Brain Stimulation Evolves for Refractory Epilepsy

BY MICHELE G. SULLIVAN
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MADRID — Deep brain stimulation shows considerable promise for reducing intractable seizures in patients who are not candidates for epilepsy surgery, even though there have been few large-scale controlled trials to back up the practice.

"We have no idea what the best stimulation parameters are, we don't know whether to stimulate in response to epileptiform activity or continuously, and, of course, the search for the optimal target is ongoing," Dr. Paul Boon said at the annual congress of the European Federation of Neurological Societies. "Most of our information has come from uncontrolled studies and case reports, which included about 115 people worldwide."

Now, data from three new or upcoming studies might help shed light on some of these questions, said Dr. Boon of University Hospital Ghent (Belgium), where he and his colleagues are leaders in researching an epilepsy application for DBS.

'We got a 70% response rate, with no significant adverse events or changes in memory,' suggesting that DBS of the medial temporal lobe is safe and effective.

Some of the earliest studies, in the 1980s and early 1990s, used the electrodes in the brain's cerebellar regions, but with very little effect, so the cerebellum is no longer considered a target. The caudate nucleus and centromedial nucleus of the thalamus have also been examined as possible targets, but in very small numbers of patients and with varying results, said Dr. Boon.

The most promising approach to date is bilateral stimulation of the anterior thalamic nucleus, he said. Early uncontrolled studies of this application had small patient numbers, but their success led to the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy trial of 110 patients with medically refractory partial-onset seizures.

All of the patients received the implants; for the first 3 months, only half of the patient had their stimulators turned on. After this blinded treatment phase, all of the patients received neurostimulation. The results are due to be presented at the American Epilepsy Society meeting in Seattle in December. By way of detailing his financial conflicts of interest, Dr. Boon said in an interview that Medtronic Inc., the company that makes DBS hardware, has been and is providing devices and electrodes in support of the pilot trial, and has provided an educational grant.

The medial temporal lobe and the hippocampus are other potential targets. Last year, Dr. Boon and his colleagues published a study of 12 patients with refractory temporal lobe epilepsy, who were also candidates for surgery. Instead of implanting recording electrodes during the presurgical period, they implanted DBS electrodes in the medial temporal lobe.

"We aimed to adjust the simulation parameters to get a 50% reduction in spikes for 7 consecutive days," he said. "If the patient achieved that, then we went to chronic stimulation, and if they did not achieve that, then we adjusted the parameters until we met those criteria. If the patient still didn't achieve the reduction, then we removed the electrodes and proceeded to surgery."

Of the 12 patients, 10 underwent long-term DBS, and 2 had the resection. After a mean follow-up of 31 months, both of the surgical patients were seizure free. One of the DBS patients had a seizure reduction of more than 90%; five had a reduction of at least 50%, and two had a reduction of 30%-40% (Epilepsia 2007;48:1551-60).

"We got a 70% response rate, with no significant adverse events or changes in memory," he said. "This shows that DBS of the medial temporal lobe is safe, feasible, and effective."

Dr. Boon and his group are also seeking to recruit 45 patients for an upcoming study in which they will compare DBS of the hippocampus with medial temporal lobe resection or with hippocampal DBS delayed for 6 months after implantation. The 1-year CoRaStiR (Controlled Randomized Stimulation Versus Resection) trial will also be sponsored by Medtronic.

Researchers believe that DBS controls seizures by desynchronizing synchronized high-voltage cortical discharges. During chronic DBS, the stimulation is applied constantly to the epileptogenic focus, regardless of the area's own discharge.

However, there is some evidence that stimulation only in response to epileptiform activity might be more effective. This "closed-loop" stimulation would require a device that could read and analyze brain waves and then "decide" what type of stimulation to deliver—a process that clearly presents a technological challenge.

Early external devices were tested in small numbers of patients in the late 1990s and early 2000s. More recently, a California-based company, NeuroPace Inc., has developed the RNS System, which includes fully implantable intracranial components as well as external products, he said.

The device consists of an implanted neurostimulator with one or two strip leads that can be placed in different areas of the brain to allow activity to be monitored and controlled. An external programming device allows the stimulator to detect predetermined electrographic patterns; the physician can also program the type of response that the device delivers.

A treatment can consist of up to five different stimulation parameters delivered sequentially. After each stimulation, the device tries to detect further epileptiform activity; it will deliver the next stimulation if such activity is present, or cease stimulation if there is no epileptiform discharge.

In a feasibility study of 65 patients, the system was deemed safe. In a preliminary analysis of 24 patients, the response rate (defined as a seizure reduction of at least 50%) was 43% for complex partial seizures and 35% for total disabling seizures, which included simple partial motor, complex partial, and secondarily generalized tonic-clonic seizures (Neurotherapeutics 2008;5:68-74).

