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Glioblastoma Extracellular Vesicles: Targeting the Ill Effects, Using the Good

In the fight against glioblastoma, extracellular vesicles are a doubled-edged sword. On the one hand, glioblastoma-derived extracellular vesicles appear to be important culprits in suppressing patients' immune systems. But the tumor cell-released particles might also prove useful in the diagnosis and treatment of the disease. Mayo Clinic is shedding light on both edges of the sword, paving the way to improved glioblastoma management.

"Extracellular vesicles play a role in the biology of glioblastoma tumor growth. But they also have certain factors that we can exploit to better care for patients," says Ian F. Parney, M.D., Ph.D., a neurosurgeon and director of the Neurosurgical Oncology Laboratory at Mayo Clinic in Rochester, Minnesota.

Glioblastoma is the most common and deadly brain tumor, with a median survival of just 14 months, and novel approaches are needed. Immunotherapies have had limited efficacy, as patients with glioblastoma exhibit profound immunosuppression.

"Here at Mayo, we are looking at many different therapies to stimulate the immune system to fight glioblastoma," Dr. Parney says. "Extracellular vesicle pathways that mediate immunosuppression could be targeted alongside

existing immunotherapies, such as checkpoint inhibitors and vaccines, to achieve greater benefit."

A complex pathway

Recent studies have proposed that glioblastoma-derived extracellular vesicles directly inhibit patients' T lymphocytes. "Our results suggest the process is more complicated," Dr. Parney says.

In a study published in the July 2020 edition of *Neuro-Oncology*, Mayo Clinic researchers showed that extracellular vesicles work through monocytes — converting them into immunosuppressive cells that then inhibit T lymphocytes (Figure).

"Those results fit with what we already know about the biology of glioblastoma," Dr. Parney says. "Glioblastoma tumors are heavily infiltrated by monocytes. Almost 30% of the cells in some glioblastomas aren't tumor cells but monocytes subverted by the tumor to be immunosuppressive."

In addition to subverting monocytes, extracellular vesicles appear capable of co-opting standard cancer therapies to actually increase immunosuppression. Interferon gamma is normally a marker of a positive immune response. But tests in the Neurosurgical Oncology Lab found that treating glioblastoma cells with interferon gamma increased the immunosuppressive properties of extracellular vesicles.

"Similarly, standard treatments such as radiation and chemotherapy also make extracellular vesicles more potently immunosuppressive, at least in the test tube," Dr. Parney says. "Unfortunately, even if treatment generates an immune response, the tumor can shut it down."

Mayo's increased understanding of extracellular vesicles is bringing potential therapeutic targets

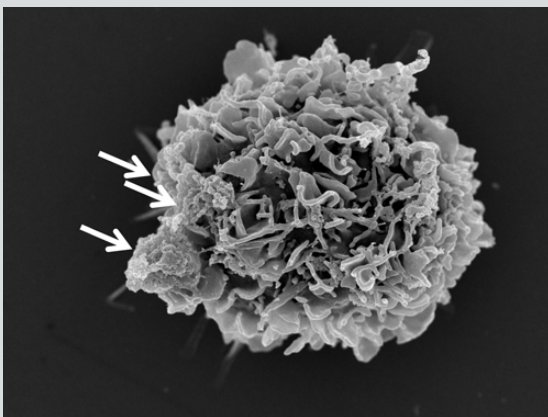


Figure. Image shows human glioblastoma extracellular vesicles (white arrows) binding to a normal human monocyte.



Ian F. Parney, M.D., Ph.D.

into focus. The Neurosurgical Oncology Lab is investigating markers of specific types of extracellular vesicles that boost immunosuppression.

“We’re hot on the trail of a few markers,” Dr. Parney says. “If we can block the release of those specific types of extracellular vesicles, we could also block the immunosuppressive capacity. That could be a future target of glioblastoma treatment.”

