Responsive Neurostimulation for Epilepsy

Despite the use of anti-epileptic drugs, up to 40 percent of patients with focal epilepsy have drug-resistant seizures. Depending on the location of the seizure focus, treatment with surgery might not be appropriate for these patients.

All three campuses at Mayo Clinic offer a new responsive neurostimulation treatment for people with medically intractable focal epilepsy (Figure 1). Results of a clinical trial of the treatment, published in the March 2014 issue of Epilepsia, showed a median 53 percent reduction in seizure occurrence in patients two years after implantation of the device and a 55 percent responder rate.

“This treatment is very innovative because it provides direct intracranial stimulation of the brain,” says William Tatum, D.O., a consultant in the Department of Neurology at Mayo Clinic in Jacksonville, Florida. “It’s very similar to what cardiologists have been doing for years in terms of defibrillation for the heart.”

Although the Food and Drug Administration only recently approved the neurostimulation device, Mayo Clinic has nearly a decade of experience with it through clinical trials beginning in 2005. “It’s very exciting to have something other than medications and surgery to offer to patients,” says Joseph F. Dratzkowski, M.D., a consultant in the Department of Neurology at Mayo Clinic in Phoenix/Scottsdale, Arizona.

Tickling the brain
At Mayo Clinic, surgery remains the preferred treatment when possible for focal epilepsy. However, neurostimulation is an option for patients who aren’t surgical candidates due to location of seizure focus. Participants in the clinical trial had focal seizures originating in up to two areas of the brain. The patients averaged three or more disabling seizures a month and had failed to respond to at least two anti-epilepsy drugs.

“The average duration of their epilepsy was over 20 years. These are significantly impacted patients,” says Gregory A. Worrell, M.D., Ph.D., a consultant in the Department of Neurology at Mayo Clinic in Rochester, Minnesota.

The neurostimulator is a battery-powered, microprocessor-controlled device, roughly the size of an ice cube, which is implanted in the patient’s skull (Figure 2). Leads connected to the neurostimulator are implanted near the patient’s seizure focus. The device is designed to detect abnormal electrical activity and to respond by delivering electrical stimulation to normalize brain activity before the patient experiences a seizure (Figure 3).

“Most of my patients are getting many stimulations a day, in some cases over a thousand,” Dr. Worrell says. “These patients clearly weren’t having a thousand seizures a day. So what the device is actually doing is tickling the brain frequently. That is suppressing the seizures before they really start. Once a seizure starts, we have a much harder time stopping it.”
Patients generally require only one day of hospitalization for device implantation. “The recovery is fairly rapid,” Dr. Tatum says. “By the next day, patients are walking and talking and ready to go.”

**Long-term improvement**

All three campuses at Mayo Clinic report generally positive outcomes for patients. Unlike anti-epilepsy drugs, whose effectiveness can decline in specific patients over time, the neurostimulator can provide continual improvement. “We have a couple of patients who have failed many different treatments who are now seizure-free,” Dr. Tatum says.

Dr. Drazkowski cites the case of a young man who was having difficulty in college because reading triggered his seizures. After determining that surgery wasn’t suitable, Dr. Drazkowski offered the option of the neurostimulator. The patient, who has had the device for eight years, no longer has major motor seizures.

“Rarely, he has seizures if he accidentally skips his medication. When he’s very stressed, he may have an aura,” Dr. Drazkowski says. “But he is now able to attend university.”

The generator’s battery has a life span ranging about a year if several thousand stimulations are required daily to up to four years if hundreds of daily stimulations are needed. Replacing the battery is a 30-minute procedure that involves opening only the skin, not the skull.

“We always ask patients if they want the battery replaced — if the device has improved their lives to that extent — and so far, everyone has,” Dr. Drazkowski says.

**Potential for new insights**

Because the neurostimulator records brain activity, the device potentially will yield data about pre-seizure brain activity. To date, that knowledge has been gained primarily through evaluations of patients in epilepsy monitoring units.

“But now, we’ll be continuously obtaining this information for long periods of time from people in an outpatient setting,” Dr. Tatum says. “We’re basically doing chronic ambulatory direct recording from the brain. There is infinitely greater potential to learn more about predicting seizures.”

