AVM: Multimodal Approach for Individualized Treatment

Mayo Clinic has neurosurgeons with expertise in the full range of treatment options for people with arteriovenous malformations (AVMs). That multimodal capability — encompassing microsurgical resection, endovascular embolization, stereotactic radiosurgery and awake surgery, as well as watchful waiting — allows treatment for these complex cases to be individualized to each patient (Figure).

“This disease has so many variables that no single strategy would work for all patients. It’s important to have all these strategies available, and to be able to perform them in a very advanced way, to ensure that the patient is receiving the best possible care,” says Rabih G. Tawk, M.D., a neurosurgeon at Mayo Clinic in Jacksonville, Florida.

Mayo neurosurgeons have pioneered surgical techniques for AVM and stereotactic radiosurgery, and developed the radiosurgery-based AVM grading score to predict outcomes after Gamma Knife treatment. As a major neurosciences center, Mayo has a large group of neurosurgeons with experience in diverse AVM treatments.

“Some of us have expertise in radiosurgery; others have experience in surgery and embolization, or embolization alone,” says Giuseppe Lanzino, M.D., a neurosurgeon at Mayo Clinic in Rochester, Minnesota. “We can be comprehensive in our approach but use our individual strengths in various techniques to the patient’s advantage.”

**Broad, team-based care**

Mayo Clinic sees more than 300 people with arteriovenous malformations each year. The goal is to maximize patient well-being while using the safest and most effective approach. Mayo Clinic neurosurgeons have the full range of treatment options available, which allows them to individualize treatment for each patient.

**Figure.** A large arteriovenous malformation (AVM) was found in a 37-year-old woman following a motor vehicle accident. On the left, catheter angiography utilizing left internal carotid artery injection shows a large frontal AVM. The patient had preoperative embolization to reduce the blood supply to the AVM, followed by surgical resection. On the right, follow-up catheter angiography one day after surgery confirms the complete obliteration of the patient’s large lesion. He was discharged home four days after surgery, and returned to work one month after surgery.
AVM and other vascular malformations every year. The complete integration of Mayo's neurological and neurosurgical services helps ensure efficient patient care.

“Having different specialists working under the same umbrella improves communication and patient flow. Often, patients are given a diagnosis and a therapeutic plan within the same day,” Dr. Lanzino says.

Patients typically are evaluated by a neurologist, who might prescribe or adjust medications, particularly if the patient is experiencing seizures. Detailed imaging, including cerebral angiography, is done to assemble the information needed to make treatment decisions.

“We now also use holography, 4-D MRI and 3-D printing to assess an AVM before treatment,” says Bernard R. Bendok, M.D., chair of neurosurgery at Mayo Clinic in Phoenix/Scottsdale, Arizona. “This allows the treating team to think through management options more clearly and to relay the consensus opinion back to the patient in a more comprehensible way.”

The treatment team considers the AVM’s size, location and blood flow, as well as whether the patient is experiencing symptoms and whether the AVM is robbing adjacent brain tissue of blood. “If the patient is asymptomatic, sometimes it is better to leave the lesion and monitor it,” Dr. Tawk says. “But if treatment is needed, we discuss which modality or modalities would be best. The goal is to solve that particular patient’s problem, with minimal risk.”

If the AVM has bled or is readily accessible, surgical resection is generally recommended. An AVM in a deeper location might be treated with stereotactic radiosurgery, to avoid damaging brain tissue during resection. Endovascular embolization might be used to stem blood flow, with possible follow-up surgery or stereotactic radiosurgery. “If we know the AVM is going to bleed heavily during surgery, we do embolization first to cut the blood supply and make the surgery safer,” Dr. Lanzino says.

Large vascular lesions are sometimes treated with volume-staged stereotactic radiosurgery. Staging treatment into multiple radiological sessions allows a higher radiation dose to be delivered to the entire AVM volume while reducing radiation exposure to the adjacent brain. In a retrospective study published in the April 2017 issue of Neurosurgery, Mayo Clinic researchers found that 34 patients with large AVMs treated with volume-staged radiosurgery at Mayo had a low rate of adverse radiation effects. The median follow-up period was eight years.

