MAYO CLINIC

NeurosciencesUpdate

Neurology and Neurologic Surgery News

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INSIDE THIS ISSUE

Advances in Denervation Surgery for Torticollis

Torticollis, also known as idiopathic cervical dystonia, is one of the most common focal dystonias in adults. Voluntary muscles in the neck contract, causing involuntary twisting, turning, or tilting of the head and neck. Contractions may be sustained or may occur in spasms, causing repetitive head movement. More typically, the posture is fixed in 1 position or a combination of positions, including forward (anterocollis), backward (retrocollis), or to the side (laterocollis).

"Patients with this condition are usually in terrible pain," explains Robert J. Spinner, MD, a neurosurgeon at Mayo Clinic in Rochester, Minnesota, "and they also have tremendous physical and functional limitations." Employment options are limited, driving is often out of the question, and especially if the head and neck are in retrocollis, walking, eating, and all aspects of self-care are affected. Quality of life suffers and patients often become depressed in response.

Medical treatments, including nonsteroidal anti-inflammatory drugs, muscle relaxants, and anticholinergics, have had only limited success. At Mayo Clinic's 3 campuses, botulinum toxin is the medical therapy most often prescribed. Joseph Y. Matsumoto, MD, a movement disorders specialist in the Department of Neurology at Mayo Clinic in Rochester, notes that botulinum toxin has proven far more effective than other medications. After careful EMG mapping, botulinum toxin is injected into a select number of affected muscles. Patients return every 3 to 6 months for follow-up injections.

Botulinum toxin can provide relief for many years. However, some patients do not respond to it, and in others, it can lose its effectiveness over time. In these situations, surgery may be an option. Selective peripheral denervation, offered at only a few institutions, has proven to be a safe and effective surgical option. It involves cutting the nerves to targeted muscles to prevent innervation and, thus, over-firing.

Denervation surgery for torticollis was pioneered in Montreal in the 1980s by Claude Bertrand, MD. Mayo Clinic has an extensive history of treating this rare disorder with denervation surgery for it. In a 2003 study, neurosurgeon Dudley H. Davis, MD, and his colleagues at Mayo Clinic in Rochester found the procedure was successful in approximately 75% of patients.

To improve outcomes, Dr Davis began to add selective single-muscle resection to the nerve

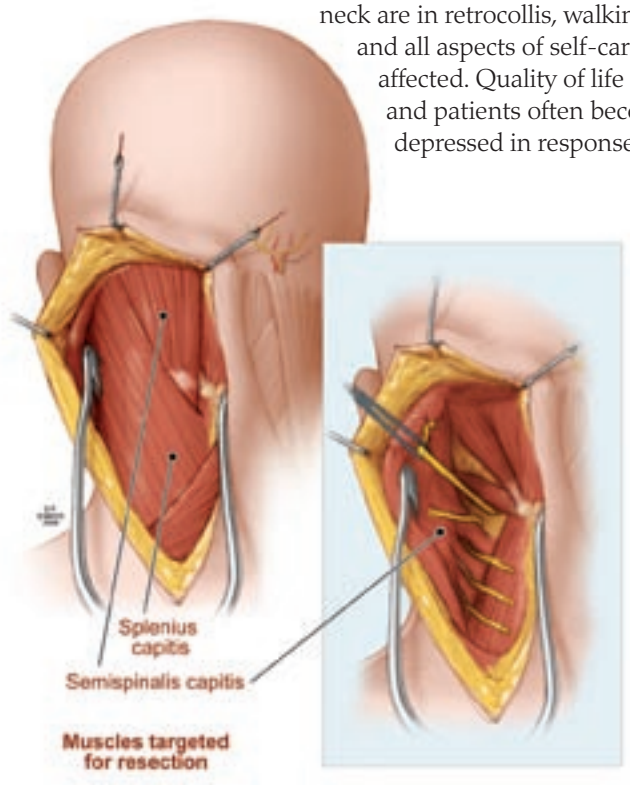
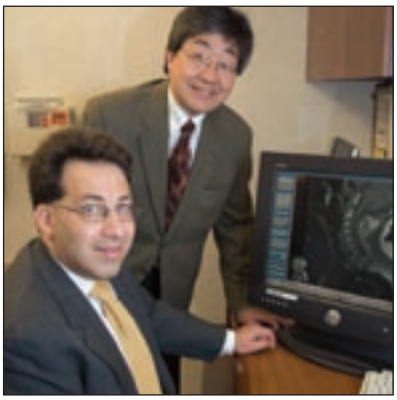


