Vagus nerve stimulation for treatment of epilepsy in Rett syndrome

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This case series presents the outcomes of seven females with Rett syndrome and medically refractory epilepsy who were treated with adjunctive vagus nerve stimulation (VNS) therapy for a minimum of 12 months. Patients ranged in age from 1 to 14 years (median age 9y) at the time of implantation, had experienced seizures for a median period of approximately 6 years, and had failed at least two trials of antiepileptic drugs before receiving VNS. The median number of seizures per month was 150 (range 12–3600). At 12 months, six females had ≥50% reduction in seizure frequency. VNS was safe and well tolerated, with no surgical complications and no patients requiring explantation of the device. Quality of life outcomes of note among these patients included reports at 12 months of increased alertness among all seven patients. No change in mood or communication abilities was noted.

Rett syndrome is a genetic disorder predominantly affecting females. It is characterized by profound cognitive impairment, communication dysfunction, stereotypical hand movements, gait abnormalities, and deceleration of head growth following a period of apparently normal development for the first 6 to 18 months of life (The Rett Syndrome Diagnostic Criteria Work Group 1988, Hagberg 1995, Burford et al. 2003). Rett syndrome is primarily caused by mutations in the methyl-CpG-binding protein 2 (MECP2) gene on Xq28, which encodes MECP2 (Sirianni et al. 1998, Amir et al. 1999). Although gene sequencing of MECP2 is not yet complete, mutations in MECP2 have been identified in 80 to 85% of patients with classic Rett syndrome, and in approximately half of those with atypical features (Kerr et al. 2001, Percy 2002).

Clinical features associated with Rett syndrome include seizures, breathing irregularities, growth failure, and oropharyngeal dysfunction (Percy 2002). Epilepsy is reported to occur in 50 to 90% of patients with Rett syndrome (Glaze et al. 1998, Steffenburg et al. 2001). Seizures can be controlled with antiepileptic drugs (AEDs) in many patients with Rett syndrome. However, some develop medically refractory epilepsy. Vagus nerve stimulation (VNS) is the first non-pharmacological therapy approved by the US Food and Drug Administration for the treatment of refractory epilepsy and treatment-resistant depression (Schachter 2002, George et al. 2005, Rush et al. 2005).

To date, more than 32,000 patients with epilepsy have received VNS therapy, which is delivered as a series of intermittent electrical pulses to the vagus nerve in the neck by an implantable device similar to a cardiac pacemaker. VNS therapy is approved for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures that are refractory to AEDs. Available evidence of the efficacy of VNS among children, the elderly, and those with other seizure types and disorders associated with additional neurological comorbidities, including Lennox-Gastaut syndrome, Landau-Kleffner syndrome, and autism, is also encouraging (Trevathan 2002, Wheless and Maggio 2002, Park 2003, Wheless 2004, Huf et al. 2005).

The automatic delivery method and lack of neurocognitive side effects associated with VNS make this therapy a potentially attractive adjunctive treatment option for individuals with Rett syndrome and refractory seizures. Concern exists, however, regarding the possibility that VNS therapy could complicate autonomic functions already compromised by Rett syndrome. This paper is the first to describe the effectiveness and tolerability of VNS therapy for the treatment of medically refractory epilepsy among patients with Rett syndrome.

Method

Five females with classic Rett syndrome and two with atypical Rett syndrome with early onset seizures and medically refractory epilepsy were treated with VNS therapy (Cyberonics Inc, Houston, Texas) for at least 1 year at our center. All seven patients were implanted with a VNS device between January 2000 and March 2003. Patients were included in the retrospective study if they had at least 1 year of follow-up. To receive VNS, patients must have failed to respond to at least two trials of AEDs. Mutations in MECP2 were identified in the five females with classic Rett syndrome; no MECP2 mutation was identified in the two atypical cases. The Institutional Review Board of Texas Children's Hospital approved the study.
Board for Human Subjects at Baylor College of Medicine and its affiliated hospitals approved this study.

Data were collected retrospectively from the patient medical records at 3, 6, 9, 12, 18, 24, and 30 months after implantation with the device. Data for all measures were not available for all patients at all time points. Follow-up data were available for five patients at 18 months, for two at 24 months, and for one at 30 months. Because follow-up data were not yet available for all seven patients after 1 year, the primary focus of this case review is the 12-month time point.

