MAYO CLINIC

Neurosciences Update

Focus on Pediatric Neurologic Surgery and Pediatric Clinical Neurology Vol. 6 Supplement 2009

Collaborative Management of Pediatric Brain Tumors

INSIDE THIS ISSUE

Recently, Nicholas M. Wetjen, MD, a pediatric neurosurgeon at Mayo Clinic in Rochester, Minnesota, helped remove a tumor that had eroded through the bones of the skull and face of a young child. The surgical team conducting the procedure included 2 skull-base surgeons, Michael J. Link, MD, a neurosurgeon, and Eric J. Moore, MD, an otorhinolaryngologist, in addition to Dr Wetjen. Each contributed their particular expertise on how best to approach the tumor and reconstructive surgery. It is an example of the depth of expertise so often needed to address the complicated care of children with brain tumors. Mayo's team includes specialists who collaborate in every aspect of pediatric care at Mayo Clinic's T. Denny Sanford Pediatric Center and the Eugenio Litta Children's Hospital.

Symptoms: Specific and Nonspecific

Recognizing and diagnosing the symptoms of brain tumor may take longer in infants and children than it does in adults. At Mayo Clinic, once a tumor is suspected, the efficient integration across pediatric neuro-oncology, neurology, neuroradiology, neurosurgery, and neuropathology smoothes the diagnostic process—a process that may take 1 to several days compared with weeks in many medical centers.

Some children have obvious neurologic signs, such as focal motor or sensory deficits or asymmetric motor skills, that suggest the diagnosis of a tumor. Other readily recognized neurologic symptoms are seizures, hydrocephalus, balance problems, lack of coordination, and failure to reach developmental milestones or the loss of those previously gained.

Often, however, the symptoms, such as vomiting and irritability, are less specific to a neurologic disorder. For example, persistent vomiting over the course of 2 to 3 weeks without other gastrointestinal tract or respiratory tract signs or fever might be a response to pressure within the brain from a tumor. Other nonspecific symptoms are lethargy, persistent headache, failure to gain weight, and frequent thirst, drinking, and urination. In older children, the signs may include head tilt and eye deviation.

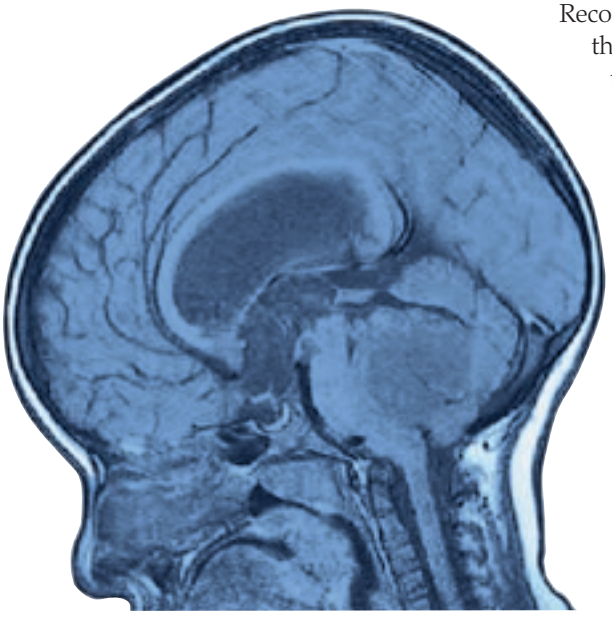


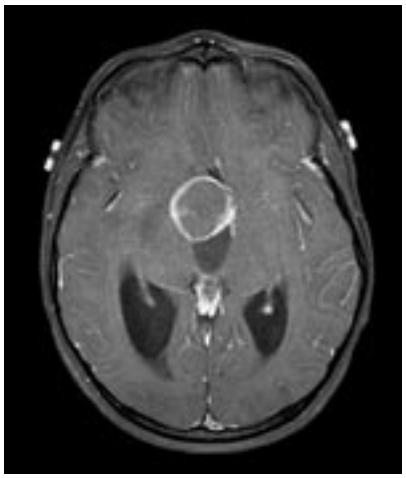
Figure 1. *Medulloblastoma in a 4-year-old boy who presented with nausea, vomiting, and imbalance. MRI demonstrated a large, hypointense tumor in the midline cerebellum with associated obstructive hydrocephalus.*

Collaborative Diagnosis

The initial work-up is conducted by one of Mayo's 10 pediatric neurologists or by one of its pediatric neuro-oncologists. Cynthia J. Wetmore, MD, PhD, a pediatric neuro-oncologist, notes that "as soon as a child comes to the clinic, the patient and the patient's family meet with a pediatric oncologist, a pediatric neurologist, and often a radiation oncologist as well as a pediatric neurosurgeon." Dr Wetjen adds, "It is rare that a new patient would not see us all in 1 day."

