

INSIDE THIS ISSUE

2 **ALS and FTD:
Insight Into
Pathologic
Factors and
Treatment Targets**

5 **Beyond Stroke:
Expanding the
Telemedicine
Care Model**

6 **Through the
Looking Glass:
Tracking Tumor
Immunotherapy
Over Time**

Update on Spina Bifida Management at Mayo Clinic

Mayo Clinic offers a full range of services for rare and common congenital spinal cord defects. Two areas of that program are prenatal open spina bifida surgery and repair in tethered cord syndrome.

Prenatal Open Spina Bifida Surgery

Mayo Clinic's practice in prenatal surgery for repair of myelomeningocele (Figures 1 and 2), the most common form of spina bifida, is now up and running. In May 2012, Mayo Clinic in Rochester, Minnesota, performed the first surgery of this type in the Upper Midwest. "It was a complete success," says Nicholas M. Wetjen, MD, the neurosurgeon on the team. Ten weeks after the prenatal repair, the infant was born at 36 weeks' gestation without complication or motor impairment and is continuing to thrive.

Forty medical specialists contributed to the procedure, which was led by surgeons Norman P. Davies, MD, in obstetrics and gynecology, Abdalla E. Zarroug, MD, in pediatric surgery,

and Dr Wetjen in neurosurgery. "This is the kind of surgery that Mayo is set up for, with a team of collaborating surgeons and numerous medical disciplines involved," says Dr Wetjen. "The patient was identified, and within three weeks we were performing the operation."

Having encountered prenatal surgery in an animal model as an undergraduate, Dr Wetjen says the surgical experience had such an impact on him that it was a major factor in his decision to become a pediatric neurosurgeon.

Prenatal repair of myelomeningocele in humans was pioneered in the 1990s, and in 2003, a randomized, prospective clinical trial for the procedure was initiated. The results, reported in *The New England Journal of Medicine* in 2011, showed that when adjusted for lesion level, prenatal surgery improved outcomes, despite the fact that infants in the prenatal group had more severe lesions than those in the postnatal surgery group and that nearly 13% of them were delivered prematurely (eg, before 30 weeks' gestation). The significant findings included reduced need for shunting at 12 months of age, improved scores on mental and motor function at 30 months of age, and decreased incidence of hindbrain herniation associated with Chiari II malformation.

The surgery is not without risks to maternal and infant health, which is one reason why it is performed at so few medical centers. Not all infants improve, and risks must be weighed against benefits. Patient selection criteria are critical. Obesity, for example, was an exclusion criterion in the clinical trial.

Having waited for the results of the clinical trial, the Mayo team went to the University of California, San Francisco, one of the three participating study centers, for specialized training. "We have organized and adapted the surgery in a way we feel is most efficient for Mayo," Dr Wetjen explains. Some of the critical aspects of the surgery are anesthesia for mother and infant and continuous irrigation and replacement of the amniotic fluid. "The neurosurgical repair is very much like what we do in a postnatal open spina bifida repair," he says. "Depending on the age of the fetus, the tissue planes may be easier to define, just more friable because the patient is so fragile."

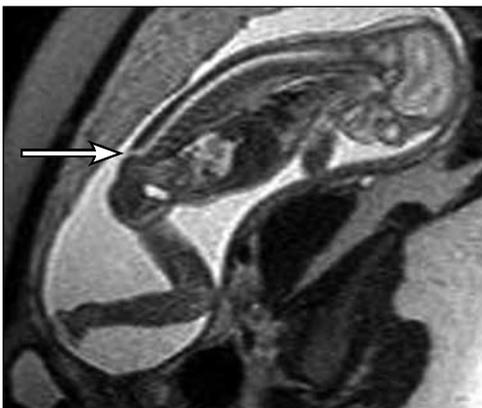
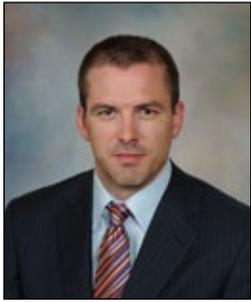


Figure 1. Fetal MRI scan demonstrating lumbo-sacral myelomeningocele.



