Managing Epilepsy II: Surgical Treatment of Epilepsy in Children

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10-20% of all epilepsy is intractable, that is, poorly controlled despite treatment with antiepileptic medications to therapeutic levels both singly and in combinations. Most intractable epilepsy begins during childhood. It has long been established that poorly controlled seizures have an adverse effect on cognitive and psychosocial development. In many cases when medications are not effective, surgery is a viable option. The preoperative evaluation involves video-EEG monitoring, high-resolution MRI, and detailed neuropsychological testing. Resection surgery is performed when the area of seizure onset is focal. Disconnection surgery such as corpus callosotomy is used if the seizures are generalized. Vagal nerve stimulation (VNS) is the procedure of choice if the area of seizure onset can not be localized or in many types of generalized seizures. Children have favorable outcomes from epilepsy surgery similar to those in adults.

Key Words: epilepsy surgery, focal cortical dysplasia, hemispherectomy, pediatrics, vagal nerve stimulation

With a prevalence of 1-2%, epilepsy is a common disorder.[10] A consensus conference on epilepsy surgery estimated that seizures are intractable in 10-20% of patients with epilepsy.[34] Until recently, the surgical treatment of epilepsy was centered on adults with complex partial seizures (CPS) of temporal origin. However, approximately 50% of seizures begin before the age of 5, and the incidence of seizures is highest during the first year of life.[10] It is common for the time from onset of seizures to surgical intervention to be 10 years or greater. As it has been demonstrated that children have good outcomes in similar proportions to adults following epilepsy surgery, the question arises as to whether a price is paid by the long delay between onset of seizures and successful treatment by surgery. The recent development of pediatric epilepsy centers has brought about a re-evaluation of these concepts. In many cases, surgery is now performed earlier and new techniques directed at the specific problems of children are being developed. It has become clear that children with epilepsy are not "little adults" and they benefit from a separate consideration of their needs.

This paper will discuss the differences between pediatric and adult epilepsy surgery, provide a rationale for early surgery, list criteria necessary for consideration of surgery, and describe the various surgical options.

Differences Between Pediatric and Adult Epilepsy Surgery

Seizure Types

CPSs associated with mesial temporal sclerosis (MTS) are by far the most common seizure type found in adults. While CPSs that originate in the temporal lobe also commonly occur in the pediatric population, especially in adolescents, there are other seizure types that are amenable to surgery in infants and children. CPSs of non-temporal origin occur more frequently in children and may be associated with area of focal cortical dysplasia (FCD) or low grade tumors.[15] Children with infantile hemiplegia, hemiconvulsion syndrome, usually caused by *in utero* infarction, present with focal motor seizures. Generalized seizures, especially akinetic (drop attacks) seizures are seen more commonly in children than adults and may be improved following corpus callosotomy.[17] Infantile spasms, until recently felt to be a generalized seizure associated with poor developmental outcome, have been shown, at least in some cases, to be amenable to focal cortical resection.[7] This would imply that infantile spasms are secondary generalized seizures caused by an abnormality that may be restricted to a single area of the cortex.

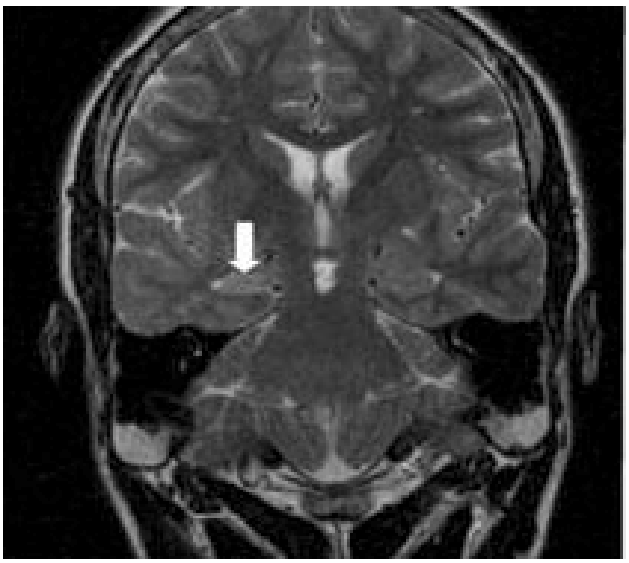

Figure 1. T2 weighted, coronal MRI of a 17-year-old male with a 7-year history of complex partial seizures. Area demonstrates shrunken right hippocampus with high signal consistent with mesial temporal sclerosis.

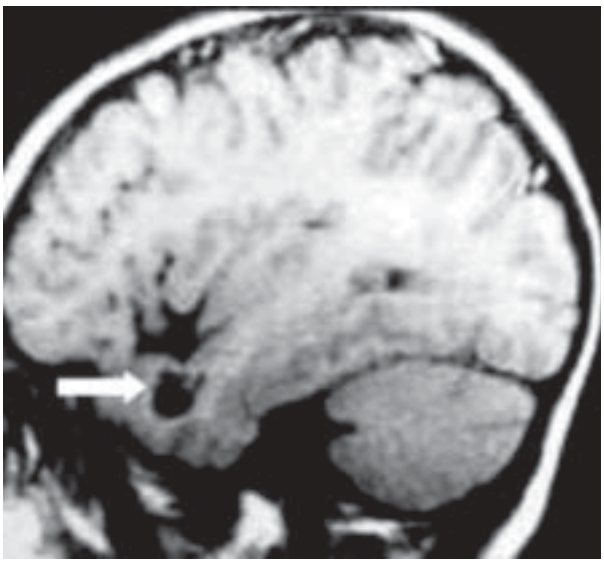

Figure 2. T1 weighted, sagittal MRI of 7-year-old male with one year history of complex partial seizures. Arrow points to low signal mass that was pathologically shown to be an oligodendroglioma.

