Individualized Approach for Complex Intracranial Aneurysms

With the development of new neurovascular techniques, treatment options for patients with intracranial aneurysms have vastly improved. However, the optimal use of the multiple possible treatment modalities — and decisions about which aneurysms to treat — require sound diagnostic and surgical skills. Neurovascular surgeons at all three Mayo Clinic campuses have the experience and expertise to successfully manage these complicated cases.

“We are able to treat complex patients with very low morbidity and mortality. Equally important, we are able to differentiate between dangerous aneurysms that need treatment and the large number of aneurysms that are absolutely innocuous and don’t need treatment,” says Giuseppe Lanzino, M.D., a consultant in Neurosurgery at Mayo Clinic in Rochester, Minnesota.

In addition to fully equipped neurological intensive care units, Mayo Clinic also provides round-the-clock coverage by fellowship-trained neurovascular surgeons. “Our depth of expertise means that we have individual neurovascular surgeons who can perform whatever the patient needs — such as extracranial to intracranial bypass, coiling, stenting or microvascular procedures,” says Bernard R. Bendok, M.D., chair of Neurosurgery at Mayo Clinic in Phoenix/Scottsdale, Arizona. “Many of these techniques were pioneered by Mayo Clinic neurosurgeons.”

Prioritizing the patient’s needs
As members of a group practice, Mayo Clinic neurosurgeons make treatment decisions based on the individual patient’s needs, free of incentives to recommend unnecessary surgery or a particular technique. “It’s important for patients to hear about all treatment options and their particular benefits,” Dr. Bendok says. “Telling the patient only about the technique preferred by the surgeon would go against the Mayo Clinic model.”

“Every aneurysm and every patient is different,” adds Leonardo Rangel-Castilla, M.D., a consultant in Neurosurgery at Mayo Clinic’s campus in Minnesota. “Being trained in both open vascular and endovascular neurosurgery gives us a full understanding of intracranial vascular anatomy and pathophysiology, and allows us to tailor treatment based on the patient’s condition and the anatomy of the aneurysm.”

When appropriate, Mayo Clinic neurosurgeons use minimally invasive techniques, such as modified eyebrow incision, endoscopic skull base surgery,
Regenerative Medicine: Potential to Improve Life After Brain Tumor Treatment

Mayo Clinic’s Center for Regenerative Medicine is developing a neuro-oncology service line to optimize quality of life for patients treated for brain tumors. Although recent improvements in cancer therapies might lengthen life spans, survivors often must live with the cognitive sequelae of radiation-induced brain injury.

Mayo Clinic’s goal is to develop regenerative strategies to mitigate those effects in patients with low-grade gliomas or other tumors who can expect to live for decades after treatment.

One potential strategy (Figure) involves oligodendrocyte progenitor cells (OPCs). Radiation renders OPCs dysfunctional, impeding their and transnasal and transcranial endoscopy. “The modern care of aneurysms requires a team that has wide expertise in these minimally invasive techniques and access to the very latest neuronavigation technology,” Dr. Bendok says.

When making recommendations about treatment, Mayo Clinic neurovascular surgeons consider a constellation of factors, such as the patient’s age and comorbidities and the aneurysm’s size, shape and location. The complex decision-making is facilitated by the surgeons’ extensive experience. “I have followed more than 1,200 patients with unruptured aneurysms,” Dr. Lanzino says. “Over the years you acquire a set of skills to analyze each patient to determine whether an aneurysm is dangerous.”

It’s also common for Mayo Clinic neurosurgeons to review cases in conference with colleagues who have decades of neurovascular experience. “We learn from sharing previous experiences. It’s a pool of experts giving a recommendation, not a single surgeon,” says Rabih G. Tawk, M.D., a consultant in Neurosurgery at Mayo Clinic in Jacksonville, Florida.