Imaging is critical to detect and localize brain tumors, but it can be difficult to conduct in children (Figures 1-3). Tests for brain tumors in children at Mayo include CT scan, MRI with diffusion-weighted and gradient-echo imaging, MR spectroscopy, and, in some cases, PET scans. Imaging studies require that children be sedated, with particular attention to age and severity of illness. Anesthesiologists with special expertise in pediatrics are another important adjunct to Mayo's pediatric brain tumor team.

If seizures are a presenting symptom, pediatric epilepsy specialists help determine if the tumor alone is causing the seizures. Mayo has extensive experience in video monitoring for epilepsy, should that be needed before surgery (see "Intractable Seizures in Children" on page 5 of



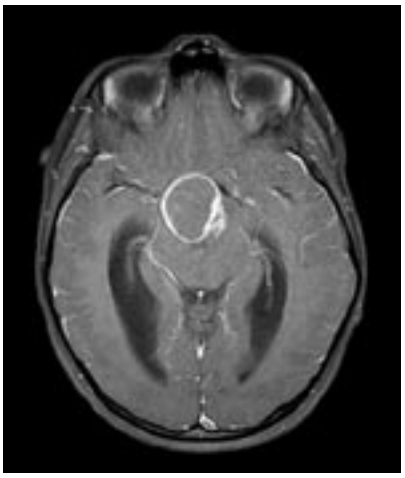


Figure 2. *Craniopharyngioma in an 8-year-old boy presenting with visual disturbance and headaches. MRI demonstrated a contrast-enhancing cystic lesion in the suprasellar cistern with obstructive hydrocephalus.*

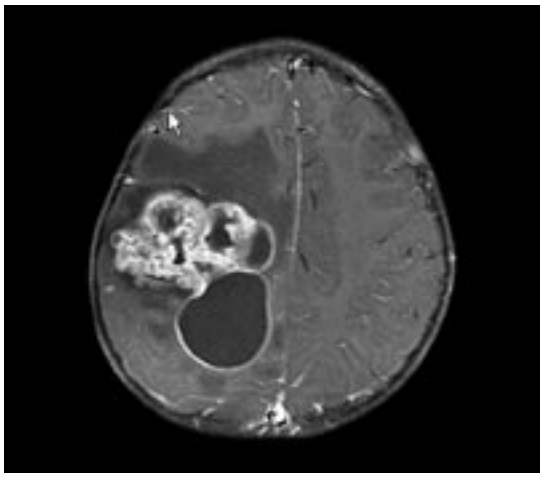


Figure 3. *Ependymoma in an 8-month-old girl who presented with lethargy and enlarged head circumference. MRI demonstrated a large, multicystic, heterogeneously enhancing mass in the left frontal lobe.*

Nicholas M. Wetjen, MD

Cynthia J. Wetmore, MD, PhD

this issue). Pediatric neuropsychologists provide behavioral and developmental testing. Specialists in pediatric endocrinology and genetics are also available as needed.

Surgical and Medical Management

Surgical resection is considered the best treatment for most types of childhood brain tumors. Because both chemotherapy and radiotherapy pose risks for the developing brain, surgically removing as much of the tumor as possible is critical. Dr Wetjen notes, "Too often we see patients in whom the tumor has been incompletely resected or an inadequate tissue sample has been collected for biopsy. Then we are dealing with both the adverse effects of previous surgery and the need to reoperate."

At Mayo, an initial biopsy specimen can often be taken and evaluated during surgery, then sent for further pathology testing. The histology results help determine the best management, whether it be surgical resection, chemotherapy, radiotherapy, or some combination of treatments. As Dr Wetmore points out, "Even if the tumor is completely resectable, adjunct chemotherapy or radiotherapy often improves long-term survival, except in children younger than 3 years in whom radiation is not recommended." Gamma knife surgery is rarely recommended for children as a primary treatment.

