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ON THE COVER: Coronal view showing thermogram obtained during intraoperative MRI laser ablation of the left mesial frontal area in a 17-year-old male patient with a history of intractable epilepsy. See article on page 4.
“It is the long history of humankind (and animal kind, too) that those who learned to collaborate and improvise most effectively have prevailed.” — CHARLES DARWIN

On New Year’s Day 2008, Cleveland Clinic abolished the traditional medical specialty-based organizational structure that had been a fixture of our hospital system since its founding nearly 90 years earlier.

In its place arose a new model of care built on patient-centered institutes. Each institute would be an integrated practice unit combining medicine, surgery, research and education, organized around a disease (cancer), organ or organ system (heart and vascular, urology), or practice area (geriatrics, women’s health).

The goal of this new infrastructure was to forge an interdisciplinary collaboration among physicians and scientists with similar interests, striving together for excellence. It was intended to enable strategic thinking, coordinate treatment, spark invention, share best practices and resources, and eliminate the organizational silos that spawn competition and inefficiency. Patients would benefit from improved communication and access, consistent care, and managed costs.

Nearly eight years later, pediatric neurosciences is a prime example of this collaborative initiative’s success. The program unites the activities of our Neurological and Pediatric Institutes, two centers of excellence dedicated to the treatment of, and scientific inquiry into, diseases of the central and peripheral nervous system — one from a disease-based approach, the other based on age. Pediatric neurosciences also taps the expertise of Cleveland Clinic Children’s, our vibrant pediatric “hospital within a hospital.”

This pooling of knowledge and capabilities from across the Cleveland Clinic enterprise makes possible the innovations in care that you will read about in the pages of Pediatric Neuroscience Pathways.

The treatment of epilepsy, for example, requires the intimate linkage of neurology and neurosurgery and the convergence of brain imaging and functional mapping. This synergy is evident in the articles describing our experience with magnetoencephalography to evaluate pediatric epilepsy surgery candidates, and our use of the emerging technique of laser ablation employing stereoelectroencephalography in pediatric patients with difficult-to-localize epilepsies.

Multidisciplinary and interinstitutional collaboration is also apparent in the exciting account in these pages of our application of deep brain stimulation to treat pediatric movement disorders.

The increasingly blurred boundaries between pediatric and adult disease provide an opportunity to tackle difficult neurological challenges across our patients’ life spans in a multidisciplinary, coordinated manner, and to implement new treatments for nervous system disorders. Our Neurocardiac Clinic, as you will read, is an example of this unique transitional care approach — managing the long-term neurodevelopmental disabilities that children with congenital heart disease experience as surgical advances make it possible for them to survive into adulthood.

It is an energizing time at Cleveland Clinic. We hope that Pediatric Neuroscience Pathways provides a snapshot of the extraordinary progress we’re making in caring for these precious young patients, and the talent and dedication of the clinicians and researchers who work together on these complex cases. Their commitment is why U.S. News & World Report consistently ranks our neurology and neurosurgery programs and Cleveland Clinic Children’s as among the best in the nation. Please contact us if we can help you or your patients.

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Combining Robotic SEEG with Laser Therapy:  
A Minimally Invasive Approach for Children with Difficult-to-Localize Epilepsy 

By Jorge Gonzalez-Martinez, MD, PhD, and Ahsan N.V. Moosa, MD

KEY POINTS

• Laser ablation of epileptogenic foci employing stereoelectroencephalography (SEEG) is a feasible treatment option in pediatric patients with difficult-to-localize epilepsies, even in the most difficult clinical scenarios, such as nonlesional scans.

• Laser therapy combined with SEEG may also be particularly suitable for deep, difficult-to-access lesions such as insular lesions, hypothalamic hamartoma and periventricular heterotopias.

• Short-term results of laser ablation-SEEG epilepsy surgery have been promising. Precise localization is key to a successful outcome.

Initially described in 2006 as a treatment for metastatic tumors, laser ablation guided by real-time MRI has shown promising results in the treatment of multiple intracranial pathologies including primary and metastatic lesions, epileptogenic foci and radiation necrosis.

The treatment of epileptogenic areas such as tubers (in tuberous sclerosis) and in mesial temporal sclerosis (via selective laser amygdalohippocampotomy), focal cortical dysplasias, hamartomas and poststroke epilepsy has been described in the literature. The advantages associated with laser ablation are attributed to the small opening required to accommodate the probe, the precision related to the probe's final location, and the relatively short ablation time associated with each treatment (which averages less than five minutes, following placement of the laser catheter).

All of these attributes can make laser ablation a safer, more cost-effective and more efficient treatment option than other approaches for pediatric patients with medically intractable focal epilepsy. Additionally, it provides access to areas where surgical treatment using conventional therapies would be contraindicated.

Pioneering SEEG’s Integration with Laser Ablation

While our epilepsy center has previously published cases of laser ablation of epileptogenic lesions, the use of the robotic stereoelectroencephalography (SEEG) technique in combination with laser ablation surgery to disrupt a specific epileptogenic network in patients with nonlesional epilepsy has not been reported. We have been performing this pioneering and innovative work in our center for the past year, with promising results in terms of seizure control and safety.

Case Description

Epilepsy history: A 17-year-old male presented with a history of intractable epilepsy since 9 years of age. He described his seizures as a “cold chill down the whole body” followed by partial awareness of subsequent events. Caregivers reported that his seizures began with a stare, changes in facial expression and pouting of the mouth, accompanied by changes in breathing pattern. Often he walked aimlessly or made quick “robotic” movements. Seizures ended with a scream that startled anyone nearby and disrupted the patient’s social life. Seizures lasted only 15 to 20 seconds but occurred as frequently as 20 times a day, and almost every hour during sleep. The patient presented to Cleveland Clinic after having failed eight different anti-epileptic drugs and vagal nerve stimulation. His neurological examination was normal.

Presurgical, noninvasive workup:

Video EEG evaluation suggested a diagnosis of left frontal epilepsy based on interictal spikes and ictal patterns in a few seizures. Several other seizures, however, were poorly localized, with bifrontal involvement. A 3T MRI brain scan did not reveal any lesion. Fluorodeoxyglucose positron emission tomography (FDG-PET) showed focal hypometabolism in the left frontal region. Ictal single-photon emission computerized tomography (SPECT) also showed hyperperfusion in the left anterior medial frontal region. A magnetoencephalogram (MEG) confirmed epileptiform discharges in the same region (Figure 1). Absence of a lesion on brain MRI and the localization in the dominant frontal lobe led to consideration of invasive monitoring with SEEG. This procedure was performed to map the epileptogenic zone and to determine the margins of the resection.
Invasive monitoring with robotic SEEG:
During SEEG monitoring, the electrode in the left anterior mesial frontal area (L’ electrode, contacts 2, 3 and 4) showed focal and persistent repetitive spikes throughout the evaluation (Figure 2). All of the recorded seizures also arose from the same region (Figure 2). This was concordant with the presurgical suspicions. Stimulation of the same regions elicited habitual seizures, further reinforcing the hypothesis. After discussion with the patient and his family, we elected to laser ablate the focus at the time of removal of the SEEG electrodes.

