

INSIDE THIS ISSUE

2 **Innovative
Monitoring in the
Neuro-ICU**

4 **Sleep Disorders:
Mayo's Deep
Experience**

6 **Standardizing
Care Pathways
for Spinal Implants**

Understanding MS in Children

Although multiple sclerosis (MS) most commonly affects people who are ages 20 to 40, as many as 5 percent of MS patients develop symptoms during childhood. Yet many features of the natural history of pediatric MS, as well as best practices for diagnosing and treating the disease, are not fully understood.

Mayo Clinic in Rochester, Minn., has been recognized by the National Multiple Sclerosis Society as a "pediatric MS center of excellence." The multidisciplinary practice focuses on evaluating and treating children with MS and other central nervous system (CNS) disorders. In conjunction with five similarly designated centers, Mayo researchers also are enrolling patients in a database to support studies on the causes and management of these CNS disorders in children.

"Our goal is to learn more about pediatric MS so we can establish treatment guidelines and standards and be in a leading position to offer the best care for these patients," says Jan-Mendelt Tillema, M.D., a pediatric neurologist at Mayo Clinic in Minnesota.

Diagnosis and treatment

For physicians, the challenges of pediatric MS begin with diagnosis. Magnetic resonance imaging (MRI) plays a large role, as it does in adults. "But magnetic resonance imaging of children can be much more difficult to interpret," Dr. Tillema says. For example, lesions may be less sharply demarcated (Figure). Distinguishing between MRI patterns in MS and acute disseminated encephalomyelitis (ADEM) — which occurs more frequently in children and adolescents than does MS — can be challenging, particularly after a single episode of signs and symptoms.

Following subsequent attacks, MRI often can show clearer evidence of disease, which is required to make the diagnosis of MS. Dr. Tillema notes that research studies with a small number of patients suggest MS attacks tend to occur more frequently in the initial phase of the disease in children than in adults — a feature he has witnessed in his own practice. "It's not uncommon for kids to have a few attacks within a year or two, whereas in adults it is more often — but not always — the case that episodes are spread out over several years," he says.

Treatment for pediatric MS relies on the same medications used in adults, although randomized controlled trials needed for Food and Drug Administration approval of such medications have not included pediatric patients. One of the major goals of the

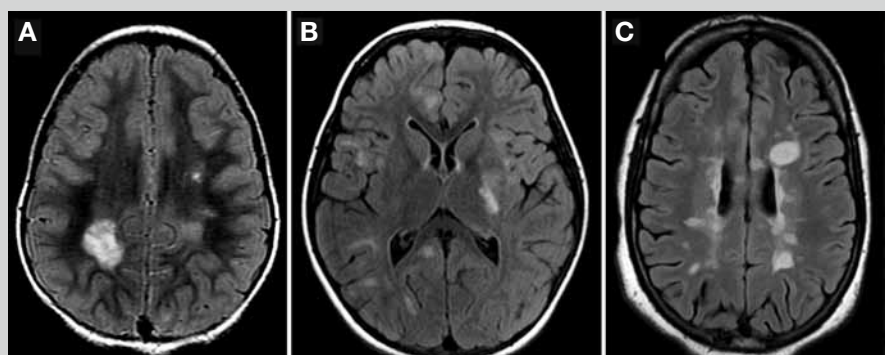


Figure. A, Axial T2 FLAIR image of a 5-year-old boy with multiple sclerosis. Newly developed lesions aren't well demarcated and show contrast enhancement after gadolinium administration. B, Axial T2 FLAIR image of a 6-year-old girl with acute disseminated encephalomyelitis in the setting of viral prodromal illness, with no gadolinium contrast. The lesions aren't well demarcated and show involvement of both cerebral white and gray matter. C, Post-gadolinium T1 image of a 17-year-old male with clinical symptoms of mild ataxia and mild unilateral weakness. Numerous well-demarcated lesions are visible. Subsequent clinical events corresponding with new MRI lesions developed over time.



Jan-Mendelt Tillema, M.D.



Moses Rodriguez, M.D.

pediatric centers of excellence is to facilitate large-scale research initiatives.

"There is increasing experience in using MS medications in kids. Based on studies of these cases, we know more about the similarities and differences in both efficacy and side effect profiles in children," Dr. Tillema says. "The future target is to find the safest and best drugs to treat MS in children, rather than extrapolating that information from adult studies."

