Clinical commentary

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Managing Lafora body disease with vagal nerve stimulation

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ABSTRACT – A 17-year-old female, of consanguineous parents, presented with a history of seizures and cognitive decline since the age of 12 years. She had absence, focal dyscognitive, generalized myoclonic, and generalized tonic-clonic seizures, all of which were drug resistant. The diagnosis of Lafora body disease was made based on a compatible clinical, EEG, seizure semiology picture and a disease-causing homozygous mutation in the *EPM2A* gene. A vagus nerve stimulator (VNS) was inserted and well tolerated with a steady decrease and then stabilization in seizure frequency during the six months following insertion (months 1-6). At follow-up, at 12 months after VNS insertion, there was a persistent improvement. Seizure frequency during months 7-12, compared to pre-VNS, was documented as follows: the absence seizures observed by the family had decreased from four episodes per month to 0 per month, the focal dyscognitive seizures from 300 episodes per month to 90 per month, the generalized myoclonic seizures from 90 clusters per month to eight per month, and the generalized tonic-clonic seizures from 30 episodes per month to 1.5 per month on average. To our knowledge, this is the second case reported in the literature showing efficacy of VNS in the management of seizures in Lafora body disease.

Key words: vagal nerve stimulation, Lafora body disease, progressive myoclonus epilepsy

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Progressive myoclonus epilepsy (PME) is a rare complex neurological syndrome characterized by a series of neurological deficits including progressive myoclonus, drug-resistant epilepsy, cognitive impairment and, often, ataxia. It encompasses more than a dozen clinical entities, each with distinct genetic aetiology and clinical findings (Minassian *et al.*, 2016; Shbarou and Mikati, 2016). Lafora body disease (LBD), one of the main PME types, is characterized by an age at onset between 12 and 17 years old in previously healthy adolescents with frequent fragmentary, symmetric, generalized myoclonus and/or generalized tonic-clonic seizures (GTCS), visual hallucinations, progressive cognitive impairment and behavioural deterioration, ataxia, and dysarthria (Jansen and Andermann, 2007; Turnbull *et al.*, 2016). It is caused by mutations in two genes, *EPM2A* and *NHLRC1 (EPM2B)* (Lohi *et al.*, 2007). Patients with LBD may respond at

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first to anticonvulsants but with time they become pharmaco-resistant (Andrade *et al*., 2007). To date, only one case is reported in the literature showing the utility of VNS in LBD (Hajnsek *et al*., 2013); herein, we report the second such case.

Case study

History and workup

A 17-year-old female presented to the Neurology clinic at Duke Medical Center for evaluation of seizure disorder and cognitive decline. Seizures started at the age of 12 years and were of multiple types: first, absence seizures consisting of episodes of staring, blinking, and upward gaze deviation, lasting at times for few seconds and up to one minute. These seizures were further verified as absence seizures by video-EEG monitoring. During the six months prior to the visit, these absence seizures were occurring at a frequency of an average of approximately four episodes per month. The second type of seizure was focal dyscognitive seizure. These consisted of an initial loss of vision or of seeing flashes of light followed by unresponsiveness for about one minute. These were occurring at a frequency of an average of approximately 300 episodes per month. The third type of seizure was generalized sudden myoclonic jerks that occurred as a rule in clusters, which usually lasted for approximately 15 minutes and occurred at a frequency of an average of approximately 90 clusters per month. The first episode occurred after the start of carbamazepine, but these persisted even after stopping that medication with transient short-lived incomplete improvement with the use of valproic acid and levetiracetam. Her myoclonic seizures led to falls once every 1-2 weeks. The fourth type of seizure was GTCS that, as a rule, would start as the above focal dyscognitive seizure and would progress to adversive head movements and then generalized tonic-clonic activity, usually lasting 1-2 minutes. Sublingual clonazepam would seem, at times, to abort this progression to GTCS. These were occurring at the beginning (age 12) as two episodes per week but later increased progressively to an average of approximately 30 episodes per month despite being on medications. Often, her seizures would be precipitated by mental activity requiring concentration, by bright light, or by an attempt to move such as initiation of walking.

At that time, the patient had failed numerous medications including: valproate, levetiracetam, carbamazepine, zonisamide, clonazepam, lamotrigine, phenobarbital, lacosamide, and piracetam. She had also failed the Atkins diet which was stopped six months before her evaluations by us. When seen, she was on the following which were kept unchanged during the following year: oral clonazepam (4.5 mg by mouth, daily), sodium valproate (300 mg by mouth, twice daily), lacosamide (150 mg by mouth, twice daily), sustained-release levetiracetam at 500 mg (1,500 mg by mouth, twice daily), phenobarbital (40 mg by mouth, twice daily), piracetam, (1,200 mg by mouth, three times daily), escitalopram (20 mg by mouth, daily), calcium carbonate-vit D3, ferrous fumarate, and multivitamin tablet.