Laser ablation:
Under general anesthesia, a small lesion centered at the previous location of the L’ electrode (left mesial frontal area, contacts 2, 3 and 4) was created (Figure 3). The lesion’s volume was approximately 1 cm³. The treatment period, from the time of insertion of the laser probe to the end of the lesioning phase, was five minutes. Afterward, the probe was removed, the incision was closed with one stitch and anesthesia was reversed. The patient was discharged from the hospital the next morning.

Outcome:
At the three-month postoperative follow-up, the patient was seizure-free. He has had no change in personality or memory. However, his family reports a new “problem”: “Since surgery, we don’t know if he is at home or not!” (because his seizure-associated screams have ended).

Conclusions:
Our preliminary experience with the described method clearly illustrates the feasibility of a unique combination of robotic SEEG, laser ablation and intraoperative MRI in the management of children with difficult-to-localize epilepsy. While we acknowledge that further study is needed, the success of this procedure suggests the possibility of a diagnostic-therapeutic combination that offers unparalleled minimal invasiveness, duration of treatment and brevity of recovery time, without compromising efficacy.

Suggested Reading


FIGURE 1. Left frontal localization supported by noninvasive testing.

FDG-PET: showed focal hypometabolism in the left frontal region
Ictal SPECT: showed focal hyperperfusion in the left frontal region
MEG: showed focal discharges in the same region

Cleveland Clinic’s preliminary experience merging robotic SEEG with laser ablation surgery to treat patients with nonlesional epilepsy has shown promising results in terms of seizure control and safety.
FIGURE 2. Intracranial SEEG confirms ictal onset localized to left anterior mesial superior frontal gyrus (L’ 2-4).

FIGURE 3. Images (coronal and axial views) showing thermograms obtained during intraoperative MRI laser ablation of the left mesial frontal area.
Magnetoencephalography for Evaluation of Pediatric Epilepsy Surgery Candidates

By Richard C. Burgess, MD, PhD, and Sumiya Shibata, MD, PhD

KEY POINTS

- Magnetoencephalography (MEG) is a sophisticated brain functional mapping and neuronal activity localization tool that can aid evaluation and surgical planning in the treatment of neurological disorders such as epilepsy and brain cancer.
- MEG is particularly useful in the evaluation of pediatric epilepsy patients due to its noninvasiveness, lack of radiation exposure and use in an outpatient setting.
- Cleveland Clinic’s MEG lab has assisted in the care of more than 1,000 patients since its launch in 2008.

For pediatric epilepsy patients being considered for a targeted surgical resection, magnetoencephalography (MEG) is a localization tool that can significantly impact surgical strategy. MEG provides a direct measurement of neuronal activity and can be used to accurately pinpoint the location (within 3-4 mm) of physiological interneuronal communication or aberrant discharges.

MEG measures the extremely weak magnetic fields generated by neuronal activation. It can identify the location and duration of the net synaptic transmissions of clusters of nerve cells. It provides localization information about both normal and abnormal brain function, enabling the creation of a functional map of the cortex. MEG can isolate the source of aberrant neuronal activity and can determine the spatial relationship of eloquent cortex to nearby pathological regions, thus helping guide the evaluation and treatment of patients with epilepsy or brain tumors.

Since brain magnetic fields are several orders of magnitude weaker than ambient magnetic noise from the environment, the MEG scanner is housed in a magnetically shielded room. Its sensors consist of detection coils and their corresponding superconducting quantum interference devices (SQUIDs), which use superconductivity produced by temperatures very close to absolute zero to amplify the weak neuronal signals. Approximately 300 detection coils, housed in a dewar containing liquid helium, surround the patient’s head to provide a dense spatial sampling of the neuromagnetic activity of the entire brain.

Because the MEG recording is reference-free and the neuromagnetic signals are not attenuated by bone and scalp, MEG has a higher sensitivity and more precise localization capability for brain signals than does electroencephalography (EEG). In addition, MEG’s temporal resolution is on the order of milliseconds. Using the high spatial and temporal resolution provided by MEG recording, the location, strength and orientation of the brain signal’s source can be accurately inferred using specialized computer processing based on mathematical modeling.

There are approximately 30 clinical MEG centers in the United States, and most commercial health insurance carriers now provide reimbursement for MEG scans.

Cleveland Clinic’s MEG Experience

Since the MEG lab’s inception at Cleveland Clinic in 2008, we have applied MEG in more than 1,000 patients for precise localization of epileptic seizures, accurate mapping of functional areas in the brain, and uncovering of interictal spikes that cannot be identified using scalp EEG. In many patients these results have been of critical assistance in the planning for surgery.

MEG is an especially valuable tool in the evaluation of pediatric patients with epilepsy. A scan is safe, noninvasive and painless. MEG uses no ionizing radiation, generates no magnetic fields and requires no injections. The machinery is quiet and almost never produces a feeling of claustrophobia. MEG is usually an outpatient procedure. Parents may accompany children into the MEG testing room to calm and comfort them.

MEG confirmation of the epileptic focus and refinement of its location make it possible to select patients with medically refractory epilepsy who may benefit from surgical resection. It is particularly helpful in MRI-negative patients, or when MRI has identified multiple lesions. In some cases MEG may allow epilepsy surgery to proceed without the need for long-term intracranial EEG monitoring.

In addition, MEG’s ability to delineate the spatial relationship between the pathological region and nearby eloquent cortex helps guide the surgical trajectory. For example, the somatosensory evoked field (SEF) elicited by electrical stimulation of the median nerve is used to functionally map somatosensory cortex. SEF can precisely determine the central sulcus, even in cases where the primary somatosensory area has been altered by space-occupying lesions or moved by seizure disorders.

At Cleveland Clinic, MEG findings have been used to determine therapeutic management in an increasing number of pediatric patients. The recent examples described below demonstrate MEG’s utility.

Case Study I

A 10-year-old girl with tuberous sclerosis complex and attention deficit hyperactivity disorder suffered from medically refractory epilepsy, with weekly seizures. Video EEG evaluation suggested that the seizures arose from the right side of her brain. However, brain MRI scan showed multiple lesions in the left side and none in the right side. Fluorodeoxyglucose positron emission tomography was nonlateralizing, exhibiting bilateral hypometabolism.

MEG showed interictal epileptiform discharges, all originating from a restricted location in the deep gray matter of the right middle frontal gyrus (Figure 1). Careful scrutiny of a repeat brain MRI scan in the region identified by MEG revealed a subtle, ill-defined hyperintensity extending centrally to the ventricle.

Placement of intracranial electrodes was guided by the MEG and MRI results. Based on the intracranial recording, it was possible to perform a limited resection of the epileptic focus, sparing motor function (Figure 1). Postoperatively, the patient had a mild hemiparesis on the
left side that soon resolved with physical therapy. The surgery not only eliminated this young girl’s seizures but also profoundly affected her behavior. She has become calm and has improved verbal expression. In this case, MEG was of crucial help in identifying the focal epileptogenic zone so that the patient could undergo successful epilepsy surgery.

