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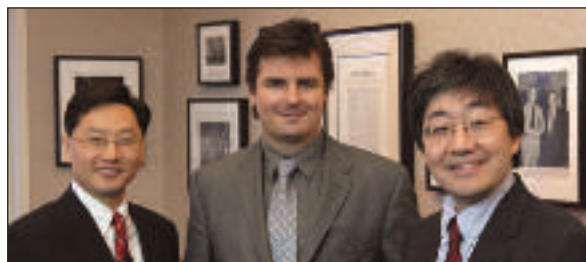
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Deep Brain Stimulation: Program Expansion



Kendall H. Lee, MD, PhD, S. Matthew Stead, MD, PhD, and Joseph Y. Matsumoto, MD

Deep brain stimulation (DBS) is a type of functional restorative surgery. During the procedure, electrodes are surgically implanted to stimulate neuronal activity deep in the brain. Developed in the 1980s, DBS was principally used to treat movement disorders associated with essential tremor (ET) and Parkinson disease (PD). For patients with PD, surgical intervention to reduce or stop excessive neuronal firing previously took the form of pallidotomy and thalamotomy, procedures that ablate these sites. Unlike ablation surgery, DBS is reversible; tissue is not destroyed, and the stimulator can be turned off. Postsurgical adjustments can be made, allowing for highly individualized therapy.

In 1997, neuroscientists from Mayo Clinic Jacksonville received training at European medical centers that were refining this technique. Neurologist Ryan J. Uitti, MD, and neurosurgeon Robert E. Wharen, Jr, MD, were among the first to perform DBS for ET in research studies in the United States. Today, the applications of DBS include other movement disorders as well as certain nonmotor syndromes and conditions.

The DBS Program

The Mayo Clinic experience at all 3 sites has expanded to include new treatment avenues and innovative research to refine and improve DBS surgery. DBS is now offered to treat dystonia, chronic pain, cluster headache, and Tourette syndrome.

Interdisciplinary teams dedicated to DBS meet regularly at each site. These teams evaluate patients, formulate treatment recommendations, and provide multiple perspectives on current practice and future clinical and research directions for the DBS

programs. The Mayo Clinic DBS team in Jacksonville is headed by Drs Wharen and Uitti. The DBS team at Mayo Clinic Arizona is headed by neurologist Virgilio H. Evidente, MD, and neurosurgeon Mark K. Lyons, MD. Neurosurgeon Kendall H. Lee, MD, PhD, and neurologist S. Matthew Stead, MD, PhD, lead the DBS team in Rochester.

Successful DBS depends on 3 key features: careful patient selection, precise targeting of neural structures in the surgical procedure, and intense, individualized postoperative programming and follow-up. Evaluation, surgery, and follow-up care are provided at each site.

Patient Selection

DBS is generally reserved for patients in whom pharmacologic and other treatments are no longer effective or who have disabling adverse effects. Not all patients with a given disorder are candidates. Dr Lee believes the program is fortunate to have the input of neurologists and others at the forefront of their fields on the DBS team to tackle the complexities of DBS candidacy. Dr Lee observes, "The neurosurgeon can be confident of the decision to operate because by the time of surgery, the patient has had a very thorough evaluation."

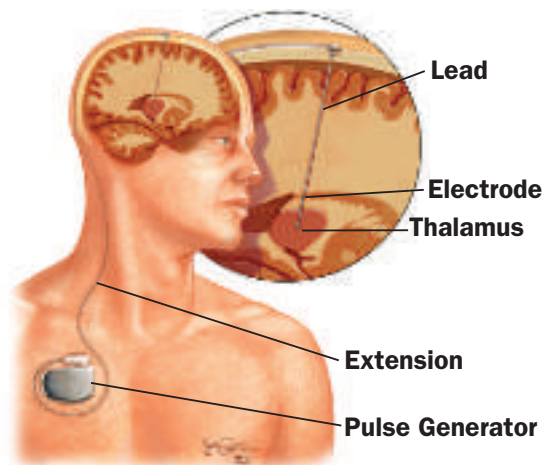


Figure. DBS of the targeted group of nerve cells requires implantation of the stimulation electrode, which is secured to the skull and then connected to an infraclavicular neurostimulator (pulse generator).

