Pediatric Neuroscience Pathways
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On the cover: Cartoon diagram showing a tightly parallel bundle of axons representing a white matter tract. Superimposed ellipsoids represent the anisotropic diffusion pattern of embedded water molecules. Note that the ellipsoids are elongated along the direction of the axons. Diffusion-weighted MRI has the ability to interrogate water diffusion and determine the direction of maximal diffusivity.
Welcome from the Editors

Cleveland Clinic’s pediatric neuroscience program has the honor and distinction of being ranked among the top three pediatric neurology and neurosurgery programs in the United States by *U.S. News & World Report* for 2012-2013. The elements of this success are the world-renowned teams of physicians, scientists, nurses, therapists, technologists and other caregivers who collaborate to provide multidisciplinary care to children with neurological disorders.

Cleveland Clinic’s pediatric neuroscience program includes a wide range of doctors in many specialties. Integration of these teams in both the Neurological Institute and Children’s Hospital offers seamless collaboration between adult and pediatric specialists in every discipline. Thanks to this integration, pediatric neuroscience physicians offer cutting-edge treatments for the widest imaginable spectrum of neurological disorders.

The reader will find several examples of this integration in these pages. For example, children with severe dystonia may receive relief through deep brain stimulation at Cleveland Clinic because the pediatric movement disorders team is integrated with a celebrated team of adult specialists in neurological restoration. Similarly, children with difficult-to-localize epilepsy may benefit from surgery planned with stereotactic-depth EEG because the pediatric epilepsy team works closely with prominent adult and pediatric neurosurgeons who have extensive experience with this technique. In addition, treatment of pediatric hydrocephalus is enhanced by the clinical and experimental study of its progression and consequences in adults. These synergistic collaborations provide opportunities for unparalleled innovations in pediatric clinical care, education and research.

Cleveland Clinic’s premise is “Patients First.” Whether the activity is providing today’s newest, most innovative treatments or researching and developing the treatments of the future, this focus on patient care is the compass for pediatric neuroscience. We proudly offer this compilation of research and innovations for use in your own cutting-edge practice for care of children with neurological disorders.

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Diffusion Tensor Imaging and Tractography in the Evaluation for Pediatric Epilepsy Surgery

Stephen E. Jones, MD, PhD

With little doubt, medical imaging has significantly impacted medical care during the past century, with the greatest impact for neurological disease being the advent of cross-sectional imaging from computed tomography (CT) X-rays in the 1970s and magnetic resonance imaging (MRI) in the 1980s. In the past 30 to 40 years, these modalities, particularly MRI, have advanced and matured. With its significant advantage of a complete lack of ionizing radiation, the future for MRI in neurological imaging is particularly open-ended and exciting. As with other aspects of medical imaging, neurological imaging has been extending from purely structural imaging to the imaging of physiology or function. While the most notable advances of the latter include BOLD (blood-oxygen-level-dependent) functional MRI (fMRI), MR perfusion and resting-state connectivity, the most notable development in structural imaging of the brain uses complicated diffusion-weighted imaging (DWI) to provide information about the brain’s circuitry patterns.

The intrinsic signal used to create the familiar grayscale images of MRI derive from the tiny magnetic moment associated with every proton. Medical care is fortunate to have an unusual combination of factors that permit practical imaging from this tiny signal: the relatively large coupling constant of protons to radiation that passes easily through the body, the presence of two protons with every water molecule, and the 70 percent water composition of human tissues. In addition, not only can MRI visualize the density of protons, but variations in scanning parameters can reveal physics characteristics, particularly the diffusion properties of water.

The diffusion of water in tissues is strongly influenced by the anisotropy of the underlying substrate. For example, in areas of the brain that are highly organized and uniform, such as the corpus callosum, water flows relatively freely parallel to the fiber direction, while it is impeded in directions perpendicular to the fiber direction. Figure 1 depicts a set of strongly parallel axons forming a white matter fiber tract as well as superimposed ellipsoids representing anisotropic diffusion of water molecules located within this region. Diffusion-weighted MRI can interrogate the diffusion preference along different directions, producing 3-D maps that show the direction of maximal water diffusion. For example, Figure 2 shows an axial color map, where the different colors represent the maximally preferred direction of water diffusion, and the intensity of the color represents the predilection for that direction.

While the MRI images accurately describe the preferred water diffusion direction in the localized vicinity of one voxel (typically 2-3 mm), adjacent voxels can be connected along these directions to produce a longer line that spans large distances across the brain. The inset of Figure 2 is an enlargement of a small region in the corpus callosum, where the arrows represent the direction of maximal diffusion of water in individual voxels. These arrows appear to naturally connect to form lines, or tracts. Known as tractography, in its simplest form the technique is called diffusion tensor imaging (DTI), with more recent advanced techniques known as HARDI (high-angular-resolution diffusion imaging). While this line strictly represents the properties of water diffusion, the working hypothesis of tractography is that the path correlates well with the underlying axonal structure, or white matter pathways. Figure 3 shows an example of producing a single path closely corresponding to the corticospinal tract.

Although initially used as a research tool to investigate the brain’s structure, DTI has now become a commonplace tool for neurosurgeons planning the resection of lesions. For example, the goal of presurgical planning is to identify the safest approach to lesions that avoids major white matter tracts, such as the cortico-spinal tract or the optic radiations (Figure 4). The utility of DTI is demonstrated in neurosurgical literature reports describing how maintaining a separation of greater than 5 to 10 mm between the surgical margin and the white matter tract minimizes postoperative morbidity.
Anticipated Applications of DTI and Tractography

Today, the utility of DTI and tractography for presurgical planning is well documented and applies to neurosurgical procedures in both the adult and pediatric populations. The anticipated application of DTI and tractography is gestating in worldwide research efforts, including at Cleveland Clinic, which will have particular applications to pediatric neurology. First, the presence and progression of developmental neurological diseases can currently be visualized with track-density maps. Often this visualization is best appreciated with asymmetrical diseases, such as Parry-Romberg syndrome (Figure 5) and Rasmussen encephalitis. A second application involves superior detection of epileptogenic foci in epilepsy patients, and in the pediatric population a majority of these are due to malformations of cortical development (MCD). Many of these lesions have abnormal architecture not only within the cortex but also in the subjacent white matter, occasionally extending along radial-glial fibers toward the periventricular margins. Many patients with MCD can be cured with proper resection of the lesion, but this requires visualization of the location, and a considerable proportion of MCD are “MRI invisible” using conventional techniques. Thus, there is great hope that advanced techniques, such as DTI and tractography, may help reveal the location of MCD. For example, high-resolution DTI focusing on the cortical-subcortical regions may reveal deranged architecture of water diffusion profiles, which could indicate cortex abnormalities, all of which appear normal on conventional MRI.

Figure 1. Cartoon diagram showing a tightly parallel bundle of axons representing a white matter tract. Superimposed ellipsoids represent the anisotropic diffusion pattern of embedded water molecules. Note that the ellipsoids are elongated along the direction of the axons. Diffusion-weighted MRI has the ability to interrogate water diffusion and determine the direction of maximal diffusivity.

Figure 2. DTI color map of an axial section of the brain. The colors encode the direction of maximal diffusion (green = anterior-posterior; red = left-right; blue = superior-inferior). The brightness of the color represents the predilection for water diffusion in that direction. The inset shows an enlargement of a small section of the corpus callosum with small superimposed arrows located at each voxel. Note how the arrows are easily visually connected to produce lines, or tracts.
Figure 3. Example of DTI tractography. A single tract is produced from connecting the directions of maximal water diffusion in multiple voxels, starting from the corticospinal tract in the pons. It is essential to understand that the visualized tracts primarily represent the diffusion of water and secondarily may represent the underlying white matter pathways.

Figure 4. Utility of DTI for presurgical planning. This young patient has a tumor in the right temporal-occipital lobe, near the expected location of the optic tracts. DTI tractography more accurately shows the location of the optic tracts and influenced the pathway for surgical resection.

Figure 5. Deterministic tracking of bilateral corticospinal tracts in a patient with Parry-Romberg syndrome, which causes a progressive hemifacial atrophy with associated hemi-degenerative changes in the brain. Qualitatively, the image shows fewer DTI tracts on the patient’s right than on the left, which corresponds to the affected side.

Figure 6. Sagittal view of the brain of an epilepsy patient who had numerous intracranial electrodes implanted after high-resolution DTI. The lines show tractography from an electrode in Broca’s area, connecting a subset of electrode contacts. The colors of the lines represent the magnitude of electrophysiological connectivity, as produced by cortico-cortical evoked potentials (CCEP). Such knowledge could reduce the degree of invasive evaluations for intractable epilepsy.
images. A third application of DTI to pediatric neuroimaging regards brain connectivity. Many diseases may manifest themselves as subtle alterations of diffusion properties along the pathways between portions of the brain. In epilepsy, for example, in addition to the primary epileptogenic focus, there is often a network of other lesser epileptogenic regions in the brain (sometimes far away). DTI has the exciting potential application to measure the connectivity between cortical regions in addition to determining the location of the connecting pathway. An example of recent research at Cleveland Clinic is shown in Figure 6, in which high-resolution tractography is compared with electrophysiological measurements obtained from an epilepsy patient with multiple intracranial electrodes. Not only are the connecting paths visualized in this sagittal image, but the color of each path corresponds to the DWI connectivity, which modestly correlates to the electrophysiological connectivity. The eventual goal would be to obviate the need for extensive invasive intracranial electrodes by using high-resolution DTI and tractography.

Conclusion

MR tractography and DTI are recently developed methods of advanced neurological imaging, clinically used today mainly for presurgical planning. However, a growing body of research indicates the capabilities of DTI for identification of (1) deranged white matter architecture subjacent to subtle MCD, (2) distal cortical regions involved in an epileptogenic network and (3) abnormal brain connectivity within epileptogenic zones.

SUGGESTED READING


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In surgical candidates with focal lesions acquired after the brain is already mature, the EEG, seizure signs and symptoms, and MRI all typically give evidence of focal epilepsy. In patients with early brain lesions, however, the findings may be more complicated.

At Cleveland Clinic we are exploring the boundaries of possibility for epilepsy surgery to expand the pool of children who may benefit. Some of our most exciting results have been in children with early focal brain lesions and generalized EEG abnormalities.

How can we understand this phenomenon when we are accustomed to thinking of a focal EEG seizure as the “gold standard” for identifying a focal epileptogenic zone? This takes us to the concept of plasticity, with downstream differences in the epilepsy and EEG based on whether the focal lesion interacted with a mature or developing brain.

Focal brain lesions acquired later in life are imposed on a mature brain, which usually results in focal EEG discharges at the lesion location. But early focal brain lesions interact with a developing brain, and in these cases there may be aberrant circuitry resulting in generalized EEG. The most common epileptogenic lesions that occur early in life are cortical malformations or perinatal infarctions, but other early lesions may result in similar effects. The downstream generalized EEG patterns tend to be hypsarrhythmia in infants and generalized slow spike-wave complexes in older children.