MEG has been established as a means for promptly re-examining structural imaging, as exemplified by the results of the repeat MRI in this case. In addition, we have studied the prognostic value of coupling MEG results with postprocessing of the MRI scan and have found a remarkable improvement in outcome when the locations identified by MEG and voxel-based MRI morphometric analysis program (MAP) are concordant and are resected (100 percent seizure-free [examples are shown in Figure 2] vs. nonconcordant [only 39 percent seizure-free]).

Case Study II

A 12-year-old boy presented with refractory complex motor seizures triggered by “surprise” tactile stimulation. His brain MRI showed encephalomalacia in the frontal lobes bilaterally as well as in the left parietal lobe due to perinatal hypoxia/ischemia. Video EEG evaluation suggested that the seizures arose from the left frontotemporal region.

The SEF response to right median nerve stimulation identified the central sulcus on the left side, and the spontaneous MEG recording showed a single cluster of interictal dipoles anterior to the central sulcus (Figure 3). The excellent temporal resolution of MEG enabled tracking of the epileptic discharges along a consistent propagation pathway from medial to lateral and anterior to posterior. In this case, MEG provided high-resolution mapping of both the normal brain function and the nearby epileptic focus. MEG’s role in surgical planning is especially important in patients whose epileptic focus is close to eloquent cortex.

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REFERENCE

Ultrasound-Guided Chemodenervation in Children: Botulinum Neurotoxin Injections Can Provide Safe, Effective Relief from Spasticity

By Mohammed Aldosari, MD

**KEY POINTS**

- Botulinum neurotoxin (BoNT) is a safe, effective option for treating muscle spasticity in children.
- Treatment between ages 2 and 6 years can reduce surgical procedures and improve gait pattern.
- Ultrasound guidance can facilitate needle placement to improve delivery of BoNT and reduce complications.

Botulinum neurotoxin (BoNT) selectively blocks the release of acetylcholine at the cholinergic nerve terminal, causing temporary, focal chemodenervation of muscles and resultant reduction in spasticity.

In 1993, Koman et al. published preliminary results of the first clinical trial using BoNT for spasticity in patients with cerebral palsy (CP). Their rationale for using BoNT was that spasticity reduction would provide a therapeutic window for intervention and supportive therapies.

Since that time, BoNT use has proved to be a safe and effective option for the treatment of muscle spasticity in the pediatric population and is widely accepted.

BoNT treatment is recommended between ages 2 and 6, when gait patterns and motor function are still flexible. When BoNT is used in combination with other modalities, early treatment can delay the need for, and reduce the frequency of, surgical procedures and result in a favorable gait pattern.

Although initial studies focused on BoNT use in ambulatory children with mild impairments, recent studies, including a double-blind, sham-controlled trial, suggested that BoNT can be safe and effective in children with severe CP (Gross Motor Function Classification System levels IV and V). Dystonia, excessive drooling and tics are examples of other clinical indications for utilizing BoNT as adjunct therapy in the pediatric population.

**Injection Guidance Techniques**

Precise delivery of BoNT into targeted muscles provides a marked local improvement in spasticity while reducing the probability of undesired effects in adjacent muscles and adverse systemic side effects.

Correct needle placement, especially in small or deep-seated muscles, is challenging, even for an experienced operator. Several studies have shown that the utilization of anatomical landmarks and muscle palpation alone provides inadequate guidance for reliable needle placement. In 2005, Chin et al. found that needle placement by anatomic localization alone failed in 22 percent of cases when the gastroc-soleus was injected, and it failed in at least 87 percent of cases when the tibialis posterior muscle or flexor carpi radialis muscle was injected.

Electromyography and electrical muscle stimulation provide effective guidance and are widely used in the adult population. These methods have limited use in children, however, because they are painful and time-consuming and require the patient’s cooperation. Of the other imaging techniques explored as potential alternatives in pediatric cases, particularly to guide injections into deep-seated muscles, ultrasound has proved to be the most convenient and practical.

**Visualizing Anatomy and Needle Placement**

Ultrasound provides information about muscle size and fibrosis, both of which can be important factors in decision-making. Additionally, the modality enables the operator to directly visualize the entire process, including needle placement. This allows the operator to gain a better understanding of the individual’s anatomy while performing the injection, facilitating target selection and further improving injection technique.

In patients who are uncooperative or sedated, ultrasound can be very helpful in identifying small muscles involved in spasticity and focal dystonia, such as single fascicles of finger flexors. Ultrasound also allows clear differentiation of structures near target muscles, making it helpful in preventing subcutaneous or intravenous injection.

Ultrasound guidance can also help avoid the pain that arises when the needle comes into contact with the periosteum, and in cases where the psoas muscle is injected, ultrasound imaging safeguards against accidental injection into the intestines.

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Ultrasound helps identify small muscles involved in spasticity and local dystonia, while allowing clear differentiation of structures near target muscles to safeguard against subcutaneous or intravenous BoNT injection.

SUGGESTED READING


Deep Brain Stimulation for Pediatric Movement Disorders: Increasing Interest, Expanding Applications

By Mohammed Aldosari, MD; Andre Machado, MD, PhD; and Hubert H. Fernandez, MD

KEY POINTS

• Interest in and use of deep brain stimulation (DBS) to treat pediatric movement disorders has increased during the past decade.

• Though it can present technical challenges in pediatric patients, DBS has proved effective in treating medically refractory primary genetic dystonias and is being extended to secondary dystonias, including those associated with cerebral palsy, stroke and neurodegenerative conditions, as well as medically refractory Tourette syndrome.

• While measurable clinical benefits may appear modest in some cases, DBS can considerably improve pediatric patients’ quality of life, functional abilities and future development prospects while easing caregiver burden.

• It is imperative that detailed outcomes studies be conducted to improve patient selection criteria, surgical timing, lead placement targets and operative techniques.

Pharmacological treatment of pediatric movement disorders is often unsatisfactory. Medications are frequently only partially effective in terms of controlling abnormal movements. Side effects are often a dose-limiting factor.

In adults, deep brain stimulation (DBS) has become an established treatment option for various medically refractory movement disorders including Parkinson disease, dystonia, essential tremor and Tourette syndrome. DBS is also demonstrating efficacy for an expanding range of neurological and psychiatric disorders that have failed pharmacological therapies.

Evolving DBS Use in Pediatrics

During the past decade, interest has grown regarding the use of DBS in children to treat various movement disorders. Pediatric DBS use is particularly promising since early treatment may have a significant impact in young patients, such as improving functional abilities, quality of life and social integration, and enabling the completion of education and the possibility of employment.

DBS has been shown to be highly effective for the treatment of medically refractory genetic primary dystonias and, in some cases, the near elimination of dystonic movements and dystonia-related disability. DBS’s success in these disorders has inspired its application to secondary dystonias, including those associated with cerebral palsy (CP), stroke and neurodegenerative conditions.

