New Approach to Autoimmune Epilepsy

Autoimmune disorders have long been recognized as potential causes of seizures. In the extreme, autoimmune mechanisms can lead to limbic encephalitis, an acute disorder. However, accumulating evidence indicates that autoimmune factors may play a bigger role in seizure disorders than previously suspected, often without full features of limbic encephalitis. Patients with such disorders may respond to immunosuppressant therapies.

Mayo Clinic researchers have developed a new approach to diagnosing and treating autoimmune epilepsy. In research published in the May 6, 2014, issue of Neurology, 29 patients at Mayo Clinic with suspected autoimmune epilepsy were given an immunotherapy trial. The patients presented with epilepsy of recent onset, but often lacked other features of limbic encephalitis. The majority was found to have an anti-neural autoantibody (Figure 1).

Eighteen study participants (62 percent) achieved a reduction in seizure frequency of at least 50 percent. Ten patients (34 percent) became seizure-free. The findings provide evidence of a causative role for autoimmunity epilepsy and justification for continuing long-term immune suppression in some cases.

“Our work suggests that less severe, more pure epilepsy presentations may occur in people with neural antibodies, and these patients may respond quite well to immunotherapy,” says Jeffrey W. Britton, M.D., a consultant in the Department of Neurology at Mayo Clinic in Rochester, Minnesota.

Importance of early diagnosis

Patients in the retrospective study were tested at Mayo’s autoimmune neurology clinic. An autoimmune cause was suspected based on frequent or medically intractable seizures and the presence of at least one neural antibody, inflammatory changes indicated in spinal fluid or on MRI, or a personal or family history of autoimmunity. The time from onset of seizures to the start of immunotherapy was significantly shorter in patients who responded to treatment, indicating early therapy favors a beneficial response.

Mayo Clinic has a distinguished history in the research, diagnosis and treatment of autoimmune neurological disorders. “The discovery of antibodies targeting channels or receptors on the surface of nerve cells in the brain has really exploded in the past few years,” says Sean J. Pittock, M.D., a consultant in the Department of Neurology at Mayo Clinic’s campus in Minnesota. “We are now recognizing many disorders of the nervous system previously considered degenerative or idiopathic to be autoimmune.”

For patients with medically intractable epilepsy, the implications are significant: Their conditions may be reversed or significantly improved with immunotherapies (Figure 2).

“Having a biomarker for these patients is revolutionary, and paramount to understanding and treating them,” says Joseph F. Drazkowski, M.D., a consultant in the Department of Neurology at Mayo Clinic in Phoenix/Scottsdale, Arizona.
The prevalence of autoimmune epilepsy isn’t known. Recent research suggests that people with autoimmune disease are almost four times likelier to have epilepsy than are people without autoimmune disorders. “Autoimmune-mediated epilepsy is probably a lot more common than we think,” Dr. Britton says.

In addition to the presence of neural antibodies, clinical features suggestive of autoimmune epilepsy include:
- Acute to subacute onset, with seizures occurring every three months or less
- Multiple types of seizure or faciobrachial dystonic seizures
- Resistance to anti-seizure medication
- Personal or family history of autoimmunity
- History of recent or past neoplasia
- Viral prodrome
- Evidence of CNS inflammation

Dr. Britton notes that autoimmune-mediated seizures are often thought to occur only in conjunction with cancer. However, he says, many people with autoimmune epilepsy don’t have cancer. Nonetheless, at Mayo, patients with a positive neural antibody test are assessed further to exclude cancer.

“We often see depression, anxiety, personality changes and memory dysfunction out of proportion to the amount of epilepsy the patient is experiencing,” says Matthew T. Hoerth, M.D., a consultant in the Department of Neurology at Mayo Clinic’s campus in Arizona.

