

NEUROSCIENCES UPDATE

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NEUROLOGIC SURGERY AND CLINICAL NEUROLOGY NEWS FROM MAYO CLINIC

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Neurofibromatosis: A Clinic Without Walls at Mayo Clinic Rochester

Neurofibromatosis (NF) is a complex, autosomal dominant, systemic disease. Highly variable in presentation and severity, it is actually not 1 disease, but at least 2 clinical entities, NF1 and NF2 (Table 1). Both cause tumors of the nerve sheath—neurofibromas in patients with NF1; schwannomas in patients with NF2—and both reflect mutations in the genes that regulate tumor suppression. The *NF1* gene is located on chromosome 17, the *NF2* gene on chromosome 22.

NF1

The more common NF1, with an incidence of 1:3,000, is characterized by subcutaneous tumors that can lead to disfigurement and



Michael J. Link, MD, and Robert J. Spinner, MD

by neurofibromas that can compress nerves, cause pain, and lead to nerve destruction and loss of function. The number of tumors can vary from several to several thousand. Tumors are common in the spinal cord and peripheral nerves but can occur in any part of the nervous system and affect any organ or function.

Some patients are asymptomatic, but there are those who have so many tumors that their condition is thought to be beyond treatment. As Robert J. Spinner, MD, a neurosurgeon and NF expert at Mayo Clinic Rochester, says, "Many of these patients are neglected. Surveillance is important. Treatment in selected cases may, in fact, be possible."

NF2

With an incidence of 1:40,000, NF2 is rare but can have devastating effects. It is characterized by bilateral vestibular schwannomas (acoustic neuromas) that can lead to tinnitus, dizziness, and deafness. Cranial nerve tumors can cause blindness, speech difficulties, facial weakness, and swallowing disorders. NF2 patients are also prone to schwannomas on the spinal cord, meningiomas anywhere in the head or spine, and spinal ependymomas.

Michael J. Link, MD, who serves in both neurosurgery and otolaryngology, sees many of the NF2 patients who come to Mayo Clinic Rochester. Most of them are young adults, and, as he says, the disease "slowly and steadily robs them of their function—hearing, facial sensation,

Table 1. Diagnostic Signs of Neurofibromatosis

Diagnostic Signs in NF1

Diagnosis requires at least 2 of the following:

- Café au lait spots (6 or more)
- Two or more neurofibromas of any type or 1 plexiform neurofibroma (Figure 1)
- Multiple freckles in the axillary or groin regions
- Osseous lesion or thinning of long bone cortex with or without pseudarthrosis
- Optic glioma
- Two or more Lisch nodules on slit-lamp examination (Figure 2)
- A first-degree relative with NF1

Diagnostic Signs in NF2

Imaging evidence of 2 vestibular schwannomas (acoustic neuromas)

OR

Vestibular schwannoma on 1 side and a first-degree relative with either NF2 or 2 of the following:

- Neurofibroma
- Meningioma
- Glioma
- Schwannoma
- Juvenile posterior subcapsular lenticular opacity



Figure 1. Large plexiform neurofibroma on the back.

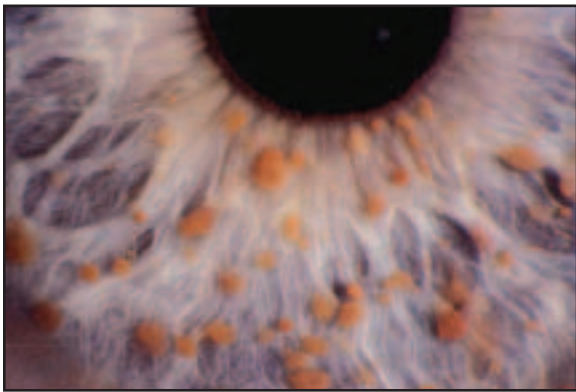


Figure 2. Close-up view of Lisch nodules, a common finding in patients with NF1.

swallowing. A meningioma of the optic nerve can be devastating to patients who are deaf and rely on their sight. NF2 can affect all the cranial nerves. You can't predict what's going to happen and when. These patients need lifelong follow-up."

