MAYO CLINIC

Neurosciences Update

Neurologic Surgery and Clinical Neurology News

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INSIDE THIS ISSUE

Battling Glioblastomas

Joon H. Uhm, MD, a neurologist and neuro-oncologist at Mayo Clinic in Rochester, Minnesota, is at war, literally and figuratively, against a formidable opponent—glioblastoma. The average survival rate for patients with a glioblastoma who have aggressive treatment, including surgical resection (Figure 1), radiation, and chemotherapy, is about 14 months. Only 27% survive 2 years. A glioblastoma is called a "grow and go" tumor—it grows at an extremely rapid rate in a given brain site, but it also "goes," moving to new sites within the brain (Figure 2). It is no wonder that Dr Uhm describes the fight in military terms. "It's a battle that takes a huge team effort, on both the patient care and research fronts," he says. "Across Mayo's 3 sites we have assembled the team we need to address both the 'grow' and 'go' properties of glioblastomas."

Immunotherapy

The latest member of that team brings a new weapon to Mayo's arsenal—immunotherapy. Ian F. Parney, MD, PhD, joined the Department of Neurosurgery at Mayo Clinic in Minnesota this past summer. An expert in surgical management of brain tumors and in immunologic research, his goal is to harness the power of the immune system to create a therapeutic vaccine. Called a dendritic vaccine, it would stimulate an immune response against glioblastoma tumor cells and disrupt their ability to suppress the immune system itself. He is collaborating with immunologist Allen B. Dietz, PhD, head of Mayo's Human Cellular Therapy Laboratory.

"One of the reasons I came here," says Dr Parney, "is that Mayo has the infrastructure to take this research from the laboratory to the patient. Making a vaccine that is safe for patients is a difficult and resource-intensive process. Mayo is unique in having an institutional human cell therapy laboratory, capable of producing clinical-grade cellular treatments."

The other reason he came to Mayo was "the opportunity to work with a renowned group of clinicians who provide a multidisciplinary approach to every patient, every time, all the time. We provide treatment planning options for patients—surgical resection, radiotherapy, and chemotherapy—and evaluate and follow-up patients after their treatment." The integrated approach to practice includes weekly teleconferencing across Mayo's 3 sites to discuss difficult cases as well as ongoing research.

Dr Uhm adds that the neurologists, neurosurgeons, medical oncologists, neuroradiologists, radiation oncologists, neuropathologists, and physical medicine and rehabilitation physicians who make up the CNS Tumor Practice Integration Team work continuously to optimize patient care, including fast-tracking and streamlining the initial evaluation for patients with aggressive tumors like glioblastoma.

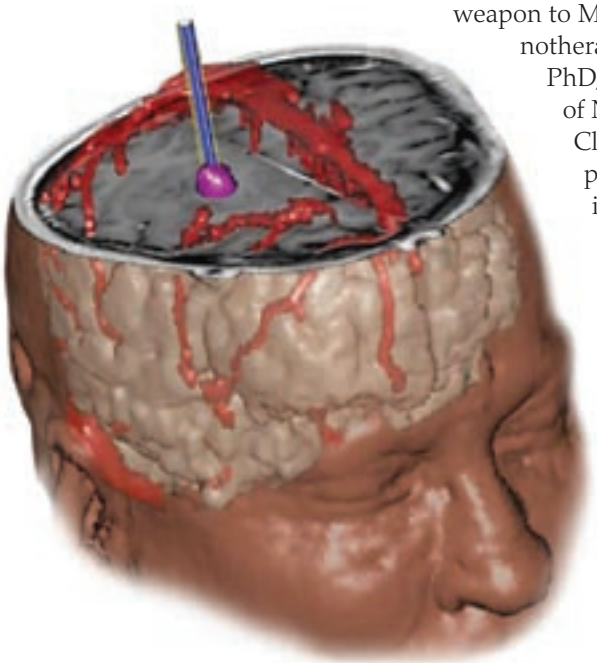


Figure 1. *In addition to surgical expertise, technologies such as 3-dimensional surgical models help Mayo neurosurgeons plan the safest surgical approaches.*

