New Approaches to Immunotherapy for Glioblastoma

Although immunotherapy is revolutionizing cancer care, its use in glioblastoma has lagged behind the progress seen in other types of cancer. Mayo Clinic is advancing new applications of immunotherapy for glioblastoma, with a focus on more-potent and combination therapies for optimal effectiveness.

“We certainly believe that immunotherapy can be useful for neuro-oncology, as it is now for other indications in solid tumor oncology,” says Maciej M. Mrugala, M.D., Ph.D., a neuro-oncologist at Mayo Clinic in Phoenix/Scottsdale, Arizona. “We are beginning to understand some of the mechanisms that make glioblastoma relatively nonimmunogenic, and finding potential ways to activate the cascade of the immune system for self-healing.”

Mayo Clinic’s enterprisewide efforts range from laboratory exploration to clinical trials in patients with newly diagnosed and recurrent glioblastoma. Preliminary results of separate clinical trials assessing a dendritic cell vaccine and checkpoint inhibitor combination therapy have been promising.

“We’re beginning to find that combining immunotherapy with standard glioblastoma therapy provides synergy,” says Ian F. Parney, M.D., Ph.D., a neurosurgeon at Mayo Clinic in Rochester, Minnesota. “Some of these findings could be translated into routine clinical practice within the next few years.” Other immunotherapeutic strategies under investigation at Mayo include chimeric antigen receptor (CAR)-T cell therapy, injections of stromal vascular fraction (SVF) into the surgical cavity at the time of glioblastoma resection (Figure 1), and the role of extracellular vesicles in brain tumor immunology.

Beyond testing new immunotherapies, Mayo Clinic researchers are seeking explanations for glioblastoma’s low immunogenicity. “We must understand how the immune system is being tricked so that the brain can fight this cancer,” says Alfredo Quinones-Hinojosa, M.D., chair of Neurosurgery at Mayo Clinic in Jacksonville, Florida. “The future is going to involve directly affecting the microenvironment of these cancers.”

A more potent vaccine
Glioblastoma’s low mutational variance limits the number of antigens that can be targeted, making successful immunotherapy challenging. But Mayo Clinic has developed a dendritic cell vaccine that showed promising results in a preliminary clinical trial in patients with newly diagnosed glioblastoma.

“The average overall survival of the 20 patients in the trial was substantially longer than we would expect for patients receiving standard treatment,” Dr. Parney says. “In addition, about 20% of patients in the study survived from four to five years, which is quite unusual in glioblastoma.”
The vaccine is based on dendritic cells taken from an individual patient, enhanced in the laboratory and then combined with tumor proteins from a Mayo Clinic library of clinical grade brain tumor cell lines. A larger study is planned in patients with newly diagnosed glioblastoma. Dr. Parney notes that a separate trial of the vaccine in patients with recurrent glioblastoma, already underway, has also had encouraging early results.

**Checkpoint inhibitors and CAR-T cell therapy**

Immune checkpoint inhibitors, which have had generally disappointing outcomes in glioblastoma, may be more efficacious when combined with standard brain cancer therapies. Early results from a Mayo Clinic phase II clinical trial of pembrolizumab indicate that surgery before administration of that checkpoint inhibitor might boost its effectiveness.

“We don’t have complete results yet from the trial, but it’s very exciting that we’re seeing this effect already,” Dr. Parney says. He suggests that the release of tumor proteins during resection might work with pembrolizumab to stimulate the immune system. The clinical trial is also assessing how well pembrolizumab works in conjunction with radiation and chemotherapy.

Like checkpoint inhibitors, CAR-T cell therapy has shown benefit in patients with certain cancers. Mayo Clinic, a pioneer in CAR-T cell therapy for acute lymphoblastic leukemia and non-Hodgkin’s lymphoma, is now working to apply that approach to glioblastoma.