**For more information**

Spinal Vascular Malformations

Spinal vascular malformations are a rare but important cause of progressive myelopathy. Untreated, they can result in severe disability, including loss of mobility and bladder function. Treatment for spinal vascular malformations is relatively straightforward. However, the condition can go undiagnosed because early signs and symptoms often are similar to those in more common conditions such as degenerative spinal disease.

“Unfortunately, patients might have symptoms for months before a correct diagnosis is made,” says Giuseppe Lanzino, M.D., a consultant in the Department of Neurologic Surgery at Mayo Clinic in Rochester, Minnesota. “After treatment, most patients with spinal vascular malformation experience improvement. But the degree and extent of improvement is strictly correlated to their condition at the time of correct diagnosis.”

Characteristic signs

About 80 to 90 percent of spinal vascular malformations are spinal dural arteriovenous fistulas (SDAVFs) (Figure). They present most often in patients ages 60 to 79. In a study published in the November 2010 issue of *Neurosurgery*, Mayo Clinic researchers reported a mean age of 63.6 years and a mean interval from symptom onset to diagnosis of 24.7 months among 154 patients who underwent surgery for SDAVF at Mayo Clinic from 1985 to 2008.

Before referral to Mayo Clinic, 31 patients in the study had undergone some form of invasive treatment for symptoms that, in retrospect, could be attributed to SDAVF. “Uniformly, patients reported worsening of symptoms after every surgical intervention not directed at obliteration of the fistula,” Dr. Lanzino says.

All 154 patients in the study experienced some form of subjective and objective motor weakness. Other neurological signs and symptoms included:

- Decreased sensation in the lower extremities
- Pain
- Paresthesias
- Dysesthesias
- Sphincter dysfunction

On MRI, the characteristic signs of SDAVF include edema on the T2 sequence that involves the conus medullaris, and indications of the presence of an abnormally enlarged blood vessel on the sagittal T2 sequence.

Definitive diagnosis requires catheter angiography, a procedure that can be difficult for elderly patients with atherosclerosis. “It is critical that these patients are evaluated in centers where large numbers of spinal angiograms are done,” Dr. Lanzino says.

Once the fistula is found, treatment consists of surgical disconnection or endovascular embolization. “Surgery is still the preferred treatment modality because it’s associated with very low complication rates and is more effective in guaranteeing obliteration of the fistula,” Dr. Lanzino says. In the December 2013 issue of *World Neurosurgery*, researchers at Mayo Clinic in Phoenix/Scottsdale, Arizona, described a minimally invasive approach for intradural ligation of SDAVF.

Less common spinal vascular lesions, such as venous malformations and cavernous malformations, often can be successfully treated with surgery. As with SDAVF, Dr. Lanzino notes, “prompt diagnosis and referral to a center with experience are key.”

For more information


Autoimmune GI Dysmotility: A New Direction

Mayo Clinic has a distinguished history of investigating neural autoimmune disorders. An important aspect of this work concerns the occurrence of autonomic disease in an immune setting and the discovery that immunotherapy can be beneficial for patients with autonomic disease.

Although autonomic disease is typically associated with syncope, neuropathy and sweating problems, chronic gastrointestinal (GI) dysmotility also may be a component. Autoimmune GI dysmotility (AGID) is a newly described clinical entity that is a limited manifestation of autoimmune dysautonomia, and can occur as an idiopathic phenomenon. Signs and symptoms include early satiety, nausea, vomiting, bloating, diarrhea, constipation and involuntary weight loss. The onset may be subacute, and neurological manifestations may or may not be an accompaniment.

In the September 2014 issue of Neurogastroenterology & Motility, Mayo Clinic researchers report the first objective evidence that immunotherapy may reverse autoimmune GI dysmotility (Figure 1). The study illustrates the importance of considering an autoimmune basis for acquired idiopathic GI motility disorders.

“The concept that you can have predominantly GI dysmotility — without necessarily having a lot of symptoms in other areas — and the conclusion that it is due to an immune mechanism affecting the nervous system of the gut is rather novel,” says Sean J. Pittock, M.D., a consultant in the Department of Neurology at Mayo Clinic in Rochester, Minnesota, and co-founder of the autoimmune neurology clinic there. “But if the immune system can cause inflammation of the optic nerve, spinal cord or cerebral cortex, then why can’t it cause a problem with the gut? After all, the gut contains 100 million neurons — more than the spinal cord or the peripheral nervous system.”