“In our small study, we found that patients with AVMs typically considered too large for radiosurgery could be safely managed with this approach. Overall, 71 percent of patients achieved AVM obliteration with a low rate of radiation-related complications,” says Bruce E. Pollock, M.D., a neurosurgeon at Mayo Clinic’s campus in Minnesota.

Stereotactic radiosurgery is sometimes followed by surgical resection. “An AVM treated with radiosurgery might still have a small portion that doesn’t respond, even after five years. But then it’s relatively easy to do surgery on that smaller AVM,” Dr. Lanzino says.

Mayo Clinic has experience with even the most challenging AVMs. Dr. Tawk cites a patient with a ruptured AVM and aneurysm who was initially treated with endovascular embolization to stem the AVM’s high blood flow. “Once she recovered good functional outcome, we brought her back in and performed surgery with her in a seated position, to get access to the aneurysm,” Dr. Tawk says.

Surgery in the sitting position carries risk, including air embolism. “But with help from our colleagues in anesthesiology, we were able to do this procedure safely,” Dr. Tawk says. “The AVM is gone, and the patient is doing great.”

Awake surgeries

Mayo Clinic also uses awake surgery for select patients with intracranial neurovascular pathologies. That option can be particularly helpful for patients with an AVM that is causing seizures.

In a retrospective review of nine procedures, published in the September 2017 issue of World Neurosurgery, Mayo Clinic neurosurgeons reported that awake surgery can be safe for these select patients while offering the advantages of greater safety, a shorter hospital stay and reduced cost. Two patients in the study had a Spetzler-Martin grade 2 AVM with seizure activity. One of the AVMs was near Wernicke’s area; the other patient’s lesion abutted right-sided hand, lip and tongue sensorimotor activity. Language and motor mapping were used in the respective awake surgeries, and both achieved complete AVM resection.

“The functional delineation of tissue surrounding the AVMs permitted the surgeon to more confidently remove the pathologies,” Dr. Bendok says. “The patients had no permanent postoperative neurologic deficits, and both are seizure-free.”

Dr. Lanzino notes that decisions about whether and how to treat AVM should take into account the patient’s long-term likelihood of bleeding. Many people with an AVM are young and face a lifelong risk of bleeding. ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations) was halted after about three years because of results indicating that the
risk of death or stroke was significantly lower in the group of trial participants who received medical management versus the interventional therapy group. That trial had several limitations. “We don’t treat AVM patients to take away the risk of bleeding for three years — we take the risk away for a lifetime,” Dr. Lanzino says. “What ARUBA has shown is that if treatment is undertaken, it must be done safely. At Mayo Clinic, we have a long tradition of research and of treating even the most complex lesions. We have in-depth knowledge of this disease, which guides our treatment decisions.”

**For more information**


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**Novel MOG Assay Aids Diagnosis of Demyelinating Diseases**

Andrew McKeon, M.D., M.B., B.Ch., and Sean J. Pittock, M.D., autoimmune neurologists and members of the autoimmune neurology laboratory at Mayo Clinic in Rochester, Minnesota, answer questions about Mayo Clinic’s new test.

**Q:** Mayo Clinic has developed the first test available in the United States to identify the myelin oligodendrocyte glycoprotein (MOG) antibody in patients’ blood. How does this test help with the diagnosis of inflammatory demyelinating diseases?

The MOG antibody can distinguish a spectrum of autoimmune demyelinating diseases from multiple sclerosis (MS). Testing positive for the MOG antibody indicates that a patient doesn’t have classical MS.

That’s important because diseases associated with the MOG antibody — as well as diseases associated with the water channel aquaporin-4 (AQP4) antibody, which was discovered at Mayo Clinic — are commonly misdiagnosed as MS. Yet some MS medications have been reported to worsen diseases that mimic MS.

Mayo Medical Laboratories offers testing for both MOG and AQP4 antibodies. Patients who have more than one episode of optic neuritis absolutely should have testing. An optic neuritis seems to be a very common presentation of MOG. Our test has great sensitivity and specificity. It uses a completely novel method of flow cytometry developed by Mayo Clinic to identify patient antibody binding to the MOG protein that is expressed on living cells.