“We are hoping to launch a clinical trial that would involve placing CAR-T cells directly into the tumor or spinal fluid, or possibly giving the therapy systemically,” Dr. Mrugala says. “There is evidence that CAR-T cells entered into the bloodstream can find their way to spinal fluid and brain tissue and cause very positive responses in patients.”

**SVF in the surgical cavity**

At Mayo Clinic’s campus in Florida, researchers are using animal models to investigate immunotherapies placed directly into the surgical cavity at the time of glioblastoma resection. “The most effective window of therapy is while the patient is in the operating room, when the surgical cavity is open,” Dr. Quinones-Hinojosa says. “This approach is an opportunity to do something about the residual cancer cells left behind when we debulk the tumor.”

One strategy under investigation involves modifying adipose-derived mesenchymal stem cells to secrete anti-tumor proteins. More recently, the researchers have begun studying the effects of SVF placed in the surgical cavity. That work required designing a laboratory methodology to assess the therapeutic mechanisms of SVF on glioblastoma cells.

The SVF used in these studies can be grown directly on the animal models’ brains as well as in the laboratory. “Both avenues could unravel the effect the immune cells impose on cancer growth,” Dr. Quinones-Hinojosa says. “This has the potential to be an amazing new tool for manipulating the immune system.”

Another potential tool is extracellular vesicles. “We have some exciting data showing that extracellular vesicles released by brain tumor cells are important in shutting down the immune system or reducing immunosuppressive changes in monocytes,” Dr. Parney says.

Extracellular vesicles might also provide the basis for a liquid biopsy. Mayo Clinic researchers have identified a panel of approximately 45 microRNAs in extracellular vesicles that are dysregulated in glioblastoma and detectable in blood. Unlike MRI, extracellular vesicles can provide a window of therapy to glioblastoma rests on the enterprise’s commitment to translational science.

“We have a large team of clinician-scientists — neuro-oncologists, radiation oncologists and immunologists — as well as basic scientists, all working together,” Dr. Mrugala says. “In addition, knowing how to care for patients in these clinical trials is critical. Our teams of physicians and support staff understand the side effects of immunotherapies (Figure 2). The safety and comfort of our patients is always paramount.”

![Figure 2](image_url)

On the left, fluid-attenuated inversion recovery (FLAIR) MRI shows the brain of a 26-year-old man with B-cell lymphoma before treatment with CAR-T cell therapy at Mayo Clinic. On the right, FLAIR MRI seven days after CAR-T cell therapy shows bilateral thalamic lesions (arrows) that developed at the time of clinical symptoms consistent with neurotoxicity. The patient’s symptoms resolved within days, and subsequent MRIs were normal.
McArdle Sign Can Provide Reliable Clinical Detection of MS

Mayo Clinic has described a new clinical sign that is highly specific for the diagnosis of multiple sclerosis (MS). In a technician-blinded study, Mayo researchers found that McArdle sign — a clinical phenomenon in which neck flexion induces rapid, reversible weakness — is also moderately sensitive for a diagnosis of MS when compared with other myelopathy conditions that mimic MS.

“This is a unique sign that to our knowledge has not been used in clinical practice elsewhere,” says Brian G. Weinshenker, M.D., a neurologist at Mayo Clinic in Rochester, Minnesota. “The sign is easily demonstrated at the bedside, so this finding can be immediately translated into practice.”

MS is commonly misdiagnosed, due to the lack of clinical signs and MRI findings specific to the disease. Dr. Weinshenker notes that approximately 20% of patients referred to his practice with a diagnosis of MS don’t have the disease; some of these patients have taken MS disease-modifying therapies for years. Similar observations have been made at other large medical centers.

“McArdle sign is another arrow in our quiver — a specific finding that indicates MS and not another myelopathy,” Dr. Weinshenker says.

Dr. Weinshenker first observed the phenomenon in the 1980s, in a patient with advanced MS. “He would arch his neck every time he took a step. When we asked him to put his chin down, he couldn’t walk,” Dr. Weinshenker says.