The ‘three M’s’ of treatment
Mayo’s standardized approach is based on three M’s: maximum reversibility of seizures, maintenance of reversibility and minimal therapeutic dosage. Patients receive high-dose immunotherapy, usually for six to 12 weeks, with objective testing at baseline and after therapy to define the extent of reversibility. “We want seizure freedom or at least seizure reduction for each patient,” Dr. Pittock explains.

Reversibility is maintained with oral immunosuppressants such as prednisone, azathioprine, mycophenolate, methotrexate or rituximab — at the minimum effective dosage, to minimize side effects. The results are generally positive, if patients are selected correctly.

“Most of the patients get at least some benefit from immunotherapy. Prior to this they were having absolutely no results from anti-seizure drug therapy,” Dr. Hoerth says.

Future directions
Mayo’s autoimmune epilepsy group is refining its standardized diagnostic and treatment protocol and designing randomized controlled trials to help better define the clinical characteristics suggestive of autoimmune epilepsy and the treatments required.

Dr. Britton notes that when he began practicing neurology 20 years ago, antibody-mediated neurological disorders were considered unresponsive to therapy. “But it’s very clear that’s not true,” he says. “There are some patients who respond extremely well. That gives some hope to people who have autoimmunity as a possible cause of their epilepsy.”

For more information
Laser Surgery for Focal Epilepsy

For patients with focal, medication-resistant epilepsy, temporal lobectomy has been the standard treatment. Although effective in up to 80 percent of patients, the procedure generally involves several days of hospitalization and at least six weeks for recovery.

A minimally invasive laser surgery option is available at all Mayo Clinic campuses. It has been offered for only about two years, so outcome measurements are somewhat preliminary. “But the results are very promising. The vast majority of our patients who have had the surgery are seizure-free,” says Jerry J. Shih, M.D., a consultant in the Department of Neurology at Mayo Clinic in Jacksonville, Florida.

The procedure is most appropriate for patients with conditions such as temporal lobe epilepsy or mesial temporal sclerosis, in which seizures originate from focal areas of the hippocampus (Figure 1). These conditions are often resistant to anti-seizure medications, and seizures typically worsen as the patient ages.

“This minimally invasive laser procedure is rapidly becoming an excellent treatment option for patients with focal seizures from a defined seizure focus. The results thus far in selected patients seem to be as good as surgical resection,” says Robert E. Wharen Jr., M.D., a consultant in the Department of Neurosurgery at Mayo Clinic's campus in Florida.

Precise MRI guidance

Unlike temporal lobectomy, which involves craniotomy, laser surgery is done through a burr hole in the back of the skull. A laser-tipped catheter is directed to the hippocampus to ablate the site where seizures originate. The patient, under general anesthesia, is in a stereotactic frame.

Real-time MRI guidance generates a temperature map of the patient’s brain (Figure 2). “With this new technique, you not only know the temperature at the tip of the laser, you actually monitor the precise temperature of the brain in the area you’re heating,” says Richard S. Zimmerman, M.D., a consultant in the Department of Neurosurgery at Mayo Clinic in Phoenix/Scottsdale, Arizona. “That allows you to heat the brain tissue just enough and not too much.”

Advantages for patients

Because laser ablation is minimally invasive, patients typically are hospitalized only overnight. Many are ready to resume normal activities within two to three weeks. Laser surgery can also lower the risk of damaging the patient’s memory and language abilities.

Candidates for laser ablation typically haven’t found relief from multiple epilepsy medications and have experienced decreased quality of life. “Most of our patients have been on at least four or five anti-seizure drugs at high doses. Yet they continue to have seizures, they can’t drive legally, and they often have difficulty maintaining employment,” Dr. Shih says.

Some of these patients have expressed reluctance to undergo surgery. “They are uncomfortable with what an open procedure entails, and therefore have not been able to get the potential benefit of epilepsy surgery,” Dr. Shih says. “But they are requesting this minimally invasive option.”