CP is the most common nongenetic cause of secondary dystonia. About 10 to 15 percent of patients with CP develop a dyskinetic or extrapyramidal movement disorder. The involuntary movements typically start during early infancy and may be slowly progressive. Affected patients are frequently severely disabled in their motor function, although their cognitive function may be normal or near normal.

Several case reports and case series have been published about the therapeutic outcome of DBS in patients with dyskinetic/extrapyramidal CP, reporting varying results. Although most reports show that the direct clinical benefit in reducing dystonic movements is less dramatic than the level of reduction observed in idiopathic dystonia, a moderate but clinically significant improvement in dyskinesia in patients with dyskinetic/extrapyramidal CP has been shown after DBS surgery. More important, quality of life, functional abilities, pain and caregiver burden can be considerably improved after DBS, even without clinically measurable changes in dystonia severity.

One important note is that traditional dystonia rating scales do a poor job of distinguishing small but meaningful improvements in levels of function (such as wheelchair control and activities of daily living) that are important in this population of patients. Many of these patients and their families perceive their improvement after DBS in quite a different way than is reflected by clinical rating scales, and small changes in function or mobility seem to bring essential benefit for these patients. There are reports of improvement of severe oromandibular dystonia with DBS, allowing children to speak and eat for the first time.

Other causes of secondary dystonia, including those associated with neurodegeneration with brain iron accumulation, glutaric aciduria, mitochondrial cytopathies, autoimmune inflammatory disease of the basal ganglia, Lesch-Nyhan syndrome, and secondary dystonias of unknown etiologies, have shown similarly promising responses to DBS therapy.

Another promising application is the use of DBS in children and adolescents with medically refractory Tourette syndrome (TS). Some patients with TS experience worsening symptoms associated with severe physical, emotional, social, academic and occupational difficulties. In some cases, surgical management might be their only remaining option. A growing body of experience indicates that tics uniformly improve after DBS. Moreover, the neuropsychological and psychiatric comorbidities frequently improve with DBS therapy.

Recent Advances in Operative Techniques

Clinical outcomes have been shown to be dependent on precise placement of DBS leads. Pediatric patients undergoing DBS present unique technical challenges.

In adults, the traditional method for DBS lead implantation involves physiological localization while patients are awake. Physiological localization methods have included microelectrode recording and/or intraoperative test stimulation to assess for therapeutic effects and
stimulation-induced adverse events. Since these methods often require the patient to be calm and cooperative during several hours of testing, they are not appropriate for most children.

Consequently, real-time interventional MRI (iMRI) guidance has been developed for implanting DBS leads. iMRI allows as-needed intraoperative imaging. Utilizing iMRI to guide placement of DBS leads in children has been associated with highly accurate electrode placement, which results in improved clinical outcomes.

Cleveland Clinic was one of the first centers in the United States to implement intraoperative MRI in deep brain stimulation surgery, including in children.

In our experience, patients can stay with their parents in an induction room until just before starting general anesthesia, thereby reducing the anxiety associated with entering the operating room. Once the surgical team devises a plan, DBS leads or temporary MRI-compatible probes are inserted into the targeted brain areas, and new MRI images are obtained. The final location for the leads is then determined. The pulse generator can also be implanted under general anesthesia. Postoperative programming of the devices is performed by specialized professionals with extensive experience in DBS and movement disorders.

Future Directions

The application of DBS to the pediatric population is rapidly evolving. DBS is expected to become an early and effective treatment option for an expanding range of pediatric movement disorders. Detailed studies of outcomes to improve patient selection criteria, timing of the surgery, lead placement targets and operative techniques are urgently needed.

The development of more sensitive rating scales to assess important functional changes will help in evaluating the clinically meaningful benefits of DBS, especially in children with secondary dystonias. Innovative operative technologies are also expected to improve outcomes and decrease potential surgical complications.

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SUGGESTED READING


Neurocardiac Clinic: Addressing the Unique Needs of Children with Congenital Heart Disease

By Neil R. Friedman, MBChB

KEY POINTS

• With improved survival of children with congenital heart disease, attention is shifting to management of the long-term neurodevelopmental disabilities these children suffer.
• Brain injury and neurodevelopmental deficits result from a combination of impaired fetal brain development and circulation, potential coexisting genetic syndromes, complications of cardiopulmonary bypass surgery, and pre- and postsurgical hemodynamic instability.
• A multidisciplinary approach is needed to address the unique needs of children with complex congenital heart disease, including neurodevelopmental screening and detailed evaluation, ongoing care and monitoring, and education and assistance for patients and families.

The seat of the soul and the control of voluntary movement — in fact, of nervous functions in general — are to be sought in the heart. The brain is an organ of minor importance. — ARISTOTLE (from De Motu Animalium, 4th century B.C.)

The debate about the importance and interdependence of the heart-brain relationship is an ancient one. The ancient Egyptians believed the heart was the center of knowledge, recording all the good and bad deeds of a person’s life, such that the hearts of Egyptian mummies were carefully embalmed and preserved, while their brains were discarded along with other internal organs and stored outside the burial sarcophagus. The cardiocentrists, epitomized by Aristotle (384-322 BC), believed the heart was the seat of the soul and of reason, whereas the cerebrocentrists, including Plato (ca. 427-347 BC), Hippocrates (460-370 BC) and Herophilus (ca. 335-280 BC), believed the brain served this function.

Fortunately, since the days of these venerable philosophers, the advancement of science has enabled us to understand the brain’s primary role in human cognition, development and emotion, as well as the profound relationship between cardiac and neurological pathologies.

Survival Gains but with Neurodevelopmental Issues

Advances in congenital heart surgery during the past 40 years have been dramatic, to the point that there are currently more adults surviving with congenital heart disease (~1.2 million) than there are children with the condition.

Congenital heart disease (CHD) remains one of the most common birth defects, affecting nearly 1 percent (~30,000-40,000) of births per year in the United States. The era of neonatal corrective surgery, which still defines current management trends, began in the early 1970s with Sir Brian Gerald Barratt-Boyes, a pioneering New Zealand cardiothoracic surgeon. His introduction of hypothermia and cardiac arrest for corrective neonatal surgery meant that children with CHD were exposed to decreased chronic hypoxia and less palliative surgery, with reduced morbidity from recurrent bypass.

With improved survival, neurological injury has become the major extracardiac complication from cardiopulmonary bypass (CPB) and CHD. Early morbidity includes stroke, seizures and epilepsy, but increasingly attention is being paid to the long-term neurodevelopmental disabilities these children suffer.

Although initially attributed to the effects of CPB surgery, the incidence of neurodevelopmental disability did not decrease despite extensive efforts through the 1980s and 1990s to optimize bypass surgery variables. It is now well-recognized that impaired fetal brain development and circulation, coexisting genetic syndromes, and pre- and postsurgical hemodynamic instability are equally important factors contributing to brain injury and neurodevelopmental outcome.