Around the same time, Dr. Weinshenker read a case report in the Journal of Neurology, Neurosurgery, and Psychiatry that described the phenomenon in a patient in England. The authors of that 1987 report were students of the neurologist M.J. McArdle, and named the phenomenon after him.

No further reports on McArdle sign were published. But over the next several decades, Dr. Weinshenker evaluated the sign in his clinical practice and taught it to Mayo Clinic residents. Finger extensor muscles, which are among the first muscles to weaken in people with MS, provide a convenient means of testing: The physician attempts to overcome a patient’s resistance of finger extension, checking for a decrease in strength when the test is performed with neck flexion compared with neck extension.

“I found lots of patients who demonstrated this phenomenon to varying degrees,” Dr. Weinshenker says. “It was often the only clinical sign of MS. Patients with symptoms of the disease might have a completely normal clinical exam, with normal reflexes and strength — but they lost strength with neck flexion. The patients are usually shocked when I find this sign.”

Quantitative evaluation

Mayo Clinic researchers have now quantitated McArdle sign. Their pilot study, described in the August 2019 issue of Mayo Clinic Proceedings, included 50 patients with MS, 25 patients with other causes of myelopathy, five patients with finger weakness due to peripheral nerve lesions, and 25 healthy participants.

For each participant, a technician attempted to overcome maximal resistance of finger extension in successive trials of neck extension and flexion. Any clinically perceived decline in strength with neck flexion was rated.

McArdle sign was then quantitated in each participant, using a torque measurement device developed at Mayo Clinic for the study by Lawrence Berglund, a biomedical engineer. The device allowed for both isometric and isoinertial testing. The peak strengths in neck flexion and extension were recorded for each study participant (Figure).

“We found that a 10% or greater decrease in strength during neck flexion was 100% specific and about 70% sensitive for MS, compared to other myelopathies,” Dr. Weinshenker says. “A decrease in strength of 5% to 10% is a gray area that is suggestive of MS, but not entirely specific.”

Both the average isometric and isoinertial torque reductions correlated with the blinded clinical evaluation of McArdle sign. “The clinical detection of a flexion-induced decrease in strength is quite reliable when compared with the decrease in strength measured by our device, especially...”
when the decline is moderate or marked,” Dr. Weinshenker says.

The pathophysiology of McArdle sign is uncertain. But the Mayo Clinic researchers speculate it might be due to a nerve conduction block induced by the mechanical stretching of the spinal cord with neck flexion. “We’re undertaking studies with motor evoked potentials to address this possibility,” Dr. Weinshenker says.

If that possibility is borne out, McArdle sign potentially might help identify patients who would benefit from treatment with conduction-enhancing medications such as dalfampridine. Dr. Weinshenker notes that only about one-third of patients with MS respond well to dalfampridine; in his experience, people who exhibit a strong McArdle sign are often the best responders. The phenomenon might indicate that despite demyelination, these patients have sufficient viable axons to overcome conduction block with medication. “But the pathophysiology of this phenomenon must be further addressed,” Dr. Weinshenker says.

The immediate value of McArdle sign is its straightforward application to patient care. “When you observe a clinical sign in very extreme form, you can be more confident in a diagnosis of MS; it is more valuable when present than when it is absent,” Dr. Weinshenker says. “We hope that McArdle sign’s clinical value for diagnosis will spread beyond Mayo Clinic.”

For more information


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**AVMs: Advanced Technology and Expertise for Complex Pathology**

Although rare, arteriovenous malformations (AVMs) in the brain can have devastating consequences. Brain AVMs account for about 2% of all hemorrhagic strokes each year and are often the cause of brain hemorrhage in children and young adults. AVMs vary greatly in terms of risks posed to patients, and there are several treatment options — further complicating care for patients with this intricate vascular pathology.

“Successful AVM management requires a deep dive into all these issues,” says Bernard R. Bendok, M.D., chair of Neurosurgery at Mayo Clinic in Phoenix/Scottsdale, Arizona. “The treatment strategy must be matched to the particular AVM and the patient. There are multiple techniques for managing AVMs, and it’s ideal to be seen at a center that excels in all of them.”

