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Vagal nerve stimulator placement for medically refractory seizures in a child treated with phrenic nerve pacing for congenital central hypoventilation syndrome

Case report

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Congenital central hypoventilation syndrome (CCHS) is a rare, idiopathic disorder characterized by a failure of automatic respiration. Abnormalities such as seizure disorder, failure to thrive, and Hirschsprung disease have been associated with CCHS. In this report, the authors discuss the use of vagal nerve stimulation (VNS) to treat a medically refractory seizure disorder in a child who had previously undergone placement of bilateral phrenic nerve stimulators for treatment of CCHS. Concomitant use of phrenic and vagal nerve stimulators has not previously been reported in the literature. No adverse reactions were noted with both devices working. Diaphragmatic pacing (DP) was clinically unaffected by VNS. The patient experienced a marked reduction in seizure frequency and severity following vagal nerve stimulator placement. Based on this case, the authors conclude that VNS is a potentially safe and efficacious treatment option for seizure disorder associated with CCHS in patients undergoing DP.
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Key Words • **vagal nerve stimulation** • **vagal nerve stimulator** • **VNS** • **congenital central hypoventilation syndrome** • **diaphragmatic pacing** • **phrenic nerve stimulator**

Congenital central hypoventilation syndrome is a rare neurological condition resulting from failure of automatic respiration. In 1962, Severinghaus and Mitchell[8] coined the term "Ondine's curse" for some patients suffering from severe central apnea due to a failure of automatic respiration subsequent to brainstem surgery. In 1970, Mellins et al.[6] reported the congenital occurrence of this syndrome in infants suffering from inadequate autonomic respiration, predominantly occurring nocturnally. The incidence of CCHS is estimated at between 1/10,000 to 1/200,000 live births and is associated with the *paired-like homeobox 2B (PHOX2B)* gene.[10] The median survival in patients with CCHS is approximately 20 years of age.[9]

Initial signs of CCHS in infants include hypoventilation during sleep or apnea during both waking and sleeping. Treatment of CCHS typically involves a tracheostomy and long-term mechanical ventilation. Patients with severe CCHS who require continual ventilation significantly benefit from DP via implantation of bilateral phrenic nerve pacing electrodes.[5] The goal of DP is to achieve hemoglobin saturation (≥ 95%) and end-tidal CO_2 between 30 and 45 mm Hg.[1] Patients with CCHS may have an associated seizure disorder.[4,7] We describe the use of VNS to treat medically refractory seizures in a child with CCHS already undergoing DP during the day using bilateral phrenic nerve stimulators. This is the first published report of these 2 devices being used simultaneously in the same patient.

Abbreviations used in this paper: CCHS = congenital central hypoventilation syndrome; DP = diaphragmatic pacing; VNS = vagal nerve stimulation.

Case Report

History and Presentation. This full-term girl was delivered via cesarean section to a 37-year-old mother after failure to progress and an unsuccessful forceps delivery. Pregnancy was complicated by premature membrane rupture 4 days prior to delivery and intrapartum fever. Both the mother and father suffered from bipolar disorder. The mother was medicated during pregnancy with lithium and Thorazine and was suspected of alcohol and/or intravenous drug abuse.

The patient required endotracheal intubation and mechanical ventilation at birth due to cyanosis and hypoventilation. General physical examination revealed no dysmorphic features, and laboratory examinations were within normal limits, revealing no metabolic dysfunction. A chest radiograph showed no evidence of cardiomegaly or pulmonary disease. Electrocardiograms and echocardiograms revealed no abnormalities. Computed tomography and MR images of the head, electroencephalograms, and brainstem auditory evoked responses also revealed normal findings.

The patient received phototherapy for neonatal jaundice. She passed meconium spontaneously within the 1st day of life, but she developed moderate abdominal distention with feedings. A rectal suction biopsy was performed, which revealed ganglion cells, ruling out Hirschsprung disease (which may also be associated with CCHS). A tracheostomy was placed at 1 month of age. Roughly 5 months after delivery, the patient was discharged to a medical foster home. She continued to require 24-hour mechanical ventilation.

During infancy, the patient developed generalized tonic-clonic seizures, which were treated with the antiepileptic medications divalproex and lamotrigine. Seizures were sometimes associated with hypoxic episodes. Notably, the patient also developed multiple bradycardic episodes during Valsalva, such as for defecation or micturition.

Operations. Over the next 4 years, the patient had multiple hospital admissions for respiratory distress and seizures. At roughly 4 years of age, she suffered cardiac arrest after an episode of status epilepticus. At 5 years of age, she underwent implantation of bilateral thoracic phrenic nerve stimulating electrodes (Avery Biomedical Devices) and several months of diaphragmatic conditioning. Respiratory function has remained stable since, with 10 hours of continuous DP during the day and mechanical ventilation at night.

After phrenic nerve stimulator placement, however, she continued to suffer from generalized tonic-clonic seizures despite improved respiratory status and oxygenation. Her seizure disorder was also refractory to treatment with multiple antiepileptic medications, including at that time valproic acid and lamotrigine, plus a ketogenic diet. Magnetic resonance imaging of the brain again revealed no focal abnormalities. Electroencephalography demonstrated generalized epilepsy without demonstrable focal onset.

This patient's course was complicated by developmental delay affecting speech and fine motor skills. She also suffered from a behavioral disorder characterized by poor cooperation and altered mood. She was able to function independently for activities of daily living, and she divided her school day between mainstream and life skills classrooms, with assistance from a one-to-one nurse. Her adoptive mother and neurologists requested VNS therapy to diminish the burden of seizures and medication on her function and development as well as ongoing medical needs posed by very poorly controlled seizures.

