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Discoveries in Neuromuscular Disease: Novel Subtypes of Myofibrillar Myopathy

In 2008, Duygu Selcen, MD, a pediatric neurologist and research scientist at Mayo Clinic in Rochester, Minnesota, received a phone call from a pathologist at the University of Manitoba in Winnipeg, Canada. Marc R. Del Bigio, MD, wanted her input in determining the molecular basis of a fatal muscle disease affecting Canadian Aboriginal infants of Cree ancestry. The children had rigid muscles and fatal respiratory insufficiency in infancy. Dr Del Bigio told her that the muscle biopsy specimens he had examined appeared to be like those found in a type of muscular dystrophy called *myofibrillar myopathy* (MFM), even though the disease took a different course. All of the affected children died in infancy except one, who died at three years of age.

It is not surprising that Dr Del Bigio contacted Dr Selcen. The Muscle Research Laboratory at Mayo Clinic, established more than 40

years ago by her mentor, Andrew G. Engel, MD, receives more than 1,000 muscle biopsy specimens a year for histologic analysis. By the time Dr Selcen received the call, she and her colleagues had already made some important discoveries about the molecular basis and distinctions among types of MFM.

MFM encompasses a group of chronic, slowly progressive diseases of the skeletal muscle, the heart muscle, and the peripheral nerves. Symptoms can include weakness, paresthesias, peripheral neuropathy, muscle wasting, stiffness, aching, and cramps. In most patients, the disease presents in late adulthood, but a subtype of rapidly progressing MFM, identified by Dr Selcen and colleagues, can occur in childhood.

Tracking the Genes and Identifying New Subtypes

The term *myofibrillar myopathy* was coined 15 years ago, grouping together genetically heterogeneous neuromuscular disorders that previously were thought to be distinct but which share common morphologic characteristics. The common pathologic features include disorganization and degradation of the contractile filaments of striated muscle (myofibrils) originating at the Z disk.

The molecular abnormalities of MFM include the accumulation and aberrant expression of proteins. Only two of the genes had been identified until 2004, when Drs Selcen and Engel uncovered two more genes that cause MFM. Both of the newly identified genes were implicated in Z-disk structure and biology. The first gene, *myotilin*, helps to distinguish a subtype of MFM from the classic limb-girdle

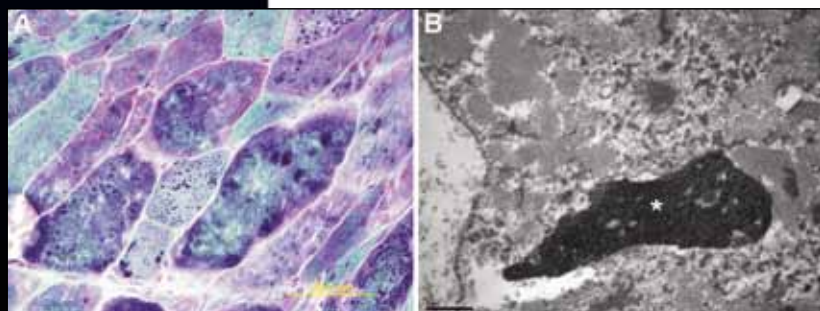


Figure. A. Trichrome stained section from a patient with Bag3opathy demonstrates abnormal inclusions in many muscle fibers. B. Electron micrograph of an abnormal muscle fiber shows an apoptotic nucleus (asterisk) and granular degradation products.



Duygu Selcen, MD

phenotype, highlighting the genetic heterogeneity of MFM and shedding new light on Z-disk mechanisms. The second gene, *ZASP*, defined a new form of MFM. *ZASP* is expressed more in cardiac than skeletal muscles and, prior to Dr Selcen's discovery, was known to cause only cardiomyopathy, not peripheral neuromuscular disease.

Discovery of Novel Pediatric MFM Subtype

More recently, Dr Selcen and colleagues discovered a mutation in yet another protein, a product of the *BAG-3* gene, which has antiapoptotic features. Their finding isolated a previously unidentified severe, rapidly progressive, fatal childhood type of MFM. It marked the first time that *BAG-3*, typically associated with cancer, was implicated in human muscle disease. The finding is of immediate clinical significance because the symptoms of cardiomyopathy often occur before the disease shows up in the peripheral muscles. Affected children and adolescents may be candidates for heart transplantation, but if they have the *BAG-3* gene mutation, spine rigidity and respiratory failure will develop eventually, regardless of improved heart function. Now, under Dr Selcen's direction, the Mayo team is developing animal models to test antiapoptotic drugs in an effort to halt the progression of the disease.