In addition to temporal lobe epilepsy, Mayo Clinic has successfully treated hypothalamic hamartomas with laser ablation. The hamartoma’s location deep in the brain generally precludes resection; Gamma Knife surgery has been used in some patients, but with incomplete success. “Laser ablation offers a less invasive treatment for some patients with hypothalamic hamartoma,” says W. Richard Marsh, M.D., a consultant in the Department of Neurosurgery at Mayo Clinic in Rochester, Minnesota.

Although the results of laser ablation are preliminary, some success stories stand out. The first patient to undergo the procedure at Mayo Clinic's campus in Florida was a 29-year-old woman who had seizures since age 6 months. After losing her driver’s license, she had to rely on family and friends to drive her to work. The patient is now seizure-free, and regained her license.

At Mayo Clinic’s campus in Arizona, Dr. Zimmerman cites a patient in her late 50s who had lifelong, medication-resistant seizures. Although developmentally delayed, she had...
independence within a group home setting. “Any damage to her memory or language from open surgery could result in her moving from semi-indepen-
dence to total dependence in a nursing home,” Dr. Zimmerman says. After laser ablation, the patient is seizure-free; she con-
tinues to live in the group home but is now able to work part
time in her family’s business.

**Remaining challenge**

Some Mayo patients continue to experience seizures after laser surgery. Pinpointing all tissue involved in seizure activity, particularly in patients without
abnormality on MRI, remains a challenge during minimally invasive surgery.

“We’ve shown that minimally invasive surgery can work, and we’ve shown that it’s safe,” Dr. Marsh says. “What we’d like to learn
now is the correct amount of tissue to ablate to optimize seizure control.”

**Multidisciplinary expertise**

Mayo’s integrated practice facilitates the smooth running of minimally invasive epilepsy surgery. In addition to neurosurgeons, the procedure requires highly trained epileptologists, neuro-
radiologists and allied health workers. “This is a good example of something we are increasingly seeing in neurology: the impor-
tance of a multidis-
ciplinary team,” says Gregory A. Worrell, M.D., Ph.D., a con-
sultant in the Depart-
ment of Neurology at Mayo Clinic’s campus in Minnesota. “Mayo has the tools and experi-
ence to create the best possible environment for a safe and effective procedure.”

**Prognostic Factors in Childhood Epilepsy**

About two-thirds of children with epilepsy will ultimately achieve seizure freedom. Many of them will be able to stop taking medication and remain seizure-free. Within this fairly positive broad view, the challenge for neurologists is defining the prognosis for an individual patient.

“If you’re the parent of a child with epilepsy, you really want to know which third your child falls into,” says Elaine C. Wirrell, M.D., a con-
sultant in the Department of Neurology at Mayo Clinic in Rochester, Minnesota.

Population-based, longitudinal research at Mayo Clinic is uncovering prognostic factors for children with epilepsy. The retrospective studies involve the records of 467 children in Olmsted County, Minnesota, ages 1 month through 17 years who were newly diagnosed with epilepsy from 1980 to 2009.

“Because the research is population based, we’re getting a good sampling of difficult as well as relatively easily controlled epilepsies,” Dr. Wirrell says. “We are recognizing that there are certain predictors for the likelihood of remission or lack of it.”

**Neuroimaging abnormalities**

About 20 percent of children with epilepsy are deemed medically intractable (Figure). In children, uncontrolled seizures result in consider-
able comorbidity, including intellectual disabil-
ity, physical injury, depression and anxiety, and failure to achieve independence. Surgery offers the benefit of quicker seizure control. “But surgery is irreversible and not without risk. There’s often a tendency to wait and try more medications,” Dr. Wirrell says.

Accurate and early prediction of medical intractability is crucial for the choice between drug-based therapy and surgery. Yet factors associated with medically intractable epilepsy have been characterized less well in children than in adults.

