MAYO CLINIC

Neurosciences Update

Neurologic Surgery and Clinical Neurology News

Vol. 6, No. 1, 2009

INSIDE THIS ISSUE

Management of Cavernous Malformations

New information and technologies have improved the management of cavernous malformations (CMs). CMs are well-circumscribed, multilobulated malformations made up of channels or caverns lined by a layer of endothelium (Figure 1). A subset of vascular malformations, they have a characteristic radiographic and pathologic appearance. Their pathogenesis is not completely understood, but the clinical presentation includes seizures of all types, hemorrhage, and acute or subacute focal deficits. They can occur anywhere in the brain—very often in the brainstem and, rarely, in the spinal cord (Figure 2).

There is a high incidence of asymptomatic CMs, which are often discovered as an incidental finding on MRI. Because the endothelial tight junctions are defective, all CMs, regardless of whether they are symptomatic, show evidence of microhemorrhages that occur over time. Overt hemorrhage is less common but can have potentially devastating and life-threatening consequences and is likely to recur in patients with a single CM-related hemorrhagic event.

Improvements in Surgery

At Mayo Clinic, surgery is recommended if the CM is symptomatic and in an accessible location. If not, the CM is observed closely until intractable seizures, repeat hemorrhage, or worsening focal symptoms develop.

The definition of "inaccessible location" has changed. "Today," notes Giuseppe Lanzino, MD, a neurosurgeon at Mayo Clinic in Rochester, Minnesota, "surgery can be done with a good degree of safety, even in areas traditionally considered inoperable such as the brainstem and thalamus." He attributes improved safety to better microscopes and optics, more sophisticated understanding of the brainstem and its surgical anatomy, and better ability to monitor cranial nerve function intraoperatively. He also points to the newer technology available at Mayo such as frameless stereotactic surgery, which has improved localization by providing real-time navigation during surgery.

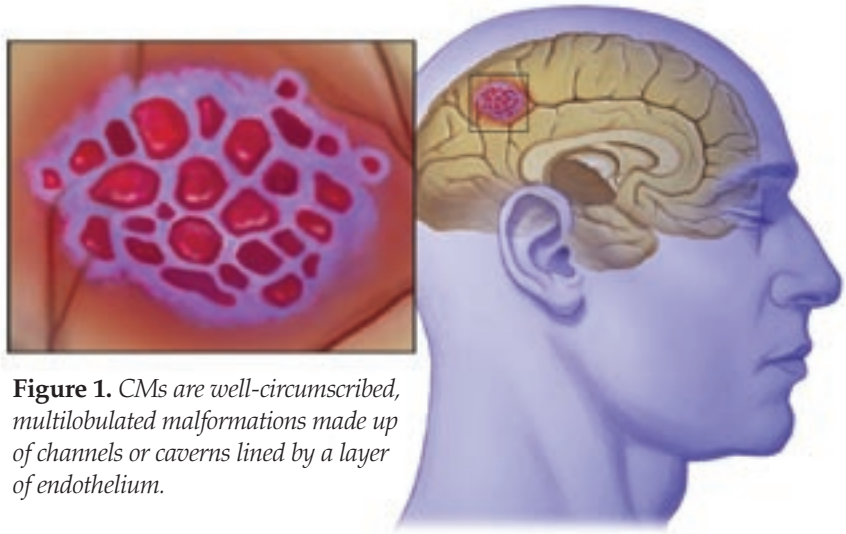


Figure 1. *CMs are well-circumscribed, multilobulated malformations made up of channels or caverns lined by a layer of endothelium.*

Improved Detection Through Advances in MRI

"Another major advance has been in MRI imaging, which has helped us understand and identify these lesions," adds Kelly D. Flemming, MD, a vascular neurologist with expertise in CMs at Mayo Clinic in Rochester. In the past decade, gradient echo imaging has helped identify CMs with greater precision (Figure 3). Most recent is susceptibility-weighted imaging, which can identify tiny CMs that conventional MRI sequencing would miss. Mayo Clinic is fortunate to have these MRI tools for several reasons, Dr Flemming says. The first is that multiple CMs may be indicative of a genetic form of the condition. The second is that, in patients with CM-related seizures, susceptibility-weighted imaging can more precisely and accurately identify the symptom-causing CM, which, if small, may have been missed on traditional MRI.

