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Brief Communication

Effects of Vagus Nerve Stimulation on Progressive Myoclonus Epilepsy of Unverricht-Lundborg Type

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Summary: *Purpose:* A 34-year-old woman with progressive myoclonus epilepsy of Unverricht-Lundborg type was considered for vagus nerve stimulation (VNS) therapy.

Methods: After demonstration of intractability to multiple antiepileptic regimens and progressive deterioration in cerebellar function, the patient was implanted with a vagus nerve stimulator and followed for 1 year. Neurological status, seizure frequency, and parameter changes were analyzed.

Results: VNS therapy resulted in reduction of seizures (more than 90%) and a significant improvement in cerebellar function demonstrated on neurological examination. The patient reported improved quality of life based in part on her ability to perform activities of daily living.

Conclusions: VNS therapy may be considered a treatment option for progressive myoclonus epilepsy. The effects of VNS on seizure control and cerebellar dysfunction may provide clues to the underlying mechanism(s) of action. **Key Words:** Vagus nerve—Progressive myoclonus epilepsy—Electrical stimulation—Epilepsy—Seizure.

Progressive myoclonus epilepsy of Unverricht-Lundborg type (PME-UL) is a rare, autosomal recessive disorder characterized by spontaneous, stimulus-sensitive, and action myoclonus, tonic-clonic seizures, and cerebellar dysfunction (ataxia, dysarthria, tremor). Age of onset is usually in childhood, and the disease course is variable, ranging from limitations in performing activities of daily living to complete incapacitation. Dementia is usually mild and occurs late in the course of the disease (1).

Using linkage analysis, Lehesjoki et al. (2) identified the gene locus for PME-UL (EPM1) on chromosome 21, band q22.3. The EPM1 gene has been associated with a gene encoding a cysteine protease inhibitor, cystatin B (3). The specific mechanism whereby one gene abnormality allows development of typical clinical and neuropathological features has not been determined. Treatment of PME-UL typically consists of antiepileptic drugs, usually in polytherapy regimens. Valproic acid (VPA), clonazepam, and phenobarbital (PB) have produced symptomatic benefit, but phenytoin (PHT) has led to progressive deterioration (4). Reduced seizure frequency and improved neurological function have also been reported in EPM1 patients treated with piracetam (5), zonisamide (ZNS) (6), baclofen (7), and *N*-acetylcysteine, a sulfhydryl antioxidant (8).

Vagus nerve stimulation (VNS) reduces seizure frequency in some patients with intractable localization-related epilepsy (9). We report a case in which a patient with PME-UL had improved seizure control and reduced cerebellar dysfunction after implantation of a vagus nerve stimulator.

CASE REPORT

The patient was a 34-year-old woman of Finnish descent who developed myoclonus at age 12 years. She had her first generalized tonic-clonic seizure 2 years later. Her paternal great grandfather had a history of seizures, but the clinical semiology and nature of the illness were unknown. There were no other risk factors for seizures or epilepsy.

The patient was initially diagnosed as having primary generalized epilepsy. Electroencephalograms revealed bursts of bilaterally synchronous 2.5- to 4-Hz spike/

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slow-wave and polyspike/slow-wave discharges, which were activated by photic stimulation. She was treated with various antiepileptic drugs (AEDs), including PHT, PB, VPA, and clonazepam, either alone or in combination. Treatment with PHT worsened her myoclonus and tremor. Later, she developed impaired cognition, tremor, and dysarthria, and a diagnosis of progressive myoclonus epilepsy was made 12 years after the first symptoms appeared.

The patient had focal, regional, and generalized myoclonus, which occurred on an almost daily basis. Precipitants included video games, stress, and laughter. Clustering of seizures coincided with stress, alcohol use, use of oral contraceptives, and singing at parties. When attempts were made to simplify her AED regimen, deterioration resulting from increased myoclonus led to difficulties performing activities of daily living, including drinking from a cup and washing dishes.

Generalized tonic-clonic seizures usually lasting 2 to 3 minutes occurred every 2 to 3 months. Secondary injuries included a fractured nose (three times), periorbital trauma, and fractures of the teeth and ribs.

Physical examination revealed a pleasant young woman with mild flattening of affect, monoprosody, bradyphrenia, and drowsiness. She had moderately severe ataxic dysarthria characterized by explosive, hesitant, and staccato articulation with long pauses for word finding and a slow speech rate. Extraocular movements were conjugately full but contaminated by square wave jerks. There was mild ptosis bilaterally as well as fine eyelid and mouth tremors.

Tremor involved most muscle groups and was aggravated by postural input or action. Myoclonus appeared intermittently at rest. Both upper extremities exhibited decreased tone with suspension. There was mild polyminimyoclonus of the fingers (ataxic type), more prominent on the right. Moderate ataxia was present in the arms and legs, and Romberg's sign was present. Gait was widely based, mildly stooped, and moderately slowed. There was loss of hand and arm swing, inability to perform tandem gait, and a tendency to turn en bloc. Reflexes were increased bilaterally in a symmetric distribution.