Pathology

The most common pathology in adult seizure surgery is MTS. While not uncommon in adolescents **(Figure 1)**, MTS is uncommon in infants and children. "Lesional" epilepsy, that is, the occurrence of intractable seizures in the presence of intra-axial structural lesions, is common in children. Low grade tumors such as dysembryoplastic neuroepithelial tumor (DNET), ganglioglioma, astrocytoma, oligodendroglioma occur with regularity **(Figure 2)**.[2] Improved neuro-imaging (improved pulse sequences, 3D volumetric imaging, and high-resolution imaging) have allowed increased recognition of FCD.[25] As a result, the incidence of FCD has increased and it is now the most common focal developmental disorder in children with intractable epilepsy, occurring in 20-30% of all surgically treated cases of pediatric epilepsy.[11]

Extensive, hemispheric abnormalities present most commonly in childhood. These lesions may be developmental (hemimegalencephaly, Sturge-Weber syndrome), caused by *in utero* insults (hemiplegia, hemiconvulsion syndrome), or acquired (Rasmussen's encephalitis). Hemimegalencephaly is a disorder of neuronal migration that is limited to one hemisphere and frequently presents with intractable, focal motor seizures. The brain on the involved side is enlarged, and has thickened gray matter with poor gray-white differentiation. Sturge-Weber syndrome is a phakomatosis (abnormal development of the brain associated with a skin abnormality) and presents with a port-wine stain on one side of the face, and a cortical vascular malformation of the brain on the same side. Rasmussen's encephalitis is a progressive disease with seizures and progressive hemiatrophy of the brain thought to be viral or post-viral in origin that can lead to severe neurological and mental deficits if not adequately treated with medication or surgery.

Localization

Finding the area of the brain from which the seizures are originating is essential prior to a resection procedure. As seizures are an electrochemical phenomenon, the electroencephalogram (EEG), which records the brain's electrical activity, is the test that is essential for diagnosis and localization. While surface (scalp) EEG is a good first approximation, it is essentially an average of the electrical output of large areas of the brain. The EEG's ability to localize a seizure focus is also hampered by the relatively great distance from the recording electrode to the site of origin of the seizures. Because of the need to localize the seizure focus as accurately as possible, in many cases invasive procedures are performed to position a recording electrode as close to the suspected focus as possible. In adult epilepsy centers, this is often accomplished with the patient awake, on the operating table, just prior to the resection. Performing awake brain surgery with neuropsychological testing requires a level of cooperation of which most children are not capable. Accordingly, pediatric epilepsy centers tend to use long-term, invasive recording to determine the site of origin of the seizures and to allow stimulation studies to map eloquent areas of the brain (such as motor and speech cortex) that must be preserved during resection surgery. The most common technique for invasive recording is placement of grids with electrodes on the surface of the brain or depth electrodes within the brain.

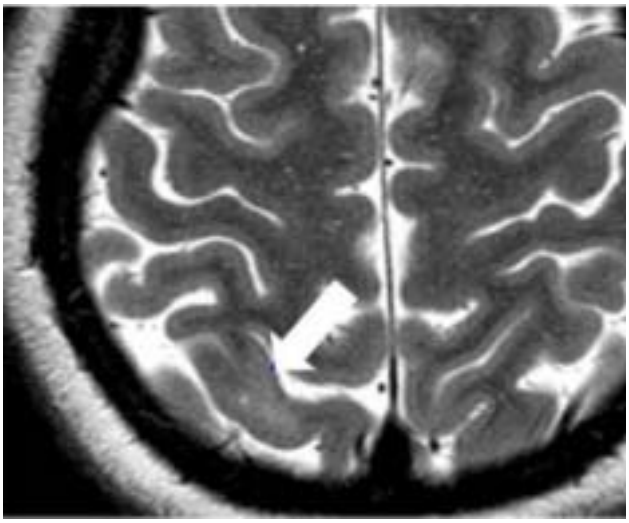

Figure 3. T2 weighted, axial MRI using a surface coil to demonstrate a small area of focal cortical dysplasia characterized thickening of a gyrus and indistinct gray-white junction (arrow).

Types of Surgeries

The most common procedure in adult and pediatric epilepsy surgery is a temporal lobectomy. There are, however, a higher percentage of extra-temporal seizures in children, necessitating an increased incidence of non-temporal resections in children. If eloquent cortex is involved and resection is not possible, multiple subpial transections may be performed.[13,14,30] This technique interrupts the "U" fibers that interconnect adjacent areas of cortex, and prevent spread of seizures. Corpus callosotomy and hemispherectomy are more commonly performed in children than adults.

Developmental Issues

The infant or child with intractable seizures does not face loss of employment or driving privileges as does the adult and this may make the adverse effect of seizures more difficult to appreciate, but prolonged or frequent seizures may damage the immature brain and cause loss of attainment of developmental milestones. Infantile spasms in particular are associated with poor developmental and neurologic outcomes.[7,42] In some cases, infantile spasms are of focal onset and may be cured by resection of the seizure focus with resulting normal outcomes.[7]

Rationale for Early Surgery

Intellectual and Biological Effects of Seizures

Children with uncontrolled seizures are at risk of injury, cognitive impairment, and abnormal psychosocial development.[22,26] These risks appear to be associated more with recurrent than prolonged seizures.[42] A study evaluating intelligence in groups of children with seizures has shown a decrease of an average of 10 intelligent quotient (IQ) points on follow-up.[5] This underlies the importance of controlling the seizure at the earliest possible stage.