At each clinic visit, the number and dosage of AEDs, seizure frequency, and utility of magnet activation were recorded. Other variables tracked by caregiver report included the effect of VNS therapy on hyperventilation and/or breath holding, swallowing dysfunction, and changes in alertness, mood, and communication. All data collected for this study were taken from caregiver reports during clinic visits and are, therefore, subjective in nature. Standard, validated questionnaires were not used to assess quality of life changes over time. Weight measurements were obtained using an electronic scale, with values recorded to the nearest 0.1 kg.

Implantation of the VNS device was performed in accordance with previously published methods (Borthwick-Duffy et al. 1997). Stimulus was initiated in the operating room for two patients and after a 2-week recovery period for five patients. Stimulus parameters were adjusted using a standardized protocol beginning with a generator output of 0.25 mA, pulse width 500 ms, frequency 30 Hz, on time 30 seconds, and off time 5 minutes for all patients. Magnet output was started at 0.50 mA with a pulse width of 500 ms and an on time of 60 seconds. Each week, the duty cycle and magnet outputs were increased by 0.25 mA to reach 1.50 mA and 1.75 mA, respectively. Thereafter, off time was decreased every 3 months depending on seizure response. At 12 months, the parameters for all seven patients were duty cycle 1.50 mA, pulse width 500 ms, frequency 30 Hz, and on time 30 seconds. The off times were 3 minutes for two of the seven patients, 1.8 minutes for one patient, and 1.1 minutes for four patients. AED changes were kept at a minimum during the first year of VNS therapy.

At the onset of a seizure, caregivers were instructed to hold the VNS magnet over the generator for 3 seconds, remove, and wait 1 minute. If the seizure continued then they were instructed to repeat the procedure for up to five times.

Results

The demographic features of these seven patients can be seen in Table I. At the time of VNS implantation, patients had experienced seizures for a median period of approximately 6 years (range 12 mo–12 y 6 mo). The frequency of seizures at the time of implantation ranged from 12 seizures per month to several seizures per hour (median 150/mo). The two patients in this study who were experiencing infantile spasms were both MECP2 negative (Table II). Before receiving VNS, at least two and as many as eight AED treatments failed to control patients’ seizures.

Table II displays the diagnoses and outcomes for each patient. After 3 months of VNS therapy, five of the seven females had experienced seizures at least a 50% reduction in seizure frequency, and at 12 months six females had experienced at least a 50% reduction in seizure frequency. Four out of seven patients had at least a 90% reduction at 12 months. The two patients with 24 months of follow-up maintained more than a 90% reduction in seizure frequency from baseline. By 6 months, caregivers reported that using the magnet at the onset of, or during, a seizure shortened the duration of the postictal state or stopped seizures 50 to 75% of the time for three patients. One patient did not benefit from the magnet and the magnet

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Seizure type</th>
<th>Duration of seizures at implant, y</th>
<th>% reduction in seizure frequency (3mo)a</th>
<th>% reduction in seizure frequency (12mo)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MECP2 +</td>
<td>Symptomatic generalized</td>
<td>Generalized tonic clonic, generalized tonic</td>
<td>12.5</td>
<td>&gt;90</td>
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<tr>
<td>2</td>
<td>MECP2 +</td>
<td>Symptomatic generalized</td>
<td>Complex partial</td>
<td>8.8</td>
<td>Slight increase in seizure frequency</td>
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<tr>
<td>3</td>
<td>MECP2 –</td>
<td>Symptomatic generalized</td>
<td>Infantile spasms, generalized tonic</td>
<td>2.2</td>
<td>&gt;75</td>
</tr>
<tr>
<td>4</td>
<td>MECP2 –</td>
<td>Symptomatic generalized</td>
<td>Infantile spasms, generalized tonic, atonic</td>
<td>1.0</td>
<td>&gt;50</td>
</tr>
<tr>
<td>5</td>
<td>MECP2 +</td>
<td>Symptomatic localized</td>
<td>Complex partial</td>
<td>5.9</td>
<td>No change</td>
</tr>
<tr>
<td>6</td>
<td>MECP2 +</td>
<td>Symptomatic generalized</td>
<td>Generalized tonic clonic</td>
<td>6.4</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>MECP2 +</td>
<td>Symptomatic generalized</td>
<td>Atypical absence, complex partial</td>
<td>2.3</td>
<td>&gt;90</td>
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</tbody>
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aPercentage change from pre-implant baseline. MECP2, methyl-CpG-binding protein 2.
was not used for three patients.

