Vagus nerve stimulation may be a sound therapeutic option in the treatment of refractory epilepsy

Estimulação no nervo vago pode ser uma excelente opção no tratamento de epilepsias refratárias

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The prevalence of epilepsy is approximately 1%, and between 70 and 80% of these patients have good control of seizures with drug therapy1,2. However, the remaining 20 to 30% who are refractory to antiepileptic drugs have an important burden regarding their labor, social and cognitive aspects as a result of their seizures, its etiology and sometimes the effects of their drug treatment2,3.

People with medically refractory epilepsy may be included in pre-operative protocols for epilepsy surgery, and as a result, to undergo microsurgical resection for curative treatment2,3. Another group of patients can be treated surgically only with palliative surgery, such as those based on the disconnection of the epileptogenic process. These surgeries are aimed at reducing the number of attacks and at improving the quality of life3,6,7.

Vagus nerve stimulation (VNS) is a palliative therapy that has been shown to be effective not only in the treatment of epilepsy refractory to medical treatment but also the one refractory to surgical treatment8. It is a procedure less invasive than disconnective surgeries, such as callosotomy and multiple subpial transections3,6,7.

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In order to study the results of VNS, the patients treated by this approach at the Institute of Neurology, Curitiba have been retrospectively analyzed, and the impact of the procedure on the seizures, the implantation procedure and the neurostimulator calibration procedures have been described in detail.

**METHODS**

**Population**

Between October 2007 and June 2012, six patients with generalized epilepsy refractory to medical treatment underwent VNS surgery at the Institute of Neurology, Curitiba. Of these, three were females and three males. The age ranged from 7 to 44 years old. Three had generalized epilepsy in the past and had undergone callosotomy, two had epilepsy with focal and generalized features and one had posterior temporal lobe epilepsy. Patients that underwent callosotomy also showed focal irritative activity/epileptogenic foci. All patients were refractory to drug treatment, three of which had already undergone previous callosotomy. In five cases, a video-electroencephalogram (video-EEG) was performed and showed generalized, focal or multifocal irritative or epileptogenic activity. Table 1 presents these data.

**Surgical procedure**

The surgery is performed with the patient under general anesthesia and endotracheal intubation. Two small skin incisions of about 4 cm are performed. The first one is on a horizontal fold of skin on the anterolateral surface of the neck, with a section of the platysma muscle, muscle dissection and exposure of the plans until the left vagus nerve, between the common carotid artery and internal jugular vein using an operating microscope. The electrode is wrapped around the vagus nerve (Fig 1). A second incision is made below the clavicle, and the subcutaneous space is opened to place the generator, which is connected subcutaneously to the electrode already placed around the vagus nerve. The system is tested through telemetry to verify the operation of the generator. Finally, the incisions are closed in two layers after assessing hemostasis, and dry dressings are placed over the surgical wounds.

**Table 1. General data related to vagus nerve stimulation treated patients.**

<table>
<thead>
<tr>
<th>Gender/ Age (years)</th>
<th>Age at implantation (years)</th>
<th>Clinical condition</th>
<th>Irritative/ epileptogenic zone</th>
<th>Neuroimaging findings</th>
<th>Time since implantation</th>
<th>Efficacy (patients’ rating)</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 M, 21</td>
<td>21</td>
<td>Multifocal epilepsy</td>
<td>Generalized irritative activity, left occipital/supratentorial epileptogenic zone</td>
<td>Bilateral temporal arachnoid cysts, supratentorial asymmetric ventricular dilation</td>
<td>Four years</td>
<td>80% decrease in seizure frequency</td>
<td>Transient cough, precordialgia, irritability</td>
</tr>
<tr>
<td>#2 F, 27</td>
<td>27</td>
<td>Epilepsy since the first year of life, multifocal, mild cognitive impairment, previous callosotomy</td>
<td>Right rolandic irritative zones, indefinable epileptogenic zone</td>
<td>Anterior 2/3 callosotomy</td>
<td>Three years and nine months</td>
<td>80% decrease in seizure frequency</td>
<td>Transient anxiety</td>
</tr>
<tr>
<td>#3 M, 50</td>
<td>50</td>
<td>Generalized epilepsy since the first year of life, tetraparesis, marked cognitive impairment, previous callosotomy</td>
<td>Generalized irritative activity, with anterior temporal focal paroxysms in F7</td>
<td>Volumetric reduction of the brain, right frontal encephalomalacia, anterior 2/3 callosotomy</td>
<td>Eight months (later explanted)</td>
<td>50% decrease in seizure frequency, mood improvement, started walking again</td>
<td>Surgical wound infection</td>
</tr>
<tr>
<td>#4 F, 29</td>
<td>29</td>
<td>Seizures onset within the first year of life, previous callosotomy, right crural monoparesis, mild cognitive impairment</td>
<td>Multifocal neocortical irritative activity and epileptogenic zone</td>
<td>Volumetric reduction of the left brain hemisphere, anterior 2/3 callosotomy, left fronto-parieto-temporo-occipital gliosis</td>
<td>Three years and one month</td>
<td>80% decrease in seizure frequency, mood improvement, started walking again</td>
<td>Transient hoarseness</td>
</tr>
<tr>
<td>#5 F, 41</td>
<td>41</td>
<td>Neocortical epilepsies of the left temporal lobe, mild verbal abilities compromise</td>
<td>Left temporal irritative activity, left postero-temporal epileptogenic zone</td>
<td>Frontal horn cystic formation of the left lateral ventricle</td>
<td>One year and four months</td>
<td>40% decrease in seizure frequency</td>
<td>Transient cough, chest pain; calibration-dependent dyspnea</td>
</tr>
<tr>
<td>#6 M, 7</td>
<td>6</td>
<td>Multifocal epilepsy, severe cognitive impairment</td>
<td>Generalized and multifocal irritative activity</td>
<td>No significant findings</td>
<td>Six months</td>
<td>90% decrease in seizure frequency</td>
<td>None</td>
</tr>
</tbody>
</table>
Programming the neurostimulator