Determining the optimal treatment strategy requires detailed understanding of an AVM’s anatomy (Figure 1). Mayo Clinic uses the latest imaging technology, including 3D modeling software and augmented reality visualization, to guide decision-making.

“When surgery is indicated, these imaging modalities help us to find a safe corridor and complete the surgery in an elegant fashion,” says Chandan Krishna, M.D., a neurosurgeon at Mayo Clinic’s campus in Arizona. “AVM is a pathology that requires not just one set of eyes, or clinicians working in silos, but a team approach.”

**Assessing an AVM’s risks**
The most potent factor influencing an AVM’s risk to the patient is prior hemorrhage. But signs of AVM bleeding can be subtle. “Susceptibility-weighted imaging might be required to see the hemorrhage,” Dr. Bendok says. “In addition, small hemorrhages that are thought to be caused by hypertension might actually be due to a micro-AVM.”

Other important factors affecting an AVM’s risk include size and location. In general, small AVMs and AVMs located deep in the brain are likelier to bleed. A brain aneurysm, which is found in about 20% of people with an AVM, also increases bleeding risk.

“The aneurysm can pose greater danger to the patient than the AVM itself,” Dr. Bendok says. “In that situation, if the AVM isn’t treatable, treating the associated aneurysm might reduce the risk of bleeding.”

Full understanding of an AVM’s potential danger requires detailed imaging, starting with cerebral angiography. “Aneurysms and venous stenosis may not be seen on regular MRI,” Dr. Bendok says. “Also, sometimes an AVM that is being monitored undergoes changes that can
be detected only on advanced imaging. AVMs are three-dimensional — it’s important to go beyond 2D views of a 3D problem.”

To obtain clear views of cerebral anatomy and real-time blood flow (Figure 2), Mayo Clinic uses 3D models produced from MR angiography. “This technology quite accurately determines the amount of blood flow through the major blood vessels,” Dr. Krishna says.

Holography and augmented reality visualization provide additional information. “This combined imaging gives a better understanding of the flow dynamics to the AVM and the draining vessels, and how they intertwine with the underlying anatomy and functioning of the brain,” Dr. Krishna says. “We can also see the normal vein tracks around the AVM, and then superimpose a functional MRI to plan a safe and effective surgical corridor. The more information we have, the safer the surgery becomes.”

**Matching treatment to patient needs**

As a major tertiary center, Mayo Clinic offers the full range of treatment options for AVMs, including microsurgical resection, endovascular embolization and stereotactic radiosurgery. A new hybrid operating room allows patients to undergo angiogram and surgery in a single setting.

Small AVMs can sometimes be treated with glue embolization to avoid surgery. Glue embolization can also be used to treat an aneurysm within an AVM. “Our 4D MRI is very helpful in showing us the impact of embolization on the AVM,” Dr. Bendok says.

Radiosurgery can successfully treat AVMs that are less than 2 to 3 centimeters in diameter. Patients are closely monitored for recurrence of bleeding after radiosurgery, as it may take a few years for the AVM to resolve. Radiosurgery can also be used to treat AVMs considered inoperable, including AVMs located in the brainstem.

For larger AVMs, Mayo Clinic uses staged radiosurgery (Figure 3): multiple radiation sessions, each aimed at a portion of the lesion. “Dividing the AVM into two or three pieces and treating each component three months apart has a 50% chance of obliterating the AVM,” Dr. Bendok says. “Any remaining lesion becomes safer to remove surgically later.”

This use of combination treatments requires experience and expertise in multiple treatment strategies. “Mayo Clinic is able to integrate all of these modalities,” Dr. Bendok says.

“Every AVM is unique — even AVMs with the same size and location are dramatically different from one another,” Dr. Krishna says. “Careful study of the anatomy and all possible surgical solutions is critical for optimal management of this condition.”