Figure. ***Torticollis Surgery.*** *The current surgical strategy combines selective peripheral nerve denervation and targeted muscle resection.*



Robert J. Spinner, MD, and Joseph Y. Matsumoto, MD

resection. As Dr Spinner explains, "Successful denervations can be difficult because anatomy is variable and there are multiple nerve inputs to muscle. Fine branches of a given nerve may not be identified in surgery, or another nerve may give off a twig. Even after a nerve has been cut, there is some potential for regrowth—the sprouting or collateralization of nerves—which is not well understood, even in animal models." By removing muscle, the potential for continued innervation is also removed. Resecting muscle along with nerves has improved the original denervation procedure.

Dr Spinner, having learned the procedure from Dr Davis, further refined it 2 years ago by resecting more than 1 muscle. Muscles to be resected are targeted with careful, precise, preoperative EMG recordings by Dr Matsumoto. Dr Spinner emphasizes that it is a highly selective procedure. "If, for example, 12 muscles are overfiring, the surgeon cannot divide or resect all of them without causing patient disability. What we do, based on Dr Bertrand's work and Dr Davis's experience and our own, is target the muscles that we know are the most important contributors to the problem." The 10 patients who have undergone this refined surgical approach thus far have had positive outcomes.

Early Detection of Alzheimer's Disease

How Early and by What Means?

Richard J. Caselli, MD

The research frontier in treatment for Alzheimer's disease (AD) is being defined by the search for disease-modifying therapies—therapies that would alter the course of the disease by delaying its onset, slowing it down, or stopping its progression. Such treatments will likely be expensive and carry some risk, so it is ever more critical to be able to predict who is going to get the disease and when.

Redefining Early Detection

How early is "early" in a disease that strikes the elderly? Richard J. Caselli, MD, a Mayo Clinic neurologist and his colleagues in the Arizona Alzheimer's Disease Center, are finding out that "early" may be as young as middle age in individuals at risk. In the first longitudinal investigation of its type, they have discovered subtle cognitive changes that predate clinical signs of AD by as many as 10 to 15 years in carriers of apolipoprotein ε4.

Apolipoprotein (APOE) is a gene isoform or protein, present in all humans, that helps transport lipids. Three types or alleles—ε2, ε3, and ε4—can be inherited in any of 6 combinations. While APOE ε2 appears to be protective against AD, APOE ε4 is a serious risk factor. In people with 2 copies of APOE ε4, the risk of developing AD is 12 times greater than the risk in the general population. Approximately 25% of the population has at least 1 copy of APOE ε4, and the presence of APOE ε4 is thought to explain about 50% of cases of AD.

In the mid 1990s, Dr Caselli and collaborators began conducting extensive behavioral and neuroimaging studies every 2 years on APOE ε4 homozygotes (those with 2 copies), heterozygotes (those with 1 copy), and noncarriers. At the same time, Ronald C. Petersen, PhD, MD, and colleagues at Mayo Clinic in Rochester, Minnesota, began to characterize a condition called mild cognitive impairment (MCI), subtle cognitive changes that predate clinical symptoms of AD by 3 to 5 years. Now Dr Caselli and colleagues have found that in those known to be at extremely high risk (ie, APOE ε4 homozygotes) subtle changes in cognitive status occur much earlier and may represent a pre-MCI stage of AD. Substantiation of these findings could alter the timetable for early therapeutic interventions in those with established risk factors. As Dr Caselli says, "Alzheimer's research has focused on the elderly, but it appears that we need to look earlier in the lifespan. We are now including people as young as 20 years old in our samples."

Defining Risk

Knowing whom to treat is as important as knowing when to intervene. Early detection will likely depend on identifying combinations of risk factors. At Mayo Clinic's 3 locations, investigators are uncovering a wide array of AD predictors and methods of detection.