Diagnostic and delivery vesicles

The advantageous aspects of extracellular vesicles start with their potential to provide a liquid biopsy for glioblastoma. In a study published in the January 2020 issue of *Journal of Neuro-Oncology*, Mayo Clinic identified a panel of microRNAs in extracellular vesicles that are dysregulated in glioblastoma and detectable in blood. MRI — the standard means of assessing tumor response — can’t clearly differentiate actual tumor growth from pseudoprogression following treatment.

“A blood test that can detect glioblastoma-derived extracellular vesicles would conceivably distinguish between tumor and inflammation. That would be very helpful,” Dr. Parney says.

A liquid biopsy might even prove possible for the initial diagnosis of glioblastoma. Recent work in the Neurosurgical Oncology Lab found that the microRNAs in glioblastoma-derived extracellular vesicles contain a signature. “The signature tracks back to the tumor itself. That allows us to distinguish quite well between plasma from a patient with glioblastoma and from a healthy donor,” Dr. Parney says.

The researchers also found that the microRNA signature in the plasma of a patient with glioblastoma reemerges when the tumor recurs. “That information could potentially help us track glioblastoma treatment,” Dr. Parney says.

He notes that extracellular vesicles might eventually serve as delivery vehicles for glioblas-

toma treatment. Mayo Clinic has clinical-grade glioblastoma tumor cell lines and a good manufacturing practice facility. “It’s not a big jump to say we could genetically modify those clinical-grade tumor cells so that their extracellular vesicles deliver a gene therapy,” Dr. Parney says.

Boosting existing immunotherapies

Although single-agent immunotherapies haven’t so far proved rewarding against glioblastoma, Mayo Clinic sees synergy from combining immunotherapy with standard treatments. Adding therapies that target extracellular vesicle pathways might further boost treatment response.

Knowledge of extracellular vesicles might also provide guidance on the optimal timing of combined treatment. “For example, if we know that the immune response is depleted right after chemotherapy, we might then try to block the immunosuppressive pathway that is mediated through extracellular vesicles,” Dr. Parney says.

As immunotherapies evolve, Mayo Clinic is focused on translating laboratory research into new treatments. “Glioblastoma-mediated immunosuppression is complex, and extracellular vesicles exert multiple effects,” Dr. Parney says. “But targeting these particles looks like a fruitful strategy to help prevent immunosuppression in glioblastoma.”

For more information

Himes BT, et al. The role of extracellular vesicles and PD-L1 in glioblastoma-mediated immunosuppressive monocyte induction. *Neuro-Oncology*. 2020;22:967.

De Mooij T, et al. Short non-coding RNA sequencing of glioblastoma extracellular vesicles. *Journal of Neuro-Oncology*. 2020;146:253.

Cervical Myelopathy: Discoveries Paving the Way to Better Care

Cervical myelopathy is common and debilitating, yet consensus on optimal treatment is lacking. As many as 25% of patients require re-operation for symptom recurrence. Through groundbreaking research, Mayo Clinic is learning more about spinal cord mechanics to guide improved surgical treatment.

“We want to better understand how much stress is actually on the spinal cord so we can determine the best surgical approach for each patient,” says Kingsley Abode-Iyamah, M.D.,

a neurosurgeon at Mayo Clinic in Jacksonville, Florida. “If surgery doesn’t optimally position the spinal cord, the patient can have ongoing and worsening symptoms of myelopathy.”

To that end, Mayo Clinic is using the first finite element model of the healthy and myelopathic C2-T1 cervical spine. The model, described in a study published in the February 2020 issue of *Clinical Biomechanics*, predicts how common surgical interventions affect spinal cord mechanics.

As expected, the study found that after

surgery, patients had decreased spinal cord movement in the surgical area. “But interestingly, we also found that surgery didn’t necessarily eliminate all the strain on the spinal cord,” Dr. Abode-Iyamah says. “While the area that was decompressed showed decreased strain, other areas of the spinal cord started to see new stress.”