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Clinical evaluations are tailored to the disorder and conducted by a neurologist. These evaluations typically include tests of memory, cognitive function, and speech and language and may include a psychiatric evaluation for depression or other disorders. In selected patients, functional MRI is done to map areas of activity in the brain before surgery. Because DBS may exacerbate certain symptoms, the procedure may be contraindicated as a treatment for movement disorders in patients who have major depression, autonomic dysfunction, and cognitive or communication impairment.

Parkinson Disease

Neurologist Joseph Y. Matsumoto, MD, stresses the fact that DBS is not a cure for PD, but rather a tool to eliminate disabling motor symptoms and to help patients reduce medication. Autonomic disorders, cognitive decline, and speech difficulties, all of which may be part of disease progression, are not improved by DBS. However, in the right patients, DBS can be an effective therapy for PD, improving function and reducing dyskinesias and symptom fluctuations related to on-off medication effects.

The main indication for DBS in PD is the patient's need for increased frequency and levels of medication. The first step is to be sure the patient has idiopathic PD and not a disease with parkinsonian features such as multiple-system atrophy (Table). Symptoms must be severe, but not so severe that patients would not have functional improvement from DBS.

Patients must also be responsive to dopamine agonists such as levodopa—even if only at a high dose. If not, they will likely not respond well to DBS. To be sure they are responsive, patients are usually videotaped preoperatively both on and off their medication.

DBS has generally been reserved for PD patients under the age of 70 years who are on high doses of medication and in the later stages of the disease. However, recent studies suggest DBS may be considered earlier in the disease process.

Essential Tremor

Patients with severe, medically intractable ET almost always have symptom relief with DBS. Most become tremor-free, are able to stop their medications, and have few, if any, adverse effects. Age does not seem to be a factor. Dr Matsumoto calls DBS a “life-altering” procedure for most patients. The effects of DBS for tremor from trauma or multiple sclerosis (MS)

are not as dramatic. A concern is that DBS for ET might affect speech, but current experience suggests that it does not appear to have severe effects.

Other Conditions

Once thought best for patients with primary idiopathic generalized dystonia, DBS has been successful in segmental or focal dystonias such as writer's cramp and spasmodic torticollis. Patients with chronic pain and those with cluster headache also may benefit. DBS has also been successful in some patients with Tourette syndrome, although this application is under study. Tourette symptoms fluctuate over time, so long-term follow-up, currently under way in an international study, is critical. In fact, the DBS team cautions that long-term follow-up in all new applications is needed to fully assess success.

Success has also been seen in patients with cluster and SUNCT headaches (ie, short-lasting, unilateral, neuralgiform headache attacks with conjunctival injection and tearing). In 2006, the DBS team in Arizona performed the first successful hypothalamic DBS in North America for the rare headache syndrome called SUNCT. In Rochester, DBS was used to treat 2 patients successfully for cluster headaches. Other conditions under consideration for DBS treatment at Mayo Clinic include epilepsy, depression, and obsessive-compulsive disorder.

**The Surgical Procedure: Precision Targeting
Creating a Map of the Brain**

Structural targets differ according to the condition addressed by DBS. Locating targets during surgery requires brain mapping and neuronal monitoring. The patient is fitted with a stereotactic head frame, an MRI is obtained, and the image is merged with a brain atlas. This context helps the surgeon guide the trajectory of an initial microelectrode through a small hole in the skull to the targeted locus. Using brain-mapping software developed at Mayo Clinic, the DBS team has a history of exceptional targeting accuracy.

Mayo Clinic Rochester is one of only a few institutions with an intraoperative MRI suite; Mayo Clinic Jacksonville also will have one with the opening of its new hospital in April 2008. Reducing the time between scan and surgery minimizes brain shift (the settling of the brain as the head shifts), so the target position can be better preserved. Just as important, MRI during surgery allows immediate confirmation that the target has been reached. Drs Lee and Stead are working to refine the use of intraoperative MRI. Their eventual goal is to create “frameless” surgery, which would eliminate the bulky and often uncomfortable stereotactic head frame.

As the targeting microelectrode passes through various brain structures, it transmits electrical activity

**Table. Criteria for DBS
in Patients With PD****Classic clinical features of PD****Slowly progressive signs****Lack of early dysautonomia and early cognitive impairment****Normal eye movement (to distinguish PD from progressive supranuclear palsy)****Lack of cerebellar and pyramidal involvement (to distinguish PD from striatonigral degeneration or olivopontocerebellar atrophy)****Robust and continued response to levodopa****Disabling motor symptoms despite optimized medication****Absence of dementia, depression, personality disorder, uncontrolled hypertension, and bleeding diathesis****Ambulation on medication****Disabling symptom fluctuations due to medication on-off effects**

emitted by cells. These cellular signatures are translated into auditory and visual tracings that are monitored. The DBS team believes this type of monitoring is a major factor in their successful target location.