Two of the 29 Alzheimer's Disease Centers funded by the National Institutes of Health (NIH) are at Mayo Clinic. The Mayo Clinic Alzheimer's Disease Research Center, a partnership between Mayo Clinic in Rochester, Minnesota, and Jacksonville, Florida, is directed by Dr Petersen in Minnesota with codirectors Neill R. Graff-Radford, MD, and Steven G. Younkin, MD, PhD, in Florida. The Arizona Alzheimer's Disease

Center is a consortium of Arizona institutions, of which Dr Caselli is the Clinical Core Director. In addition to basic science and clinical trials research, coordinated research at these 2 centers and Mayo's 3 sites is fostering discovery of reliable biomarkers for risk. Mayo Clinic in Arizona also has state funding to conduct regularly scheduled tissue sample analysis, neuroimaging, and neuropsychological testing across the lifespan. The Mayo Clinic Study on Aging in Minnesota, supported by a separate NIH grant, conducts similar studies on more than 2,000 subjects without dementia who have been enrolled to date.

"The ultimate goal of Alzheimer's research is to prevent the disease, and the only way to prevent it is by knowing which patients are at risk before they get it," states Dr Graff-Radford. "To do that we need to stratify the population into levels of risk," adds Dr Petersen, "which is what we're doing throughout Mayo Clinic's AD research programs." Biomarkers under investigation at Mayo include structural changes in the brain, genetic predisposition, changes in blood chemistry, altered cognitive status, and other behavioral signs of early onset.

Neuroimaging

Identifying correlations between behavioral changes and shifts in the volume, density, and activity of brain structures is a major step forward in defining risk before symptom onset in AD. Mayo's innovation in MRI is rapidly expanding the methods of detecting presymptomatic AD and other dementias. Led by neuroradiologist Clifford R. Jack, MD, who won the American Academy of Neurology's Potamkin Prize for Research in Pick's, Alzheimer's, and Related Diseases in 2008, researchers at Mayo Clinic in Rochester are using voxel-based (volumetric) morphology, diffusion tensor imaging, and various other new analytical techniques to identify volumetric shifts in white matter as well as in specific brain structures that signal early signs of AD.

The Arizona Alzheimer's Disease Center is investigating MRI changes in brain density and volume, in white matter and gray, and in the integrity of neurovasculature in APOE carriers and noncarriers. They have also used positron emission tomography (PET) to study these patients. Numerous PET scan studies have shown that AD is associated with an abnormally low glucose metabolic rate in regions of the precuneus and posterior cingulate, the parietotemporal, and the frontal cortex. Dr Caselli and his colleagues found that reduced glucose metabolism in these same brain regions correlated with APOE ϵ4 gene dose (ie, the number of ϵ4 alleles in a