Neurofibromatosis Clinic

Because NF is a systemic disease with multiple potential effects, patients with NF are best served by multispecialty groups with experience in NF diagnosis and management. Several years ago, Mayo Clinic Rochester established the Neuro-

fibromatosis Clinic in which internationally recognized NF specialists see more than 300 NF patients each year. Truly a "clinic without walls," Mayo's NF Clinic provides easy access to specific subspecialties throughout Mayo Clinic's Rochester campus. The NF Clinic, caring for both pediatric and adult patients, ensures coordinated, comprehensive care from genetic screening, education, and counseling to diagnosis, surgical management of acute symptoms, rehabilitation services, and continuous monitoring. The entry point is typically through medical genetics under Dusica Babovic-Vuksanovic, MD, a director of the NF Clinic, but patients may enter through any of the participating subspecialties (Table 2).

Genetic Screening and Education

The NF genes were identified 10 years ago. Two years ago, genetic testing became widely available. In a family with NF, some members may have unrecognized symptoms. With a 50% chance that the disease will be passed on, all family members should be screened, either clinically or through DNA testing. Dr Babovic-Vuksanovic emphasizes the importance of testing, not only in prenatal screening, but in children who do not yet meet the clinical criteria. Dr Link adds that testing is also critical in NF2 patients younger than 35 years who

may not meet NF2 criteria, but present with a single, large vestibular schwannoma.

When Is a Tumor NF and When Is It Not?

Enlarged nerves and/or multiple tumors are not by themselves diagnostic of NF, although patients with these conditions may receive an erroneous diagnosis of NF. A recent article by Dr Spinner and colleagues in the November-December 2006 issue of *Clinical Neuropathology* detailed 1 such case in which an incorrect assumption of NF was supported by traditional imaging studies, but the correct diagnosis was actually benign metastasizing leiomyomatosis. MRI can localize focal nerve lesions but cannot identify the underlying pathology. To do so often requires a biopsy.

For the past several years, P. James B. Dyck, MD, a peripheral nerve neurologist at Mayo Clinic Rochester, Kimberly K. Amrami, MD, a peripheral nerve radiologist, and Dr Spinner have been using targeted fascicular biopsies to overcome diagnostic uncertainty in patients with unexplained neuropathies and abnormal imaging studies. Using a Mayo-developed, high-resolution peripheral nerve MRI with coils dedicated to the extremities, Dr Amrami can pinpoint location of a lesion with exceptional precision. Dr Spinner performs the biopsy, and Dr Dyck the histologic analysis. They are successfully identifying the disease process in many patients in whom suspected NF turns out not to be NF. The distinction is critical. Some patients they work with have already had masses removed that were diagnosed incorrectly as neurofibromas, when in fact they have a treatable condition such as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) that can be managed with intravenous immunoglobulin, corticosteroids, plasma exchange, or a combination of these therapies.

As Dr Dyck explains, the nerves in chronic demyelinating conditions such as CIDP try to heal through remyelination. Macrophages strip the myelin, Schwann cells replace it, and macrophages again attack it. This repetitive cycle of injury and repair causes stacks of Schwann cell processes to enlarge the nerve (apparent on imaging), which has an "onion bulb" appearance under the microscope. A great aid in differential diagnosis, this type of targeted fascicular biopsy requires special attention:

- neurologists with peripheral nerve expertise
- specialized peripheral nerve MRI equipment
- a peripheral nerve radiologist with special skills in interpreting peripheral nerve images
- a neurosurgeon capable of conducting a fascicular biopsy without damaging the nerve and causing a neurologic deficit