Dr Lanzino adds that at Mayo, epilepsy specialists are part of a multidisciplinary team that manages patients with a CM and seizures. They help localize the area of the brain from which the seizures arise—an area that may differ from the location of the CM. He noted, "At Mayo Clinic, we sometimes insert electrodes during surgery and

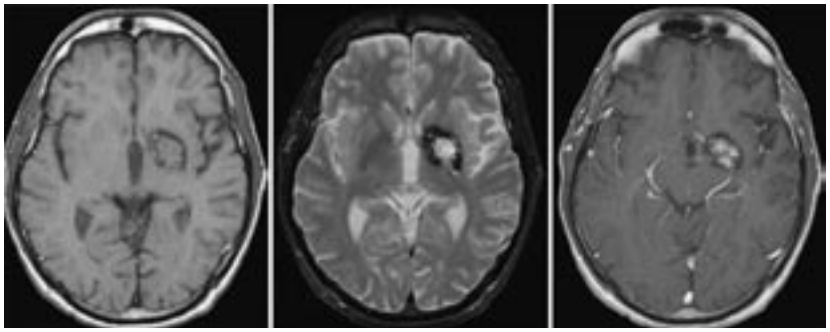


Figure 2. *MRI scans of the brain, including T1-weighted (left), T2-weighted (center), and contrast-enhanced (gadolinium) T1-weighted (right) images, reveal the typical CM appearance in the left basal ganglia. The imaging reveals a mixed density lobulated lesion reflecting the lesion behavior. The low T2 signal reflects hemosiderin, and the hyperintensity reflects acute and subacute blood.*

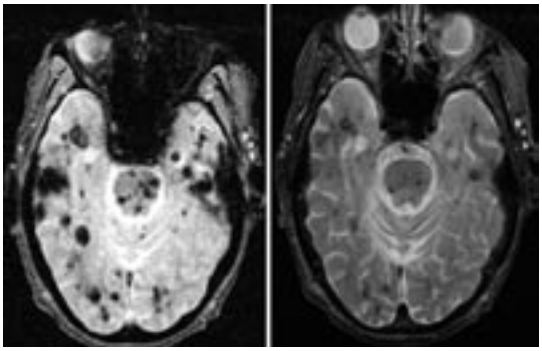


Figure 3. *MRI scans of the brain, including gradient echo sequences (left) and standard T2-weighted images (right) of a patient with multiple intracranial CMs. These images are characteristic of the familial form. The gradient echo sequence (left) allows better visualization of the individual lesions than the T2-weighted sequence (right).*

from the information transmitted can arrive at the actual source of the seizures which may or may not be the CM."

New Issues in Management and Risk Factors

In cases of a sporadic CM in which the CM has been removed, the chances of developing another lesion are rare. Thus, if removed surgically, the possibility of future CM hemorrhage is usually eliminated. Such is not the case with familial CMs.

Kelly D. Flemming, MD, and Giuseppe Lanzino, MD

Familial CMs

A familial form of the disease often causes multiple lesions (Figure 3). The genetic predisposition is particularly prominent in the Hispanic American population. Approximately 50% of Hispanic Americans with a CM have a familial form, compared with 10% to 20% of white patients with a CM. The familial form is autosomal dominant, and 4 genes have been isolated, 3 of which can be clinically tested. Mayo offers genetic counseling as well as genetic screening for patients with a suspected familial CM.

