MRI in Fetal Neuroimaging
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Plus 14 other updates on our activities in pediatric neurology and neurosurgery
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On the cover: Fetal MRI showing a normal twin pregnancy (see article, page 4).
Welcome from the Editors

Cleveland Clinic’s guiding principle is “Patients First,” which drives our focus on high-quality, compassionate care — including the cutting-edge treatments we offer to our youngest patients. This approach is the foundation of our multidisciplinary pediatric neuroscience program, which has the honor and distinction of being ranked among the top 10 pediatric neurology and neurosurgery programs in the United States by U.S. News & World Report for 2013-2014.

Our pediatric neuroscience program includes world-renowned specialists from Cleveland Clinic’s Neurological Institute and Cleveland Clinic Children’s who provide integrated care to patients with a wide spectrum of neurological disorders. These pediatric and adult-care physicians from every related discipline collaborate with one another and with scientists, nurses, therapists, technologists and other caregivers to provide exceptional care. They are continually working to identify and implement clinical innovations for optimal outcomes.

In this issue of Pediatric Neuroscience Pathways, you will learn about the latest clinical innovations, emerging research, and new diagnostic and treatment modalities within our pediatric neuroscience program, including:

- **Fetal neuroimaging**: What you need to know about fetal MRI studies as an evolving modality to guide clinical decision-making.

- **Continuous EEG monitoring**: Cleveland Clinic is one of the only centers in the country providing continuous technologist review of EEG tracings backed with interpretation by physician specialists in EEG and epilepsy, 24 hours a day, 7 days a week — find out how we do it and what we’ve learned.

- **Epilepsy surgery**: Seizure outcomes in stereotactic EEG-guided resections, surgery for tuberous sclerosis and functional outcomes of hemispherectomy.

- **Medical/surgical treatment of pediatric epilepsy and related conditions**: Treating comorbidities, plus surgery vs. autoimmune therapies for Rasmussen encephalitis.

- **Pediatric rehabilitation**: Use of augmentative and alternative communication for Angelman syndrome.

- **Pediatric psychiatry**: Clarifying misperceptions about electroconvulsive therapy in adolescents, how quality of life in epilepsy extends beyond seizure control, and insights into the long-term impact of childhood emotional trauma.

- **Pediatric neurology**: Concussion assessment and management, plus practical management of chronic daily headaches in adolescents.

- **Pediatric behavioral health**: Outcomes of early intervention in autism spectrum disorders.

Also, we are thrilled to announce that Cleveland Clinic will be hosting a CME-certified International Pediatric Epilepsy Surgery Symposium in October 2014 that will focus on emerging surgical treatments and pathology-driven approaches. Please plan to join us and share your astute observations and experience. We will be issuing a call for abstracts and posters, as detailed on page 44.

We hope you enjoy the articles in this issue, which highlight our focus on providing the newest, most innovative treatments and diagnostic options to shorten the gap between today’s research and tomorrow’s patient care. Toward this shared goal, each article includes “Take-Home Points” focused on actionable information that you can apply in your own progressive practice for the care of children with neurological disorders.

Elaine Wyllie, MD  
Professor, Epilepsy Center  
Co-Editor

Mark Luciano, MD, PhD  
Professor, Department of Neurological Surgery  
Co-Editor
MRI can be particularly useful for fetal neuroimaging in the following settings:
• When limited fields of view restrict the technical utility of prenatal ultrasound
• When clarification of ultrasound findings is needed
• For possible additional findings on MRI

Cleveland Clinic’s Imaging Institute works closely with our maternal-fetal medicine (MFM) specialists to provide state-of-the-art, ultrafast fetal MRI studies. For pregnancies complicated by serious maternal or fetal conditions, Cleveland Clinic opened a unique Special Delivery Unit (SDU) in early 2012 to provide comprehensive care in the perinatal period for the newborn and/or mother. Our team comprises pediatric radiologists, MFM specialists and neonatal neurologists.

**Technique and Best Practices**

The American College of Radiology recommends that fetal MRI be performed only after 20 weeks of gestational age. Before this age, MRI is unlikely to add significant incremental information in view of the small size of the fetus. Additionally, the effect of MR energy deposition in early fetuses is incompletely understood.

A 1.5-tesla (1.5T) MRI system is routinely used for fetal MRI. Although some centers are using 3T systems, specific absorption rate, a measure of energy deposition from the system, should be measured and maintained within the recommended levels. Higher-resolution surface MRI coils are used, with the patient best imaged supine or in the left lateral decubitus position. Sedation is not routinely performed.

There are currently no fetal indications for contrast administration. Interpretation of MRIs is often performed in correlation with images from prenatal ultrasound.

**Potential Risks**

The principal theoretical risk of fetal MRI relates to excess tissue heating, which has been associated with growth retardation and congenital malformations in various animal models.