Neurofibromatosis Specialists

NEUROSURGERY

William E. Krauss, MD
Michael J. Link, MD
Robert J. Spinner, MD

NEUROLOGY

P. James B. Dyck, MD

MEDICAL GENETICS

Dusica Babovic-Vuksanovic, MD

OTORHINOLARYNGOLOGY

Charles W. Beatty, MD
Colin L. Driscoll, MD
Brian A. Neff, MD

RADIOLOGY

Kimberly K. Amrami, MD

Table 2. Participating Subspecialties in the Neurofibromatosis Clinic at Mayo Clinic Rochester

- Audiology
- Dermatology
- Developmental pediatrics
- Endocrinology
- Medical genetics
- Neurology
- Neurosurgery
- Oncology
- Ophthalmology
- Otolaryngology
- Orthopedic surgery
- Pain clinic
- Plastic surgery
- Physical medicine and rehabilitation
- Psychology
- Radiology
- Social services
- Speech pathology

- a pathology laboratory with expertise in processing peripheral nerve tissue
- As Dr Dyck notes, “Mayo Clinic Rochester may be the only center in the country that has all 5 of these components.”

Neurosurgical Advances in NF

Surgery is the main option for symptomatic nerve tumors in NF. The obvious challenge is to remove them with as little damage to the nerve as possible. This is particularly difficult with neurofibromas that invade the connective tissue within the nerve, although it can also be challenging in schwannomas, which displace, rather than invade, the nerve.

Specialized imaging and advances in microsurgery have made it possible to operate on tumors once thought impossible to address—those embedded in the nerve. Dr Spinner explains that sometimes tumors that appear to be taking up a large amount of the nerve may actually be coming from a single fascicle or small branch of the larger nerve. In such cases, microsurgical techniques can often remove the tumor(s) while preserving nerve function.

Intraoperative monitoring is also making NF surgery safer and more successful. William E. Krauss, MD, a neurosurgical colleague of Dr Spinner’s, points out that monitoring motor activity in the spinal cord is now possible. He also notes that improved implants are helping to reduce deformities—of particular importance after multiple spine operations. And, he adds, inpatient rehabilitation is an important part of patient care. At Mayo Clinic, inpatient rehabilitation is available to patients in the same building where they have surgery.

Tumor Treatment in NF2

The surgical goal for vestibular schwannomas in NF2 patients is to preserve the eighth nerve if possible and its blood supply so as to maintain hearing on at least 1 side. The average growth rate of tumors is 1 mm per year. Brian A. Neff, an otorhinolaryngologist at Mayo Clinic Rochester, explains that “although there is no direct correlation between tumor size and symptoms, the challenge is to remove

the tumor before it becomes so large that it risks affecting the facial nerve during surgery.”

Mayo Clinic also offers Gamma Knife radiosurgery, which has the advantage of reducing meningiomas or vestibular schwannomas through focused radiation with minimal or no facial nerve damage. The decision to use it depends on the patient’s age, general health, hearing status, and tumor size, a decision that involves the neurosurgeon, otolaryngologist, and radiation oncologist. NF2 patients with hearing loss may be also be candidates for cochlear or brainstem implants, both of which are offered at Mayo Clinic.

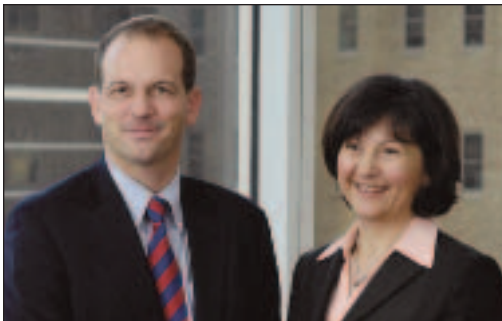
Patient Education and Follow-up

A small percentage of NF1 patients develop malignancies that can become life-threatening very quickly. As Dr Krauss says, “A big part of our practice is monitoring or surveillance of tumor growth.” Because rapid changes in tumor size and neurologic function and the development of pain are indicators of malignant transformation, it is important that patients are educated about this critical component of their care.”