MFM Subtype Unique to Canadian Aboriginals

What of the Canadian Aboriginal infants? Dr Del Bigio was right: the muscle biopsy specimens shared multiple characteristics with MFM, particularly the abnormal accumulation of specific proteins. However, when Dr Selcen conducted further immunostaining tests, a protein that is always at increased levels in MFM was totally absent. Its absence provided the clue that led Drs Selcen and Del Bigio and their colleagues to pinpoint *CRYAB* as the disease gene—a discovery that will enable genetic testing, genetic counseling, and, eventually, disease prevention in this population.

Dr Selcen is both a clinician and a researcher. She routinely sees patients with MFM and other muscle diseases for clinical assessment and disease management. Her ongoing investigations at Mayo's Muscle Research Laboratory on malfunctioning genes and gene products in muscle disease have led to the identification of specific subtypes of childhood MFM, discoveries that have immediate management implications and hold the promise of identifying therapeutic interventions in the future.

Surgical Management of Intractable Seizures in Children With Epilepsy

One in five children with epilepsy has intractable seizures—defined as seizures that fail to respond to at least two appropriate antiseizure medications. Surgery may be an option, but the path to that decision is complex. At many institutions, the evaluation process can take months.

At Mayo Clinic in Rochester, Minnesota, the surgical work-up can be done in one or two weeks and includes state-of-the-art functional brain mapping and seizure locus studies. If the child is documented to be a good surgical candidate and the family decides to proceed, surgery can then



Figure 1. Mayo Clinic's EEG video monitoring unit is specifically designed for children and families and provides 24/7 monitoring by trained technicians.

be scheduled promptly.

At Mayo Clinic in Rochester, pediatric neurologists Elaine C. Wirrell, MD, Lily C. Wong-Kisiel, MD, and Katherine C. Nickels, MD, and pediatric neurosurgeon Nicholas M. Wetjen, MD, are experts in pediatric epilepsy. They are part of a multidisciplinary epilepsy team that includes neuroradiologists and pediatric neuropsychologists.

As Dr Wetjen explains, “The turnaround time here is quick because the care is not fragmented, and there is immediate communication between team members. For example, a child with lesional epilepsy (eg, tumor, cavernous malformation) may come in on a Monday; have an evaluation that includes imaging, inpatient video-EEG monitoring with several recorded seizures, a SISCOM study (subtraction ictal SPECT coregistered to MRI), and neuropsychological evaluation by Thursday; and, in some cases, be in surgery by Friday. The pace is not always that fast, however. The typical range for most epilepsy patients is two to four weeks from initial consult to surgery.”

Determining Surgical Candidacy

A pediatric epileptologist determines the frequency, severity, and duration of seizures; whether the seizure onset is focal; and whether other conditions coexist. An MRI and scalp EEG help identify seizure etiology (eg, cortical dysplasia, vascular malformations, arteriovenous malformation, tumor, trauma, stroke, rare metabolic conditions) and the presence (or absence) of a specific lesion and its location. A pediatric neuropsychologist then evaluates baseline cognitive function and helps establish lateralization of function. Other tests to localize function may include functional MRI, PET, or intracarotidsodium amobarbital (Wada) testing.

Inpatient Pediatric EEG Monitoring

Surgical candidates then undergo continuous EEG monitoring in the Eugenio Litta Children’s Hospital, the 85-bed pediatric facility located within Mayo’s Saint Marys Hospital.

Four rooms, as well as the pediatric intensive care unit, are hardwired with ceiling cameras for behavioral observation and continuous EEG monitoring via external or intracranial EEG leads (Figure 1). Inpatient video-EEG monitoring is needed to record several seizures by EEG and video and to minimize risks of medication withdrawal, a process that is often required to record seizures. Monitoring may take from 24 hours to several days to record a sufficient number of seizures. Digital recording allows analysis of the EEG in a number of formats.

The video-EEG monitoring unit is specifically designed with children and families in mind.

