Advanced Neurological Expertise for Complex Cases

Specialized care for Angelman syndrome
Approximately one in 15,000 children is born with Angelman syndrome annually; 90% of these children have seizures. In 2008, MassGeneral Hospital for Children (MGH/C) opened the first Angelman syndrome clinic in the United States. Founded by pediatric epileptologist and neurologist Elizabeth Thiele, MD, PhD, director of the Pediatric Epilepsy Program at MGH/C and director of the Carol and James Herscot Center for Tuberous Sclerosis Complex; and pediatric epileptologist Ronald Thibert, DO, MsPH, co-director of the Angelman Syndrome Clinic and director of the Dup 15q Clinic, the Angelman Syndrome Clinic provides consultations, recommendations and ongoing multidisciplinary care for more than 70 families. This care, says Dr. Thiele, can involve pediatric gastrointestinal specialists, neuropsychologists, psychiatrists and neurologists specializing in sleep disorders, as well as pediatric epileptologists and the services of Massachusetts General Hospital’s Lurie Center for Autism (see massgeneral.org/luriecenter). An experienced clinic coordinator organizes subspecialty consultations, imaging and other tests to minimize time away from home for families that have traveled long distances. Because MGH/C is a comprehensive pediatric specialty hospital fully integrated into a world-class academic medical center, individuals with Angelman syndrome can be seamlessly transitioned from pediatric to adult care.

Dup 15q Clinic unique in the country
Dup 15q is a clinically identifiable syndrome resulting from duplications of chromosome 15q11-13. These duplications can lead to seizures, attention deficit and anxiety disorders, scoliosis, gross and fine motor delays, speech and language delays, sensory processing disorders, cognitive delays, autism spectrum disorder, sleep disorders and behavior challenges as well as physical characteristics. The incidence of dup 15q is still being assessed, according to Dr. Thibert. However, current estimates indicate that one child in 15,000 will be born with the disorder each year.

The MGH/C Dup 15q Clinic, started in late 2010, is the first in the country and is currently the only clinic offering specialized multidisciplinary care to families affected by duplications of chromosome 15q. Currently, specialists within the clinic are following more than 40 families from across the United States and providing advice to physicians abroad who are treating patients with dup 15q. Patients at the MGH/C Dup 15q Clinic are evaluated in the Epilepsy Clinic and receive highly coordinated, individualized multidisciplinary care as needed. For many children, the specialists involved are the same as those treating children with Angelman syndrome. The difference, says Dr. Thibert, is that children with dup 15q are more likely to have an autism spectrum disorders than children with Angelman. As a result, care involves more emphasis...
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on neuropsychology and psychiatry. Often these children are referred immediately to the Lurie Center for Autism to help connect families to a full-range of autism programs and services.

Improving care for patients with tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is a genetic multisystem disorder that occurs in approximately one in 5,500 individuals and can affect every organ system. In 95% of cases, the complex affects the brain, and about 85% of people with TSC have epilepsy.

Mass General’s Herscot Center for TSC provides consultations and care for children and adults with TSC. For both the pediatric and the adult side of care, specialists in every organ that can be affected are completely engaged in care. As with the other gene-related syndrome clinics at MGH/C, patients and families benefit from research conducted by MGH/C TSC specialists as well as coordinated and individualized medical, psychological and social services care provided by professionals with in-depth experience in this disorder. According to Dr. Thiele, current research includes efforts that may help to identify signs and symptoms of TSC for earlier diagnosis, the natural history of epilepsy in TSC and the mental health issues of TSC.

For more information, please visit www.massgeneral.org/livingwithtsc

Evolutions in dietary therapy

The ketogenic diet has been used since the 1920s to control seizures in some people with epilepsy. While effective in controlling or reducing seizures in two thirds of children who have failed medical therapy, the diet is very restrictive, making it challenging for patients and families. Many centers today offer a modified Atkins diet as an alternative to the ketogenic diet. MGH/C clinical researchers have developed a third approach, a low glycemic diet, which appears to be as effective as the classic ketogenic diet in controlling refractory seizures. Clinical trials of this high-fat, limited-carbohydrate diet are currently underway at Mass General in both adults and children.

Bench research leads to new treatment

For more than two decades, investigators in the Pediatric Epilepsy Research Lab at MGH/C have been involved in the study of the biological processes involved in seizure initiation and propagation with the goal of developing new approaches to epilepsy treatment. Their efforts have paid off in the form of the first new treatment for neonatal seizures that has successfully gone from bench to bedside. According to Kevin Staley, MD, chief of pediatric neurology at MGH/C and Joseph P. and Rose F. Kennedy Professor of Child Neurology and Mental Retardation at Harvard Medical School, neonatal seizures are typically treated with phenobarbital, a solution introduced a century ago that has many disadvantages. The new treatment, which is currently being evaluated in Europe and in a cooperative trial involving MGH/C, Mass General, Boston Children’s Hospital, and Brigham and Women’s Hospital, uses phenobarbital and bumetanide, a drug targeted at an age-dependent mechanism which MGH/C researchers tied to the high incidence of seizures in neonates. In addition, says Dr. Staley, the lab has generated a novel high throughput model of chronic epilepsy that allows for rapid screening of drugs that may be effective in intractable epilepsy.

