ALS: Genetic Discoveries, Hope for Treatment

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig’s disease, is a rapidly progressive neurodegenerative disease. There is no treatment, and ALS is almost always fatal within three to five years of diagnosis. Recent discoveries about the genetic basis of the disease—including the identification by researchers at Mayo Clinic in Jacksonville, Florida, of a repeat expansion in the C9ORF72 gene (Figure 1)—as well as novel stem cell therapies offer new paths for developing treatments.

“What makes the chromosome 9 finding so exciting is that it helps explain a relatively large percentage of patients who have ALS,” says Rosa Rademakers, Ph.D., who directs the Frontotemporal Dementia and Related Disorders Laboratory at Mayo Clinic’s campus in Florida. “If therapies can be developed based on this finding, then a significant group of patients can be helped.”

At Mayo Clinic in Rochester, Minnesota, researchers are conducting a clinical trial of stem cell therapy for ALS. Although the safety trial appears to be progressing well, efficacy hasn’t yet been measured.

“I am optimistic about stem cell therapy; it is one of the more promising approaches we have right now for ALS,” says Nathan P. Staff, M.D., Ph.D., a consultant in the Department of Neurology at Mayo Clinic’s campus in Minnesota. “However, in contrast to the explosion of progress in the science behind what causes ALS, treatment strategies remain much more challenging.”

Clumps of RNA

The C9ORF72 repeat expression is an unusual mutation. “This piece of RNA consists of six base pairs that, in normal individuals, are repeated three or four times. Individuals with the mutation have hundreds or thousands of repeated copies,” Dr. Rademakers says. “These large aggregates of RNA form clumps in the nucleus of cells. The clumps attract other binding proteins and as a result, the cell is misregulated.”

The mutation is present in about 30 percent of people with familial ALS and 5 percent of sporadic ALS cases—as well as in 25 percent of people with familial frontotemporal dementia (FTD). “Increasingly, we realize that ALS and FTD may be two ends of a spectrum,” Dr. Rademakers says. “A fair number of patients with ALS have symptoms of FTD, and vice versa. In post-mortem studies, we see the same disease protein deposited in the brains of people with FTD and spinal cords of people with ALS.”

The clinical manifestations of the C9ORF72 mutation are correspondingly diverse. “Patients can present with memory problems and receive a diagnosis of Alzheimer’s disease. Or they might undergo personality changes and have a diagnosis of bipolar disorder,” Dr. Rademakers says. “The age of disease onset also varies. There are even individuals who live into their 70s and never develop symptoms.”

These variations suggest that unknown modifying factors are at work. “We are very interested in identifying the genetic modifying factors that can determine whether someone gets ALS or FTD, and at an earlier or later age,” Dr. Rademakers says. Current efforts focus on whether known genetic risk factors for FTD and ALS—for example, the ATXN2 mutation associated with ALS—may be responsible for determining when and if people with the C9ORF72 mutation develop disease, and which disease they develop.

Figure 1. Fluorescence in situ hybridization (FISH) of frontal cortex neuron from a patient who is positive for the C9ORF72 repeat expansion. A Cy3-labeled oligonucleotide probe (red) indicates RNA foci in the nucleus (blue).
Once considered rare, spontaneous intracranial hypotension (SIH) is now more commonly diagnosed and recognized as an important cause of headaches. SIH is typically the result of spontaneous cerebral spinal fluid (CSF) leak at the spine level; orthostatic headaches, low CSF pressure, and diffuse pachymeningeal enhancement on MRI are diagnostic hallmarks. However, SIH has a broad spectrum of clinical and imaging manifestations, and atypical cases are increasingly seen.

“The variability in just about every aspect of this disorder is substantial,” says Bahram Mokri, M.D., an emeritus professor of neurology at Mayo Clinic in Rochester, Minnesota. “It can be difficult to diagnose and treat this syndrome.”

Seeking biomarkers
In addition to forming clumps that disrupt cell function, abnormal C9ORF72 RNA creates toxic peptides. Based on that finding, Dr. Rademakers is working with Leonard Petrucelli, Ph.D., director of the Neurodegenerative Diseases Laboratory at Mayo Clinic’s campus in Florida, to identify a biomarker for ALS. Work is also underway to identify additional genetic causes of ALS. One invaluable resource is the brain bank for neurodegenerative disorders at Mayo Clinic’s campus in Florida, which has more than 5,000 brains, including 50 with the C9ORF72 repeat expansion.