Risk of Hemorrhage

The most common predictor of future hemorrhage is prior hemorrhage. There is debate about some other risk factors. Traditionally, pregnancy and medications like aspirin or warfarin, prescribed to prevent heart attack and stroke, have been considered risk factors for hemorrhage in patients with a CM. Dr Flemming hypothesized that this may not be the case in an investigation of the natural history of CM. Begun in 1989, with 292 patients enrolled, the project is among the largest of its kind. When completed, it should help provide further guidelines for management of CM.

Advances in the Management of Spinal Cord Tumors

Performing more than 3,000 neurosurgical procedures a year, the neurosurgery practice at Mayo Clinic is one of the largest neurosurgery practices in the United States. Patients can be evaluated and treated by a team of specialists in a matter of days rather than months.

Spinal cord tumors can be broadly classified by location relative to the spinal cord and the dura mater (Figure 1). Those outside the dural sac and cord are called extradural extramedullary tumors. Those within the dural sac but exterior to the cord are called intradural extramedullary. Because of their location within the dural sac and cord, intradural intramedullary tumors were considered inoperable as recently as a decade ago. Mayo Clinic neurosurgeons were among the first to resect such tumors, and today, improved imaging and microsurgical techniques continue to advance surgery for tumors of this type.

Differential Diagnosis and Management: A Team Effort

The symptoms of spinal cord tumors vary and depend on a number of factors, including location, rate of tumor growth, involvement of skeletal structures of the spinal column, and whether the tumor is creating pressure against or invading the spinal cord or adjacent nerves. Symptoms can include numbness, tingling, pain, sensory and motor impairments, and changes in

bowel and bladder function. In children, spinal or vertebral column abnormalities such as scoliosis may be present as well.

Diagnosis can be difficult. Various conditions mimic tumors and vice versa. Possibilities include cystic formations, cavernous malformations, and dural arteriovenous fistulas. The symptoms associated with inflammatory conditions that affect the spinal cord, such as multiple sclerosis, and the nerve roots, such as chronic inflammatory demyelinating polyradiculoneuropathy, as well as viral, bacterial, or parasitic infections, and degenerative disorders of the nervous system, can also be confused with symptoms of tumor.

At Mayo Clinic, patients are usually seen first by a neurologist. "Our job is to sort out what's really going on, to decide when the neurologic disability—or threat of it—is severe enough to warrant intervention and the nature of that intervention," explains Daniel H. Lachance, MD, a neurologist at Mayo Clinic in Rochester, Minnesota. He notes, for example, that some patients may have a tumor found incidentally on an MRI, but the symptoms are caused by another process—"a situation," he says, "that requires detailed explanation to the patient." Other patients may come for treatment of a herniated disc only to find they also have a tumor. Still others may have had an attempted and nondiagnostic biopsy or other surgical intervention, or perhaps radiotherapy, yet have progressive disability with few answers as to why. "At Mayo," Dr Lachance notes, "in these difficult situations, management decisions are greatly enhanced by the collaborative approach and the depth of experience among our team members."

The diagnostic and management team typically includes specialists from neurology, neuroradiology, and neurosurgery, but may also include experts in radiation oncology, medical genetics, orthopedics, physical medicine and rehabilitation, and other specialties.

Daniel H. Lachance, MD, and William E. Krauss, MD

Mayo's High-Field Imaging

MRI is one of the best tools for detecting the presence of a spinal cord tumor (Figure 2). Yet, traditional MRI may not always distinguish the type of mass present. Mayo is one of the few institutions to have high-field 3-Tesla MRI scanning (Figure 3), which can help distinguish tumor from other types of diseased tissue and can detect smaller tumors that may be missed on traditional MRI scans.