Stimulation has been performed in all cases in the left vagus nerve. The stimulation protocol consisted of activating the neurostimulator just 15 days after the implantation procedure. The initial parameters and current neurostimulation parameters are shown in Table 2. Adjustments in neurostimulation parameters have been made in monthly visits in the first six months of follow-up. The default current intensity is 0 mA, set to 0.25-mA increases at every next visit. The default stimulus frequency is 20 to 30 Hz, with a pulse width of 250 to 500 usec current, on-time (time on) of 30 seconds and wait time (time off) of five minutes. These parameters can be reduced in case of lack of tolerability to stimulation. The relationship between the stimulus frequency, intensity, time-on and time-off is optimized over time. Fig 2 brings a flowchart for setting and adjusting the neurostimulator.

RESULTS

Mean follow-up was 26.6 months. Seizure frequency decreased in all patients. One patient reported a 40–50% reduction in seizure frequency (patients #3 and #5), and the remaining four patients estimated an 80% or greater reduction in seizure frequency (n=4). Three patients no longer required frequent hospitalizations. In one of the patients (#5), the reduction in seizure frequency occurred after her first year of follow-up. Two patients previously restricted to wheelchairs started to walk, probably because of improved mood. One system was explanted because of infection (patient #3), but otherwise no other relevant adverse event was seen. Individual follow-up time, efficacy data and adverse events are summed up in Table 1.

DISCUSSION

Effectiveness of VNS

When refractory to medical treatment, symptomatic generalized epilepsy or those epilepsies with secondary bilateral synchrony are associated with high morbidity. In addition, these patients usually are not candidates for curative resective epilepsy surgery. Surgical options include palliative callosotomy and VNS. Callosotomy is a rather aggressive surgery, but leads to a satisfactory control of tonic-clonic and atonic seizures. Callosotomy leads to a decrease in the frequency and severity of epilepsy seizures in a bracket between 40 and 70%. Procedural complications include disconnection syndrome, infection, mutism, hemorrhage and focal neurological deficits. VNS is performed without intracranial surgery, with a minimally invasive technique. According to Nei et al., who compared 50 epileptic patients who underwent callosotomy to 21 epileptic patients who underwent VNS, the reduction of tonic and atonic seizures was similar for all seizure types, including partial and generalized, but there was a greater reduction in callosotomy. However, there was one death among patients submitted to callosotomy, illustrating the greater morbidity of this procedure as compared to VNS. In another study of 16 adults with medically refractory generalized epilepsy, a 43.3% average decrease in seizure frequency has been observed after treatment with VNS.

The reduction in seizures in three of our patients who had previously undergone callosotomy mirrors that of the available literature. Elliot et al. evaluated 110 patients who had previously undergone intracranial surgery for epilepsy and later on treated by VNS, and concluded that previous surgery...
did not affect VNS outcome. Our data add to the previous information and brings thoughts on the possibility of VNS implant prior to surgical procedures, as already suggested by other authors.  

In addition to patients with symptomatic generalized epilepsy, those experiencing idiopathic generalized epilepsies may also respond to the VNS, as reported by Kostov et al., who reported an average 61% decrease in seizure frequency in 12 of these patients undergoing VNS, with concomitant reduction in the medication they had been on. 