Patients also benefit from Mayo Clinic’s highly skilled interventional radiologists, neuroradiologists and vascular neurologists. “Vascular wall imaging can tell us if the walls of an aneurysm are inflamed and indicate whether there is a high risk of rupture,” Dr. Tawk says. “Our neuroradiologists and vascular neurosurgeons work together to develop these imaging modalities.”

Before complex surgeries, Mayo Clinic also has the resources to engage in simulations of the procedure on a computer or a 3-D printed model of the patient’s anatomy. “We can use these pre-surgical simulations to determine the best surgical techniques for that patient, to plan the procedure and then practice it on a physical model,” Dr. Bendok says.

Collective wisdom and pre-surgical preparation are especially important for patients with complex intracranial aneurysms. Dr. Tawk describes a patient who came to Mayo Clinic’s campus in Florida after three unsuccessful attempts elsewhere to have a flow diverter implanted for treatment of an aneurysm that was causing double vision (Figure).

“The complication was that the vessel dissected, and there were stents that were placed in the carotid artery before the aneurysm. Crossing those stents is very complex,” Dr. Tawk says. “I ended up going step by step, first crossing the stents and then putting a balloon inside the stents and opening them up to create a pathway to the aneurysm where I needed to place the flow diverter. We successfully implanted the device, and a day later the patient went home.”

At the forefront of clinical trials

Since the 1990s, Mayo Clinic has participated in major clinical trials leading to new treatment approaches for intracranial aneurysms. Most recently, Mayo Clinic was part of the multicenter International Study of Unruptured Intracranial Aneurysms (ISUIA), which defined indications for treatment and possible complications, as well as the Pipeline for Uncoilable or Failed Aneurysms (PUFS) trial, which led to the approval of flow diverters. Dr. Bendok serves as principal investigator of the Hydrogel Endovascular Aneurysm Treatment (HEAT) coiling trial.

Other Mayo Clinic studies have addressed the long-term safety of flow diverters, as described in the October 2017 issue of Journal of Neurosurgical Sciences, and the long-term clinical outcomes of stent-assisted embolization for wide-neck aneurysms, as reported in the February 2016 issue of Neurosurgery.

“Studies done at Mayo Clinic guide the treatment decisions of doctors worldwide,” Dr. Lanzino says. “Our expertise is based partly on the fact that we not only treat patients but also study the disease.”

For more information


Reparative response. The resulting white matter degeneration is a major contributor to radiation-induced cognitive impairment after brain cancer treatment. However, preclinical research has shown that healthy, functioning exogenous OPCs maintain their normal function upon implantation into a previously irradiated brain — migrating widely, generating oligodendrocytes and remyelinating lesioned areas.

“In our lab we have seen that the irradiated brain is quite changed in some way that promotes the migration of these oligodendrocyte progenitor cells into the brain. I think that has tremendous potential,” says Terence (Terry) C. Burns, M.D., Ph.D., a consultant in Neurosurgery at Mayo Clinic in Rochester, Minnesota, and principal investigator in Mayo Clinic’s Regenerative Neurosurgery and Neuro-Oncology Laboratory.

In his clinical practice Dr. Burns sees patients whose low-grade gliomas were irradiated more than a decade earlier.

“The patient might be only 50-something years old but is walking like an 80-year-old, and has symptoms of dementia,” Dr. Burns says. “Fortunately, the tumor has been held at bay for many years. But at what cost?”

In a study published in the May 2015 issue of Glia, Dr. Burns and colleagues demonstrated that the transcriptional profile of radiated microglia closely mirrors that acquired by microglia during aging. “The white matter also atrophies and loses volume,” he says. “Our studies suggest that brain radiation may accelerate aging-like changes in the brain. It’s as though aging is happening in fast forward in the brain. We are now trying to minimize the amount of brain exposed to radiation, and come up with strategies to help rejuvenate the radiated brain.”