Currently, the most effective and commonly used MS medications for children must be injected. Complications may include lowered white cell count and liver irritation or injury, so children must have frequent lab evaluations. Other common side effects include reactions at the injection site and flu-like symptoms such as fatigue and malaise.

Although these adult medications appear to be beneficial in reducing MS attacks, "we see some pediatric patients whose side effects or anxiety over injections are so disturbing that families choose to discontinue the medication," Dr. Tillema says. "Fortunately, as more medications are coming out, there are alternatives. But these decisions can be difficult for patients and families."

Focus on pediatric issues

Like adults, children with MS may benefit from consultation with a neuropsychologist, rehabilitation specialist and ophthalmologist, if vision problems develop. At Mayo, evaluations with all of these specialists typically are prescheduled. "If there are any other comorbidities, we have the opportunity to consult our other pediatric specialists if needed," Dr. Tillema says.

Pediatric MS is uniquely challenging because its repeated attacks on the CNS occur during childhood development. According to an article in the January 2013 issue of *Journal of Child Neurology*, in a recent study of pediatric patients, researchers from Mayo and other pediatric MS centers of excellence identified cognitive impairment in 35 percent of study

participants with MS and 18 percent of participants with clinically isolated syndrome.

At Mayo, these data are used not only for research but also as guidance for families facing potential school-related problems. The results of neuropsychological testing can help parents and school officials understand the difficulties faced by children with MS as they mature. "We frequently see older kids who want to transition to college or a future career. These children can encounter problems in school," Dr. Tillema says.

As a major center for adult MS, Mayo can also offer pediatric patients a smooth transition in their medical care for a lifelong disease. Moses Rodriguez, M.D., a neurologist and MS specialist at Mayo Clinic in Minnesota, for many years has worked closely with Mayo's pediatric neurologists treating these patients. Dr. Rodriguez was also among the neurologists who initiated the national network of pediatric MS centers of excellence.

"The combination of expertise is a real strength for patients," Dr. Tillema says. "It helps not just with transition for future care but also with current care. The uncertainties that come with the physical and emotional challenges of MS can be very distressing to both patients and their caregivers. Mayo Clinic's expertise in pediatric MS allows our treatment team to provide families with answers to many of these questions, and with optimal neurological care."

For more information

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Pediatric MS Centers of Excellence. National Multiple Sclerosis Society. <http://www.nationalmssociety.org/about-multiple-sclerosis/pediatric-ms/pediatric-ms-centers-of-excellence/index.aspx>.

Innovative Monitoring in the Neuro-ICU

Perhaps uniquely among physicians, neurologists follow a carefully scripted examination to localize and diagnose patients' problems. In critically ill patients, the neurological examination is limited but remains the most reliable tool for monitoring a patient's condition. Because of these limitations, patient monitoring systems serve a crucial role. Mayo Clinic utilizes innovative neurointensive care unit (neuro-ICU) monitoring as an essential

adjunct in both patient care and research.

Cerebral oxygenation monitoring and real-time EEG

The neuro-ICU at Mayo Clinic in Rochester, Minn., is now equipped with a monitor that can measure regional cerebral oxygen saturation (Figure). Like pulse oximeters, cerebral oxygenation monitors use near-infrared light to measure

oxyhemoglobin and deoxyhemoglobin levels in blood. The noninvasive technology utilizes optode-containing pads that are attached to the patient's forehead.

Cerebral oxygenation monitoring is especially helpful for evaluating patients after aneurysmal subarachnoid hemorrhage. Those patients are at risk of developing delayed cerebral ischemia, a major contributor to poor outcome after subarachnoid hemorrhage. Near-infrared technology can detect disturbances in cerebral perfusion, which have been implicated in the development of delayed cerebral ischemia.

"Cerebral oxygenation monitoring is another tool — in addition to transcranial Doppler, which we've used for many years — that warns of early changes in cerebral perfusion in patients at risk of ischemia," says Sara E. Hocker, M.D., a neurointensivist at Mayo Clinic in Minnesota. "Having this noninvasive option is a huge advantage for patients."

Mayo's commitment to innovative monitoring extends to providing continuous, real-time EEG monitoring. Neuro-ICU patients not only are monitored continuously; EEG technicians also watch the tracing around the clock. "That allows us to react quickly to seizure activity rather than waiting until the next day to find out the patient had five or six seizures overnight," Dr. Hocker says. Real-time EEG helps Mayo neurointensivists define the number, duration and nature of seizures and autonomic spells, and sometimes has implications about the patient's prognosis.