Nicholas M. Wetjen, MD

Repairing Tethered Cord Syndrome

Occult spinal dysraphism, or tethered cord syndrome (TCS), can take several forms, but generally the terms refer to a malformation of the spinal cord in which the cord is tethered to what is usually a developmental abnormality at the base of the spine. The cord malformation may not be able to be repaired; however, by untethering it, further neurologic deficits can be prevented. TCS may be suspected when there is abnormal hair or discoloration of the skin at the tethering site. A fat pad or dimple above the gluteal cleft, especially one with fluid discharge, is highly suspicious for an underlying abnormality. Early diagnosis is critical, and definitive diagnosis requires an MRI scan. Dr Wetjen points out that pediatricians may be reluctant to refer an infant for MRI because it requires anesthesia, but he adds that Mayo's pediatric anesthesiologists are very experienced in conducting MRI in infants and children.

If neurologic symptoms are not present at the time of diagnosis, patients are monitored over

time in Mayo's Cerebral Palsy/Spina Bifida Clinic. The clinic includes physicians and other specialists from neurology, neurosurgery, urology, and physical medicine and rehabilitation.

When symptoms are present—and, in some cases, as a preventative measure—surgery is required to untether the cord. If the dural spinal tract is leaking fluid, emergency surgery is performed to prevent bacteria from entering the spinal canal. Dr Wetjen states that apart from emergency situations, surgery is best conducted when the child is between six and 12 months of age, and this is one reason why early diagnosis is so important.

In addition to seeing referred patients, Dr Wetjen occasionally reviews the medical history, MRI scans, and videos sent by parents who are considering adopting children with confirmed spinal abnormalities. "It is a type of complimentary electronic consult," he explains. A father of adopted children, Dr Wetjen feels a special bond with adoptive parents and understands the many unknowns they face.

Mayo Clinic in Minnesota has a multidisciplinary team to manage the ongoing neurologic, bowel, and bladder issues and chronic pain that may be associated with spina bifida into adulthood. With the expansion into prenatal surgery for myelomeningocele, Mayo is well prepared to manage spinal cord abnormalities across the life span.

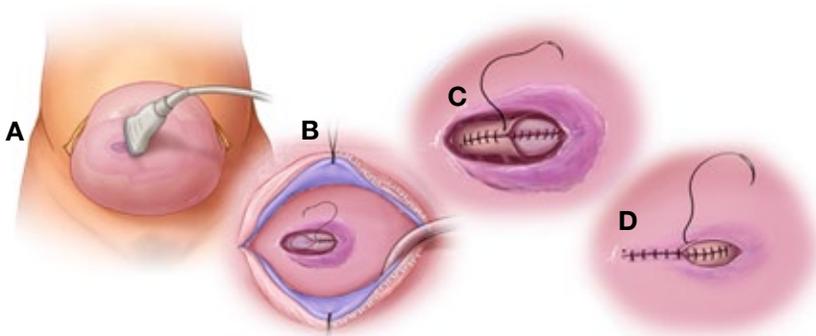


Figure 2. Prenatal open myelomeningocele repair. A, Ultrasonography of the abdomen and uterus is used to plan the incision that exposes the myelomeningocele defect of the fetus. B, The uterus is opened, the defect is exposed, and, with continuous infusion of warm irrigation to replace the amniotic fluid, the neural placode is exposed, dissected, and closed under microscopic magnification. C, The dura is closed in a watertight manner or, in some cases, is grafted because native dura is inadequate for closure. D, The dysplastic skin edges are trimmed, the lumbar myofascia elevated, and the skin closed over the neural placode and dural closure before closing the hysterotomy and abdominal incision.



View our YouTube video on the Myelomeningocele, use the QR code here or search Myelomeningocele 2012 on www.youtube.com/mayoclinic.

ALS and FTD: Insight Into Pathologic Factors and Treatment Targets

Every year, 6,000 people in the United States receive a diagnosis of amyotrophic lateral sclerosis (ALS), which typically is fatal within 3 to 5 years of onset. The related neurologic disorder, frontotemporal dementia (FTD), is the second most common form of early-onset neurodegenerative dementia, after Alzheimer's disease. The discovery by researchers at Mayo Clinic in Florida of a genetic mutation strongly associated with both ALS and FTD is offering insight into the diseases'

development, as well as opening new lines of research for eventual treatments.