Distinctive neurodevelopmental profiles in children with CHD are now recognized and include problems such as:

› Learning disabilities
› Language delay
› Behavioral difficulties (attention deficit hyperactivity disorder [ADHD], executive dysfunction)
› Difficulties with communication (pragmatic language) or adaptive behaviors
› Visual-spatial dysfunction and coordination (fine motor, oromotor) difficulties
More than 400 children have been evaluated in Cleveland Clinic’s Neurocardiac Clinic since its opening in 2011, providing unique insights into the long-term disabilities they face and the impact of these disabilities on their quality of life.

Approximately 30 to 50 percent of children who have undergone cardiopulmonary bypass for complex CHD will require remedial school services, and 15 percent will need full-time special education. Early identification of neurodevelopmental impairments offers the best opportunity for intervention and treatment, thereby allowing the child to reach his or her fullest potential and minimize disabilities.

Recognizing these problems, the American Heart Association in 2012 released a scientific statement recommending periodic developmental surveillance, screening and evaluation of children with CHD.1

An Interdisciplinary Approach to CHD Care

In late 2011 Cleveland Clinic established a comprehensive, dedicated Neurocardiac Clinic as part of our Neurocardiology Program to address the unique needs of children with complex CHD. This interdisciplinary clinic provides early screening and detailed evaluation of children at risk for neurodevelopmental disabilities, ongoing care and monitoring of neurodevelopmental problems, and education and assistance for patients and families. Specialists include pediatric neurologists, cardiologists, developmental pediatricians, behavioral health/psychologists, and speech, occupational and physical therapists.

More than 400 children have been evaluated in the clinic, providing unique insights into the long-term disabilities these children face and the impact of these disabilities on their quality of life.

Tackling Migraines, ADHD Medication Concerns

New research by our group has highlighted the frequency and severity of migraine headaches in this population — a condition that is under-recognized and undertreated and has a significant impact on quality of life.

Current work also involves assessing the safety and optimal monitoring of ADHD medications in this vulnerable population, given the frequency of ADHD and of concerns regarding the use of ADHD medication in children with CHD. Stimulant medications such as methylphenidate or amphetamine-based products are often most effective for ADHD but carry certain potential cardiac risks such as increased heart rate and potentially elevated blood pressure.

Other ADHD treatment options include alpha 2 adrenergic agonists (short- or long-acting guanfacine), which may cause modest, dose-dependent decreases in blood pressure and heart rate (although typically asymptomatic), or atomoxetine, a selective norepinephrine uptake inhibitor, which may cause an increase in heart rate and blood pressure. Physicians generally should avoid prescribing atomoxetine for patients with known serious structural cardiac abnormalities, cardiomyopathy or serious heart rhythm abnormalities that could elevate the risk for noradrenergic effects.

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REFERENCE

Dose Response Curves and Predictors of Response to Methylphenidate and Mixed Amphetamine Salts in School-aged Children and Youth with Attention Deficit Hyperactivity Disorder

By Michael Manos, PhD; Eric Geyer, BA; Ralph D’Alessio, BA; Kimberly Giuliano, MD; and Michael Macknin, MD

KEY POINTS

- Despite psychostimulants’ effectiveness in treating children with attention deficit hyperactivity disorder, dose response across children varies considerably and has not been studied in depth.
- This response variability often goes unnoticed by physicians, which can compromise optimal treatment.
- In addition to a linear dose response, psychostimulants are capable of producing five other patterns of response in individuals — some with predictable results and others with unpredictable outcomes.
- The idiosyncratic nature of children’s responses to psychostimulants necessitates close monitoring during titration to optimize treatment.

Substantial evidence from clinical trials confirms that psychostimulants improve symptoms in children with attention deficit hyperactivity disorder (ADHD) and that their pharmacokinetic properties are well-documented.1

There remains, however, a dearth of information regarding how behavior changes during stimulant titration.

The prescribe-and-wait method in which the physician uses the skill and art of medical practice to determine the best dose is common and may be informed only by the physician’s personal experience with his or her patients.2 In clinical practice, however, stimulant dose response varies considerably across ADHD subtypes, patient age and gender, type of stimulant, and other variables that have been only peripherally studied.3

To date, factors that inform and predict response to stimulants remain elusive. Because the relationship between dose and response tends to be predominantly linear (i.e., as dose increases, behavioral improvement increases), clinicians have a tendency to expect this pattern and subsequently may not systematically observe and measure response as it occurs. Response variability often goes unnoticed,4 and when it is overlooked, optimal treatment can be compromised.

Early clinical practice parameters suggested that dosing should be carried out according to gross body weight, beginning with 0.3 mg/kg in a twice-daily regimen and titrating upward until undesirable side effects emerged or behavior improved. This method was untenable, however, because pharmacological factors such as drug absorption, metabolism and excretion rates produce great interindividual variability.5

Though a linear dose response — improvement as a direct function of increasing dose — is found consistently at the group level of analysis, individual children vary considerably in behavior change across dose levels.6 In addition to a linear response, there are five other patterns of response in individuals. A curvilinear response is incremental improvement at a low and moderate dose followed by a decrement at a high dose. A threshold response is the absence of observed improvement at a low or moderate dose with abrupt therapeutic benefit at a high dose. Variable response curves are marked by irregular response to dose changes — improvement at a low dose, deterioration at a moderate dose and improvement again at a high dose. Placebo responders are those who show equal reaction between medicine and a nonmedicine placebo capsule. Finally, some individuals just do not respond to pharmacotherapy and show no change during standard dosing.

Three curves are predictable in that they tend to yield results in specific regimens and have a readily recognizable course of action. Behavior that improves as dose increases (linear) indicates to the physician that optimal dose may be achieved by ramping up the dose. If behavior deteriorates at higher doses (curvilinear), the best dose is achieved by using the dose just prior to behavior deterioration. If no response is observed with the initial doses, a further increase in the dose may still yield an optimal response (threshold).

The remaining three curves, however, are unpredictable and do not guide the physician as to the next action during titration. Curves that inconsistently improve response (variable), despite an increase or a decrease in the dose, give little guidance to the physician as to the next action, such as to terminate, change or extend the titration. The same is so when individuals respond to treatment regardless of the medicine or dose (placebo). Finally, some children do not respond to medicine except at unusual dose levels (no change), and these are seldom pursued in primary care. Dose curves are illustrated in Figure 1.

These distinctions describe dose response patterns that confound titration of psychostimulants during pharmacotherapy for children with ADHD. They also identify characteristic patterns with implications for pediatric practice for ADHD treatment. We investigated these patterns in the Medication Monitoring Clinic of Cleveland Clinic’s ADHD Center for Evaluation and Treatment. A sample of 249 children and youth meeting DSM-III or DSM-IV diagnostic criteria for ADHD was evaluated using a four-week double-blind placebo-controlled protocol. Physicians prescribed twice-daily dosing of methylphenidate, single daily dosing of mixed amphetamine salts (MAS) or sculpted dosing of MAS (MAS-S — higher dose in the morning; 5 mg dose at about 3 p.m.) for youths ages 5 to 17 years. Data were collected at baseline and across the pharmacological protocol, which specified four possible dose response sequences (BL = baseline, A = placebo, B1 = 5 mg, B2 = 10 mg, B3 = 15 mg):

1. BL - A - B1 - B2 - B3
2. BL - B1 - A - B2 - B3
3. BL - B1 - B2 - A - B3
4. BL - B1 - B2 - B3 - A
Each participant was randomized to one of the four dosing sequences. Teachers and parents rated symptom presence at baseline and at the end of each treatment week using the Abbreviated Symptom Questionnaire: for parents. Total N = 249; linear = 106; curvilinear = 65; threshold = 18; variable = 19; no change = 20; placebo = 21.