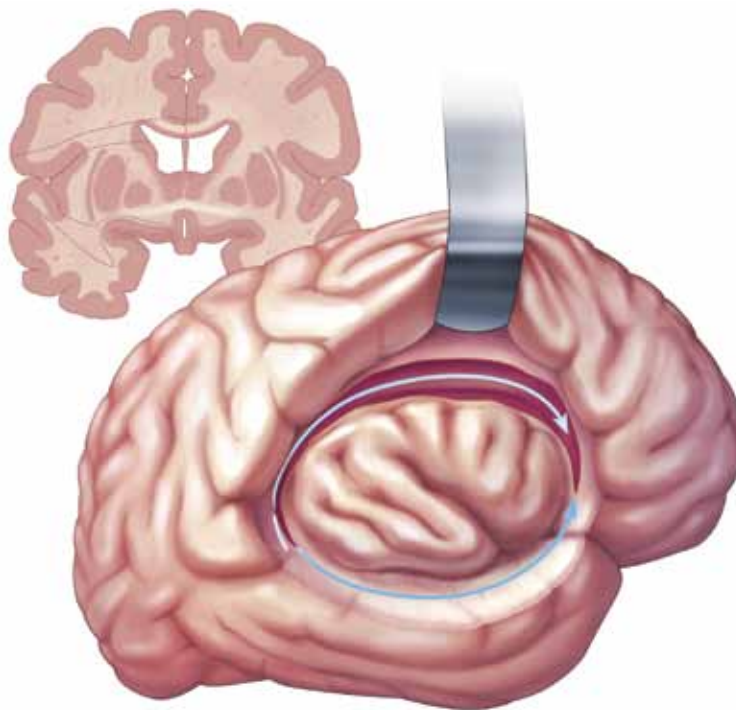


Figure 2. Rather than removing the entire hemisphere, a hemispherotomy involves a much smaller resection (arrows) followed by image-guidance technology to disconnect the diseased hemisphere from the healthy one.

Child-life specialists not only provide toys, movies, computer games, and other entertainment, but also help children and families through procedures that may be uncomfortable or unfamiliar. The single-patient rooms allow parents to stay with their child throughout the child’s hospitalization. The nurses and EEG technicians are, according to Dr Wetjen, “remarkably attentive and good at what they do.” Dr Wirrell agrees, saying, “Our EEG technologists are superb and dedicated to their patients. I have not worked with one who is not devoted to the child.”

Dr Wirrell also notes that “unlike many centers that offer monitoring, we have the ability to monitor the patient every second of the day or night, so if the patient or family member is sleeping or the seizure is subtle, our technologists are still able to pick it up.” Continuous monitoring by trained technicians not only increases safety, but also reduces the length of time a patient stays in the monitoring unit.

Localizing Seizure Focus Through SISCOM

Pioneered at Mayo Clinic, SISCOM fuses the MRI image with the SPECT image, an innovation particularly useful in localizing seizure focus when seizures have a focal onset. A radioactive tracer is injected as soon as possible during a seizure. The first imaging study is performed shortly after the seizure; the second is done after 24 hours of seizure freedom. Dr Wirrell notes, “SISCOM can



Elaine C. Wirrell, MD



Nicholas M. Wetjen, MD

be very helpful in pediatric epilepsy in which the MRI frequently does not show a clear structural abnormality.”

If imaging studies establish a clear focus that is not in an area of critical brain function, the child may have surgery for resection. If the focus cannot be precisely localized or if it is in an area of eloquent cortex, intracranial electrodes may be implanted. Further seizures are then recorded to improve localization of seizure onset. Electrical stimulation can be performed to map important motor and language functions.

All the data for each case and the potential risks and benefits of surgery are reviewed at the epilepsy team conference where, according to Dr Wirrell, “everyone provides input, and there is always plenty of time to discuss each patient fully.” The attending neurologist then meets with the family to review the recommendations.

Multiple Surgical Options

Depending on the nature of the problem, the patient may have surgical resection or disconnection. Resections are generally conducted for tumors, vascular malformations, and areas of cortical dysplasia. Cortical disconnection (corpus callosotomy) is used to treat drop attacks.

For patients whose epilepsy arises from an entire hemisphere, Dr Wetjen and colleagues may perform a peri-insular hemispherotomy instead of the traditional hemispherectomy. Rather than removing the entire hemisphere, a hemispherotomy involves a much smaller resection monitored by image-guidance technology to disconnect the diseased hemisphere from the healthy one (Figure 2). As a result, there are fewer postoperative complications such as hydrocephalus and superficial siderosis.