Joon H. Uhm, MD

Ian F. Parney, MD, PhD

Research and Treatment: A Single Effort

In the war against glioblastomas at Mayo Clinic, it is difficult to distinguish between the research and treatment fronts, because they have merged into a single effort. "Our first priority is patient care," says Dr Uhm. "All our research has direct relevance to the patient, and because most of our clinicians are conducting research, the research and clinical care complement each other." He cites the programmatic SPORE (Specialized Projects of Research Excellence) grants as an example. Led by Brian P. O'Neill, MD, a neuro-oncologist at Mayo Clinic in Minnesota, and funded by the National Cancer Institute (NCI), these projects focus on clinical trials for new drugs, new diagnostic tests, and molecular prognostic indicators to determine which patients will benefit from a given drug.

Ongoing Research

While much of Mayo's research focuses on the "grow" properties of glioblastomas, Dr Uhm has a specific interest in the "go" properties. His colleague, Joseph C. Loftus, PhD, at Mayo Clinic in Phoenix/Scottsdale, Arizona, has isolated a protein that plays a key role in enabling a glioblastoma to move from site to site in the brain. As a clinician, Dr Uhm hopes to help bring Dr Loftus's critical findings to the bedside. In conjunction with a pharmaceutical company, this physician-scientist team is developing a clinical trial for a drug that would target the protein and prevent tumor migration.

Among the other approaches to tumor treatment under study at Mayo are oncolytic viruses, which can infect and kill tumor cells while leaving normal cells intact. Evanthia Galanis, MD, an oncologist at Mayo Clinic in Minnesota, and her colleagues are evaluating the potential of oncolytic viruses to destroy glioblastomas.

New methods of attacking a glioblastoma must be wed to research that determines who will benefit from treatment. As Dr Uhm explains, tumors from 2 different patients may look the same under the microscope; one patient's tumor may respond well, while the other may not. Jann N. Sarkaria, MD, a radiation oncologist at Mayo Clinic in Minnesota, and colleagues have found that certain tumors express a protein that prevents the tumor from responding well to standard chemotherapy regimens. Knowing which tumors do and which do not have this protective protein will help Dr Sarkaria's team identify patients most likely to benefit from certain types of chemotherapy.

Clinical Trials

The goal of determining the molecular basis and action of glioblastomas, their effect on the immune system, and their response to oncolytic viruses, molecular manipulation, and immunotherapy is to generate new treatments. As Dr Parney notes, "Mayo can provide experimental treatments through the clinical trials offered through the Mayo Clinic Cancer Center and the North Central Cancer Treatment Group (NCCTG)."

The NCCTG is a national clinical research group funded by the NCI. Researchers across Mayo's 3 sites contribute to the development, execution, and review of all high-priority NCI-funded trials. Kurt A. Jaeckle, MD, a neuro-oncologist at Mayo Clinic in Jacksonville, Florida, where basic science and gene therapy cancer research is ongoing, chairs the NCCTG's Neuro-oncology Committee.

Other avenues for participation in clinical trials include institutionally funded trials through the Mayo Clinic Cancer Center, the only NCI-designated National Cancer Center with sites in 3 geographic locations. As Dr Uhm says, "The motto 'One Cancer Center; Three Front Doors' is an apt description of Mayo's cancer treatment and research integration of which our brain tumor program is an excellent example."

Most new drugs, including the immune-based therapies for glioblastomas, are combined with radiotherapy, explains Dr Uhm. Radiation oncology researchers at Mayo are continuously developing new protocols to complement advances in chemotherapy.