Halting Tumor Growth: Clinical Trials and Basic Science

As part of Mayo Clinic’s ongoing clinical trials in NF, Dr Babovic-Vuksanovic recently led a phase 2 trial on the antifibrotic drug pirfenidone; the results of this trial were published in the November 2006 issue of *Neurology*. Research is also under way to develop animal models of NF1 and NF2. Dr Babovic-Vuksanovic, investigating the molecular underpinnings in NF tumor growth, explains that NF genes express in highly variable ways, particularly in NF1. Dr Neff agrees. He is investigating schwannoma pathophysiology, the NF2 gene, and the protein pathways involved in tumor formation. His goal is to identify proteins that may lend themselves to targeted inhibition to halt tumor growth. Additionally, he is attempting to develop animal models for NF2 schwannomas using bioluminescence, which allows tumor growth in mice to be tracked via special cameras that record emitted light from the tumors.

Clinically applied research at Mayo Clinic and other medical centers holds promise for the future for NF patients. For now, comprehensive symptom management at a multispecialty center with a focus on differential diagnosis, multiple systems management, and ongoing follow-up care and monitoring is considered the best approach.



William E. Krauss, MD, and Dusica Babovic-Vuksanovic, MD

Stroke Genetics: The Keys to Prevention

In the United States someone has a stroke every 45 seconds. Every 3 minutes someone dies of stroke.

Hypertension, high cholesterol, diabetes, smoking, obesity, and lack of exercise—these are known risk factors for cerebrovascular disease and stroke. But these risk factors tell only part of the story. Genetic predisposition may explain much of the remaining risk. The weight of epidemiologic evidence leaves no doubt that genetic factors play a role in stroke susceptibility. Genetics may also play a role in how well brain tissue responds to a blocked artery—defining individual differences in the degree of damage and recovery after stroke. The effectiveness of stroke prevention drugs may also differ according to genetics, making pharmacogenomics a potentially critical issue in stroke prevention.

Treatment is available for acute stroke, but every physician knows that prevention is key. The future of prevention depends on unraveling the molecular pathways and genetic mechanisms that define risk. This knowledge will dramatically impact public health worldwide. Armed with genetic information, future medical practitioners may be able to identify those at risk years before symptoms develop; provide them precise, focused, presymptom counseling; and offer them molecular-based, targeted, preventive medical intervention for conditions that lead to stroke.

In a major first step toward accomplishing these goals, Mayo Clinic is leading 2 multicenter studies designed to identify the molecular and genetic bases of ischemic stroke: the Ischemic Stroke Genetics Study (ISGS) and the Siblings With Ischemic Stroke Study (SWISS).

Ischemic stroke was chosen for study because it represents 85% of all strokes. In addition, unlike previous studies, both ISGS and SWISS are addressing ischemic stroke subtypes (Table) in an effort to discover if they differ according to genetic variation. These subtypes are determined at Mayo Clinic through validated, standardized classification methods.

Single Genes Versus Genome-Wide Scanning

Individual gene mutations have been identified for relatively rare conditions that can cause stroke such as mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (known as MELAS). However, only a tiny portion of ischemic

strokes can be accounted for by these straightforward, mendelian or mitochondrial conditions and patterns of inheritance. In complex conditions such as cerebrovascular disease, multiple genes, gene clusters, and gene interactions must be identified. To find them, the entire genome must be scanned.

Five years ago, a genome-wide scan would have been technically impossible. But with completion of the Human Genome Project, a new technology, based on single nucleotide polymorphisms, or SNPs, has made scanning the genome a reality. Now, these single base-pair regions of variation or SNPs can be tracked through the entire genome.

There are 2 approaches to genome-wide studies. The first, used in ISGS, is to look for candidate genes—those genetic mutations that seem likely to be associated with conditions such as hypertension or blood clotting abnormalities that can lead to stroke. In case-control studies like this, rates of polymorphisms (ie, genes working together toward a selected outcome) can be compared between stroke patients and stroke-free controls.

