MAYO CLINIC

NeurosciencesUpdate

Neurologic Surgery and Clinical Neurology News

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INSIDE THIS ISSUE

Reaching Remote Tumors: Endoscopic Neurosurgery at Mayo Clinic

One of the biggest advances in neurosurgery over the past decade has been the development of endoscopic techniques for treating tumors in the skull base and brain. Lesions that formerly required craniotomy and brain retraction are now being accessed directly via natural pathways through the nose and sinuses. All three Mayo Clinic campuses have surgeons who are experienced with these endoscopic techniques and are using them in an increasing number of cases.

"All of our pituitary adenomas are now treated endoscopically. We are able to visualize areas of the sella we couldn't see before, which makes a complete resection more likely," says Naresh P. Patel, M.D., a neurosurgeon at Mayo Clinic in Phoenix, Ariz.

Other tumors treated endoscopically at Mayo include meningiomas, clival chordomas, nasal tumors, chondrosarcomas and craniopharyngiomas, as well as lymphomas and melanomas. "Endoscopic surgery, especially for extradural central skull base tumors, has essentially replaced or eliminated some of the very extensive and at times disfiguring transfacial approaches previously necessary," says Michael J. Link, M.D., a neurosurgeon at Mayo Clinic in Rochester, Minn.

A specialized skull base team comprising a neurosurgeon and an otolaryngologist work together during endoscopic procedures, supported by neuroradiologists and interventional neuroradiologists. "That combined expertise is necessary to offer our patients the best possible results in terms of reducing morbidities as well as optimizing the outcome from the operation," says Devyani Lal, M.D., an otolaryngologist and endoscopic skull base surgeon at Mayo in Arizona.

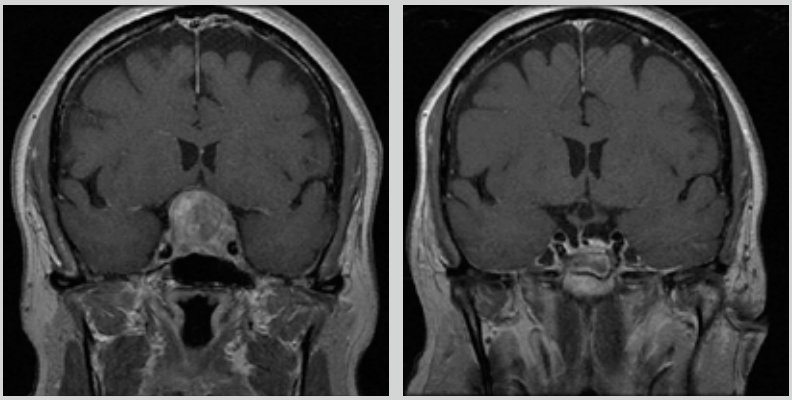

Figure. *MRI scans from a 64-year-old woman presenting with a history of progressive bitemporal vision loss. On the left, a preoperative coronal MRI demonstrates a large pituitary tumor with suprasellar extension. The optic chiasm is markedly compressed, and tumor is abutting the bilateral carotid arteries. On the right, postoperative coronal MRI after endoscopic surgery demonstrates complete resection of the tumor. The optic chiasm is well decompressed, and the pituitary stalk is intact. Packing is visible in the sphenoid sinus below the sella.*

Advantages over microscopic surgery

The proximity of certain skull base tumors to vital neurovascular structures increases the risk of morbidities arising from surgical removal. Although microscopic surgery has been the gold standard, for certain skull base lesions an endoscopic approach is less invasive and offers important advantages, particularly in visualizing tumors.

Unlike the microscope, which focuses light narrowly on the tumor, the endoscope works


Naresh P. Patel, M.D.


Devyani Lal, M.D.


Rabih G. Tawk, M.D.

more like a flashlight, focusing light outward. "With the microscope, it's like looking through a keyhole in a door. You have a very narrow, straight-on view," says Rabih G. Tawk, M.D., a neurosurgeon at Mayo Clinic in Jacksonville, Fla. "The endoscope brings your eye right next to the tumor."