The mechanisms are unknown, but certainly the first year of life is characterized by processes leading to increased neuronal connectivity, such as myelination, axonal growth and synaptogenesis. Disruption of these processes during infancy could lead to patterns of epileptogenicity that are different from those that start later in life.

We published our larger experience in Neurology (see Suggested Reading below). We blindly and retrospectively reviewed the preoperative video EEG from the 415 children who underwent epilepsy surgery at our institution between 1994 and 2004. We identified 50 children, median age of 8 years at surgery, who had abundant generalized ictal and interictal epileptiform discharges on their preoperative EEG, comprising 30 to 100 percent of all their recorded EEG abnormalities.

The study group was selected based solely on the presence of abundant generalized epileptiform discharges on preoperative EEG. But when we unblinded ourselves and studied these 50 patients in detail, we found another unifying feature: They all had a focal MRI lesion that occurred early in life. Ninety percent of the lesions were prenatal, perinatal or acquired in the first two years of life. The latest lesion occurred by 5 years of age. The patients ranged in age from 6 months to 24 years at the time of their preoperative evaluations, but their focal epileptogenic lesions, usually cortical malformations or perinatal infarctions, all occurred during early brain development. Seventy-two percent of children had no seizures after surgery, at a median follow-up of two years. The results were similar to those in a comparison group of 159 children with early focal lesions and focal EEG findings who underwent epilepsy surgery at Cleveland Clinic.

By appreciating the opportunities for successful epilepsy surgery in children with generalized EEG discharges and an early focal lesion, we expand the pool of candidates who may gain relief from seizures for a lifetime.
SUGGESTED READING


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See next two pages for a case study related to this article.
Case Study: Successful Epilepsy Surgery Despite Complicated EEG

The following case is illustrative. A girl presented to Cleveland Clinic at 4 years old. Her development was on track and her neurological examination was normal, but at 3 years old she had developed severe epilepsy with daily clusters of facial tonic seizures often evolving to lip smacking, confused speaking and unprotected falls. She was on four antiepileptic medications and had failed a total of five.

Her MRI showed a round, circumscribed lesion in the right parietal lobe, posterior to the sensorimotor cortex (Figure 1). The lesion had no significant mass effect and did not enhance with gadolinium, so it wasn’t clear whether it was a low-grade tumor or a malformation of cortical development.

Whereas her MRI showed a focal lesion, her EEG showed only generalized epileptiform discharges (Figure 2). These were abundant, nearly continuous during sleep, and lacked any focal features. EEG seizures also were generalized at the onset and maximal on the left (Figure 3). As seizures evolved, the left-sided predominance became even more apparent (Figure 4).

In summary, this girl had medically intractable epilepsy, a right parietal lesion on MRI and generalized findings on EEG, sometimes maximum on the left. Would epilepsy surgery stop her seizures, or was her MRI abnormality just the “tip of the iceberg” of a more diffuse process?

At Cleveland Clinic, each surgical candidate is discussed in detail at an epilepsy management conference, with input from all of the specialists. Once a consensus has been reached, the recommendations are presented to the family for informed consent.

In this case, the family was told that based on previous experience in similar cases, epilepsy surgery could be expected to resolve the epilepsy. However, this plan was clearly at the boundaries of epilepsy surgery because of the generalized EEG. After detailed informed consent with a full discussion of the possible risks and benefits, the parents elected to proceed.

The lesion was resected at Cleveland Clinic in 2009, and histopathologic analysis showed that it was an oligoastrocytoma, World Health Organization grade II. The girl recovered from the surgery uneventfully and was discharged from the hospital after five days.

Since surgery, she has had no seizures and has taken no antiepileptic medications, and her postoperative EEG shows no epileptiform discharges. This favorable result proves that the focal lesion was causing the epilepsy, even though the preoperative EEG features were generalized.
Figure 2. Interictal EEG showing our patient’s abundant generalized slow spike-wave complexes.

Figure 3. EEG at onset of one of our patient’s seizures, showing a generalized pattern with fast activity higher on the left (highlighted in blue).

Figure 4. EEG seizure 10 seconds after onset, with more pronounced left-side predominance (highlighted in blue). Despite the generalized and contralateral ictal and interictal EEG features, this child was free of seizures after resection of her right parietal oligoastrocytoma.
Project COPE – Improving Knowledge and Access to Care for Youth with Epilepsy in Ohio

Tatiana Falcone, MD

The primary goal of Project COPE (Collaboration for Outreach and Prevention Education) is to improve access and knowledge about mental healthcare for children and adolescents with epilepsy by facilitating development of a community-based, culturally and linguistically competent mental health model. The project’s objectives are to create a culturally and linguistically competent network of care that enhances the capacity of primary care providers (PCPs), pediatric neurologists and pediatric epileptologists to detect, refer and/or treat mental health problems in youth with epilepsy; to create an effective triage network to improve access to mental healthcare for youth with epilepsy; and to educate and assist families in accessing mental health services for their children with epilepsy.

Youth with epilepsy have increased mental health needs compared with the general population. We hypothesized that children with epilepsy will have barriers to accessing mental health care and an increased need for educational services. To further understand the needs of youth with epilepsy in Ohio, a needs assessment survey was conducted.

A parent survey was administered to 359 families with children up to the age of 18 who were diagnosed with epilepsy. Surveys also were distributed to epileptologists, school nurses, pediatricians and other key informants.

The findings about epilepsy and mental health included:

- Access to educational services is a major barrier for youth with epilepsy.
- Parents lacked knowledge about the existing educational services available to their children.
- Information about the resources available to these patients was poorly disseminated.
- Ninety-eight percent of families felt empowered and involved in the decision-making for epilepsy and mental health services. Seventy percent of families and patients felt they had very little knowledge about epilepsy.
- Most concerns were related to quality of life, poor seizure control and psychiatric comorbidities.
- Contrary to our belief, most families (76 percent) felt it was easy to access epilepsy services. The wait time for an epilepsy appointment was less than one week for 72 percent of the families. Nearly all (96 percent) of the families had a PCP, and 58 percent reported receiving care from their PCP at least one time a year. Almost 92.6 percent reported receiving care from their PCP at least two times a year.
- Most patients in our survey (76 percent) have to travel two hours or less to see their specialist (e.g., epileptologist, child psychiatrist). Only five families in our sample had to travel more than 10 hours for care.
- Seventy percent of our patients felt that they had very poor knowledge about epilepsy and felt sad, frustrated and overwhelmed when they learned about the diagnosis.
- Seventy-three percent of the families felt that they were given information about epilepsy and psychiatric comorbidities mostly by the specialist (e.g., pediatric epileptologist, child psychiatrist).
- Pediatricians in the Cleveland community felt that epileptologists provided most of the epilepsy care and that child psychiatrists provided most of the mental healthcare for youth with epilepsy.
- Overwhelmingly, all PCPs in our sample felt the allotted time for appointments makes it difficult to support and guide the medical home model.
- Pediatricians providing hospital-based services felt closer to the medical home model because they had access to case management and specialists readily available during admission and after discharge to help coordinate care for youth with epilepsy.
- Epileptologists, child psychiatrists and PCPs identified reimbursement as a barrier for epilepsy and mental healthcare for youth with epilepsy for as many as 75 percent of their patients.

Additional survey findings are detailed in Figures 1 to 3.

Psychoeducation is one of the underrecognized unmet needs of children. Therefore, it is important to engage pediatricians in it. Stigma continues to be an important barrier for families and youth with epilepsy. Educating first responders will help us decrease stigma and improve access to mental health services for youth with epilepsy.

The Access Issue in Youth with Special Healthcare Needs

In Ohio, it is estimated that there are 32,159 youths with epilepsy. The number of children with special healthcare needs (CSHCN) is 570,913. The federal government has estimated that around 227,000 of these youths are uninsured.

CSHCN are a vulnerable population, according to the Ohio Family
Health Survey. CSHCN have greater difficulty accessing the appropriate level of mental health services. Overall, these patients have higher unmet needs than does the general population. About 6.2 percent of these patients who are eligible for Medicaid services continue to be uninsured, perpetuating the unmet medical and psychiatric needs.

**Conclusions**

There are important and underrecognized unmet needs in youth with epilepsy.

Psychoeducation is a key piece to help families of youth with epilepsy cope with some of the comorbidities these patients face. Although many services are provided in our community, parents and children do not know about these services and do not access them.

It is important to engage PCPs in the psychoeducation of youth with epilepsy. Stigma continues to be an important barrier for patients and families in accessing mental health services.

Educating first responders (school nurses, parents, pediatricians) will help us decrease stigma and improve access to mental health services by youth with epilepsy.

This project was developed with funding from the Health Resources Services Administration Maternal and Child Health Bureau under grant H98MC2026n.

**SUGGESTED READING**


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Hemispheric Epilepsy and Hemispherectomy in Children

Ajay Gupta, MD, and William E. Bingaman, MD

Certain epilepsies are caused by congenital or acquired disorders that extensively involve all or most of one cerebral hemisphere. These disorders usually present with catastrophic epilepsy during infancy and require urgent diagnostic evaluation and treatment. After careful consideration of several complicating factors, hemispherectomy may be the most effective treatment for these children.

**Indications for Hemispherectomy:**
**Common Disorders with Hemispheric Epilepsy**

Common disorders for which hemispherectomy is indicated are congenital malformations such as hemimegalencephaly, hemispheric or extensive multilobar cortical dysplasias, perinatal or acquired ischemic strokes, Sturge-Weber syndrome and Rasmussen syndrome. Congenital malformations may occur as isolated disorders or in association with certain sporadic or inheritable genetic conditions. Figures 1 to 3 show brain MRI findings in children who are candidates for hemispherectomy.

A thorough clinical evaluation — assessing age of seizure onset, course of the neurological symptoms, family history, presence of neurocutaneous markers, dysmorphic features or congenital anomalies involving multiple organ systems, and abnormal neurological findings — helps in making a specific diagnosis, determining disease progression and planning treatment. Video EEG monitoring is the initial key tool in establishing the diagnosis of epilepsy, localizing the seizure-onset zone, and planning surgical strategy. Brain MRI, supplemented by FDG-PET, helps in determining the underlying epilepsy substrate and extent of hemispheric involvement as well as the anatomical and functional integrity of the unaffected hemisphere. Other tests required may include an eye examination, neuropsychological assessment and metabolic/genetic consultation.

**Timing and Planning of Hemispherectomy**

Hemispherectomy in children with catastrophic epilepsy is challenging and requires careful analysis of several complex age-related issues.

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**Figure 1:** T2-weighted sagittal image of hemimegalencephaly showing diffuse right hemispheric enlargement and dysplasia. Midline shift with bulging of anterior falx to the left and compression of the right lateral ventricle suggest a mass effect due to increased volume of the brain parenchyma. Dysplastic changes are diffuse with a thick and disorganized cortex, poor gray-white matter differentiation, and abnormal signal in the white matter. Note the basal ganglia are also dysplastic with abnormal increased signal.