Nadia N. Laack, MD, a radiation oncologist, and her colleagues are investigating the long-term effects of radiation on cognitive development and growth. Dr Wetmore, who directs a basic research laboratory, and colleagues are also investigating tumor resistance to radiation in children and ways to target tumors without harming normal brain development. Mayo Clinic holds a National Cancer Institute SPORE (Specialized Programs of Research Excellence) grant in brain cancer under which numerous other pediatric research initiatives are ongoing.

Recently joining the group is pediatric neurologist Gesina Keating, MD, who has expertise in the care of children with tumors of the nervous system, as well as the neurologic complications of other cancers in children. Her interests range from the acute management of newly diagnosed tumors in children to their ongoing care and long-term follow-up, with plans to establish a transition program for the continued neurologic needs of patients as they reach adult age.

Mayo offers state-of-the art neurosurgical techniques and technology, including the ability to conduct electrophysiologic and speech and language monitoring during surgery, frameless stereotactic surgery for real-time intraoperative localization and navigation, and intraoperative MRI. Mayo neurosurgeons have extensive experience in tumor resection in both the adult and pediatric practice. Experience matters. A recent study found that it is a major factor affecting pediatric brain tumor surgical outcomes.

Unlike adults, 95% of children who have chemotherapy in the United States are treated through protocols specified by the National Cancer Institute (NCI). Most of those involved in the direct management of pediatric brain tumors at Mayo Clinic in Rochester are members of the Children's Oncology Group (COG) through the NCI, and all postsurgical therapy is directed by a member of COG.

Taking Care of the Whole Patient and the Whole Family

The T. Denny Sanford Pediatric Center at Mayo

Clinic in Rochester, Minnesota, is located in the Gonda Building. It serves more than 45,000 children a year. Every aspect, from the nature-themed environment to the specialized furniture, restrooms, and drinking fountains at several different heights, is designed for children of all ages. It is a colorful, welcoming environment, but more important, it is staffed by pediatric experts from every specialty who, working together in a central location, can coordinate care efficiently and to the patient's best advantage.

Mayo's Eugenio Litta Children's Hospital is staffed by more than 150 physicians. Distinct from, but located within Mayo's Saint Marys Hospital, patients have access to all Mayo's technological advances and the expertise of Mayo's entire staff of physicians. The facility includes playrooms for all ages and a teen lounge. Tutors are available from the Rochester Public School system for children absent from school for long periods of time. Rehabilitation specialists, including physical therapists and speech-language pathologists and others with expertise in pediatrics, work with patients as needed during recovery.

Diagnosis of a brain tumor in a child affects the entire family. During the hospital experience, social workers as well as child-life specialists who support children and families before, during, and after surgery work with patients and their families. The hospital has special family support space with laundry, kitchen, and shower facilities. Pets are permitted to visit. And because many patients come from a distance, Mayo is fortunate to have the Ronald McDonald House located only blocks from both the clinic and hospital. Supported by charitable contributions and available to patients and their families with a Mayo Clinic referral, it has 45 rooms, each available at a minimum cost, accommodating up to 5 persons per room, for as long as needed—be it 6 days or 6 months.

Dr Wetmore notes that, at Mayo Clinic, "We have a commitment to our pediatric brain tumor patients and their families that extends from our breadth and depth of interdisciplinary expertise to our research on brain tumor treatment and to our child-centered, state-of-the art facilities."

Occipital-Cervical Spine Surgery in Children

Children with Down syndrome are screened for neck instability before they are allowed to participate in the Special Olympics. More than 15% of those with Down syndrome have occipital-cervical junction abnormalities.

Nicholas M. Wetjen, MD, a pediatric neurosurgeon at Mayo Clinic in Rochester, Minnesota, would like to see effective screening for occipital-cervical instability in children with other genetic conditions that put them at risk, including Klippel-Feil syndrome and achondroplasia (dwarfism) (see sidebar on page 4). Before his staff appointment, Dr Wetjen completed his neurosurgical residency at Mayo and received extensive training in pediatric neurosurgery and in pediatric occipital-cervical spine surgery at the University of Utah with Douglas L. Brockmeyer, MD, a world-renowned expert in this specialized area.