For more information about MGH/C’s Pediatric Epilepsy Program, please call 617-726-6540.

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Clinical and Research Programs Enhance Neurocritical Care

Under the directorship of Sarah Murphy, MD, MGH/C has launched a comprehensive, multidisciplinary pediatric neurocritical care program within the 14-bed pediatric intensive care unit. This program provides optimal protection of the brain in critically ill and injured children while advancing the standard of care. It complements established programs, including MGH/C’s pediatric stroke service, which is one of the oldest and largest in North America; the hospital’s renowned neurosurgery department; and expert neuroradiologists who use innovative techniques involving the most advanced imaging and monitoring equipment to improve care for children with neurologic injuries or illness (see Technology and Innovation Improve Safety on page 4). Expansion plans are in process to bridge neonatal and pediatric critical care.

According to Dr. Murphy, who is board certified in neurocritical and pediatric critical care, management of patients in the pediatric neurocritical service is enhanced by interaction with Mass General’s adult neurocritical care specialists and by bench and translational research on neurologic illness and disease. One current research project involves using infrared light therapy for concussions in a rodent model of traumatic brain injury. Near-infrared light has been shown to have a beneficial effect on healing and to have an anti-inflammatory effect outside the central nervous system. Over the past 10 years, researchers have investigated near-infrared light for the treatment of adult stroke. At MGH/C, principal investigator Michael Whalen, MD, has begun investigating this approach in the treatment of traumatic brain injury. In the first published report to document a beneficial role for near-infrared light in cognitive outcome after traumatic brain injury, Dr. Whalen showed that one two-minute treatment of near-infrared light on injured brains, beginning one hour after injury, improves cognitive functioning. A second line of inquiry, led by Josephine Mun-Yee Lok, MD, demonstrated the importance of growth factor neuregulin-1 (NRG1) as a therapeutic target following traumatic brain injury. NRG1 ameliorates disruption of the blood-brain barrier; this barrier is frequently compromised in traumatic brain injury.

Studies have shown that telemedicine is feasible in the adult critical care setting, but use of this technology in pediatric critical care is under explored. MGH/C uses telemedicine to link pediatric critical care specialists on home call with staff, patients and families at the downtown, North Shore, Newton-Wellesley and Nantucket Cottage Hospital locations. Using the technology, on-call physicians can have real time, high-quality voice and video communication, including access to monitors. This link is used for patient assessment, communication with families and multidisciplinary team members, and changes in care management. Recently MGH/C intensivists published a study based on their experience, demonstrating that nighttime telecommunication is technologically feasible. Furthermore, nighttime telemedicine reduced parental anxiety. Additional studies will help establish the role of this technology in improving outcomes for patients in the pediatric critical care setting.

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Technology and Innovation Improve Safety

Next-generation imaging equipment available at the Athinoula A. Martinos Center for Biomedical Imaging at Mass General and innovative approaches to using these tools allow MGH/C’s neuroradiologists to diagnose even subtle abnormalities in brain tissue and to understand more about the impact of injury and illness on the developing brain. These new approaches are being developed by a team of specialists with extensive experience in intraoperative monitoring and mapping of brain function in children in collaboration with other MGH/C and Mass General specialists and subspecialists.

Resources at the Martinos Center include the 7-Tesla MRI. This specialized equipment, found at only a handful of medical centers in the country, produces extremely detailed images of the brain in children with problems ranging from epilepsy and brain tumors to disorders of cranial nerves and cerebral spinal fluid. The strength of a magnetic field is measured in Tesla units; the higher the field strength, the more detailed the image acquired by MRI machines. Aided by these precise images, neurosurgeons can remove seizure loci or tumors while avoiding critical structures.

Steven Stufflebeam, MD, director of clinical magnetoencephalography (MEG) at the Martinos Center, is using a combination of imaging technologies including MEG, high-density electroencephalography (EEG), fMRI and optical imaging to understand how the brain processes neural information. The MEG maps brain activity noninvasively by recording magnetic fields produced by electrical currents occurring naturally in the brain. Combining information generated by the MEG with images from other imaging technologies provides neurosurgeons with precise structural and mechanistic detail that helps them treat epilepsy, neoplasms and other disorders with reduced damage to important electrical activity in the brain. Current approaches to map neural activity prior to epilepsy surgery involve using electrodes implanted against the surface of the brain. The use of multiple imaging technologies eliminates the need for this invasive procedure, reducing hospital admissions and easing treatment burden for patients and families.