Continuous EEG is also of particular benefit to patients undergoing therapeutic hypothermia after cardiac arrest. Mayo Clinic helped pioneer the use of that therapy, which has been shown to improve neurological outcome after out-of-hospital cardiac arrest due to ventricular fibrillation.

In 2009, Mayo began continuous EEG monitoring of patients during therapeutic hypothermia and rewarming after cardiac arrest. According to an article in the January 2013 issue of *Neurology*, a Mayo retrospective study of the records of 54 patients treated with that protocol from 2009 to 2012 found continuous EEG to have prognostic value. EEG severity grading during both therapeutic hypothermia and rewarming — as well as incidence of seizures, nonreactive background and epileptiform discharges — correlated with treatment outcome.

Enhancing research

In addition to improving patient treatment, innovative monitoring plays a key role in Mayo's many research efforts in the neuro-ICU. Following the study of continuous EEG in therapeutic hypothermia, researchers at Mayo



Figure. The EQUANOX™ Model 7600 cerebral/somatic regional oximeter with EQUANOX™ Advance Adult Sensors. Photo courtesy of Nonin Medical, Inc.

are using cerebral oxygenation monitoring to learn more about cerebral oxygenation during the procedure. Issues under investigation include the frequency of cerebral desaturation when peripheral oxygen appears normal; the duration of desaturation events; their occurrence during the cooling versus the rewarming period; and the impact on patient outcomes, particularly cognitive outcomes.

Continuous EEG monitoring is also frequently used in research on epilepsy, including a recent Mayo study characterizing the predictors of outcome in refractory status epilepticus. According to an article in the January 2013 issue of *JAMA Neurology*, that study documented an association between the severity of status epilepticus, and clinical course and outcome. In addition, real-time EEG is facilitating a Mayo study of the ketogenic diet as adjunct therapy for refractory status epilepticus. The prospective study, done in collaboration with researchers at Johns Hopkins University, examines the diet's feasibility and safety and eventually will seek to determine efficacy in managing refractory status epilepticus.

"We would like to know whether we can wean study participants from anesthetic agents sooner because of the ketogenic diet. Continuous EEG monitoring will be very helpful in that setting," Dr. Hocker notes.

For more information

Crepeau AZ, et al. Continuous EEG in therapeutic hypothermia after cardiac arrest: Prognostic and clinical value. *Neurology*. 2013;80:339.

Hocker SE, et al. Predictors of outcome in refractory status epilepticus. *JAMA Neurology*. 2013;70:72.



Sara E. Hocker, M.D.

Sleep Disorders: Mayo's Deep Experience



Michael H. Silber, M.B.,
Ch.B.

The Center for Sleep Medicine at Mayo Clinic in Rochester, Minn., has a comprehensive, multidisciplinary practice treating children and adults. With a strong clinical focus, the center has consultants with experience diagnosing and treating sleep disorders ranging from the rare to the well-known. After initial clinical evaluation, patients may be referred for polysomnography in the center's 24-bed sleep lab.

The center's 22 consultants include neurologists, psychiatrists, pediatricians and pulmonologists. The neurologists who treat adults at the center specialize in sleep medicine. Although Mayo's sleep medicine specialists treat the full spectrum of neurological sleep disorders, particular areas of interest include Willis-Ekbom disease, also known as restless legs syndrome; rapid eye movement (REM) sleep behavior disorder and narcolepsy.

Willis-Ekbom disease (restless legs syndrome)

Mayo Clinic has a national reputation in treatment for and research on Willis-Ekbom disease, the most common sleep-related movement disorder seen at Mayo. Michael H. Silber, M.B., Ch.B., co-director of the Center for Sleep Medicine at Mayo in Minnesota, currently serves as chair of the medical advisory board of the Willis-Ekbom Disease Foundation, which is revising the national algorithm for treating the condition.

"At Mayo, we are very interested, and have experience, in the management of complex cases of Willis-Ekbom disease," Dr. Silber says. "We see lots of patients with treatment-related problems, in which there have been drug failures and drug side effects."

Although therapies, notably dopamine agonists, are available to treat Willis-Ekbom disease, managing the condition remains difficult. The results of a recent Mayo study of the long-term effects of treatment with the dopamine agonist pramipexole suggest that the drug's efficacy decreases over time, leading to increased dosages and adjunct therapies. According to an article in the December 2012 issue of *Sleep Medicine*, augmentation developed in 42 percent of patients in the Mayo study over a mean follow-up period of eight years. Side effects, including daytime sleepiness and impulse control disorders, were reported by 74 percent of study participants.