Among all the surgical techniques studied, anterior cervical discectomy and fusion (ACDF) increased adjacent-level strain and stress the most. The researchers suggest this might be due to a lack of spinal canal widening in the procedure compared with ACDF with laminectomy or double-door laminoplasty. Increased canal width allows for more spinal cord displacement, especially in extension, which may decrease the likelihood of spinal cord impingement elsewhere along the canal. The researchers also found that double-door laminoplasty allowed for more normal motion of the spine, as that procedure doesn’t fuse the vertebral bodies.

“These results have the potential to change our approach in treating these patients,” Dr. Abode-Iyamah says. “The goal is to return the patient’s spine to the best alignment that will minimize stress and strain on the spinal cord.”

Another area of interest is a genetic component to cervical myelopathies. Previous work by Dr. Abode-Iyamah and colleagues implicated a mutation known as Val66Met polymorphism in the pathophysiology of cervical spondylotic myelopathy (CSM).

Mayo Clinic is enrolling patients in a new study to determine how the polymorphism might affect the recovery process of people with CSM. “We hope to learn if there’s an adjunct treatment we might give these patients before or after surgery to help their recovery,” Dr. Abode-Iyamah says. “We would also like to find a way to screen patients and catch CSM early.”

The importance of early intervention

Diagnosis of cervical myelopathy is often delayed. The most common early sign of the disease — loss of dexterity — can be attributed by patients and even physicians to normal aging.

Telemedicine Offers Benefits in the COVID-19 Era and Beyond

Mayo Clinic has enhanced its use of telemedicine during the coronavirus disease 2019 (COVID-19) outbreak to safeguard health care workers while optimizing patient care. Mayo’s positive experience provides a potential model for post-pandemic care.

“The disease process isn’t generally associated with pain,” Dr. Abode-Iyamah says. “Patients tell us, ‘There’s nothing wrong with my neck. But I can’t button my shirt or put my earrings in.’ Or ‘My handwriting has gotten bad’ or ‘My balance isn’t quite what it used to be and I am having more falls.’ Those problems should trigger physicians to think about cervical myelopathy.”

As the disease progresses, symptoms can include upper extremity numbness, neck pain and gait disturbance. Some individuals become wheelchair dependent. “Unfortunately, by the time some patients get to us, they are very debilitated,” Dr. Abode-Iyamah says. “Cervical myelopathy really sneaks up on people. But the earlier you intervene, the better the outcome.”

At Mayo Clinic, patients with suspected cervical myelopathy have MRI to check for spinal cord

compression (Figure). If the MRI and clinical findings correlate and result in a diagnosis of cervical myelopathy, surgery is typically recommended.

“We don’t know how fast the disease will progress once patients present with symptoms, and we want to halt that progression,” Dr. Abode-Iyamah says.

“All of our work, in both research and clinical care, is focused on improving the functioning of the spinal cord,” he adds. “We want to target our interventions so our patients get the best possible care.”

For more information

Stoner KE, et al. A comprehensive finite element model of surgical treatment for cervical myelopathy. *Clinical Biomechanics*. 2020;74:79.



Kingsley Abode-Iyamah, M.D.



Figure. Preoperative MRI of a patient with cervical myelopathy shows compression of the spinal cord.

“Prior to COVID, telemedicine was approved primarily for rural areas. During COVID, telemedicine has become a powerful tool for delivering care at our academic campuses. Post-COVID, we don’t envision going back,” says William D. Freeman, M.D., a



William D. Freeman, M.D.

neurocritical care specialist at Mayo Clinic in Jacksonville, Florida.

Mayo Clinic has pioneered the use of telemedicine for patients in underserved areas, particularly for the treatment of stroke. In response to the COVID-19 pandemic, government regulators eased significant obstacles to telemedicine involving, for example, state licensure and health insurance reimbursement. As a result, Mayo Clinic extended its Emergency Medicine Telehealth (TeleEM) program to its campuses in Arizona, Florida and Rochester, Minnesota.



Bart M. Demaerschalk, M.D.