When possible, the patient is awake during surgery, and intraoperative stimulation tests of movement, speech, and other behavioral output can assist in confirmation of target placement. However, in conditions such as generalized dystonia, it is not possible for the patient to be awake during the procedure. Similarly, functional response (ie, symptom improvement) to stimulation in various psychiatric disorders is difficult to monitor during surgery, making physiologic monitoring and precise brain mapping more critical.

Implanting the Device

When the target is confirmed, an electrode with 4 contacts is implanted and attached subcutaneously by a thin, insulated wire to a battery-operated, programmable pulse generator (neurostimulator). The stimulator, usually implanted just under the clavicle, stimulates neuronal activity at the electrode site in the brain (Figure on page 1).

Follow-up and Programming: Partnership With the Patient

Follow-up care includes evaluation and medication adjustment by neurologists and stimulator programming adjustments. Nurse programmers with extensive training and expertise adjust stimulus parameters to fit individual patient needs. As Dr Stead observes, "To say our nurses go an extra mile is an understatement. Many institutions follow a rote algo-

rithm, which keeps programming visits short. Our nurses take as much time as necessary with as many visits as necessary, even within a single day, to accommodate the delayed effects of program adjustment." Most patients need fairly frequent programming during the first 6 months after surgery.

Future Directions for DBS

The therapeutic mechanisms of DBS are not fully known, but uncovering them is providing unique insights into neuronal window on the brain. For example, animal model studies by Dr Lee and colleagues suggest that in PD, DBS causes glutamate release and activation of dopamine neurons in the substantia nigra compacta, leading to enhanced dopamine release in the basal ganglia (see, for example, *European Journal of Neuroscience*, 23:1005-14, 2006). Findings such as these may lead to refinements in the design of the next generation of DBS devices.

In the future, DBS may be used to stimulate cells surrounding a lesion site in stroke, as well as for obesity, addiction, and other disorders. Mayo Clinic's DBS team is approaching the extension of DBS systematically, with enthusiasm tempered by the recognition that DBS is in its infancy. For example, Mayo Clinic clinicians will participate in a multicenter trial to study the use of DBS to treat depression. Also, the DBS Clinic plans to be part of a national patient registry when they begin using DBS for obsessive-compulsive disorder. Research-based refinements in the procedures, targeting, and technology as well as studies of the mechanism and long-term outcomes of DBS will guide these new therapeutic uses.

Integrated Approach to Minimally Invasive Spine Surgery

The National Institutes of Health estimates that back pain affects approximately 8 of 10 people at some point during their lives. Surgery is usually reserved for patients who have pain that is refractory to other therapies, severe decrease in function, or invasive or progressive tumors.

Increasing numbers of patients are requesting "minimally invasive" spine surgery (also known as "minimal access" or "microendoscopic" surgery), hoping that it will decrease surgical time, complications, postoperative pain, and recovery time. Internet and media claims often lead to patients' unrealistic expectations. Members of the interdisciplinary spine surgery team at Mayo Clinic are famil-

iar with those expectations and are equally familiar with actual outcomes.

Expectations for Minimally Invasive Spine Surgery

What are reasonable expectations for minimally invasive procedures?

Minimally invasive surgery does not change surgical indications. Traditional criteria still apply. Barry D. Birch, MD, a neurosurgeon at Mayo Clinic Arizona, explains that minimally invasive and traditional techniques are in fact different paths to the same end.

Neurosurgeons at all Mayo Clinic sites routinely perform minimally invasive surgery to repair single-level, focal herniated disks (microdiscectomy); dural arteriovenous (AV) fistulas (minimally invasive dural AV fistula ligation); and 1- and 2-level disk degeneration (minimally invasive spinal fusion).

The incision in minimally invasive spine surgery is usually 2 to 2.5 cm, much smaller than in



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Figure 1. Radiographic localization of tubular retractor for microendoscopic discectomy.



Figure 2. View through tubular retractor during microendoscopic discectomy.