The discovery—which was first reported in the September 21, 2011, online issue of *Neuron*—involves an expanded hexanucleotide (GGGGCC) repeat in a portion of the *C9ORF72* gene. The Mayo study found the chromosome 9 mutation to be the most common genetic abnormality in both familial ALS (present in 23.5% of study patients with the disease) and familial FTD (present in

11.7% of study patients with the disease).

“The hexanucleotide repeat appears to be the most common cause found to date of familial ALS and familial FTD. This finding aids the identification of the diseases,” says Kevin B. Boylan, MD, who is medical director of the ALS clinic at Mayo Clinic in Florida. “Using DNA testing for the hexanucleotide repeat and other genes that have been linked to familial ALS, we can now identify the cause of familial ALS in 60% to 70% of people with that disease.”

One of the study’s most important findings is the establishment of a genetic link between ALS and FTD. Recent research has suggested that ALS and FTD may represent a spectrum of disease: up to half of ALS patients have symptoms of FTD, and up to half of FTD patients have clinical symptoms of motor neuron dysfunction. Both diseases also have been known to occur in the same family. “The chromosome 9 discovery has established that the occurrence of these diseases within a family can be caused by the same mutation,” Dr Boylan says.

That discovery, in turn, has implications for diagnosis. The diagnostic criteria for familial ALS have included having a family member with a diagnosis of ALS; a family history of dementia was not thought to be an important risk factor. “But now we realize that it may be relevant,” Dr Boylan says. “A patient with ALS may have no family history of the disease but may have a parent who had dementia. In such cases, DNA testing for chromosome 9 repeat expansion might determine whether the patient has the familial form of ALS.”

The *C9ORF72* discovery also has potential for new treatments. Among the efforts Mayo researchers are pursuing is the development of animal and induced pluripotent stem cell models of disease related to the *C9ORF72* repeat expansion. These model systems would provide a basis for preclinical evaluation of potential gene therapy and screening of experimental medications to control expression of the mutation. “The chromosome 9 discovery is guiding us toward the future development of means to protect nerve cells from the adverse effects of the mutation,” Dr Boylan says.

Characteristic Effects on Patients

In addition, Mayo researchers are documenting the specific effects of the chromosome 9 mutation on patients. A 2012 study of patients from Mayo Clinic in Florida and in Rochester, Minnesota, identified 43 probands and 10 affected relatives with the hexanucleotide repeat. Tests showed that, although variability existed, most people with the mutation had a characteristic spectrum of demographic, clinical, neuropsychological, neuroimaging, and

especially neuropathologic findings. Among the 14 postmortem cases in the study, all showed abnormal pathological inclusions containing TDP-43 protein, commonly found in ALS and FTD. Neuronal inclusions in cerebellar granule cells were found in 11 of the 14 cases.

“This work is still in progress,” Dr Boylan says. “Although we have a basic understanding of the phenotype associated with the *C9ORF72* repeat expansion, there are still unanswered questions, especially with regard to the time course of cognitive impairment in mutation carriers with or without ALS.”

Dr Boylan notes that the cerebellum was not previously thought to be a site for important diagnostic information regarding ALS and FTD. “But these results are sufficiently specific that postmortem examinations can determine whether patients had the chromosome 9 mutation and whether their families are at risk for ALS or FTD,” he says. “This is noteworthy because a primary pathologic finding in this class of disorders is the presence of ubiquitin-positive neuronal and glial inclusions in which the DNA/RNA binding protein TDP-43 is a major component. In contrast, the ubiquitin-positive neuronal inclusions found in cerebellar neurons in patients with the *C9ORF72* repeat expansion and in some other ‘extramotor’ brain regions, such as the hippocampus and frontal neocortex, do not appear to contain TDP-43. These findings may reflect disruption of molecular pathways in addition to those involving TDP-43.”

Among the many questions raised by the *C9ORF72* discovery is the specific way the mutation is transmitted. Data suggest that a high proportion of people with the genetic variant have a shared haplotype, yet many of these people seem to have no family history of ALS or FTD.

“The central question is whether the mutation can be clinically silent or whether there may be changes in the structure of the repeat expansion as it is transmitted from generation to generation that alter its pathogenic potential,” Dr Boylan says. “Or are there other genes that either help protect a person with the mutation from developing ALS or FTD or may be conducive to developing it? The possibilities are not mutually exclusive, and more work is needed to resolve these questions.”