Surgical Advances

The most common spinal cord tumors in adults are ependymomas, relatively slow-growing tumors that account for approximately 60% of intramedullary tumors and tend to occur in patients 40 to 60 years of age. Approximately 40% occur in the lower spine. "Our goal is to remove ependymomas in their entirety," says William E. Krauss, MD, a neurosurgeon at Mayo Clinic in Rochester. "Improvement in microsur-

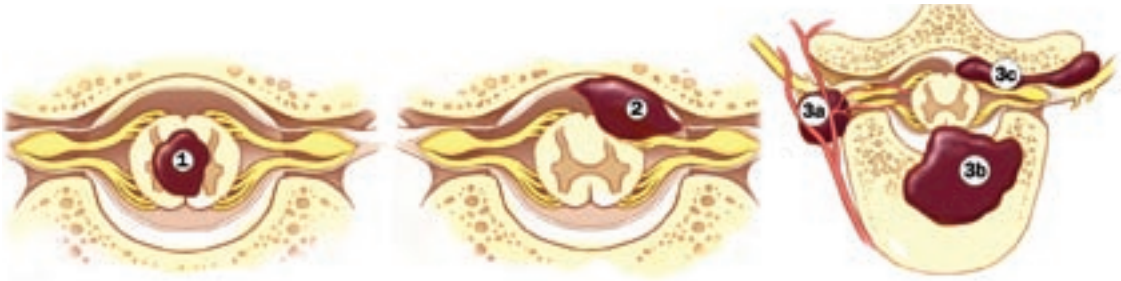


Figure 1. *Anatomic classification of spinal tumors. Intradural tumors: 1) intramedullary spinal cord tumor (usually ependymoma or astrocytoma); 2) intradural extramedullary mass lesion arising from the dura, compressing the dorsal root and cord, typical of a meningioma. Extradural tumors: 3a) paraspinal mass lesion representing a number of pathologies with the potential to compress or invade autonomic ganglia, nerve root, dorsal root ganglia, and radicular arteries; 3b) mass primarily arising from bone, invading spinal canal and compressing intraspinal structures, potentially destabilizing the vertebral column, a pattern typical of metastatic disease from a number of primary cancers, especially breast, lung, and prostate; 3c) mass invading spinal canal through the intervertebral foramen, potentially arising from nerve root as in a primary nerve sheath tumor (schwannoma), or progressing from a paraspinal mass, a pattern typical of lymphoma.*

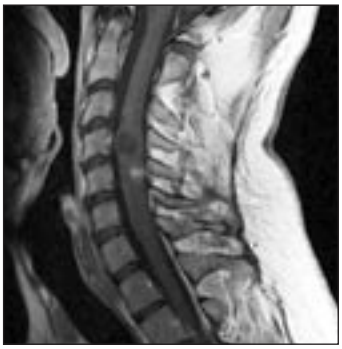


Figure 2. *MRI image of a hemangioblastoma.*

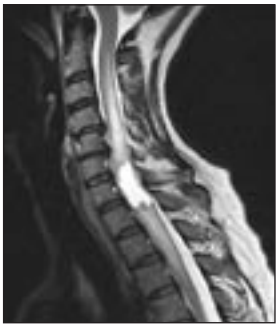


Figure 3. *Example of 3-Tesla MRI image of an astrocytoma.*

gical instrumentation and technique, combined with ultrasonic aspiration, gives us a very good success rate." If the tumor is growing rapidly or cannot be resected entirely, surgery is followed by radiotherapy.

Astrocytomas are the second most common type of intramedullary tumors in adults and the most commonly occurring type in children. Astrocytomas are typically found in the cervical and upper thoracic region of the spine. Tumors with well-defined borders may be removed surgically. Invasive tumors and those associated with progressive neurologic deterioration are usually managed through biopsy followed by radiation or stereotactic radiotherapy.

Monitoring Motor Function During Surgery

Monitoring sensory function through evoked potentials has long been a part of spinal tumor surgery. Approximately 10 years ago, Mayo began monitoring motor evoked potentials as well. As Dr Krauss explains, "The motor pathway is more difficult to monitor than the sensory pathway because measurements of motor function can be suppressed by anesthesia. The expertise of our neuroanesthesia colleagues is critical to the successful use of this technology." Monitoring motor evoked potentials has improved the ability to preserve motor function in spinal cord tumor resection.