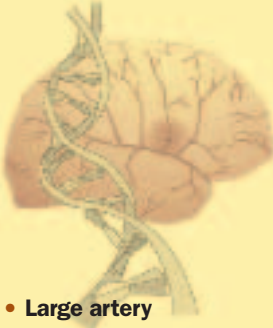
The second approach, used in SWISS, is to conduct a model-free, genome-wide scan. The model-free design enables an unbiased assessment of all the genes and biochemical pathways that may be relevant to stroke. By scanning the entire genome without reference to preselected gene candidates, new hypotheses can emerge. Robert D. Brown, Jr, MD, chair of neurology at Mayo Clinic Rochester and an investigator in both studies, points out that because up to one-third of ischemic strokes are of uncertain origin, a model-free design is an important advantage in hypothesis development.

Using both the model-free and candidate-gene approaches, Mayo Clinic investigators hope to consider as many possibilities as possible to uncover the molecular mechanisms that lead to stroke.

ISGS: Another Look at Candidate Genes

A previous candidate-gene study, conducted in Iceland, identified an association between genes related to thrombosis and stroke. A 5-center study, initiated and led by James F. Meschia, MD, a neurologist at Mayo Clinic Jacksonville, ISGS followed

Table. Ischemic Stroke Subtypes Addressed in ISGS and SWISS



- Large artery atherosclerosis
- Small vessel occlusion (also known as lacunar stroke)
- Cardioembolism
- Stroke of other etiology
- Stroke of undetermined etiology



Robert D. Brown, Jr, MD



James F. Meschia, MD

up on those leads in a more diverse North American population.

With more than 1,200 subjects enrolled, recruitment is complete, and analysis ongoing. Of the 2 genes proposed in the Icelandic study, ISGS data confirmed that a gene which appears to be involved in inflam-

matory vascular processes, *PDE4D*, contributes to genetic predisposition for stroke. The influence of a second gene, *ALOX5AP*, associated with lipid metabolism, was not confirmed. A third gene, *IL1RN*, previously found to be involved in inflammation, although not by the Icelandic study, was also confirmed. These results were published in the September 2005 issue of *Annals of Neurology*, and further findings will be published in the coming months.

SWISS: A Model-Free, Genome-Wide Scan of Sibling Pairs

Because stroke is heterogeneous in nature, genome-wide studies have been difficult to undertake. To enrich the genetic database and overcome this impediment, Dr Meschia, principal investigator of SWISS, designed it to study sibling pairs. Concordant pairs (2 siblings with strokes) and discordant pairs (2 siblings, one of whom has had a stroke and one of whom has not) compose the study population. Some families enrolled in the study have both concordant and discordant pairs. This is the first study of its type in the world—in its subject selection (sibling pairs), ischemic stroke subtyping, and model-free, genome-wide design.

Recruitment for SWISS

Because stroke affects elderly people, finding sibling pairs who have survived stroke can be challenging. As Dr Meschia points out, “A few years ago, it was considered impossible to conduct an adequately powered study on siblings.” However, a multicenter design, involving 50 medical centers in the United States and Canada, has made the study possible. Enrollment of 300 concordant sibling pairs and 200 discordant siblings will provide adequate statistical power to conduct data analyses.

Participation is straightforward. Individuals who have had 1 or more ischemic strokes and meet study inclusion criteria are given a set of invitation letters asking their siblings to participate. Siblings willing to participate donate a small, 1-time blood

sample taken in their home by a home health agency phlebotomist.

To date, more than 230 sibling pairs have been recruited. Mayo Clinic Rochester is the primary enrollment center, with Mayo Clinic Arizona, Mayo Clinic Jacksonville, and the other 47 centers actively participating. Home health agencies in every state are helping to obtain DNA from family members who may live several states away from the enrolled siblings. Genotyping is done at the National Institute on Aging, with Mayo Clinic Jacksonville directing the analysis.

Patients who learn about the study have been more than willing to participate. Bart M. Demaerschalk, MD, a neurologist at Mayo Clinic Arizona and a coinvestigator in the SWISS study, has never had a patient turn down the opportunity, stating, “They all seem genuinely interested in the research question and in contributing to this overall knowledge base.” He goes on to say, “We really need broad involvement in the SWISS trial beyond the contributing medical centers. In particular, we need the involvement of primary care physicians, family practitioners, internists, and other medical and surgical specialists who have patients with a shared family history of stroke.”