“ALS is even more complicated than we thought,” Dr. Rademakers says. “At least 50 percent of our familial cases and even more of our sporadic cases remain unexplained by the C9ORF72 repeat expression. There are definitely more genes involved.”

Stem cell therapy safety trial
The stem cell therapy in clinical trial at Mayo Clinic’s campus in Minnesota was developed in the Regenerative Neurobiology Laboratory, under the direction of Anthony J. Windebank, M.D. The treatment (Figure 2) uses intrathecal autologous fat-derived mesenchymal stem cells. Eventually, the researchers hope to show that the re-engineered stem cells can deliver neural growth factors to patients, promoting nerve regeneration.

The dose-escalation safety trial involves 27 patients and is nearly complete. Treatment has been generally well-tolerated, with reported mild adverse events that are not likely related to treatment. No patients have developed progressive weakness worse than that expected with ALS.

Although some patients in the trial report changes in spasticity and muscle twitching and a perceived slowing of disease progression, “the placebo effect can be very strong in these studies,” Dr. Staff says. Efficacy trials might start next year.

One possible benefit of stem cell therapy is its potential to act on multiple etiologic factors in ALS. “The neuroprotection offered by stem cell therapy is not a one-drug, one-target sort of approach. The stem cells likely are changing the immune system a little bit, and the growth factors that are released can have local effects,” Dr. Staff says. “We are still far from an ability to halt ALS entirely. But I am hopeful that the molecular studies underway will hasten that.”

Complexities of Low CSF Volume Headache
Spectrum of presentation
Mayo Clinic has been at the forefront of advances in SIH diagnosis and treatment. Over the past 25 years, Dr. Mokri and Dr. Piepgras have seen an estimated 700 patients with SIH. Initially, it wasn’t uncommon for patients to be referred after misdiagnosis and treatment for conditions such as migraine or tension headache.

Based on work at Mayo Clinic, it now appears that the core pathogenic factor in SIH is decreased CSF volume rather than decreased CSF opening pressure. “Patients can have normal CSF pressure and yet have this syndrome,” Dr. Mokri says. “MRI findings and clinical features seem to be variables that are dependent on the CSF volume.”

Even orthostatic headache, the most common symptom of SIH, appears to vary. The time from change in the patient’s posture from recumbent to standing and appearance of headache, or relief upon lying down — usually assumed to be a few minutes — can be much longer. The headache might be throbbing, but often is not, and pain can range from dull to severe. The headache is often but not always bilateral, and can be frontal, fronto-occipital, holocephalic or occipital.

Indeed, Dr. Mokri notes that not all patients with orthostatic headache have CSF leaks, and headaches related to CSF leaks are not all orthostatic: “Sometimes, orthostatic features may dampen, and the pain transform into a chronic daily headache.”

The nonheadache manifestations of CSF leak also vary greatly, including but not limited to:

• Neck or intercapsular pain
• Tinnitus, change in hearing and dizziness
• Nausea and emesis
• Gait unsteadiness
• Diplopia
• Trouble with memory or cognitive function
• Movement disorders, such as chorea or parkinsonism

“Patients can be profoundly affected,” Dr. Piepgras says. “The headache might be so disabling that the patient can’t be up and working.” He cites one patient seen at Mayo Clinic with a spinal CSF leak and brain sag so severe that a syrinx developed in the patient’s spinal cord — which resolved after identification and repair of the leak.

A significant minority of patients with SIH display clinical signs of heritable disorders of the connective tissue matrix (Figure 1). Although the etiology of spontaneous CSF leaks remains unknown in many patients, connective tissue weakness may play a role in the formation of meningeal diverticula and zones of dural weakness, resulting in CSF leaks.

Sealing CSF leaks
At Mayo Clinic, patients who haven’t responded to initial conservative treatment — bed rest, hydration and time — are usually first treated with an epidural blood patch. Many require more than one patch. Although the overall success rate with each patch is about 30 percent, Dr. Mokri notes that, in his clinical experience, patients acknowledge the cumulative improvement when asked after several treatments to compare their symptoms with those before treatment started.

Another treatment option is epidural injections of fibrin glue or blood and fibrin glue.

Surgery is considered if these less invasive treatments fail, and the source of the CSF leak is located. Mayo Clinic neuroradiologists have experience with CT myelogram and MRI with gadolinium contrast in these cases. Pinpointing a slow-flow leak remains a challenge; radioisotope cisternography can be helpful in providing evidence of slow-flow CSF leak but is less helpful in determining the precise site.