**Q:** Which inflammatory disease phenotypes are associated with the MOG antibody?

Our work indicates that testing is positive in:

- 60 percent of children and 40 percent of adults with acute disseminated encephalomyelitis (Figure 1)
- 30 percent of patients with neuromyelitis optica who lack the AQP4 antibody

**A1.** Sagittal T2 fluid-attenuated inversion recovery (FLAIR) image of an adult patient demonstrates multifocal T2 hyperintense lesions in the frontal, occipital and temporal lobes, and the corpus callosum and brainstem (arrows), consistent with acute disseminated encephalomyelitis. A2. Sagittal T2 FLAIR image nine months later following immunotherapy shows almost complete resolution of the T2 hyperintense lesions.

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Andrew McKeon, M.D., M.B., B.Ch.

Sean J. Pittock, M.D.
20 percent of patients with a longitudinally extensive transverse myelitis
10 percent of patients with recurrent optic neuritis (Figure 2) and 2 percent of patients with a single optic neuritis

Q: How does the presence of the MOG antibody affect disease course?
It may actually indicate a more favorable prognosis. For example, in patients with recurrent optic neuritis, the visual outcomes are better with MOG-associated disease than AQP4-associated disease. The diseases are bizarrely different — AQP4 targets astrocytes while MOG targets oligodendrocytes — yet the phenotypes look quite similar. We are planning a study to learn more about these phenotypes.

We’ve also found that the persistence of the MOG antibody is associated with disease relapses. Many of these patients will see a very rapid drop in MOG antibodies and test negative within six months. Those patients are at low risk of another attack. But if the antibody persists, the patient is at higher risk of another attack. This is a very interesting phenomenon and quite unusual in the field of autoimmune neurology.

Q: What are the implications for treatment?
In general, we would treat each attack, maybe aggressively, with steroids. The persistence of the MOG antibody might indicate a need for medication to prevent disease relapse and possibly reduce disability progression. But whether all of these patients should be put on heavy-hitting immune-suppression isn’t 100 percent clear. Many of these patients might have one or two optic neuritis attacks over five years and have normal visual outcomes.

Q: What other antibody tests might become available?
We expect to discover more antibodies. For example, we know that only about 20 percent of people with recurrent episodes of optic neuritis have the MOG or the AQP4 antibody. The other 80 percent of people behave very similarly clinically but don’t have either of those biomarkers. This area is ripe for discovery.

Q: How does the Autoimmune Neurology Laboratory facilitate Mayo Clinic’s translational science?
The lab is a multidisciplinary group that includes people with very strong clinical backgrounds as well as scientific backgrounds. Having that clinical expertise in a laboratory environment helps us to focus on the needs of patients who will have this type of testing. The lab also has a large repository of specimens that allowed us to develop the MOG assay relatively quickly. This type of testing, for relatively common but treatable diseases, directly benefits patients.
Subspecialized Neuro-Ophthalmology Care

Mayo Clinic provides subspecialized team care for people with neurological disorders affecting their vision and visual pathways. At all three Mayo Clinic campuses, neuro-ophthalmologists work closely with Mayo’s neurologists and neurosurgeons to treat people with any problems involving sight or eye movement that arise from the nervous system, including issues caused by:

- Tumors
- Migraine
- Stroke
- Multiple sclerosis (MS)
- Radiation treatment
- Idiopathic intracranial hypertension
- Cerebral venous sinus thrombosis (Figure)
- Parkinsonian disorders
- Traumatic brain injury

“Neuro-ophthalmologists are sort of a rare breed. We are a subspecialty of both neurology and ophthalmology, and there aren’t many of us practicing full time,” says Marie D. Acierno, M.D., a neuro-ophthalmologist at Mayo Clinic in Phoenix/Scottsdale, Arizona. “We have unique training to evaluate patients from the neurological, ophthalmological and medical standpoints.”