Children’s responses to individual psychostimulant medications varied across age. Predictable dose response curves (linear, curvilinear and threshold) were associated with younger children (< 10 years), and unpredictable curves (variable, no response and placebo) were associated with older children (> 9 years). The idiosyncratic nature of children’s responses to psychostimulants necessitates close monitoring during titration to optimize treatment. Results underscore the need to use more sophisticated dosing strategies at older ages.

REFERENCES
PTEN Mutations and Autism: The Search for Individualized Treatments Gets Underway

By Thomas W. Frazier, PhD

New research out of Cleveland Clinic Children’s Center for Autism has focused on a genetic subgroup of children with autism spectrum disorder (ASD) — those with mutations of the PTEN gene — to identify a unique pattern of brain abnormalities and cognitive deficits. We are now building on these insights with new investigations that promise greater understanding of the biological mechanisms causing autism — and that ultimately may lead to individualized treatments.

Turning to a Genetic Subgroup for Answers

Disorders along the autism spectrum are frequently debilitating and lead to lifelong impairments in social interaction coupled with inflexible behavior. Research has identified a strong genetic component to autism, but identifying effective treatments has been difficult due to high variability in the underlying biology.

One approach to this problem is to study genetic subgroups of autism. Our group applied this strategy to individuals with PTEN mutations who also have autism spectrum disorder (PTEN-ASD). The PTEN gene was identified as a tumor suppressor gene by Charis Eng, MD, PhD, Chair of Cleveland Clinic’s Genomic Medicine Institute. Dr. Eng also noticed that parents with mutations in the PTEN gene were having a disproportionately large number of children with autism and very large heads, a feature consistent with brain overgrowth.

Our research group recruited 17 children with PTEN-ASD (mean age, 11.5 years) and compared them to patients with autism with no known genetic cause and to healthy controls. The primary goal was to identify specific patterns of brain abnormalities and thinking skills unique to PTEN-ASD. The secondary goal was to determine whether these patterns are linked to the molecular effects of PTEN mutations.

Findings: Useful Clinical Signals Emerge

Our study found that patients with PTEN-ASD had overgrowth of the white matter connections as well as spots where white matter development was clearly abnormal (Figure 1). These brain changes correlated with cognitive problems, such as reductions in information processing speed and memory, and motor difficulties in the PTEN-ASD group relative to both other study groups. These findings enabled us to determine that reduction in the PTEN protein drives brain overgrowth and white matter abnormalities that, in turn, drive these patients’ cognitive and behavioral impairment (Figure 2).

At a practical level, these data suggest that any child presenting with large head size and developmental or cognitive delays should receive genetic counseling and possible testing for a PTEN mutation. Such testing is particularly important because individuals with PTEN-ASD may have increased cancer risks due to the role of PTEN as a tumor suppressor and regulator of cell growth and proliferation.

Our findings also suggest that therapists treating patients with PTEN-ASD should speak slowly and clearly, with frequent repetition and attention questions, to ensure that children understand the information being communicated. Given the high rate of motor difficulties seen in patients with PTEN-ASD, patients also should be regularly referred for occupational and, in many cases, physical therapy.

Other Proteins Apparently Not Implicated

Interestingly, we did not find that other proteins related to PTEN were abnormal, suggesting that PTEN mutations cause reductions in PTEN protein levels but do not seem to cause changes in the typical PTEN biological pathways. This may indicate that reductions in PTEN protein levels are working through other mechanisms, such as interactions with mitochondrial or metabolic pathways or other noncanonical biological routes.

In the Works: A Longitudinal Study and Medication Trial

Future research is needed to pin down the exact molecular effects of PTEN protein loss and develop additional treatment targets. However, based on the low PTEN protein levels observed in this study, we have received funding as part of a consortium examining rare genetic causes of autism to longitudinally follow patients with PTEN-ASD over two years and begin a medication trial. The latter is especially exciting because it was designed based on knowledge of PTEN and associated pathways and would represent one of the first attempts to develop an individualized gene-based treatment approach for children with autism.

We hope to build on the findings reported here by using processing speed, memory and brain white matter changes as outcomes to provide more-sensitive treatment targets than those used in typical medication trials focused on autism symptoms or other behavioral aspects that often require long periods for changes to be detectable.

Ultimately, we believe this study and the planned follow-up research we are just beginning represent a new paradigm for autism research: Find the gene or set of genes causing autism, comprehensively study and follow patients with those genetic changes, and use the knowledge gained to develop individualized treatments.
Dr. Frazier (fraziet2@ccf.org; 216.448.6440) is Director of Cleveland Clinic's Center for Autism and a staff member of the Genomic Medicine Institute and the Center for Pediatric Behavioral Health.

More Findings of Note

In addition to these PTEN studies, Cleveland Clinic Children's Center for Autism is conducting pacesetting research in other aspects of autism. Below are profiles of two other significant recent publications by the center’s investigators.

Largest-ever study of clinically ascertained ASD in twins
In this study, we compared concordance in 568 monozygotic (identical) and dizygotic (fraternal) twin pairs, of whom 471 were affected with ASD, and identified a strong genetic component to ASD. Among the key findings:

› Shared environment was not supported as a causative factor, whereas genetic influences were strong.

› Social interaction and repetitive/inflexible behaviors appear to be driven by highly overlapping genetic influences.

This research supports the search for genetic influences on autism and suggests that environment may play only a minor role.

Largest-ever study of behavioral characteristics of females with ASD
This study, supported by the Simons Foundation Autism Research Initiative, analyzed data from 304 females and 2,114 males with ASD. It found that females had:

› Lower levels of restricted interests but greater irritability and externalizing behavior

› Weaker social communication skills, lower overall cognitive ability and poorer daily living skills

Our findings suggest that ASD may be underidentified in females and that this underidentification may be due to a focus on male-centric representations of autism in diagnostic instruments or to genetic or developmental protective factors.

REFERENCES


Should Radiation Therapy for Choroid Plexus Carcinoma Patients with Li-Fraumeni Syndrome Be Avoided?