Stimulation parameters for these patients were within the range typically used to treat other epilepsy populations. The number of AEDs taken by the patients during the first year of therapy with VNS changed little. Two patients had a single new AED added to their regimen and three patients had a reduction in either the number or the dosage of medication.

At baseline, breath holding and/or hyperventilation was reported as occurring almost continuously for three patients and for approximately 25% of the time for two patients. Two patients did not have any breathing irregularities. There was no change in these breathing irregularities at 12 months. One patient’s caregiver reported decreased appetite and coughing/choking on food after 1 month of VNS and the patient subsequently underwent placement of a gastrostomy feeding tube. One patient’s caregiver reported decreased appetite after 6 months of VNS, which persisted through the 12-month observational period. No patients lost weight during this 12-month observational period. No other patients reported any VNS-related side effects and no patient required explantation of the device. In addition, no prolonged recovery or surgical complications were observed. Quality of life outcomes of note among these patients included reports at 12 months of increased alertness among all seven patients. No change in mood or communication abilities was noted.

Discussion
In this case series of females with Rett syndrome, VNS therapy had a clinically significant effect in reducing seizures at 12 months in six of the seven patients. No difference in response rate was seen between patients who were MECP2 positive or negative. One patient who was MECP2 positive initially responded to VNS therapy, but then had a return of her seizures by the 12-month follow-up visit. This patient also derived no benefit with VNS magnet activation at the start of a seizure. An additional benefit seen with VNS therapy included an increase in alertness reported for all seven patients. There was no predictor of response to VNS therapy in this case series.

Some of the clinical characteristics found in patients with Rett syndrome, particularly breathing irregularities, oropharyngeal dysfunction, and growth failure, were thought to possibly contraindicate the use of VNS therapy for the treatment of seizures among this population. One patient had decreased appetite and coughing/choking on food after 1 month of VNS therapy. These symptoms did not resolve despite reductions in VNS stimulation parameters and the patient subsequently underwent placement of a gastrostomy feeding tube. Decreased appetite without weight loss was reported in one other patient after 6 months of VNS therapy. The symptoms seen in these two patients may have been related to VNS therapy, but in our experience these symptoms were more likely a result of the natural clinical history of Rett syndrome. No patient was reported to have any exacerbation of their baseline breathing irregularities. Nonetheless, patients with Rett syndrome should be monitored closely at the initiation of treatment with VNS to ensure that their clinical symptoms are not aggravated by the therapy.

As a retrospective study relying on caregiver reports, this study has inherent limitations. With any new dramatic intervention, particularly among a population with such a marked level of disability, the possibility of a placebo effect must be taken into account. However, the length of this study should help mitigate the placebo effect. Responses to VNS were sustained for more than a year. Such sustained results are characteristic of a placebo effect, which is generally short term in nature. Reductions in AED therapy could have accounted for some of the improvements reported for quality of life; however, improvements in quality of life were reported during the first year of treatment with VNS when medications were held relatively constant. Therefore, VNS appears to have played a role in improving these patients’ quality of life.

The absence of neurocognitive side effects and pharmacokinetic interactions with AEDs and other drug therapies make VNS a palliative treatment option, particularly for children and patients with additional comorbidities (Handforth et al. 1998, Wheless and Maggio 2002). The self-administering nature of the treatment also is well suited for patients with disabilities requiring a high level of dependence on others for care (Huf et al. 2005). Additional studies of the use of VNS therapy among patients with Rett syndrome and epilepsy are warranted.

References

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**List of abbreviations**

<table>
<thead>
<tr>
<th>AED</th>
<th>Antiepileptic drugs</th>
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<tbody>
<tr>
<td>MECP2</td>
<td>Methyl-CpG-binding protein 2</td>
</tr>
<tr>
<td>VNS</td>
<td>Vagus nerve stimulation</td>
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</tbody>
</table>

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