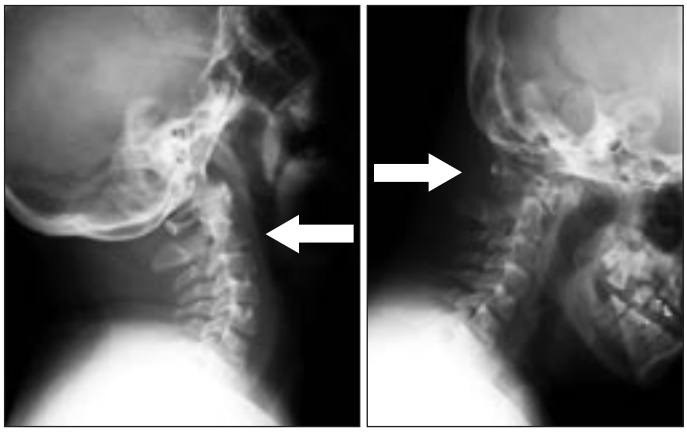


Figure 1. *Extension (left) and flexion (right) lateral radiographs of the neck demonstrating excessive movement at the atlanto-occipital joint in a patient with Down syndrome.*

Symptoms and Cause

Congenital instability can be caused by ligament laxity, abnormal bone segmentation, or bone deficiencies and other abnormalities in the occipital-cervical junction. These problems may affect the enclosed nervous system structures. For example, because of impaired bone development at the junction of the skull and spine, the cerebellum may be abnormally low, and the brain stem may be compressed in the upper cervical spine. Excessive range of motion in the neck can create tissue build-up which then compresses the spinal cord and affects the functions of the lower cranial nerves or the peripheral nerves exiting the upper cervical spine. There may be a risk of stroke if the vertebral artery is stretched or compressed with excessive range of motion in the neck. Symptoms of occipital-cervical instabil-

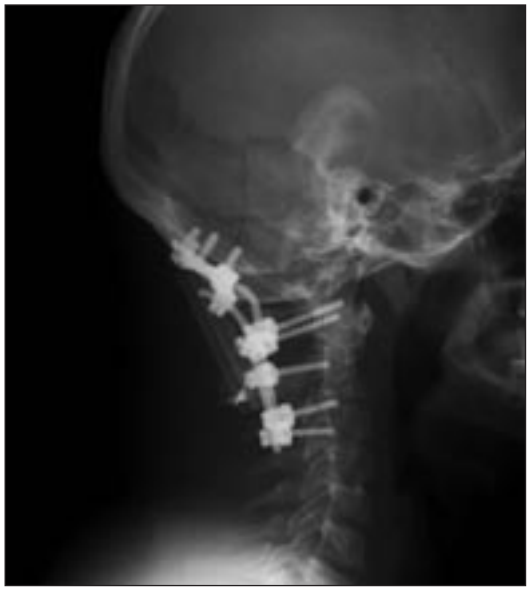


Figure 2. *Postoperative lateral cervical spine radiograph after occipital-cervical instrumentation and fusion.*

ity include neck pain, respiratory and swallowing difficulties, disorders of eye movement, sensory impairment, and weakness of the upper and lower limbs. The most common symptom is occipital and upper neck pain.

These problems also can occur in otherwise healthy children and adults and in those who have suffered trauma to the area. And cervical instability may be at issue in children with persistent torticollis that is not relieved by a course of physical therapy.

Surgical Intervention

At Mayo Clinic in Rochester, imaging studies before surgery include MRI, CT scanning, and x-ray studies. The combination allows views of the degree of motion in flexion and extension (x-ray), the bony anatomy (CT), and the soft tissue (MRI). Occasionally, MRI with contrast is used to map the arterial anatomy, particularly if the neurologic deficits occur in a specific head and neck position.

The goal of surgery is to stabilize the junction, a procedure that usually involves fusing the bony anatomy of the craniovertebral junction using titanium plates and screws and bone grafts from either the hip or the rib. Bone grafts incorporate better and are considered stronger than artificial materials. The combination of hardware and bone grafts usually allows the neck to heal without the need for a halo, except in those with very soft bones.

The youngest patient Dr Wetjen has operated on was 16 months old, but surgical treatment of patients that young is rare. For the procedure to be effective, the bones must be dense enough and large enough to accommodate the instrumentation, and surgery is usually reserved for children at least 3 years old. Children tend to heal well because they have rapid bone growth. Problems may arise in syndromes in which disorders of bone metabolism play a role.