Figure 3. Anteroposterior lumbar x-ray view after placement of a decompression device.

traditional approaches. A tubular retractor system is used to dilate, rather than dissect muscle, which decreases muscle fiber damage (Figures 1 and 2). The surgery is conducted through a 3-dimensional viewing system microscope with the patient under general anesthesia and takes as long as or longer than traditional procedures.

A smaller incision and less muscle damage mean a less painful immediate postoperative period, so patients can often leave the hospital within 24 hours. However, as Dr Birch cautions, a more comfortable perioperative period and smaller incision in spine surgery (as opposed to abdominal surgery) does not translate into a shorter, less painful overall recovery. As Dr Birch puts it, "Recovery from a surgical procedure that alters the environment around the nerves hinges on nerve recovery more than on the size of the incision." He goes on to state, "There are no differences in outcomes reported either in the literature or anecdotally between minimally invasive techniques and traditional ones. What prevents patients from returning to work after laminectomy and discectomy is not soft tissue damage, but postoperative nerve inflammation, and that outcome is the same, regardless of approach."

Minimally invasive surgery done by an experienced surgeon can greatly reduce the trauma associated with some traditional techniques. For example, dural AV fistula ligation usually involves a multilevel laminectomy in which bone is removed, the dura opened, and the fistula ligated. Neurosurgeons at Mayo Clinic Arizona pioneered a microscopic technique that eliminates laminectomy and has allowed many patients to return to normal activities sooner than those treated with traditional techniques.

Matthew A. Butters, MD, in the Department of Physical Medicine and Rehabilitation at Mayo Clinic Arizona, notes that, regardless of surgical technique, the extent of rehabilitation depends on the nature and extent of the surgery and on patient age, medical issues, and prior level of deconditioning.

Surgery for Spinal Stenosis

Spinal stenosis creates pressure on the nerves in the spinal canal from degenerative disk and joint disease, overgrowth of bone in the canal, and the hypertrophy of ligaments. It can arise from injury or normal aging. Symptoms include leg cramping, weakness, numbness, fatigue, and pain from intermittent neurogenic claudication. The critical distinguishing feature of lumbar stenosis is symptom exacerbation when

walking and symptom improvement on sitting.

While technically not "minimally invasive" or "microendoscopic," surgery with an intraspinal process decompression system (X STOP; St Francis Medical Technologies, Inc, Alameda, California) for relief from spinal stenosis is less invasive than laminectomy. With this procedure, a titanium spacer is placed between the spinous processes of the lumbar spine (Figure 3). The device prevents the spine from extending (and narrowing) in the standing position, thus relieving nerve pressure. Unlike laminectomy, device placement can be done with the patient under local anesthesia with a 3- to 4-hour hospital stay. There is no postoperative nerve inflammation and less risk of spinal fluid leakage or nerve root damage, because no bone is removed and nerves are neither exposed nor manipulated.

Neurosurgeons at Mayo Clinic Arizona and Mayo Clinic Jacksonville have found this surgery best for patients who have moderate stenosis, regardless of age. Dr Birch calls it "another tool in the toolbox to treat lumbar spinal stenosis," but like his neurosurgery colleague, Naresh P. Patel, MD, cautions that "it is not a cure." As Dr Patel says, "It removes symptoms, but only laminectomy can treat the problem by removing bone and ligament pressing on the nerves. However, spinal space does increase after placement of the device." Because the procedure is new, it is unknown whether the long-term results will be as durable as those with laminectomy. If symptoms return, the device can be removed and a laminectomy performed. So far, it appears to be an excellent stopgap between epidural corticosteroid injection therapy and laminectomy.

Minimally Invasive Fusion Surgery

Fusion surgery is generally performed for degenerative disks, trauma, and spondylolisthesis. It requires a bone graft or the insertion of a synthetic graft that has been injected with human recombinant bone morphogenetic protein, a bone growth stimulant. Neurosurgeons at all 3 Mayo sites have had good results with this procedure. Mark A. Pichelmann, MD, a neurosurgeon at Mayo Clinic Rochester, explains that minimally invasive fusion reduces hospital stays from approximately 4 or 5 days to approximately 1 or 2 days. Major advantages are that blood loss is minimal and blood transfusions and postsurgical drains are not needed. It can be done from the patient's side using a procedure called extreme lumbar interbody fusion, or XLIF, or using a posterior approach called transforaminal lumbar interbody fusion, or TLIF.