**Figure 2:** Axial FLAIR brain MRI image of a child with Rasmussen syndrome with left hemispheric atrophy most prominent in the insular region, mildly dilated atrium of the left ventricle, and increased signal in the peri-insular subcortical and cortical ribbon.

**Figure 3:** Axial FLAIR brain MRI image of a 5-year-old with a remote ischemic stroke in the distribution of the right middle cerebral artery with severe right hemispheric encephalomalacia and atrophy.
The first issue is the risk of performing surgery on a child. The lowest reported perioperative mortality rate in children is approximately 1 percent from our and a few other experienced centers. Mortality may be higher in infants undergoing hemispherectomy with weight < 10 kg (small blood volume). However, the mortality rate with epilepsy surgery must be weighed against the mortality of medically treated intractable seizures, which is approximately 0.3 percent per year in children of all ages. Another important risk of epilepsy surgery is the possibility of incurring new postoperative neurological deficits. In children with pre-existing motor, visual and language deficits undergoing hemispherectomy, the risk of new or worsening postoperative deficits is usually low. Young age confers distinct advantages because of developmental plasticity. The second issue is the timing of and goals for hemispherectomy. There is evidence that a shorter duration of frequent seizures before surgery may lead to better long-term cognitive outcomes in children under the age of 2 years. The third issue is the prediction of success after surgery in eliminating or controlling seizures. Prediction of success requires careful selection of candidates based on clinical, EEG and imaging tests. The majority of patients are expected to become seizure-free or show dramatic improvement, as outlined below.

**Surgical Approach, Techniques and Complications**

The most commonly employed hemispherectomy technique remains functional hemispherectomy. Benefits over anatomic removal of the hemisphere include less tissue removal, shorter operative time, less blood loss and perhaps less chance of hydrocephalus after surgery. More recently, less-invasive techniques such as peri-insular hemispherotomy and hemispheric deafferentation have been proposed as alternatives to large resections. Our practice, based on our experience over the past 15 years, is to adapt the appropriate surgical hemispherectomy technique based on the underlying pathology. Hemispherectomy is a major surgical procedure, and complications in the perioperative period include death, hemorrhage, aseptic meningitis, infection, coagulopathy, hypothermia and hydrocephalus requiring ventriculoperitoneal shunting. Mortality reported in the literature is 0.5 to 3 percent. However, the risks of perioperative mortality and morbidity could be further reduced if patients are carefully screened before surgery and the surgery is performed at a specialized pediatric epilepsy center with experience in critical care perioperative management.

**Outcome After Hemispherectomy**

At Cleveland Clinic, we capture longitudinal seizure outcome data after epilepsy surgery at every postoperative visit. Figure 4 shows long-term seizure outcomes in 222 patients after hemispherectomy (1997-2011). The rate of seizure freedom is 88 percent after one year, 83 percent after two years, 75 percent after five years, and 69 percent after eight years and beyond. Even among patients who do not become seizure-free after surgery, significant reduction (> 75 percent) in the frequency of seizures is usually seen in an additional 20 to 25 percent of patients. After surgery, children are often well-controlled on fewer medications and demonstrate improvement in their behavior and social interactions. Our experience shows that global improvement in physical and intellectual function tends to go hand in hand with seizure outcome after hemispherectomy.

**The Cleveland Clinic Hemispherectomy Program: Our Experience and Organization**

Cleveland Clinic’s hemispherectomy program is one of the nation’s premier and most experienced programs in pediatric epilepsy surgery. Our results and complication rates in more than 200 procedures performed over the past 15 years are among the best in the country. Pediatric epileptologists, epilepsy neurosurgeons, and anesthesia and critical care specialists with interest and experience in taking care of children with catastrophic epilepsy form a core team for this program at Cleveland Clinic. Active outcome and clinical research programs in pediatric epilepsy disorders supplement our clinical program to improve the lives of patients who are being considered for epilepsy surgery.

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**Figure 4. Long-term seizure freedom following hemispherectomy (N = 222)**

<table>
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<th>Seizure-free (%)</th>
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</tr>
<tr>
<td>Seizure-free (%)</td>
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</table>

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MEG is a measure of the magnetic fields caused by neuronal activation. The instrument uses no X-ray radiation, generates no magnetic fields and requires no injections. The child simply lies quietly on a bed with his or her head resting in a special helmet. MEG’s imaging capabilities offer a high spatial resolution along with a high temporal resolution — a combination that no other modality for studying the brain currently offers. The flow of electrical current through any conductor produces a magnetic field, which can then be recorded using sensitive magnetic sensors. Because the strength of the magnetic field produced by the brain is so small, very specialized instrumentation is required to pick up the signal. These sensing systems consist of small, high-resolution coils coupled to devices called superconducting quantum interference devices (SQUIDs), which must operate very close to absolute zero temperatures in order to achieve superconductivity. Approximately 300 are arrayed around the head in a dewar containing liquid helium to provide whole-head coverage with high resolution. By analyzing the patterns of the signals recorded by all these sensors, the location, strength and orientation of the sources can be inferred. MEG recordings are done both spontaneously and in response to specific external stimuli. MEG technology is similar to the electroencephalogram (EEG) in that it can record function over time. MEG, however, has a higher source resolution than EEG, its recordings are

Case Study: MEG Paves the Way for Successful Epilepsy Surgery

A MEG was recorded at Cleveland Clinic of a 10-year-old boy with medically refractory epilepsy with daily seizures. Video EEG evaluation suggested that the seizures arose from the left side of the brain but did not provide further localizing information. MRI and neurological examination were normal. Ictal SPECT (single photon emission computed tomography) and interictal FDG-PET (fluorodeoxy-glucose-positron emission tomography) were not helpful.

MEG showed interictal epileptiform discharges from a restricted location in the deep gray matter of the posterior insula and inferior parietal cortex (Figure 1). All the interictal spikes were estimated to originate from the same region (Figure 2). Careful scrutiny of the MRI in the region identified by the MEG revealed a subtle blurring of the gray-white border in the deep parietal lobe (Figure 3). Placement of intracranial electrodes, at 11 years of age, was guided by the results from the MEG and MRI. Based on the results from intracranial recording, it was possible to perform a limited resection of the seizure focus, sparing language and motor cortex (Figure 4). At 13 years of age, the boy remained free of seizures on reduced antiepileptic medication. In this case, MEG was very helpful in identifying the focal epileptogenic zone so that the child could have successful epilepsy surgery.
reference-free, its signals are not attenuated by bone and scalp, and it is easy to obtain a multichannel, whole-head, high-spatial-density recording. As with PET and fMRI, the results of MEG are coregistered with the anatomic images and reconstructed in 3-D to show the exact areas of activity.

While some metallic implants or other objects (such as dental orthotics) may cause interference, the preparation of the patient and the post-processing of the data can mitigate these sources of noise. Cleveland Clinic’s MEG laboratory successfully records in children with orthopaedic implants, heart pacemakers, vagus nerve stimulators, implanted pumps and other devices. The increased sensitivity of MEG means that even in some cases where there is no conclusive evidence of the epileptic source on scalp EEG, it is possible to pick up abnormal activity with MEG. For patients with epilepsy, MEG allows for better estimation of the origin of their epileptic discharges without intracranial insertion of electrodes. It also can help to better refine the exact implant location of electrodes when they are necessary.

**Cleveland Clinic’s MEG Lab Can Identify Cortical Functioning and Lateralize Language in Children**

Since the MEG lab’s inception at Cleveland Clinic, nearly 200 children, some as young as 8 months old, have had a MEG to help localize their seizures. In many cases, this assisted the planning for epilepsy surgery.

The MEG may be used to help identify specific areas of cortical functioning. Median nerve stimulation — the application of stimulation at the wrist to make the thumb twitch — may be used to delineate the primary somatosensory cortex in each hemisphere. The brain’s response to this stimulation is also used as a fiducial point during post-processing of the MEG data.

In addition, the MEG may be used to help lateralize language in children who are being considered for epilepsy surgery. Most people are left-hemisphere dominant for language, but early trauma or early onset of seizures may force reorganization of language into the right hemisphere. There is also a slightly higher incidence of atypical lateralization in people who are left-handed, especially if there is a strong family history of sinistrality or left-handedness. Language lateralization is not used in all cases, but if surgery is being considered for the left hemisphere and there is a question as to hemispheric dominance for language, it may be ordered. The language lateralization protocol is primarily a passive listening task. The children are asked to remember five words, and when they hear one of the five words, they indicate it by lifting their fingers. The children are asked to make an indication not as a test of memory but as a way of ensuring that they do not fall asleep during the task. The words are delivered via specialized earphones that fit inside the ear. After the children have heard the three blocks of words, the procedure is repeated, taking about 10 minutes overall. Analysis of the data allows for a determination of language lateralization.

As with the other testing to evaluate young patients, the results of MEG are utilized in concert with other diagnostic information. Sending the patient for a MEG recording is most often chosen for patients who are considered potential candidates for epilepsy surgery but who are MRI-negative, or where the activity from scalp EEG recordings is nonlocalizable or generalized.

**SUGGESTED READING**


**Patricia Klaas, PhD**, is an associate staff member in Cleveland Clinic’s Center for Behavioral Health, Lou Ruvo Center for Brain Health, and Epilepsy Center, along with the departments of Neuroscience, Neurology, and Psychiatry and Psychology. Her specialty interests include epilepsy, magnetoencephalography, pediatric neuropsychology and evaluation of cognitive changes associated with epilepsy. She can be contacted at 216.636.5860 or klaasp@ccf.org.

**Richard Burgess, MD, PhD**, is a staff member in Cleveland Clinic’s Epilepsy Center. His specialty interests include clinical neurophysiology, computer processing of electrophysiologic signals, continuous computerized neurophysiologic assessment, dipole modeling, epilepsy, forward modeling of electrophysiologic signals, magnetoencephalography and medical informatics. He can be contacted at 216.444.7008 or burgesr@ccf.org.

**John Mosher, PhD**, is a staff member in Cleveland Clinic’s Epilepsy Center. His specialty interests are electroencephalography, magnetoencephalography recording and analysis for detection of abnormal activity, localization of possible seizure onset zones, imaging analysis, and registration with MRI, fMRI, PET and SPECT images. He can be contacted at 216.444.3379 or mosherj@ccf.org.
In children with refractory and focal epilepsy, subdural mapping techniques have been the hallmark of extraoperative invasive monitoring techniques for refractory epilepsy in the United States for more than 30 years. With subdural methodology, the grid of electrodes is laid directly on the surface of the brain and provides spatially accurate information from the cortical surface in contact with the electrodes. However, the array of electrodes in a grid is limited in the ability to sample deeper brain structures, bilateral brain regions and a wider functional network connecting different brain regions. The stereoelectroencephalogram (SEEG) technique is able to overcome these limitations, and it does so with less morbidity risk relative to subdural grid electrodes. For carefully selected candidates who are not ideal for subdural grid electrode evaluation but are potential candidates for surgical treatment, the SEEG technique holds promise.