At Mayo, that research is enhanced by the close collaboration of clinicians and scientists. Similar to its counterparts at Mayo in Arizona and Minnesota, the ALS clinic in Florida provides clinical care, as well as performs research. Each Mayo ALS clinic is certified as a Center of Excellence by the ALS Association. “Working as an integrated unit allows us to study ALS on a broad scale and to transfer that information to patient care,” Dr Boylan says.



Kevin B. Boylan, MD

Beyond Stroke: Expanding the Telemedicine Care Model



Bart M. Demaerschalk, MD

In 2007, Mayo Clinic launched a novel approach to treating stroke patients who live in remote communities. Stroke telemedicine connects neurologists at Mayo's hospital in Phoenix, Arizona, to physicians in rural Arizona hospitals via audiovisual robots and other technology. The Mayo specialists remotely evaluate patients and make treatment recommendations to the physicians at the other sites. Telemedicine has proved so successful with stroke patients in Arizona that Mayo is expanding the program to other states, as well as to other neurologic conditions, including epilepsy and concussion.

Rural areas have as few as 1.78 neurologists for every 100,000 people, according to the American Academy of Neurology. Before Mayo initiated the teleneurology network in Arizona, about 90% of stroke patients in remote hospitals were transferred to a neurologic center. That transfer rate is now 30% or less.

"Without teleneurology, patients must be transported for hundreds of miles and over long periods to gain the neurologic expertise that doesn't exist in their communities," says Bart M. Demaerschalk, MD, professor of neurology and director of teleneurology and telestroke at Mayo Clinic in Arizona. "It's a huge advantage to provide the patients and their referring doctors with neurologic expertise at the point of care."

Mayo's network of real-time neurologic consultations operates on a hub-and-spoke system. The hubs are Mayo hospitals, where neurologists are available around the clock. When contacted by a network physician, the Mayo specialist uses a desktop or laptop computer, an iPhone, or an iPad to activate the remote hospital's

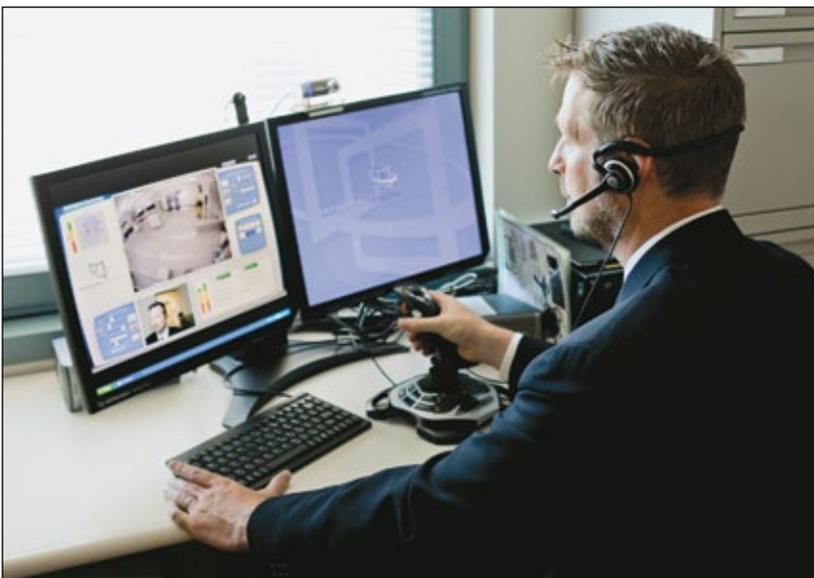
telemedicine robot and send it to the patient's bedside. The Mayo neurologist's face is visible on the robot's screen and the physician's voice is audible while he or she evaluates the patient and recommends treatment.

The network has grown to 10 remote hospitals in Arizona, with another five sites planned to join in 2012. The Mayo hospital in Phoenix also serves as a hub for Heartland Regional Medical Center in St. Joseph, Missouri. In 2010, Mayo's hospital in Jacksonville, Florida, became a telestroke hub, and soon, it will add a second spoke hospital. Mayo in Rochester, Minnesota, is becoming a hub for hospitals in the Mayo Clinic Health System network in Minnesota and Wisconsin and will continue to expand in 2013. Discussions on the potential for telemedicine have begun with officials in India, Bhutan, Mexico, Canada, and Spain. "Mayo Clinic is emerging as a national teleneurology network with the opportunity for international connectivity," Dr Demaerschalk says.