**Leading NIH’s Lewy Body Dementia Initiative**

Dennis W. Dickson, M.D., and Pamela J. McLean, Ph.D., discuss Lewy body dementia and a National Institutes of Health (NIH) initiative aimed at better understanding the disease. Dr. Dickson directs the Brain Bank for Neurodegenerative Disorders at Mayo Clinic in Jacksonville, Florida. Dr. McLean directs the Neurobiology of Parkinson’s Disease Laboratory at Mayo Clinic’s campus in Florida. Together they co-direct a team of international investigators in the multiyear, multimillion-dollar NIH initiative.

**Q: What challenges does Lewy body dementia pose for patients and clinicians?**

Lewy body dementia is a progressive, incurable disease that causes severe physical and cognitive decline. Although it’s the second most common dementia after Alzheimer’s disease, Lewy body dementia is underdiagnosed and can be definitively identified only postmortem. Death occurs on average about eight years after the start of clinical manifestations.

Those manifestations vary widely among patients. In addition to cognitive problems, they include motor problems such as Parkinsonism, sleep disorders — especially dream-enactment behavior — and problems with autonomic control. Postmortem brain analysis finds aggregates of alpha-synuclein known as Lewy bodies (Figure) within neurons, as well as variable...
Mayo Clinic has a long history of Lewy body dementia research and clinical studies, in addition to providing clinical care and support for people with the disease.

**Figure.** Lewy body dementia is characterized by intraneuronal protein aggregates that are detected in several regions of the brain.

deposits of beta-amyloid protein, a key feature of Alzheimer’s disease.

Thus, Lewy body dementia has components of both Parkinson’s disease and Alzheimer’s disease, and a great deal of overlap with the symptoms and pathologies of other dementias. It is important to make the correct diagnosis because patients who experience delusions and hallucinations might be prescribed first-generation antipsychotic medications, which can worsen Lewy body dementia symptoms and even be life-threatening.

**Q: What does the NIH hope to accomplish through the Lewy body dementia initiative?**
The goal is to learn more about the proteins involved in Lewy body dementia so we can characterize disease progression and identify potential therapeutic targets. We don’t yet understand what individual roles alpha-synuclein and beta-amyloid might play in Lewy body dementia or if there are synergistic interactions between those two proteins.

This initiative is a multidisciplinary project that follows the NIH’s Center Without Walls model, in which several institutions collaborate to achieve a single high-priority goal. We expect to generate a great deal of data, which will be shared with academic institutions and pharmaceutical companies interested in drug discovery. No single institution has all the answers, especially in a disease as complex as Lewy body dementia.

**Q: What specific efforts are planned?**
We will start by analyzing Lewy body dementia tissue samples in the brain bank on Mayo Clinic’s campus in Florida. The brain bank contains more than 8,000 specimens, including nearly 1,000 brains donated by people with Lewy body dementia. Through those analyses we hope to confirm and characterize the pathology of Lewy body dementia, and choose samples from the most severely affected individuals to discover the molecular underpinnings of the disorder.

We will then distribute the samples to our Mayo colleagues and the collaborating institutions for further analysis. Those centers will gather genetic and genomic information and look for changes in proteomics, lipids and RNA. Since all the samples originate from a single laboratory, we’re able to cut down on the variability that poses a problem when samples come from different locations. The goal is to obtain complementary information on all the major macromolecules in the brain.

In addition to alpha-synuclein and beta-amyloid, tau is found in some Levy body donor brains. Those individuals unfortunately had both Alzheimer’s disease and Lewy body dementia. We hope our studies can address whether these dementias are discrete disorders or a single entity that exists on a disease spectrum.

**Q: How will the effects of Lewy bodies on brain mechanisms be explored?**
The effects of alpha-synuclein and beta-amyloid species from the donor brains will be tested on patient-derived neurons grown in petri dishes in Mayo’s Neurobiology of Parkinson’s Disease and Translational Cell Biology of Parkinson’s Disease laboratories. We want to decipher the cellular dysfunction these protein species promote and determine which species are most toxic. Understanding what these proteins are doing to the cells will give us new targets for therapeutics.