Perhaps, the great lesson that we have learned from our cases comes from patient #5, in whom calibration of titration was delayed by the onset of dyspnea, but later on, when possible, led to an improvement in seizure frequency and severity, as would be expected by the current literature, which has reported a greater efficacy in patients with partial epilepsy.

In addition to drug or surgical refractoriness, there are other indications for VNS. Patwardhan et al. described the case of a 30-year old patient in whom phenytoin, valproic acid, topiramate and carbamazepine were withdrawn due to Stevens-Johnson syndrome, who went into status epilepticus. After nine days of barbiturate coma, the patient underwent VNS implantation, which allowed total seizure control for 19 days. The association of VNS, phenobarbital and levetiracetam allowed the patient to be discharged seizure-free. Indeed, another case of status epilepticus treated with VNS had been previously described in a 13-year old patient. 

An indirect measure of efficacy is the lower utilization of health services by these patients. We observed this phenomenon in our population: our patient #1 had a 70% decrease in the frequency of his visits; patients #1 and #2, who were usually admitted to the hospital because of recurrent seizures (one to several episodes of status epilepticus), no longer require hospital care. After implantation and calibration of the VNS, our patients #2 and #4 stopped attending scheduled visits and attended follow-up visits only when summoned.

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* Programming intervals can vary according to tolerability during the rump up.
** Pulse width and frequency can be reset to the previous values depending on tolerability.
*** Clinical outcomes are evaluated at each visit, and programming intervals can be increased.

Fig 2. Neurostimulator Programming Flowchart
Other effects of VNS

Another aspect of VNS therapy is the improvement in mood, cognition and quality of life, in which our sample, though small, echoes the literature. Of our patients, two showed, in addition to the reduction in seizures, a marked antidepressant effect, and, despite being previously bound to wheelchairs, started doing efforts to walk again after VNS. However, two of our patients showed a slight increase in anxiety-related complaints, which we attribute to increased autonomy and greater exposure to daily life situations.

Neurostimulator calibration

Heck et al. described in detail the recommendations for neurostimulation equipment calibration. The same group examined 154 patients in different calibration parameters, such as pulse duration, frequency, time online, time off and output current, and the relationship of these parameters with the reduction in the number of seizures. In their study, there were no evident changes in the reduction of seizures with different parameters, however, in a subgroup with time off ≤ 1.1 minute, the average reduction changed significantly from 21 to 39%.

Our strategy is to change one parameter at a time to monitor the response which particular change is more appropriate.

The interval between the adjustments is of 15 days until a set of parameters is reached, when the patient begins to show clinical responses. We found that when approaching a current intensity close to 1.5 mA (1.0–1.5 mA), it is desirable to increase the interval between the adjustments to allow a better observation of the clinical response to the new parameters. Different patients may respond better or worse with more or less current; there is not a standard current for all patients. It is important to note that excessively large intervals may bring unnecessary delays in seizure control. During the visits, the patient should be observed for their seizures, as well as in issues related to their quality of life, such as behavior, way of relating, mood and concentration, among others.

Adverse events

Ben-Menachem summed-up side-effects of VNS stimulation in some studies and divided them in early complications of VNS implantation and in side-effects seen in long-term VNS stimulation. Among the early complications of VNS implantation, they described infections (3 to 6%), laryngeal irritation are known side effects of VNS, however respiratory changes during sleep were poorly described in literature. Malow et al. studied four epileptic patients with previous obstructive sleep apnea who have been treated with VNS and concluded that these symptoms may worsen. To eliminate this problem, the authors suggest reducing the frequency of the stimulus without changing the other parameters.

Although none of our patients have presented apnea, patients #1, #4 and #5 had transient cough or dysphonia at each calibration, and patient #5 presented dyspnea, which could be circumvented by a slower neurostimulation calibration parameters.

Post-operative infections can occur between 3–6%, but most are treated with oral antibiotics, and it is rarely necessary to remove the generator or the electrodes. Patient #4, despite good reduction in seizure frequency and independence gain, required the device explantation due to infection. This patient had cognitive impairment, a condition that may have contributed to the contamination of the surgical wound. An irrigation system with vancomycin and Ringer lactate solution was described by Liechty to prevent the removal of the generator.

In conclusion, our data set echoes and adds to previous experience, showing significant gains in terms of reduction in seizure frequency, decreased use of health services, autonomy and quality of life. Adverse events related to neurostimulation were transient and circumvented by the temporary reduction in neurostimulation parameters. In one case, the explantation of the neurostimulator was required due to local infection. The set of outcomes shows that VNS treatment had a positive impact on seizure control and in the lives of our patients.

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2. Kwan P, Sperling MR. Refractory seizures: try additional antiepileptic drugs (after two have failed) or go directly to early surgery evaluation? Epilepsia 2009;50:S57-S62.