Initially, the telemedicine network focused on stroke because of the importance of timely evaluation and treatment in limiting the extent of brain injury. Mayo Clinic studies have found that telemedicine is both clinically effective and cost-effective for treating stroke. In a 2010 study, 276 patients were randomly assigned to stroke consultation using a digital observation camera vs telephone consultation. Correct emergency stroke treatment decisions were made 96% of the time with telemedicine technology, but only 83% of the time with telephone consultation. A study in 2011 found that the incremental cost-effectiveness ratio for telestroke over a person's lifetime was less than \$2,500 per quality-adjusted life-year. The threshold of \$50,000 to \$100,000 per quality-adjusted life-year is commonly cited as the cutoff point for cost-effectiveness in the United States.

Broad Range of Time-Sensitive Conditions

Now, Mayo is expanding telemedicine to neurologic emergencies other than stroke. "Status epilepticus, coma, meningitis, encephalitis, spinal cord compression, brain tumor, Guillain-Barré syndrome, and traumatic brain injury, for example, all have the potential to cause death and disability. Like stroke, they also are time sensitive," Dr Demaerschalk notes. "Neurology lends itself well to the audiovisual encounter of telemedicine because much clinical neurology is conducted by taking the history from the patient and by a largely visual examination, all of which can be done from a distance with technology."



Teleneurology provides Mayo specialists with information beyond a simple audiovisual interaction with the patient. Speech, language, calculation, and other cognitive functions can be assessed with problems, figures, diagrams, words, and sentences that are projected onto the telemedicine robot's screen. Even tests that require touch and other neurologic instruments can be remotely assessed.

"We train all the nurses in the remote hospitals to be the hands of the neurologist on the other end of the camera," Dr Demaerschalk says. "A trained bedside assistant can shine a flashlight to assess pupillary reaction, apply a pin prick to the skin to determine whether the patient has any sensory loss or numbness, use a reflex hammer to test deep tendon reflexes, and assess individual muscle groups for strength. We watch the assessment, and the nurses accurately report back to us what they observe, detect, and feel."

Electroencephalography also lends itself well to telemedicine. Mayo already uses remote monitoring of patients in the inpatient epilepsy units at its hospitals in Arizona, Florida, and Minnesota. Neurologists can observe a patient during a seizure and remotely can interpret CT or MRI brain scans, as well as the continuous EEG monitoring performed on patients in the units.

"This technology is easily extended to a

remote hospital in the teleneurology network," Dr Demaerschalk says. "The Mayo neurologist can then provide the local physician with a diagnosis—whether epilepsy or not—and a treatment recommendation."

Mayo neurologists are evaluating telemedicine solutions for a broad range of neurologic conditions, including movement disorders such as Parkinson's disease, dementia, neuromuscular disorders, and coma. "Our hypothesis is that telemedicine may lend itself well to these other neurologic problems," Dr Demaerschalk says. "But we want to be very systematic and rigorous about the careful development of the consultative paradigms and examinations, to ensure they're reliable and valid assessments that translate into efficacious, safe, high-quality, and cost-effective care, as has been the case for stroke."



View our YouTube video on the telestroke program, use the QR code here or search Telestroke Update 2012 on www.youtube.com/mayoclinic.

Through the Looking Glass: Tracking Tumor Immunotherapy Over Time

Glioblastoma, one of the most aggressive and invasive tumor types, represents a major challenge to immunotherapy because of its powerful local and systemic immunosuppressive properties. Ian F. Parney, MD, PhD, a neurosurgeon and research scientist at Mayo Clinic in Rochester, Minnesota, is working to understand the immunobiology of glioblastomas at the cellular and molecular levels in an effort to optimize immune-related treatments.

