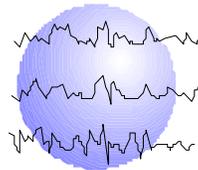


VAGUS NERVE STIMULATOR AS A TREATMENT FOR SEIZURES ASSOCIATED WITH HYPOTHALAMIC HAMARTOMAS

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REVISED ABSTRACT

RATIONALE: The epilepsy syndrome associated with hypothalamic hamartomas can be medically intractable and not amenable to resective surgery. This syndrome may also be associated with difficult to manage, aggressive or self-injurious behaviors. The vagus nerve stimulator (VNS) approved in 1997 as an adjunctive treatment for intractable partial seizures has proven to be helpful in many seizure types and for many epilepsy syndromes. We report on 4 patients with intractable seizures due to a hypothalamic hamartoma who had a VNS implanted for seizure control.

METHODS: 4 patients with hypothalamic hamartomas (3 males, 1 female, ages 11-24 years) were implanted with the VNS. All patients had the VNS turned on within 24 hours of implant and were then ramped up (duty cycle output of 1.5 mamps, on-time of 30 sec, off-time of 5 min., magnet output of 1.75 mamps, pulse width 500 msec, pulse frequency of 30 Hz) over several weeks. The duty cycle was held constant for at least 2 months, then adjusted based on individual responses. Seizure counts and quality of life (QOL) issues were documented by a caregiver at subsequent follow-up visits. Follow-up ranged from 1 year (1 patient) to greater than 2 years (3 patients).

RESULTS: 3 of 4 patients had a greater than 50% reduction in total seizure counts and/or >50% reduction in specific seizure type (GTC, CPS, atypical absence and drop). These 3 patients also had overall improvement in alertness and daily QOL. Anticonvulsant medications were significantly reduced in 1 patient. One patient had no reduction in seizure activity and no improvement in QOL in spite of changes in duty cycle. The VNS was ultimately turned off in this patient after 1 year due to lack of efficacy and perceived side effects. No serious adverse events were reported with any of the 4 patients. The details of each patients' response will be shown.

CONCLUSION: The VNS is an effective treatment for patients with seizures and hypothalamic hamartomas.

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INTRODUCTION

Seizures associated with hypothalamic hamartomas is a well-recognized syndrome. Seizure types are often multiple and medically intractable. Resective surgical approaches are usually unsuccessful in achieving seizure control even when seizure onset appears to be localized. Other treatment approaches, including the ketogenic diet, have added little to seizure management. In addition to the debilitating seizures, cognitive deterioration and behavioral problems contribute to the quality of life issues associated with this syndrome.

The NCP system for vagus nerve stimulation was approved for adjunctive treatment of partial onset seizures in patients 12 years of age and older in 1997. Since some of the seizures associated with hypothalamic hamartomas are complex partial, we implanted four patients with intractable seizures associated with hypothalamic hamartomas with the vagus nerve stimulator in an attempt to improve seizure control. This report summarizes those results.

METHODS

Table 1 summarizes the characteristics of the four patients. Two patients were children, two were adults at the time of implant. Three of the four patients had significant behavior problems, particularly aggressive behavior. Two of the four patients had onset of seizures at less than 18 months of age. All patients had the VNS turned on within 24 hours of implant and were then ramped up (duty cycle output of 1.5 mamps, on-time of 30 sec., off-time of 5 min., magnet output of 1.75 mamps, pulse width 500 msec, pulse frequency of 30 Hz) over several weeks.

RESULTS

Table 2 summarizes the results of vagus nerve stimulation on seizure control and quality of life. Three of four patients had a greater than 50% reduction in total seizure control and/or a greater than 50% reduction in a specific seizure type. These three patients also had an overall improvement in alertness and daily quality of life. One patient had no reduction in seizure activity and no improvement in quality of life in spite of changes in duty cycle. The VNS was ultimately turned off in this patient after 1 year due to lack of efficacy and perceived side effects. No serious adverse events were reported with any of the 4 patients.