Digital connections with patients rose from fewer than 500 a day pre-pandemic to more than 8,000 a day in April 2020. "Since then, although our inpatient and outpatient in-person visits have been restored, we are still conducting nearly 5,000 digital connections a day," says Bart M. Demaerschalk, M.D., a neurologist at Mayo Clinic in Phoenix/Scottsdale, Arizona, chair of Stroke and Cerebrovascular Diseases and medical director of Mayo Clinic's Telestroke Service. "We have demonstrated that our digital connections not only are scalable — they are also sustainable. Survey responses from our patient population and our providers have been highly favorable."

As described in the October 2020 issue of Mayo Clinic Proceedings, some of the many benefits of telemedicine during the pandemic include:

- Conservation of personal protective equipment (PPE)
- Reduced exposure of staff to the COVID-19 virus
- Efficient use of emergency department exam rooms

The lessons learned during the pandemic are likely to change future health care. "COVID has pushed us to try new approaches," says Rabih G. Tawk, M.D., a neurovascular surgeon at Mayo Clinic's campus in Florida. "Patients have become more proficient with technology. We have found that many follow-up visits can be done over video. Not every patient needs to spend time and expense to travel."

Facilitating a multidisciplinary approach

Telemedicine aligns well with Mayo Clinic's integrated practice and multispecialty approach to patient care. The TeleEM team is

able to remotely gather specialists in neurocritical care, critical care, telestroke, teleneonatology, pediatric intensive care and cardiology (Figure).

"The biggest benefit of telemedicine pre-, during or post-COVID is that we can offer subspecialized care to the right person in the right place at the right time," says Deena M. Nasr, D.O., a neurologist at Mayo Clinic in Rochester, Minnesota, and the site medical director for Mayo's telestroke core team in the Midwest. "It's the new standard of quality care for subspecialized areas."

The benefits are apparent at multiple stages of patient care. During the pandemic, telemedicine has made triage in Mayo Clinic's emergency departments more efficient.

"Stable patients with suspected COVID-19 but no respiratory distress don't require full emergency department exam rooms," Dr. Demaerschalk says. "Those patients can be tested for COVID and remotely examined by a physician, which keeps critical emergency department rooms open for more acutely ill patients."

Patients can also be monitored remotely. Dr. Demaerschalk notes that considerable amounts of PPE are consumed by health care workers briefly entering patients' rooms to assess pain and the need for therapeutics. Remote monitoring minimizes those contacts.

Daily hospital rounds also can be done remotely. "Instead of a large group of nurses, trainees and a neurological consultant gathering

at the bedside, we usually now have a representative from our neurological hospital team put on PPE and enter the COVID environment," Dr. Demaerschalk says. "The other team members gather together and are able to ask questions and to discuss the diagnosis and management plans without putting themselves at risk or unnecessarily utilizing PPE."

Even before the COVID-19 pandemic, Mayo Clinic began using telemedicine in ambulances transporting patients to the emergency departments at Mayo's campuses in Arizona and Florida. For the past five years, Mayo Clinic stroke neurologists have been able to remotely conduct National Institutes of Health (NIH) Stroke Scale testing before patients arrive at the hospital.



Rabih G. Tawk, M.D.



Deena M. Nasr, D.O.

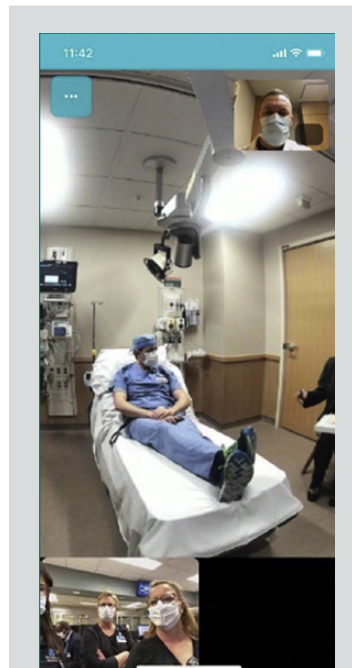


Figure. Photograph illustrates the ability of multiple participants to examine a patient remotely.