Stabilization of the Spine

In the past, spinal tumor resection could lead to profound deformities of the spine. Today, Mayo neurosurgeons work to stabilize the spine through spinal fusion or spinal reconstruction. Dr Krauss notes, "We now have a much better knowledge of which patients are at risk for developing spinal deformities." Dr Lachance adds that many of the spinal reconstruction procedures performed at Mayo are extremely complex. The team involved in reconstruction may include surgeons from a number of subspecialties, such as orthopedic and thoracic surgery, who operate in tandem with neurosurgeons. This intraoperative collaboration is a benefit of Mayo's team approach.

Microstimulators Hold Promise for Some Medically Refractory Headaches

Occipital nerve stimulation (ONS) for medically refractory headache pain has been available since the late 1990s. Offered at all 3 Mayo Clinic sites, it is most commonly used to treat migraine and cluster headaches that do not respond to conventional medications. Mayo Clinic in Phoenix/Scottsdale, Arizona, has been involved in several studies of ONS, including work on a microstimulator that is not yet commercially available.

In traditional ONS, a thin wire containing electrodes is implanted under the skin in the back of the head. The wire extends to an implantable, battery-driven impulse generator (IPG) (Figure on page 6). Using a remote, handheld programmer, the patient controls the rate and intensity of the pulses. The pulses create paresthesias, often experienced as a light tingling or buzzing, in the area of the occipital nerve and the distal branches of the second and third cervical nerves. Although the mechanism is not entirely understood, peripheral nerve stimulation may influence deep brain centers that are responsible for pain modulation, and may gate or block pain signals from ascending from the trigeminal-cervical complex in the lower brainstem and upper cervical spinal cord.

Advantages of Microstimulators

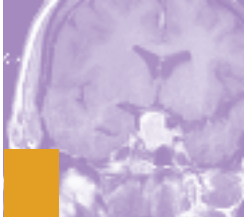
Terrence L. Trentman, MD

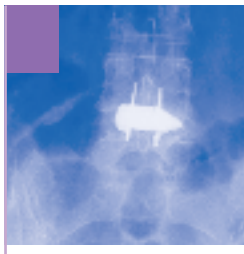
In traditional ONS, the IPG is implanted below the clavicle, in the flank, or in the lower abdomen. The wires can thus extend more than a meter from the leads to the IPG, a situation that can create mechanical stress, wire migration, and breakage.

Terrence L. Trentman, MD, former head of Mayo's Pain Clinic in Arizona, reports that "lead migration has been one of the biggest frustrations that we've experienced with the occipital stimulator. Microstimulators obviate that risk." They do so because both the electrodes and the IPG are contained within the stimulating device, which is about the size of a paperclip.

Richard S. Zimmerman, MD, a neurosurgeon at Mayo Clinic in Arizona, notes another advantage: "The microstimulator is less invasive and the surgery carries fewer risks. Traditional stimulators have long wires and require 3 incisions.

Continued on page 6





Research Highlights

Variants in a Gene on the X Chromosome Associated With Increased Susceptibility to Alzheimer Disease

Researchers at Mayo Clinic have discovered the first sex-linked susceptibility gene for late-onset Alzheimer disease. The research, published in the February 2009 issue of *Nature Genetics*, showed that women who inherited 2 copies of a variant in the *PCDH11X* gene, found on the X chromosome, are at considerably greater risk of developing Alzheimer disease.

Discovery in Perry Syndrome Suggests Common Mechanism May Underlie Many Neurodegenerative Diseases

A Mayo Clinic–led international consortium of researchers has discovered a genetic defect that results in profound depression and parkinsonism in a disorder known as Perry syndrome. Results were published in February 2009 issue of *Nature Genetics.*

Posterior Reversible Encephalopathy Syndrome in Neuromyelitis Optica Spectrum Disorders

The study shows that brain lesions in some patients with neuromyelitis optica spectrum disorder may be accompanied by vasogenic edema and manifest as posterior reversible encephalopathy syndrome. The study was published in the February 24, 2009, issue of *Neurology*.