In an article published in the May 2016 issue of Neurosurgical Focus, Dr. Burns noted that studies using animal models of acute demyelination, including toxin-induced demyelination, have shown that OPCs generate new oligodendrocytes to swiftly remyelinate a lesioned area, avertting permanent axonal injury. Of particular interest are preclinical studies suggesting that OPCs implanted in the forebrains of radiated animal models improve cognitive function, and OPCs implanted in the hindbrains improve motor function.

Exogenous OPCs are being explored for use in clinical trials of childhood leukodystrophies, multiple sclerosis and Huntington’s disease. “At this point, the most promising source of the cells may be from embryonic or induced pluripotent stem cells, so it is essential to determine early if there are any safety concerns,” Dr. Burns says.

“There are a lot of questions to be answered, but what we have seen so far suggests OPCs as a promising avenue for treating radiation-induced brain injury,” he adds. “Nevertheless, we’re not focusing exclusively on OPCs. Unlike other forms of brain injury — for example, traumatic brain injury, stroke and Alzheimer’s disease — radiation-induced brain injury allows us to intervene possibly even before the damage...
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Tracking cognitive function in glioma patients
At Mayo Clinic, low-grade gliomas are an initial target for neuro-oncology regenerative medicine. Currently, patients with these tumors can expect to live for approximately 15 years after treatment. “We’re making rapid progress, so I am hopeful in 15 years, we’ll actually have much more effective treatments,” Dr. Burns says. “For now, we need to buy time for patients and do our best to preserve their quality of life.”

Before treating patients with low-grade gliomas, Dr. Burns schedules neuropsychological assessments, which are repeated after surgery and periodically after chemotherapy and radiation.

“Cognitive outcomes are often ignored in cancer treatment, but I feel we need to be systematic about compiling and analyzing these data,” he says. “How much worse is cognitive function after treatment, and in which domains? We believe the hippocampus is particularly sensitive to radiation, based on memory performance, but impairments in executive function and multitasking may reflect injury to other white matter tracts. What about the contralateral cingulate gyrus? We need the integrated data to determine when and how best to use the tools we have of surgery, radiation and chemotherapy, to maximize benefit and minimize cognitive impacts.”

Children are another patient population severely affected by radiation-induced brain injury. Survivors of childhood medulloblastoma can experience an IQ loss of as much as 25 points, due to the long-term effects of radiation treatment. “Children could have the most to gain from our regenerative strategies, since their brains are still developing and the demyelinating impacts of radiation can worsen over time,” Dr. Burns says.

“In the brain tumor field, we’ve not devoted enough attention to cognitive performance and quality of life because the enemy has been the tumor,” he adds. “The regenerative neuro-oncology service line initiative at Mayo Clinic will help ensure we not only get rid of the tumor but translate regenerative strategies to patients to preserve and optimize brain performance despite the tumor.”

For more information


Objective Criteria for Migraine
Mayo Clinic researchers are using brain MRI to develop objective biomarkers for the classification of migraine. The existing, subjective criteria are based on the expert opinions of contributors to the International Classification of Headache Disorders (ICHD). The Mayo Clinic researchers hope to validate or refine those criteria and perhaps identify new migraine subtypes, paving the way for better targeted therapies.

“We currently have limited ability to practice precision medicine for patients with migraine,” says Todd J. Schwedt, M.D., a consultant in Neurology at Mayo Clinic in Phoenix/Scottsdale, Arizona, and a member of the committee that helps compile the ICHD. “Only about 40 to 45 percent of patients respond to any one of the first line migraine-preventive therapies, and we are not able to accurately predict which patient will respond to which therapy. I think there’s a reason for that — our current classification does not identify all the heterogeneity that exists among groups of patients with migraine.”

The MRI studies led by Dr. Schwedt are currently used only for research. However, identification of new patient subgroups from these studies might eventually be used in the clinical domain.

“I’m a firm believer that there are additional subtypes of migraine beyond those that are commonly recognized,” Dr. Schwedt says. “Imaging is one way we might identify these subgroups.”