“We realized that if we got our eyes on the patients earlier, we could tailor the care they needed,” Dr. Freeman says. “It’s sort of like NASCAR — we know what the patients need by the time they roll up.”

The early assessments have cut 8 to 10 minutes from the time needed to obtain CT scans. “In large vessel occlusion strokes, one minute of faster treatment saves about 1.9 million neurons,” Dr. Freeman says. “Doing the NIH Stroke Scale in the ambulance potentially saves 19 million neurons.”

Potential new uses

Telemedicine might possibly be used for the diagnosis of patients presenting with certain new subacute neurological conditions. Mayo Clinic has launched a study comparing the accuracy of a provisional video telemedicine diagnosis and an in-person reference standard diagnosis for each of 2,600 study participants.

“We will compare the provisional diagnosis from the telemedicine consultation with the definitive reference diagnosis offered after in-person evaluation and any diagnostic studies,” Dr. Demaerschalk says. “Our goal is to more clearly understand where video telemedicine

consultations have added value and where there may be vulnerabilities.”

Mayo Clinic is also working to incorporate robotic technology into care for patients who require neurological surgery. Robot-assisted spinal surgery is performed at all three campuses. Eventually, Mayo Clinic neurosurgeons might have the capability to robotically examine patients or even perform minimally invasive procedures on patients in other states or countries.

“That work is very much in its infancy,” Dr. Freeman says. “But we’re trying to think on a worldwide scale and to pioneer the next wave of robotic technology.”

Mayo Clinic’s use of technology is a key aspect of patient-centered care. “We have always seen the potential for wider use of telemedicine. But COVID really solidified that need,” Dr. Nasr says. “This patient-centered approach exemplifies the Mayo Clinic model of care.”

For more information

Russi CS, et al. Emergency medicine telehealth for COVID-19: Minimize front-line provider exposure and conserve personal protective equipment. *Mayo Clinic Proceedings*. 2020;95:2065.

Longitudinal Study Maps the Transition to Alzheimer’s Disease

Mayo Clinic has found that cognitive and behavioral changes can be detected nearly two decades before the onset of Alzheimer’s symptoms. That time lag — longer than previously demonstrated — is similar to the gap between preclinical biomarker changes and symptom onset.

“Our work shows that plenty is happening during the preclinical period that needs to be addressed to help prevent dementia,” says Richard J. Caselli, M.D., a neurologist at Mayo Clinic in Phoenix/Scottsdale, Arizona. “It’s never too early to try to avoid setting up the cascade of events that will kick in, on average, by our early 50s.”

Mayo Clinic’s finding, described in the March 2020 issue of *Alzheimer’s & Dementia*, is one of many insights from an extensive study of neuropsychological aging underway at Mayo Clinic since 1994. Cognitively healthy adults age 21 and older in Maricopa County, Arizona, are recruited for the longitudinal study.

Participants have initial genetic testing to gauge their relative risk of developing Alzheimer’s disease, as well as neuropsychological testing that is repeated every two years. Some participants also have MRI (Figure 1, see page 6) and PET imaging, performed in conjunction

with Banner Alzheimer’s Institute in Phoenix.

Mayo Clinic is one of the few centers conducting longitudinal personality-based testing as a potential aid for identifying the transition from cognitive health to mild cognitive impairment (MCI) in individuals at risk of dementia.

“We have found subtle but statistically significant differences in personality that coincide with the transition from preclinical Alzheimer’s disease to incident MCI,” Dr. Caselli says. “During that transition, we see an increase in neuroticism and a decrease in openness, along with subclinical behavioral measures of somatization, depression, anxiety and irritability.”

The genetic component of the longitudinal research, focused particularly on the APOE e4 allele, aims to identify and quantify an individual’s risk of developing Alzheimer’s disease.