Noninvasive Stereotactic Radiosurgery for Spinal Tumors

For patients with spinal tumors that are refractory

to standard care and for those whose health or age makes surgery too high risk, noninvasive radiosurgery may be an option. Mayo Clinic Arizona has recently acquired a specialized linear accelerator with an image-guided targeting system that allows the delivery of high-dose, focal radiation either as a single, 1-time dose or through a hypofractionated regimen (once a day for 5 days). Controlling tumor growth with this technique has been excellent.

Integrated Care

Mayo Clinic's spine teams provide comprehensive

care from diagnosis through management and follow-up. As Dr Butters says, "Integrated care is one of the biggest pluses in Mayo Clinic's spine care, with daily interactions among all the subspecialties and biweekly review of cases by a team that includes neurosurgeons, physiatrists, neuroradiologists, and anesthesiologists." Intervention always includes patient education and counseling. Interdisciplinary collaboration and judicious application of innovative surgical techniques and other forms of symptom management provide patients with both reasonable expectations and optimal outcomes.



P. James B. Dyck, MD

Radiculoplexus Neuropathies: Nerve Biopsy Studies Suggest Treatment Options

Case Reports

Patient 1

A 24-year-old man had burning pain in the left shoulder and upper arm severe enough to disrupt sleep and daily activities. Asymmetric pain was accompanied by weakness 2 days later, leading to atrophy of the shoulder girdle muscles. The condition cleared over the ensuing 6 months.

Patient 2

A 47-year-old woman, recently diagnosed with diabetes mellitus, had sharp, lancinating pain that began in her right hip and thigh and within 2 months had spread to the contralateral hip, thigh, and leg. Orthostatic hypotension and lower limb weakness developed. Two years later, her pain had resolved, but she was left with right footdrop.

Patient 3

A 56-year-old man did not have diabetes mellitus, but his clinical course followed the same pattern as patient 2, except that leg pain was accompanied by contact allodynia (pain to light touch) and he had thoracic involvement. He required hospitalization for pain control. His symptoms were preceded by an unintentional 40-pound weight loss, and he continued to lose weight. The pain cleared within a year, but because of residual leg weakness, he used a wheelchair.

Discussion

The case stories are hypothetical, but the symptoms are real. They represent a group of monophasic illnesses that have been known by many names in attempts to define their clinical features, anatomic locus, and etiology (Table). Today, they are referred to as radiculoplexus neuropathies, defined at Mayo Clinic as disease of the nerve roots, plexus, and peripheral nerves, any or all of which may be

involved. Each case report describes one of the radiculoplexus neuropathies: brachial plexus neuropathy (BPN) in patient 1; diabetic lumbosacral radiculoplexus neuropathy (DLRPN) in patient 2; and nondiabetic lumbosacral radiculoplexus neuropathy (LRPN) in patient 3.

These conditions have long been thought of as distinct clinical entities—but are they? Actually, they have more in common than previously thought. New discoveries have opened the door to the possibility of moving beyond symptomatic treatment into therapies that address underlying mechanisms.

Three Diseases or One? The Unifying Pathophysiology in BPN, DLRPN, and LRPN

In 1972, Mayo Clinic neurologists Peter Tsairis, MD, Peter J. Dyck, MD, and Donald W. Mulder, MD, defined the natural history of BPN and advanced the term "brachial plexus neuropathy" to describe the condition of pain followed by weakness of the upper limbs. The etiology of BPN remained a mystery.

In the mid 1990s, Dr Dyck, along with P. James B. Dyck, MD, and their colleagues in the Peripheral Nerve Laboratory at Mayo Clinic Rochester, began a series of studies in patients with DLRPN and LRPN on the natural history of these lower limb neuropathies. They also studied nerve biopsy specimens, which revealed large inflammatory infiltrates in vessel walls, suggestive of microvasculitis. Their continued biopsy and histopathology studies of nerves from patients with BPN, DLRPN, and LRPN demonstrated increasing similarities among these apparently disparate neuropathies. By 2000, they had confirmed their hypothesis that the 3 conditions shared the same underlying pathophysiology: ischemic nerve injury secondary to a nonsystemic microvasculitis caused by an immune-mediated inflammatory attack.

