

# Time Will Tell If Gamma Knife Surgery Is Worth Possible Risks

BY BRUCE JANCIN  
Denver Bureau

BRECKENRIDGE, COLO. — Gamma knife surgery shows some promise for drug-resistant epilepsy, but the definitive proof of its effectiveness remains a few years away, C. Akos Szabo, M.D., said at a conference on epilepsy syndromes sponsored by the University of Texas at San Antonio.

Radiation-induced changes, both good and bad, require time to evolve. The durability of the improvement seen to date as well as the possibility of future late side effects remain open questions, explained Dr. Szabo, a neurologist who is director of the epilepsy surgery program at the university's South Texas Comprehensive Epilepsy Center.



**It may take 10 years of successful results for gamma knife surgery to gain acceptance.**

DR. SZABO

Gamma knife surgery—also known as stereotactic radiotherapy—has been around for a long time. Worldwide, 200,000 procedures have been performed, chiefly for treatment of benign and malignant brain tumors, trigeminal neuralgia, and vascular malformations. Only relatively recently have investigators pursued in earnest the gamma knife's potential as a less invasive therapy for epilepsy that spares patients the risks associated with craniotomy and cold-steel resective surgery.

Proposed candidates for gamma knife surgery have a single well-defined temporal lobe seizure focus. The procedure utilizes a collimator to focus a hemispheric array of 201 beams of gamma radiation from cobalt-60 sources on a 5,500- to 9,000-mm<sup>3</sup> targeted volume of brain tissue. The dose at the target margin is 24 Gy. The operation is done in a single sitting, with separate anterior and posterior exposures.

The sole reported prospective study of gamma knife surgery to date was conducted in Marseille, Prague, and Graz, Austria. It involved 21 patients with refractory mesial temporal lobe epilepsy deemed suitable for temporal lobectomy but who instead had stereotactic radiotherapy. One died of myocardial infarction, leaving 20 with 2-year follow-up.

"Of course, this type of study would have to go on for 10 years before it would gain any type of acceptance within the epilepsy surgery community," Dr. Szabo observed.

Targets of the focused radiation included the

anterior parahippocampus, head and body of the anterior hippocampus, the rhinal sulcus, and the basal and lateral amygdala.

The tricky thing about gamma knife surgery is the seizures don't begin to improve until 9-12 months later. During the interim they actually get worse; for the first months following surgery, patients may begin to have complex partial seizures rather than their usual simple partial seizures.

Still, at 2 years the median seizure frequency was reduced to 0.33 per month, compared with 6.16 per month before treatment, and 65% of patients were seizure free. Quality of life measures improved significantly (*Epilepsia* 2004;45:504-15).

With the target tissue's close proximity to the optic nerve, it was unsurprising that

8 patients in the European study had quadrant visual field defects resulting from the gamma knife. Another patient experienced narrowing of the visual hemifield, a more disabling side effect.

Radiation-induced brain swelling, often accompanied by extremely severe headaches, was a common late side effect, peaking in occurrence at 1 year.

Of gamma knife-treated patients, 62% required corticosteroids for this condition, and 15% were hospitalized. However, the brain swelling resolved over time, and at 2 years none of the study participants had any neuropsychologic impairment.

The big problem for proponents of gamma knife surgery, Dr. Szabo noted, is that conventional open temporal lobectomy is a relatively mature operation whose long-term benefits and risks are well documented.

A 2003 evidence-based practice parameter issued by the American Academy of Neurology concluded that two-thirds of patients become essentially seizure free following anterior temporal lobectomy, while 10%-15% are unimproved. Three percent of patients develop permanent neurologic deficits, and an equal percentage experience permanent cognitive or behavioral deficits.

Thirty-day mortality was 0.4% in the patient series analyzed by the AAN panel, but none of the deaths was deemed surgery related (*Neurology* 2003;60:538-47).

## Suicide Attempt May Precede First Seizure

NEW ORLEANS — Suicide attempt is associated with a fourfold increase in the risk of developing a first unprovoked seizure in adults and children older than 3 years, Dale Hesdorffer, Ph.D., said at the annual meeting of the American Epilepsy Society.

Major depression is associated with almost a doubling in the risk of first unprovoked seizure, she said.

"There's clearly an underlying susceptibility for all these

problems," said Dr. Hesdorffer of Columbia University, New York City.

"This has been shown in several studies, but we don't know what it could be. It's completely undetermined at this point."