An early key finding was that age-related memory decline in carriers of that allele diverges from age-related memory decline in noncarriers before the age of 60 (Figure 2, see page 6).

All of this work has facilitated the design of trials aimed at preventing dementia. “Sadly, we still don’t have a therapy known to be effective for dementia. But unlike 20 years ago, we



Richard J. Caselli, M.D.

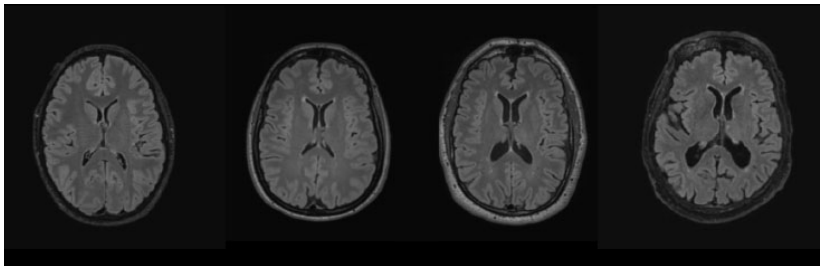


Figure 1. MRI illustrates the mild shrinkage in cortical volume resulting from normal aging. From the left, imaging shows the brains of a 22-year-old female, a 44-year-old female, a 62-year-old male and an 83-year-old male.

now have preventative trials,” Dr. Caselli says. “Because of the length of our study and the wide age range of our cohort, we are able to help researchers determine what should be measured and when it should be measured.”

Complex pathogenesis

Mayo Clinic’s research has contributed to the increasing awareness of the complexities of dementia pathophysiology. “There are a number of both inherited and acquired factors that increase our vulnerability and that don’t seem to conform to any single pathway,” Dr. Caselli says. In addition to APOE e4, roughly 30 other genes have a milder but statistically significant effect on dementia risk. Acquired and environmental risk factors include head injury and air pollution.

The 2020 study of early cognitive and behavioral changes assessed neuropsychological changes in an APOE e4-enriched cohort of individuals. All members of the cohort were cognitively normal when they entered the longitudinal study. Among individuals who went on to develop MCI, behavioral measures changed in the pre-MCI period — despite the absence of any clinically identified behavioral problems. Depression also tended to increase more rapidly in individuals who went on to develop MCI compared with participants who didn’t.

“During the transition from normal aging to MCI, there is a change in personality and behavioral measures, including depression scores,” Dr. Caselli says. “This temporal pattern suggests that depression, rather than being a risk factor, is more likely an early manifestation of neurodegeneration.”

Amyloid buildup, long considered the first in a linear sequence of events leading to dementia, has now been shown to occur at the same time as tau formation, brain atrophy and memory decline. In a theoretical article published in the November 2020 issue of *Alzheimer’s & Dementia*, Mayo Clinic researchers proposed an alternative to the amyloid cascade hypothesis: that amyloid formation is part of the brain’s protective response to various genetic and environmental neurotoxic factors.

The researchers noted that amyloid precursor protein, which leads to the production of amyloid beta plaques, is vital for brain development and structure and has a diverse array of functions. The researchers suggest that dysregulation of this complex system might include, yet go well beyond, amyloid beta accumulation and toxicity. Similar proposals made by other investigators haven’t received sufficient merit, according to the Mayo researchers.

The updated amyloid hypothesis aligns with the findings of Mayo Clinic’s neuropsychological research. “We see people starting to develop cognitive decline right from the beginning. We don’t have to wait for the amyloid buildup,” Dr. Caselli says.

The complexities of Alzheimer’s disease pose significant challenges for researchers, clinicians and patients. But as a clinician-researcher, Dr. Caselli emphasizes that for most people, cognitive decline is a long process that needn’t preclude activity. He cites a patient who, after a diagnosis of MCI, fulfilled his lifelong dream of hiking the 800-mile Arizona Trail alone. “Even for people who have MCI, life isn’t over yet,” Dr. Caselli says.