AGID appears to be relatively uncommon; most GI symptoms are caused by other diseases or have a functional basis — for example, irritable bowel syndrome. The term dysmotility refers to abnormal movement of food, nutrients and waste through the digestive tract. With AGID, the presumption is that the nerves controlling the GI tract are being targeted by immune cells, resulting in altered neural function and thus, altered GI transit.

AGID can be disabling. “Patients who have these problems are miserable. They have no appetite. They have terrible abdominal pains and constipation. Often these patients undergo lots of diagnostic testing and multiple consultations,” says Lawrence A. Szarka, M.D., a consultant in the Division of Gastroenterology and Hepatology at Mayo Clinic in Rochester, Minnesota.

The Mayo Clinic research was a retrospective case study of 23 patients seen at Mayo Clinic for suspected AGID, in whom an immunotherapy trial was undertaken. Seventeen of the patients improved after the six- to 12-week immunotherapy trial. Autoimmune serological evaluation revealed a neural-specific antibody in 12 of the 17 responders (71 percent). Symptomatic improvements were generally accompanied by objective evidence of improved GI motility and autonomic function on repeated scintigraphic, manometric and autonomic function tests.

“The observation that the immune system may be attacking parts of the nervous system and causing disorders that we might have explained away as a functional problem opens up possibilities for new, directed therapies to help the patient’s GI symptoms,” says Joseph A. Murray, M.D., a consultant in the Division of Gastroenterology and Hepatology at Mayo Clinic in Rochester, Minnesota.

“Treatment options for gastroparesis — a condition where the stomach does not empty food — are extremely limited, and the ones that exist merely facilitate gastric emptying or treat the symptoms. The idea that there may be a treatment that targets the underlying cause of gastroparesis is exciting,” says Yuri A. Saito Loftus, M.D., a consultant in the Division of Gastroenterology and Hepatology at Mayo Clinic in Rochester, Minnesota.

AGID diagnostic panel

Mayo Clinic’s standardized approach to autoimmune neurological conditions is based on

Figure 1. Colonic motility is assessed at 24 and 48 hours after ingestion of a tracer. Regions of interest are assigned numbers: 1, ascending colon; 2, transverse colon; 3, descending colon; 4, sigmoid colon/rectum; 5, stool. The estimated geometric center (Gc) is the average distance traveled by the ingested tracer. Normal Gc is 3.0 to 4.8 at 48 hours, indicating tracer should be in the descending colon or sigmoid colon/rectum. On the left, motility test in a patient with autoimmune GI dysmotility before intravenous immune globulin (IVIg) therapy shows Gc of 1.5 at 48 hours, indicating most tracer is in the proximal ascending colon. On the right, Gc is 3.8, in the normal range, at 48 hours after IVIg therapy.
three M’s: determine the maximum reversibility of signs and symptoms, which also serves as a diagnostic test; maintain that maximal reversibility; and do so with minimal therapeutic dosage, thus reducing the likelihood of side effects.

To establish a diagnosis, patients are asked about a history of autoimmune disease — such as lupus or vitiligo — or cancer. They undergo neural antibody evaluation (Figure 2), which includes an autoimmune GI dysmotility panel that is the only one of its type in the U.S. In addition, patients with suspected AGID have objective testing, particularly GI transit studies. Additional tests may include a gastroduodenal manometry or a colon motility study. Both tests measure intestinal contractions, and the pattern of contractions confirms or refutes a neurological basis for the slow GI transit.

When AGID is suspected, patients are given a 12-week “diagnostic” trial of intravenous immune globulin or methylprednisolone. A response to immunotherapy in the acute treatment phase of suspected AGID has diagnostic as well as therapeutic importance. Although a lack of response doesn’t imply a nonautoimmune etiology, clinical improvement obtained with immunotherapy is probably the single most important diagnostic test performed in the evaluation of a patient with a suspected AGID. It is imperative that baseline objective testing provide reference points for evaluating clinical improvement with immunotherapies. If symptoms and objective testing show improvement, the next step is to maintain that level of reversibility with the minimum effective dosage of maintenance oral immunosuppressants.

“Patients generally come in with subacute and often rapid onset of symptoms. The age range is usually in the mid-20s to 50s,” Dr. Pittock says. “When we give them immunotherapy, the improvement can be dramatic. Patients can go from persistent nausea, vomiting and weight loss to feeling normal within a few weeks.”