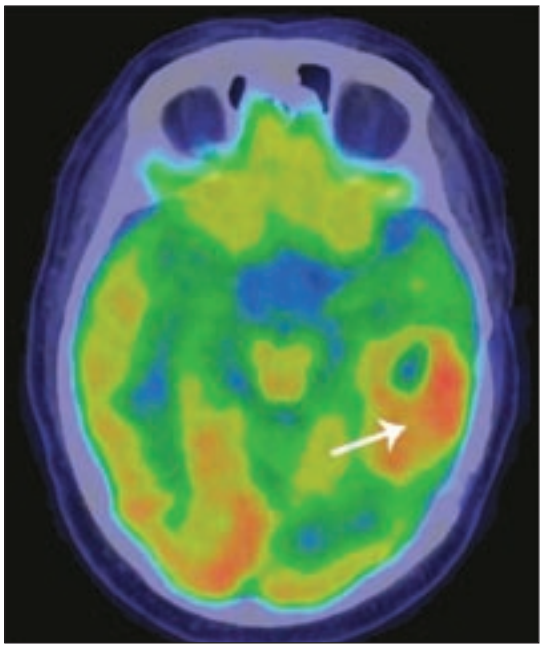


Figure 2. *PET scan of glioblastoma multiforme (arrow).*

Surgical and Imaging Advances

Dr Parney is animated as he describes the latest imaging technology available at Mayo. It helps in surgical planning, makes surgery safer, and improves the possibility of preserving function. Examples include functional MRI (fMRI); diffusion tensor imaging, which allows mapping of white matter tracts; image-guidance technology; and the ability to correlate functional imaging with intraoperative electrophysical mapping. Intraoperative MRI with a high-field-strength (1.5 Tesla) magnet allows surgeons to re-register the image-guidance system after the tumor has been removed to compensate for brain shift during surgery. Dr Parney notes the shared enthusiasm among the radiologists and physicists who participate in Mayo's imaging research for future advances such as intraoperative fMRI.

Reviewing Mayo's war against glioblastomas, Dr Uhm concludes, "We have major research invested in determining what makes a glioblastoma go and grow and in clinical trials to target those 2 components. Now, as we advance toward a therapeutic vaccine, we are working to harness the surveillance capabilities and weaponry of the immune system in our fight against these aggressive and deadly tumors."

Neurointerventionalist Neurosurgeons Join Mayo Clinic

The face of interventional neuroradiology and endovascular neurosurgery is changing. For more than 30 years, the vast majority of neurointerventionalists have been neuroradiologists. In the past 5 to 7 years, however, increasing numbers of neurosurgeons are also training to become neurointerventionalists. Reflecting this wider professional umbrella, the American Society of Interventional and Therapeutic Neuroradiology recently changed its name to the Society of NeuroInterventional Surgery.

This change has been reflected at Mayo Clinic where 2 dual-trained neurosurgeons, Ricardo A. Hanel, MD, and Giuseppe Lanzino, MD, have joined the staff of Mayo Clinic in Jacksonville, Florida, and Mayo Clinic in Rochester, Minnesota, respectively. Dual training is rare. As Dr Lanzino points out, a major benefit is that hands-on experience with both open and endovascular procedures helps guide optimal management. Dr Hanel agrees, noting that dual training gives the neurosurgeon a different perspective and greater flexibility in considering treatment options.

At Mayo Clinic in Minnesota, Dr Lanzino has joined an interventionalist team that includes neuroradiologists Harry Cloft, MD, PhD, and David F. Kallmes, MD, as well as 9 neurologists and 4 neurosurgeons who specialize in vascular disorders. In addition to open procedures, Dr Lanzino performs endovascular surgery 1 day a week. His colleagues Drs Cloft and Kallmes do so 5 days a week. Together, they provide round-the-clock coverage for endovascular neurosurgical cases.

