Does Vagal Nerve Stimulation Treat Drug-Resistant Epilepsy in Patients with Tuberous Sclerosis Complex?

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Tuberous sclerosis complex (TSC) is a genetic disease caused by mutation of TSC1 and TSC2 genes. The incidence is 1 per 6000 live births.[1] The clinical manifestations are widespread, but the neurologic involvement could cause pervasive developmental disorders, mental retardation, and epilepsy. Epilepsy occurs in 88% of the patients, and drug resistance appears in 63% of all the patients with epilepsy.[1] After drug failure, resective surgery, ketogenic diet, everolimus, and vagal nerve stimulation (VNS) may be indicated to stop seizures. Chu-Shore et al[1] in a recent review reported that, among 39 patients undergoing resective surgery, 25.6% became seizure free, and 1 case underwent VNS with good results.

The goal of our work is to describe and discuss our experience in treating drug-resistant epilepsy in patients with TSC with VNS. Drug resistance was defined according to the current definition by Internation League Against Epilepsy. We report the results obtained in 4 patients, implanted at the mean age of 7 years (range, 3–14 years), with a mean follow-up of 7 years (range, 4–12 years).

At the last follow-up, all but 1 patient reached class IA (McHugh). Particularly, one patient is currently seizure free without medications, one patient presented with occasional nondisabling morpheic seizures and is without medication, one patient (presenting with drop attacks) currently had only brief seizures with impairment of awareness (only valproic acid), and the last patient experienced only a reduction of about 50% of the frequency of the seizures. The stimulation parameters were mean current of 1.875 mA (range, 1.5–2.25 mA), mean duty cycle of 16%, and mean total charge of 364 mC (range, 185–466 mC).

Data from the literature disagree and concern small series of patients. Parain et al.[2] reported 10 patients, of whom 5 reached class IA McHugh after VNS. Major and Thiele[3] found an outcome IA only in 19% in a sample of 16 patients implanted at the mean age of 15 years. Elliott et al.[4] reported 2 out of 11 implanted patients in Engel class 1. In summary, no patient became fully seizure free. Moreover, in all of the series, the number of antiepileptic drugs was unchanged before and after surgery. The authors did not investigate if VNS could treat drug-resistant epilepsy in TSC and if VNS could be considered as a first-step therapy in TSC epilepsy in detail.

Comparing our results with the available literature data, some emerging issues became clear: the first is if VNS could stop drug-resistant epilepsy in TSC and the second one is if VNS could stop drug-resistant epilepsy per se.

In our experience, VNS treats epilepsy (class IA McHugh) in almost 3 out of 4 patients, whereas a fourth patient is in class 2A. These results seem to suggest that VNS could treat epilepsy in TSC.

In addition, 2 patients in class IA of our series stopped antiepileptic drugs, confirming that VNS seems to be able to control seizures per se.

In the literature, there is a conservative attitude regarding drugs withdrawal after VNS, also in case of good results. Orosz et al.[5] showed that best outcomes are achieved in the subgroup without change in drug regimen.

It is our opinion that drugs should be withdrawn as soon as possible once the effects of stimulation are stable, similarly to resective surgery.

Our findings seem to suggest that VNS can treat drug-resistant epilepsy in TSC. To better evaluate the efficacy of VNS, we suggest withdrawing drugs after about 1 year of being seizure free or class IA and to continue the therapy with VNS alone.

A common method to monitor the efficacy of VNS therapy is to check the seizure frequency and the improvement in behavioral skills. We suggest the evaluation of bioelectrical markers that are able to define the changes in the activity of the brain. In detail, the compressed spectral array (CSA) condenses the raw ongoing electroencephalogram to provide a 2-dimensional graphic display of frequency and power versus time, allowing a quantified dimension of electrical brain activity, which can be compared along time. For example, in **Figure 1**, we show the CSA recorded on left occipital area (O1) in our sample. The patients with good outcome presented with a peak in the alpha band, whereas the patients with bad outcome showed a peak in the delta band.