Other options include endoscopic surgery in

the rare case of a patient with gelastic or laughing seizures, in which there is a third ventricle hypothalamic hamartoma; radiosurgery or microsurgical resection for seizure-causing arteriovenous malformations; and neuromodulation using vagus nerve stimulation, deep brain stimulation, or cortical stimulation for focal, multifocal, and generalized seizures. Implanted pacemaker stimulation, another form of neuromodulation, is a future possibility. As Dr Wetjen says, “We don’t know yet if pacemaker stimulation will be effective in patients with epilepsy, but Mayo is always looking for better ways to manage the treatment of patients. The infrastructure is here if it is appropriate to make those kinds of advances.”

Caring for the Whole Family

“Epilepsy impacts siblings as well as the patients and their parents. I find developing long-term relationships with the whole family important and fulfilling,” says Dr Wirrell. Adds Dr Wetjen, “I like to spend a lot of time making the children feel comfortable. The mothers and fathers want the best possible care, and it’s critical to provide extensive and effective ongoing communication throughout each patient’s care. Our whole team is attentive to the ongoing mental, social, and educational development of the children under our care.”

Like the rest of the epilepsy team, Drs Wetjen and Wirrell are acutely aware of the importance of the developing brain, and, as Dr Wetjen notes, “Epilepsy is not a static situation, but an actively changing one. It’s very hard to separate the problems related to continuing epilepsy from the effects of epilepsy medications, but certainly, if it is possible, stopping the seizures is best. We can’t do it in every case, but that’s the hope, that’s the goal.”

DBS at Mayo Clinic: Pediatric Practice and Research Update

Mayo Clinic in Rochester, Minnesota, conducts about 100 deep brain stimulation (DBS) procedures a year. The list of disorders treated includes essential tremor and Parkinson disease, as well as dystonia, chorea, Tourette syndrome, epilepsy, and certain types of centrally mediated neuropathic pain. Four years ago, the DBS practice expanded to include children, as well as adults.

As is true in adults, successful DBS treatment in children depends on careful patient selection, precise neural targeting, and extensive, individualized stimulator programming. At Mayo, an interdisciplinary committee with

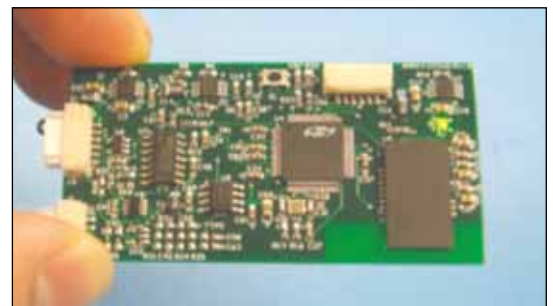


Figure 1. Circuit board of the Wireless Instantaneous Neurotransmitter Concentration Sensing System device. The device is able to wirelessly detect neurotransmitter level changes in the brain.

membership from the departments of neurology, neurosurgery, psychiatry, neuropsychology, pain neurology, nurse programming, and speech pathology reviews every DBS candidate, weighs risk factors against potential benefits, and comes to consensus about disease management.

Kendall H. Lee, MD, PhD, the neurosurgery director of the DBS program at Mayo Clinic in Minnesota, and his colleague Matt Stead, MD, PhD, a pediatric neurologist, note that the three patients with Tourette syndrome whom they have treated have responded well. The symptoms in one of the patients, who was 19 years old at the time of surgery, all but disappeared after programming adjustments to the DBS stimulator.

DBS for dystonia in children can help eliminate some symptoms. As Dr Stead explains, "It is the best treatment we have to offer for dystonia that is medically refractory. Patients differ in response, but, on average, both adults and children experience about a 50% improvement with DBS."

Asked about the outcomes for children with chorea, Dr Stead notes that none have had complete symptom remission, but all have had improvement. As an example, he cites a five-year-old child who was nonverbal before surgery and was able to begin speaking after DBS.

Mayo Clinic is one of the few institutions in the world to offer DBS for intractable epilepsy in children. The program's youngest patient, and the youngest in the world to undergo DBS, was a three-year-old child with Lennox-Gastaut syndrome. "The response was excellent, with marked seizure reduction," says Dr Lee. Dr Stead adds, "There is no treatment available for this very serious condition, so we were pleased to see how well DBS worked."