At the Florida campus, Dr Hanel is part of a team that includes 2 neurointerventionalists, 2 vascular neurosurgeons, and 5 vascular neurologists. Together they make up one of the largest neurovascular teams in the region, and in the past year, the volume of cases involving vascular lesions has markedly increased. For example, during that time, the number of aneurysms treated at Mayo Clinic in Florida increased 7-fold. About 60% of those were

Ricardo A. Hanel, MD

Giuseppe Lanzino, MD

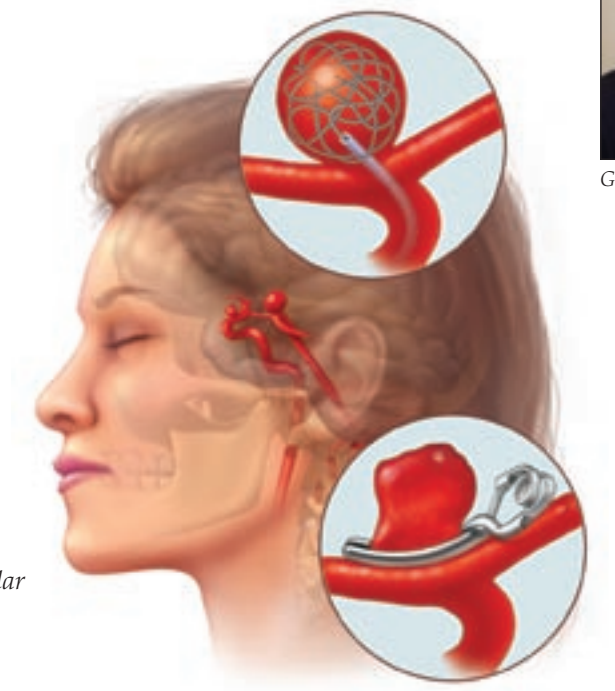


Figure 1. ***Interventional Treatment Options.*** *Management options for brain aneurysms include conservative management with control of risk factors, or an interventional treatment with either endovascular coiling or surgical clipping, as shown in the figure.*

Brian W. Chong, MD

treated endovascularly and the rest by craniotomy and clipping.

Weighing Risks and Benefits

Neuroendovascular procedures include embolization for arteriovenous malformations (AVMs), arteriovenous fistulas, and cerebral aneurysms; thrombolysis for cerebral emboli; and angioplasty and stenting for cerebrovascular stenosis. Neuroendovascular surgery is less invasive than open surgery and can translate into shorter recovery times.

Five years ago, the vast majority of aneurysms were clipped in an open procedure rather than coiled in endovascular surgery. Today that ratio is reversed. Neuroendovascular surgery provides another, sometimes safer, option for managing some neurovascular lesions. Studies have shown, for example, that neurointervention for basilar tip aneurysms gives patients a 2-fold improvement in morbidity and mortality compared with outcomes from an open procedure.

As Dr Hanel notes, however, just because it is less invasive, a neuroendovascular procedure may not always be the best option. For example, a craniotomy might be the better choice for a middle cerebral aneurysm with a large neck that requires several stents and carries the risk of clotting. The open procedure might actually take much less time and be the more straightforward approach. A dual-trained neurosurgeon is in a good position to weigh the potential risks and benefits and to communicate them directly to the patient.

Endovascular Neurosurgery Fellowship—Crossing Subspecialty Lines

Another change in the profession has been certification of training programs by the Accreditation Council for Graduate Medical Education and recognition of endovascular surgery as a subspecialty by the American Medical Association. A fellowship, called Endovascular Surgical Neuroradiology, is open to physicians with training in neurology, neurosurgery, or radiology and is offered at Mayo Clinic. Brian W. Chong, MD, a neuroradiologist at Mayo Clinic in Phoenix/Scottsdale, Arizona, and his neurosurgical colleague, Richard S. Zimmerman, MD, have been strong supporters of crossing specialty lines within neurointervention. They see the training program as an embodiment of that effort. Dr Chong notes that the name of the subspecialty and the number of disciplines to which it is open "speak to the multidisciplinary nature and the multiple skills needed to practice neurointervention."