As a fully integrated group practice, Mayo Clinic can offer patients the subspecialized evaluations they need in a single day. “A patient might come in to have neuro-imaging, then have a visual-system assessment and then go on to see the neurosurgeon,” Dr. Acierno says. “It’s important to transfer all this information,” she adds. “For example, because the pituitary gland sits across the visual pathway, a pituitary tumor of sufficient size can compromise the visual field. A complete neuro-ophthalmological evaluation can help a neurosurgeon make a better surgical decision for the patient.”

For nonsurgical cases, neuro-ophthalmologists provide expertise for patients with visual disorders associated with an underlying condition, such as migraine.

“As our neurologists work to control the frequency and severity of a patient’s migraine episodes, the neuro-ophthalmologist can advise on the visual disturbance that a patient might have during the episodes,” Dr. Acierno says. “These disturbances are often frustrating and worrisome for patients. As neuro-ophthalmologists, we can let these patients know that their ocular and visual systems are intact and that this experience is part of their migraine events.”

Patients who experience visual loss after a stroke can also benefit from a neuro-ophthalmological evaluation. “These patients might not realize that the visual loss isn’t coming from the ocular system itself, but emanating from the brain or the nervous system if the stroke has affected the visual cortex of the brain,” Dr. Acierno says.

In addition, people with MS are a large part of Mayo’s neuro-ophthalmological practice. “We have many referrals of patients with MS who experience optic neuritis, eye-movement disorders, problems with ocular motility or double vision,” Dr. Acierno says.

For Mayo’s neuro-ophthalmologists, collaboration extends beyond the fields of neurology and neurosurgery. Dr. Acierno often works with radiation oncologists to treat patients who experience visual problems after radiation treatment for cancer. She also hopes to start a combined service — with neurologists, neurosurgeons and bariatric surgeons — for people with idiopathic intracranial hypertension.

“Many of these patients can lose vision due to the elevated intracranial pressure and may require surgery to decompress the optic nerve or a shunt to relieve pressure from cerebrospinal fluid,” Dr. Acierno says. “That surgery might be done by a neuro-ophthalmologist or by a neurosurgeon. In addition, our neurologists work to control these patients’ headaches. But it’s also important for these patients to lose weight, which might involve bariatric surgery.

“As a center of excellence in the neurosciences, Mayo Clinic has subspecialists in place to offer the best care for patients,” she adds.

Figure. Image shows significant papilledema in a young female diagnosed with Henoch-Schönlein purpura IgA vasculitis. The papilledema is due to elevated intracranial pressure secondary to a cerebral venous sinus thrombosis, presumably associated with the vasculitis. She has visual field compromise and is being closely medically managed on an anticoagulant and a diuretic prior to determining if optic nerve decompression surgery is warranted. Her treatment at Mayo Clinic involves a multidisciplinary approach including specialists in neurology, neuro-ophthalmology, hematology and rheumatology.
Mayo Clinic offers minimally invasive surgery using a tubular retractor system that substantially lowers the risk of damaging eloquent tissue during removal of deep-seated lesions. The procedure can be an option for selected patients with subcortical high-grade glioma (Figure), metastatic brain tumors or vascular lesions.

“It’s a stealth approach. You go deep within the brain, you cause minimal disturbance — it’s like no one knew you were there,” says Kaisorn L. Chaichana, M.D., a neurosurgeon at Mayo Clinic in Jacksonville, Florida. “Patients also have less blood loss and recover much faster than they do with open surgery.”

The typical approach to deep-seated lesions — involving large craniotomies, extensive cortical and subcortical dissection, and retractor blades — can be associated with significant morbidity. “One advantage of our keyhole procedure is that the incision can be just 1.5 to 2 inches long,” Dr. Chaichana says. “The bone opening is a little bit larger than a silver dollar, and we work through a tube with a diameter that’s a little bit smaller than a dime.”

The tubular retractor splays the brain’s white matter tracts, exposing the tumor surface and providing a small working channel for lesion dissection and removal. “Bladed retractors stretch the white matter tracts and often sever them. The tubular retractor pushes the tracts aside, and the tracts go back into place when you pull out the tube,” Dr. Chaichana says.

The minimally invasive procedure also uses exoscopic visualization, which provides greater magnification than microscope technology. “The exoscope is very ergonomic for the surgeon, and allows us to get light down into areas where we couldn’t before,” Dr. Chaichana says.