**Q: What other Mayo Clinic researchers and institutions are involved in the NIH initiative?**
Our Mayo Clinic colleagues include Guojun Bu, Ph.D., Owen A. Ross, Ph.D., and Woldieter Springer, Ph.D., at the Florida campus, and John D. Fryer, Ph.D., at the Arizona campus. The participating institutions are University College London, Columbia University, University of Arizona, St. Jude Children’s Research Hospital and University of Texas Health Science Center at San Antonio.

**Q: What other efforts are underway at Mayo Clinic to learn more about Lewy body dementia?**
Dr. Dickson’s team has additional projects, supported by the Harry T. Mangurian Jr. Foundation, focusing on the interface between normal aging and Lewy body dementia. With funding from an NIH U01 grant, Mayo Clinic neuroradiologist Kejal Kantarci, M.D., and colleagues are working to apply advanced imaging technology to detect the progression of Lewy body dementia and to discover biomarkers for the disease. Bradley F. Boeve, M.D., leads Mayo’s Lewy Body Dementia Association Research Center of Excellence, as well as conducts research on sleep disorders in Lewy body dementia, including experimental therapeutic trials.

Figure. Lewy body dementia is characterized by intraneuronal protein aggregates that are detected in several regions of the brain.
Research Highlights in Neurology and Neurosurgery

Avoiding Carotid Artery Injury: Experience May Be More Important Than Technique
Transsphenoidal resection has evolved into the standard of care for most pituitary adenoma operations. Recently, the endoscopic endonasal approach has gained popularity as an alternative to microsurgery for transsphenoidal resection. Numerous studies attempting to assess the differential risk of internal carotid artery injury between the two techniques have had equivocal and contradictory results. In the first systematic review comparing the two techniques in the modern era, Mayo Clinic researchers found that operator inexperience may be a more important risk factor than choice of surgical technique. The researchers performed a systematic literature review of publications from 2002 to 2017 that reported the outcomes of internal carotid artery injury in cases involving microsurgery or the endoscopic endonasal approach. In an effort to look beyond the learning curve pertinent to the early adoption of surgical skills, the researchers focused on surgeries performed by operators whose experience included at least 250 cases. Within this population of highly experienced neurosurgeons, the researchers noted a dramatic decrease in the overall rate of cerebrovascular complications, with a consistently reproduced improvement in safety correlated with increasing operator experience. The researchers also observed a de facto parity between microsurgery and the endoscopic endonasal approach for transsphenoidal resection, with most highly experienced surgeons reporting a less than 0.5% incidence of internal carotid artery injury. The researchers emphasize the need for consolidated care in pituitary centers of excellence, improvement of high-fidelity simulators and skull base mentorship between senior and junior staff. (Perry A, et al. Beyond the learning curve: Comparison of microscopic and endoscopic incidences of internal carotid artery injury in a series of highly experienced operators. World Neurosurgery. 2019;131:e128.)

Absence of Orthostatic Hypotension May Distinguish PSP From Other Pathologies
The clinical diagnosis of progressive supranuclear palsy (PSP) can be challenging due to the variability of its phenotype and overlap with other parkinsonian disorders. Autonomic dysfunction has emerged as a frequent feature of atypical parkinsonisms; however, data on autonomic dysfunction in PSP, a tauopathy, have been inconsistent or contradictory. In a retrospective study, Mayo Clinic researchers found that the absence of orthostatic hypotension was the strongest autonomic parameter distinguishing autopsy-confirmed PSP from alpha-synuclein pathology. The researchers reviewed the cases of 14 patients with PSP, 18 with multiple system atrophy and 24 with Lewy body disease. The reviews included the results of antemortem autonomic testing and clinical evaluations by Mayo Clinic movement disorder specialist consultants, as well as postmortem examinations. Although multiple system atrophy and Lewy body disease were frequently associated with orthostatic hypotension, none of the patients with autopsycopirmed PSP had orthostatic hypotension. The researchers note that their data support the conclusion that the cardiovascular adrenergic system is relatively spared in PSP, as well as affirming the value of identifying orthostatic hypotension as a means of reaching an accurate diagnosis in a patient with atypical parkinsonism. The results also demonstrate the value of comprehensive autonomic testing to distinguish this class of neurodegenerative disorders. (van Gerpen JA, et al. Progressive supranuclear palsy is not associated with neurogenic orthostatic hypertension. Neurology. 2019;93:e1339.)