Structural and functional MRI
The Mayo Clinic research uses both structural and functional MRI of people with migraine and other types of headaches, and healthy controls. Structural MRIs evaluate factors such as the volume of various brain regions, cortical thickness, surface area, curvature of the brain and brain shape (Figure 1). Diffusion tensor imaging is used to assess white matter integrity. Functional MRI involves both resting state functional connectivity, to assess how areas of the brain are connected and communicate, and event-related functional MRI to determine how participants’ brains
respond to a painful stimulus (Figure 2).

“So far, we’ve built classification models for both episodic and chronic migraines, using structural as well as functional data and a combination of the two,” Dr. Schwedt says.

In a study published in the August 2017 issue of *Cephalalgia*, Dr. Schwedt and colleagues used machine-learning techniques and data from resting-state functional MRI of pain-processing regions to develop biomarkers that distinguish between individuals with migraine and healthy controls. Six brain regions — the bilateral amygdala, right middle temporal, posterior insula, middle cingulate and left ventromedial prefrontal — had the most discriminative power.

The researchers were able to classify individual brain MRIs as belonging to a person with migraine or a healthy control with an overall accuracy of 81 percent and a best accuracy of 86 percent. Migraineurs with longer disease durations were classified more accurately than those with shorter disease durations.

“We can look at the functional MRI and tell you with greater than 80 percent accuracy whether that MRI belongs to somebody who has chronic versus episodic migraine, or chronic migraine versus a healthy control,” Dr. Schwedt says.

In a subsequent study published in the July 2017 edition of *Headache*, structural MRIs measured regional cortical thickness, volumes and cortical surface areas in the brains of migraineurs and healthy controls. Automatic data-driven analysis clustered the MRIs into two subgroups. People with migraine in the first subgroup had more severe allodynia symptoms during migraine attacks, more years with migraine and higher Migraine Disability Assessment scores. Headache frequency and aura status weren’t significantly different between the two subgroups.

“Allodynia occurs in the majority of people during a migraine attack. It’s been suggested that allodynia might affect migraine treatment response and disease prognosis, and our study suggests that it affects brain structure,” Dr. Schwedt notes. “The presence or severity of allodynia could be considered when defining migraine subgroups.”

The imaging studies may also shed light on whether anomalies in brain structure or function are present at birth or result from migraine attacks. “We have found that the more severe a person’s migraines, the greater accuracy we have classifying that person according to brain MRIs. That probably means that the brain changes occur secondary to recurrent attacks,” Dr. Schwedt says. “But it’s possible that certain brain structures or functions at baseline predispose a person to migraine. We need large, longitudinal studies to determine directionality.”

Another focus of research compares MRIs of people with migraine and people with post-traumatic headaches. Although symptoms are often similar or identical for both types of headache, the researchers have found differences in brain structure between the two groups. “That suggests there might be differences in the underlying pathophysiology of migraine and post-traumatic headache,” Dr. Schwedt says.

“Our ultimate goal is to identify objective differences among people with migraine and other headache types that predict treatment responses and allow us to provide more-targeted therapies for these patients,” he says.

**For more information**


Mayo Clinic in Jacksonville, Florida, has a multidisciplinary amyotrophic lateral sclerosis (ALS) clinic, providing a team approach for patients with that rapidly progressing disease. Appointments are coordinated so that patients see a neurologist specializing in ALS as well as a complement of allied staff in a single visit. The multidisciplinary clinic offers comprehensive and efficient treatment and support for patients with ALS.

“There is a very narrow time window for meaningful interventions to relieve the symptoms of ALS. It’s important to address these changes in a timely manner,” says Bjorn E. Oskarsson, M.D., a consultant in Neurology at Mayo Clinic’s campus in Florida. “For example, if a patient ends up waiting months for a wheelchair evaluation and further months to get insurance approval, the patient might no longer be able to use the device by the time it arrives."

Mayo Clinic was among the first centers in the United States to create a multidisciplinary ALS clinic. The ALS Association has certified all three Mayo Clinic campuses, in Florida, Arizona and Minnesota, as Certified Treatment Centers of Excellence.

