Research Into Seizure Prediction Devices Advances

No adverse events have been reported in the two ongoing phase III implanted device studies.

BY JEFF EVANS
Senior Writer

CHICAGO — Ongoing clinical trials for two implanted devices designed to interrupt or predict seizures herald an area of clinical research that has quickly gained ground during the last 5 years, Dr. Brian Litt said at the annual meeting of the American Neurological Association.

Research into seizure prediction, most of which has occurred in the past 15 years, has been "very controversial," mostly because of people getting too excited about findings very early on, said Dr. Litt of the departments of neurology and bioengineering at the University of Pennsylvania, Philadelphia.

Early studies were plagued by overreliance on abstract functions rather than on clinical physiological parameters, and they lacked statistical rigor. As a result, the databases were biased toward seizures because much of the data were taken from inpatients who had many seizures during hospital stays.

"Those data are not what it's like to live with epilepsy; you might have one seizure a month, you might have four a month. But clearly the preponderance of the data is interictal," he said.

A data set heavily enriched with seizures makes it much more likely that attempts to predict seizures at broad intervals will, in fact, detect a seizure. This made it impossible to reproduce the claims of seizure prediction that were announced in early studies.

"We also found that listening to patients was really important," Dr. Litt said, because many patients tell their physicians that sometimes hours or days before a seizure onset, they have a feeling—or prodrome—that tells them they are likely to have a seizure. And the patients may or may not have a seizure.

"The model [for predicting seizures] has to account for this," he said.

These lessons taught Dr. Litt and his colleagues that they were very unlikely to predict an exact seizure, but that it was likely they could identify periods of time in which the probability of a seizure's occurring is greatly increased.

No efficacy data are yet available for the two devices that are being tested in phase III trials, but no adverse events have occurred.

In Medtronic Inc.'s Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trial, about 150 adult patients with medically refractory partial-onset epilepsy will receive the Intercept Epilepsy Control System.

The implanted device, which bilaterally stimulates the anterior nucleus of the thalamus but does not sense or respond to EEG activity, will be turned on in some patients but not in others during the trial's double-blind phase. Medtronic decided to continue the SANTE trial after it recently passed its midterm analysis, according to Dr. Litt.

The Responsive Neurostimulator system from NeuroPace Inc. will be tested in about 240 adult patients to determine if it can reduce the frequency of medically uncontrolled and disabling partial-onset seizures.

All of the patients will be implanted with the device, which scans EEG recordings for particular patterns associated with seizure onset or impending seizures, and then stimulates epileptogenic foci through intracranial electrodes. Only some patients will have the device turned on during the double-blind phase of the randomized trial.

In a safety study of about 50 patients with more than four seizures per month who were implanted with the Responsive Neurostimulator, 43% of those with complex partial seizures and 35% of those with disabling motor seizures had a 50% or greater reduction in seizures, Dr. Litt said.

"Is this a home run? No. Does it mean that it's effective? No. Does it mean that there's proof of principle enough to perhaps go forward? I think it does," Dr. Litt said.

"Remember, this is a first-generation device. Judge this as a work in progress, like the first pacemaker," he added.

Dr. Litt has contributed patents through the University of Pennsylvania for NeuroPace's Responsive Neurostimulator device. He is a consultant to BioNeuronics Corp., and he helped to found BioQuantix Corp. through the University of Pennsylvania.

Major questions still remain in understanding and mapping epileptic networks in the brain, such as where to place electrodes, where to sense seizure onset, and where to stimulate the brain. Researchers also want to know how seizures are generated over time.

To answer these questions, Dr. Litt and his associates have examined seizures in patients with Responsive Neurostimulator devices, which save about a minute of data prior to stimulation and also for a short period afterward.

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Analyses of the 2-second period before a seizure began in thousands of events distinguished between effective and ineffective types of stimulation. For particular stereotyped seizure onsets, the researchers used specific characteristics of synchrony, frequency of activity, and the relationship between the stimulus and the seizure waveform to determine if stimulation would be effective or not.