The SEEG methodology implies a rigorous pre-implantation scrutiny of all available findings obtained during the noninvasive phase. Based on the noninvasive test results, a hypothesis for the likely seizure-generating zone or seizure network is formulated. This is followed by a tailored implantation of SEEG electrodes with the capability to sample depths of brain areas in question to confirm the hypothesis. During this phase, the exploration is focused to sample the anatomic lesion (if present), the more likely structure(s) of seizure onset and the possible pathway(s) of propagation of the seizure discharge. Small 2-mm pinholes are made, and the desired targets are reached using small and flexible electrodes (1.2 mm in diameter) with the precision of the stereotactic technique, allowing them to be recorded from lateral, intermediate or deep brain structures in a 3-D arrangement, thus accounting for the dynamic, multidirectional spatiotemporal organization of the seizures (Figure 1). A surgical resection is offered only after confirmation of the hypothesis and careful delineation of functional and seizure-generating areas.

In addition to the general selection criteria for invasive extraoperative monitoring, additional specific indications are used to choose SEEG (vs. other methods of invasive monitoring such as subdural grids/strips) as the recommended method of invasive monitoring.

These criteria include:

1. The possibility of a deep-seated seizure-onset area or a region that cannot be accessed with the help of grid electrodes (e.g., mesial structures of the temporal lobe, opercular areas, cingulate gyrus, interhemispheric regions, posterior orbitofrontal areas, insula and depths of sulci).
2. Failure of a previous subdural invasive study to clearly outline the exact location of the seizure-onset zone.
3. The need for extensive bihemispheric explorations.
4. Presurgical evaluation suggestive of a functional network involvement (e.g., limbic system) in the setting of normal MRI.

Between March 2009 and June 2012, 32 children with difficult-to-localize refractory focal epilepsy underwent SEEG procedures. The mean age was 8 years (range, 5 to 17 years). All the patients had a diagnosis of refractory focal epilepsy, with an average failure of five antiepileptic drugs per patient. On average, 13 depth electrodes were implanted per patient (range, 7 to 22 electrodes; total of 416 implanted electrodes). Analyses of the SEEG recordings led to potential electrographic localization of the epileptogenic focus in the majority of patients (n = 30). Twenty-five patients underwent surgical resection following SEEG evaluation. From this group, 14 patients (56 percent) were seizure-free at the end of the follow-up period. Only one minor complication related to the SEEG procedures was observed (complication rate was 3 percent), which corresponded to a small frontal intraparenchymal hemorrhage with no clinical significance. No other complications were observed in this series. Given the total number of implanted electrodes, the calculated risk of complications per electrode in this series was 0.2 percent.

In conclusion, we have found the SEEG method to be promising in a most challenging group of young patients who were not considered ideal candidates for subdural grid evaluation. The SEEG method is a safe, less morbid and more efficient invasive monitoring alternative for children that yields localizing information in the following contexts: (1) in patients with deep-seated or difficult-to-cover region(s) such as depths of sulci, mesial structures of the temporal lobe, opercular regions, cingulate gyrus, interhemispheric regions, posterior orbitofrontal cortex and insula; (2) following failure of a previous subdural invasive study to clearly outline the exact location of the seizure-onset zone; (3) in children with multiple multilobar or bihemispheric lesions with a need for extensive bihemispheric explorations; and (4) in children in whom presurgical evaluation shows findings consistent with an anatomo-functional network involvement (e.g., limbic system) in the setting of normal MRI. Equally important are the SEEG method’s minimally invasive characteristics, which are particularly appealing in the pediatric population, as they avoid large craniotomies and minimize blood transfusion and postoperative pain. In performing SEEG in this highly selected group, we were able to overcome the relative limitations of the current standard method of invasive monitoring, offering to this challenging group of patients an additional opportunity for seizure freedom that likely would not be possible with subdural monitoring.
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Deepak Lachhwani, MD, is a staff pediatric epileptologist in Cleveland Clinic’s Epilepsy Center. His specialty interests include children with complex epilepsies, children with epilepsy and Sturge-Weber syndrome, diagnostic video EEG for pediatric seizure disorders, interpretation of continuous EEG monitoring in the critical care setting, and invasive EEG monitoring for presurgical evaluations. He can be reached at 216.444.5559 or lachhwd@ccf.org.

SUGGESTED READING


Pediatric Neurology and Neurorestoration

Deep Brain Stimulation (DBS) has become an established treatment in adults for medically refractory Parkinson disease and essential tremor. DBS also has been found to be effective for the treatment of medically refractory primary dystonia and has been approved by the FDA under a humanitarian device exemption. DBS has been used in secondary dystonias as well, including those associated with cerebral palsy, stroke and heredodegenerative conditions, but with limited efficacy. Primary and secondary dystonias frequently affect children; however, only a few studies have focused on the role of DBS in dystonic children and adolescents. Dystonia in children tends not to respond well to pharmacotherapy. Thus, DBS will have the greatest impact on children through improvement in quality of life, social integration, education and ability to work.

The standard technique for lead placement during DBS is to use microelectrode recording after using a stereotactic head frame when the patient is awake. Children do not tolerate the “awake surgery” well. They, and even more so their parents, are frightened by the idea of invasive brain surgery in the awake state. The advantage of intraoperative MRI and CT guidance is that they allow lead placement under general anesthesia. Cleveland Clinic’s functional neurosurgeons recently used both these techniques to place the DBS leads in various targets, with excellent results.

### Pediatric DBS Before Intraoperative MRI or O-arm CT Guidance

Cleveland Clinic’s Center for Neurological Restoration performed eight pediatric DBS surgeries between 2003 and 2011. All were performed via the standard procedure of brain mapping by microelectrode recording during the awake state. Six patients had primary dystonia, and two had secondary dystonia. All were refractory to multiple medications and severely disabled by dystonia. Consistent with the literature, the outcome was excellent in the patients with primary cases (Figure 3) and modest in the patients with secondary cases (Figure 4).

### Pediatric DBS After Intraoperative MRI or O-arm CT Guidance

After successfully trying the real-time intraoperative MRI or CT guidance for DBS lead placement in adults, our functional neurosurgeons started using this technique in children in March 2012. In the four months following, four children with primary dystonia underwent DBS using this new technology while under general anesthesia throughout the procedure. The lead placement is accurate in all of them. It is too early to report the clinical improvement in these patients.
Establishment of Pediatric Deep Brain Stimulation Program

Cleveland Clinic formed a multidisciplinary pediatric DBS program comprising the Pediatric Neurology Center, the Center for Neurological Restoration, Child Psychiatry, Neuropsychology, and Physical and Occupational Therapy. We have experts in each of the above centers dedicated to the care of children. All children with medically intractable dystonia are evaluated by the above team of doctors and specialists. These evaluations are presented during a multidisciplinary DBS conference to decide on candidacy. After the surgery, the same team follows the children periodically for assessment of clinical improvement when DBS programming is optimized. DBS surgery is an invasive brain surgery not without complications. So the decision to pursue this surgery should be reserved for the appropriate candidate during the proper window of opportunity, not too early and not too late. Delay in deciding to pursue the surgery may produce many irreversible changes such as contracture or fixed deformity. Similarly, it is not wise to do the surgery too early without trying other relatively noninvasive medical options.

Primary generalized dystonia presents at an early age, is severely disabling and is usually resistant to medical therapy. Globus pallidus internus DBS for patients with primary generalized dystonia has revolutionized the treatment of primary generalized dystonia, and its long-term benefit has been well documented. There has been a reluctance to consider DBS at an early stage in children with primary generalized dystonia despite the recent literature corroborating the efficacy and safety of early DBS in pediatric patients. This may be due to the lack of awareness or fear of brain surgery on the part of children, their parents and primary caregivers, and neurologists. The fear becomes further compounded by the idea of awake brain surgery. Preliminary observations in four children with DBS placement using intraoperative MRI or CT guidance under general anesthesia show that all of them tolerated the procedure very well, the experience was very positive for both the children and their families, and lead placements also were accurate based on neurophysiological monitoring. This new technique will definitely boost the pediatric DBS program, helping many children suffering from disabling disorders such as dystonia.

Suggested Reading


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Andre Machado, MD, PhD, is the Director of Cleveland Clinic’s Center for Neurological Restoration. His specialty interests include stereotactic and functional neurosurgery, surgery for Parkinson disease, movement disorders and deep brain stimulation. He can be reached at 216.444.4270 or machada@ccf.org.

Milind Deogaonkar, MD, is an associate staff member in Cleveland Clinic’s Center for Neurological Restoration. He can be reached at 216.444.2210 or deoganm@ccf.org.
We started by asking what is specifically compressed when the brain is squeezed by expanding ventricles. Previous work by others had indicated that the low-pressure vessels, such as capillaries and venules, were the most vulnerable and that neurons themselves would be resistant to the compression. In our first studies, we did indeed also find decreased vascularity and, specifically, a decreased density of capillaries in the early weeks of hydrocephalus development. This reinforced a general hypothesis that hydrocephalus disrupted neuronal function in part by decreasing cerebral blood flow. However, our longer-term findings, after 12 weeks of hydrocephalus, were a surprise: There was a dramatic two- to threefold increase in capillary density that suggested the creation of new vessels — angiogenesis. Could new blood vessel growth in chronic hydrocephalus be an adaptive response to a low-blood-flow state and relative hypoxia?

Subsequent studies further suggested an angiogenic response to chronic hydrocephalus. Hypoxia, an established trigger for angiogenesis, was observed. CSF oxygen saturation was lower in chronic hydrocephalus, improved with shunting and decreased again with shunt removal. Receptors for vasoactive endothelial growth factor (VEGF), a promoter of angiogenesis, increase in the hydrocephalic hippocampus and caudate and decrease with shunting. Finally, VEGF levels are measurable in human and animal CSF and are elevated in hydrocephalus. In many but not all cases, increased VEGF receptor densities correlated with increased density of capillaries.

Although the story emerging is consistent with an adaptive angiogenic response to chronic hydrocephalus, the role of VEGF increases and angiogenesis is still unknown. VEGF’s effects on blood vessel permeability and tissue edema also have been suggested to play a pathophysiologica role in fluid accumulation. VEGF may indeed be increasing capillary density in some situations, but whether this translates into more blood flow to tissue is uncertain. Other known effects of VEGF, such as neuroprotection, also may be pivotal in any attempt to mitigate the injury of hydrocephalus. This is especially intriguing since we have observed increased VEGF receptors on neurons in the hydrocephalus-affected hippocampus.

In order to explore the role of VEGF changes in hydrocephalus, current studies focus on the net effect of blocking VEGF systems in experimentally induced hydrocephalus. Does VEGF stimulation in chronic hydrocephalus result in an adaptive response? Can we use this physiological response as an avenue to improve function in children or adults with chronic ventriculomegaly? These are the questions, visions and hopes that will guide this research in the coming years.