Kindling refers to neural processes that cause lasting changes in brain function in response to repeated stimuli. Thus, recurrent seizures in children may result in subsequent decreases in seizure threshold, i.e.,repetitive seizures may "kindle" another source of seizure onset over time. While kindling occurs in mammalian species in experimental models, it is not clear if it occurs in humans.[32,33] The probability, however, is that it does, and this makes a powerful argument for early operative intervention when seizures are not well controlled by antiepileptic drugs (AEDs).

Psychosocial Effects of Seizures

A child with poorly controlled seizures is likely to be excluded from normal social situations, school and, eventually, vocational opportunities. A negative self-image becomes reinforced and frequently leads to psychosocial difficulties and dependence on public assistance as an adult.[35]

Neural Plasticity

As compared to the adult brain, the immature brain of the infant and young child has a remarkable ability for functional recovery following surgery.[23] The younger the child is, the greater the ability to recover. Thus, resection surgery may produce a better functional result if performed early in life.[41]

Outcome Analysis

While the reasons listed above build a strong case for performing epilepsy surgery in the pediatric population, they would lose validity if surgical outcomes were not as good in children as adults. Fortunately, this is not the case.

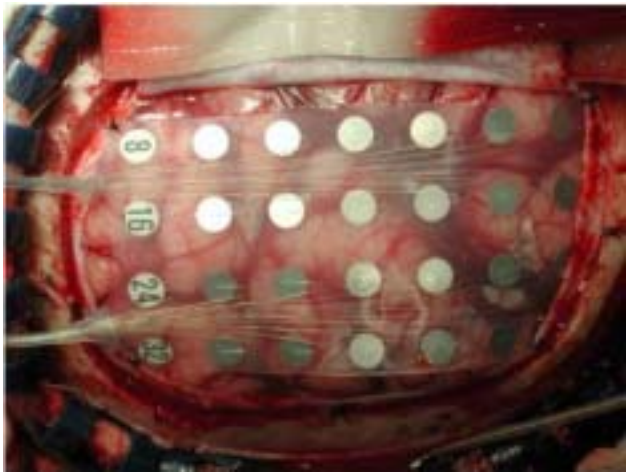

Figure 4. Frontoparietal craniotomy with 32 contact grid in place.

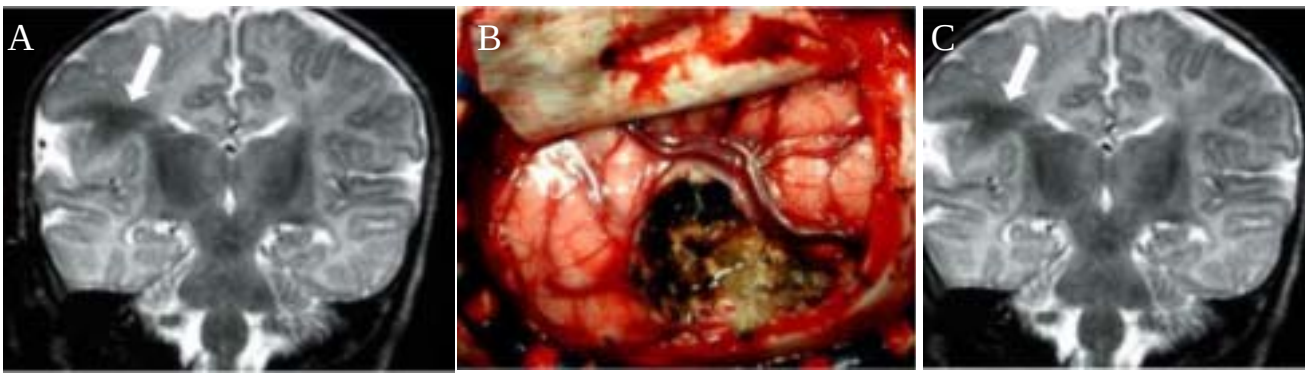

Figure 5. One-year-old child with focal cortical dysplasia and intractable complex and simple partial seizures. A: Preoperative T2 weighted, coronal MRI demonstrating low signal abnormality extending from the cortical surface towards the ventricle. This is consistent with Taylor's balloon cell FCD. B: Intraoperative photograph following resection of the area of seizure onset demonstrated by grid implantation and chronic monitoring. Known area of FCD behind the large vein was not resected because it was felt to be motor cortex. C. Postoperative T2 weighted image demonstrating residual FCD. An approximate 80% resection was performed. The child remains seizure free 3 years following resection.

Many studies have demonstrated essentially similar outcomes for seizure control following surgery when adult and pediatric patients are compared.[4,18,39] In addition, analyses demonstrate that when seizure control is achieved during childhood, the patient is more likely to be employed and productive than if control occurs as an adult.[38]

Who is a Candidate for Resection Epilepsy Surgery?