For more information

Caselli RJ, et al. Neuropsychological decline up to 20 years before incident mild cognitive impairment. *Alzheimer’s & Dementia*. 2020;16:512.

Banner Alzheimer’s Institute. <https://www.banneralz.org/>.

Caselli RJ, et al. An agnostic reevaluation of the amyloid cascade hypothesis of Alzheimer’s disease pathogenesis: The role of APP homeostasis. *Alzheimer’s & Dementia*. 2020;16:1582.

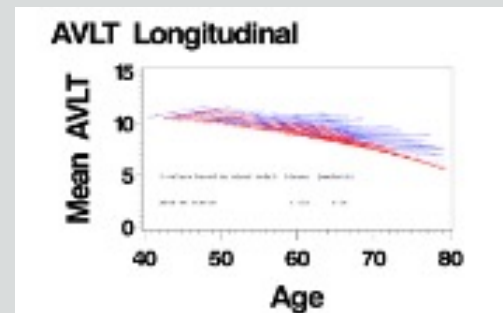
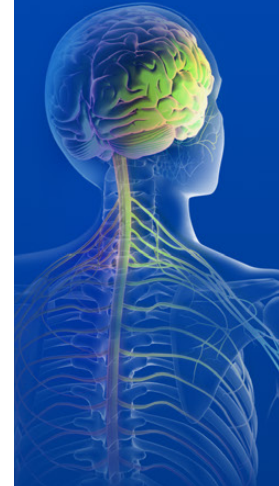


Figure 2. Graph shows the more rapid decline in memory experienced by APOE e4 carriers (red) compared with noncarriers (blue). Each line represents an individual patient in Mayo Clinic’s longitudinal study.



Research Highlights in Neurology and Neurosurgery

Minimally Invasive Spinal Surgery for Elderly Patients

As a consequence of normal aging, more than 90% of individuals over age 50 have evidence of lumbar disc degeneration. About one-third of patients presenting with degenerative lumbar spinal disease require surgical intervention. Minimally invasive spinal surgery has generally been associated with lower complication rates and improved patient-reported outcomes. However, there are limited data comparing outcomes of minimally invasive surgery versus open lumbar spine decompression in the subgroup of older adults. A Mayo Clinic study suggests that minimally invasive spinal surgery is safe for these patients and may pose a lower risk of complications compared with open surgery. The researchers reviewed the records of 107 individuals ages 65 and older who were treated for degenerative disc disease at Mayo Clinic between 2016 and 2018. The patients were grouped according to the type of surgery performed: minimally invasive or lumbar decompression. The individuals' characteristics, such as demographics and comorbidities, as well as perioperative and postoperative complications were collected. The median age of the patients studied was 73 years. Demographics and comorbidities in the minimally invasive and open surgery groups were similar. Patients who had minimally invasive surgery had significantly lower estimated blood loss, operative time and length of hospital stay. No individual who had minimally invasive surgery required rehospitalization. The rates of complications and pain improvement also favored the minimally invasive group, although these rates weren't significantly different. (Yolcu YU, et al. Minimally invasive versus open surgery for degenerative spine disorders for elderly patients: Experiences from a single institution. *World Neurosurgery*. 2021;146:e1262.)