Dendritic cell vaccine, a commonly used cancer immunotherapy, offers an approach that has worked well in mouse models but has not been as effective as hoped in humans. Dr Parney explains that standard mouse models that use human brain tumor cells do not replicate the tumor-immune system interactions found in human glioblastoma. Designed to provide a platform from which to study tumor biology, such models do not have a functioning immune system. If they did, they would reject human tumor cells. To better address tumor effects on the immune system, Dr Parney and his

colleagues use a mouse model with an intact immune system called GL261, which they have modified to replicate many of the immunosuppressive processes found in human glioblastoma.

But there is an additional factor to be considered: time. Sophisticated tools are available to test the effect of vaccines on the immune system response. Among them are immunologic staining, focal microscopy, and flow cytometry, a very sensitive way to detect single immune cells in the blood. However, such tissue-slice methods provide only a snapshot in time because they

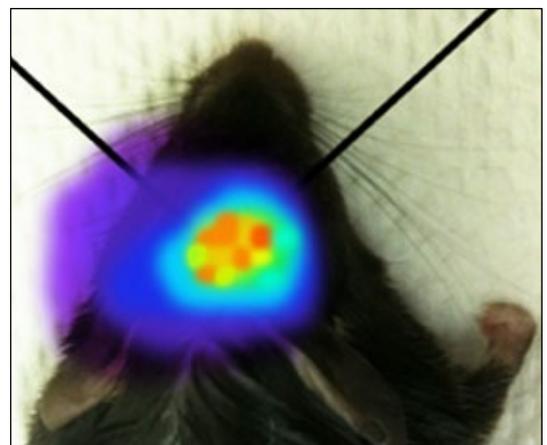


Figure 1. Bioluminescence imaging. Light heat map generated from a mouse with an intracranial glioma that has been genetically modified to express the gene luciferase.



Ian F. Parney, MD, PhD

are conducted *in vitro*. “What is needed is the ability to observe the effects over time,” says Dr Parney. “A treatment may have a rapid or a delayed effect that may not be evident on static observation.”

Windows Into the Brain

Dr Parney’s laboratory is taking several approaches to move beyond the snapshot and into observing dynamic effects of changes in tumors and alterations in the immune response *in vivo*. These methods include the established technique of bioluminescence, a specialized MRI scanner unique to Mayo Clinic, and a novel intracranial window mouse model now under development in Dr Parney’s laboratory.

Bioluminescence

Bioluminescence is a straightforward imaging process. Using the luciferase gene researchers can genetically modify tumor cells to express an enzyme that converts to a fluorescent protein. As the tumor grows, it produces increased amounts of luciferase that, when viewed under a specialized camera, produce a type of heat map (Figure 1). Although it does not produce a high-resolution image, bioluminescence can help to distinguish mice that have developed tumors from those that have not—a necessary first step

in studying treatment effects. And the images provide general evidence of changes in tumor volume in response to treatment.

7-Tesla MRI

For high-resolution brain images, Dr Parney and his team rely on a 7-Tesla MRI scanner that has been modified for mouse brain imaging by Mayo’s Nuclear Resonance Imaging Core Facility (Figure 2). Collaborating with Mayo Clinic researchers Istvan Pirko, MD, in neurology and Aaron J. Johnson, PhD, in immunology, the laboratory has developed computer-generated models of mouse brain tumors to measure tumor volume. A recent proof-of-principle study combined the MRI scans with other techniques, such as flow cytometry, to demonstrate that tumors injected with a specific immunologic protein reduced in size over time. Dr Parney explains that such high-resolution MRI allows imaging of other dynamic changes, such as the volume of tumor blood, and will thus be an invaluable aid in developing new vaccines.

Intracranial Window

The intracranial window, as its name implies, is literally a window into the mouse brain. While the MRI shows changes in tumors, the intracranial window would allow direct observations of real-time immune cell activity in a living mouse brain. In this novel approach under development in Dr Parney’s laboratory, the burr hole in the skull of mice injected with tumor cells would be covered with a plastic slip from which tumor and immune system activity could be observed using a two-photon laser microscope (Figure 3). For example, mice with genetically engineered tumor cells that fluoresce in one color can be injected with white blood cells from mice with cells that have been genetically engineered to fluoresce in a different color. The action of white blood cells in the tumor can then be tracked in real time through the intracranial window. Other aspects critical to tumor biology also can be imaged, including blood vessel growth and, in some cases, metabolic activity.