The Mayo studies have pinpointed abnormal neuroimaging as a strong prognostic factor in childhood epilepsy. In a study published in the June 2013 issue of *Epilepsia*, the Mayo research-
ers identified 381 children in the study cohort who were followed for at least three years after diagnosis. Seventy-five of the children, or nearly 20 percent, were deemed medically intractable within two years of diagnosis. After a median follow-up of 11.7 years, 49 percent of those children remained medically intractable. The researchers then analyzed the children’s records for neuroimaging abnormalities, neurologic examinations at diagnosis and mode of epilepsy onset (focal, generalized or unknown).

“We found that the only predictive factor for medical intractability — and it was a very significant factor — was neuroimaging abnor-
mality,” Dr. Wirrell says. “If a child appears medically intractable early on and the MRI is abnormal, the epilepsy is unlikely to go away. In that situation, early surgery is extremely important to minimize the risk of prolonged seizures and other comorbidities.”

Similarly, in a study published in the May 2013 issue of Epilepsia, the Mayo researchers found that neuroimaging abnormality is also the most significant predictor of pharmacoresistance in childhood epilepsy. About one-third of children with epilepsy who initially appear pharmacoresistant ultimately achieve seizure freedom without surgery. But only 8.6 percent of pharmacoresistant children with an abnormal MRI do so.

“In those children, early surgical intervention should be strongly considered to limit comorbidities,” Dr. Wirrell says. “Conversely, a more cautious approach may be appropriate for children with normal imaging, as many remit with time.”

Mortality risks
Mortality rates in children with epilepsy are four to five times higher than in the general pediatric population. However, the specific causes of seizure-related deaths in children haven’t been elucidated. To do so, the Mayo researchers pooled their data with colleagues from Connecticut, Canada and the Netherlands.

In a study published in the July 2013 issue of Pediatrics, the researchers found that among the 2,229 subjects followed for more than 30,000 person-years, only 69 deaths occurred. Ten of those were attributed to sudden unexpected death in epilepsy, and three to other seizure-related causes. Among the remaining deaths, 48 were due to other natural causes.

Most of the deaths occurred in children with neurodisability or an underlying brain condition and were secondary to infections and other complications. The death rate among children with “uncomplicated” epilepsy was not much greater than expected for the general population.

“The risk of death in an otherwise healthy, intellectually normal child with epilepsy is low,” Dr. Wirrell says. “That information is very reassuring and helps us provide better counseling to families.”

For more information


Unlocking the Complex Genetics of Epilepsy

In two-thirds of people with epilepsy, the cause is unknown. Although genetics is believed to play an important role in many epilepsy syndromes, few specific genes have been implicated. Learning more about the genetic causes of epilepsy may facilitate the development of better-targeted therapies for this complex disorder.

The Epilepsy Phenome Genome Project (EPGP), one of the largest epilepsy research studies ever attempted, is examining the pathophysiology and clinical expression of idiopathic epileptic syndromes. All Mayo Clinic campuses are among the 27 centers participating in this international study.

Detailed phenotypic and genetic information has been collected from almost 3,000 patients with idiopathic or genetically based epilepsies. The study cohort also includes parents of participants with epilepsies that have a strong genetic predisposition.

“The purpose of the study is to identify relationships among family history, genetic factors and different types of seizures,” says Gregory D. Cascino, M.D., a consultant in the Department of Neurology at Mayo Clinic in Rochester, Minnesota. “What we’ve seen thus far looks very promising in terms of better understanding the causes of epilepsy and the prognosis for specific types of patients.”

De novo mutations
The study results underline the complexity of genetically based epilepsies. “We’re finding that these genes are influenced by a host of other factors that we don’t yet fully grasp. This isn’t going to be as easy as good old-fashioned Mendelian genetics,” says Joseph I. Sirven, M.D., a consultant in the Department of Neurology at Mayo Clinic in Phoenix/Scottsdale, Arizona.

