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Responsive Neurostimulation in Epilepsy: Wall to Block Seizures or Bridge to Resection?

Mesial Temporal Resection Following Long-Term Ambulatory Intracranial EEG Monitoring With a Direct Brain-Responsive Neurostimulation System

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Objective: To describe seizure outcomes in patients with medically refractory epilepsy who had evidence of bilateral mesial temporal lobe (MTL) seizure onsets and underwent MTL resection based on chronic ambulatory intracranial EEG (ICEEG) data from a direct brain-responsive neurostimulator (RNS) system. Methods: We retrospectively identified all patients at 17 epilepsy centers with MTL epilepsy who were treated with the RNS system using bilateral MTL leads, and in whom an MTL resection was subsequently performed. Presumed lateralization based on routine presurgical approaches was compared to lateralization determined by RNS system chronic ambulatory ICEEG recordings. The primary outcome was frequency of disabling seizures at last 3-month follow-up after MTL resection compared to seizure frequency 3 months before MTL resection. Results: We identified 157 patients treated with the RNS system with bilateral MTL leads due to presumed bitemporal epilepsy. Twenty-five (16%) patients subsequently had an MTL resection informed by chronic ambulatory ICEEG (mean = 42 months ICEEG); follow-up was available for 24 patients. After MTL resection, the median reduction in disabling seizures at last follow-up was 100% (mean: 94%; range: 50%-100%). Nine (38%) patients had exclusively unilateral electrographic seizures recorded by chronic ambulatory ICEEG and all were seizure-free at last follow-up after MTL resection; 8 of 9 continued RNS system treatment. Fifteen (62%) patients had bilateral MTL electrographic seizures, had an MTL resection on the more active side, continued RNS system treatment, and achieved a median clinical seizure reduction of 100% (mean: 90%; range: 50%-100%) at last follow-up, with 8 of 15 seizure-free. For those with more than 1 year of follow-up (N = 21), 15 (71%) patients were seizure-free during the most recent year, including all 8 patients with unilateral onsets and 7 (54%) of 13 patients with bilateral onsets. Significance: Chronic ambulatory ICEEG data provide information about lateralization of MTL seizures and can identify additional patients who may benefit from MTL resection.

Commentary

Approximately 30% to 40% of individuals suffering from epilepsy have seizures that are resistant to medications, and a large subset of these patients have mesial temporal lobe epilepsy (MTLE)—the most common focal epilepsy syndrome. Most of the time, the seizures originate from only one temporal lobe. This is good news for patients, because unilateral MTLE is one of the most surgically remediable epilepsy disorders, with one half to two-thirds of patients achieving long-term seizure freedom after resection or ablation of the mesial temporal lobe structures.[1,2] However, the subset of patients who do have bilateral seizure onset are much more challenging to treat. Prior to the introduction of neuromodulation therapies, there were few safe surgical options for bilateral MTLE. Today in the United States, implantation of a responsive neurostimulation (RNS) device has become a common surgical approach to treat bilateral MTLE, with electrodes placed into the mesial temporal structures for constant recordings and closed-loop stimulation. Long-term studies suggest that patients treated with RNS for MTLE experience a reduction in median seizure frequency of approximately 50% after 2 years and 70% after 6 years of therapy, with 15% of patients achieving at least a year of seizure freedom.[3,4]

Nearly all US epilepsy centers rated level 4 by the National Association of Epilepsy Centers now have experience with RNS for seizure reduction in MTLE. However, the present study by Hirsch and colleagues explores a different benefit of the device: long-term ambulatory intracranial EEG monitoring

that can be used as a bridge to resection.[5] The authors examined 157 patients at 17 centers who received RNS implants for presumed bilateral MTLE, and identified 24 who eventually underwent unilateral temporal lobe resection guided by the intracranial EEG data, and who had postsurgical follow-up. These included 22 patients who underwent anterior temporal lobectomy, and 2 who received selective amygdalohippocampectomy. Interestingly, 9 patients were found to have exclusively unilateral seizures after RNS monitoring, suggesting that at least 5% of individuals in the entire cohort may have been misdiagnosed as having bilateral MTLE. Five of these 9 individuals did not have intracranial EEG prior to RNS placement, which raises the point that some seizures in MTLE may rapidly spread to the contralateral temporal lobe, and be misinterpreted as originating contralaterally based on scalp EEG alone.[6] The other 15 patients did have bilateral MTLE, but more than 90% of seizures originated on one side, so a palliative resection on that side was ultimately pursued. After resection, all but one patient continued to receive treatment with RNS, and many of these individuals continued to have bilateral stimulation, with the electrode ipsilateral to resection either pulled back to the posterior hippocampus or swapped out for a temporal neocortical strip electrode. Overall, of the 21 patients with more than 1-year follow-up after resection, 71% were seizure free—a success rate comparable to resection as an initial procedure for unilateral MTLE.

Now that it is clear that RNS can be used for long-term ambulatory intracranial EEG to guide future resection, should we be considering this approach in more patients? In certain patients with questionable signs of bilateral epileptogenicity, making a definitive diagnosis of unilateral versus bilateral MTLE can be challenging. In one study of RNS patients implanted in the bilateral temporal lobes, approximately one-third of patients required more than 1 month of recordings before capturing bilateral seizures.[7] Clearly, this suggests that contralateral seizures may be missed during inpatient intracranial EEG sessions of only 1 to 3 weeks. Furthermore, the frequency of seizures from either side can be difficult to ascertain during a short inpatient stay, and seizures experienced during a rapid medication wean in the hospital may not always resemble those experienced in a patient's natural setting.[8] Also, it is possible that a subset of surgical failures in MTLE are due to undiagnosed contralateral epileptogenicity. In a recent magnetic resonance imaging study of patients undergoing MTLE surgery, abnormal functional connectivity involving the contralateral hippocampus was found to be associated with seizure recurrence.[9] A better appreciation of contralateral hippocampus pathophysiology may aid treatment decisions in some MTLE patients. This understanding may be improved by neuroimaging or intracranial EEG network studies,[10] or by using an implant to gather long-term ambulatory data.

Overall, the study by Hirsch and colleagues demonstrates that when considering neuromodulation treatments for epilepsy, the potential diagnostic value of the device should be considered along with the therapeutic benefit. There are limits to current technology, including the number of electrodes implanted, the amount of data stored, and risks inherent to an implanted intracranial device. Furthermore, seizure outcomes with neuromodulation for epilepsy do not rival those after resection, as complete seizure freedom remains uncommon. Nevertheless, as we continue to improve current neurostimulation treatment paradigms and uncover novel technologies for neuromodulation, the diagnostic value of long-term ambulatory intracranial EEG must be carefully considered.

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