For patients who experience difficulties with dopamine agonists, Mayo neurologists have experience prescribing alternatives, including gabapentin, pregabalin and opioids. Iron supplements may be prescribed for patients with iron deficiency, which has been associated with Willis-Ekbom disease.

REM sleep behavior disorder

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by dream-enactment behavior and abnormal motor activity during REM sleep. RBD has been considered rare, but recent Mayo Clinic research suggests the incidence may be higher than previously thought, particularly in men older than age 70. "We have a lot of experience with REM sleep behavior disorder," Dr. Silber notes.

Clonazepam has been the most common first line treatment for RBD. But the medication's possible side effects — which include cognitive impairment, dizziness and unsteadiness — are of



particular concern in elderly patients. A recent Mayo study compared longitudinal outcomes for RBD treated with clonazepam and melatonin. According to an article in the March 2013 issue of *Sleep Medicine*, the results indicated that although both treatments reduced RBD behaviors and injuries, melatonin-treated patients reported fewer adverse effects. “We’re starting to recommend that treatment start with melatonin and then move to clonazepam if it doesn’t work,” Dr. Silber says.

Mayo physicians have also been at the forefront of research linking RBD to neurodegenerative disorders. A recent collaborative study with researchers from the University of Minnesota, updating research begun in the 1990s, reported that the vast majority (81 percent) of men initially diagnosed with idiopathic RBD developed a parkinsonian disorder or dementia. The mean interval from onset of RBD to emergence of the neurodegenerative disorder was 14 years, with the range extending to 29 years.

“Unfortunately, at this point there are no medications that can prevent that progression from happening,” Dr. Silber says. “But this predisposed group will be an excellent model for testing such drugs as soon as they become available.”

Narcolepsy

Narcolepsy has been studied and treated at Mayo Clinic since at least the 1930s. Mayo researchers completed one of the first epidemiologic studies of the disease, defining its prevalence and incidence.

As with other sleep disorders, Mayo physicians have experience treating complex cases of narcolepsy. A range of stimulant medications are available — the major challenge, establishing a dose that is effective while minimizing adverse side effects. A Mayo study, according to an article in the June 2005 issue of *Sleep*, demonstrated a significantly higher occurrence of psychosis, substance misuse and psychiatric hospitalizations in patients with narcolepsy who used high-dose stimulant therapy compared with those using standard doses. Mayo physicians also have experience with the range of selective serotonin reuptake inhibitors and norepinephrine reuptake inhibitors prescribed for cataplexy, as well as sodium oxybate, which helps improve nighttime sleep and may help with daytime sleepiness.

Research on the progression of narcolepsy is yielding intriguing results that may ultimately improve treatment. Mayo participated in a recent international study on narcolepsy without cataplexy. Previous research has focused mostly on narcolepsy with cataplexy, which is associated with hypocretin deficiency and the presence of the HLA-DQB1*0602 gene; it is considered



a lifelong condition requiring treatment with potentially addictive medications. Narcolepsy without cataplexy, in which hypocretin levels are often normal, is less common.

According to an article in the September 2012 issue of *Sleep*, in a retrospective study of 171 cases of narcolepsy without cataplexy, Mayo researchers and colleagues found that nearly one-fourth (24 percent) of the patients studied had hypocretin deficiency. All of these patients were HLA-DBQ1*0602 positive. Of the 127 patients the researchers were able to recontact, 33 percent with low hypocretin had developed typical cataplexy by 26 years after onset of narcolepsy, whereas only 1 percent of patients with normal hypocretin had developed cataplexy. Although more research is needed, the study suggests that the presence of hypocretin deficiency in HLA-positive patients may allow physicians to better predict the lifelong evolution of narcolepsy and thus guide treatment.

For more information

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William E. Krauss, M.D.



Barry D. Birch, M.D.



Mark A. Pichelmann, M.D.

Standardizing Care Pathways for Spinal Implants

Team medicine — cooperation across sites and specialties — has long been a hallmark of patient care at Mayo Clinic. Now, Mayo neurosurgeons and orthopedic surgeons are taking that collaboration in a new direction, by developing standardized care pathways for spinal implants across all Mayo sites.

“When we started this effort, there was wide variation in the implants used across the Mayo enterprise,” says William E. Krauss, M.D., a neurosurgeon at Mayo Clinic in Rochester, Minn. “Now just about every implant we use in lumbar and cervical spine procedures is one that everybody has agreed on.”