Some patients who test positive for antibodies don’t respond to immunotherapy. Research continues in an effort to learn more about the association between autoimmune antibodies and GI dysmotility. One recent development is the discovery of an antibody that targets dipeptidyl-peptidase-like protein-6 (DPPX), a regulatory subunit of neuronal Kv4.2 potassium channels, which causes hypermotility resulting in diarrhea.

“Testing for this antibody may become part of our AGID diagnostic panel in the near future,” Dr. Pittock says. “We are still very much learning how to approach these conditions.”

Those efforts are facilitated by strong collaboration between clinician-researchers. “At Mayo, we work closely with our colleagues when diseases cross specialties,” Dr. Murray says. “Patients get a single answer, not different answers from multiple specialists. As neurologists and gastroenterologists, we may come to the patient’s problems from different perspectives. But ultimately we come to consensus on what is good for the whole patient.”

For more information

Laser Ablation of Brain Lesions

One of the greatest challenges of treating patients with brain lesions is balancing the need to maximize cytoreduction while minimizing approach-related morbidity. For patients with metastatic brain tumor or radiation necrosis, open surgery not only poses risks of functional loss but also can require cessation of chemotherapy, thereby disrupting ongoing cancer treatment.

At Mayo Clinic in Rochester, Minnesota, minimally invasive laser surgery is available to treat certain brain lesions. The technology is similar to that used at Mayo Clinic to treat patients with focal, medication-resistant epilepsy. The MRI-guided laser ablation has
been used to treat metastatic brain tumors and radiation necrosis for only about nine months, but preliminary results are promising.

“We can potentially treat these tumors, or at least control them locally, and spare the patient from undergoing craniotomy,” says Jamie J. Van Gompel, M.D., a consultant in the Department of Neurologic Surgery at Mayo Clinic in Rochester, Minnesota. “We can also potentially reduce or avoid steroid therapy, which can cause weight gain and other problems for patients when used chronically.”

**MRI precision**

The laser surgery (Figure 1) is performed by Dr. Van Gompel and by Ian F. Parney, M.D., Ph.D., a consultant in the Department of Neurologic Surgery at Mayo Clinic in Rochester, Minnesota. The procedure is done through a 4-millimeter burr hole in the back of the skull. A laser catheter is positioned optimally in the tumor; in some cases, more than one catheter may be used to maximize the volume of tumor that can be ablated. The patient, under general anesthesia, is then placed in an MRI scanner. Real-time MRI guidance generates a temperature map of the patient’s brain while laser ablation is underway.

The procedure takes about four hours. There is a small risk of missing the target and causing a bleed in the lesion. However, that risk is minimized by the laser’s hemostatic properties.

“The advantage of this system is that we can put a laser catheter deep into these problem areas,” Dr. Van Gompel says. “When we do that, we avoid the approach-related morbidities that might occur with brain retraction.”

The system facilitates precise navigation of the laser and monitoring of brain tissue temperature during ablation. “Under MRI guidance, we can watch as we heat the tissue,” Dr. Van Gompel says. “We can input specific reference points on the MRI, so we don’t heat beyond a specific zone. We can also heat tissue to a precise threshold and monitor the temperature very accurately.”

In patients who have undergone the procedure at Mayo Clinic, lesions have been well-treated without complications. Dr. Van Gompel cites the example of a patient (Figure 2) whose colorectal cancer metastasized to a single brain lesion. After treatment with Gamma Knife radiation, the patient developed a nodular recurrence that was treated with laser ablation.

“He left the hospital the day after the procedure with no pain medications,” Dr. Van Gompel says. “He felt well and was able to continue with his chemotherapy without disruption.”

Mayo Clinic recently added a second laser ablation system that, rather than targeting a single sphere, can fire around the laser’s tip — allowing for more conformal treatment. Dr. Van Gompel expects that Mayo Clinic neurosurgeons may soon be able to treat recurrent gliomas with laser ablation.