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3-Dimensional fusion of structural MRI, tractography, MEG and PET data used in planning epilepsy surgery for a child with intractable seizures. Images courtesy of Brad Buchbinder, MD and Steven Stufflebeam, MD.
Media attention on potential long-term effects of sports-related concussions has created a lot of fear among parents, coaches and athletic directors, says Peter Greenspan, MD, director of the MGH/C Youth Sports Concussion Clinic. Much of this fear, however, results from information that has not been rigorously tested. At the MGH/C clinic, children, adolescents and young adults through college who have sustained concussions from playing sports or other recreational activities are individually assessed and provided education that separates fact from fear.

The clinic is staffed by specialists in neurology, physical medicine/rehabilitation and sport psychology; expedited access to neurosurgery, neuropsychology, psychiatry, sports medicine and physical therapy is available when required. All new patients receive a computerized test of cognitive function, and follow-up patients are tested if indicated. Care plans are based on algorithms created from the input of all relevant specialists to match patient symptoms with referral and testing needs. Even patients who do not need multidisciplinary assessment benefit from the combined input of neurologists, neuropsychologists, neurosurgeons, physical medicine and rehabilitation specialists, psychiatrists, and sports medicine and trauma physicians via these data-derived care plans. These experts constantly update treatment algorithms based on the literature and emerging data from every related specialty.

Thanks to philanthropy, MGH/C’s Youth Sports Concussion Clinic includes educational presentations and question-and-answer sessions for patients and families. These sessions, which are led by a physician and a sports psychologist, provide an opportunity for patients and parents to learn what is known about concussions, to ask questions and to share experiences with other families. Philanthropic support has also made possible research studies initiated by MGH/C clinical researchers to answer questions about the impact of concussions on the developing brain. MGH/C concussion specialists also currently participate in national studies.

**CONCUSSION FACTS**

- Approximately four million concussions per year in the U.S.
- Until fully recovered, patients are at increased risk of neurological problems if injured again
- Some patients have more long-term symptoms

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<thead>
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<th>Time</th>
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<td>21 days</td>
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<td>28 days</td>
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Advanced Neurosurgical Expertise for Complex Cases

Pediatric neurosurgeons at MassGeneral Hospital for Children (MGH/C) diagnose and treat all neurological conditions of infants, children and adolescents, says Ann-Christine Duhaime, MD, MGH/C’s director of pediatric neurosurgery and the Nicholas T. Zervas Professor of Neurosurgery at Harvard Medical School. MGH/C neurosurgeons often collaborate with adult specialists at Massachusetts General Hospital and with experts at Massachusetts Eye and Ear Infirmary (MEEI) and Spaulding Rehabilitation Hospital to ensure optimal outcomes for even the most complex disorders and diseases of the brain. High surgical volumes, extensive experience treating disorders and illnesses of the brain, and on-site access to leading-edge imaging equipment, like the 7 Tesla MRI and the MEG, have given the members of the pediatric neurosurgery service at MGH/C special expertise in the management of pediatric brain and spinal cord tumors; epilepsy surgery; other types of functional neurosurgery, including spasticity and movement disorders; vascular problems; hydrocephalus and brain cysts; craniofacial disorders; neurosurgical trauma; and congenital anomalies of the spine and brain, including spinal dysraphism (tethered cord syndrome). This clinical expertise is enhanced by research within the Pediatric Neurosurgery Laboratory, including Dr. Duhaime’s investigations of how the immature brain responds to injury and experimental treatments, how it repairs itself at different ages, and the best methods for assessing infants and children to predict outcome and response to treatment. These studies are performed in collaboration with Dr. Murphy and other investigators from the Critical Care Service, Pediatric Emergency Department, Trauma Program and the Martinos Center, integrating this translational work across the Mass General community.

Leading-edge treatment and monitoring equipment
The MGH/C neurological surgery team uses the most advanced technologies available in research studies and during surgical planning and intervention, including the state-of-the-art imaging technologies and approaches described above (see Technology and Innovation Improve Safety, page 4). In 2011, the team gained access to a new, specially designed, two-room operating suite containing an intraoperative 3-Tesla MRI. Having this equipment available in the operating suite allows surgeons to conduct image-guided procedures using readily accessible, highly detailed, real-time images. In addition, it increases patient safety and quality of care by eliminating the need to transport patients to another area of the hospital for imaging. Surgical teams also have access to stereotactic image-guided technology, ultrasound and laser equipment and expert intraoperative functional monitoring of the brain and spinal cord.