The multidisciplinary ALS clinic teams include:
- Neurologists specializing in ALS
- Nurse coordinators who arrange care for patients
- Respiratory therapists who measure respiratory function and advise on respiratory equipment
- Speech therapists who assist with swallowing difficulties and speech-generating devices
- Dietitians who advise on foods appropriate for swallowing difficulties and on enteral and parenteral feeding
- Physical therapists to assist with safety and mobility
- Occupational therapists to assist with adaptive equipment
- Social workers to help with navigating the health care system
- Palliative care specialists
- Representatives from the ALS Association to connect patients and their families with support groups and other resources

In addition, pulmonologists, otorhinolaryngologists and interventional radiologists at Mayo Clinic have expertise and experience with advanced respiratory care, tracheotomies and the placement of feeding tubes for patients with ALS.

“We meet together as a team and care for patients in a structured way. Our most recent patient survey shows that patients are very satisfied with this approach to their care. The multidisciplinary clinic is a sort of medical home for them,” Dr. Oskarsson says.

The ALS treatment teams also include research coordinators. In addition to offering the opportunity for patients to participate in clinical research trials, investigators at Mayo Clinic’s campus in Florida are following up on their discovery of a noncoding repeat expansion in the C9orf72 gene that is the most common cause of ALS (Figure). Every patient with ALS is asked to contribute specimens to further Mayo Clinic’s efforts to find biomarkers and novel therapies for ALS.

“In addition to these large projects, we collect a lot of information from our patients to help us improve their quality of life — for example, finding ways to prevent falls,” Dr. Oskarsson says.

**Figure.** The GGGGCC repeat expansion — shown in red — is located between two noncoding exons (1a and1b) of the C9orf72 gene. RNA transcribed from the repeat expansion can accumulate into very small structures, termed RNA foci, in cells of the brain and spinal cord. In the bottom left image, the RNA foci appear as small red structures within the nucleus, which is stained blue, of a cell. In addition, this RNA can undergo an atypical form of translation, thereby producing dipeptide repeat proteins that aggregate into clumps, or inclusions, within neurons. In the bottom right image showing cells of the cerebellum, the inclusions appear as brown spots, many of which can be found near the nucleus of cells, which are stained blue.

**Telemedicine for ALS**

To further serve patients with ALS, Mayo Clinic’s campus in Florida has launched a telemedicine initiative. After initial diagnosis in Jacksonville, patients with ALS can be followed remotely at a clinic in Pensacola, located in the Florida panhandle about five hours west of Jacksonville. A second remote clinic is planned for Panama City, about four hours west of Jacksonville.

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Research Highlights in Neurology and Neurosurgery

**Survival Rates for People With Synucleinopathies With Parkinsonism**
Comprehensive studies of the survival rates and causes of death of people with synucleinopathies compared with the general population haven’t been performed. Mayo Clinic researchers have determined the age- and sex-adjusted risk of death for several synucleinopathies — including Parkinson’s disease (PD), dementia with Lewy bodies, PD dementia and multiple system atrophy — as well as the median time from diagnosis to death and the causes of death. The population-based study analyzed the medical records of residents of Olmsted County, Minnesota, who had a clinical diagnosis of synucleinopathy with parkinsonism between 1991 and 2010. For each patient an age- and sex-matched Olmsted County resident without parkinsonism was also identified. Of the 461 residents with synucleinopathies, 309 (67 percent) had PD, 81 (17.6 percent) had dementia with Lewy bodies, 55 (11.9 percent) had PD dementia and 16 (3.5 percent) had multiple system atrophy with parkinsonism. Patients with any synucleinopathy died a median of two years earlier than referent participants. Patients with multiple system atrophy with parkinsonism had the highest risk of death compared with referent participants, followed by those with dementia with Lewy bodies, PD dementia and PD. The most frequent cause of death among patients was neurodegenerative disease and among referent participants was cardiovascular disease. The researchers conclude that people with synucleinopathies have increased mortality compared with the general population although the increase is only moderate for people with PD. (Savica R, et al. Survival and causes of death among people with clinically diagnosed synucleinopathies with parkinsonism: A population-based study. *JAMA Neurology*. 2017;74:839.)