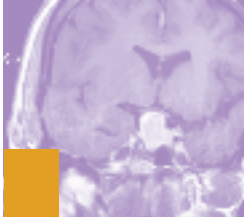
The interdisciplinary nature of the subspecialty is second nature to neurovascular physicians throughout Mayo Clinic. For example, Dr Chong is 1 of 3 neuroradiologists who conduct endovascular surgery at Mayo Clinic in Arizona, and he has his own outpatient clinic. However, he collaborates regularly with the other neurovascular specialists. He and Dr Zimmerman consult on every aneurysm patient. As Dr Chong says, "Although we are from different disciplines, together we act as one. I attribute this entirely to the multispecialty model of care that defines Mayo. It works well because that is what Mayo Clinic is—multiple disciplines taking care of the patient in concert."

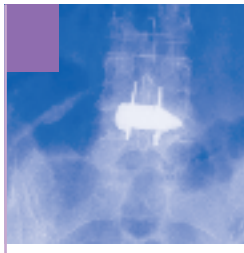
Providing Options and Tailoring Treatment

Deciding on the optimal procedure is best arrived at in a climate where there is no vested interest in the approach taken and there is close and open communication between neurosurgery and neuroradiology. A young patient with an unruptured AVM, for example, might benefit from open surgery, radiosurgery, embolization, or a combination of all 3 approaches, depending on the size and location of the AVM and the patient's age, history, and perspective.

At Mayo, multispecialty cooperation extends beyond neurosurgery and radiology. For example, as noted by Dr Cloft, Mayo Clinic in Minnesota is one of the few institutions in the world with "the anesthesia resources that allow us to conduct an angiogram that includes possible endovascular surgery right then and there." The interventionalist can discuss the results with a neurosurgeon while the patient and anesthesia team wait in the operating room. As he says, "It is a patient-friendly atmosphere. A lot of our patients travel some distance to Mayo Clinic, and they don't want to wait days for a decision."

Whether in the person of a dual-trained neurosurgeon or in the case-by-case consultation between neurovascular specialties, having the perspective of both neurointervention and open surgery is critical in providing optimal care for surgical candidates. Drs Hanel and Lanzino, both dual-trained, cite the collaboration among members of the neurovascular teams throughout Mayo Clinic as making the difference for patients because treatment is always individually tailored.





Research Highlights

Advanced Imaging Technology Used at Mayo Clinic Improves Spinal Surgery Outcome

The largest study yet using 3-dimensional (3D) image-guided technology to place screws in the spine for spinal fusion procedures was published by Mayo Clinic physicians in the online edition of the *Journal of Neurosurgery: Spine.* Using a 3D image-guided system to help place screws in the spines of patients results in safe and accurate surgery with a decrease in the number of misplaced screws and subsequent injuries, seen in more traditional operations.

Mayo Clinic Finds It Generally Safe to Withdraw Antiseizure Medication in Children With Epilepsy

A Mayo Clinic study presented at the American Epilepsy Society's annual meeting found that it is generally safe to withdraw antiseizure medications in children with epilepsy who have achieved seizure freedom while on the medication. Researchers found that these children were not at high risk of subsequently developing intractable epilepsy.

200-Year-Old Mystery Solved: Intraneural Ganglion Cyst

Beauchene intraneural cyst of the ulnar nerve is an important specimen. Its brief description was previously hidden in a catalogue and had long been miscited. Its availability has allowed its establishment as a bona fide example of an intraneural ganglion cyst and to confirm its articular origin.

Long-term Risk of Hemorrhage in Unruptured Intracranial Aneurysms

A Mayo Clinic study presented at the 6th World Stroke Congress found that the risk of rupture of a brain aneurysm depends on the location and size of the aneurysm. Additionally, patients whose aneurysms were more than 13 mm in diameter were at least twice as likely to experience rupture, compared with those whose aneurysms were 12 mm in diameter.