The surgery usually reduces normal head and neck motion by approximately 50%. Long-term follow-up data have shown that fusion surgery of this type does not seem to have a detrimental effect on the overall growth of the cervical spine. The bones tend to remodel around the instrumentation.

Which Patients To Treat and When?

Only a few medical centers in the world perform the extremely complicated procedure of occipital-cervical spine fusion in children. The goal is to treat the problem before it creates neurologic damage, which may not be reversible. But who should be treated and when?

"A major issue," notes Dr Wetjen, "is that some children with these abnormalities do not have symptoms, and they may or may not be at risk for neurologic deficits. We need more information on the natural history of these spinal abnormalities to know which patients need intervention and when to intervene." To that end, he and approximately 15 other pediatric neurosurgeons across the country are forming the Pediatric Craniocervical Society to build a database of patients with these abnormalities. By pooling their data, they hope to learn more about the long-range outcomes in asymptomatic patients and how long these patients should

Syndromes Associated With Occipital-Cervical Instability

- **Down syndrome**
- **Klippel-Feil syndrome**
- **Achondroplasia**
- **Neurofibromatosis type 1**
- **Goldenhar syndrome**
- **Congenital spondyloepiphyseal dysplasia**
- **Morquio syndrome**
- **Larsen syndrome**
- **Osteogenesis imperfecta**
- **Kniest syndrome**

be followed with imaging studies. They hope to identify which types of abnormalities pose the greatest risk of developing cervical spine instability and neurologic impairment and to establish criteria for typical and atypical head and neck movement. The database will include a description of the surgical procedures in patients with these disorders to better refine operative management. Finally, they hope to establish screening programs for those with conditions that pose a risk of neurologic injury.

Surgical Management of Intractable Seizures in Children With Epilepsy

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 can take months. At Mayo Clinic in Rochester, Minnesota, 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 surgical candidate and the family decides to proceed, surgery can then be scheduled promptly.

At Mayo Clinic in Rochester, Minnesota, pediatric neurologists Elaine C. Wirrell, MD, and Katherine C. Nickels, MD, and pediatric neurosurgeon Nicholas M. Wetjen, MD, are experts in pediatric epilepsy. They are part of the multidisciplinary epilepsy team that includes 2 pediatric epileptologists, neuroradiologists, neurosurgeons, as well as 2 new pediatric neuropsychologists.

As Dr Wetjen explains, "The turnaround time here is quick because the care is not fragmented, and there is immediate communication between 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—***S***ubtraction ***I***ctal ***S***PECT ***CO***registered to ***M***RI—and 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."

Elaine C. Wirrell, MD

Katherine C. Nickels, MD

Determining Surgical Candidacy

A pediatric epileptologist determines the frequency, severity, and duration of seizures and whether other conditions coexist. An MRI

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

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 location. A pediatric neuropsychologist then evaluates baseline cognitive function and helps establish lateralization of function. Other tests to localize function may include functional MRI 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 (see article on "Pediatric Brain Tumors," this issue). Four rooms as well as the pediatric intensive care unit are hardwired with ceiling cameras for behavioral observation and continuous EEG monitoring via external or intracranial EEG leads (Figure 1). Inpatient video-EEG 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 video-EEG 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 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 also reduces the length of time a patient stays in the monitoring unit.