Clinical Relevance of Stroke Genetics Studies Risk Factor Stratification

As Dr Demaerschalk points out, discussing an individual patient’s risk for stroke in a concrete, quantifiable way is more likely to have a positive impact on risk-factor modification than today’s more generalized approach. Dr Meschia adds that, for example, the findings from stroke genetics studies might modify parameters of acceptability for levels of cholesterol or blood pressure in an at-risk individual.

New Interventions

Defining the gene clusters associated with disease also defines the relevant proteins, enzymes, pathways, and receptors. The hope is that this knowledge will translate into molecular targets for yet-to-be-developed drug therapies. The example of cholesterol-lowering drugs, which target a specific receptor site, highlights how genetic and molecular studies can revolutionize prevention.

Genetic information could also improve current interventions. For example, it is anticipated



Bart M. Demaerschalk, MD

Stroke/Cerebrovascular Disease Specialists

NEUROLOGY

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Bart M. Demaerschalk, MD
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Alejandro A. Rabinstein, MD
David O. Wiebers, MD
Eelco F. M. Wijdicks, MD

Contact Information for SWISS, the Siblings With Ischemic Stroke Study

For more information, go to <http://clinicaltrials.mayo.edu>, and use the key word *stroke*. Potential participants may contact one of these Mayo Clinic sites:

Mayo Clinic, Jacksonville, Florida
Alexa N. Richie—phone: 904-953-9612,
 e-mail: richie.alexa@mayo.edu
Dale M. Gamble—phone: 904-953-7839,
 e-mail: gamble.dale@mayo.edu

Mayo Clinic, Rochester, Minnesota
Colleen Albers, RN—phone: 507-284-5225,
 e-mail: albers.colleen@mayo.edu

Mayo Clinic, Scottsdale, Arizona
Erica Boyd, RN—phone: 480-342-1326,
 e-mail: boyd.ERICA@mayo.edu

Additional information is available at www.clinicaltrials.gov, with key words *siblings* and *stroke*.

that differences in plaque stability are genetically based. Genetic information could help determine, for example, which patients with carotid artery stenosis should proceed to a carotid intervention.

Clinical and Scientific Integration

Although each study has its own unique design, both SWISS and ISGS are

- multicenter, collaborative investigations across institutions and within the National Institutes of Health
- funded by the National Institute of Neurological Disorders and Stroke with the National Institute on Aging conducting the genotyping
- representative of scientific and clinical integration across Mayo Clinic's 3 sites, Jacksonville, Rochester, and Arizona
- an example of Mayo Clinic's long history of epidemiologic research into stroke prevention

As Dr Brown points out, the integration of basic science with population studies and clinical issues translates into optimal clinical care and is exemplary of Mayo Clinic's approach to medical research.

Management Challenges in Myasthenia Gravis

Myasthenia Gravis/
 Neuromuscular
 Disorders Specialists

NEUROLOGY

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 Andrew G. Engel, MD
 C. Michel Harper, MD
 Daniel H. Lachance, MD
 Ruple S. Laughlin, MD
 Vanda A. Lennon, MD, PhD
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 Margherita Milone, MD, PhD
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 Claude Deschamps, MD

IMMUNOLOGY

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OPHTHALMOLOGY

James A. Garrity, MD
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 Brian R. Younge, MD

Diagnosis and treatment of myasthenia gravis (MG) can be challenging. A well-developed animal model of MG has helped define the nature of the antigen—the skeletal muscle acetylcholine receptor—and the immune response. However, many aspects of disease pathogenesis and natural history such as the triggering mechanisms, role of genetics, and factors that contribute to exacerbation and remission are not fully understood. Like other chronic autoimmune diseases, there is wide individual variability in physiologic and environmental symptom triggers and responses to treatment. Treatments themselves differ in type and in action onset as well as duration. As C. Michel Harper, MD, a Mayo Clinic Rochester neurologist specializing in neuromuscular disorders and MG, notes, “Medication requires careful monitoring and adjustment relative to both potency and timing.”