Potential New Therapeutic Target for Progressive Multiple Sclerosis

A Mayo Clinic study presented at the American Neurological Association annual meeting found that 2 particular enzymes were elevated in patients with progressive multiple sclerosis. The levels of these enzymes also were associated with patients' levels of disability.

Parkinson Disease: Pathways to Prevention

Mayo Clinic researchers are changing concepts about the molecular basis for Parkinson disease and generating new ways of identifying those at risk before the disease strikes.

Mayo Clinic Identifies Best Treatments for Long-term Survival in Brain Tumor Patients

A Mayo Clinic study published in *Neuro-Oncology* found that patients with low-grade gliomas survived longest when they underwent aggressive surgical procedures to remove the entire tumor. If safely removing the entire tumor was not possible, patients survived significantly longer when surgery was followed by radiation therapy.

Symptom Awareness Can Improve Stroke Recovery

A Mayo Clinic study published in *Emergency Medicine Journal* shows a majority of stroke patients don't think they're having a stroke and delay seeking treatment until their condition worsens.

Researchers Find Drugs Being Tested for Alzheimer Disease Work in Unexpected and Beneficial Ways

Researchers at Mayo Clinic, with their national and international collaborators, reported in the journal *Nature* that they have discovered how a class of agents now in testing to treat Alzheimer disease works and say these drugs may open an avenue of treatment for this disease and others.

To read more about Mayo Clinic neurosciences research and patient care, visit www.mayoclinic.org.

Intractable Seizures in Children: Surgical Management at Mayo Clinic

Elaine C. Wirrell, MD, a pediatric neurologist, and Nicholas M. Wetjen, MD, a pediatric neurosurgeon, joined Mayo Clinic in Rochester, Minnesota, this year and are making a difference for children with intractable seizures. Experts in pediatric epilepsy, they are part of the multidisciplinary epilepsy team that includes 2 pediatric epileptologists (Katherine C. Nickels, MD, has also recently joined the team), neuroradiologists, neurosurgeons, and 2 new pediatric neuropsychologists.

One in 5 children with epilepsy has intractable seizures—defined as failure to respond to at least 2 appropriate antiseizure medications. Surgery may be an option, but the path to that decision is complex. At many institutions, the evaluation process may take months. At Mayo Clinic, the surgical work-up can be done in 1 to 2 weeks and includes state-of-the art functional brain mapping and seizure locus studies. If the child is documented to be a good candidate and the family decides to proceed, surgery can then be promptly scheduled.

As Dr Wetjen explains,"The turnaround time here is quick because the care is not fragmented, and there is immediate communication among the team members. For example, a child with lesional epilepsy (eg, tumor, cavernous malformation) may come in on a Monday; have an evaluation that includes imaging, inpatient video EEG monitoring with several recorded seizures, a SISCOM study, and a neuropsychological evaluation by Thursday; and, in some cases, be in surgery by Friday. The pace is not always that fast, however. The typical range for most epilepsy patients is 2 to 4 weeks from initial consult to surgery."

Determining Surgical Candidacy

A pediatric epileptologist determines the frequency, severity, and duration of seizures and whether other conditions coexist. An MRI and scalp EEG help identify seizure etiology (eg, cortical dysplasia, vascular malformations, arteriovenous malformation, tumor, trauma, stroke, or rare metabolic conditions) and the presence or absence of a specific lesion and its focus. A pediatric neuropsychologist then evaluates baseline cognitive function and helps establish lateralization of function. Other tests to localize function may include functional MRI (fMRI) or sodium amobarbital (WADA) testing.

Inpatient Pediatric EEG Monitoring

Surgical candidates then undergo continuous EEG monitoring in the Eugenio Litta Children's Hospital, the 85-bed pediatric facility located within Mayo's Saint Marys Hospital. Four rooms as well as the pediatric intensive care unit are hard-wired with ceiling cameras for behavioral observation and continuous EEG monitoring via external or intracranial EEG leads (Figure 1). Inpatient EEG video monitoring is needed to record several seizures by EEG and video and to minimize risks of medication withdrawal, a process that is often required to record seizures. Monitoring may take from 24 hours to several days to record at least 3 seizures. Digital recording allows analysis of the EEG in a number of formats.