These imaging techniques are shedding new light on tumor and immune responses in living mice. They are providing the opportunity to observe the effects of vaccines over time and to refine immunologic vaccines. Dr Parney points out that his team is fortunate to have access to the Mayo Clinic Human Cell Therapy Laboratory, a Good Manufacturing Practices facility, which can produce clinical-grade tumor vaccines and readily translate their findings to clinical practice.

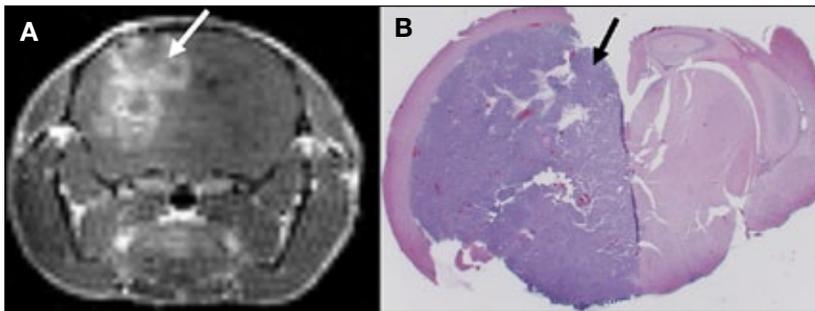


Figure 2. Mouse MRI scan and photomicrograph. A, MRI scan showing a glioma (white arrow) in the right frontal lobe of a mouse. B, Photomicrograph of brain from the same mouse showing tumor stained purple with hematoxylin and eosin (black arrow).

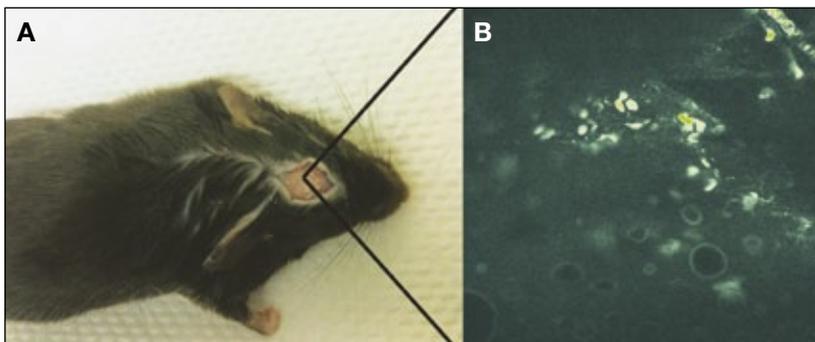


Figure 3. Intravital imaging. A, A permanent cranial window has been created in a living mouse. B, Malignant glioma cells, expressing green fluorescent protein, can be visualized growing in the brain of this living mouse using a two-photon laser microscope magnification 20X.

Research Highlights in Neurology and Neurologic Surgery



Potential New Therapy for Neuromyelitis Optica

Neuromyelitis optica (NMO) is a potentially debilitating central nervous system disorder involving myelitis and inflammation of the optic nerves. Often misdiagnosed as multiple sclerosis, NMO can cause blindness in one or both eyes, weakness or paralysis in the legs or arms, painful spasms, loss of sensation, and bladder or bowel dysfunction from spinal cord damage. Severe NMO attacks can cause permanent visual or motor disability. In a recent study presented at the 2012 annual meeting of the American Neurological Association, Mayo Clinic researchers reported that eculizumab, a drug typically used to treat blood disorders, appears to stop NMO attacks in patients with active and severe symptoms of the disease. Previously, Mayo Clinic researchers discovered an antibody—NMO-IgG—in NMO patients that activates the damaging C5 complement protein. Eculizumab is a monoclonal antibody that binds to C5, preventing its activation. In the recent study, Sean J. Pittock, MD, and coauthors found that of the 14 study participants who received eculizumab treatment intravenously every two weeks for one year, 12 were symptom-free for the duration of the study. Although eculizumab therapy is not a cure, the authors report that it could potentially lead to longer attack-free periods for thousands of NMO patients worldwide.