Mark Luciano, MD, PhD, FACS, is Head of Congenital and Pediatric Neurosurgery and Co-Director of the Pediatric Neurology Center at Cleveland Clinic. His specialty interests include pediatric and adult neurocongenital anomalies, hydrocephalus, neuroendoscopy, neuro-oncology, pediatric neurosurgery and spasticity. He can be reached at 216.636.5860 or lucianm@ccf.org.

Abhishek Deshpande, MD, PhD, is a neuroscience researcher. He received his medical degree from Manipal University in India and his doctorate in cell and molecular biology from Kent State University in Ohio. He was honored as a recipient of a Young Investigator Development Grant from the Hydrocephalus Association for the study of angiogenesis in hydrocephalus and is currently participating in a pilot study to block VEGF in hydrocephalus. He can be reached at deshpaa2@ccf.org.
REFERENCES


After more than a century of descriptive studies in pediatric stroke, the first interventional treatment trial for arterial ischemic stroke is taking place. The Thrombolysis in Pediatric Stroke (TIPS) Trial is a long-awaited five-year, multisite international study funded by the NIH. It is a safety and dose-finding study of intravenous tPA in children with acute arterial ischemic stroke (AIS) (clinicaltrials.gov/ct2/show/NCT01591096?term=pediatric+stroke&rank=1).

The start of the 21st century saw the beginnings of a remarkable collaborative effort in pediatric stroke. The International Paediatric Stroke Study (iPSS) was established in 2003 as an international registry with the long-term goal of developing a multicenter clinical research and trials network focused on pediatric stroke and outcomes. The iPSS also has led to the development and establishment of pediatric stroke centers throughout the world with the aim of promoting an increasing awareness of pediatric stroke, more rapid and comprehensive evaluation of AIS and the development of pediatric stroke protocols (app3.ccb.sickkids.ca/cstrokestudy/).

The first funded trial utilizing the IPSS network investigated the application of a modified pediatric NIH stroke scale in acute AIS in children. It was funded by the NIH and was a multicenter prospective cohort study involving 15 North American sites between January 2007 and October 2009. A second, more ambitious study investigating the association between infection and vasculopathy in arterial ischemic stroke in children is in the final year of enrollment. This too was funded by a grant through the NIH.

The Role of Arteriopathy

“No agreement has been reached so far as to the importance to be ascribed to general and special vascular factors.”

— Sigmund Freud, 1897

Arteriopathies account for about one-third of childhood AIS and have been identified as an important target for research. Etiologies include genetic, infectious, inflammatory, traumatic and “iatrogenic” (e.g., postirradiation) causes (Table 1). In an elegant study by Fullerton et al, the incidence of stroke recurrence risk was 66 percent in the presence of an arteriopathy, as compared with approximately 20 percent in “all comers,” underscoring the need for appropriate vascular imaging and stroke prevention studies.

The TIPS trial marks the coming of age of pediatric stroke and is a testament to the dedication of purpose and collaboration of such entities as the IPSS and European collaborative groups.

REFERENCES


Pediatric Neurology

Neil Friedman, MBChB, is on staff at Cleveland Clinic’s Center for Pediatric Neurology. His specialty interests include fetal and neonatal neurology, neuromuscular diseases, neurological complications of congenital heart disease, and pediatric stroke and cerebrovascular disease. He can be reached at 216.636.5860 or friedmn@ccf.org.

Table 1: Arteriopathies in pediatric stroke

<table>
<thead>
<tr>
<th>Vasculitis</th>
<th>Monogenic disorders</th>
</tr>
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<tbody>
<tr>
<td>Primary</td>
<td>Fabry disease</td>
</tr>
<tr>
<td>Primary angitis of the central nervous system</td>
<td>Neurofibromatosis type I</td>
</tr>
<tr>
<td>Secondary</td>
<td>Down syndrome</td>
</tr>
<tr>
<td>Postinfectious</td>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>Varicella</td>
<td>ACTA 2 gene</td>
</tr>
<tr>
<td>Other</td>
<td>SAMHD1 gene</td>
</tr>
<tr>
<td>Infectious</td>
<td>Moyamoya disease (primary)</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>Moyamoya syndrome (secondary)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>Neurofibromatosis type I</td>
</tr>
<tr>
<td>Associated with collagen vascular disease</td>
<td>Down syndrome</td>
</tr>
<tr>
<td>or systemic vasculitides</td>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>Vasoconstrictions syndrome</td>
<td>Williams syndrome</td>
</tr>
<tr>
<td>Dissection</td>
<td>Post-cranial irradiation</td>
</tr>
<tr>
<td>Traumatic</td>
<td>ACTA 2 gene</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>SAMHD1 gene</td>
</tr>
<tr>
<td>Vasculopathies</td>
<td>Microcephalic osteodysplastic primordial dwarfism, type II (MOPD II)</td>
</tr>
<tr>
<td>Transient/focal cerebral arteriopathy*</td>
<td>Fibromuscular dysplasia</td>
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<td></td>
<td>PHACE syndrome</td>
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* Cause is uncertain

Review Articles

Postural Orthostatic Tachycardia Syndrome in Children – An Emerging Entity

Manikum Moodley, MD

At Cleveland Clinic, children and adolescents with postural orthostatic tachycardia syndrome (POTS) may receive state-of-the-art care from specialists dedicated to diagnosis and treatment of syncope and autonomic disorders. This multidisciplinary collaboration between pediatric neurology and cardiology offers the most modern approach to this complex group of disorders.

The scope of pediatric autonomic disorders is currently not well recognized as most publications on various aspects of autonomic function tend to concentrate mainly on adult disorders. In recent years, however, investigators have begun to appreciate the value of childhood genetic autonomic disorders as models to advance the understanding of pathophysiologic mechanisms involved in autonomic dysfunction. It is therefore incumbent on pediatric caregivers to be more aware of the existence of this expanding spectrum of pediatric autonomic disorders, as early recognition is essential for appropriate investigation and management of this group of pediatric patients who may otherwise suffer debilitating symptoms and signs.

Symptoms of Autonomic Dysfunction in Children

Because the autonomic nervous system innervates multiple organ systems, the clinical manifestations of autonomic disorders are extremely varied and include abnormalities in the cardiovascular, respiratory, gastrointestinal, ophthalmologic, neurologic, sudomotor and urologic systems.

**Postural Orthostatic Tachycardia Syndrome in Children**

The list of pediatric autonomic disorders is ever-expanding, with many presenting in early childhood as congenital/genetic disorders and others, like POTS, presenting in the adolescent/teen age group. POTS is a well-known entity in adult patients but less well-known in children. Fortunately, it has been increasingly recognized in children and adolescents as of late.

POTS in adults is defined as the development of orthostatic symptoms associated with sustained increment of heart rate ≥ 30 beats per minute (bpm) and/or an absolute heart rate ≥ 120 bpm, within 10 minutes of active standing or head-up tilt test. In children and adolescents, a heart rate increment of 35 or 40 bpm is considered excessive.

**Symptoms of Pediatric POTS**

The symptoms of orthostatic intolerance and sympathetic overactivation in POTS are listed in Table 1. In addition, a spectrum of somatic symptoms may occur, including fatigue, nausea, abdominal pain, migraine, sleep disturbance, widespread myofascial pain and cognitive dysfunction, as well as psychiatric symptoms of depression and anxiety. The most common adolescent presentation involves teenagers within one to three years of their growth spurt.

**Diagnostic Evaluation**

The most important part of the evaluation of patients with suspected POTS is a detailed history and clinical examination followed by several diagnostic studies, as listed in Table 2.

**Treatment**

Both nonpharmacological and pharmacological interventions are useful in the management of POTS (Table 3).

**Conclusion**

POTS is common among adolescents, and its presence should be recognized by family physicians, pediatricians and child neurologists so that appropriate and timely interventions can be instituted. Its pathophysiological basis is complex, with multiple interacting models explaining its myriad manifestations. Common mechanisms are denervation (neuropathic POTS), hyperadrenergic states and deconditioning. Many questions still surround pediatric POTS;
foremost among them are its diagnostic criteria, diagnostic evaluation and pharmacologic management. However, despite all the above limitations, recognition of this disorder, which is invariably very disabling, is important because some useful multidisciplinary treatment options exist.

Manikum Moodley, MD, is a staff member in Cleveland Clinic’s Center for Pediatric Neurology. His specialty interests include general pediatric neurology, neonatal neurology, neuromuscular diseases, pediatric multiple sclerosis and other white matter disorders, neurofibromatosis, and pediatric autonomic disorders. He can be reached at 216.444.5559 or moodlem@ccf.org.

REFERENCES


Table 2. Diagnostic evaluation

<table>
<thead>
<tr>
<th>(1) Hematological/biochemical</th>
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<tbody>
<tr>
<td>• CBC</td>
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<tr>
<td>• CMP</td>
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<tr>
<td>• Serum ferritin</td>
</tr>
<tr>
<td>• 25-OH vitamin D</td>
</tr>
<tr>
<td>• TSH</td>
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<tr>
<td>• Paraneoplastic antibodies (in neuropathic POTS, pandysautonomia and severe GI dysfunction)</td>
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<table>
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<tr>
<th>(2) Cardiac evaluation</th>
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<tbody>
<tr>
<td>• EKG</td>
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<tr>
<td>• Echocardiography</td>
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<tr>
<td>• Holter monitoring</td>
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<table>
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<tr>
<th>(3) Autonomic function tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cardiovagal</td>
</tr>
<tr>
<td>• Heart rate response to deep breathing</td>
</tr>
<tr>
<td>• Valsalva ratio</td>
</tr>
<tr>
<td>• Adrenergic</td>
</tr>
<tr>
<td>• Head-up tilt test</td>
</tr>
<tr>
<td>• Sudomotor</td>
</tr>
<tr>
<td>• QSART/Q-Sweat</td>
</tr>
<tr>
<td>• Thermoregulatory sweat test</td>
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<tr>
<th>(4) Genetic evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Familial cases/genetic autonomic disorders (e.g., HSAN)</td>
</tr>
<tr>
<td>• POTS with hypermobile joints (Ehlers-Danlos syndrome)</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>(5) Gastroenterology evaluation</th>
</tr>
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<tbody>
<tr>
<td>• Severe GI dysfunction including gastroparesis</td>
</tr>
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</table>

Table 3. Treatment

Summary of treatment options for pediatric POTS

(1) Nonpharmacological

• Water and salt supplementation
• Compression stockings (20-30 mm Hg)
• Avoid excessive standing and heat
• Iron supplementation where necessary
• Psychophysiologic training (pain, anxiety)
• Family education

(2) Pharmacological

• Fludrocortisone
• Beta blockers
• Midodrine
• Clonidine
• Pyridostigmine
• SSRIs
• Methylphenidate
• DDAVP
• IVIG (in cases of autoimmune neuropathy – GBS)
Mitochondrial Dysfunction and Cyclic Vomiting Syndrome
Sumit Parikh, MD

Cleveland Clinic now has the only dedicated clinic in the entire Northeast and eastern Midwest United States for children with cyclic vomiting syndrome (CVS), a debilitating condition characterized by explosive, recurrent, prolonged and severe attacks of vomiting with no other underlying etiology. Children with CVS vomit many times an hour for a period of hours to days. The episodes occur weekly or monthly and are self-limited and stereotypical in nature, with patients experiencing a complete return to normal health between episodes.