"The bottom line is that seizures in which stimulation is not effective are ones that are likely more evolved or perhaps began in a different place in the network and spread to these regions before the stimulation occurred," he said.

Although Dr. Litt's model for seizure generation has not been statistically proven, his group's research suggests that seizures "may occur in a reproducible cascade of events" in which there are periods of increased complex epileptiform activity in the hours or days before a seizure, followed in the 2 hours before the seizure by short seizurelike bursts of activity, or "seizlets," that last 1-5 seconds. These seizlets appear to build exponentially as the seizure approaches and activity ramps up.

To prove that this cascade of events exists, the investigators have built detectors that can quantitatively detect seizures in large chunks of data. When seizure and nonseizure events are mixed up and randomized, the two events can be distinguished with a certain latency, which increases as the likelihood of correctly predicting a seizure event increases, he said.

Other investigators who have collaborated with Dr. Litt may have come across a good method for validating the performance of algorithms that are designed to predict seizures.

This method also may have discovered the first evidence for the EEG patterns of a definitive preictal period (J. Neurophysiol. 2006 Oct. 4 [Epub DOI:10.1152/jn.00190.2006]).

Pinpointing the location of seizures has benefited from research using high-frequency EEG.

High-frequency EEG readings were not recognized as clinically significant until recent studies showed that the characteristic waveform flattening, or "electro-decrement," of intracranial EEG before a seizure is actually high-frequency activity that was filtered out by intracranial EEGs that were calibrated to filter settings of pen and paper EEG machines from the 1950s, Dr. Litt said.

For many seizures, a rise in high-frequency epileptiform oscillations can indicate an impending seizure 40 minutes in advance (Brain 2004;127:1496-506).

Investigations of the density of these high-frequency epileptiform oscillations during a period of time around specific electrodes in the brain have helped to map the distribution of nodes that are "heating up" before seizure onset, he explained.

These maps have suggested that the focal point of a seizure is not really like a single point, as was previously thought, but is "more like a cloud. It's areas that are buzzing and trying to initiate synchrony that seem to be going from one place to the other to generate the seizure, and which ones actually start the seizure may vary," he said. ■

Variant of MET Gene Linked to Increased Risk of Autism

BY DOUG BRUNK
San Diego Bureau

Researchers have discovered that a common genetic variant of the MET receptor tyrosine kinase on chromosome 7q31 is associated with a 2.27-fold risk of having autism.

This new finding corroborates other works in autism which "indicate altered organization of both the cerebral cortex and the cerebellum, both of which are disrupted in mice with decreased MET signaling activity," wrote the investigators, who were led by Daniel B. Campbell, Ph.D., of the department of pharmacology at Vanderbilt University in Nashville, Tenn.

"There is co-occurrence of autism with a number of neurological and cognitive disorders, including epilepsy, atypical sleep patterns, and mental retardation. Together with well known dysfunction of cortical information processing, the role of MET signaling in interneuron development is relevant as a central component of the hypothesized GABAergic pathophysiological changes in autism," Dr. Campbell and his associates said.

The MET gene, which is known for its role in cancer metastasis, is also involved in the regulation of the immune system and in gastrointestinal repair, the investigators said.

The researchers conducted genetic analysis of 743 families who had at least one child with autism (Proc. Natl. Acad. Sci. U.S.A. 2006 Oct. 19 [doi:10.1073/pnas.0605296103]). They found that people with two copies of the MET gene variant were 2.27 times more likely to have autism as were people in the general population.

The risk of autism among study participants who had only one copy of the genetic variant was also high: a relative risk of 1.67 compared with the general population.

In a statement about the study, the researchers noted that the MET gene variant is common, seen in an estimated 47% of the population. However, in the study, Dr. Campbell and his associates emphasized that having the variant is not a standalone marker for a diagnosis of autism.

"We hypothesize that the [variant] can, together with other vulnerability genes and epigenetic and environmental factors, precipitate the onset of autism," they said.

The study was supported in part by a grant from the National Institute of Mental Health and National Institute of Child Health and Human Development. ■