NeuroPace is recruiting up to 240 patients with refractory partial-onset seizures for a randomized, sham-controlled trial of the system, with 2-3 years of follow-up. During the initial 4-month double-blinded phase, half of the patients will have the system turned on and half of them will have it remain off, after which all of the patients will receive stimulation. ■

Cortical Malformation Type Determines Deficits in Epilepsy

BY MICHELE G. SULLIVAN
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MADRID — Patients with microcephaly, hemimegalencephaly, tuberous sclerosis, and polymicrogyria have an earlier onset of epilepsy and are more likely to experience comorbid neurologic and cognitive deficits than are patients with other malformations, according to an observational study performed in Austria.

"In comparison, patients with focal cortical dysplasia very rarely had cognitive impairment or neurologic deficits," Dr. Giorgi Kuchukhidze said at the annual congress of the European Federation of Neurological Societies.

Dr. Kuchukhidze, a neurologist at the Medical University of Innsbruck, Austria, discussed the results of his prospective study of 237 epilepsy patients, all of whom were seen at the university's tertiary epilepsy referral center. All of the patients had a cortical malformation as the root cause of their seizure disorder.

"Certain EEG patterns and clinical pictures create a strong suspicion of malformations of cortical development," he said. However, the prognosis for such patients is not always grim. "Up to 70% of patients with these malformations can become seizure-free after antiepileptic surgery."

The most commonly observed malformations in the cohort were focal cortical dysplasia (62; 26%) and polymicrogyria (49; 21%). There were also 30 patients with periventricular nodular heterotopia, 27 with ganglioglioma, 26 with tuberous sclerosis, 14 with microcephaly, 13 with hemimegalencephaly, 8 with dysembryoplastic neuroepithelial tumor, 6 with subcortical laminar heterotopia, and 2 with lissencephaly/pachygyria.

The mean age of seizure onset was 12 years, but this varied with the type of malformation. "The majority of patients with microcephaly, hemimegalencephaly, and tuberous sclerosis had seizure onset during the first year of life, whereas in most of the patients with focal cortical dysplasia, ganglioglioma, and periventricular heterotopia, the seizures manifested during the second decade of life," Dr. Kuchukhidze said.

Delayed developmental milestones were seen in 39% of the patients, and various levels of cognitive impairment were present in 43%. "These were apparent in the majority of patients with microcephaly, tuberous sclerosis, hemimegalencephaly, and polymicrogyria," he said.

Generalized seizures—either West's or Lennox-Gastaut syndrome—were significantly associated with microcephaly, tuberous sclerosis, and diffuse focal lesions. Temporal lobe epilepsy was significantly associated with single focal lesions and focal cortical dysplasia. Medically refractory epilepsy was present in 150 patients (63%). Forty-three patients underwent epilepsy surgery, and 26 of them (60%) have been seizure-free for at least 1 year after the procedure. ■

DATA WATCH

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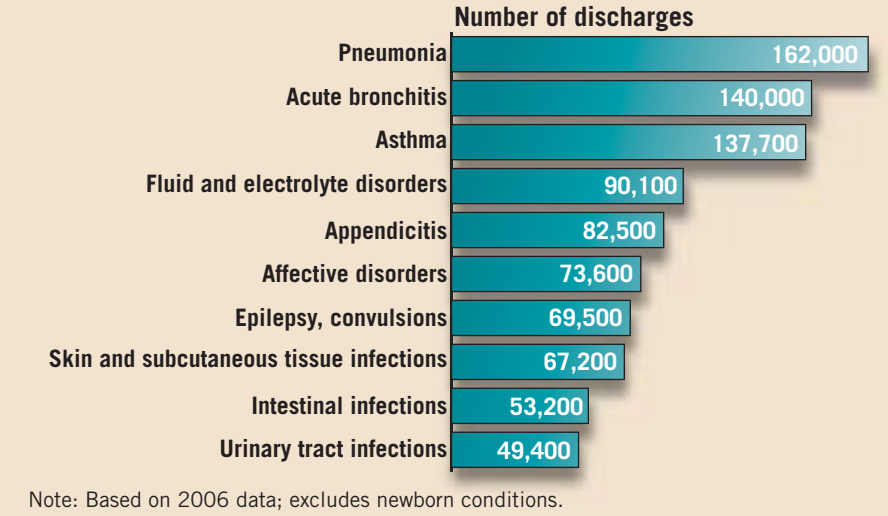

Note: Based on 2006 data; excludes newborn conditions.
Source: Agency for Healthcare Research and Quality

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