At 11 years of age, she underwent left vagal nerve stimulator implantation (Cyberonics model 101) using standard technique.[2] Because no information was available regarding potential adverse interaction between the simultaneous use of phrenic and vagal nerve stimulation in the same patient, the vagal nerve stimulator was activated in an intensive care unit under close observation. No complications were associated with the stimulator implantation or activation. A dramatic decrease in seizure incidence and severity as well as a shortened postictal period was noted following the vagal nerve stimulator placement. Vagal nerve stimulation also notably improved the patient's alertness, cognitive function, and behavior, according to her mother and other caretakers. Furthermore, VNS-associated seizure improvements allowed for reduction in doses of anticonvulsant medications. There was no change in the timing or effect of phrenic pacing or overall respiratory status after VNS therapy was introduced.

Postoperative Course. Four years after institution of VNS therapy, vagal nerve stimulator generator replacement was undertaken for battery failure that had resulted in increased seizures. Generator replacement was complicated by a methicillin-resistant *Staphylococcus aureus* infection, requiring removal of the VNS system, antibiotic therapy, and subsequent replacement (Cyberonics generator model 102), with no further complications and complete return of therapeutic benefit. Again, no adverse interaction between the two systems was noted. A subsequent second generator change for end of battery life was uneventful. To date, the patient has been treated successfully with VNS for 7 years and 9 months (Fig. 1).

The highest VNS settings used in this patient to date in the setting of concurrent phrenic nerve stimulation were as follows: output current 2.0 mA, signal frequency 20 Hz, pulse width 250 msec, on time 30 seconds, off time 1.8 minutes, magnet output current 2.5 mA, magnet on time 60 seconds, magnet pulse width 500 msec.

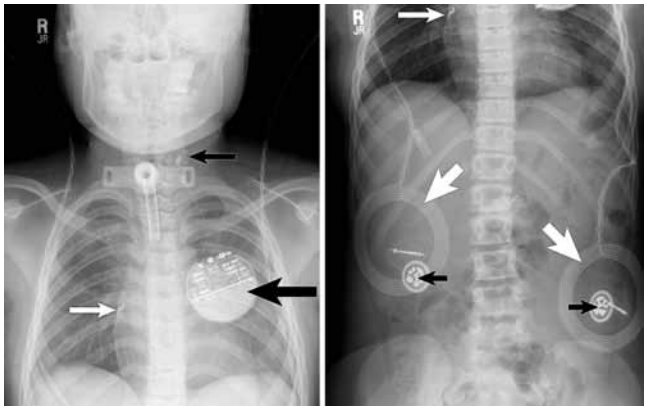

Fig. 1. Vagal and phrenic nerve stimulators in place in this patient. **Left:** The vagal nerve stimulator leads wrap around the left vagus nerve adjacent to the tracheostomy *(small black arrow)*. The vagal nerve stimulator generator is in place below the left clavicle *(large black arrow)*. The tip of the right phrenic nerve lead is visible *(white arrow)*; the left lead is obscured by the vagal nerve stimulator generator. **Right:** The phrenic nerve system radio antennae (external; *large white arrows*) overlie the radio receivers (internal; *black arrows*). The right phrenic nerve lead is again visible *(small white arrow)*, connected to its radio receiver.

Discussion

Diaphragmatic pacing is most useful in the treatment of children and adults with hypoventilation who have intact phrenic motor neurons and an anatomically intact phrenic nerve.[3] Children with CCHS frequently suffer from a medically refractory seizure disorder, which can be particularly disabling and dangerous due to their additional proclivity to suffer from hypoxic spells.[4]

Phrenic nerve stimulation complications are rare but include sleep apnea, infection, equipment failure, and interference with cardiac pacemakers.[3,5] The latter observation has led to concern that phrenic nerve stimulation might interfere with therapeutic VNS for epilepsy, or vice versa.

No adverse interaction or interference between simultaneous phrenic nerve pacing and VNS was noted in this patient. Significant clinical benefit accrued from markedly enhanced seizure control without compromise of respiratory status. When the intensity of VNS therapy was increased over time, no interference with DP emerged. The delivery of additional VNS using a magnet swipe during a seizure also failed to interfere with DP. This patient has now undergone simultaneous DP and VNS therapy for almost 8 years without known complications related to dual use.

Patients with CCHS who undergo treatment with DP and who also suffer from intractable seizures could potentially benefit significantly from VNS. Withholding VNS therapy in this patient population due to a potential adverse device interaction, therefore, may represent a significant potential lost opportunity for therapeutic benefit.

Conclusions

The patient described here has benefited significantly from simultaneous phrenic nerve pacing and VNS. Bilateral phrenic nerve pacemakers enable increased mobility without daytime ventilation, enhancing participation in school, physical therapy, and other daily activities. No interactions between phrenic nerve pacing and the VNS were encountered in this patient.

Concurrent phrenic nerve pacing and VNS may be safe and particularly relevant in the small and difficult to manage population of patients with CCHS and medically refractory epilepsy. Until more experience with concurrent use is gained, reasonable precautions including primary activation of VNS therapy under close observation may be warranted.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Selden, Duty. Acquisition of data: Selden, Duty. Analysis and interpretation of data: all authors. Drafting the article: Selden, Wozniak. Critically revising the article: Selden, Wozniak. Reviewed final version of the manuscript and approved it for submission: all authors.

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