Various endoscopes offer differing angles of vision, which is particularly helpful for resection of hormone-secreting pituitary tumors. "Achieving remission requires removing the hormone-secreting portion of the tumor, which may be hidden somewhere in a corner of the sella," Dr. Patel notes. "Sometimes, we can angle a microscope a bit to see more superiorly or inferiorly, but it's very difficult to see farther off to the left or the right. The endoscope actually can be advanced into the sella after some of the tumor has been removed. The visualization is incredible."

Endoscopic surgery also can be used to treat tumors, such as esthesioneuroblastoma, that extend to the anterior skull base. "With the endoscope you can look up toward the skull base and resect the bone, the tumor and the dura — which can be invaded by tumor — and even take out tumor that's abutting the brain," Dr. Patel says.

The endoscope can also provide visualization downward into the spine, giving surgeons access to lesions of the clivus and C1 or C2 areas. Another advantage is that it can help the surgeon find and repair a CSF leak, which can occur after removal of a large skull base tumor.

A number of technological advances have enhanced endoscopic surgery techniques. Improvements in light intensity and delivery systems, as well as the advent of high-definition imaging, allow better visualization of deep operative cavities. The development of better surgical tools is rendering surgical resection safer and more effective; the use of image guidance allows surgeons to pinpoint tumor location when the patient's anatomy is abnormal or distorted by the tumor. "We can now accurately know our proximity to adjacent structures beyond our visible fields," Dr. Tawk says. "The use of intraoperative CT and MRI also provides great feedback while the patient is still undergoing surgery."

This enhanced visualization and access to tumors can provide oncologically sound resection with negative margins while avoiding a large open craniotomy and brain retraction. "The endoscopic approach does not compromise oncologic resection for decreased morbidity and cosmesis," Dr. Lal says. She notes that early results from multiple centers are encouraging, although long-term follow-up data are awaited.

Help with the learning curve

Unlike the microscope, most endoscopes provide only a 2-D view, although 3-D endoscopes are being developed. "You lose depth perception, so there is a learning curve associated with endoscopic skull base surgery," Dr. Tawk says. "But once you acquire experience, you can overcome this limitation."

Mayo in Arizona offers an annual course in endoscopic sinus and skull base surgery. Guided by international faculty, participants learn endonasal surgery techniques and practice in a cadaver laboratory. Dr. Lal directs the four-day course.

"Once a neurosurgeon sees that endoscopic view, it's very difficult to go back to the microscope," she says. "With the endoscope you do a better resection, and your postoperative reconstruction work is much tighter. That panoramic view really affects the results you obtain from resection of these tumors."

Concussion: Mayo's Multidisciplinary Approach

Few neurologic conditions have sparked as much public discussion as concussion. Injuries sustained by professional athletes and U.S. soldiers in combat zones have focused attention on the long-term effects of repetitive concussive injury. Once dismissed as "just having your bell rung," concussion is the focus of a multidisciplinary group of physicians at Mayo Clinic who provide enhanced treatment for patients as well as research the role of concussion in age-related neurodegenerative disease.

"Our practice has always considered concussion for what it is — a traumatic brain injury along the spectrum of injury severity and mechanism," says Allen W. Brown, M.D., a physiatrist at Mayo Clinic in Rochester, Minn., who specializes in rehabilitation after acquired brain disorders.

The integrated approach, which is pursued at all three Mayo campuses, is especially appropriate for concussive traumatic brain injury because symptoms vary widely among individuals and span the fields of neurology, physiatry, psychiatry and psychology. "Concussion must be approached from every angle," says Bradley F. Boeve, M.D., a neurologist at Mayo in Min-

nesota. "Just treating headache or memory problems does not treat the whole patient. That is the value of a multidisciplinary program."