“The surgery itself may be difficult, particularly if the repair must be in front of the spinal cord, often in the thoracic area,” Dr. Piepgras says. “But if you find the tear and

Figure 1. Imaging of a 23-year-old woman who developed orthostatic headaches and pain in the posterior neck and shoulder muscles. She had joint hypermobility and a family history of joint hypermobility, CSF leaks, and aortic aneurysms and dissection. Treatment for tension headaches had been ineffective. A. Head MRI sagittal view shows descent of the cerebellar tonsils, flattened anterior pons, obliteration of pre-pontine cistern and crowded posterior fossa. B. Gadolinium-enhanced MRI coronal view transecting the sella. Note enlarged pituitary, obliteration of prechiasmatic cistern and crowded posterior fossa. C. Spine MRI (heavily T2-weighted axial image) shows a meningeal diverticulum. D. Hyperdynamic CT myelography indicates leaking meningeal diverticulum (arrow). It was surgically removed, and the small orifice of its connection to the dura was sutured. Headaches resolved.
stitch it up, the patient is cured.”

Successful treatment can sometimes result in rebound intracranial hypertension (Figure 2). Patients may re-present with headache that isn’t necessarily orthostatic, and occasionally with papilledema. “The hypertension usually settles down in a matter of months,” Dr. Mokri says. Acetazolamide may help ease symptoms.

Dr. Mokri notes that when he began practicing, a diagnosis of low CSF volume headache was largely unknown. Once MRI with contrast became available, he and Dr. Piepgras began seeing patients with diffuse meningeal enhancement and orthostatic headache often referred to Mayo Clinic with diagnoses such as chronic meningitis.

“But to me, it didn’t make sense that fixed meningeal pathology would cause such an intermittent position-related headache,” Dr. Mokri says. “And so we began researching and publishing.”

For more information


Awake Brain Surgery in Arizona

Awake brain surgery offers significant advantages for patients, reducing the possibility of morbidity and increasing the likelihood of complete resection when surgery involves critical brain areas. Neurologic surgeons at Mayo Clinic in Phoenix/Scottsdale, Arizona, have experience performing this complex procedure for treating brain tumors and focal epilepsy, and soon will offer awake brain surgery for cavernomas and arteriovenous malformations.

“Neurological testing of patients during surgery adds a layer of safety,” says Bernard R. Bendok, M.D., chair of the Department of Neurologic Surgery at Mayo Clinic’s campus in Arizona. “We know right away if we are at risk of affecting speech or other critical functions, versus waiting until the patient wakes up.”

Awake brain surgery requires close collaboration among neurologic surgeons, neurologists, neuroanesthesiologists and neuroradiologists as well as intraoperative monitoring technicians.

Mayo Clinic’s awake brain surgery protocol incorporates these services. “It takes all of them, working in tandem like an orchestra, to make awake brain surgery successful,” Dr. Bendok says.

At Mayo Clinic, selected patients are offered the option of awake brain surgery or more-traditional procedures. Candidates for awake brain surgery must be cooperative and have sufficient cognition to communicate during the procedure. If patients become distressed during surgery, deeper sedation or general anesthesia remains an option.

“In my experience patients usually have no significant discomfort during the procedure,” Dr. Bendok says. “If there is some memory of the awake portion, the patient remembers being comfortable. If done correctly, awake brain surgery is not an unpleasant experience.”

Before surgery, functional MRI (Figure) is used to pinpoint critical areas of the patient’s brain. Those pre-surgery images can be registered through an intraoperative image navigation sys-
tem during the procedure, to guide the surgeon. Scalp numbing is used to minimize or avoid incisional pain during and after surgery. During cranial incision and closing, the patient is under intravenous (IV) sedation. “During the ‘awake’ portion, the patient hovers between IV sedation and mild sedation,” Dr. Bendok says.

Music chosen by the patient is played and neurological function is tested throughout the awake portion of surgery. “The patient is talking to a neurologist he or she has met before, so there is a rapport,” Dr. Bendok says. “Someone is holding the patient’s hand, which is very comforting.”

Forgoing general anesthesia allows for neurological examination during and immediately after surgery. “The patients are able to talk to you right away and their recovery is more rapid, whereas with anesthesia, they’re groggy for a couple of hours,” Dr. Bendok says. Patients are often sent home the next day.

Minimally invasive techniques
Mayo Clinic also offers a range of minimally invasive brain surgeries, including:
• Endoscopic treatment for skull base and brain tumors, aneurysms, and vascular malformations.