Indeed, people with genetically based epilepsy often have no family history of the disease. In a research letter published in the Sept. 12, 2013, issue of Nature, EPGP researchers identified novel de novo mutations implicating at least
two genes — GABRB3 and ALG13 — in infantile spasms and Lennox-Gastaut syndrome (LGS). Several other gene mutations also were seen in the exomes of EPGP patients with infantile spasms or LGS, suggesting that genetic diagnostics will need to focus on the entire genome. In addition, the study found that many of the mutations seemed to converge on certain specific biological pathways.

“These findings are very important because they point out that a spontaneous gene mutation may predispose people to a genetic epilepsy even if they lack a family history,” Dr. Cascino says. “The specific biological pathways also suggest a direction for drug development and treatment personalization in epileptic encephalopathies.”

**Other EPGP findings**

The EPGP researchers have also found:

- A spectrum of clinical, electroencephalogram (EEG) and developmental characteristics among 135 study participants with LGS of unknown cause. In research published in the November 2013 issue of *Epilepsia*, the EPGP researchers also found that half of adults in the study with LGS of unknown cause had completed secondary school, indicating that these patients can attain cognitive achievements.

- Evidence of a shared genetic susceptibility to epilepsy and migraine. In a study published in the February 2013 issue of *Epilepsia*, the EPGP researchers found the shared genetic susceptibility applied to study participants with focal and generalized epilepsies, and migraine with aura.

**Data for treatment breakthroughs**

A principal goal of EPGP is the creation of a DNA repository and data bank. The size of the study cohort and range of epilepsies represented (Figure) is unique. The strength of the data offers potential for eventual breakthroughs that individualize patient treatment.

“In the future I believe we will treat our patients based on what we know about the genetics of their diseases,” says William Tatum, D.O., a consultant in the Department of Neurology at Mayo Clinic in Jacksonville, Florida. “Individuals have a genetically predisposed susceptibility to side effects of a medication. We may be able to select medications based on the channels of the brain that are operational in patients with particular epilepsies. Our work with the human genome is making this a reality.”

**Enrolling patients in new study**

Mayo Clinic in Rochester, Minnesota is enrolling patients in the Human Epilepsy Project, a multicenter, prospective study of people with newly diagnosed focal epilepsy. The study’s purpose is to identify clinical characteristics and biomarkers predictive of disease outcome, progression and treatment response. The researchers also seek to identify patients at high risk of pharmacoresistance who may benefit from more-aggressive initial therapy and earlier consideration for surgical treatment.

Study participants must:

- Be between the ages of 12 and 60
- Have had at least two focal seizures in the previous 12 months
- Have taken seizure medication for less than four months

Participants will be followed for three years to characterize their clinical course and evolution of neuroimaging, electrophysiology, neuropsychiatric comorbidities and biochemical features.

“We know that about a third of patients who develop epilepsy ultimately will have difficulty controlling their seizures,” Dr. Cascino says. “With this study, we hope to learn more about who is likely to have a benign disease that responds to therapy.”

**For more information**


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**Figure.** The international study has a large cohort representing a range of epilepsies, including idiopathic generalized epilepsy (IGE), localization-related epilepsy (LRE), infantile spasms (IS), Lennox-Gastaut syndrome (LGS), polymicrogyria (PMG) and periventricular heterotopia (PVH).
Research Highlights in Neurology and Neurosurgery

Outcome of iEEG Monitoring and Surgery in MRI-Negative Temporal Lobe Epilepsy
The surgical success rate is much lower in temporal lobe epilepsy (TLE) patients with normal MRI than in patients with mesial temporal sclerosis. Standard anterior temporal lobectomy in patients with normal MRI is also associated with significant cognitive impairment. A study conducted at all Mayo Clinic campuses found that anterior temporal lobectomy guided by intracranial electroencephalography (iEEG) in patients with MRI-negative TLE is associated with a high rate of post-surgical seizure freedom. The researchers analyzed the records of 32 patients with MRI-negative TLE who underwent chronic iEEG evaluation for seizure localization. Of the 17 patients who subsequently had iEEG-guided anterior temporal lobectomy, 13 (76.5 percent) had Engel class I outcome. However, only two of six patients (33 percent) who underwent temporal neocorticectomy had Engel class I outcome. (Lee R, et al. Outcome of intracranial EEG monitoring and surgery in MRI-negative temporal lobe epilepsy. Presentation at: American Academy of Neurology Annual Meeting; 2014; Philadelphia, Pa.)