Recognizing what patients need

The vast majority of traumatic brain injuries — an estimated 70 to 90 percent — are mild or concussive. Although Mayo physicians treat soldiers and professional athletes, most of the practice consists of patients who suffer concussion from routine work- and sports-related injuries. Concussion doesn't always involve loss of consciousness or post-traumatic amnesia, and neurologic imaging is typically normal. Thus, concussion is a clinical diagnosis, with headache the most common symptom. Other symptoms include dizziness, nausea, vomiting, balance problems, mood changes, and difficulty with concentration and memory.

For most patients these symptoms ease with rest, limited activity and symptom management. But patients whose symptoms persist for weeks or months can benefit from rehabilitative intervention. At Mayo, a comprehensive evaluation — which may include behavioral neurologic testing, orthopedic consultation for physical injuries, and psychological assessment — is often pre-scheduled based on the individual patient's needs. Afterward, a document is prepared that summarizes the team's recommendations for follow-up care at Mayo or in the patient's community.

Psychological evaluation is a key component of Mayo's treatment model. "Just as important as the intricacies of the brain injury, is who the injury happened to," notes Thomas Bergquist, Ph.D., L.P., a clinical neuropsychologist at Mayo in Minnesota. A variety of psychological and environmental factors are known to influence recovery after brain injury. As just one example, Dr. Bergquist says, "patients' personality styles can drive their symptomatic complaints. A patient with concussion who perceives his or her circumstances as more stressful is going to present in a different manner from someone who isn't wired that way." For patients with persistent symptoms who are experiencing their situations as highly stressful, cognitive behavioral therapy can decrease negative thinking and significantly improve quality of life.

Unraveling controversies associated with concussion

For physicians, one of the biggest challenges is advising patients about the long-term effects of concussion and about when it's safe to return to play or to work. Second impact syndrome, a complication that arises when a patient recovering from an initial concussion sustains a subsequent concussive injury, "dramatically increases the chances of some permanence to the brain injury," Dr. Boeve says.

Repetitive injuries have been implicated as contributing to the neurobehavioral symptoms of retired professional athletes who are diagnosed postmortem with chronic traumatic encephalopathy (CTE), a condition characterized by degeneration of brain tissue and accumulation of tau and other proteins. But Dr. Boeve notes that many former athletes show no symptoms of CTE or any other neurologic disorder. In an article published in the April 2012 edition of *Mayo Clinic Proceedings*, Mayo neurologists compared the medical records of male students in Rochester who played high school football between 1945 and 1956 with non-football-playing male students from the same schools and time period. The study found no increased risk of developing dementia, Parkinson's disease or amyotrophic lateral sclerosis for the former football players.

"Yet this was in the era of leather helmets with no face masks, less regard for concussion and no rules against 'spearing' or head-first tackling," Dr. Boeve says. "There's little doubt that repeated injuries to the head aren't good for you. But when are they clearly bad for you? In other words, why is it that some people have neuropsychiatric problems years later after head injuries while others do not? These are important scientific and societal questions for which we do not have answers yet."

Possible factors may include the nature of the injury, the cumulative number and severity of the injuries, a person's genetic predisposition, other medical co-factors, and injuries that occur outside of sports or a job. "Because abnormal tau protein deposition is a key feature of CTE, it makes sense that the tau haplotype or some other variants in the tau gene, or other genetic or environmental factors that affect the dynamics of tau deposition and clearance in the brain, have some play," Dr. Boeve says. "But TDP-43 deposition is also relatively common in CTE, and this protein is likely involved in inflammation or response to neuronal injury, or both. Also, there may be some other proteins that we don't even know about yet."

Documenting the incidence of traumatic brain injury

Few objective estimates of the incidence of traumatic brain injury include all ages and injury mechanisms, both sexes and the full spectrum of events, from very mild to fatal. But in a study published in the November 2011 issue of

Allen W. Brown, M.D.

Bradley F. Boeve, M.D.

Thomas Bergquist, Ph.D., L.P.