Depending on the lesion’s location, the minimally invasive surgery takes about 2.5 hours. Patients generally go home on the second postoperative day. “Typically, patients who have open resection stay in the hospital for five or six days and often need rehabilitation,” Dr. Chaichana notes.

Tubular retraction can also be an effective tool for diagnosing deep-seated lesions, to guide adjuvant therapy when extensive surgical resection isn’t appropriate. In a study published in the November 2017 issue of the Journal of Neurological Surgery Part A: Central European Neurosurgery, Dr. Chaichana and colleagues reported that a tubular retractor system with exoscopic visualization can safely access deep-seated lesions to provide adequate tissue for diagnosis and molecular evaluation. The researchers noted that tubular retraction yields more tissue than stereotactic needle biopsy and provides enhanced visualization.

“You can see the pathology up close. You know exactly what tissue you’re getting,” Dr. Chaichana says.

These minimally invasive techniques require a high level of expertise. “This procedure is technique-heavy. Surgeons who typically do this must be skilled in minimally invasive surgery, endoscopic as well as exoscopic,” Dr. Chaichana says.

In addition to skilled neurosurgeons, the procedure requires subspecialized expertise in neuro-imaging. “You need a high-quality neuroradiology team that’s able to identify the location of white matter tracts and to monitor them,” Dr. Chaichana says.

“This surgery is done on the highest-risk patients,” he adds. “At Mayo Clinic, we’re committed to providing a minimally invasive procedure for this group.”

For more information
Most Patients With Suspected Idiopathic Transverse Myelitis Have a Specific Myelopathy

Idiopathic transverse myelitis is often proposed as a diagnosis for patients who don’t meet the diagnostic criteria for the condition. In a retrospective study of patients referred to Mayo Clinic for idiopathic transverse myelitis, Mayo researchers found that a majority had an alternative specific myelopathy diagnosis. Among the 226 adult patients referred to Mayo Clinic in Rochester, Minnesota, for idiopathic transverse myelitis from 2010 to 2015, only 41 (18 percent) met the diagnostic criteria. Mayo Clinic made an alternative specific myelopathy diagnosis in 158 of the patients referred (70 percent). The most common specific diagnosis was multiple sclerosis or clinically isolated syndrome (75 patients), followed by vascular myelopathy (41 patients). Other diagnoses included neurosarcoidosis, neuromyelitis optica spectrum disorder, and myelin oligodendrocyte glycoprotein myelopathy. A myelopathy wasn’t confirmed in 27 of the 226 patients. Fifty-five patients (24 percent) required treatment changes according to their final clinical diagnoses. The researchers note that the diagnostic criteria for idiopathic transverse myelitis were published 15 years ago — before advances in neuroimaging and the discovery of highly specific biomarkers of myelitis or an underlying cause — and that revised criteria are indicated. Based on the most common specific myelopathy diagnoses found, the researchers recommend that physicians carefully consider clinical history with particular attention to hyperacute onset of symptoms, indicating the possibility of an acute vascular myelopathy, and the possibility of a first clinical attack of multiple sclerosis or a progressive myelopathy indicating primary progressive multiple sclerosis. Physicians should also obtain cervical and thoracic MRI with sagittal and axial pre-gadolinium and post-gadolinium images. (Zalewski NL, et al. Evaluation of idiopathic transverse myelitis revealing specific myelopathy diagnoses. *Neurology*. 2018;90.e96.)