Table. Earlier Terminology for Radiculoplexus Neuropathy

Earlier terms for brachial plexus neuropathy (BPN)

Parsonage-Turner syndrome

Multiple neuritis or local neuritis of the shoulder girdle

Neuralgic amyotrophy

Earlier terms for diabetic lumbosacral radiculoplexus neuropathy (DLRPN)

Diabetic amyotrophy

Diabetic myelopathy

Diabetic mononeuritis multiplex

Diabetic polyradiculopathy

Diabetic motor or paralytic neuropathy

Femoral or femoral-sciatic neuropathy of diabetes

Paralytic neuropathy of diabetes

Proximal diabetic neuropathy

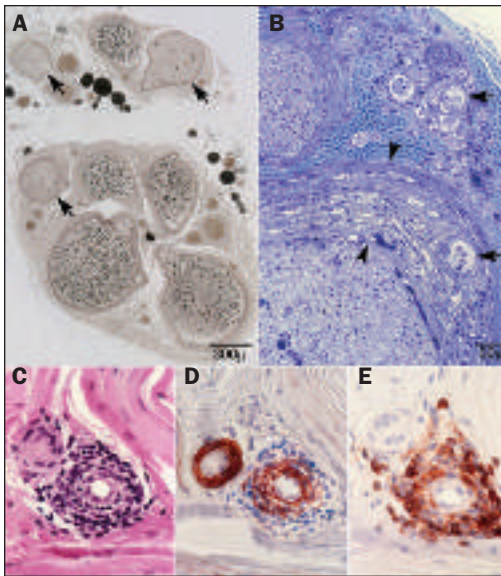


Figure. A-B, Transverse sections of sural nerves from patients with DLRPN showing multifocal fiber degeneration and loss (A, arrows), abortive repair with injury neuroma (microfasciculation) (B, arrows), and thickened perineurium (B, between arrowheads). C-E, Serial sections of a microvessel at a region of focal microvasculitis from the sural nerve of a patient with DLRPN. These findings are typical of ischemic injury and repair due to microvasculitis and are commonly seen in both DLRPN and LRPN nerves. (Modified and reprinted, with permission, from Dyck PJB. Radiculoplexus neuropathies: diabetic and nondiabetic varieties. In: Dyck PJ, Thomas PK, eds. *Peripheral Neuropathy*, 4th ed. Philadelphia; Elsevier, 2005; volume 2, chapter 86:1993-2015.)

Undoing Previous Assumptions

In retrospective and prospective studies these investigators confirmed other unifying features of these clinical entities as well—findings that were at odds with previous assumptions. They found that the conditions may involve not only the plexuses, but the spinal nerve roots and peripheral nerves—hence the term “radiculoplexus neuropathy.” Once thought to involve proximal, but not distal nerves, the process does include distal nerve damage. In DLRPN and LRPN, autonomic nerves can also be involved.

Finally, DLRPN has been shown to be distinct from slow, insidious diabetic polyneuropathy in its acute onset, its overall presentation, and its mechanism. Like LRPN and BPN, it is brought on by an immune-mediated response.

These findings settled a long-standing debate about the nature of DLRPN, which was originally thought to be a metabolic-mediated disorder brought on by hyperglycemia. They confirmed the relationship of DLRPN to the then-underrecognized nondiabetic form of the disease, LRPN. And although BPN differs in clinical presentation and anatomic locus, the fact that it shares the same pathophysiologic process suggested that all 3 disorders might benefit from immune-modulating therapies.

Etiology

The triggering mechanisms remain unclear—possibly an infectious process initiates symptoms. Patients with BPN may have a genetic predisposition, and the illness may be triggered by trauma or pregnancy. In patients with DLRPN, the illness may be triggered by an excessive exercise program or too vigorous control of blood glucose.

There remains the striking and unexplained weight loss that occurs with some of the lumbosacral radiculoplexus neuropathies. One possibility is that

vasculitis may elevate cytokines, reducing hunger. But as Dr P. James B. Dyck notes, “It is clear that some of these patients seem to induce the syndrome themselves. I have seen numerous patients who find out they are mildly diabetic and start exercising, eating right, losing weight, and feeling great, until they find they can’t control the weight loss.” The fact that radiculoplexus neuropathy can occur after bariatric surgery only adds to the possibility of weight loss–induced disease. Although a majority of those with DLRPN and LRPN have considerable weight loss, some do not.

Management

The degree of suffering from radiculoplexus neuropathies is often underappreciated. Typically, patients require narcotic medication to control pain and can become clinically depressed by ongoing weakness and life-altering disability as the illness progresses. Symptoms can be confused with disk disease or other structural damage. The rapid and severe weight loss in DLRPN and LRPN may suggest a diagnosis of cancer. With little information available, many patients fear the illness is terminal. Because DLRPN was thought to have a metabolic cause, patients were often told to focus on improving regulation of their blood glucose. Now, it is beginning to be understood that DLRPN typically occurs in the face of mild, well-controlled diabetes.