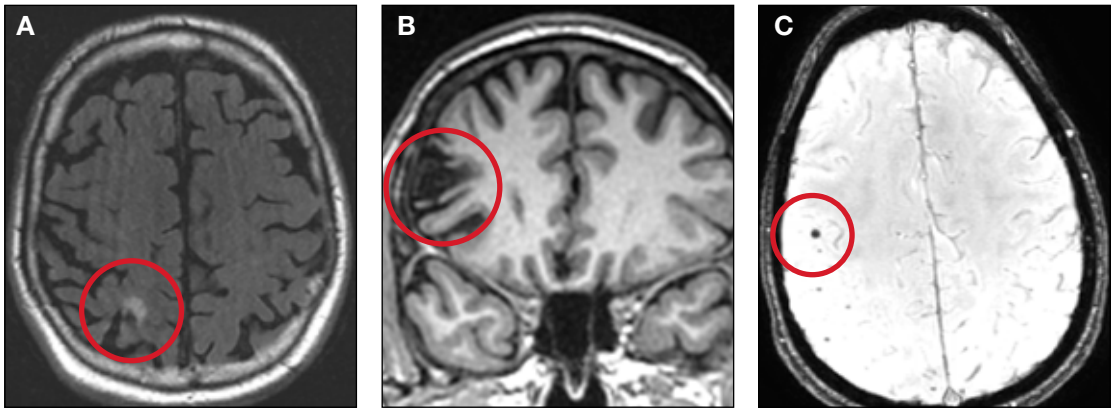

Figure. ***A****, MRI showing contusion in right parietal cortex associated with prior traumatic brain injury.* ***B****, MRI showing encephalomalacia in right frontal cortex associated with prior traumatic brain injury.* ***C****, MRI showing hemosiderin deposition indicative of prior hemorrhage.*

Epidemiology, Dr. Brown and colleagues documented an incidence rate of 558 traumatic brain injuries per 100,000 person-years in Olmsted County, Minn., from 1987 to 2000. Among the 1,257 medical records reviewed, 56 percent of cases were male and 53 percent of cases were symptomatic. Mayo researchers also developed the Mayo Classification System for TBI Severity, which captures a larger number of cases than single-indicator systems.

In this research, as well as in clinical care, Mayo's integrated approach is essential. "Every individual who experiences a concussive traumatic brain injury has a unique genetic background, set of psychosocial circumstances and clinical problems. Consideration of these characteristics is the key driver of efficient medical evaluation and effective management," Dr. Brown says. "At Mayo Clinic we customize the approach to remain focused on the needs of our patients and their families."

For more information

Savica R, et al. High school football and risk of neurodegeneration: A community-based study. *Mayo Clinic Proceedings*. 2012;87:335.

Leibson CL, et al. Incidence of traumatic brain injury across the full disease spectrum: A population-based medical record review study. *Epidemiology*. 2011;22:836.

Malec JF, et al. The Mayo Classification System For Traumatic Brain Injury Severity. *Journal of Neurotrauma*. 2007;24:1417.

Uncovering Genetic Causes of Epilepsy

Epilepsy affects about 2.4 million Americans. Roughly 70 percent of cases are idiopathic, although a genetic basis is strongly suspected in most of them. The Epilepsy Phenome/Genome Project (EPGP), one of the largest epilepsy research studies ever attempted, seeks to understand the pathophysiology and clinical expression of idiopathic epileptic syndromes. All three Mayo Clinic campuses are among the 29 centers participating in this international study, which is funded by the National Institutes of Health through the National Institute of Neurological Disorders and Stroke.

The study involves collecting detailed phenotypic information from patients with idiopathic or genetically based epilepsy. State-of-the-art bioinformatics will then be used to identify the potential contribution of genomic and somatic variability to the epilepsy phenotype, to developmental anomalies of the central nervous system and to the varied therapeutic responses of patients treated with anti-epilepsy medications.

About 4,200 patients are enrolled in the study, including 320 at Mayo Clinic in Rochester, Minn. Although some of them were Mayo patients, many others were sent by physicians

throughout the U.S. who learned about the study. "We have finished the patient enrollment and are now gathering information and doing the analysis," says Gregory D. Cascino, M.D., a neurologist who is the primary EPGP investigator at Mayo in Minnesota. "We're already beginning to analyze patterns, but the process may take several years."