By Tanya Tekautz, MD; Michal Bahar, MD; and Johannes Wolff, MD

KEY POINTS

- Choroid plexus carcinomas (CPCs) are often associated with Li-Fraumeni syndrome (LFS), a disorder usually characterized by an underlying germline mutation of the TP53 tumor suppressor gene.
- We conducted a literature analysis to test our supposition that radiation therapy should be avoided in CPC patients with LFS, since a TP53 mutation could confer primary radioresistance.
- Analysis showed an apparent survival disadvantage with the use of radiation therapy for LFS patients with CPC, and an increased risk of secondary malignancies associated with radiation therapy.
- Considering these findings and the fact that long-term survival without radiation therapy is possible in LFS patients with CPC, we propose that these patients should be classified separately and treated with radiation-sparing protocols.

The rare, highly invasive pediatric brain tumors known as choroid plexus carcinomas (CPCs) are often associated with Li-Fraumeni syndrome (LFS). This hereditary disorder, usually characterized by an underlying germline mutation of the TP53 tumor suppressor gene, predisposes carriers to sarcomas and malignancies of the brain, breast and adrenal glands.

CPC cases, which primarily involve infants and children younger than 2 years of age, account for less than 5 percent of all brain tumors. Their scarcity has precluded randomized clinical trials, meaning that decisions regarding the course of treatment for CPC patients must be derived from a limited record of case studies, small series reports and expert opinion.

Surgical resection of the tumor to the maximal extent possible is generally considered the preferred initial treatment, followed by adjuvant therapy, although the role and benefits of chemotherapy and radiation therapy are not well-defined. Radiation therapy improves survival in many patients with high-grade embryonal brain tumors and is often recommended for CPC patients. However, the significant, irreversible and progressive neurocognitive deficits and growth impairment it causes, especially in very young children, make its use controversial.

Previous research has demonstrated TP53’s crucial role in cell cycle control, genomic stability and response to DNA damage, such as from ionizing radiation. Mutation of TP53, as occurs in LFS, not only abrogates the P53 protein’s normal tumor suppressive function but also may disrupt cellular regulatory networks, thus enabling tumor cells to avoid genotoxic signals such as from gamma radiation, circumventing senescence and programmed cell death.

Testing the Radioresistance Hypothesis

For this reason, we hypothesized that LFS patients who harbor the TP53 mutation will have primary radioresistance, with treatment and survival implications. Supportive evidence comes from research by Boyle et al.,1 showing that eight TP53 mutation-carrying fibroblast strains from seven LFS donors showed increased cellular resistance to ionizing radiation, although at varying levels. Also, Malkin and colleagues2 reported a 22 percent five-year overall survival rate among nine CPC patients with LFS and TP53 germine mutations, compared with 100 percent five-year overall survival for 11 non-LFS CPC patients with TP53 wild-type tumors — a difference presumably due to heightened chemo- and radiation therapy resistance in the TP53-mutant strains.

We conducted a literature analysis to test our supposition that radiation therapy should be avoided in CPC patients with LFS, using a database of 11 research articles chronicling the treatment outcomes of 28 CPC patients with LFS. We compared overall survival among patients treated with radiation therapy, chemotherapy or surgery alone. The results of our meta-analysis were recently published in Anticancer Research3.

Of the 28-patient cohort, 24 had germline TP53 mutations, two had phenotypic characteristics of LFS (one without TP53 mutation and the other untested), and two had positive p53 staining but no TP53 mutations. Median age at diagnosis was 12 months. All patients underwent surgical resection, with gross total resection of the primary tumor achieved in 15 cases, partial resection in one case, and unknown results in 10 cases.

Twenty-seven patients received chemotherapy treatment at diagnosis, using a variety of regimens.

Eleven patients received radiation therapy, including five who were treated after tumor recurrence. Of those 11, six died from disease recurrence or progression and three from secondary malignancies. Two radiation recipients were alive and disease-free at the study’s completion.

Seventeen patients did not receive radiation therapy. One of those developed a secondary malignancy, seven died of cancer progression and nine remained alive at the study’s completion.

Survival and Tumor Progression Concerns

Analysis showed a marginally significant (p = 0.056) survival advantage for patients who did not receive radiation compared with those who did (two-year overall survival 0.58 ± 0.12 percent vs. 0.18 ± 0.1 percent, respectively).

It is possible that cancer deaths among patients who underwent deferred radiation therapy may actually reflect instances where radioresistance developed at relapse, rather than representing primary radiation therapy failure. Therefore, we reanalyzed our data by excluding those five patients who received treatment at recurrence.
Our results continued to show a survival advantage for the non-radiation therapy patients, although at a level that did not reach statistical significance ($p = 0.3$), likely due to the small sample size.

The heightened rate of tumor progression or relapse after radiation therapy apparent from our analysis is worrisome. The research by Boyle and colleagues suggests a mechanism of action: Doses of gamma radiation below the level required for universal cellular lethality may induce selective survival of tumor cells with additional genetic aberrations, accelerating tumor growth potential. Also, cells from LFS patients with or without $TP53$ mutation show a reduced capacity to repair or eliminate chromosomal damage of the sort caused by ionizing radiation, which may contribute to these patients’ cancer predisposition.

Admittedly, a retrospective literature review such as ours has limitations imposed by the publication bias of the case reports and case series upon which it is based. However, a prospective randomized clinical study also would have inherent reliability restrictions due to the rarity of CPC cases and resultant small data sample size. Our meta-analysis provides the best possible evidence to date regarding radiation therapy outcomes in CPC patients with LFS.

**A Recommendation to Avoid Radiation**

In summary:

- LFS-derived cells are radioresistant.
- There is an apparent survival disadvantage with the use of radiation therapy for LFS patients with CPC.
- There is an increased risk of secondary malignancies associated with radiation therapy in LFS-CPC patients.
- Radiation therapy causes detrimental pediatric neurological effects.
- Long-term survival in LFS patients with CPC is possible without radiation therapy.

In light of the foregoing considerations, we propose that radiation therapy should be avoided in all LFS patients with CPC (i.e., those with $TP53$ mutations). These patients should be classified separately and treated with radiation-sparing protocols.

At a meeting organized by Cleveland Clinic Children's in conjunction with the 2014 International Society of Paediatric Oncology Annual Congress in Toronto, an international group of pediatric oncologists concurred with this proposal, deciding to no longer recommend radiation as first-line treatment for CPC with LFS. Testing for $TP53$ mutations and assessing family histories are vital in the management of newly diagnosed CPC patients.

**REFERENCES**


Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) are used extensively to evaluate neurological conditions such as stroke, neurocognitive decline, neoplasm and epilepsy.

MRI and MRA help characterize disease states noninvasively and without radiation in pediatric as well as adult patients. By using a reduced field of view, contrast enhancement and saturation pulses to eliminate artifacts inside blood vessels, it is possible to obtain high-resolution MRI (HRMRI) images that delineate blood vessel walls rather than indirectly studying the internal contours of a blood vessel by imaging the flowing blood. HRMRI scans typically are obtained using a 3.0 Tesla whole body scanner.

Homing In on Vascular Abnormalities

Stroke is among the top 10 causes of pediatric mortality in the United States and results in significant morbidity in more than half of survivors. High-resolution MR vessel wall imaging (VWI) helps identify abnormalities that result in either hemorrhagic or ischemic strokes. Identification of a cerebral vasculopathy in pediatric stroke is critical considering the increased risk of stroke recurrence in these cases.