Characterizing Amphiphysin-IgG Autoimmunity
Amphiphysin is an intracellular protein regulating synaptic vesicles. Amphiphysin–immunoglobulin G (IgG) autoimmunity was first recognized in stiff person syndrome with breast cancer. Braintem, cerebellar and neuropathy presentations, as well as lung cancer, were subsequently described. Although reports indicate that neuropathy is the most common neurological presentation, detailed understanding of the amphiphysin-IgG-associated peripheral nervous system involvement is lacking. Mayo Clinic researchers have found that amphiphysin-IgG autoimmune neuropathy has a recognizable phenotype, is frequently immune responsive and can prompt early diagnosis of breast cancer. The researchers reviewed the records of 53 Mayo Clinic patients with amphiphysin-IgG who were examined by indirect immunofluorescence and Western blot between 1995 and 2018. Among the 53 patients, 33 (60%) had neuropathy, including 21 patients with amphiphysin-IgG alone and 12 with coexisting autoantibodies. The neuropathies in isolated amphiphysin-IgG autoimmunity included polyradiculoneuropathy, diffuse sensory neuronopathy and facial neuropathy with gastroparesis. Pain, breast cancer and central nervous system (CNS) involvements commonly coexisted with these neuropathies. Neuropathy frequently prompted breast cancer diagnosis. Stiff person spectrum disorder was the most common CNS involvement. In contrast, patients with coexisting autoantibodies commonly had lung cancer. Among all patients studied, 58% responded to immunotherapy. Patients with amphiphysin-IgG alone had more favorable immunotherapy responses than did patients with coexisting autoantibodies. (Dubey D, et al. Amphiphysin-IgG autoimmune neuropathy: A recognizable clinicopathologic syndrome. Neurology. 2019;93:e1873.)

To read more about Mayo Clinic neurosciences research and patient care, visit www.MayoClinic.org/medical-professionals.
**Education 2020 and 2021 Neurology and Neurologic Surgery Continuing Medical Education Programs**

### 2020 courses

**April**
- **Advances in Brachial Plexus Reconstruction: A Surgical Skills Course 2020**
  - April 23-25, 2020
  - Mayo Clinic, Rochester, Minn.

**June**
- **Skull Base and Aneurysms Rhoton Course: Microsurgical and Endoscopic Approaches 2020**
  - June 1-5, 2020
  - Mayo Clinic, Jacksonville, Fla.

**July**
- **Neurology in Clinical Practice 2020**
  - July 9-11, 2020
  - The Westin Grand Cayman Seven Mile Beach Resort, Seven Mile Beach, Cayman Islands

- **1st Annual Complex Spinal Disorders and Techniques Hands-On Workshop: Innovations in Procedural Training**
  - July 16-18, 2020
  - Mayo Clinic, Jacksonville, Fla.

### 2021 courses

**February**
- **Practical Neuroradiology: Excellence Through Evidence and Guidelines**
  - Feb. 7-11, 2021
  - Four Seasons Resort and Residences, Whistler, British Columbia, Canada

**March**
- **4th Annual Mayo Clinic Advances and Innovations in Complex Neuroscience Patient Care: Brain and Spine 2021**
  - March 4-6, 2021
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### Resources

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Contact Us

- **Phoenix/Scottsdale, Arizona**
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Mayo Clinic welcomes inquiries and referrals, and a request to a specific physician is not required to refer a patient.

**Expanding 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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