Cleveland Clinic’s CVS clinic is the third of its kind in the country and represents a multidisciplinary approach among pediatric headache, gastroenterology, neurometabolism and psychology specialists. Three of the team members serve on the National CVS Association (CVSA) Medical Advisory Board.

While CVS can occur at any age, most patients are children and experience onset in their late preschool years. Adults are affected by this condition, though true incidence and prevalence numbers are not known. Females are affected slightly more than males. The patient is prone to motion sickness, and there is often a family history of migraine headaches. In fact, most CVS patients transition to having migraines themselves as adolescents.

The episodes can begin at any time, though most begin in the early morning hours. There can be associated triggers, such as positive or negative stress, certain foods, motion, and viral illness. There is associated pallor, anxiety and a decrease in the patient’s activity level. The individual is sensitive to the environment and might have photo- and phonophobia as during a migraine. There might be loosening of the stools or actual diarrhea. Autonomic symptoms include low-grade fever and mild hypertension. Vomiting is often worse at the beginning of the cycle and gradually subsides. The lull in vomiting is followed by a period of sleepiness. There is often associated midline abdominal pain that is not typically severe and, less often, actual headache. The vomiting itself is usually bilious and infrequently bloody. Gastric herniation or esophageal tears from frequent vomiting are rare complications. The spells usually end as abruptly as they started, and the child is “magically” well again.

CVS is frequently misdiagnosed because it is still considered a novel diagnosis and there is no single test or procedure to aid diagnosis confirmation. Viral gastroenteritis and food poisoning are often invoked as the primary culprits — until the spells keep recurring. Despite increasing awareness of this condition, diagnosis is typically delayed two to three years after onset of symptoms. The diagnosis is now made after careful review of the patient’s history, along with the exclusion of other pathology including epilepsy, increased intracranial pressure, abdominal malrotation, gastrointestinal volvulus or obstruction, and renal colic due to hydronephrosis.

Of recent interest are findings of mitochondrial dysfunction in a number of these patients and a clinical response to mitochondrial medications such as levocarnitine and coenzyme Q10 (CoQ10). As part of our CVS clinic we have developed a standardized intake and evaluation protocol. The evaluation prior to diagnosis includes studies when well and during a bout of vomiting, including metabolic testing in blood and urine, amylase and lipase levels, an upper GI series, and abdominal ultrasound. Neuroimaging and EEGs are obtained selectively.

We have seen almost 200 patients with this condition and have reported on our first 100 or so. Our patients’ mean age at diagnosis was 8.9 ± 5.0 years, with 58 percent being males. The average duration of each vomiting cycle was 24 hours, with 18 episodes of vomiting per cycle and a peak vomiting intensity of five vomits per hour. Episode triggers were identified in 66 percent of patients and included stress and/or anxiety in many. Autonomic symptoms, including fever and hypertension, were observed in 25 percent of patients.

Neuroimaging did not show an etiology of vomiting in any of these patients. Abdominal ultrasounds, however, showed abnormalities in 15 percent of patients during an acute episode and in 7 percent of patients when well, most commonly affecting the renal system. Sixty-one patients had an upper gastrointestinal series, all of which were normal. Ninety percent of patients completed metabolic testing in blood and urine during a bout of vomiting, a period of wellness or both, with 38 percent showing abnormalities suggestive of mitochondrial dysfunction.

These findings have been reported at meetings of the North American Society for Pediatric Gastroenterology, the Child Neurology Society and the United Mitochondrial Disease Foundation. A publication is pending.

Treatment of these conditions is available and includes both abortive and prophylactic therapy. Acutely, anti-nausea and anti-migraine medications are used along with a sedative. Chronically, the patient is started on a medication such as amitriptyline, cyproheptadine and/or CoQ10. A protocol for appropriate management has been developed by the CVSA Medical Advisory Board and is available at cvsaonline.org.

Sumit Parikh, MD, is a staff member in Cleveland Clinic’s Center for Pediatric Neurology. His specialty interests include the diagnosis and treatment of patients with mitochondrial cytopathies, inborn errors of metabolism, cognitive and developmental regression, autism and developmental delays. He can be reached at 216.444.5559 or parikhs@ccf.org.

Suggested Reading

Obstructive Sleep Apnea and Unusual Sleep Positioning in Children with Down Syndrome

Jyoti Krishna, MD

Children with Down syndrome commonly have sleep apnea, especially obstructive sleep apnea (OSA), with prevalence rates as high as 50 to 75 percent. Not unexpectedly, parents of these children frequently report sleep-related concerns. While classic symptoms include snoring, witnessed apnea or other respiratory difficulty, other common observations include restless sleep or unusual sleeping positions, such as a hyperextended neck posture. Some children may be observed sleeping in a peculiar body position that involves sitting cross-legged with the trunk flopped forward such that the head is resting on the bed. It has been suggested that these peculiar positions are assumed in order to maintain a patent airway.

We recently conducted a retrospective study using polysomnogram (PSG) data from Cleveland Clinic’s Sleep Disorders Center to evaluate body position in 17 children with Down syndrome. These children were compared with 17 age- and gender-matched non-syndromic, neurologically intact controls. We found no difference between the two groups with regard to total sleep time, sleep efficiency, rapid eye movement time, supine sleep time, oxygenation or apnea-hypopnea index. Despite this, we confirmed that a significant number (53 percent) of children with Down syndrome slept sitting up bent forward at the waist for part of the total sleep time. Since this posture was not seen more frequently in children with or without OSA, it does not appear to be a marker for sleep apnea. These results provide helpful information for physicians who counsel parents of children with Down syndrome.

Although the unusual body positioning in sleep need not in itself raise concerns about OSA, there are cogent reasons to perform OSA screening in all children with Down syndrome. Parental reports are not known to be very reliable in screening for OSA. As a result, the American Academy of Pediatrics recently published guidelines that recommend PSG in all children with Down syndrome by the age of 4 years, or sooner if the child has typical symptoms.

Once PSG confirms OSA, the treatment depends on the area of obstruction. This sleep-related breathing disorder in children with Down syndrome stems from a myriad of anatomical and metabolic factors (Table 1). Thus, the reason for airflow obstruction may be anatomically located in more than one part of the airway or be related to factors outside the airway itself. Investigations to help with localization include upper airway endoscopy and, in some cases, radiography including cephalometry and cine MRI of the upper airway. Otolaryngology opinion is needed to help with these investigations and management.

Table 1. Possible causes of sleep-related breathing disorder in children with Down syndrome

<table>
<thead>
<tr>
<th>(1) Anatomic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Midfacial hypoplasia</td>
<td></td>
</tr>
<tr>
<td>• Narrow palatal arch</td>
<td></td>
</tr>
<tr>
<td>• Mandibular hypoplasia</td>
<td></td>
</tr>
<tr>
<td>• Relative macroglossia and glossoptosis</td>
<td></td>
</tr>
<tr>
<td>• Hypertrophy of adenoids and tonsils</td>
<td>(both palatine and lingual)</td>
</tr>
<tr>
<td>• Laryngotraacheal abnormalities</td>
<td></td>
</tr>
<tr>
<td>• Nasal obstruction from sinusitis or deviated septum</td>
<td></td>
</tr>
<tr>
<td>(2) Metabolic</td>
<td></td>
</tr>
<tr>
<td>• Obesity</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>(3) Central</td>
<td></td>
</tr>
<tr>
<td>• Hypotonia</td>
<td>Abnormal hypoxic ventilatory drive</td>
</tr>
</tbody>
</table>

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SUGGESTED READING

National Down Syndrome Society: ndss.org


Biomarkers in Youth with Major Depressive Disorder

Tatiana Falcone, MD

Depression has an enormous impact on individuals and society. About 121 million people worldwide suffer from depression, and fewer than 25 percent of those have access to effective treatments. With a lifetime prevalence of more than 15 percent in the year 2020, depression will be the second most disabling illness in the world as projected by the World Health Organization.

Depression is already the leading cause of disability as measured by the years lived with a disability, and among 15- to 44-year-olds, depression is the second cause of disability-adjusted life years. The point prevalence of depression is approximately 1 to 2.5 percent in school-age children and 2 to 8.3 percent in adolescents. Among adolescents, 14 to 25 percent experience at least one episode of depression before adulthood. The lifetime prevalence of depression in adolescents of 15 to 20 percent is similar to the lifetime prevalence found in adult populations with depression, suggesting that depression in adults often begins in adolescence. Individuals born in the 20th century are at a greater risk of developing depression, and depressive disorders are manifesting at a younger age in children.

Depression in youth, on average, lasts 7 to 9 months and recurs in up to 70 percent. Multiple negative sequelae are related to depression, including impairment in school performance and interpersonal relationships. Suicidal ideation and attempts are frequent in adolescents. A survey of adolescents showed that 19 percent had seriously considered suicide in the past year, 15 percent had made a plan and 8 percent reported that they had made an attempt. Since 1950, the suicide rate among adolescents has quadrupled and represents 12 percent of the mortality rate for this age group. Suicide is now the third-leading cause of death among adolescents in the United States.

The Link Between Inflammation and Depression

Adults with depression often have immunological alterations that can be detected in blood samples by clinical detection methods. A recent meta-analysis of more than 180 studies and more than 40 immune measures provides overwhelming evidence that immunological abnormalities are associated with mood disorders in adults. This evidence points to activation of the innate immune inflammatory response and alteration in the ability of the immune cells to express inflammatory cytokines. Inflammation is an important biological factor that might increase the risk of major depression. Astrocytes and microglia are the major immunocompetent cells in the brain, and their activation points toward inflammation and immune reactions indicated by the release of cytokines and S100B, an astrocytic protein that has been measured in serum at increased levels in adults with severe mood disorders and depression.

There is strong evidence linking major depressive disorder (MDD) with immunological abnormalities, inflammation and cytokine production. Likewise, strong evidence suggests that inflammation may contribute to the pathophysiology of MDD, and this is supported by multiple studies.

Biomarkers have the potential to help us understand the development, diagnosis and prognosis of depression and to monitor treatment response. The episodic course of mood disorders, particularly in adolescents, makes biomarker validation a very important goal to further our understanding of the pathophysiology of this disease.