With one of the largest MG practices in the country, Mayo Clinic Rochester has conducted pioneering work in the mechanisms of MG, distinguishing it from related neurologic autoimmune

disorders and developing diagnostic tests and clinical tools to manage it. Mayo Clinic's Neuromuscular Clinic takes a coordinated team approach to the care of MG patients that includes specialists from neurology, thoracic surgery, neuro-ophthalmology, immunology, and radiology.

Diagnostic Challenges**Symptoms**

MG can be classified according to symptom distribution—ocular or generalized. Ocular MG is restricted to the eye muscles. Ptosis and diplopia, fluctuating in duration and severity, are the presenting symptoms in 50% of patients and can later affect as many as 90%.

Generalized MG typically starts in the cranial nerves, only later progressing to the peripheral nerves of the arms and then the legs. There is greater proximal than distal weakness, leading to problems in standing up, climbing stairs, and combing one's hair. Bulbar symptoms include dysarthria, dysphagia, difficulty chewing, and

facial weakness. Axial weakness can affect muscles of the neck and diaphragm. Generalized MG may cause in unexpected falls, especially in younger patients. General fatigue without weakness, however, is not a symptom of MG.

Tests Conducted at Mayo Clinic Rochester

The diagnosis of MG requires a combination of clinical, electrophysiologic, and laboratory findings. At Mayo Clinic, electromyographic (EMG) testing is conducted and interpreted by physicians whose practice is dedicated to neuromuscular disorders. Specialized EMG techniques include repetitive stimulation studies and single-fiber EMG, considered the most sensitive test of neuromuscular transmission.

Transient relief of ocular muscle weakness after injection of edrophonium chloride (Tensilon) suggests a diagnosis of MG. Rather than relying on subjective measures of improvement, neuro-ophthalmologists use the Lancaster red-green test, which provides precise, objective measures of extraocular muscle imbalance before and after edrophonium injection.

In addition to traditional blood tests, patients undergo antibody tests developed by Vanda A. Lennon, MD, PhD, and colleagues in neuroimmunology. Some of these tests are unique to Mayo Clinic, and a recent retrospective study shows they have sensitivity and specificity of MG diagnosis of 90%. This combination of laboratory and clinical findings not only provides initial diagnosis, but also aids in monitoring the

response to treatment over the course of the disease.

Treatment— A Balancing Act

MG treatment targets the immune system, itself an interlocking network in which regulatory T cells and antibodies produced by B cells both excite and suppress the immune response. This is one reason for the variability in response to therapy both within and between patients. The medications of choice are immunosuppressants, most commonly prednisone. Because of the adverse effects of corticosteroids, corticosteroid-sparing drugs such as azathioprine are often prescribed. However, they can take longer to reach peak effect—sometimes 4 to 6 months compared

with prednisone's 6 to 8 weeks.

At Mayo Clinic, these drug types are often used in combination to enhance or lessen immunosuppression. Mayo Clinic's approach includes intravenous immunoglobulin, plasma exchange, or both. However, as Dr Harper suggests, although these agents can be effective in a crisis, their expense and relatively short duration of benefit preclude them from being suitable long-term therapy.



C. Michel Harper, MD

Treatment Regimen Cautions

All the standard MG drugs have dose dependency and carry some adverse effects, including liver damage, osteoporosis, cataracts, diabetes, fluid retention, and thinning skin. Dr Harper adds that the more the immune system is suppressed, the more susceptible patients are to certain infections (eg, tuberculosis, fungal infection) or cancers (eg, lymphoma, leukemia, solid tumors) later in life. Whether cancer susceptibility is part of the disease process or is drug related is unknown. Because of the number of MG patients at Mayo Clinic, neurologists and radiologists are particularly attuned to detecting cancer in these patients. Fifteen percent of those with MG develop thymus gland tumors within the first few years. For these patients, surgical removal of the tumor is critical. When the tumor cannot be cured by surgery, neurologists, medical oncologists, and radiation therapists collaborate to tailor treatments using drugs and radiotherapy, which are often effective in controlling residual tumor growth. Surgical removal of the thymus is also indicated in patients with moderate to severe MG who are less than 55 years old.