**Predictive Models for Autoimmune Epilepsy**
A significant proportion of cryptogenic epilepsies have been attributed to an autoimmune cause. Establishing an autoimmune etiology greatly affects treatment and prognosis. Mayo Clinic researchers have validated the Antibody Prevalence in Epilepsy (APE) scoring system as a model to predict the detection of neural antibodies based on a patient’s clinical presentation and initial neurological evaluation. The researchers conducted a retrospective study of patients who had autoimmune encephalopathy, dementia or epilepsy antibody testing at Mayo Clinic. An APE score was assigned to each patient, based on clinical characteristics. Among patients who received immunotherapy, a Response to Immunotherapy in Epilepsy (RITE) score was designed. Serum and cerebrospinal fluid (CSF) from 1,736 patients were analyzed for neural autoantibodies. Among the patients studied, 262 had epilepsy of unknown etiology; central nervous system-specific antibodies were detected in 44 (16.8 percent) of them. The sensitivity and specificity of an APE score of at least 4 (out of a possible 15) to predict the presence of specific neural autoantibody were 97.7 percent and 77.0 percent, respectively. Among the 77 patients who received immunotherapy, the sensitivity and specificity of a RITE score of at least 7 (out of a possible 19) to predict favorable seizure outcomes were 87.5 percent and 83.8 percent, respectively. The researchers note that a scoring system based on clinical features and initial neurological assessment may enable earlier clinical diagnosis while special neural antibody results are awaited. (Dubey D, et al. Predictive models in the diagnosis and treatment of autoimmune epilepsy. *Epilepsia*. 2017;58:1181.)

**Plasma Total Tau Level as a Marker of Cognitive Decline**
The utility of plasma total tau level as a prognostic marker for cognitive decline and dementia isn’t well-understood. The results of research at Mayo Clinic suggest that elevated plasma total tau levels are associated with cognitive decline, but results differ based on cognitive status and the duration of follow-up. The analysis included 458 participants enrolled in the population-based Mayo Clinic Study of Aging. All participants had available plasma total tau levels, amyloid-beta positron emission tomography imaging and a complete neuropsychological exam at the same visit, as well as at least one follow-up visit. Among all participants, higher levels of plasma total tau were associated with significant declines in global cognition, memory, attention and visuospatial ability over a median follow-up of three years. In additional analyses restricting the follow-up to 15 months, plasma total tau didn’t predict decline among cognitively normal participants. However, among participants with mild cognitive impairment, higher plasma total tau levels were associated with greater decline in both visuospatial ability and global cognitive at 15 months. The association between plasma total tau levels and cognition is independent of elevated brain amyloid-beta. (Mielke MM, et al. Association of plasma total tau level with cognitive decline and risk of mild cognitive impairment or dementia in the Mayo Clinic Study of Aging. *JAMA Neurology*. In press.)

To read more about Mayo Clinic neurosciences research and patient care, visit http://www.mayoclinic.org/medical-professionals.
“It’s pretty common for patients to have difficulty getting back here to Jacksonville after they have received a diagnosis. Telemedicine is a great option for these patients,” Dr. Oskarsson says.

He and a nurse coordinator communicate with the patient using digital video cameras and other technology. A social worker and a respiratory therapist, who assesses breathing function, are with the patient at the remote clinic. “Based on the breathing function and on patient-reported rating scales, I give recommendations for treatment,” Dr. Oskarsson says.

Whether patients are assessed remotely or in Jacksonville, the goal is to provide optimal care as the disease progresses. “With ALS, we might see a patient go from moderate disability to end-of-life care within a year,” Dr. Oskarsson says. “At Mayo Clinic we take a holistic approach to respond to every patient’s needs.”