Diagnosis

The diagnoses of radiculoplexus neuropathies are ones of exclusion, so evaluation at Mayo Clinic Rochester consists of the following: extensive clinical examination and history; laboratory studies, including tests for diabetes; spinal fluid examination to exclude malignancies (the protein is often elevated); imaging studies to rule out a structural etiology; electrophysiologic tests (compound muscle and sensory nerve action potentials and nerve conduction velocities); quantitative sensory and autonomic tests; and possible peripheral nerve biopsy and histology studies conducted in the Peripheral Nerve Laboratory (Figure).

Treatment

The finding that the underlying mechanism of the radiculoplexus neuropathies was an autoimmune inflammation of vessel walls with ischemic damage to peripheral nerves suggested immune-modulating treatments might be effective. Several case reports of varying levels of success with methylprednisolone, prednisone, or intravenous immunoglobulin (IVIg) led to clinical trials. Mayo Clinic clinicians are currently participating in multicenter, double-blind, placebo-controlled trials of intravenous methylprednisolone for DLRPN and LRPN. Preliminary results show some improvement in pain and sensory loss and

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on some measures of motor function. Although there have been concerns about using intravenous corticosteroids in patients with diabetes, most DLRPN patients in these studies have blood glucose levels controlled well enough that intravenous corticosteroids have not caused adverse effects.

Dr P. James B. Dyck notes, "We've had many people think this treatment is a miracle. Patients arrive in wheelchairs and come back later walking on their

own. However, these are monophasic illnesses, and spontaneous improvement over time is expected."

More studies are needed, but recognition of a unifying immune-mediated pathophysiology highlights the possibility of new treatment options for the often debilitating symptoms of radiculoplexus neuropathies.

Neuro-oncology Provides Access to System-wide Patient Care and National Clinical Trials

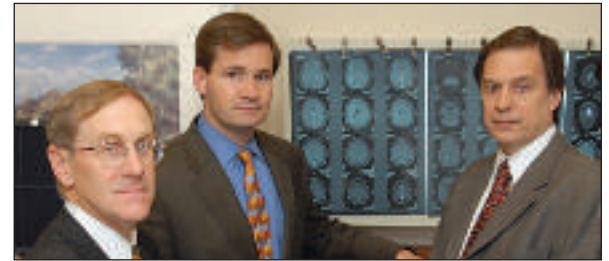
"Comprehensive care"—2 words that are often overused and underrepresented as a working reality. The neuro-oncology program at Mayo Clinic provides comprehensive care, grounded in 4 integrated components:

- Multidisciplinary expertise in central nervous system cancers by on-site specialists dedicated to providing the latest advances in medical and neurosurgical treatments
- Participation in the Mayo Clinic Cancer Center, the only multisite National Cancer Institute (NCI)-designated Comprehensive Cancer Center with sites in 3 different geographic regions
- Development of and access to national treatment trials (including NCI-approved trials) through the Mayo Clinic Cancer Center and the North Central Cancer Treatment Group (NCCTG)
- Partnership between Mayo Clinic and the patient and the patient's referring physician within the context of Mayo Clinic's culture of collaboration in every aspect of care

Multidisciplinary Expertise: The On-site and 3-Site Team Approach

Kent C. New, MD, a neurosurgeon on the Mayo Clinic Jacksonville neuro-oncology team, calls the multidisciplinary approach to the patient "one of the most important aspects of our program." With appointments in both neurology and oncology, Kurt A. Jaeckle, MD, heads the neuro-oncology program at Mayo Clinic Jacksonville. He agrees with Dr New: "I've never practiced at a facility like Mayo, where there is such open communication among several specialists regarding the patient's care, often during the patient's appointment." The multispecialty team includes members from neurology, neurosurgery, medical oncology, neuroradiology, radiation oncology, neuropathology, neuropsychology, and neuro-oncology nursing.

Teleconferencing allows interaction with the neuro-oncology teams at Mayo Clinic Rochester and Mayo Clinic Arizona. These conferences extend dis-



Robert E. Wharen, Jr, MD, Kent C. New, MD, and Kurt A. Jaeckle, MD

cussion of unusual, difficult, or rare cases. While oncology conferences are a feature of some hospitals, the multicenter contribution of Mayo Clinic experts provides a depth and breadth of experience and resources that are relatively uncommon.