Two types of patients were enrolled in the study:

- Patients with idiopathic epilepsy who have a first-degree relative with epilepsy.
- Patients with diagnoses of epilepsies that have a strong genetic predisposition, including infantile spasms, Lennox-Gastaut syndrome, periventricular nodular heterotopia or polymicrogyria. Patients in this group were required to have both parents available to provide blood samples and complete a questionnaire.

In addition to providing blood samples, all study participants are undergoing EEG, MRI and diagnostic interviews. Patients' medical records from Mayo or other centers also are being reviewed. "The purpose of the study is to identify genes involved in genetically determined epilepsies, to help with diagnosis and to understand the clinical manifestations," Dr. Cascino says. The researchers also hope to discover if certain genetic factors may indicate that a patient's epilepsy is more likely to be medically refractory.

This type of genetic information is important to family members after a diagnosis of epilepsy. "Families are interested in knowing not only about treatment options, but also the possible cause of epilepsy," Dr. Cascino says. "They want to understand the likelihood of developing seizures themselves or of passing a seizure disorder on to their offspring."

Prospective study on prognosis

Mayo Clinic in Minnesota also is participating in the Human Epilepsy Project, a planned multicenter, prospective study of patients with newly diagnosed focal epilepsy. Although enrollment hasn't yet begun, participants in this study must be between the ages of 12 and 60, must have had all seizures within the past two years and at least two seizures in the previous 12 months, and must have been on seizure medication for less than four months. Patients will be followed for a minimum of three years. The study's primary goal is to identify clinical characteristics and biomarkers predictive of disease outcome and progression, as well as treatment response.

"We hope to learn what we can about the prognosis for these newly diagnosed patients, as well as which anti-epilepsy medications are effective and which cause side effects," Dr. Cascino says. "This is a very exciting project because the number of new epilepsy diagnoses in the United States is conservatively estimated at 200,000 a year, and very little is known about prognostic factors."

This participation in international, multicenter research studies is possible because Mayo has extensive experience with epilepsy as well as the resources to conduct EEG and MRI according to highly specific research protocols. Notes Dr. Cascino: "As a major comprehensive epilepsy program, Mayo is available not only for patient care but also for cutting-edge research."

Gregory D. Cascino, M.D.

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Neurosciences Research

Research Highlights in Neurology and Neurologic Surgery

Interaction of Beta-Amyloid and Brain Injury Biomarkers in Neurodegeneration

The appearance of beta-amyloid and brain injury biomarkers in cognitively normal people each confers risk of the future development of cognitive impairment due to Alzheimer's disease (AD). But the interaction of these biomarkers is poorly understood. In a study of 191 participants in the Mayo Clinic Study of Aging, researchers at Mayo Clinic in Rochester, Minn., found that higher rates of hippocampal volume loss occurred in cognitively normal individuals who had abnormal levels of both beta-amyloid and brain injury biomarkers, compared with other cognitively normal study participants with only one or no abnormal biomarker classes. The study participants, who were cognitively normal, underwent MRI, fluorodeoxyglucose (FDG) PET and PiB-PET imaging at least twice over a period greater than one year. The participants were then grouped according to preclinical AD criteria. The researchers also included 26 patients with mild cognitive impairment or dementia from the Mayo Clinic Study of Aging or the Mayo Alzheimer's Disease Research Center who underwent comparable imaging and had beta-amyloidosis. Among the cognitively normal study participants, 25 had both high PiB retention and low hippocampal volume or FDG hypometabolism — a biomarker of AD-related synaptic dysfunction. The rate of hippocampal volume loss for these participants was greater than that of other cognitively normal participants, and comparable to the level of participants with mild cognitive impairment or dementia due to AD. (Knopman D, et al. Acceleration of brain injury biomarker abnormalities in cognitively normal elderly with beta-amyloidosis. Presentation at: American Academy of Neurology Annual Meeting; 2013; San Diego, Calif.)