Intractability of Seizures

How many AEDs should be tried before the child is deemed medically intractable is dependant on the situation and remains a matter of judgment. Use of one AED produces good control in approximately 80% of cases. It is clear, however, that when one major AED fails, the chances that another AED will produce significant improvement are low and the chances of drug toxicity are high.[29,37] Many (and perhaps most) epileptologists believe that surgery should not be a last resort and that all available medications do not need to be tried prior to consideration of operative intervention. A reasonable course would be the use of three to four AEDs in monotherapy at maximal tolerated dosages. Currently in progress in the United States and Canada is a randomized trail of early versus late (after failure of two medications) surgery in patients 12 years of age or older.

Focal Onset of Seizures

By definition, seizures of generalized onset are not treatable by resection surgery (corpus callosotomy and vagal nerve stimulation remain options, see below). The diagnostic studies discussed below are used to determine the laterality (which hemisphere) and location of the seizure focus.

Resection of Seizure Focus will not Result in Neurologic Deficit

The goal of surgical resection is removal of the area generating the seizures while avoiding creation of a new neurologic deficit. Thus, prior to resection, it is important to determine the location of eloquent cortex and its proximity to the area of seizure onset. Exceptions are made when the seizures are frequent and/or prolonged and, if not controlled, will result in focal neurologic or cognitive abnormalities.

Evaluation

Clinical Evaluation

A thorough history, physical, and neurological examination is essential. The seizure pattern in many cases can predict the area of brain involved: Jeffersonian march of seizures for motor strip involvement, visceral aura and oro-alimentary automatisms (lip smacking) with temporal seizures. When focal abnormalities are present (e.g., hemiparesis, hemianopsia), they may provide clues to the location of the epileptogenic zone.

EEG

By showing spikes or sharp waves, an EEG remains the standard in the diagnosis and localization of seizures. However, a routine EEG usually consists of a 20-30 minute sample of brain activity and, especially when surgery is a possibility, prolonged video-EEG monitoring is essential. Inpatient EEG combined with constant video and computerized recognition of seizure onset allows recording of the actual event for which the child and family sought medical attention. Correlation between the clinical episode and EEG allows a definitive diagnosis between epileptic and non-epileptic events and in many cases can localize the area of the epileptic zone. Prolonged video-EEG monitoring may last for hours to weeks. A reduction or cessation of AEDs may be necessary to obtain seizures within a reasonable time. Sometimes seizure provoking maneuvers such as sleep deprivation may have to be done if seizures do not occur within a reasonable period of observation in the hospital.

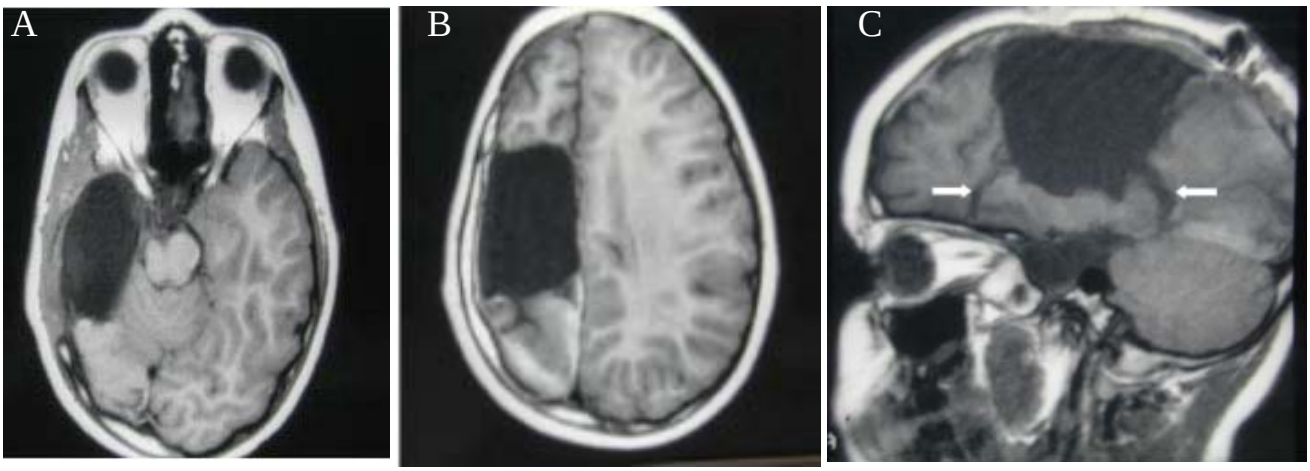

Figure 6. Components of functional hemispherectomy: (A) Extended temporal lobectomy; (B) Removal of central, suprasylvian cortex plus corpus callosotomy; (C) Disconnection of residual frontal and occipital lobes (arrows).

Imaging Studies

MRI has become the imaging modality of choice in the evaluation of seizures disorders. When the temporal lobe is the region of interest, thin coronal sections can reveal hippocampal atrophy with a high degree of sensitivity and specificity. Three currently used MR imaging techniques have improved detection of seizure foci: improved pulse sequences, 3D volumetric imaging, and high-resolution imaging.[9,25,28,40] Hardware developments in the early to mid 90's allowed the development of pulse sequences that have improved the ability to detect small areas of signal abnormality in a reasonable period of time. The development of the T2 fast spin echo (FSE) sequence was a significant improvement over conventional methods of dual echo spin echo T2 imaging sequences. The T2 FSE sequence allows rapid acquisition times with heavy T2 weighting that can better demonstrate an area of signal abnormality. The development of the fluid attenuation inversion recovery (FLAIR) sequence optimized detection of periventricular signal abnormality.