An extensive workup for inborn errors of metabolism, mitochondrial disease, and autoimmune processes was unrevealing. An MRI without contrast showed sulcal spaces and ventricles that were prominent for age. A muscle biopsy showed changes suggesting LBD. The Comprehensive Epilepsy Panel and Comprehensive Mitochondrial Nuclear Gene Panel revealed an *EPM2A* nonsense homozygous mutation, c.166G>T p.Glu56Stop (E56X), which is predicted to be a disease-causing mutation characterized by loss of protein function through protein truncation (http://www.ncbi.nlm.nih.gov/clinvar/variation/205431/).

VNS insertion and response

She was, as per the above, having an estimated average of 424 seizure episodes per month during the six months before the VNS was inserted. The VNS was implanted and was first set at an initial output current of 0.25 mA, signal frequency of 20 Hz, pulse width of 250 μseconds, signal on time of 30 second, signal off time of 5 minutes, magnet current of 0.5 mA, magnet on time of 60 seconds, and magnet pulse width of 500 μseconds. This was increased progressively to reach an output current of 2 mA, signal frequency of 20 Hz, pulse width of 250 μseconds, signal on time of 30 seconds, signal off time of 5 minutes, magnet current of 2.25 mA, magnet on time of 60 seconds, and magnet pulse width of 500 μseconds by three months of VNS insertion. Over the six months following VNS insertion, the seizure frequency gradually decreased and then stabilized. At the time of follow-up, 12 months after VNS insertion, parameters were still as above. Her seizure frequency during that six-month period was the following: an average of 100 episodes per month as compared to an average of about 424 episodes per month pre-VNS (a decrease of 75%; *figure 1*). The absence seizures observed by the family had decreased from an average of about four episodes per month to 0 episodes per month (a decrease of 100%). The focal dyscognitive seizures decreased from an average of about 300 episodes per month to 90 episodes per month (a decrease of 70%). The myoclonic jerks of the entire body had decreased from an average of about 90 clusters per month to eight clusters per month (a response rate of 91%). However,

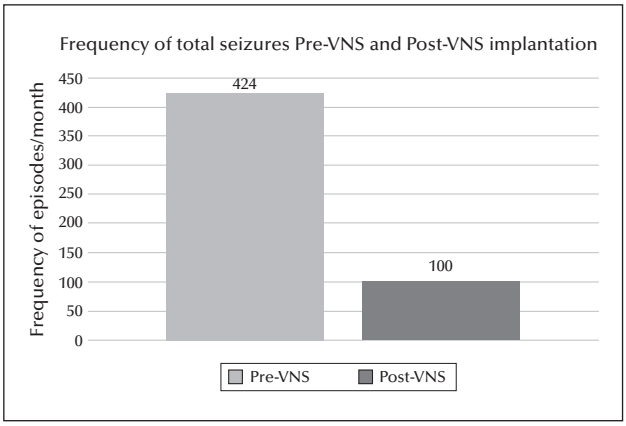

Figure 1. Frequency of total seizures pre-VNS and post-VNS implantation.

falling due to these seizures continued to occur at the same frequency of one every 1-2 weeks. The GTCS decreased from an average of about 30 episodes per month to 1.5 episodes per month (a decrease of 95%) (*see figure 2 for a summary of the data*).

Discussion

Our patient showed improvement in her various types of seizures. This is similar to the previously reported case of the effectiveness of VNS in LBD in which, after one year of follow-up, the patient demonstrated cessation of the GTCS and status epilepticus episodes, in addition to a significant decrease in myoclonus and moderate reduction in cerebellar symptomatology (Hajnsek *et al.*, 2013). One general limitation of the case report that can be noted is that we are dealing with a retrospective single case and the placebo effect cannot be eliminated when assessing the usefulness of VNS in decreasing the frequency of the seizures discussed above.

The mechanism by which VNS can help LBD is not clear but it may involve alterations in neurotransmitter modulation of cortical irritability. Prior studies have shown that VNS can exert its effects through multiple potential mechanisms including glutamatergic, serotoninergic, noradrenergic, and GABAergic mechanisms, in addition to desynchronization of neuronal activity, general effect on arousal, and possible modifications of hippocampal plasticity with resultant anti-seizure effects (Krahl *et al.*, 2003; Hassert *et al.*, 2004; Groves *et al.*, 2005; Dorr and Debonnel, 2006; Follesa *et al.*, 2007; Aalbers *et al.*, 2011; Raedt *et al.*, 2011; Muñoz-Ballester *et al.*, 2016). In fact, studies on the mouse model of this disease have indicated a disruption in the homeostasis of the glutamate transporter GLT-1 (EAAT2), resulting in reduced capacity of glutamate transport. This is consistent with the anti-seizure mechanisms of action of VNS which include, as mentioned above, anti-glutamatergic effects (Muñoz-Ballester *et al.*, 2016).