Cerebrospinal Fluid Shunting for Patients With High-Grade Glioma

Hydrocephalus is a known complication of high-grade glioma in the primary central nervous system. Shunting of cerebral spinal fluid (CSF) can relieve the symptoms of hydrocephalus and might also extend patient survival. However, information on clinical outcomes after this procedure is limited, and the risk of complications isn’t well-defined. In a retrospective study, Mayo Clinic researchers found that shunting can be an effective treatment for the symptoms of hydrocephalus in people with high-grade glioma, but the procedure carries a significant risk of complications. The researchers reviewed clinical outcomes for 41 people with pathologically confirmed grade III or grade IV glioma who had CSF shunting at Mayo Clinic to relieve the symptoms of hydrocephalus. A major complication occurred in 17.1 percent of the patients, with two suffering an intracranial hemorrhage. Prior administration of bevacizumab was significantly associated with the incidence of hemorrhage. Three patients (7.3 percent) died during admission, and eight (19.5 percent) died within 30 days of shunt placement. The presence of ependymal or leptomeningeal enhancement was more common in patients who died within 30 days. Six patients (18.1 percent) required readmission to the hospital within 30 days of discharge. Seven patients (17.1 percent) needed revision surgery. The median time from shunt placement to death was 150.5 days. The researchers compared those outcomes to outcomes for people with normal pressure hydrocephalus who had CSF shunting at Mayo Clinic. The shunt-treated high-grade glioma patients had increased hospital stays and 30-day mortality but no difference in the incidence of revision surgery. The researchers suggest that the risks and benefits of CSF shunting for patients with high-grade gliomas should be carefully considered, particularly in patients with advanced disease. (Rinaldo L, et al. Outcomes following cerebrospinal fluid shunting for high-grade glioma patients. *Journal of Neurosurgery*. In press.)

Effects of TDP-43 Pathology on Disease Mechanism in ALS/FTD

The cytoplasmic mislocalization and aggregation of TAR DNA-binding protein-43 (TDP-43) is a common histopathological hallmark of the amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) disease spectrum (ALS/FTD). However, the composition of aggregates and their contribution to the disease process haven’t been elucidated. Mayo Clinic researchers and colleagues used an adaptation of proximity-dependent biotin identification to explore the mechanisms through which TDP-43 pathology contributes to neurodegeneration. The researchers’ proteomic analysis of pathological TDP-43 aggregates led to the unexpected discovery that cytoplasmic TDP-43 aggregates are highly enriched for nuclear pore complexes as well as transport factors. The findings imply that TDP-43 may not only be mislocalized as a consequence of defects in nucleocytoplasmic transport but also directly inhibit the nuclear import and export of macromolecules by sequestering components in this pathway. (Chou CC, et al. TDP-43 pathology disrupts nuclear pore complexes and nucleocytoplasmic transport in ALS/FTD. *Nature Neuroscience*. 2018;21:228.)

To read more about Mayo Clinic neurosciences research and patient care, visit http://www.mayoclinic.org /medical-professionals.
Education 2018-2019 Neurology and Neurologic Surgery Continuing Medical Education Programs

2018 courses

**June**
- Microsurgical Approaches to Aneurysms and Skull Base Diseases 2018
  - June 14-16, 2018
  - Mayo Clinic Simulation Center, Jacksonville, Fla.

**July**
- Neurology in Clinical Practice 2018
  - July 19-21, 2018
  - Westin Chicago River North, Chicago

**August**
- Microvascular Surgery Skills Training
  - Aug. 6-10, 2018
  - Mayo Clinic, Rochester, Minn.

**October**
- Mayo Clinic Neuroscience and Oncology Innovation Summit
  - Oct. 18-20, 2018
  - The Ritz-Carlton Key Biscayne, Miami
  - Key Biscayne, Fla.

**November**
- Mayo Clinic Convergence Neuroscience 2018
  - Nov. 8-10, 2018
  - The Ritz-Carlton Amelia Island, Amelia Island, Fla.
- Microsurgical Approaches to Aneurysms and Skull Base Diseases 2018-November
  - Nov. 15-17, 2018
  - Mayo Clinic Simulation Center, Jacksonville, Fla.
- Epilepsy and EEG in Clinical Practice 2018
  - Nov. 15-17, 2018
  - The Ritz-Carlton Orlando Grande Lakes
  - Orlando, Fla.
- Mayo Clinic Multidisciplinary Spine Care Conference 2018
  - Nov. 16-17, 2018
  - The Ritz-Carlton Amelia Island
  - Fernandina Beach, Fla.

2019 courses

**March**
- Principles of Pain Management and Palliative Care: Essential Tools for the Clinician 2019
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  - June 18-21, 2019
  - Mayo Civic Center, Rochester, Minn.

Information and registration
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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