Neill R. Graff-Radford, MD

Ronald C. Petersen, PhD, MD

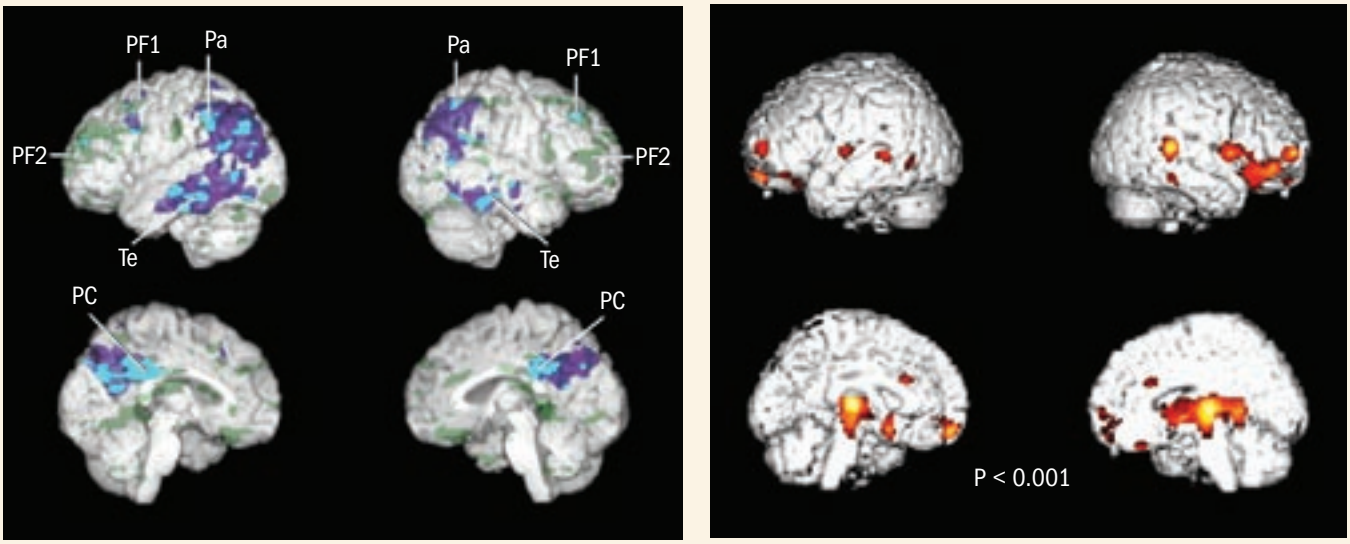


Figure 1. ***Preclinical Cerebral Metabolic Rates of Glucose (CMRgl) Changes in APOE ϵ4 Carriers.*** *Fluorodeoxyglucose PET studies of cognitively normal individuals at risk for AD. Left, Eleven healthy APOE ϵ4 homozygotes were compared with 22 healthy ϵ4 noncarriers. Purple indicates regions known to be affected by AD; blue overlapping purple, regions of reduced cerebral metabolism in the healthy ϵ4 homozygotes; and green, regions of reduced metabolism in prefrontal brain known to be differentially affected by aging. Pa indicates parietal; PC, posterior cingulate; PF1 and PF2, prefrontal; Te, temporal. (Reprinted, with permission, from N Engl J Med 1996;334:752-758.) Right, Two-year declines in brain metabolism seen in APOE ϵ4 heterozygotes compared with noncarriers. (Reprinted, with permission, from Proc Natl Acad Sci U S A 2001;98:3334-3339.)*

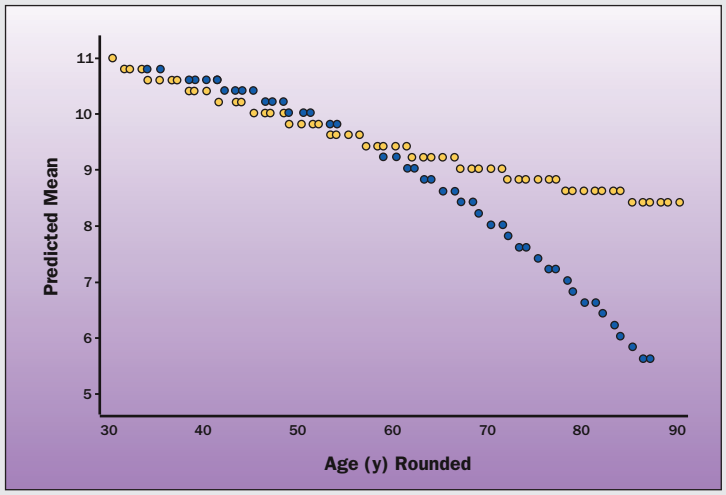


Figure 2. ***Performance of APOE ϵ4 Homozygotes and Heterozygotes on the Auditory Verbal Learning Test.*** *A statistical technique, called "longitudinal growth modeling," shows cognitively healthy carriers (denoted by blue circles) and noncarriers (yellow circles) of the APOE ϵ4 allele have nearly equivalent rates of memory decline between the ages of 30 and 60 years, but at the age of 60 years, the rate of decline accelerates in ϵ4 carriers. This difference represents "normal aging"; individuals who developed MCI and AD were not included in this analysis.*

person's APOE genotype) (Figure 1). They and others have concluded that PET may be a useful diagnostic tool and a quantifiable measure of the effects of gene-modifying therapies in the future.

Mayo Clinic in Rochester has recently begun using a molecular-based imaging technique to detect pathologic alterations in the brain. The imaging tracer being used is called Pittsburgh compound B (PiB). It detects a form of the amyloid protein that is deposited in the brain. The proteins amyloid beta 42 (Aβ42) and amyloid beta 40 (Aβ40) are major components of the plaques associated with AD and a major part of the disease process.