RBD Associated With Reduced Alzheimer's Pathology

Rapid eye movement (REM) Sleep Behavior Disorder (RBD) is characterized by coordinated motor behavior during REM sleep with accompanying loss of muscle atonia. RBD is a suggestive feature of dementia with Lewy bodies (DLB), along with cognitive impairment and three core features: parkinsonism, fluctuating cognition and visual hallucinations. Patients with Lewy body-related neuropathology at autopsy often have concomitant Alzheimer's disease pathology, which is associated with hippocampal atrophy on MRI. In a post-mortem study, researchers at Mayo Clinic in Jacksonville, Fla., and Rochester, Minn., found that the presence of probable RBD is associated with less severe Alzheimer's pathology and Alzheimer's-like atrophy in low-to-high likelihood DLB. The researchers identified 75 consecutive low-to-high-likelihood, autopsy-confirmed DLB cases — 35 with probable RBD and 40 without probable RBD — from patients who had undergone antemortem MRI at the Mayo Clinic Alzheimer's Disease Research Center. On post-mortem examination, pathologic burden of markers for AD (hyperphosphorylated neurofibrillary-tau, alpha-synuclein and beta-amyloid) from the hippocampus was quantified, along with hippocampal volumes. The results showed lower hippocampal neurofibrillary-tau and beta-amyloid burden, and larger hippocampal and parietotemporal cortical volumes in cases with a history of probable RBD, compared with those without a history of probable RBD. Further analysis indicated that a history of probable RBD increased the odds of predicting pathology associated with DLB likelihood. Parkinsonism approached significance in a model with hippocampal volume and probable RBD, but not fluctuations or visual hallucinations. The study results suggest the presence of RBD is a stronger predictor of DLB likelihood than the currently established core features. (Murray M, et al. Hippocampal and parietotemporal atrophy in dementia with Lewy bodies. Presentation at: American Academy of Neurology Annual Meeting; 2013; San Diego, Calif.)

Long-Term Effects of Therapeutic Hypothermia on Cognitive Function

Therapeutic hypothermia has been shown to improve neurologic outcome after out-of-hospital cardiac arrest due to ventricular fibrillation. Most studies of comatose survivors of cardiac arrest focus on mortality or functional outcome based on physical limitations. Researchers at Mayo Clinic in Rochester, Minn., studied the long-term cognitive abilities of patients who received therapeutic hypothermia after surviving cardiac arrest. The medical records of cardiac arrest survivors who underwent therapeutic hypothermia from June 2006 to Mayo 2011 were reviewed. The results of brain imaging, serum neuron-specific enolase measurements and EEG were recorded. Of the 133 patients identified, 77 (58 percent) were alive at mean follow-up of 21 months. Median age was 67 years. The researchers also interviewed 56 patients (73 percent of those alive) using the Telephone Interview for Cognitive Status. Among those patients, 33 (60 percent) were considered cognitively normal and 22 (40 percent) were cognitively impaired. Of the 38 patients who were working at the time of their cardiac arrest, 30 (79 percent) had returned to work. Cognitive outcome was not associated with age, time to return of spontaneous circulation, brain atrophy, leukoaraiosis or neuron-specific enolase level. (Moore S, et al. Cognitive outcomes of patients undergoing therapeutic hypothermia after out-of-hospital cardiac arrest. Presentation at: American Academy of Neurology Annual Meeting; 2013; San Diego, Calif.)