Spinal Surgery: Joining Neurologic and Orthopedic Expertise

Over the past decade, significant advances have occurred in surgery to correct scoliosis and spinal deformity. Improvements in spinal implants and biologics that promote bone fusion have led to better outcomes and easier recovery for adolescents with idiopathic scoliosis (Figure 1) and adults with degenerative scoliosis, for whom scoliosis surgery poses particular challenges.

“More surgeries are being offered because we’re getting better at doing these procedures,” says Jeremy L. Fogelson, M.D., a consultant in the Department of Neurologic Surgery at Mayo Clinic in Rochester, Minnesota. “These surgeries are complex but have been very beneficial in working with colleagues in the Department of Otorhinolaryngology-Head and Neck Surgery, Mayo Clinic neurologic surgeons can approach these procedures through the ear bone or nose.
• Laser surgery for focal, medication-resistant epilepsy.
• Use of a catheter to aspirate a brain hemorrhage.
• Use of a hand artery to more safely reach a brain aneurysm.

“At Mayo Clinic we like to consider every option for the patient and pick the one that best fits the patient’s needs,” Dr. Bendok says. “The goal is to reduce the risks of surgery and provide patients with faster recoveries and excellent long-term outcomes.”
terms of quality of life. We are helping patients become active again.”

Dr. Fogelson treats pediatric and adult patients, and has training in both neurosurgery and orthopedic spinal deformity surgery. “It is very helpful to learn from both fields — one with a more neurologic viewpoint, and the other with a musculoskeletal focus,” he says. “That allows me to see issues and to manage complications from the perspective of both specialties.”

At Mayo Clinic, the treatment team for spinal deformity surgery includes anesthesiologists and nurses with experience in complex spine surgery. Intraoperative image guidance facilitates safe placement of implants; sensory and motor function of the spinal cord is monitored in real time, to minimize the chances of neurological deficits. “In some of the more challenging cases, we assemble surgical teams from several departments, including pediatric orthopedic surgery,” Dr. Fogelson says. “This facilitates better outcomes and lower complication rates.”

Dr. Fogelson frequently collaborates with Anthony A. Stans, M.D., and A. Noelle Larson, M.D., consultants in the Department of Orthopedic Surgery and at the Children’s Center at Mayo Clinic in Rochester, Minnesota. In the case of a 16-year-old girl with congenital kyphosis that progressed over time, Dr. Stans and Dr. Fogelson worked together to remove the malformed vertebrae via a vertebral column resection to restore normal alignment (Figure 2). Post-surgery, the patient has improved posture and was able to return to most sports.

**Idiopathic scoliosis trial**

Dr. Larson is one of the principal investigators for the Minimize Implants Maximize Outcomes (MIMO) Study Group, a randomized multicenter study at 12 sites. The randomized trial will compare clinical and radiographic outcomes in two cohorts: one with low-implant density, the other with high-implant density. Participants must be ages 10 to 17, and have a diagnosis of idiopathic scoliosis for which surgery is recommended and a Cobb angle of 45 to 65 degrees.

“Every time we implant a pedicle screw, there is a risk it might be inserted incorrectly and cause complications. We’re trying to find the right balance between number of screws and best outcome,” Dr. Larson says.

**Multispecialty treatment for adults**

Adults can develop scoliosis related to arthritis in the spine, leading to back and leg pain and difficulty walking. “We try to avoid surgery if possible, but in selected patients it can improve quality of life substantially,” Dr. Fogelson notes. Surgery typically involves laminectomies to remove pressure on nerves, and fusion to stabilize the scoliosis. One of the main challenges is preventing the spine from failing above the fusion. This condition, known as proximal junctional kyphosis, is usually related to osteoporosis and is one reason why patient selection is key.

Dr. Fogelson cites the case of a 64-year-old woman who had noticed progressive collapse of her spine over several years. She had back pain and also leg pain from a pinched nerve. Comorbidities included multiple sclerosis, osteoporosis and gastrointestinal disorders.

Mayo Clinic consultants in neurology, endocrinology and gastroenterology all confirmed the patient was an acceptable candidate for surgery. The procedure involved a fusion of the upper thoracic spine down to the sacrum, completed in one day with one posterior incision (Figure 3). The patient reports overall improvement in pain, posture and appearance, and marked improvement in quality of life.

“After surgery, these patients are generally able to walk much longer distances and stand up straighter,” Dr. Fogelson says. “They typically experience relief from back and leg pain and stop taking narcotic medications.”

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**Figure 2.** X-rays of a 16-year-old girl with congenital kyphosis, before and after vertebral column resection to restore normal alignment.