Coronary Heart Disease Is Associated With Nonamnestic Mild Cognitive Impairment

The association of coronary heart disease (CHD) with prevalent nonamnestic mild cognitive impairment (na-MCI) but not with amnestic mild cognitive impairment suggests that CHD and na-MCI may have similar underlying etiologies. This study was published in the December 2008 issue of *Neurobiology of Aging*.

Patterns of Neuropathy and Autonomic Failure in Patients With Amyloidosis

A study published in the November 2008 issue of *Mayo Clinic Proceedings* recommends that physicians should test for symptoms of generalized autonomic failure in patients who have peripheral neuropathy of unknown origin. Early recognition of autonomic failure may lead to earlier diagnosis of the underlying pathogenesis of amyloidosis, as well as earlier treatment for patients with this condition.

Increased Cardiovascular Mortality After Early Bilateral Oophorectomy

Bilateral oophorectomy performed in patients younger than 45 years is associated with increased cardiovascular mortality, especially with cardiac mortality. However, estrogen treatment may reduce this risk. Results of this study were published in the January 2009 issue of *Menopause*.

Mayo Clinic Researchers Assess the State of Stroke Telemedicine

In the January 2009 issue of *Mayo Clinic Proceedings*, Mayo researchers document how stroke telemedicine is a lifesaving practice and note that it deserves further advancement. Since its inception, stroke telemedicine has developed nationally and internationally as a reliable means of aiding patients.

Intracranial Electroencephalography Seizure Onset Patterns and Surgical Outcomes in Nonlesional Extratemporal Epilepsy

In the December 2008 issue of *Journal of Neurosurgery*, Mayo Clinic physicians reported that the prospect of an excellent outcome in nonlesional extratemporal lobe epilepsy prior to intracranial monitoring is poor. However, intracranial EEG can further stratify patients and help identify those with a greater likelihood of Engel class I outcome after surgery.

Mayo Clinic Surgeons Find Surgical Removal of Cavernomas Leads to Excellent Epilepsy Outcomes

In the February 13, 2009, issue for *Journal of Neurosurgery*, Mayo Clinic surgeons reported that the surgical removal of cavernomas most often leads to an excellent epilepsy outcome. In cases of temporal lobe cavernomas, the more extensive the guided resection, the better the seizure outcome.

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

Microstimulators (continued from page 4)

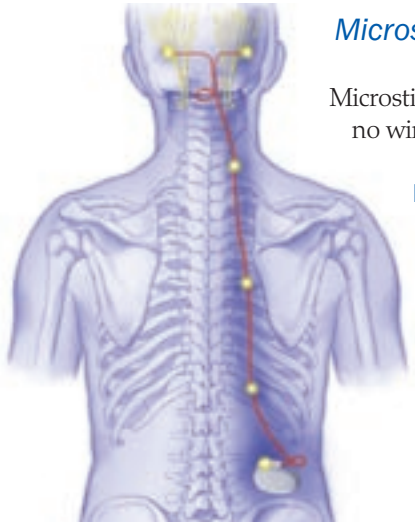


Figure. *Traditional occipital nerve stimulation system.*

Microstimulators require only 1 incision and no wires."

Patient Response to ONS at Mayo Clinic Arizona

Dr Trentman points out that ONS "is reserved for patients for whom all other treatments have failed—people who not only have chronic daily headache, but also have had continuous, severe headaches for years and have tried everything from multiple types of medication to psychological, behavioral, and alternative approaches to pain management."

Recently, Drs Trentman and Zimmerman, along with neurologist David W. Dodick, MD, and others, conducted the first test of microstimulators. In a small series of patients with medically refractory chronic cluster headache, 75% reported a positive response 3 months after implant. They have also found microstimulation to be effective in patients with hemicrania continua.