The technique described herein refers specifically to imaging designed to assess the blood vessel walls. A gadolinium-based contrast agent is infused into the patient, allowing for vessel wall enhancement. To eliminate enhancement of flowing blood, a saturation pulse is employed to cancel the signal of blood perfusing the brain. By creating a signal-nulled “black blood” appearance, we can distinguish abnormal wall enhancement from enhanced blood.

Physicians collaborate to identify cases that might benefit from further analysis with VWI and to help plan tailored treatment for several stroke subtypes, including central nervous system vasculitis, dissection, and focal cerebral arteriopathy of childhood.

Large Vessel Occlusions

For instance, it may be unclear what is blocking blood flow in a vessel, such as in the internal carotid artery of the 10-year-old ischemic stroke patient whose catheter angiogram is shown in Figure 1A.

Post-contrast VWI (Figure 1B) shows proximal collapse of the vessel and luminal irregularity, and pre-contrast T1 imaging (Figure 1C) shows high signal intensity along one side of the wall, indicating blood beneath the intima of the wall and confirming a dissection as opposed to a thrombus.

Evaluating Vessel Wall Inflammation

The term vasculitides describes a diverse group of diseases that result in inflammation of a blood vessel wall, which may reduce blood flow to the area of the brain that the blood vessel supplies. HRMRI can be utilized to identify the most diseased segments, potentially helping to target blood vessels for biopsy. The technology can also help monitor response to treatment (see Figures 2A-2B).

SUGGESTED READING


FIGURE 1A. A catheter angiogram shows blocked blood flow in the carotid artery of a 10-year-old ischemic stroke patient.

FIGURE 1B. Axial contrast-enhanced T1 HRMRI at the level of the petrous bone in the 10-year-old patient shows proximal collapse of the vessel and luminal irregularity.

FIGURE 1C. Pre-contrast T1 HRMRI of the 10-year-old patient’s blocked carotid artery shows high signal intensity along one side of the wall, indicating blood beneath the intima of the wall and confirming a dissection as opposed to a thrombus.

FIGURES 2A AND 2B. These images show resolution of contrast enhancement along the walls of the right internal carotid artery and right middle cerebral artery origin on VWI before and after treatment of varicella zoster virus-associated vasculitis.
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Cleveland Clinic Joins National Pediatric MS Research Collaborative

Cleveland Clinic has been selected by the National Multiple Sclerosis Society to join the national Network of Pediatric MS Centers (NPMSC).

Cleveland Clinic’s Pediatric MS Center becomes the 12th participating center in the research network, which unites investigators working to better understand the causes of MS and related central nervous system demyelinating disorders, the disorders’ characteristics in children and teens, and how best to treat them. The NPMSC was established in 2006.

The MS Society’s decision to expand the research network and commit additional funding will support research activities at the individual centers and at the University of Utah Data Coordinating and Analysis Center, which is responsible for patient registry and center collaboration. It also enables network members to leverage additional funding sources for specific research issues. Since 2013, the MS Society has provided $2.8 million to support the NPMSC.

Cleveland Clinic’s Pediatric MS Center is a collaboration between the Mellen Center for Multiple Sclerosis and the Center for Pediatric Neurology, whose pediatric MS program has been evaluating and managing children with MS since 2006. The effort is led jointly by Mary Rensel, MD, a staff neurologist in the Mellen Center, and Manikum Moodley, MBChB, FCP, FRCP, a staff pediatric neurologist at Cleveland Clinic Children’s.

“Being part of this network will allow us to build on our existing collaborative research and connect with other specialists across the country,” said Dr. Rensel. “It will enhance our knowledge about pediatric MS and provide additional research opportunities for this rare diagnosis. The NPMSC is a strong fit with Cleveland Clinic’s emphasis on patient-focused care and research.”

Cleveland Clinic’s Mellen Center for Multiple Sclerosis provides advanced specialized care, supported by an extensive program of research and education. The center is one of the largest and most comprehensive programs for MS care and research in the world. Basic and clinical research conducted at Cleveland Clinic sheds new light on MS every year.
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The Cleveland Clinic Way
By Toby Cosgrove, MD,
CEO and President, Cleveland Clinic
Visit clevelandclinic.org/ClevelandClinicWay for details or to order a copy.

About Cleveland Clinic

Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, more than 3,000 physicians and researchers represent 120 medical specialties and subspecialties. We are a main campus, more than 80 northern Ohio outpatient locations (including 16 full-service family health centers), Cleveland Clinic Florida, Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Cleveland Clinic Canada, Sheikh Khalifa Medical City and Cleveland Clinic Abu Dhabi.

In 2015, Cleveland Clinic was ranked one of America’s top five hospitals in U.S. News & World Report’s “Best Hospitals” survey. The survey ranked Cleveland Clinic among the nation’s top 10 hospitals in 13 specialty areas, and the top hospital in heart care for the 21st consecutive year. Cleveland Clinic Children’s was ranked as a national leader in 10 of 10 pediatric specialties.
Pediatric Neuroscience Pathways is published to provide the latest information about our diverse services and research related to pediatric neurological care. This publication is written for physicians and should be relied on for medical education purposes only. It does not provide a complete overview of the topics covered and should not replace the independent judgment of a physician about the appropriateness or risks of a treatment or procedure for a given patient.

Cleveland Clinic Children’s provides comprehensive medical, surgical and rehabilitative care for infants, children and adolescents. Our more than 300 pediatric physicians accommodate more than 800,000 outpatient visits and 18,000 inpatient admissions per year at the children’s hospital and outpatient facilities on our main campus, at the Cleveland Clinic Children’s Hospital for Rehabilitation and outpatient facilities on our Shaker campus, and at community hospitals, family health centers and other locations across Northeast Ohio.

Cleveland Clinic Children’s & Pediatric Institute is one of 27 institutes at Cleveland Clinic designed to offer highly integrated care and conduct innovative research across multiple settings. It is backed by the full resources of Cleveland Clinic, a nonprofit academic medical center ranked among the nation’s top hospitals (U.S. News & World Report).

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By Jorge Gonzalez-Martinez, MD, PhD, and Ahsan N.V. Moosa, MD

Magnetoencephalography for Evaluation of Pediatric Epilepsy Surgery Candidates
By Richard C. Burgess, MD, PhD, and Sumiya Shibata, MD, PhD

Ultrasound-guided Chemodenervation in Children: Botulinum Neurotoxin Injections Can Provide Safe, Effective Relief from Spasticity
By Mohammed Aldosari, MD

Deep Brain Stimulation for Pediatric Movement Disorders: Increasing Interest, Expanding Applications
By Mohammed Aldosari, MD, Andre Michels, MD, Ph.D, and Robert H. Fernandes, MD

Neurosurgery Clinic: Addressing the Unique Needs of Children with Congenital Heart Disease
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Pediatric Behavioral Health

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