Association Between Macronutrient Intake and Risk of Dementia

Macronutrients (ie, carbohydrates, fat, and protein) have been associated with glucose metabolism and with neuronal integrity and function. High caloric intake has been correlated with increased risk of cognitive impairment, and reduced caloric intake with reduced amyloid β deposition. To investigate the relation between the percentage of daily calories from specific macronutrients and mild cognitive impairment (MCI) or dementia, Mayo Clinic researchers conducted a population-based prospective study of elderly persons monitored over a median of 3.7 years. Study participants were assessed by an initial neurologic evaluation, neuropsychological testing, and a 128-item food-frequency questionnaire that helped to establish the percent of caloric intake from each macronutrient category. Cognitive testing was conducted at 15-month intervals. Findings showed that among the 937 participants who were cognitively normal at baseline, MCI or dementia developed in 200 and that the risk of either condition was increased in participants with dietary patterns showing a high percentage of carbohydrate intake and reduced in those with a high percentage of fat and protein intake. The authors concluded that a diet high in carbohydrates and low in fats and proteins may increase the risk of MCI or dementia in elderly persons (Roberts et al. *J Alzheimer's Dis.* 2012;32[2]:329-39).

Glycine Receptor Aids Identification of Autoimmune Hyperexcitability Disorders

Glycine is essential for mediating inhibitory neurotransmission and regulating motor neuron excitability in the brainstem and spinal cord. Disorders ascribed to loss of this input include stiff-man syndrome (SMS; also known as *stiff-person syndrome*), variant SMS, and progressive encephalomyelitis with rigidity and myoclonus (PERM). Autoantibodies for the glycine receptor GAD65-IgG are detected in 80% of patients with classic SMS. Among other autoantigens pertinent to SMS phenotype is the glycine-gated chloride channel GlyR α 1-IgG, which has been associated with the rare, PERM phenotype. Mayo Clinic researchers conducted a retrospective case-control study to investigate whether GlyR α 1-IgG occurs in more common forms of brainstem and spinal cord hyperexcitability disorders. Serum and cerebrospinal fluid specimens collected from 81 patients with a diagnosis of SMS and phenotypically similar disorders and from 80 neurologic control subjects and 20 healthy control subjects were tested for GlyR α 1-IgG. The results indicated that serologic tests for GlyR α 1-IgG complement tests for GAD65-IgG in aiding diagnosis of autoimmune brainstem and spinal cord hyperexcitability disorders. Treatment and outcome data from the medical records of the SMS phenotype patients showed that immunotherapy responses were more frequent in GlyR α 1-IgG-positive cases (6 of 7 improved) than in seronegative cases (7 of 25 improved). This finding suggests that GlyR α 1-IgG testing may predict immunotherapy responsiveness, although the range of immunotherapy treatments used and the retrospective nature of the study preclude definite conclusions (McKeon et al. *Arch Neurol.* 2012 Oct 22. doi:10.1001/jamaneurol.2013.574).

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

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Education Opportunities

Multiple Sclerosis 2013: Update and Practical Management

March 1-2, 2013, Mayo Clinic Education Center, Phoenix, Arizona

This course provides a research update and instruction in management strategies for physicians and health care providers who treat multiple sclerosis.

Mayo Clinic Headache Symposium

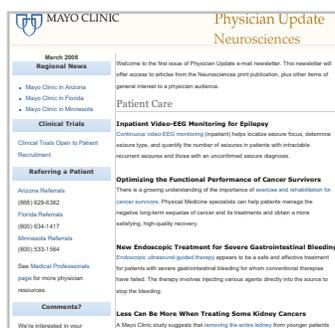
May 3-5, 2013, Hotel Nikko San Francisco, San Francisco, California

This course provides attendees with an update in the diagnosis and management of both primary and secondary headache disorders. The format include lectures, expert panel discussions, interactive question and answer sessions, and small-group discussions.

Clinical Trials Update

Study of Thymectomy in Acetylcholine Receptor–Positive Myasthenia Gravis: Patients with generalized MG with or without treatment with Mestinon and Prednisone are randomly assigned to receive thymectomy or not and are observed for three years.

For more information about other Mayo Clinic research studies, please visit the Research section on www.mayoclinic.org/medicalprofs.



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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

MAYO CLINIC | 4500 San Pablo Road | 200 First Street SW | 13400 East Shea Boulevard
mayoclinic.org | Jacksonville, FL 32224 | Rochester, MN 55905 | Scottsdale, AZ 85259

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