**Figure 3.** X-rays of a 64-year-old woman with progressive kyphoscoliosis before and one year after surgery.
Research Highlights in Neurology and Neurosurgery

Effect of Relapses on MS Disability Accrual
Most patients with multiple sclerosis (MS) enter a progressive phase of disease; few reach severe disability before onset of this phase. Previous studies suggested that primary progressive MS (PPMS) portended a worse prognosis than relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS). These studies considered time to disability milestones from onset of MS rather than from onset of the progressive phase of the disease. Researchers at Mayo Clinic in Rochester, Minnesota, used the onset of progressive disease course as a uniform starting point to study the rate of post-progression disability accrual in a large cohort of MS patients: 322 patients with PPMS and 533 patients with bout-onset progressive MS (BOPMS). In the BOPMS group, 112 patients had single-attack progressive MS and 421 had SPMS. The effect of relapse on time to Expanded Disability Status Scale (EDSS) score of 6 was analyzed. The results indicate that patients with BOPMS reach severe disability faster than do patients with PPMS. Only 3.1 percent of PPMS patients and 10.7 percent of single-attack progressive MS patients had relapses after onset of progressive MS, whereas 29.5 percent of SPMS patients had relapses. Post-progression relapses typically occurred within five years of progression onset and in patients under age 55. Female sex and progression onset after age 50 were modestly associated with shorter time to EDSS score of 6. Results of the study suggest that intervention to prevent post-progression relapses would be most effective within five years of progressive onset or until age 55, especially for patients with BOPMS. (Paz-Soldan MM, et al. Relapses and disability accumulation in progressive multiple sclerosis. Neurology. 2015;84:81.)

Consolidation of Neuronal Assemblies After Seizures
The establishment of memories involves reactivation of waking neuronal activity patterns and strengthening of associated neural circuits during slow wave sleep (SWS), a process known as cellular consolidation. During seizures, a subpopulation of neurons is activated repetitively and synchronously for an extended time, while most neurons remain silent. Researchers at Mayo Clinic in Rochester, Minnesota, hypothesized that the activation of neuronal assemblies during seizures should be observable as persistent changes in pairwise correlation during nonrapid eye movement sleep from a pre-seizure baseline. Continuous wide-bandwidth recordings of six patients undergoing intracranial monitoring for drug-resistant epilepsy were analyzed. Nine seizures, and seizure-free recording before and afterward, were analyzed. Periods of continuous SWS and wakefulness were identified before and after a seizure and served as a control. Analysis revealed reactivation of seizure-related neuronal activity during subsequent SWS, but not during wakefulness. The neuronal assemblies most strongly activated during seizures showed the largest correlation changes, indicating that consolidation might selectively strengthen neuronal circuits activated by seizures. The results suggest that seizures “hijack” physiological learning mechanisms and also suggest the potential for therapy targeting neuronal dynamics during post-seizure. (Bower MR, et al. Evidence for consolidation of neuronal assemblies after seizures in humans. Journal of Neuroscience. 2015;35:999.)

Anti-thrombotics and Intracerebral Hemorrhage
Hypertension has been considered the main risk factor for primary intracerebral hemorrhage (ICH). With improved treatment of hypertension, the overall incidence of ICH has remained unchanged — although it has decreased in people below age 60 and increased in those over age 75. Cerebral amyloid angiopathy (CAA) increases with age and is recognized as a major risk factor for ICH. Several studies have shown an increase in the use of anti-thrombotic medications over the past 30 years, raising the question of whether the shift in ICH demographics is secondary to a combination of CAA and increased use of anti-thrombotic medications. Researchers at Mayo Clinic in Rochester, Minnesota, evaluated the influence of anti-thrombotic medications on ICH etiology. The retrospective study examined the records of patients admitted to Mayo Clinic hospitals with a primary ICH from 2009 to 2012. Etiologies were classified using an algorithm that, among other factors, incorporated patient age, history of hypertension, use of anti-thrombotic medications and imaging. Among the 292 cases studied, hemorrhage etiology was hypertension in 50.6 percent, indeterminate in 29.5 percent and CAA in 19.9 percent. The researchers found a nonsignificant trend toward older age and CAA-associated ICH compared with other causes. There was no difference between CAA-ICH and other-cause ICH with respect to the proportion of patients on anti-thrombotics in general or anticoagulants in particular. The findings do not suggest that higher occurrence of ICH in older patients or in patients with CAA-ICH is due to higher frequency of anticoagulant use. (Braksick SA, et al. Influence of anti-thrombotics on the etiology of intracerebral hemorrhage. Journal of Stroke and Cerebrovascular Diseases. In press.)

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