This standardization of medical supplies is an outcome of Mayo’s ongoing efforts to ensure the best quality care for patients at all sites. “The goal is to examine preoperative and postoperative care for patients with spinal disorders and to determine a best-practices model on which all sites cooperate,” says Barry D. Birch, M.D., a neurosurgeon at Mayo Clinic in Phoenix, Ariz.

Forging supply chain agreement

Spinal implants — the plates, rods and screws that are surgically placed to help obtain spinal fusion — are essential components of treatment for spinal instability (Figure). The most recent round of spinal-implant procurement began with discussions among neurosurgeons and orthopedic surgeons at all three Mayo sites — as well as in the Mayo Clinic Health System, which provides care in communities in the Midwest — about which implants should be used for various procedures. After numerous meetings within sites, teleconferences among sites and discussions with Mayo’s procurement executives, agreement was reached. As a result, Mayo is now able to source nearly all of its spinal implants from three medical-supply companies.

“A single company may not have all the instrumentation we need for all parts of the spine. With three companies we cover almost all our bases,” says Mark A. Pichelmann, M.D., a neurosurgeon at Mayo Clinic in Jacksonville, Fla. “For very special needs we also have the capability to

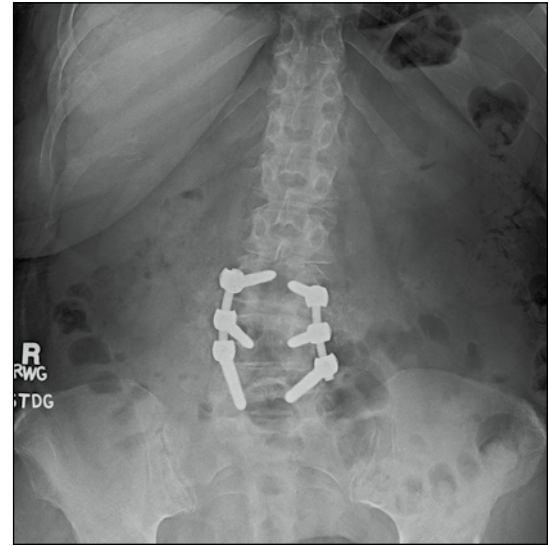


Figure. Spinal implants for treatment of lumbar scoliosis and spondylolisthesis

bring in a fourth or fifth vendor. It’s not at all constricting in terms of how we practice medicine.”

Indeed, the surgeons quickly realized a side benefit: Standardized instrumentation means fewer surgical-equipment trays. “We save a lot of shelf space in the operating room, and our staff become very proficient in the use of the two or three systems we have in place,” Dr. Pichelmann says.

Standardizing the supply chain also offers potential cost savings. In an era of rising costs and increasingly complex health care, Mayo understands the need to reduce the cost of care. Standardization whenever possible is one way of reducing costs without compromising patient care. “When all Mayo sites cooperate, the practice is both cost-effective and beneficial in terms of improved patient outcomes,” Dr. Birch says.

For Mayo physicians, this type of collaboration is an extension of their usual teamwork. “We work together on a clinical basis, discussing cases and sharing patients,” Dr. Krauss says. “This is an opportunity for us to work together to standardize supplies.”

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Research Highlights in Neurology and Neurologic Surgery

Cardiac Disease Linked to Higher Risk of Mild Cognitive Impairment

Mild cognitive impairment (MCI) is an important stage for the early detection of and intervention for dementia. Nonamnesic MCI (naMCI) has been hypothesized as having a vascular etiology. In a prospective, population-based cohort study, researchers at Mayo Clinic in Rochester, Minn., found that cardiac disease is an independent risk factor for naMCI, with a stronger association in women than men. Researchers evaluated 2,719 people ages 70 to 89 from Olmsted County, Minn., at baseline and every 15 months, using the Clinical Dementia Rating scale, a neurological evaluation and neuropsychological testing. Of the 1,450 study participants without MCI at the beginning of the study, 669 had heart disease and 781 didn't. Over the course of the four-year study, 59 participants with heart disease (8.8 percent) developed naMCI. In comparison, 34 of the participants without heart disease (4.4 percent) developed naMCI. The association varied by sex, with cardiac disease and naMCI occurring more often together in women than in men. Cardiac disease wasn't associated with amnesic MCI. The results support the hypothesis that naMCI has a vascular etiology, and suggest that prevention and management of cardiac disease and vascular risk factors may reduce the risk of naMCI. (Roberts RO, et al. Cardiac disease associated with increased risk of nonamnesic cognitive impairment: Stronger effect on women. *JAMA Neurology*. 2013;70;3:374.)