Differentiating Variants of Progressive Supranuclear Palsy

The patterns of white matter tract degeneration underlying three variants of progressive supranuclear palsy — and the degree to which white matter patterns might differentiate these variants — are unclear. In a pilot study, Mayo Clinic researchers found that the patterns of white matter tract degeneration differed across the three variants, with the body of the corpus callosum showing some utility in differentiating them. Among the 49 patients with progressive supranuclear palsy who were studied, 28 had the classic Richardson's syndrome (known as PSP-RS), 12 had the parkinsonism variation (PSP-P), and nine had the speech and language variation (PSP-SL). All study participants had diffusion tensor imaging, and the results were compared. Degeneration of the superior cerebellar peduncle was greatest in PSP-RS, while PSP-SL showed the most widespread degeneration of association fibers, corpus callosum and internal capsule. The PSP-P variant showed the most restricted patterns of white matter tract degeneration, with less involvement of the superior cerebellar peduncle and association fibers. The researchers note that the body of the corpus callosum provided excellent values on diffusion tensor imaging for differentiating PSP-SL from both PSP-RS and PSP-P. However, the ability to differentiate between PSP-RS and PSP-P based on diffusion tensor imaging was only moderate. The results indicate that PSP-RS and PSP-P are more similar to each other than either is to PSP-SL. (Whitwell JL, et al. Diffusion tensor imaging analysis in three progressive supranuclear palsy variants. *Journal of Neurology*. In press.)

Pseudophlebitic Pattern Is Associated With More-Aggressive Dural Arteriovenous Fistulas

The pseudophlebitic pattern is an increasingly recognized angiographic manifestation of chronic venous congestion in the setting of a cranial dural arteriovenous fistula. Mayo Clinic researchers found that this pattern was associated with high rates of brain parenchymal changes and neurological symptoms. The retrospective study reviewed the records of 200 patients with dural arteriovenous fistulas evaluated at Mayo Clinic from 2008 to 2020. Angiograms were evaluated to classify dural arteriovenous fistulas and to document the presence or absence of a pseudophlebitic pattern. The researchers then studied the association between the pseudophlebitic pattern and the patients' clinical presentations and MRI findings. Among the patients studied, the presence of a pseudophlebitic pattern was associated with a significantly higher rate of hemorrhage and nonhemorrhagic neurological deficits such as cognitive changes, gait dysfunction and seizure. Several cross-sectional MRI findings were associated with the presence of a pseudophlebitic pattern, including cerebral edema, chronic hemosiderin deposition and dilated transmedullary veins. The results highlight the reliability of the pseudophlebitic pattern as a prognostic marker for a symptomatic and malignant fistula. (Brinjikji W, et al. Clinical presentation and imaging findings of patients with dural arteriovenous fistulas with an angiographic pseudophlebitic pattern. *American Journal of Neuroradiology*. 2020;41:2285.)

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

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2021 courses

October

13th Annual Stroke and Cerebrovascular Disease Review 2021 — LIVESTREAM
Oct. 13-16, 2021

Mayo Clinic Stimulation Therapies for Epilepsy 2021
Oct. 21-22, 2021
Hilton Rochester Mayo Clinic Area, Rochester, Minn.

Mayo Clinic Conference on Brain Health and Dementia 2021
Oct. 29, 2021
Mayo Civic Center, Rochester, Minn.

November

Neuroradiology: Practice to Innovation
Nov. 8-12, 2021
The Westin Hapuna Beach Resort, Kohala Coast, Hawaii

5th Annual Multidisciplinary Spine Care Conference 2021
Nov. 12-13, 2021
The Ritz-Carlton, Amelia Island, Amelia Island, Fla., or LIVESTREAM

2022 COURSES

February

Neuroradiology: Excellence Through Evidence and Guidelines
Feb. 13-17, 2022
Four Seasons Resort and Residences, Whistler, BC, Canada

Mayo Clinic Advancements in Surgical & Medical Management of the Spine 2022
Feb. 19-23, 2022
Fairmont Orchid, Kohala Coast, Hawaii

July

5th Annual Mayo Clinic Advances and Innovations in Complex Neuroscience Patient Care: Brain and Spine 2022
July 27-30, 2022
Enchantment Royal Sedona, Sedona, Ariz.

November

Neuroradiology: Practice to Innovation 2022
Nov. 7-11, 2022
The Ritz-Carlton, Grand Cayman, Seven Mile Beach, Grand Cayman, Cayman Islands

Parkinson's Disease and Other Movement Disorders 2022
Nov. 11-12, 2022
Mayo Clinic Franke Education Center, Phoenix, Ariz.

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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

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