Mechanisms of DBS

Dr Lee is also the director of Mayo's Neural Engineering Laboratory and a Mayo-based, multi-institutional DBS consortium investigating the mechanisms of neurostimulation across a spectrum of disorders. In research funded by the National Institutes of Health and benefactor grants, he, Kevin E. Bennet, chair of Mayo's Division of Engineering, and their colleagues developed the Wireless Instantaneous Neurotransmitter Concentration Sensing System (WINCS), a device that can monitor neurochemical output of targeted brain sites in real time during DBS (Figure 1).

It appears likely that DBS evokes the release of neurochemicals. DBS uses a high-frequency stimulation device applying five to 100 stimulation pulses per second. Traditional chemical

detection systems, such as mass spectrometry, are an impractical means of monitoring in vivo chemical changes in the brain during DBS stimulation. WINCS, however, is capable of electrochemical detection using fast-scan cyclic voltammetry and amperometry, sampling a subsecond at a time.

Electrochemical monitoring through WINCS during DBS surgery in animals suggests that the positive effects of DBS are based on changes in neural activity and neurochemical transmitters in interconnected structures within a given neural network.

The thalamus, for example, is known to be an effective DBS target for seizure suppression (Figure 2). Dr Lee and his colleagues have applied high-frequency stimulation (HFS), which mimics DBS, to brain slices from ferrets, monitoring changes with WINCS. They found that HFS suppressed spindle wave oscillations in the nucleus reticularis thalami and in thalamocortical relay neurons in the lateral geniculate nucleus. It also caused elevation in extracellular glutamate levels for many seconds after stimulation. Identification of the prolonged release of glutamate, which decreases neuronal input resistance and abolishes thalamic network oscillatory action in response to HFS, is a step forward in explaining how DBS inhibits seizures and tremor.

WINCS is not just a research tool. The goal is to use WINCS to monitor neurochemical changes during human DBS surgery, to improve target identification and placement precision. In the study cited above, for example, Dr Lee and his colleagues found that HFS-mediated neurotransmitter release may begin in astrocytes, which may turn out to be an as-yet-unappreciated target for DBS stimulation.



Matt Stead, MD, PhD, and Kendall H. Lee, MD, PhD

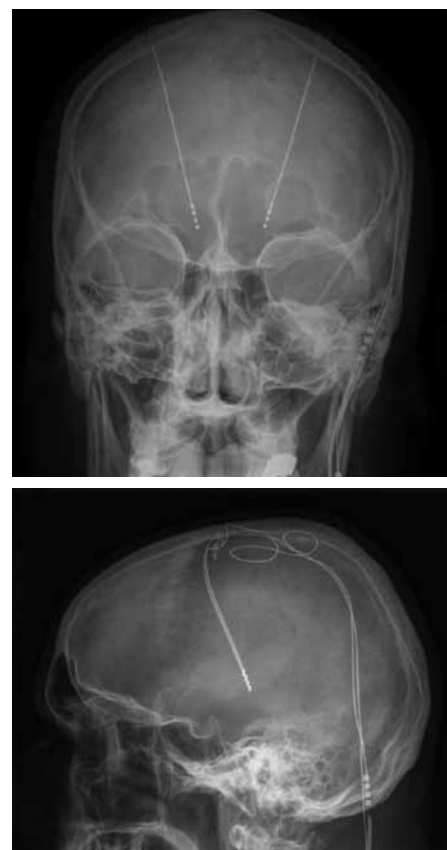


Figure 2. Skull radiograph (anterior/posterior [top] and lateral [bottom]) showing a deep brain stimulation lead in the human thalamus.



Research Highlights in Pediatric Neurology and Neurosurgery

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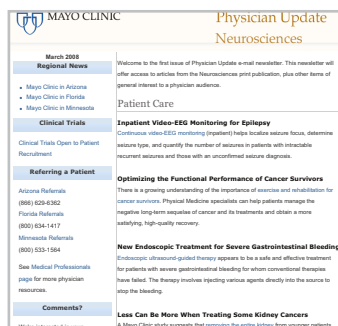
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Clinical Trials Update

1. Study of Dichlorphenamide in Periodic Paralysis. Double-blind, placebo-controlled study of dichlorphenamide (Darandide) for treatment of hypo- or hyperkalemic periodic paralysis.
2. Study of Thymectomy in Acetylcholine Receptor–Positive Myasthenia Gravis. Patients with generalized myasthenia gravis with or without treatment with Mestinon and prednisone are randomly assigned to receive thymectomy or not and observed for three years.

For more information about other Mayo Clinic research studies, please visit: <http://clinicaltrials.mayo.edu/>.



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