Role of KLK6 in Glioblastoma

Glioblastoma multiforme (GBM) is the most common and malignant form of primary intracranial tumor in adults. The prognosis for patients is extremely poor, with a median survival of only 12 to 15 months. Considerable heterogeneity exists within this tumor type, a factor contributing to GBM's poor response to treatment. Kallikreins are known to have prognostic value in certain cancers, but few studies have evaluated their role in brain tumors. Researchers at Mayo Clinic in Rochester, Minn., have demonstrated that elevated levels of kallikrein 6 (KLK6) in GBM are likely to promote the resistance of tumor cells to cytotoxic agents and are an indicator of reduced patient postsurgical survival times. The researchers examined 60 grade IV astrocytoma tumor specimens. A range of KLK6 expression was observed, with higher levels corresponding to poorer patient prognosis, even after adjusting for gender and for Eastern Cooperative Oncology Group performance scores. Tumor specimens with the highest levels of KLK6 were associated with median patient survival of 276 days, compared with median survival of 408 days associated with lower levels of KLK6. The researchers also investigated the mechanism of the enzyme. They found that GBM cells treated in the laboratory with KLK6 showed resistance to radiation and chemotherapy treatment and determined that the ability of KLK6 to promote resistance to apoptosis was dependent on activation of protease-activated receptor 1. The findings indicate that KLK6 and protease-activated receptor 1 may represent potential new therapeutic targets for developing methods of sensitizing GBM to cytotoxic agents. (Drucker KL, et al. Clinical significance and novel mechanism of action of kallikrein 6 in glioblastoma. *Neuro-Oncology*. 2013;15;3:305.)

Telestroke Is Cost-Effective for Hospitals

Researchers at Mayo Clinic in Phoenix, Ariz., have shown that using telemedicine to deliver stroke care appears to be cost-effective for rural hospitals that don't have round-the-clock staffing by neurologists. Telestroke uses audiovisual technology that allows a patient with stroke to be examined in real time by a stroke specialist elsewhere who consults via computer with an emergency room physician at the rural site. Previous studies have found that telestroke networks are effective in terms of the net costs to society for each year of life gained. The new study examined costs and benefits from the perspective of network hospitals. The researchers developed a model to compare costs and effectiveness with and without a telestroke network over a five-year period. Using data from Georgia Health Sciences University and Mayo telestroke networks, the model considered differences in rates of teleconsultations, intravenous thrombolysis, endovascular stroke therapies and spoke-to-hub transfers. The results predicted that compared with no network, a telestroke system of a single hub and seven spoke hospitals would treat 45 more patients with intravenous thrombolysis and 20 more with endovascular stroke therapies each year. But the model also indicated that telestroke would lead to an estimated 6.1 more home discharges a year, resulting in an annual savings of \$109,080 for spoke hospitals and overall cost savings for the network of \$358,435 a year. The researchers note the economic implications of a telestroke network vary for individual participating hospitals, depending on available resources and spoke-to-hub transfer rates. (Switzer JA, et al. Cost-effectiveness of hub-and-spoke telestroke networks for the management of acute ischemic stroke from the hospitals' perspectives. *Circulation: Cardiovascular Quality and Outcomes*. 2013;6:18.)

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

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2013 courses

September

Stroke and Cerebrovascular Disease Review

Sept. 26-29, 2013
Ritz-Carlton, Amelia Island, Fla.

November

Neuroradiology: Practice to Innovation

Nov. 11-15, 2013
The Ritz-Carlton, Grand Cayman, Cayman Islands

2014 courses

March

Mayo Clinic EMG, EEG and Neurophysiology in Clinical Practice

March 2-8, 2014
Mayo Clinic, Arizona

May

Neurorehabilitation Summit

May 19-20, 2014
DoubleTree, Rochester, Minn.

November

Parkinson's Disease & Other Movement Disorders for the Practitioner – 2014

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Mayo Clinic, Education Center, Phoenix

Neuroradiology: Practice to Innovation

Nov. 10-14, 2014
Ritz-Carlton Dove Mountain, Marana, Ariz.

Information and registration

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

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3. Brain, spinal cord or peripheral nerve tumors
4. Epilepsy with indications for surgery
5. Carotid disease

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