoreceptors themselves owing to presence of the device. The vagal nerve stimulator acts on the nucleus tractus solitarius in the medulla, which then projects to other nuclei in the brain that affect autonomic functions in the hypothalamus and insular cortex. The chronic stimulation of these areas can cause their decreased sensitivity and function. To our knowledge, our case is the second reported in the United States and the only that was treated with a permanent pacemaker implantation and continuation of the vagal nerve stimulator therapy.

Conclusion

Late-onset asystole is a rare but significant complication in a patient with a vagal nerve stimulator of which the clinician needs to be aware to prevent significant morbidity. Our patient was successfully treated with a permanent pacemaker insertion with resolution of her asystolic episodes.

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