Richard S. Zimmerman, MD

ONS complications can include infection and an increase in pain. Traditional ONS is first conducted on a trial basis to screen for increased pain. Dr Dodick notes that because ONS takes time to work, patients may not experience improvement in the 5- to 7-day trial period. As long as they have no adverse effects and are amenable, they will receive the device after the trial period.

Inborn Errors of Neurometabolism: Not So Rare and Not So Untreatable

Inborn errors of cellular metabolism occur much more frequently than has been thought previously. To date, more than 1,000 inborn errors of metabolism (IEMs) have been identified, affecting approximately 1 in 1,000 Americans. IEMs may be rare individually, but taken collectively, they are common. They affect not just children, but also adults, and many of the milder forms have been underrecognized.

"All IEMs are treatable," says Marc C. Patterson, MD, chair of the Division of Child and Adolescent Neurology and an IEM specialist at Mayo Clinic in Rochester, Minnesota. Deborah L. Renaud, MD, a child neurologist and metabolic specialist who began Mayo's Neurometabolic Program, agrees. They both stress that treatment is available in all cases—whether novel, disease-modifying therapies that can affect the course of the disease or symptomatic treatments that can greatly improve quality of life for the patient and the family.

Only a handful of physicians specialize in inborn errors of neurometabolism. Two of them, Drs Patterson and Renaud, are on the staff at Mayo Clinic in Rochester.

The Nature of the Disorders

Today, hundreds of IEMs have had their genes sequenced and mapped and their gene mutations isolated. Together, IEMs represent deficiencies in the proteins that make a substance, break one down, store it, or move it around within a cell. The diseases are classified into 2 general categories—large-molecule diseases, which affect the storage of large molecules such as lipids or glycogen, and small-molecule diseases, which affect energy metabolism, protein synthesis, the production of organic acids, and/or the urea cycle.

Neurologic Symptoms

Errors exist on a continuum of severity—from benign to life-threatening. The neurologic effects of IEMs can include seizures, ataxia, muscle disease, sensory impairments, dysarthria, cataplexy, global cognitive impairment, and dementia. Patients may develop normally, then development plateaus and rapidly deteriorates, and they lose developmental milestones. This can occur from early childhood into adulthood. Some never attain developmental milestones and succumb to illness in the first year of life. The key is variability, and diagnosis may be difficult unless the child is evaluated over a period of time.

One way to recognize a metabolic syndrome is the complexity of the neurologic symptoms such as developmental delay, with seizures, psychiatric symptoms, movement disorders, and other symptoms. Another way is to recognize the involvement of multiple organs such as the brain, heart, liver, and muscles.

Equally important, metabolic errors may not become symptomatic until mid to late adulthood. Symptoms may be subtle and slowly progressive. For example, one of Dr Patterson's patients noted subtle problems with balance following pregnancy and a slow deterioration in neurologic function leading to diagnosis at the age of 65 years. As Dr Patterson states,"There are quite a number of adults with undiagnosed metabolic disorders. It is not often recognized that certain IEMs can present with dementia mimicking more common disorders such as Alzheimer disease."

Early Detection: Mayo's Biochemical Genetics Laboratory

Newborn screenings for IEMs began in 1964 with screening for phenylketonuria, a condition with neurologic consequences that is treatable through diet. Since then, approximately 50 other diseases have been added to the newborn screening panel. Dr Renaud points out that early diagnosis can help prevent permanent neurologic damage. To do so, she adds, samples must be analyzed by a reliable, world-class laboratory.

Mayo Clinic's Biochemical Genetics Laboratory, under the codirection of Piero Rinaldo, MD, PhD, does all the newborn screens for Minnesota and is a reference laboratory for biochemical genetics, analyzing fluid and tissue samples from major medical centers worldwide. Results typically provide more extensive interpretation for the clinician than do those from a clinical chemistry laboratory. Working closely with clinicians, Mayo's Clinical Biochemical Genetics team is involved in every step of evaluation, education, and treatment monitoring.