3D volumetric imaging has been available since 1995, but was not clinically useful because of long imaging and reconstruction times. The development of faster and more powerful MR gradients has dramatically reduced image acquisition times. A typical 3D data set now takes 7 minutes or less to perform. The value of volumetric imaging is in the excellent gray-white differentiation obtained at 1.2 mm thick slices. The data set can be reconstructed into any plane that facilitates detection of an area of abnormality.

When small areas of cortex must be optimally evaluated, the techniques of choice are surface coil imaging or multi-channel phased array, high-resolution imaging. These imaging tools increase the signal to noise ratio, and thus improve spatial resolution. The increased sensitivity afforded by these techniques allows detection of subtle areas of gray-white blurring or cortical thickening that can indicate such abnormalities as FCD **(Figure 3)**.

Functional Imaging

Positron emission tomography (PET) and single photon emission computerized tomography (SPECT) are useful adjunctive tools in determining areas of seizure onset by detecting changes in regional metabolism and blood flow induced by the seizure. PET uses 18-fluodeoxyglucose to measure glucose metabolism.[6] It is usually performed interictally and demonstrates areas of hypometabolism. SPECT is another nuclear medicine study that uses a radiotracer (usually 99Technetium) to determine regional blood flow. SPECT images are usually of lower quality than PET, and are most sensitive when performed ictally when the tracer is injected at seizure onset.[19,27]

Intracarotid Amobarbital Test (Wada Test)

Introduced by Wada in 1949, this procedure uses amobarbital, a short acting barbiturate, to selectively anesthetize each hemisphere. This is usually performed via transfemoral angiography with the patient awake. It is used to localize language and memory function. The Wada test requires a level of cooperation that young children may not be able to supply. Functional MRI (FMRI) may prove to be of value in determining areas of eloquent cortex in this situation.[16]

Neuropsychological Testing

These tests can add valuable information about lateralization of the epileptogenic region by comparing verbal and nonverbal components.[24] Memory tests are also of help in this situation. A trained pediatric specialist can test even young children. Postoperative testing can be helpful in assessing new deficits and in developing remediation programs.

Invasive EEG

While awake surgery is performed commonly in adult epilepsy centers, most children cannot provide the level of cooperation that is necessary. Thus, most pediatric epilepsy centers use some form of operatively placed invasive monitoring (epidural or subdural electrodes, depth electrodes) if further localization of the area of seizures focus is required after all neuro-imaging studies or if the cortex around the proposed resection area must be tested

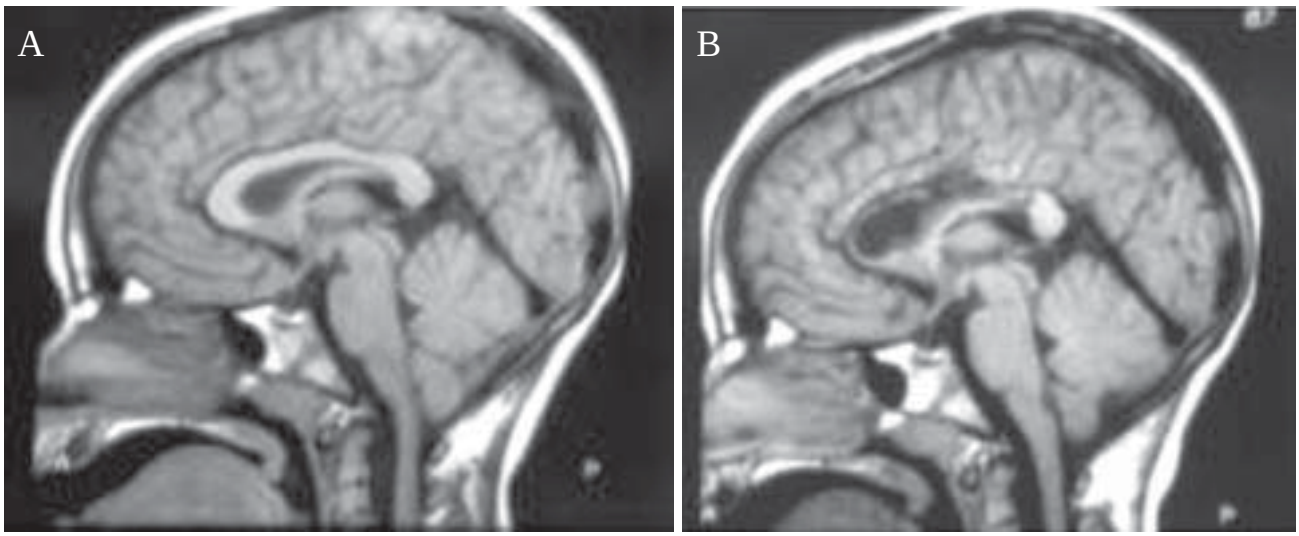

Figure 7. Ten-year-old child with mental retardation and atonic seizures. (A) Preoperative, mid-sagittal MRI demonstrating intact corpus callosum. (B) Postoperative image following anterior two-thirds resection of corpus callosum.

for function **(Figure 4)**.[42] After placement of the electrodes, the child is returned to the video-EEG area where monitoring and stimulation studies are performed over the next several days. The goal is to record 3 "typical" seizures and to map areas of eloquent cortex.