A Blood Test for AD?

Amyloid protein increases with age, and in people with AD it is deposited in the brain as plaques, generating a decline in the level of certain forms of protein in the blood. Investigators in the Mayo Clinic Alzheimer's Research Center have developed a blood test that may dramatically improve presymptom detection of AD. The test measures a ratio of amyloid proteins Aβ42 to Aβ40 in the blood. In a longitudinal study of 563 elderly subjects, they found that the 53 participants who developed MCI and/or AD had decreased levels of Aβ42 at 3 to 5 years before symptom onset. Levels of Aβ40 either increased or decreased at a slower rate. Those with the lowest ratio—low levels of Aβ42 and high levels of Aβ40—were 3 times more likely to develop AD or MCI. The research team, led by Drs Younkin and Graff-Radford in Jacksonville and Dr Petersen, Bradley F. Boeve, MD, and David S. Knopman, MD, in Rochester are in the process of recruiting 3,000 people to complete the study in the next 10 years. Although the test would not be the sole predictor, in combination with other known risk factors, it could revolutionize the process of early detection.

Genetic Risk Factors

Mayo Clinic in Jacksonville has characterized the amyloid protein and the genetics of AD and other dementias. Few genes are as powerful as APOE ϵ4 in signaling risk for AD. Genetic risk for the approximately 50% of AD not explained by it will likely be defined by gene combinations and by gene-plus-environmental factors. Scientists at Mayo Clinic in Jacksonville are conducting genome-wide association studies in search of just such gene combinations.

Behavioral Predictors and Environmental Risk Factors

In both Alzheimer's Disease Centers, researchers are looking for behavioral changes that predate AD. For example, they have found that difficult tests of verbal memory such as the Auditory Verbal Learning Test are particularly valuable in detecting both MCI and pre-MCI cognitive decline (Figure 2).

Cognitive changes are the obvious, but not the only, behavioral predictor of dementia. For example, rapid eye movement sleep disturbance, of which dream enactment behavior is the defining clinical feature, has been associated with dementia with Lewy bodies (LBD). Although dementia with LBD differs from AD, Dr Caselli and colleagues in the Arizona Alzheimer's Disease Center looked at this behavior relative to risk for AD in a small sample of healthy APOE carriers and noncarriers. They found that those with dream enactment behavior had reduced glucose uptake in areas of the brain known to be similarly affected by LBD as measured by fluorodeoxyglucose (FDG) PET scans.

Finally, lifestyle factors may also influence risk. For example, Dr Caselli and his team are finding that fatigue has a greater effect on memory in APOE homozygotes than it does in noncarriers. And, while correlations between memory impairment and cardiovascular status are weak in heterozygotes, they are robust in homozygotes. As Dr Caselli states, "Thus, it may be that in people at high risk for AD, exercise and cardiovascular health are particularly critical."

A Proposed Randomized Clinical Trial for Small Unruptured Intracranial Aneurysms

Brian W. Chong, MD

Ricardo A. Hanel, MD

As brain imaging improves, small, asymptomatic, unruptured intracranial aneurysms (UIAs) are discovered with increasing frequency, often as incidental findings. Treatment for small UIAs may include surgical intervention (craniotomy and clipping of the aneurysm), endovascular coiling, or observation, with lifestyle changes such as lowering blood pressure and smoking cessation (Figure 1).

"The question today is no longer whether we can treat small UIAs, but should we? We have the technology to fix the vast majority, but distinguishing between those that will and those that will not rupture is difficult," explains Brian W. Chong, MD, chair of the Division of Vascular and Interventional Radiology at Mayo Clinic in Phoenix/Scottsdale, Arizona. His neurosurgical colleague, Ricardo A. Hanel, MD, at Mayo Clinic in Jacksonville, Florida, agrees, listing the many considerations that go into the decision about whether to intervene: the site, size, and shape of the UIA; the patient's age and medical and family history; and the relative risks and benefits of intervention versus management through observation. They both acknowledge that in many patients the discovery of an aneurysm causes considerable anxiety, and some patients fear any type of intervention. The question of which course of management is best has been a subject of controversy.