Redefining Treatment: Curative, Disease-Modifying, and Symptomatic Management

Dr Patterson emphasizes a new mindset regarding treatment of IEMs. For too long, he says, they have been approached with a degree of therapeutic nihilism."It is a big burden of disease, but all patients are treatable. There are specific and nonspecific treatment options for every affected child and adult, making their lives better and in some cases curing the disease."

Specific Treatment

Dr Renaud cites the example of a condition called X-linked adrenoleukodystrophy. The condition can generate adrenal insufficiency at any age, with neurologic symptoms occurring in approximately 80% of affected males and up to 50% of female carriers. There is an adult-onset form called adrenomyeloneuropathy, but for many between the ages of 3 and 10 years, the natural course of the disease is the onset of blindness, loss of all developmental skills, severe disability, and death."We now know that bone marrow transplantation at the onset of neurologic symptoms can arrest the early-onset form of the disease. So treatment can be curative if the condition is caught early enough," states Dr Renaud.

Marc C. Patterson, MD, and Deborah L. Renaud, MD

Bone marrow transplantation carries risks at any age, but is particularly risky in young children. Thus, to better determine if and when to intervene, Dr Renaud and colleagues have created 2 initiatives. The first is a disease registry to follow families in which the late-onset form has been diagnosed in 1 member. The second, a multi-institutional program, is developing a newborn screening test so that boys with the diagnosis at birth can be followed prospectively. Monitoring changes in neuropsychological, ophthalmologic, and MRI test results affords the greatest chance of detecting neurologic symptoms early enough to arrest the disease.

New Treatment for Niemann-Pick C Disease

Dr Patterson and colleagues recently evaluated a novel therapy for Niemann-Pick C disease, an inherited neurodegenerative disease caused by an intracellular lipid-trafficking defect. The disease can present at any age—from before birth to late middle age. The treatment improved or stabilized swallowing capacity, auditory acuity, and ambulation in a significant number of patients aged 12 years or older (see *Lancet Neurology* 2007;6:765-72). Studies of long-term outcomes are under way.

Symptomatic Treatment

Dr Renaud notes that often in small-molecule diseases, something as simple as adding a specific vitamin or changing the diet can alter disease trajectory. Dr Patterson adds that treating seemingly unrelated physical symptoms can often improve neurologic function. For example, patients with something as correctable as constipation may experience a decrease in seizure activity and spasticity when they participate in a bowel management program. Education is another key factor. Families may have the correct diagnosis, but without explanation of "what having a missing piece of the chromosome means relative to symptoms like seizures," says Dr Patterson.

Mayo's program is focused on providing all that patients and families need, including a multidisciplinary team of specialists who provide coordinated care and are involved in every step of evaluation and management.

Mayo Clinic Neurosciences Update

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CME Opportunities

Clinical Autonomic Quantitation Workshop – May 16-17, 2009
This course will focus primarily on the 3 autonomic function tests that have CPT codes. The program will integrate 3 specific aims beginning with a series of lectures on the underlying physiology, patient preparation, indications for autonomic testing, and factors that affect the results and HCFA requirements. There will also be a demonstration of specific autonomic function tests, including the quantitative sudomotor axon reflect test (QSART), tests of cardiovagal function (heart rate response to deep breathing and the Valsalva maneuver), and tests of the adrenergic function.
Location: Mayo Clinic, Rochester, MN
Contact: (800) 323-2688 or cme@mayo.edu

Neurology in Clinical Practice – July 16-18, 2009
This comprehensive 3-day course is directed at practitioners who see a broad range of patients with neurologic disorders. The course is intended to provide a review of neurology with an emphasis on case-based presentations, recent advances, and evidence-based approaches.
Location: InterContinental, Chicago, IL
Contact: (800) 323-2688 or cme@mayo.edu

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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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