Surgical Procedures

Temporal Lobectomy

Because of the high epileptogenic potential of the hippocampus, the most commonly performed procedure in both adult and pediatric resection epilepsy surgery is temporal lobe resection. MTS is common in both groups, but children have a higher incidence of other pathologies such as tumors and FCD. A standard en bloc resection is the most common technique, but amygdalohippocampectomy with sparing of the lateral temporal lobe is also performed.[43] There is some evidence that amygdalohippocampectomy may not be as effective in children as adults, probably because of a higher incidence of lateral temporal abnormalities in the pediatric population.[8]

In patients with congruent preoperative diagnostic information that suggests temporal lobe origin of seizures, long-term seizure control (seizure free with or off AEDs) is 70-80%.[1, 31] An MRI defined preoperative lesion is a good predictor of seizure control. Potential complications specific to temporal lobectomy include diplopia from injury to the third or fourth cranial nerve, contralateral hemiparesis, and contralateral superior quadrantinopsia from injury to the inferior fibers of the optic radiations that enter the posterior temporal lobe.

Focal Cortical, Extra-temporal Resections

In children, the most common cause of a focal cortical, extra-temporal resection is FCD. As previously mentioned, the diagnosis of FCD has become more frequent with the advent of advanced MRI imaging and now accounts for 20-30% of the resection cases in children. In our experience, if the lesion is identified on MR, the epileptogenic area should be mapped using subdural grid electrodes prior to resection. We have used the Brain Lab Neuronavigational system to allow grid placement to cover the FCD plus a margin of uninvolved brain. The resection is based on the area of onset of seizures plus interictal spikes **(Figure 5)**. If the FCD involves eloquent cortex, resection is not attempted and consideration is given to multiple subpial transections (Morrell procedure). Using this technique, we have achieved a seizure free outcome in 66% (10/15) of cases (Hudgins, unpublished data).

Hemispherectomy

Hemispherectomy is the treatment of choice when the seizures occur broadly across one hemisphere, the contralateral hemisphere is uninvolved, and the child has a contralateral hemiparesis. The most frequent conditions are hemimegalencephaly, Rasmussen's syndrome, Sturge-Weber syndrome, and in utero hemispheric infarction. Many techniques of hemispherectomy have been utilized including total, functional, and peri-insular. We have primarily used the functional technique. This involves an extended temporal lobectomy, removal of the central supra-Sylvian cortex, corpus callosotomy, and disconnection of the remaining frontal and occipital lobes **(Figure 6).** This technique may need to be staged in infants because of blood loss. Hemispherectomy is one of the most effective procedures for intractable epilepsy with a success rate in properly selected patients of 80-90%.[12]

Corpus Callosotomy

Candidates for sectioning of the corpus callosum typically have generalized epilepsy and some degree of

Figure 8. Vagal nerve stimulator generator with attached electrodes.

mental retardation. The primary indication is atonic or myoclonic seizures ("drop attacks"). The procedure serves to prevent generalization of the seizure between hemispheres, and, in essence, converts a generalized seizure disorder into a partial one. The procedure can be performed through a small opening centered over the coronal suture. The right hemisphere is gently retracted laterally. The corpus callosum is differentiated from the cingulate gyrus, as it is whiter and smoother. During resection of the corpus callosum, effort is made to maintain the integrity of the underlying ependymal surface of the lateral ventricles **(Figure 7)**. Meticulous attention must be taken to avoid injury to the anterior cerebral arteries. A complication unique to corpus callosotomy is the split-brain syndrome. This refers to sensory disconnection and non-dominant hand apraxia in which the child has difficulty getting the hands to work together on a task. This tends to improve with time. Drop attacks can be diminished in approximately 80% of patients, and generalized seizures improved in 50%.[36]

Vagal Nerve Stimulation (VNS)

VNS is a relatively new procedure that has become the most widely used surgical procedure for intractable seizures **(Figure 8)**. The procedure involves implantation of a battery on the anterior chest wall and placement of electrodes around the left vagus nerve in the neck **(Figure 9)**. The left vagus nerve is used because the right vagus nerve is thought to be more involved in regulation of cardiac function. Electrical stimulation of the vagal nerve by the stimulator is transmitted to the nucleus tractus solitarius in the brainstem and then onward to many areas of the brain including the frontal lobes and the limbic system.[3]

During initiation of a seizure, cortical and thalamocortical interactions become synchronized. The seizure antagonism induced by the VNS is thought to be due to desynchronization of these interactions.[3] While it is known from both clinical and experimental studies that VNS induces changes in multiple neurotransmitters (serotonin, norepinephrine, gamma-amino butyric acid, and glutamate), the exact mechanism of its action is unknown.[21]

Candidates for implantation of a VNS are patients with intractable seizures who are not candidates for resection surgery. The VNS generator is surgically implanted into the chest, and is about the size of a stopwatch. The generator is attached to the left vagus nerve and electrical signals are released 24 hours a day, typically for 30 seconds every 5 minutes. The strength of the current is generally between 1 and 3 mA. An external device can adjust intensity, duration, and frequency stimulation parameters. If a patient senses a seizure coming on, he or she can pass a magnet over the device, activating a burst of energy that often stops the seizure. VNS therapy is thought to be effective in the treatment of both refractory partial as well as generalized epilepsy. The beneficial effect of VNS therapy improves with time. When 1864 patients were assessed 12 months after implantation, the median seizure reduction was 56%, an improvement over the 45% reduction seen 3 months following implantation.[20] It was also noted by early investigators that many patients had mood improvements following VNS placement.[20] Further investigation has recently resulted in approval in the United States for the use of VNS in the treatment of chronic and recurrent depression.