Treating movement and behavioral disorders with deep brain stimulation
Deep brain stimulation (DBS) has been used in adults, adolescents and some children for treatment of movement disorders. It works by providing a tiny, focused amount of electrical stimulation to a specific part of the brain to allow malfunctioning brain circuits to work more normally. Currently, says Dr. Duhaime, MGH/C is one of the few programs in New England to use DBS regularly in the treatment of pediatric movement disorders. Dr. Duhaime, who also specializes in epilepsy surgery in children as young as infancy, has seen that when seizures are controlled earlier in life, children have the ability to reach their full developmental and psychological potential.

Mass General is also one of the few medical centers nationally to use DBS for behavioral disorders such as depression and obsessive compulsive disorder. According to Dr. Duhaime, if behavior modulation for severe disorders that don’t respond to the usual medical management is effective in children—as it is in some adults—these children may develop to their fullest potential rather than experiencing years of disability during important developmental periods. As a result, MGH/C has begun using these brain modulatory approaches in patients of all ages, including young adults, and is one of the only centers nationally to begin investigating these techniques in adolescents.

Expert, comprehensive services for brain and skull base tumors
Children with tumors of the brain or nervous system face the possibility of significant long-term impairment to intellectual function, loss of speech, balance difficulties, hormonal and growth disorders and death. MGH/C’s Pediatric Brain Tumor Clinic provides expert multidisciplinary evaluation, treatment and care for these children, including a pediatric neurosurgeon working side by side with other surgical subspecialists in the operating room. Among the most complex and challenging of brain tumors are those occurring at the base of the skull. Depending on the location, these tumors—whether benign or malignant—can
affect cognition, movement, hearing, speech, vision or smell. Pediatric patients with these tumors receive individualized care from a multidisciplinary team that may include experts from the Mass General Cancer Center, the MGH/C Cancer Center and MEEI.

In some cases, patients benefit from the expertise of adult neurosurgeons specializing in minimally invasive techniques that increase safety and improve access to deep lesions. Mass General neurosurgeons played a key role in developing these techniques, which involve navigating a pathway to the skull base via an endoscope placed through the nose. The surgical team also has expertise in microvascular reconstruction.

At MGH/C, a high percentage of pediatric patients with tumors of the brain or skull base receive treatment at Mass General’s Francis H. Burr Proton Therapy Center, the longest continuously active proton therapy program in the United States. The inherently conformal nature of proton therapy is especially important in pediatric skull base tumors because it allows for delivery of the full therapeutic dose while minimizing damage to normal surrounding tissue. In addition, as with other conditions treated at MGH/C, patients benefit from breakthroughs in adult cancer treatments. For example, Mass General researchers have made significant contributions to the understanding and treatment of all types of neurofibromatosis (NF), including being home to the second-oldest NF clinic in the country and receiving credit for identifying some of the genes involved. According to Scott Plotkin, MD, PhD, director of the Neurofibromatosis Clinic, Mass General’s services for NF patients are unique in that they include specialized care for patients with NF1, NF2 and schwannomatosis. The clinic also sees both pediatric and adult patients and offers a seamless transition from pediatric to adult specialists. Clinical specialists provide expert reproductive care and genetic counseling to individuals with NF wishing to lower the risk of passing the disorder on to their children.

Surgeons specialized in neurofibromatosis
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Although the three conditions are unrelated, each causes development of tumors of the nervous system. Patients with NF2, for example, develop vestibular schwannomas or acoustic neuromas on both nerves to the ears, while individuals with schwannomatosis develop multiple schwannomas on cranial, spinal and peripheral nerves but no vestibular schwannomas. Safe excision of these tumors requires the experience and expertise of neurosurgeons like those at Mass General who see a high volume of patients with NF.

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First-in-Nation Clinics for Epilepsy Syndromes

Genetic disorders such as tuberous sclerosis complex, Angelman syndrome and duplications of chromosome 15q (dup 15q) can affect multiple organs, making management of children challenging outside of a major medical center. While phenotype varies among the different syndromes and by individual, the majority of children with these genetic disorders have epilepsy. In many cases, these seizures are refractory. Because seizures are so common in this population, patients are managed in specialty clinics within the MassGeneral Hospital for Children (MGHfC) Pediatric Epilepsy Program. Patients and families benefit from the expertise of epileptologists who are performing epilepsy research and treating a large number of patients with these disorders as well as from coordinated care from a team of pediatric specialists wellversed in gene-related and refractory seizures. The program also provides consultations and highly coordinated, specialized care for children with difficult-to-manage seizures unrelated to genetic syndromes. Management may include novel medical and dietary approaches and/or surgery that utilizes leading-edge technology and research to noninvasively pinpoint seizure focus.

See page one to read more.