Magnetic resonance imaging of the brain showed atrophy of the brachium pontis and the inferior aspect of the cerebellum. Muscle biopsy and evoked potential studies were normal.

Genetic testing confirmed the diagnosis of PME-UL by demonstrating the most common mutation, an expansion in the promoter of the cystatin B gene, by Southern blot analysis (*Pst*I) as well as low levels of cystatin B messenger RNA.

Despite the use of various AEDs, the patient continued to have frequent seizures and progressive cerebellar dysfunction with occasional secondary injury. Her most recent regimen included clonazepam 8 mg/d, VPA 1,750 mg/d, PB 45 mg/d, and lamotrigine (LTG) 200 mg/d. Attempts to obtain piracetam and ZNS were unsuccessful. Discussion of other potential treatment options, including VNS, surfaced at this time. It was explained to the patient that the vagus nerve stimulator was approved for use in partial epilepsy and that there was anecdotal evidence of benefit in primary and secondary generalized epilepsies, although there was no known experience with its use in PME-UL.

A vagus nerve stimulator (Cyberonics; Houston, Texas, U.S.A.) was implanted in December 1998, and indicators were set at minimal levels (Table 1), as is customary in our program. Within 3 weeks of implantation, the patient returned to the clinic and reported no appreciable change. Parameter changes were made, including maintenance of a narrow pulse bandwidth (130 microseconds), increasing the current (0.5 mA), and increasing overall stimulation time (on time, 30 seconds; off time, 10 minutes). We based these conservative changes on our previous experience with improved tolerability at lower pulse bandwidths (130 to 250 microseconds) and lack of previous reported experience with vagal stimulation in this syndrome. The changes resulted in a dramatic improvement. The patient reported no seizures, and physical examination demonstrated reduction of tremor, dysarthria, and ataxia. Polyminimyoclonus with arms outstretched was barely perceptible, and overall tremulousness of limbs, eyelids, and mouth was similarly reduced. Although her affect remained restricted, her speech showed more prosodic variation, a higher rate of word production per minute without hesitation, less staccato and explosive articulation, and almost normal overall understandability. Bradyphrenia decreased, and no drowsiness appeared during the interview. Her gait improved to a narrowly based walk, still with restricted arm and head swing and stooped posture, but overall she moved at a faster rate. She still turned en bloc. No myoclonus appeared at rest. Limb ataxia on finger-to-nose

TABLE 1. *VNS parameter settings*

	Operating room settings	First change	Second change	Third change
Output current (mA)	0.25	0.5	0.75	1.0
Frequency (Hz)	15	15	30	30
Pulse bandwidth (microseconds)	130	130	250	250
On time (seconds)	7	30	30	30
Off time (minutes)	90	10	5	3
Magnet current (mA)	0.25	0.5	0.75	1.0
On time (seconds)	7	30	30	30
Pulse bandwidth (microseconds)	130	130	250	250
Postoperative interval		3 weeks	5 months	9 months

testing was mild. She attended multiple parties and family functions without exacerbation. No changes in her antiepileptic medications or VNS parameter settings were made for 5 months after her initial clinic visit.

Although the patient continued to be free of seizures, we considered the possibility of obtaining further improvement with increasing stimulation indicators. Soon after these changes (Table 1), the patient had her only generalized seizure in 6 months, but her daily functioning was improved significantly.

About 9 months after implantation, the patient noted a slight increase in breakthrough seizures and worsening of cerebellar dysfunction. She appeared to be developing a tolerance to the effects of the stimulation. The final indicator changes were made (current, 1.0 mA; on time, 30 seconds; off time, 3 minutes), and the patient returned to the level of improvement she had noted earlier in the course of stimulation. No changes in her antiepileptic drug regimen of clonazepam, VPA, PB, and LTG have been made since vagus nerve stimulator implantation.

DISCUSSION

VNS is effective at reducing seizures in patients with intractable partial seizures. More recently, some patients with symptomatic generalized epilepsy have also shown significant seizure reduction (10). Our patient with PME-UL also benefited from VNS with marked seizure reduction and improvement in cerebellar abnormalities (i.e., reduction in ataxia, tremor, and dysarthria).

Possible mechanisms by which VNS reduces seizure frequency have been reviewed by McLachlan (11). Favorable outcomes in a small number of patients with PME-UL after treatment with piracetam (5) and *N*-acetylcysteine (8) raise questions about the underlying abnormality in PME-UL and potential treatment options.

Although we are cautious about drawing conclusions from a single case report with limited follow-up, the dramatic improvement shown by our patient in both reduced seizures and overall neurological status requires further study. Although the response seen in this patient is likely attributable to symptomatic relief as opposed to direct effects on the underlying disease process, it nevertheless had a very beneficial influence on overall quality of life. This positive tandem response for both seizure control and sensorimotor function in a patient with PME-UL may help clarify the biochemical effects produced by chronic vagus stimulation. VNS may be a treatment option for patients frequently refractory to AED polytherapy, and it may also provide further insight into the motor and cognitive pathophysiology of this genetic abnormality.

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