Dr. Hesdorffer presented the results of an Icelandic population-based case-control study that compared the rates of depression and suicide attempt and the number of depressive symptoms in subjects with and

without a first unprovoked seizure. The study included 387 cases and 773 controls. Major depression prior to the onset of seizure occurred in 11% of cases and 6% of controls.

Among the cases, 6% had made a suicide attempt, compared with only 2% of controls. The association remained significant even after controlling for age, gender, number of depressive symptoms, and alcohol intake.

—Michele G. Sullivan

# Benign Rolandic Epilepsy: Less Than Benign After All?

BY BRUCE JANCIN  
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BRECKENRIDGE, COLO. — Benign rolandic epilepsy may not be so benign after all, C. Akos Szabo, M.D., said at a conference on epilepsy syndromes sponsored by the University of Texas at San Antonio.

It's true at least 90% of patients with this common and distinctive form of childhood epilepsy go into remission by their teenage years. But there is a subset, perhaps 10%, who develop deficits in verbal memory and language skills as well as behavioral problems including attention-deficit hyperactivity disorder (ADHD) and impulsivity, explained Dr. Szabo, a neurologist who directs the epilepsy surgery program at the university's South Texas Comprehensive Epilepsy Center.

The big question is: Are the interictal epileptic EEG discharges (IEDs) in children with benign rolandic epilepsy causally related to neuropsychiatric and behavioral problems, or are both the IEDs and the behavioral problems due to a common underlying neurologic dysfunction? The corollary issue is whether treating the IEDs with antiepileptic drugs (AEDs) will prevent these problems. The answers are unknown.

Relevant to these issues is a recent study by investigators at J.W. Goethe University in Frankfurt, Germany, reporting an increased prevalence of rolandic spikes in the EEGs of 483 consecutive children without epilepsy who met diagnostic criteria for ADHD as determined by experienced child psychiatrists, Dr. Szabo said.

Martin Holtmann, M.D., and his colleagues detected rolandic spikes in 6% of the ADHD patients, compared with 2% of a control group consisting of 3,726 normal children. Eighty percent with ADHD plus spikes had right-sided or bilateral epileptiform discharges.

ADHD in children with rolandic spikes was diagnosed at a significantly younger age than in those without EEG discharges. They were also more likely to be diagnosed with ADHD-combined type than ADHD-inattentive type. ADHD patients with rolandic spikes also were more likely to develop new-onset seizures during follow-up (*Epilepsia* 2003;44:1241-4).

The German investigators raised the possibility that rolandic spikes or their underlying causal defect might increase vulnerability to ADHD, advance onset of the behavioral disorder, or aggravate its course.

They added that the treatment implications of their findings remain unclear.

If ADHD symptoms in some patients are in fact related to their focal epileptic discharges, there is the possibility that antiepileptic drug therapy in lieu of or in combination with conventional stimulant therapy might ameliorate the neuropsychologic deficits of ADHD.

Another question worthy of prospective studies is whether long-term stimulant therapy might promote seizures in ADHD children with rolandic spikes.

Benign rolandic epilepsy is the most common epilepsy of childhood, accounting for roughly one-quarter of cases in school-aged children. Peak age of onset is 8-9 years. Although benign rolandic epilepsy clearly has a strong

genetic component, a recent twin study by investigators at the University of Melbourne (Australia) produced data disputing the long-held belief that it is inherited in autosomal dominant fashion (*Ann. Neurol.* 2004;56:129-32). Rather, it is probably a polygenic disorder, Dr. Szabo said.

It's called "rolandic" epilepsy because the clinical symptoms point to involvement of the lower portion of the central gyrus of Roland.

Common features include oropharyngeal somatosensory symptoms, facial motor seizures during drowsiness, and brief nocturnal generalized tonic-clonic seizures. Roughly two-thirds of patients experience 2-10 seizures in their lifetime.

The easily recognized EEG pattern shows centrottemporal high-voltage sharp waves with a transverse dipole activated by drowsiness and stage II sleep.

Dr. Szabo said he usually does not treat mildly affected children. Otherwise, monotherapy using agents effective for focal seizures is typically sufficient. Carbamazepine is the most widely utilized drug.

Europeans have reported excellent results treating affected children with sulthiame, a drug not marketed in the United States. ■

**If ADHD symptoms in some kids are related to focal epileptic discharges, the better therapy may be AEDs rather than stimulants.**