Risk Factors for Parkinson's Differ in Men and Women

Although several environmental and genetic risk or protective factors have been associated with Parkinson's disease, their interactions overall and separately in men and women remain undefined. In a retrospective study of 196 patients with Parkinson's, researchers at Mayo Clinic in Rochester, Minn., found differences between men and women in risk factors for the disease. The medical records of patients who developed Parkinson's in Olmsted County, Minn., from 1976 through 1995 were reviewed. Each case was matched by age and sex to a general population control. The researchers considered 12 risk or protective factors: personal history of head trauma; pesticide use; immunological diseases; anemia; hysterectomy, in women only; cigarette smoking; coffee consumption; education; and family history of parkinsonism, essential tremor, dementia or psychiatric disorders. The data were analyzed to explore interactions overall and in men and women separately. In the overall group, the researchers noted the independent effects of anemia, lack of coffee consumption and head trauma on the development of Parkinson's. But the results differed between men and women. In men, the researchers found an independent effect of lack of coffee consumption, head trauma and pesticide use, as well as a suggestive synergistic interaction between immunological diseases and family history of dementia. By contrast, in women, anemia was the most important factor. A suggestive synergistic interaction between anemia and higher education also was noted in women. (Savica R, et al. Risk factors for Parkinson's disease differ in men and women. Presentation at: American Academy of Neurology Annual Meeting; 2013; San Diego, Calif.)

Myotonic Discharges Help Detect Myotonic Dystrophy Type 2

Patients with myotonic dystrophy type 2 (DM2) often present with proximal weakness and pain but do not have clinical evidence of myotonia. When the physical examination is unremarkable, the diagnosis of DM2 may not be considered. In a retrospective study of 43 cases from 1993 to 2012, researchers at Mayo Clinic in Phoenix, Ariz., found that EMG evidence of myotonic discharges facilitates the diagnosis of DM2. Medical records with diagnostic codes associated with myotonic discharges or myotonic dystrophy were reviewed for clinical information. Of the 43 patients identified with those codes, six (14 percent) were initially determined on the basis of clinical information not to have a myotonic disorder, but ultimately were diagnosed with DM2. On initial clinical exam, most patients in this group (67 percent) reported weakness with no objective strength deficit. Other symptoms included pain, numbness, restless legs syndrome and gait difficulty. All six patients had profuse myotonic discharges on EMG. Three patients (50 percent) were initially misdiagnosed with fibrillation potentials or increased insertional activity on EMG. The average time from onset of symptoms to diagnosis of DM2 was 6.4 years. The researchers note that early diagnosis of DM2 — facilitated by EMG evidence — may improve patient education, reduce evaluations and provide the opportunity for therapy. (Hlubocky A, et al. Myotonic discharges help detect clinically unsuspected myotonic dystrophy, type 2. Presentation at: American Academy of Neurology Annual Meeting; 2013; San Diego, Calif.)

Risk Factors for First Clinical Event After RIS

Radiologically isolated syndrome (RIS) is defined as MRI findings suggestive of multiple sclerosis (MS) in people without typical MS symptoms and with otherwise normal neurologic findings. A multinational consensus on the risk factors for progression from RIS to a first clinical event has not been achieved. In an international retrospective study, researchers from Mayo Clinic in Phoenix, Ariz., and elsewhere identified age, family history of MS and the presence of spinal lesions as significant predictors of a first clinical event. RIS subjects from 15 databases in four countries (the U.S., France, Turkey and Italy) were identified and prospectively followed. Comprehensive data were available in 375 RIS patients. The time from RIS finding to the first clinical event was compared across different groups. The mean clinical follow-up time was 4.6 years. Among the cases studied, a spinal cord lesion was observed in 38.7 percent; CSF profiles were abnormal in 40.9 percent; and a positive family history for MS was present in 9.9 percent. The mean age at RIS diagnosis was 37.1 years. The findings support previous evidence that the risk of progression from RIS to MS is predicated on the presence of established parameters in MS. Future directions for research involve worldwide, standardized efforts to capture prospective clinical and radiological data and strategies. (Okuda D, et al. Radiologically isolated syndrome: Five-year risk for an initial clinical event from a multinational cohort. Presentation at: American Academy of Neurology Annual Meeting; 2013; San Diego, Calif.)

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February
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March
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April
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May
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May 3-5, 2013
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May 17-19, 2013
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June
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July
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September
Stroke and Cerebrovascular Disease Review
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Nov. 11-15, 2013
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