VNS is generally well tolerated, and stimulation associated adverse events are usually mild, transient and reversible upon reduction of output current and/or signal frequency. Patients typically accommodate many of the adverse events after several months of treatment. The significant adverse effects noted from randomized, controlled clinical trials were voice alteration and shortness of breath. These events were rated as mild or moderate in 99% of the time and occurred only during the "on" phase (during stimulation) of VNS therapy.[20] Operative and peri-operative adverse events with VNS placement are unusual. A few instances of infection, vocal cord paresis, Horner's syndrome, unilateral facial weakness, lead breakage, bradycardia, and asystole have been reported.

Conclusions

Most seizure disorders begin during childhood and 10-20% will be intractable to medical management. As repetitive, poorly controlled seizures result in cognitive decline, psychosocial mal-development, and a low, but constant rate of death, vigorous attempts should be made to manage this problem. Epilepsy surgery in children has been shown to be effective, safe and to provide better outcomes as relates to function in society than when it is performed in adulthood. Every child who fails management with 2 AEDs should be referred to a comprehensive epilepsy center so that all options, including surgery, may be considered.

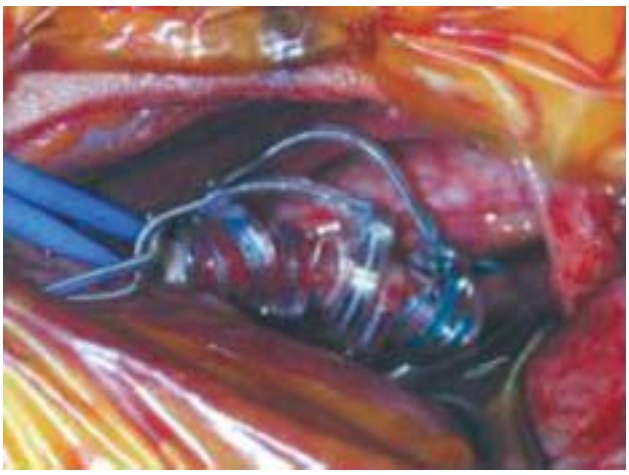

Figure 9. The position of the electrode loops in the vagus nerve. The caudal loop is the anchor, containing no metal contact strip (left). The other two loops contain the bipolar contacts. The internal carotid artery is medial to the electrodes.

References

1. Adelson PD: The surgical treatment of temporal lobe epilepsy in children, in Albright AL, Pollack IF, Adelson PD (eds): **Principles and Practice of Pediatric Neurosurgery.** New York: Thieme, 1999, pp 1111-1126
2. Babb TL, Brown WJ: Pathological findings in epilepsy, in Engel J Jr, (ed): **Surgical Treatment of the Epilepsies.** New York: Raven Press, 1987, pp 511-540
3. Bailey P, Bremer F: A sensory cortical representation of the vagus nerve with a note on the effects of low pressure on the cortical electrogram. **J Neurophysiol 1:** 405-412, 1938
4. Benbadis SR, Chelune GJ, Stanford L, et al: Outcome and complications of epilepsy surgery, in Wyllie E (ed): **The Treatment of Epilepsy: Principles and Practice. 2nd ed.** Philadelphia: Williams and Wilkins, pp 1103-1118, 1997
5. Bourgeois BFD, Prensky AL, Palkes HS: Intelligence in epilepsy: a prospective study in children. **Ann Neurol 14:**438-444, 1983
6. Chee MW, Morris HH Antar MA, et al: Presurgical evaluation of temporal lobe epilepsy using interictal temporal spikes and positron emission tomography. **Arch Neurol 50:**45-48, 1993
7. Chugani HT, Shields WD, Shewman DA, et al: Infantile spasms: 1. PET identifies focal cortical dysgenesis in cryptogenic cases for surgical treatment. **Ann Neurol 27:**406-413, 1990
8. Clusmann H, Kral T, Gleissner U, et al: Analysis of different types of resection for pediatric patients with temporal lobe epilepsy. **Neurosurg 54:**847-859, 2004
9. Colombo N, Tassi L, Galli C, et al: Focal cortical dysplasias: MR imaging, histopathologic, and clinical correlations in surgically treated patients with epilepsy. **AJNR 24**:724-733, 2003
10. Cowan LD, Bodensteiner JB, Levitrous A, et al: Prevalence of the epilepsies in children and adolescents. **Epilepsia 30:**94-106, 1989
11. Crino PB, Chourk LM: Epilepsy and cortical dysplasia. **Curr Treat Options Neurol 2:**543-551, 2000
12. Davies KG, Maxwell RE, French LA, et al: Hemispherectomy for intractable seizures: long term results in 17 patients followed for up to 38 years. **J Neurosurg 78:**733-740, 1993
13. Devinsky O, Perrine K, Vasquez B, et al: Multiple subpial transections in the language cortex. **Brain 117:**255-265, 1994
14. Dogali M, Devinsky O Luciano D, et al: Invasive intracranial monitoring, cortical resection and multiple subpial transection for the control of intractable complex partial seizure of cortical onset. **Stereotac Funct Neursurg 62:**222-225, 1994
15. Dulchowny M: Epilepsy surgery in children. **Curr Opin Neuro l 8:**112-116, 1995
16. Dupont S Samson Y, Van de Moortele PF, et al: Bilateral hemispheric alteration of memory processes in right medial temporal lobe epilepsy **J Neurol Neurosurg Psychiatry 73:**478-485, 2002
17. Fuiks KS, Wyler AR, Hermann BP, et al: Seizure outcome from anterior and complete corpus callosotomy. **J Neurosurg 74:**573-578, 1991
18. Dupont S, Samson Y, Van de Moortele PF, et al: Bilateral hemispheric alteration of memory processes in right medial temporal lobe epilepsy. **J Neurol Neurosurg Psychiatry 73:**478-485, 2002
19. Fuiks KS, Wyler AR, Hermann BP, et al: Seizure outcome from anterior and complete corpus callosotomy. **J Neurosurg 74:**573-578, 1991
20. Gilliam F, Wyllie E, Kashden J, et al: Epilepsy surgery outcome: comprehensive assessment in children. **Neurology 48:**1368-1374, 1997
21. Harvey AS, Hopkins IJ, Bowe JM, et al: Frontal lobe epilepsy: clinical seizure characteristics and localization with ictal 99mTc-HMPAO SPECT. **Neurology 43:**1969-1980, 1993
22. Heck CN, Schmidt D: Practical considerations: vagus nerve stimulation therapy questions that may be encountered from patients, their caregivers, and physician colleagues, in, Schachter SC, Schmidt D (eds): **Vagus Nerve Stimulation 2nd ed.** New York: Martin Dunitz, 2003, pp141-155
23. Henry TR: Vagus nerve stimulation for epilepsy: anatomical, experimental and mechanistic investigations, in, Schachter SC, Schmidt D (eds): **Vagus Nerve Stimulation 2nd ed.** New York: Martin Dunitz, 2003, pp 1-32.
24. Holmes GL: The long-term effect of seizures on the developing brain: clinical and laboratory issues. **Brain Dev 13:**393-409, 1991
25. Innocenti GM: Growth and reshaping of axons in the establishment of visual callosal connections. **Science**