Treating more than 16,000 new cancer patients a year, the Mayo Clinic Cancer Center is one of the largest cancer centers in the country. In addition, it meets the NCI's rigorous standards as a comprehensive care system, with clinical, research, and community-based programs aimed at translating research as rapidly as possible into effective improvements in patient care.

Access to National Treatment Trials

Members of the neuro-oncology teams contribute to the development, execution, and review of all high-priority NCI-funded clinical trials through the NCCTG. This is one of the avenues through which patients at Mayo Clinic Jacksonville can participate in clinical trials. The other avenue is through institutional clinical trials offered locally or as part of the 3-site Mayo Clinic Cancer Center.

The NCCTG is a national clinical research group funded by the NCI. With 40 separate sites located in 25 states and Canada, the NCCTG is dedicated to developing new protocols and bringing clinical trials to patients served by community clinics, hospitals, and medical centers. Dr Jaeckle serves as chair of the NCCTG's Neuro-oncology Committee, and Dr New is its primary neurosurgical representative and also a member of the NCCTG Surgery

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Committee. Mayo Clinic Jacksonville is the south-east region's entry point into the NCCTG system and Mayo Clinic Cancer Center trials that are not otherwise available in the region.

Both the NCCTG and the Mayo Clinic Cancer Center support the basic science research on which clinical trials are based. Recent discoveries in molecular targeted therapies, for example, have made previously held distinctions between systemic treatments and those reserved for brain cancer less important than they once were. These new agents are often able to target and penetrate brain tissue just as they do in tumors located in other parts of the body. Robert E. Wharen, Jr, MD, chair of neurosurgery in Jacksonville and a member of the neuro-oncology team, was involved in bringing one of them, HN66000, a targeted gene therapy, to a phase 3 clinical trial. Other avenues of investigation at Mayo Clinic include immunotherapy, a form of biotherapy (versus chemotherapy). Dr New, in collaboration with Allan B. Dietz, PhD, researcher at Mayo Clinic Rochester, is currently examining methods of using tumor vaccines to target and attack brain tumors. Several institutional or NCCTG trials are offered in Jacksonville; they involve molecular targeted therapies, either alone or in combination; radiotherapy techniques that include stereotactic radiosurgery and intensity-modulated radiotherapy; and convection-enhanced delivery.

Surgical and Radiologic Management

Brain imaging is critical to presurgical tumor location and successful tumor excision. Advanced PET and high-field-strength (1.5 Tesla) MRI scanners are used for diagnostic purposes and tumor location. Presurgical imaging may include functional MRI

and diffusion tensor MRI. This imaging technique can now yield images of the fiber tracts in the brain, a major advance.

An intraoperative MRI scanner is planned for the new Mayo Clinic Hospital in Jacksonville, scheduled to open in April 2008. An intraoperative MRI eliminates the need to transport patients under anesthesia and in unsterile conditions for the MRI, which has been previously necessary with conventional scanners. Real-time MRI enables the surgeon to adjust for any brain shifts during surgery, thus achieving more accurate target localization, and also aids in identifying any remaining tumor during the operation.

Radiotherapy is provided using linear accelerators, which offer increased treatment flexibility. The standard fractionated treatment for a malignant brain tumor is 30 treatments over 6 weeks. A linear accelerator allows not only single-fraction treatments but also hypofractionated treatments in which a single fraction a day is administered over a 5- or 10-day course.

Treating the Patient, Not Just the Disease

With years of combined experience, the neuro-oncology team helps patients and families negotiate the complexities and consequences of their disease. Advanced management strategies and collaboration with the NCCTG and the Mayo Clinic Cancer Center make the neuro-oncology program at Mayo Clinic Jacksonville a patient-centered reality.

More information on NCCTG neuro-oncology clinical trials is available at <http://ncctg-mayo.edu/>. Further information on Mayo Clinic Cancer Center clinical trials can be found at <http://cancercenter.mayo.edu/>.

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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Neurosurgical Consultation
507-284-8008

Neurologic Consultation
507-284-1588

Non-Neurologic Consultation
800-533-1564

Jacksonville

4500 San Pablo Road
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13400 East Shea Boulevard
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480-301-6539 (within Maricopa County)
866-629-6362 (nationwide)