Studying the association between serum markers of inflammation and symptoms of depression in youth with mood disorders is advantageous because studies of adults are constrained by years

Table 1. Two inflammatory markers in a group of 29 adolescents with MDD vs. 29 healthy controls

<table>
<thead>
<tr>
<th>Marker</th>
<th>F Value</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>IL-1α</td>
<td>0.71</td>
<td>0.40</td>
</tr>
<tr>
<td>IL-1β</td>
<td>0.18</td>
<td>0.67</td>
</tr>
<tr>
<td>IL-2</td>
<td>0.02</td>
<td>0.90</td>
</tr>
<tr>
<td>IL-4</td>
<td>0.89</td>
<td>0.35</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.58</td>
<td>0.45</td>
</tr>
<tr>
<td>IL-8</td>
<td>12.38</td>
<td>0.0009</td>
</tr>
<tr>
<td>IL-10</td>
<td>1.44</td>
<td>0.23</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>0.01</td>
<td>0.91</td>
</tr>
<tr>
<td>TNF-α</td>
<td>0.08</td>
<td>0.78</td>
</tr>
<tr>
<td>S100B</td>
<td>6.46</td>
<td>0.0139</td>
</tr>
</tbody>
</table>

To evaluate the role of inflammation in pediatric patients with mood disorders, a pilot study was conducted, and patients ages 12-18 were recruited; 29 adolescents with MDD and 29 healthy controls (matched by age, gender and ethnicity) were enrolled. Patients with MDD were diagnosed by two child psychiatrists and recruited in an outpatient child psychiatry clinic. Patients included in this study had scores on the Child Depression Inventory higher than 80. All patients or controls underwent serum evaluation of S100B and nine inflammatory cytokines (IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IFN-γ and TNF-α).
of chronic symptoms and multiple medical comorbidities that can affect the levels of certain biomarkers. In addition, early interventions are important to prevent progression to full-blown disease.

There are important immunological differences in patients with mood disorders. Cytokines may prove to be important biomarkers in the course of pediatric patients with mood disorders. Further studies are needed.

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SUGGESTED READING


Levels of both markers are significantly increased in adolescents with MDD compared with healthy controls (P = .0139 for S100B; P = .0009 for IL-8). In contrast with adults, IL-8 is elevated in depressed youth while IL-1β is not.
Children with Chronic Pain Syndrome See Improvement in Anxiety and Depression After Hospital-Based Pain Rehabilitation Program

Joseph Austerman, DO

Although anxiety and depression are well characterized in the adult chronic pain literature, few studies have examined these psychological factors in the pediatric population. Even less is known about the best management approach for anxiety and depression in relation to chronic pain in children. Clinically, we have discovered that anxiety and depression play an integral part in pediatric chronic pain, similar to what has been characterized in adult chronic pain syndrome. However, little is known about the impact in overall functioning of managing anxiety and depression in children with chronic pain. To this end, we have studied the severity of anxiety and depressive symptoms in a pediatric chronic pain cohort and then determined the effectiveness of an interdisciplinary intensive pain rehabilitation program on pain, anxiety and depression.

Children aged 9 to 18 (N = 49) were admitted to an intensive interdisciplinary, hospital-based pain rehabilitation program for three weeks of inpatient treatment and one week of day hospital treatment. The treatment team consisted of a psychologist, a psychiatrist, social workers, teachers, occupational therapists, physical therapists, physiatrists, general pediatricians and recreational therapists. The children were assessed for anxiety using Screen for Child Anxiety Related Emotional Disorders (SCARED), for depression using the Center for Epidemiological Studies Depression Scale (CES-D) and for pain using the Pain Rating Scale. All assessments were done at admission and at discharge from the rehabilitation program.

At entry, the mean score for the SCARED was 29.73, which is indicative of clinical anxiety. At discharge, the mean score showed a statistically significant reduction to 23.93 (Figure 1). The mean score for the CES-D at admission was 26.42, which is indicative of clinical depression. It showed a statistically significant reduction to 21.44 at discharge. The mean score on the Pain Rating Scale at admission was 7.30 and at discharge was 7.06, which does not represent a statistically significant change in pain ratings.

Based on normative data from the SCARED and CES-D, this pediatric chronic pain population displays a higher degree of anxiety and depression than the general population. There were significant reductions in both anxiety and depression upon discharge from this interdisciplinary intensive treatment model. Surprisingly, these reductions in scores occurred despite no change in the reported pain intensity. However, patients undergoing this management approach find significant improvements in global functioning. This indicates that managing anxiety and depression is essential in treating chronic pain syndromes in children.

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REFERENCES

Constraint-Induced Movement Therapy vs. Bimanual Therapy for Children with Hemiparesis

Douglas Henry, MD

Constraint-induced movement therapy (CIMT) has been used for the past decade to improve the active movement and functional abilities in an upper extremity (UE) that is weak secondary to stroke or cerebral palsy. Many centers now offer intensive therapy sessions lasting two to six weeks with three hours of therapy per day, several days per week, for children with hemiparesis. The unaffected or dominant UE is constrained, often with a cast, while the weaker limb is subjected to intensive forced use and sensory interventions, with an attempt to activate and strengthen specific muscle groups and to improve coordination, motor planning and functional abilities. Multiple studies show that this technique improves motor outcomes in children with hemiparetic cerebral palsy, with lasting benefit.

More recently there has been interest in bimanual therapy for hemiparesis that focuses more on functional tasks requiring the use of both hands. The thinking is that this may result in more practical, or functional, gains. One randomized trial has shown improvements in the bimanual group compared to a control group.

So an obvious question is whether one method is better than the other. A few studies have sought to compare CIMT to bimanual therapy. One multicenter study (Facchin et al, 2011) enrolled 39 patients in CIMT, 33 in bimanual therapy and 33 in standard occupational therapy. Not surprisingly, the CIMT group improved more in grasp, whereas the bimanual group increased in bimanual spontaneous use of play and in activities of daily living. In another comparison study (Gordon et al, 2011), both constraint and bimanual groups showed improvements that persisted at six months, although the bimanual group showed more progress toward goals on the Goal Attainment Scale than did the CIMT group.

We see benefits of both strategies and incorporate them into our management of children with hemiparesis. Certainly, children should begin some intervention as soon as their hemiparesis is detected. However, we do not think they are appropriate for an intensive CIMT program until at least 18 months, preferably 24 months, of age, depending on their developmental level. Before that age we begin a modified constraint program that incorporates a fair amount of bimanual activity, thus promoting developmental progress. When we feel they are ready for an intensive program, we bring them into the CIMT program and focus strictly on that philosophy.

In the CIMT program, children receive occupational therapy for three consecutive hours, five days a week, for three weeks. This includes pool therapy three times a week. They wear a cast on the unaffected arm until the last two days of the program. At the end of this program we see improvements in isolated movements, strength and coordination in the affected UE. Then we return the children to standard outpatient therapy and a daily home activity program. The focus then is on both independent use of the affected limb as well as bimanual activities. For example, they are taught to open doors and turn on light switches only with their affected limb. They also practice using both extremities in functional tasks such as dressing. We often use a similar approach in patients with unilateral UE weakness secondary to other conditions, such as brachial plexus injury and hemispherectomy, with good success.

Our feeling is that bimanual training may be more relevant for lifelong functioning, but CIMT can boost a child’s bimanual abilities. Regardless of the approach, in order to see long-term improvements in UE functioning, parents need to see their commitment not as a several-week process but as a several-year process. With our current knowledge of central nervous system plasticity, we know that the more an activity is practiced, the more the responsible neurologic pathways are strengthened, both functionally and structurally. Limited functional MRI studies before and after constraint therapy support this. But parents must also consider the tradeoffs involved in focusing so much time on a weak limb at the expense of other developmental, recreational, and educational activities as well as family time. As with any intervention, the clinician’s role is to help the parents make an educated decision.

Douglas Henry, MD, is Director of Developmental and Rehabilitative Pediatrics, Cleveland Clinic Children’s Hospital for Rehabilitation. His specialty interests include gait abnormalities, toe walking, complex regional pain syndrome, fibromyalgia, cerebral palsy and traumatic brain injury. He can be reached at 216.448.6179 or henryd@ccf.org.

Suggested Reading


Chronic Pain in Children and Adolescents: Initial Evaluation of an Interdisciplinary Pain Rehabilitation Program

Gerard A. Banez, PhD

Chronic pain in children and adolescents is common, with a prevalence of at least 15 percent. A significant subset of these patients experiences a downward spiral of increasing functional disability. Children and adolescents in this subset do not attend school, interact with peers, and/or participate in sports, extracurricular activities and other personal/family activities. For severely affected patients, an interdisciplinary rehabilitation approach provides an understandable and useful model of care. This approach accepts pain as a symptom that may or may not be eradicated and focuses on independent functioning, improved coping and increased self-efficacy.

Cleveland Clinic’s Pediatric Pain Rehabilitation Program was designed to assist children and adolescents with chronic pain that interferes with their normal activities. The program blends pediatric subspecialty care, behavioral health and rehabilitation therapies in an individualized but coordinated manner. The primary goals of the program are to help children manage their pain effectively and to restore daily activity. Patients referred to the program have experienced little to no improvement with past outpatient services (medical, psychological, rehabilitative) of appropriate length, frequency and/or intensity.

Inpatient and Day Treatment

In the first two weeks of the program, children and adolescents are admitted to an inpatient rehabilitation unit. This provides the environment and structure necessary to begin the improvement process. Children are engaged in therapies and other services that address the physical, psychological and social aspects of their pain and functional impairment. In their third week, children participate as outpatients and return home with their parents at the end of each day. They continue the activities of the prior two weeks but have opportunities to apply their new skills in real-world situations.

Interdisciplinary Therapies and Services

Pediatric Medicine

Upon admission, pediatric hospitalists and medical subspecialists provide consultation, assisting with treatment planning and supervision of medical care. They monitor each patient’s progress and revise treatment as needed. When appropriate, they request and coordinate additional subspecialty assessment, although completion of medical evaluations prior to admission is preferred.

Behavioral Health Care

Psychological or behavioral health services are provided to support patients as they participate in their rehabilitation therapies, enhance pain management skills and resources, and facilitate improved emotional adjustment and familial functioning. Patients participate in individual and/or family therapy as well as a mind-body skills training group, which provides training in evidence-based pain management strategies (e.g., progressive muscle relaxation, diaphragmatic breathing, cognitive self-statements), and are exposed to complementary/alternative techniques (e.g., aromatherapy, acupressure). Each patient in the program has a written individualized functional plan with specific health and wellness goals.

Rehabilitation Therapies

Children in the program are involved in intensive physical therapy (PT) and occupational therapy (OT) on a daily basis. PT and OT sessions focus on endurance and strengthening exercises, sensory desensitization, and restoration of functioning. During the program, each patient is given evening exercises to perform independent of his or her therapy sessions. Prior to discharge, an individualized home exercise program is developed. All patients participate in morning exercise and aquatic therapy groups.

Leisure Education and Recreation Therapy

Leisure education and recreation therapy help patients develop leisure awareness and activity skills, learn to use leisure resources, and improve social interaction skills during recreational activities. These services play an important role in facilitating a return to age-appropriate activities.

Parent/Family Education

Parent/family educational activities address the physical, psychological and social aspects of pain, disability and treatment. Guidelines that emphasize the importance of encouraging normal activity and discouraging pain behaviors are presented. Family members are provided with assistance in preventing regression upon discharge.