The EEG video monitoring unit is specifically designed with children and families in mind. Child life specialists not only provide toys, movies, computer games, and other entertainment, but also help children and families through procedures that may be uncomfortable or unfamiliar. The nurses and EEG technicians are, according to Dr Wetjen,"remarkably attentive and good at what they do."Dr Wirrell agrees, saying,"Our EEG technologists are superb and dedicated to their patients. I have not worked with one who is not devoted to the child."

Dr Wirrell also notes that "unlike many centers that offer monitoring, we have the ability to monitor the patient every second of the day or

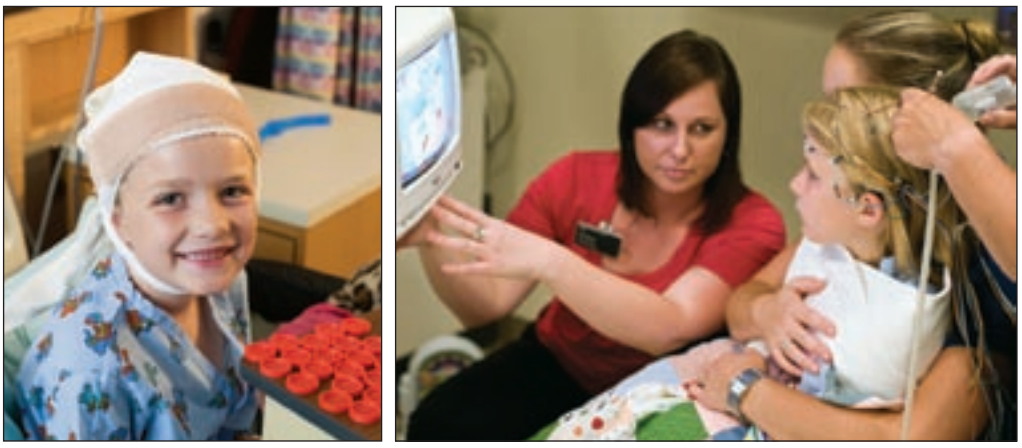


Figure 1. *Mayo Clinic's EEG video monitoring unit is specifically designed for children and families and provides 24/7 monitoring by trained technicians.*

night, so if the patient or family member is sleeping, or the seizure is subtle, our technologists are still able to pick it up." Continuous monitoring by trained technicians not only increases safety, but can reduce the length of time a patient stays in the monitoring unit.

Localizing Seizure Focus Through SISCOM

SISCOM stands for subtraction ictal single-photon emission computed tomography (SPECT) coregistered to MRI. Pioneered at Mayo Clinic, it fuses the MRI image with the SPECT image, an innovation particularly useful in localizing seizure focus when seizures have a focal onset. A radioactive tracer is injected as soon as possible during a seizure. The first imaging study is performed shortly after the seizure, and the second after 24 hours of seizure freedom. Dr Wirrell notes, "SISCOM can be very helpful in pediatric epilepsy in which the MRI frequently does not show a clear structural abnormality."

If imaging studies establish a clear focus that is not in an area of critical brain function, the child may have surgery for resection. If the focus cannot be precisely localized, or if it is in an area of eloquent cortex, intracranial electrodes may be implanted and electrical stimulation performed during an awake surgical procedure to more narrowly delineate seizure focus and to map important motor and cognitive/linguistic functions.

All the data for each case and the potential risks and benefits of surgery are reviewed at the epilepsy team conference where, according to Dr Wirrell, "Everyone provides input, and there is always plenty of time to discuss each patient fully." The attending neurologist then meets with the family to review the recommendations.