212:824-827, 1981

26. Jones-Gotman M, Smith ML, Zatorre RJ: Neuropsychological testing for localizing and lateralizing the epileptogenic region, in, Engel J Jr, (ed): **Surgical Treatment of the Epilepsies ed 2.** New York: Raven Press, 1993, pp 245-261
27. Kassubek J, Huppertz H-J, Spreer J, et al: Detection and localization of focal cortical dysplasia by voxel-based 3-D MRI analysis. **Epilepsia 43:**596-602, 2002
28. Lindsey J, Ounsted C, Richards P: Long-term outcome in children with temporal lobe seizures: social outcome and childhood factors. **Dev Med Child Neurol 21:**630-636, 1979
29. Marks DA, Katz A, Hoffer P, et al: Localization of extra-temporal epileptic foci during ictal single photon emission tomography. **Ann Neurol 31:**250-255, 1992
30. Matsuda K, Tadahiro M, Takayasu T, et al: Neuroradiological findings in focal cortical dysplasia: histologic correlation with surgically resected specimens. **Epilepsia 42:**29-36, 2001
31. Mattson RH, Cramer JA, Collins JF, et al: Comparison of carbamazapine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. **N Engl J Med 313:**145-151, 1985
32. Morrell F, Whistler W, Bleck T: Multiple subpial transection: a new approach to the treatment of focal epilepsy. **J Neurosurg 70:**231-239, 1989
33. Morrison G, Duchowny M, Resnick T, et al: Epilepsy surgery in childhood. **Pediatr Neurosurg 18:**291-297, 1992
34. Moshe SL: The effects of age on the kindling phenomenon. **Dev Psychobiol 14:**75-81, 1981
35. Moshe SL, Albala BJ: Kindling in developing rats: persistence of seizures into adulthood. **Dev Brain Res 4:**67-71, 1982
36. National Institutes of Health. Surgery for epilepsy. **Consensus Statement 8:**1-20, 1990
37. Pritchard PB, Lombroso CT, McIntyre M: Psychological complications of temporal lobe epilepsy. **Neurology 30:**227-232, 1980
38. Reutens DC, Bye AM, Hopkins IJ, et al: Corpus callosotomy for intractable epilepsy: seizure outcome and prognostic factors. **Epilepsia 34:**904-909, 1993
39. Schmidt D: Two antiepileptic drugs for intractable epilepsy with complex partial seizures. **J Neurol Neurosurg Psychiatr 45:**1119-1124, 1985.
40. Sperling MR, Saykin AJ, Roberts FD, et al: Occupational outcome after temporal lobectomy for refractory epilepsy. **Neurology 45:**970-977, 1995
41. Szabo CA, Wyllie E, Kashden J, et al: Neuropsychological effect of temporal lobe resection in preadolescent children with epilepsy. **Epilepsia 39:**814-819, 1998
42. Tassi L, Colombo N, Garbelli R, et al: Focal cortical dysplasia: neuropathological subtypes, EEG, neuroimaging and surgical outcome. **Brain 125:**1719-1732, 2002
43. Villablanca JR, Andermann F, Rasmussen T: Hemispherectomy in chronic encephalitis, in, Andermann F (ed): **Chronic Encephalitis and epilepsy: Rasmussen's syndrome**, Boston, Butterworths, 1991
44. Wylie E, Comair YG, Kotagal P, et al: Epilepsy surgery in infants. **Epilepsia 37:**625-637,1996
45. Yasargil MG, Wieser HG, Valvanis A, et al: Surgery and result of selective amygdalohippocampectomy in one hundred patients with nonlesional epilepsy, in, Silbergeld DK, Ojemman GA (eds): **Epilepsy Surgery, Neurosurgery Clinics of North America 4:**243-261, 1993