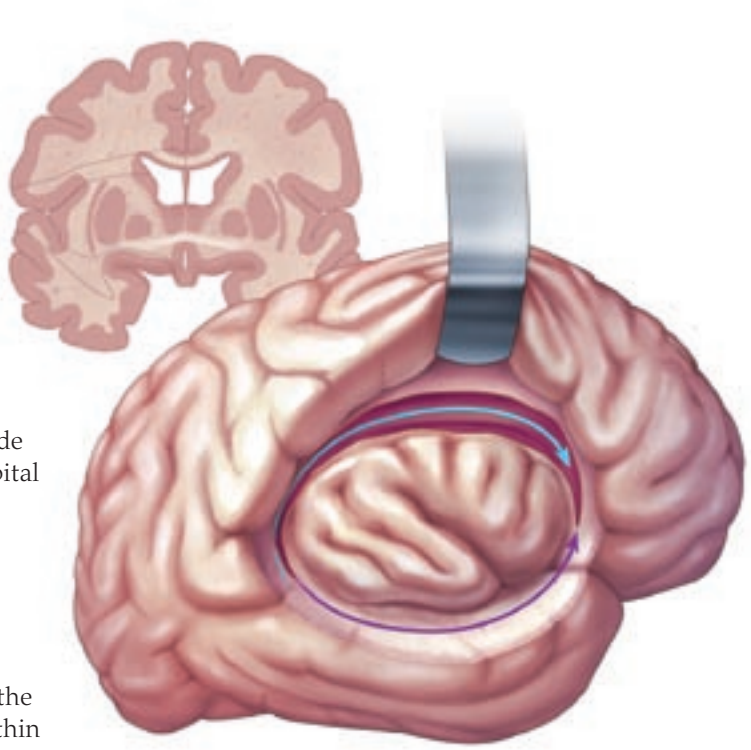


Figure 2. *Rather than removing the entire hemisphere, a hemispherotomy involves a much smaller resection followed by image-guidance technology to disconnect the diseased hemisphere from the healthy one.*

Localizing Seizure Focus Through SISCOM

Pioneered at Mayo Clinic, SISCOM 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. Cortical disconnection (corpus callosotomy) is used to treat drop attacks.

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 patients with epilepsy, but Mayo is always looking for better ways to manage patients. The infrastructure is here if it is appropriate to make those kinds of advances."

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."

CME Opportunities

Pediatric Neurology Update – August 7, 2009, Rochester, MN
This 1-day course will consist of a series of lectures by prominent child neurologists. It will address diagnosis and management issues of childhood neurologic disorders commonly encountered by primary care providers.

Pediatric Days 2009 – September 24-25, 2009, Chicago, IL
Mayo Clinic Pediatric Days is designed to provide general pediatricians, pediatric subspecialists, family physicians, physician assistants, nurses, nurse practitioners, and resident physicians with current information on various medical conditions that affect infants, children, and adolescents. The 2009 course will include a lecture on the management of new-onset seizures in children. This highly successful program presents the latest advances in the field of pediatric and adolescent medicine.

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Mayo Clinic's Pediatric Neurology and Neurosurgery Practices

The pediatric neurology and neurosurgery practices at Mayo Clinic in Rochester, Minnesota, include 10 pediatric neurologists and 1 pediatric neurosurgeon who work together with hundreds of physicians in neurology, neurosurgery, neuroradiology, neuropathology, medical and radiation oncology, and pediatrics and pediatric subspecialties to deliver care to pediatric neurology and neurosurgery patients. The pediatric neurology and neurosurgery practice is directly supported by 40 certified neuroscience or critical care nurses and hundreds of other inpatient RNs.

Pediatric neurology and neurosurgery patients at Mayo Clinic benefit from access to a team of pediatric specialists working together in 1 location to offer personally tailored multidisciplinary work-ups, facilities at Mayo Clinic's children's hospital, and the cutting-edge knowledge contributed by Mayo Clinic's pediatric neurosciences research programs.

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Welcome to the first issue of Physician Update e-mail newsletter. This newsletter will offer access to articles from the Neurosciences print publication, plus other items of general interest to a physician audience.
Patient Care
Inpatient Video-EEG Monitoring for Epilepsy
Continuous video-EEG monitoring (inpatient) helps localize seizure focus, determine seizure type, and quantify the number of seizures in patients with intractable recurrent seizures and those with an unconfirmed seizure diagnosis.
Optimizing the Functional Performance of Cancer Survivors
There is a growing understanding of the importance of exercise and rehabilitation for cancer survivors. Physical Medicine specialists can help patients manage the negative long-term sequelae of cancer and its treatments and obtain a more satisfying, high-quality recovery.
New Endoscopic Treatment for Severe Gastrointestinal Bleeding
Endoscopic ultrasound-guided therapy appears to be a safe and effective treatment for patients with severe gastrointestinal bleeding for whom conventional therapies have failed. The therapy involves injecting various agents directly into the source to stop the bleeding.
Less Can Be More When Treating Some Kidney Cancers
A Mayo Clinic study suggests that removing the entire kidney from younger patients

Expedited Patient Referrals to Mayo Clinic Departments of Neurology and Neurologic Surgery

While Mayo Clinic welcomes appointment requests for all neurologic and neurosurgical conditions, patients with the following conditions are offered expedited appointments:

1. Cerebral aneurysms
2. Cerebral or spinal arteriovenous malformations
3. Brain, spinal cord, or peripheral nerve tumors
4. Epilepsy with indications for surgery
5. Carotid disease

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