Multiple Surgical Options

Depending on the nature of the problem, the patient may have surgical resection or disconnection. Resections are generally conducted for tumors, vascular malformations, and areas of cortical dysplasia. Drop attacks are often treated with cortical disconnection (corpus callosotomy).

In patients whose epilepsy arises from an entire hemisphere, Dr Wetjen and colleagues may perform a peri-insular hemispherotomy rather than the traditional hemispherectomy. Rather than removing the entire hemisphere, a hemispherotomy involves a much smaller resection followed by image-guidance technology to disconnect the diseased hemisphere from the healthy one (Figure 2). As a result, there are fewer postoperative complications such as hydrocephalus and superficial siderosis.

Other options include endoscopic surgery for the rare patient with gelastic or laughing seizures in which there is a third ventricle hypothalamic hamartoma; radiosurgery or microsurgical resection for seizure-causing arteriovenous malformations; and neuromodulation using vagus nerve stimulation for generalized seizures. Implanted pacemaker stimulation, another form of neuromodulation, is a future possibility. As Dr Wetjen says, "We don't know yet if pacemaker stimulation will be effective in adults with epilepsy, but Mayo is always looking for better ways to manage patients. The infrastructure is here if those advances are appropriate."

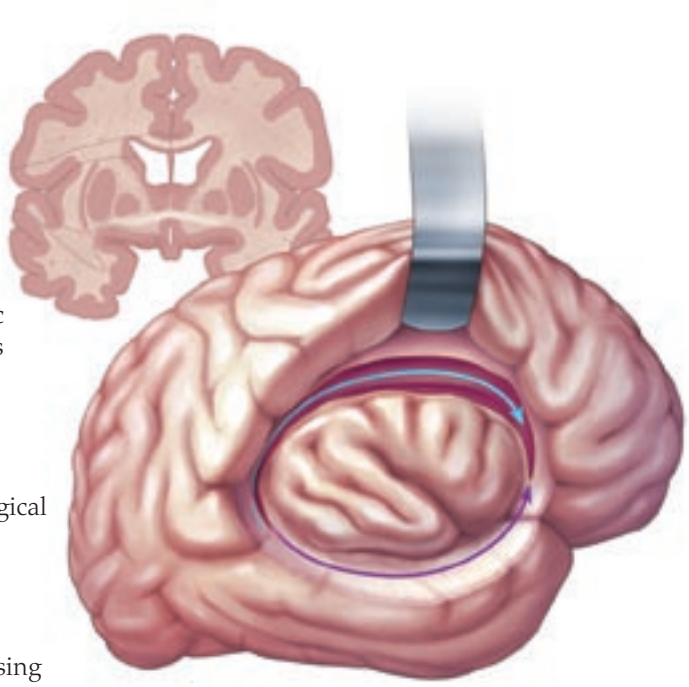


Figure 2. *Rather than removing the entire hemisphere, a hemispherotomy involves a much smaller resection followed by image-guidance technology to disconnect the diseased hemisphere from the healthy one.*

Caring for the Whole Family

"Epilepsy impacts siblings as well as the patients and their parents. I find developing long-term relationships with the whole family important and fulfilling," says Dr Wirrell. Adds Dr Wetjen, "I like to spend a lot of time making the children feel comfortable. The mothers and fathers want the best possible care, and it's critical to provide extensive and effective ongoing communication throughout each patient's care. Our whole team is attentive to the ongoing mental, social, and educational development of the children under our care."

Like the rest of the epilepsy team, Drs Wetjen and Wirrell are acutely aware of the importance of the developing brain, and, as Dr Wetjen notes, "Epilepsy is not a static situation, but an actively changing one. It's very hard to separate the problems related to continuing epilepsy from the effects of epilepsy medications, but certainly, if it is possible, stopping the seizures is best. We can't do it in every case, but that's the hope, that's the goal."

Elaine C. Wirrell, MD

Nicholas M. Wetjen, MD

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