Therapy for LBD is currently limited to symptomatic management of the epilepsy with only zonisamide and more recently perampanel, apparently showing a somewhat more favourable, albeit limited, efficacy profile than other medications (Kyllerman and Ben-Menachem, 1998; Yoshimura *et al.*, 2001; Schorlemmer *et al.*, 2013). The initial response to pharmacotherapy often involves clonazepam, levetiracetam, piracetam,

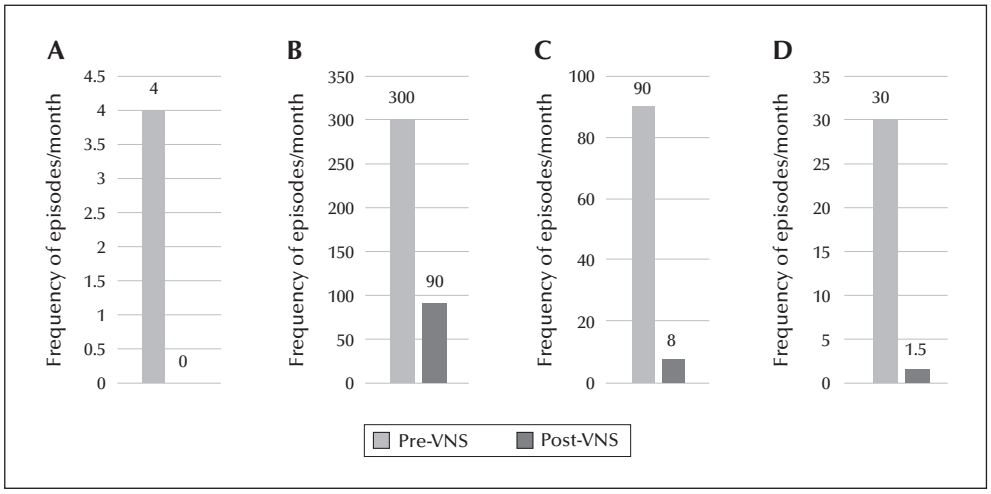

Figure 2. Frequency of generalized absence seizures (A), complex partial seizures (B), generalized myoclonic seizures (C), and generalized tonic-clonic seizures (D) pre-VNS and post-VNS implantation.

phenobarbitone, topiramate, valproate, and zonisamide. Of these medications, zonisamide was noted to have an excellent effect in controlling GTCS and myoclonus, often for 2-3 years before failing. In addition, high doses of phenobarbitone were found beneficial to avoid convulsive status epilepticus. However, carbamazepine, phenytoin, gabapentin, tiagabine, and vigabatrin may aggravate the myoclonus and should be avoided (Monaghan and Delanty, 2010). The ketogenic diet has also been reported to have some effects. Patients, as a rule, become refractory to all these therapies, hence the importance of additional alternative therapies such as VNS. In our case and in the previously reported patient, there was good tolerability, as seen in many other prior studies of VNS (Mikati *et al*., 2009; Klinkenberg *et al*., 2012). Although VNS is approved only as adjunctive therapy for focal seizures in children and adults 12 years and older, there are few controlled studies in the literature reporting effectiveness of VNS therapy as adjunctive VNS therapy for patients with drug-resistant idiopathic generalized epilepsy (Kostov *et al*., 2007). In fact, some reported cases have shown good evidence for the utility of VNS in drug-resistant epilepsies such as Lennox Gastaut syndrome, as well as a number of PMEs such as Unverricht-Lundborg disease, myoclonic epilepsy with ragged-red fibres, and Gaucher's disease (Smith *et al*., 2000; Fujimoto *et al*., 2012; Morris *et al*., 2013). Given the multiple seizure types that LBD can manifest, a therapy that can address more than one seizure type would be a favourable therapeutic option to consider. We hope that future reports will confirm our current and the previous case report observations regarding the potential utility of VNS in the management of LBD. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
The authors have nothing to disclose.

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TEST YOURSELF

(1) What are the cardinal features of Lafora body disease ?

(2) What treatments are used in the management of Lafora body disease-related seizures?

(3) For which epilepsy syndrome is vagus nerve stimulator effective?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".