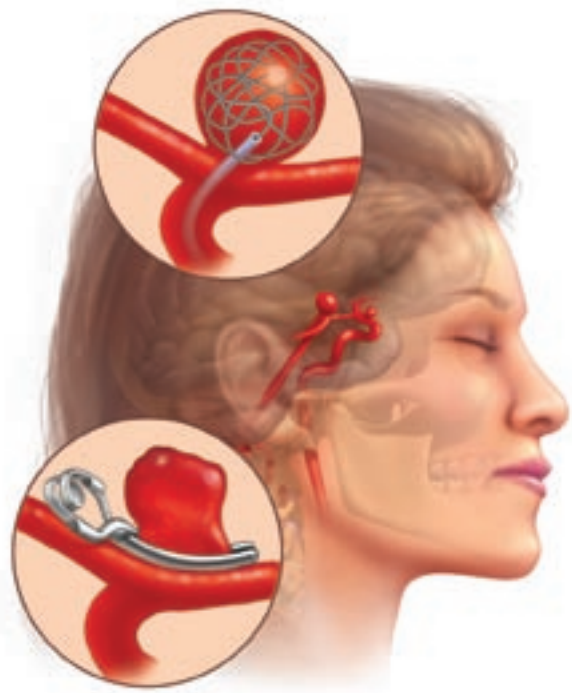


Figure 1. ***Interventional Treatment Options.*** *Management options for brain aneurysms include conservative management with control of risk factors, or an interventional treatment with either endovascular coiling or surgical clipping, as shown in the figure.*

Findings to Date

Led by Mayo Clinic in Rochester, Minnesota, the International Study of Unruptured Intracranial Aneurysms (ISUIA) set out to shed light on the issue in 1991. By far the largest study of its kind, the first phases assessed the natural history and management outcomes of UIAs in more than 5,500 patients. Management included surgical clipping, endovascular coiling, or observation. Among the many findings was that size and location mattered relative to risk for rupture: the smaller the aneurysm, the lower the risk of rupture. In asymptomatic patients without a previous subarachnoid hemorrhage, aneurysms measuring less than 7 mm in diameter had a low rupture rate, regardless of family history. Small UIAs in the posterior circulation had a slightly higher risk of rupture than in the anterior circulation. The study also found that intervention and observation were similar in outcome and risk for small aneurysms.

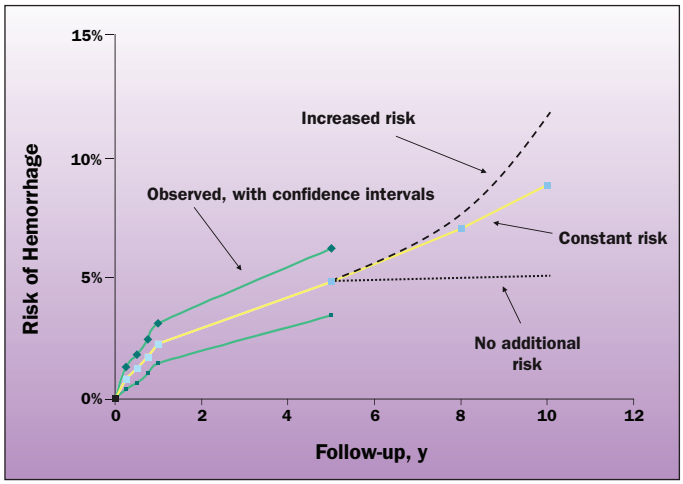
"What we did not know," explains Robert D. Brown, MD, chair of neurology at Mayo Clinic in Rochester and principal investigator of the study, "was what the outcome would be if we extended the follow-up. Would the rupture risk continue at a constant level, increase with age, or be reduced?" The latest phase of ISUIA, completed in 2008, indicates that the annual risk of rupture remains the same over an average of nearly 10 years of follow-up. For small UIAs, risk neither increased nor decreased significantly with increased age of the patient or time after discovery (Figure 2 on page 6).