DISCUSSION

The mechanism(s) by which hypothalamic hamartomas are associated with seizures and behavior/cognitive deficits. Theories range from the hamartoma being epileptogenic tissue to the hamartoma being a marker of a more widespread developmental (or migration) brain abnormality to an endocrinologic (neurotransmitter) abnormality. Since resective surgery of the lesion (if possible) rarely results in seizure control, it is more likely that the hamartoma is related to a more widespread brain abnormality resulting in more diffuse neurologic dysfunction.

Vagus nerve stimulation appears to have effects at many sites within the nervous system that may ultimately affect seizure threshold. The exact anticonvulsant mechanism of vagus nerve stimulation has yet to be elucidated but it has been shown to be effective in many seizure types and to have effect on other neurologic function (alertness, behavior and possibly depression).

Thus, potential overlapping systems (epileptogenic network associated with the hypothalamic hamartomas and the “feedback” loop from vagus nerve stimulation) may help to explain both mechanisms. Our patients help demonstrate the “broad spectrum” effect of the vagus nerve stimulator with regard to seizure type, epilepsy syndrome and the effects beyond seizure control. Since anticonvulsant medications rarely work in these patients and resective surgery may be contraindicated, the vagus nerve stimulator should be considered early in this group of seizure patients.

CONCLUSIONS

1. Vagus nerve stimulation can be effective in seizure management in patients with hypothalamic hamartomas.
2. Vagus nerve stimulation may also improve quality of life particularly with regard to behavior and alertness.
3. Vagus nerve stimulation appears to be a safe, broad-spectrum treatment for intractable epilepsy.

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TABLE 1

Patient	Gender	Age at Implant of VNS	Seizure Types/Age At Onset	Additional Associated Features
1	M	26 years	CPS, GTC (7 years)	<ol style="list-style-type: none"> 1. Mild mental retardation 2. Tuberous Sclerosis 3. Behavioral problems
2	M	13 years	CPS, GTC, Tonic Drops (1.3 years) (Lennox-Gastaut Syndrome)	<ol style="list-style-type: none"> 1. Precocious puberty 2. Aggressive and Self-Injurious behaviors 3. Moderate mental retardation 4. Anterior 2/3 corpus callosotomy in 1994
3	M	11 years	A.A., 2 nd GTC (14 mos)	<ol style="list-style-type: none"> 1. Attention deficit disorder 2. Mild mental retardation 3. Oppositional behavior
4	F	23 years	CPS, GTC, A.A., Tonic Drops., Myoclonic (3 years)	<ol style="list-style-type: none"> 1. Mild mental retardation

TABLE 2

Patient	During Baseline	Last Follow-up After Implant	Quality of Life Assessment at Last Follow-Up	Comments
1	4 CPS/mo < 1 GTC/mo	18 mos: 10 CPS/mo	No change (at 18 mos)	VNS turned off at patient request
2	CPS 2/mo 2 nd GTC 84/mo Tonic Drops 84/mo	26 mos: CPS: 0 in 4 mos GTC: < 1/mo. Drops: rare	Markedly improved behavior (less aggressive, more alert and cooperative)	Two hospitalizations for status epilepticus in two years
3	A.A. > 70/mo 2 nd GTC 126	10 mos: A.A.: 30/mo 2 nd GTC: < 50/mo (primarily limited to sleep)	Global assessment as overall better quality of life (more alert, verbal with better mood, more compliant)	No decrease in AEDs
4	CPS 1/mo GTC 2/mo A.A. "Rare"	26 mos: CPS: 0.8/mo GTC: 0/mo Drops: 0.2/mo	Overall better quality of life (particularly in professional achievements and less intense seizures)	No decrease in AEDs

Key for Table 1 and Table 2:

A.A. = Atypical Absence
GTC = Generalized Tonic Clonic

2nd GTC = Secondarily Generalized Tonic Clonic
AEDs = Antiepileptic Drugs