School Re-Entry Process

To help children keep pace during their time away from school and to facilitate re-entry into the classroom environment, all patients receive classroom services throughout the three-week program. They are asked to bring work and assignments from their home schools, and a teacher from the Cleveland Metropolitan School

| Table 1. Pain ratings and school and workdays missed |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                 | School days missed/wk | Workdays missed/wk | Hospitalization days/mo | Pain ratings (0-10) |
| Admission                       | 3.32              | 2.51             | 2.47              | 6.76             |
| Two years post-discharge         | 0.22              | 0.16             | 0.13              | 3.79             |
| Three years post-discharge       | 0.32              | 0.00             | 0.31              | 3.0              |
Pediatric Behavioral Health

District provides individualized assistance. During the final week of each patient’s program, a school re-entry meeting is held. This conference call provides the home school with information about the child’s diagnosis and functioning and the importance of focusing on the child’s abilities and activities, not on pain.

Program Impact

Evaluation of the initial 177 adolescents (mean age = 15.12 years) treated in our three-week, combined inpatient and day hospital program suggests that the program is accomplishing its goals, particularly in the area of improved functioning. Complex regional pain syndrome (n = 62) was the most common referral diagnosis, followed by headache (n = 38), abdominal pain (n = 22), fibromyalgia (n = 22) and other pain conditions (n = 33). The mean chronicity of pain was 2.16 years.

Program impact was assessed with a 12-item outcomes measure completed by patients and parents by phone post-discharge. Mixed-effects regression models examined changes over time in school days and workdays missed by children and their parents in the preceding week, number of days hospitalized in the preceding month, and pain ratings (0-10).

Follow-up analyses revealed clinically significant improvements both during and after the program (Table 1). Treatment resulted in significant reductions in school days missed by children and workdays missed by parents and the number of days hospitalized (all P values < .001), with reductions evident at one-month follow-up and maintained through 24- to 42-month follow-up (Table 2 and Table 3). Patients also reported a significant decline in pain from admission to 42-month follow-up (F(4, 358) = 12.19, P < .001) (Table 4). Longer baseline chronicity was significantly associated with smaller reductions over time in pain ratings (t(10) = 3.96, P < .001) (Table 5).

Results

Children and adolescents with pain-associated disability syndrome are among the most physically complex and psychologically challenging patients to treat. For those who have not responded to unidisciplinary and symptom-focused treatments, an interdisciplinary rehabilitation approach, which is focused on independent functioning, may be warranted. Our results support the utility of our treatment approach, with patients showing enduring improvement on real-world indices of pain and functioning 24 to 42 months following program completion. Future investigations will be aimed at determining which patients respond best to the rehabilitation approach, what combinations of services are most beneficial, and the mechanisms that underlie the improvements that result from these services.

Gerard A. Banez, PhD, is Program Director of the Pediatric Pain Rehabilitation Program and a staff member in Cleveland Clinic’s Center for Pediatric Behavioral Health. His specialty interests are pediatric chronic pain, pain-associated disability syndrome, interdisciplinary pain rehabilitation and pediatric behavioral medicine. He can be reached at 216.448.6253 or banezg@ccf.org.
Comparing the Effectiveness of Stimulant and Behavioral Treatment in Youth with Attention-Deficit/Hyperactivity Disorder in a Quasi-Naturalistic Setting

Michael J. Manos, PhD; Donald A. Caserta, MSSA; Elizabeth J. Short, PhD; Kimberly C. Giuliano, MD; and Thomas W. Frazier, PhD

Attention-deficit/hyperactivity disorder (ADHD) affects 9.5 percent of children and about 4.5 percent of adults. As such, effective interventions are sought to assist people in managing symptoms to improve their quality of life. Cleveland Clinic’s Center for Pediatric Behavioral Health conducted a study to compare the relative effects of three treatment conditions: long-acting stimulant medication (MED), intensive behavior modification (BEH) and medication/behavioral treatments combined (COM) in children with ADHD. The study was designed to answer two questions: 1. What is the relative effectiveness of behavioral intervention and long-acting medication in the treatment of ADHD? 2. What is the duration of effect of extended-release medication and behavior therapy across the day in a quasi-naturalistic setting?

We studied 25 children ages 6 to 12 years who participated in a seven-week summer treatment program. The study used a unique experimental design that alternated treatments by day with children acting as their own controls. Ratings and behavioral observations were conducted across the length of the day. Three dependent measures were investigated: ratings of symptom reduction as measured by a scale commonly used in clinical trials, parent ratings of emotional dysregulation (i.e., frustration intolerance) and the ability of the child to follow instructions. The results indicated a unique set of findings: COM and MED conditions showed improvement over BEH treatment beginning three hours post-dose and maintained 12.5 hours post-dose for two of the dependent measures: overall symptom reduction and following instructions. Results for frustration tolerance, however, indicated significant improvement in all three conditions until nine hours post-dose. Medicine sustained benefit across the day for two of three measures, and behavior modification had an additive effect on frustration tolerance.

The study addressed an important gap in the literature in that it examined the duration of effect of a long-acting medication alone relative to intensive behavior therapy alone relative to the combined effect of behavior therapy and long-acting medication. In contrast to randomized clinical trials, we used a small-N alternating treatments design in a quasi-naturalistic setting to compare active treatments rather than treatment vs. placebo alone. We were interested in when the effect of behavior therapy ends, and what, if any, augmentative effects emerge when behavior therapy is combined with long-acting medication. Most previous comparative effectiveness studies focused exclusively on global improvement of symptoms using short-acting stimulants, and they seldom measured real-world behaviors using long-acting stimulants. Thus, little information is available on the relative effectiveness of MED, BEH and COM. Treatments in this study were implemented in a camp environment that approximates daily settings children experience in play and classrooms. As such, the present study represents an effectiveness extension to previously conducted efficacy trials.

Behavioral interventions are the other side of the adage “pills don’t teach skills.” From an ecological perspective, most would agree that psychosocial interventions are important to treating ADHD in everyday settings such as classrooms, playgrounds and sports events. Previous effectiveness studies provide evidence that behavioral intervention enhances medical intervention by impacting co-occurring conditions such as anxiety. We extend this to show that behavioral treatment also contributes to managing frustration in children with ADHD.

The observation that applied behavioral intervention as monotherapy sustained frustration tolerance as effectively as medicine suggests interesting differential effects of behavioral treatment. Frustration intolerance, a form of emotional dysregulation, is a free operant in that it occurs at irregular, unpredictable intervals. Because in the summer treatment program it is met with very consistent aversive consequences (labeling the behavior and loss of points), it can come under more rigorous and vigilant self-control by the child. This may indicate possible selective effects of behavioral intervention as a monotherapy for some children with ADHD.
Michael J. Manos, PhD, is Head of Cleveland Clinic’s Center for Pediatric Behavioral Health. His specialty interests include attention-deficit/hyperactivity disorder, behavioral pediatrics, clinical behavioral pediatrics and pharmacotherapy research. He can be reached at 216.445.7574 or manosm@ccf.org.

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REFERENCES


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Cleveland Clinic Children’s Hospital & Pediatric Institute offer comprehensive medical, surgical and rehabilitative care for infants, children and adolescents. More than 300 pediatric physicians accommodate 600,000 patient visits annually at our main campus, Shaker campus, community hospitals and family health centers. Cleveland Clinic Children’s Hospital was recognized for top care in 10 out of 10 specialties by U.S. News & World Report in its “America’s Best Children’s Hospitals” survey for 2012-2013.

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Resources for Physicians

**Referring Physician Center and Hotline**
Cleveland Clinic’s Referring Physician Center has established a 24/7 hotline — **855.REFER.123** (855.733.3712) — to streamline access to our array of medical services. Contact the Referring Physician Hotline for information on our clinical specialties and services, to schedule and confirm patient appointments, for assistance in resolving service-related issues, and to connect with Cleveland Clinic specialists.

**Physician Directory**
View all Cleveland Clinic staff online at clevelandclinic.org/staff.

**Track Your Patient’s Care Online**
DrConnect is a secure online service providing real-time information about the treatment your patient receives at Cleveland Clinic. Establish a DrConnect account at clevelandclinic.org/drconnect.

**Critical Care Transport Worldwide**
Cleveland Clinic’s critical care transport teams and fleet of vehicles are available to serve patients across the globe.
- To arrange for a critical care transfer, call 216.448.7000 or 866.547.1467 (see clevelandclinic.org/criticalcaretransport).
- For STEMI (ST-elevated myocardial infarction), acute stroke, ICH (intracerebral hemorrhage), SAH (subarachnoid hemorrhage) or aortic syndrome transfers, call 877.379.CODE (2633).

**Outcomes Data**
View clinical Outcomes Books from all Cleveland Clinic institutes at clevelandclinic.org/outcomes.

**Clinical Trials**
We offer thousands of clinical trials for qualifying patients. Visit clevelandclinic.org/clinicaltrials.

CME Opportunities: Live and Online
The Cleveland Clinic Center for Continuing Education’s website offers convenient, complimentary learning opportunities. Visit ccfcmc.org to learn more, and use Cleveland Clinic’s myCME portal (available on the site) to manage your CME credits.

**Executive Education**
Cleveland Clinic has two education programs for healthcare executive leaders — the Executive Visitors’ Program and the two-week Samson Global Leadership Academy immersion program. Visit clevelandclinic.org/executiveeducation.

**Same-Day Appointments**
Cleveland Clinic offers same-day appointments to help your patients get the care they need, right away. Have your patients call our same-day appointment line, 216.444.CARE (2273) or 800.223.CARE (2273).

**Resources for Patients**

**Medical Concierge**
For complimentary assistance for out-of-state patients and families, call 800.223.2273, ext. 55580, or email medicalconcierge@ccf.org.

**Global Patient Services**
For complimentary assistance for national and international patients and families, call 001.216.444.8184 or visit clevelandclinic.org/gps.

**MyChart**
Cleveland Clinic MyChart is a secure, online personal healthcare management tool that connects patients to their medical record. Patients can register for MyChart through their physician’s office or by going online to clevelandclinic.org/mychart.

**MyConsult**
Cleveland Clinic offers online medical second opinions for more than 1,000 life-threatening and life-altering diagnoses. For more information, visit clevelandclinic.org/myconsult or call 800.223.2237, ext. 43223.

About Cleveland Clinic
Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, 2,800 physicians represent 120 medical specialties and subspecialties. We are a main campus, 18 family health centers, eight community hospitals, Cleveland Clinic Florida, the Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Cleveland Clinic Canada, Sheikh Khalifa Medical City, and Cleveland Clinic Abu Dhabi.

In 2012, Cleveland Clinic was ranked one of America’s top 4 hospitals in U.S. News & World Report’s annual “America’s Best Hospitals” survey. The survey ranks Cleveland Clinic among the nation’s top 10 hospitals in 14 specialty areas, and the top hospital in three of those areas.
Spine art ...

Width TBD!