ISUIA Phase 4: A Proposed Clinical Trial

"ISUIA brought the best evidence to date to guide us in treating these small UIAs," says Dr Hanel. However, as Dr Brown points out, in patients for whom clinical equipoise exists, the question remains, "Which management strategy is best?" Clinical equipoise is the situation in which there is uncertainty about optimal management of a medical condition because the risks and benefits of various treatment options appear

similar. Such is the case for many small UIAs, which, Dr Brown says, "suggests that a clinical trial is needed to clarify the optimal treatment."

Robert D. Brown, MD, Giuseppe Lanzino, MD, and David F. Kallmes, MD



To find out if 1 treatment serves patients better, participating institutions are poised to enter phase 4, a prospective look at best management through a randomized clinical trial. Patients with small UIAs will be randomly assigned to 1 of 2 different approaches: observation with lifestyle changes or interventional management with either aneurysmal coiling or clipping.

David F. Kallmes, MD, a neuroradiologist at Mayo Clinic in Rochester, is involved in designing the new study. As he explains, study patients must be screened for equipoise with great care to meet the highest ethical standards. He adds that techniques and materials used in interventional radiology and neurosurgical procedures to manage aneurysms are evolving. Thus, the specific procedures and the type of interventional management will not be prescribed by the study, but will be determined by each participating institution and may change over time.

The study aims to determine differences between treatment groups, not only in mortality and medical and overall functional outcome, but in cognitive and behavioral outcomes,

Continued on page 7

Figure 2. ***Long-term Follow-up of Unruptured Intracranial Aneurysms.*** *Possible outcomes during long-term follow-up (~10 years) of unruptured intracranial aneurysms: an unchanging, constant risk of hemorrhage, increasing risk of hemorrhage, and no additional risk of hemorrhage.*

CME Opportunities

Practical Clinical Neurology Review, October 29 - November 1, 2008

This course is designed for internal medicine physicians, family practice physicians, nurse practitioners, and registered nurses who encounter common neurologic problems in their clinical practice. The program format will consist predominantly of case-based presentations of a comprehensive group of neurologic disorders and clinical neurologic topics. Each presentation will focus on the clinical evaluation and treatment of clinical vignettes of common neurologic problems. Discussions will be interactive and videotapes of real and mock patients will be used during the case presentations. Small-group didactic workshops will also be presented each day to review current, evidence-based updates in the diagnosis and treatment of different categories of neurologic diseases. Location: Walt Disney World Swan & Dolphin, Orlando, Florida. Contact: 800-462-9633

Neuroradiology: Practice to Innovation November 9 - 14, 2008

Neuroradiology: Practice to Innovation is designed for the practicing radiologist whose work involves neuroradiology or those involved in the neurologic sciences, neurosurgery, neurology, and related fields. It is intended to provide a practical discussion and review of common diseases involving the brain, head/neck, and spine. It will provide an overview of common imaging strategies and incorporate evolving new modalities. Also, this course will review common endovascular and spinal interventional techniques used in neuroradiology. Location: Fairmont Kea Lani, Maui, Hawaii. Contact: 866-246-1581

A Proposed Randomized Clinical Trial for Small Unruptured Intracranial Aneurysms (continued from page 6)

quality of life, and utilization of health care resources. In patients randomly assigned to observation, an additional aim will be to define the frequency of and risk factors for aneurysm enlargement.

At Mayo's 3 sites, patients with UIAs are seen in a neurovascular clinic in which neurologists, radiologists, and neurosurgeons together arrive at the best treatment option. "The decision is highly individualized, but every bit of objective data helps. ISUIA has already helped the health care community understand that the decision to intervene when patients present with small UIAs must be made very selectively," states Giuseppe Lanzino, MD, a neurosurgeon at Mayo Clinic in Rochester. "It is hoped that the ISUIA phase 4 trial will help clarify these difficult treatment decisions."

3-Dimensional Image Guidance to Improve Surgical Outcomes

Maps show the lay of the land. A global positioning system (GPS) can pinpoint a location in relation to the larger map. In spine surgery, CT and MRI scans are the anatomic maps, and image-guidance technology is the GPS, telling surgeons the exact positions of their instruments as they operate. The instruments are equipped with light-emitting diodes that send signals to a camera connected to a computer. The computer then uses triangulation to compute the location of the instrument on the patient's anatomy and integrate it into the MRI image on a screen in the operating room. The integrated image may be 2- or 3-dimensional, depending on the type of image-guidance system used.