DBS for Medically Refractory Epilepsy
Experimental and clinical studies have suggested that electrical deep brain stimulation (DBS) of subcortical structures is a promising therapy for patients with refractory epilepsy. Bilateral stimulation of the anterior nuclei (AN) of the thalamus is useful for some patients with medically refractory partial seizure, while the efficacy of bilateral centromedian (CM) nucleus stimulation in generalized forms of epilepsy has been recently identified. Researchers at Mayo Clinic in Rochester, Minnesota, retrospectively reviewed the records of four patients who underwent bilateral AN DBS and CM DBS at Mayo. The patients weren’t candidates for resection, or were refractory to the treatment of vagus nerve stimulation or resection or both. The median age at surgery was 14 years with a median duration of epileptic history of 11 years. Average postoperative follow-up was 16 months. The average seizure frequency reduction was 63 percent; one patient had been seizure-free for 12 months. The findings suggest that bilateral stimulation of the AN and CM nucleus of the thalamus could potentially reduce seizures in medically refractory epilepsy patients who are not suitable candidates for other therapies. (Hu W, et al. Electrical stimulation of the anterior and centromedian nucleus of thalamus for treatment of refractory epilepsy: Report of four cases. Presentation at: American Academy of Neurology Annual Meeting; 2014; Philadelphia, Pa.)

Early Relapse-Recovery in MS
In multiple sclerosis (MS), the frequency of relapses occurring within five years of disease onset correlates with poor prognosis. Recovery from individual relapses inversely correlates with cumulative relapse-related disability. Poor relapse-recovery may also be associated with an earlier onset of progressive MS. In a population-based study, researchers at Mayo Clinic in Rochester, Minnesota, and colleagues found that patients with limited recovery from MS who relapse in the first five years of disease course are more likely to develop progressive MS, and do so earlier, than are MS patients with better early recovery. The records of 101 patients with relapsing-remitting MS and 83 patients with bout-onset progressive MS, who were followed for more than 20 years, were analyzed. Early relapses resulted in greater than 75 percent recovery in 143 patients, and less than 75 percent recovery in 41 patients. Early relapse-recovery occurred within three months in 169 patients, and later in 15 patients. Half the patients experiencing greater than 75 percent recovery in early relapses developed progressive MS within 33 years of disease onset, while half the patients experiencing less than 75 percent recovery developed progressive MS within 13 years. (Novotna M, et al. Early relapse-recovery impacts progressive disease course in multiple sclerosis. Presentation at: American Academy of Neurology Annual Meeting; 2014; Philadelphia, Pa.)

Predictors of Early Mortality in ALS Patients with Enteral Feeding
Patients with amyotrophic lateral sclerosis (ALS) commonly develop oropharyngeal weakness, requiring placement of an enteral feeding tube. These patients often are malnourished and have weak respiratory muscles, which may contribute to postoperative complications. To help identify ALS patients at high risk of postoperative complications or early mortality after elective enteral feeding-tube placement, researchers at Mayo Clinic in Rochester, Minnesota, reviewed the charts of ALS patients treated from 2003 to 2013. Among the 2,853 patients, 146 had elective endoscopic feeding-tube placement. Independent predictors of early mortality included nonambulatory status, hospitalization prior to tube placement, lack of riluzole use, need for feeding tube earlier in the disease course and preoperative endotracheal airway. (Braksick S, et al. Patients with amyotrophic lateral sclerosis undergoing elective percutaneous endoscopic gastrostomy or jejunostomy placement: The Mayo Clinic experience. Presentation at: American Academy of Neurology Annual Meeting; 2014; Philadelphia, Pa.)

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