“This treatment modality is in the very early stages,” he says. “But in select patients, there is a substantial advantage to this procedure.”
Research Highlights in Neurology and Neurosurgery

Suppressed Wnt Signaling Linked to Alzheimer's
The low-density lipoprotein receptor-related protein 6 (LRP6) is an essential co-receptor for Wnt signaling, and its genetic variants have been linked to the risk of Alzheimer's disease (AD). Mounting evidence also demonstrates that synaptic dysfunction and substantial amyloid buildup are present in the brains of people with AD long before clinical onset of the disease. Researchers at Mayo Clinic in Jacksonville, Florida, have discovered a defect in the Wnt signaling pathway that contributes to overproduction of amyloid-beta and synaptic dysfunction. Using mouse models, the researchers demonstrated that conditional deletion of the LRP6 gene leads to age-dependent deficits in synaptic integrity and memory. The researchers also found that neuronal LRP6 deficiency in an amyloid mouse model leads to exacerbated amyloid pathology, due to increased amyloid precursor protein processing to amyloid-beta. The findings were validated through examination of postmortem brain tissue from patients with AD, in which LRP6 levels were found to be deficient and Wnt signaling was severely compromised. The findings suggest that restoring LRP6-mediated Wnt signaling can be explored as a viable strategy for AD therapy. (Liu CC, et al. Deficiency in LRP6-mediated Wnt signaling contributes to synaptic abnormalities and amyloid pathology in Alzheimer's disease. Neuron. 2014;84:63.)

Increased Cerebral Oxygenation Precedes GTCS
One of the most devastating aspects of uncontrolled generalized tonic-clonic seizure (GTCS) is the lack of predictability. Unpredictable seizures can severely limit patients' abilities to function and put them at risk of morbidity and mortality. Currently, there is no noninvasive tool that reliably predicts the onset of seizures. Researchers at Mayo Clinic in Rochester, Minnesota, have found that increased cerebral oxygenation frequently precedes convulsive seizures. The researchers reanalyzed data gathered during a feasibility study of noninvasive cerebral tissue oximetry in patients with GTCS who were undergoing video electroencephalography (EEG) monitoring. Five patients had prolonged video-EEG and transcutaneous regional cerebral oxygen saturation (rSO2) monitoring, during which seven primary or secondary GTCSs with usable data were captured. Four of these GTCSs (57 percent) were marked by at least three sequential rSO2 values in the preictal period that were more than three standard deviations greater than the mean rSO2 value recorded during the nonictal period. On average, such values were noted 18 minutes 30 seconds prior to electrographic seizure onset. Three GTCSs (43 percent) were marked by sustained hyperoxia for eight or more consecutive readings. The recorded elevations in cerebral oxygenation resolved prior to seizure onset. The study results suggest the potential value of noninvasive cerebral tissue oximetry in predicting seizure occurrence. (Moseley BD, et al. Increased cerebral oxygenation precedes generalized tonic clonic seizures. Epilepsy Research. 2014;108:1671.)

Relative Influence of Intellectual Enrichment on Cognitive Performance
Numerous studies have found that intellectual enrichment is protective against cognitive decline and Alzheimer’s disease (AD)-related dementia. To assess the efficacy of intellectual enrichment as a preventive intervention, and to estimate the years of protection provided against cognitive impairment, researchers at Mayo Clinic in Rochester, Minnesota, examined the relative influence of intellectual enrichment factors on baseline cognitive performance and rate of decline. The research involved a prospective analysis of 1,995 participants in the Mayo Clinic Study of Aging, an epidemiologic study of the prevalence, incidence and risk factors of mild cognitive impairment (MCI) and dementia among residents of Olmsted County, Minnesota, ages 70 to 89. The study participants — among whom 1,718 were cognitively normal and 277 had MCI — completed intellectual lifestyle enrichment measures at baseline and also underwent at least one follow-up visit. The researchers grouped lifetime intellectual enrichment into two components: educational attainment and occupation, and mid- to late-life cognitive activity. Consistent with earlier studies, higher levels of both components were independently associated with a lower risk of dementia. The study also found that only baseline age, mid- to late-life cognitive activity, and APOE4 genotype were significantly associated with longitudinal change in cognitive performance from baseline. For APOE4 carriers with high lifetime intellectual enrichment, the onset of cognitive impairment was approximately 8.7 years later than the onset in participants with low lifetime intellectual enrichment. However, participants with low lifetime intellectual enrichment benefitted more from mid- to late-life cognitive activity than did participants with high lifetime intellectual activity. The results suggest that lifetime intellectual enrichment might delay the onset of cognitive impairment and be used as a successful preventive intervention to reduce the impending dementia epidemic. (Vemuri P, et al. Association of lifetime intellectual enrichment with cognitive decline in the older population. JAMA Neurology. 2014;71:1017.)

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