Surgical Intervention

Traditional thymectomy calls for a full sternotomy to remove the thymus. Mayo Clinic now also offers minimally invasive endoscopic surgery in which a small incision is made in the neck or chest, and the thymus is removed using a customized retractor and videoscope (Figure, on page 8). It has been most successful in younger patients.

Clinical Trials

Mayo Clinic is participating in an ongoing worldwide study funded by the National Institutes of Health to assess the relative outcomes of thymectomy versus medication for MG. Mayo

Myasthenia Gravis Signs, Symptoms, and Incidence

Definition: an autoimmune neuromuscular transmission disorder

Mechanism: T-cell-dependent, antibody-mediated deficiency of nicotinic acetylcholine receptors

Symptoms: fluctuating weakness of craniofacial, axial, respiratory, and limb muscles that increases with exertion

Incidence: approximately 14 of 100,000 adults

Types and distribution:
Ocular—typically presenting in men older than 60 years

Generalized—typically presenting in women in their 20s



Vanda A. Lennon, MD, PhD

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MC5520-0407

Clinic physicians routinely participate in multi-center drug trials, including a recently completed study on mycophenolate (Cellcept), with results to be published soon.

Team Approach

In general, MG patients are best served by an interdisciplinary team that can offer an array of treatment options and monitor effects. At Mayo Clinic, the MG team includes clinicians and researchers representing 5 disciplines who have an evidence-based group philosophy. Together they coordinate the balancing act that is MG treatment—from managing symptom exacerbation and fluctuating response to

medication, to surgical options, cancer detection and treatment, and ongoing monitoring of patient progress.

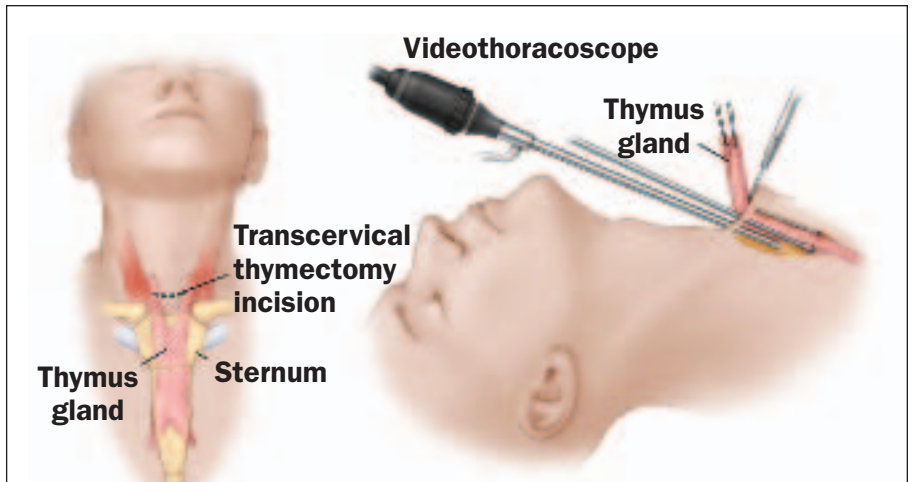


Figure. Transcervical thymectomy, a minimally invasive procedure for removing the thymus gland. A videothoracoscope, inserted through an incision in the neck, allows the surgeon to visualize and remove the thymus and perithymic tissue.

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

Mayo Clinic Departments of Neurosurgery and Neurology

Minnesota

200 First Street SW
Rochester, MN 55905
Neurosurgical Consultation
507-284-8008
Neurologic Consultation
507-284-1588
Non-Neurologic
Consultation
800-533-1564

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