In conclusion, VNS can treat drug-resistant epilepsy in TSC. In our group, 2 out of 4 patients are class IA McHugh seizure free without drugs. In the patients with good outcome, we withdraw drugs after 1 year of being seizure free or class IA McHugh. Biological markers are useful to better describe the outcome after VNS implant. CSA could provide a digital description of electroencephalogram which can easily be obtained and can be easily shared to improve the knowledge about physiology of VNS. Adjunctive Everolimus, a mammalian target of rapamycin inhibitor, reduced more than 50%[6] in 29.3% (low-exposure everolimus) or 39.6% (high-exposure everolimus) the seizure frequency in a sample of 366 patients with TSC presenting with drug-resistant epilepsy. Everolimus is defined as personalized therapy in patients with TSC because it targets the underlying molecular pathology of TSC. A combined therapy with everolimus and VNS should be a promising opportunity for patients with TSC.

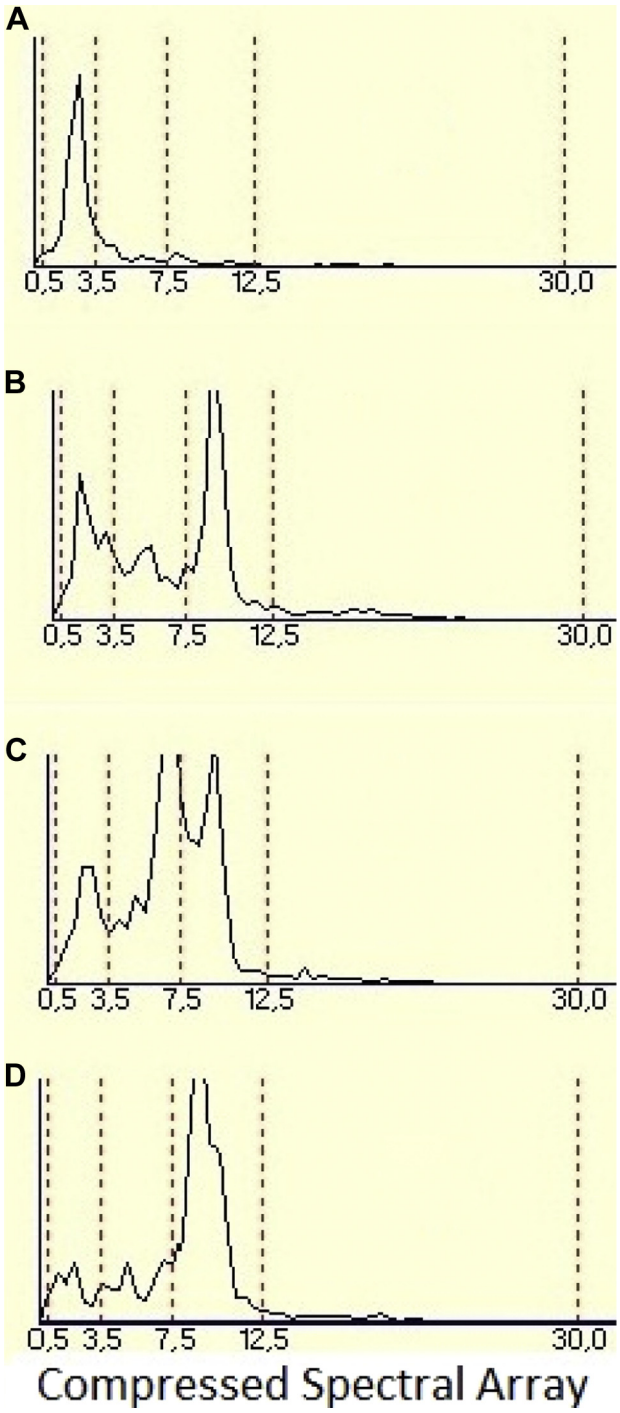

Figure 1. Compressed spectral array recorded on O1 (awake). (**A**) Bad response to vagal nerve stimulation (VNS). (**B**–**D**) Good response (class IA) to VNS. In (**A**), the peak of the spectrum power is in delta frequencies, whereas in cases (**B**–**D**), it is in the alpha frequencies.

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