Developed in the early 1990s, image guidance is a real-time navigation system that continues to improve outcomes for surgical procedures involving the spine, including spinal reconstruction. Barry D. Birch, MD, a Mayo Clinic neurosurgeon in Phoenix/Scottsdale, Arizona, notes, "It is also useful for tumor location in both the brain and the spine." William E. Krauss, MD, his neurosurgery colleague at Mayo Clinic in Rochester, Minnesota, adds, "It's often difficult for the surgeon to ascertain the exact position of hands and instruments during procedures to correct degenerative or congenital deformities or when repairing traumatic injuries, but image-guidance greatly improves navigation capabilities."

Figure 1. ***Operating Room Set-up.*** *An intraoperative photograph of Dr Nottmeier using image guidance for instrument placement. The computer has a touch-screen monitor with a sterile drape allowing the surgeon to control the computer in the operating room.*

Eric W. Nottmeier, MD, a neurosurgeon at Mayo Clinic in Jacksonville, Florida, demonstrated just how much image guidance can increase safety in a recent retrospective study. In 1,200 spinal screws placed using 3-D image guidance, there were no vascular, visceral, or spinal cord injuries, and the incidence of injury to the nerve roots was less than 1%. In the literature, the incidence of injury associated with conventional techniques can occur in up to 11% of cases.

In the upper thoracic spine, screw malposition rates are as high as 41%, in part because of the small size of the pedicles and difficulty visualizing the anatomy with lateral fluoroscopy. In Dr Nottmeier's current study of upper thoracic pedicle screws, 146 screws have been placed in the upper thoracic spine using 3-D image guidance with a 6.9% incidence of minor screw breach of the pedicle, which was of no clinical consequence.

At Mayo Clinic's 3 locations, neurosurgeons have seen improved outcomes with image guidance. Dr Krauss states, "Since we started using the 3-D system in Rochester 2 years ago, we have not had a single misplaced screw." Dr Birch notes some other advantages. "Not as many x-rays or scans are needed before the procedure. Without an x-ray or fluoroscopy unit in the field, the surgeon's radiation exposure is reduced, and from an ergonomic standpoint, it is much more comfortable to operate."

Recently, Dr Nottmeier described a new minimally invasive fusion surgery technique using 3-D image guidance. Application of translaminar facet screws to stabilize the spine can be performed with either an open or a percutaneous

Barry D. Birch, MD,

William E. Krauss, MD

Eric W. Nottmeier, MD

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3-Dimensional Image Guidance to Improve Surgical Outcomes
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approach. Often, posterolateral or dorsal facet joint fusion performed at the same time improves outcomes. However, the combined procedure has only been possible with an open approach. Using a minimally invasive percutaneous approach, Dr Nottmeier has placed facet screws with concurrent dorsal facet fusion resulting in 360° fusion.

As image guidance continues to advance the practice of spine surgery, other technologies are being developed to work in concert with it. Dr Krauss notes,"The next step, something we're working on at Mayo Clinic, is the development of robotic systems to automate screw placement and other aspects of the procedure."

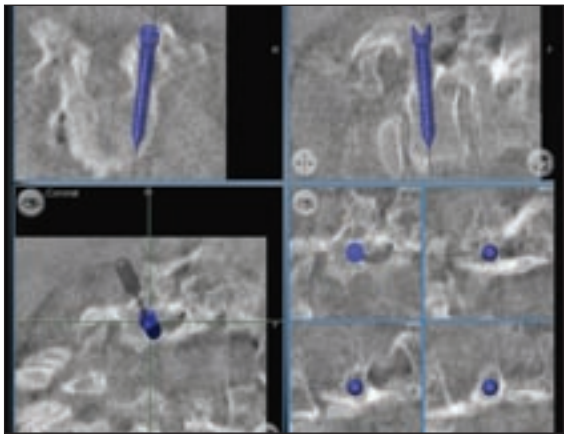

Figure 2. ***A Screenshot From the Image-Guidance System.*** *The system allows the surgeon to plan screw position and size on the computer before actual placement. This planning results in placement of the optimal-size screw at the best trajectory.*

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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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