

BRAIN STIMULATION FOR TEMPORAL LOBE EPILEPSY

Long-term Amygdalohippocampal Stimulation for Refractory Temporal Lobe Epilepsy

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Short-term deep brain stimulation (DBS) recently has been shown to be efficacious in refractory temporal lobe epilepsy. We (a) evaluated long-term DBS in medial temporal lobe structures in patients with normal magnetic resonance imaging (MRI) findings and (b) investigated the use of long-term DBS electrodes for the localization of the ictal onset zone before DBS. In three patients with complex partial seizures (CPSs), DBS electrodes were implanted in the amygdalohippocampal region to identify and subsequently stimulate the ictal onset zone. CPSs were compared before and after prolonged DBS. Side effects were carefully monitored. DBS electrodes yielded high-quality electroencephalogram recordings showing unilateral seizure onset in medial temporal lobe structures. For all patients, unilateral amygdalohippocampal stimulation was performed. After a mean follow-up of 5 months (range, 3–6 months), all patients had a greater than 50% reduction in seizure frequency. In two patients, antiepileptic drugs could be tapered. None of the patients reported side effects. This open study demonstrates the feasibility of consecutive electroencephalographic recordings and DBS in medial temporal lobe structures using DBS electrodes. These results prompt further studies in a larger patient population to establish the efficacy and safety of long-term DBS as an alternative treatment for refractory temporal lobe epilepsy.

globus pallidus is used to improve symptoms in movement disorders that are inadequately controlled by medication. Stimulation of various brain targets has been investigated for the suppression of seizures, but many questions remain to be answered regarding the feasibility, efficacy, and safety of brain stimulation for the treatment of epilepsy. In the present article, Vonck et al. advance the understanding of all these issues with regard to amygdalohippocampal stimulation for the treatment of medically refractory, unilateral, magnetic resonance imaging (MRI)-negative temporal lobe epilepsy.

Three patients with pharmacoresistant epilepsy with features suggestive of medial temporal lobe seizure origination who had negative MRI findings comprise the report. These patients required invasive monitoring as part of their evaluation for possible resection of their epileptogenic focus, but rather than undergoing implantation of conventional depth electrodes, they instead received commercially available leads used for deep brain stimulation (DBS) for recording and later stimulation purposes. Two quadripolar DBS leads (each spanning 10.5 mm from distal to proximal contacts) were implanted into each medial temporal region, with one placed more anteriorly into the amygdala and the other more posteriorly into the anterior aspect of the hippocampus. These, and supplemental standard subdural strip and/or grid electrodes, were used to obtain ictal recordings in the epilepsy monitoring unit with patients receiving tapered antiepileptic drug (AED) regimens.

Once adequate localizing information was captured and the diagnosis of temporal lobe epilepsy was confirmed, subdural strip and grid electrodes were removed, and an external pulse generator was used to deliver electrical stimulation unilaterally to the epileptogenic medial temporal region. Continuous stimulation was provided through both the amygdalar and hippocampal DBS leads; initial stimulation parameters were frequency of 130 Hz, pulse width of 450 μ sec, DBS lead contact configuration of two adjacent bipolar pairs for each lead, and amplitude of 1.0 V (set to be at a voltage just subthreshold to the appearance of stimulation artifact recorded from the hippocampal contacts when stimulation was delivered via the amygdalar contacts).

As a gauge of potential efficacy, the interictal spike count from the stimulated area was assessed for a 1-hour period each

COMMENTARY

Neurostimulation is an evolving therapy used to treat a variety of neurologic disorders. Vagus nerve stimulation is used routinely to treat pharmacoresistant epilepsy, and deep brain stimulation of the thalamus, subthalamic nucleus, and

day (during which time stimulation was discontinued) and compared with the prestimulation baseline count. If a greater than 50% reduction in spike count occurred during 7 consecutive days, then patients went on to receive implantation of the pulse generator and long-term stimulation. If this criterion was not met, stimulation parameters were adjusted until the spike count did decrease by more than 50%. Patients were maintained on the prolonged tapered medication regimen when possible. Seizure counts, adverse effects, and neuropsychological function were monitored.

Analysis of the ictal recordings demonstrated the capability of therapeutic DBS leads to record a high-quality signal. Two patients had a unilateral focal amygdalohippocampalictal onset zone, and one patient was found to have seizures arise unilaterally in a regional medial temporal lobe pattern. With the initial stimulation parameters, two patients realized a greater than 50% reduction in the interictal spike count. The third patient reached this level of apparent spike suppression after the stimulation frequency was increased to 200 Hz. With long-term stimulation by the implanted pulse generator, all patients realized a reduction in baseline seizure frequency while taking a reduced medication regimen. Complex partial seizure reduction rates at 4 to 6 months of follow-up were 97% for patient 1, 83% for patient 2, and 50% for patient 3. No stimulation-induced adverse events were identified.

Vonck et al. demonstrate in this report the feasibility of using DBS leads for both diagnostic recording purposes and for short- and long-term therapeutic stimulation of the medial temporal region. This has important practical ramifications, in that the number of brain penetrations to which a patient would be subjected is minimized, because diagnostic and therapeutic electrodes become one and the same. Further, permanently implanted therapeutic electrodes could be used to monitor and track seizures (particularly if stimulation is not delivered through them continuously but rather intermittently or contingently).

In this report, the authors suggest the ability of medial temporal stimulation to provide short-term therapeutic efficacy. Acute stimulation reduced the rate of medial temporal epileptiform discharges; although not demonstrating direct therapeutic efficacy, this finding might represent a surrogate marker for clinical effectiveness. More important, though, prolonged stimulation significantly reduced the frequency of sei-

zures at 4 to 6 months of follow-up. The durability of this response over time remains to be determined. Certainly, in the common syndrome of unilateral medial temporal lobe epilepsy to which this report applies, it will be important to assess the long-term efficacy and safety of stimulation in a much larger cadre of patients, and for the subset of patients with bilateral independent temporal lobe epilepsy (a group currently with frustratingly limited therapeutic options) to determine whether stimulation of medial temporal structures (whether unilateral, alternating bilateral, or simultaneous bilateral stimulation) is efficacious and cognitively tolerated. Particularly for syndromes with high rates of seizure freedom after resective surgery, it will be important to determine whether stimulation strategies can render patients completely seizure free.

The patients in this study received virtually continuous unilateral medial temporal stimulation, and no adverse effects were noted. Further careful studies of the neurologic and cognitive effects of prolonged brain stimulation, especially of bilateral stimulation, must be pursued to understand what deleterious effects might occur with this therapy to develop stimulation paradigms with the most favorable therapeutic window.

Although the stimulation parameters used in this report appeared to be efficacious, their selection was relatively arbitrary. Little is known about which stimulation parameters (amplitude, pulse width, frequency), electrode configurations, and paradigms (continuous vs intermittent vs contingent delivery of stimulation) are optimal. Systematic study of these issues is mandatory.

Even more fundamentally, determination of which localization-related and/or generalized epilepsy syndromes are the most responsive to brain stimulation and which brain targets are best suited for seizure detection and therapeutic stimulation in a given syndrome must occur if neurostimulation strategies are to be applied successfully.

The findings by Vonck et al. are promising and pave the way for future studies, in which additional patients will need to be assessed over longer periods of follow-up to understand better a number of critical issues.

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