Current American College of Radiology recommendations regarding the safety of fetal MRI emphasize that no studies have conclusively documented or reproducibly demonstrated harmful effects to the pregnant woman or the fetus.

**Leading Indications in Fetal Neuroimaging**

The most common neuroimaging indications for fetal MRI at Cleveland Clinic are:
• Fetal ventriculomegaly
• Agenesis of the corpus callosum
• Posterior fossa anomalies
• Spinal dysraphism

**Ventriculomegaly** is one of the most common indications for fetal MRI. Lateral ventricular measurement at the level of atria exceeding 10 mm constitutes ventriculomegaly. The etiology of fetal ventriculomegaly includes atrophic/destructive processes (Figure 1), dysgenetic abnormalities and obstructive hydrocephalus (Figure 2). MRI provides further details of ventricular configuration and contour and can point to underlying parenchymal anomalies. Changes of infection, ischemia and hemorrhage also can be readily identified on fetal MRI (Figure 3). Other anomalies of cortical maturation, including agenesis of the corpus callosum, lissencephaly, polymicrogyria, pachygyria and schizencephaly, are also better appreciated on MRI than on ultrasound.
Figure 1. Hydranencephaly. Coronal HASTE T2 sequence shows near-total loss of the supratentorial brain parenchyma, which is replaced by a large space containing cerebrospinal fluid (arrows). Posterior fossa structures are normal.

Figure 2. Severe hydrocephalus due to aqueductal stenosis. Coronal HASTE T2 sequence shows massively dilated lateral ventricles (arrows) with focal discontinuity of the right lateral ventricle (white arrow), compatible with ventricular rupture.

Figure 3. Germinal matrix hemorrhage. Axial HASTE T2 image shows irregular hypointense signal in the left germinal matrix region (arrows).

Figure 4. Agenesis of the corpus callosum. Axial HASTE T2 image shows absence of the corpus callosum with parallel orientation of the lateral ventricles. The occipital horns are dilated (arrows) when compared with the frontal horns (colpocephaly).

Figure 5. Dandy-Walker variant. Sagittal HASTE T2 image shows absence of the inferior vermis and a posterior fossa cyst (arrows) that communicates with the fourth ventricle.

Figure 6. Lumbosacral myelomeningocele with type II Chiari malformation. Sagittal HASTE T2 image shows an open neural tube defect (myelomeningocele) extending from the midlumbar level down to involve the entire sacral region (arrows). Note small posterior fossa and low-lying cerebellar tonsils. Polyhydramnios and rocker bottom foot are also noted (open arrow).
Agenesis of the corpus callosum (ACC). MRI is often performed when ACC is suspected on ultrasound. ACC can be complete or partial. Parallel orientation of lateral ventricles, colpocephaly, absence of septum pellucidum, high-riding third ventricle, interhemispheric cysts, and a classic moose horn pattern of frontal horns on coronal images are a few diagnostic features of ACC (Figure 4). Associated structural anomalies of the brain also can be ruled out on MRI.

Anomalies of posterior fossa. Posterior fossa cysts and cystlike malformations are often encountered in fetal neuroimaging with MRI. These range from incidental retrocerebellar cysts, arachnoid cysts and mega cisterna magna to the Dandy-Walker continuum that includes classic Dandy-Walker malformation, Dandy-Walker variant (Figure 5) and Blake’s pouch cyst. Diseases in the Dandy-Walker spectrum are often associated with other developmental anomalies as well as ventriculomegaly. When prenatal ultrasound is indefinite, MRI helps to elucidate anatomic details of the posterior fossa and improve diagnostic clarity.

Spinal dysraphism is part of a heterogeneous group of congenital disorders of the spine otherwise known as neural tube defects. Open spinal dysraphism or myelomeningocele (Figure 6) is one of the most severe congenital disorders of the central nervous system (CNS), with varying degrees of mental retardation, bowel and bladder dysfunction, and severe motor disabilities. Fetuses with higher (thoracolumbar) defects are associated with severe functional limitation, with progressive improvement seen with more caudal lesions.

The cerebrospinal fluid (CSF) leak through the myelomeningocele is shown to be the underlying cause for hindbrain herniation, features of type II Chiari malformation and hydrocephalus in these patients. With recent advances in fetal surgery, it is now possible to perform in utero repair of open spinal dysraphisms in selected patients. A recent multicenter randomized prospective trial (Management of Myleomeningocele Study [MOMS]; see Suggested Reading) has demonstrated significantly better clinical outcomes with fetal surgery. Specifically, fetal surgery was shown to result in a significant reduction in the need for ventriculoperitoneal shunt placement, with substantial improvement in overall neuromotor function and reversal of hindbrain herniation.

Fetal MRI, along with prenatal ultrasound, plays a key role in identifying spinal dysraphism and guiding therapy. Prenatal ultrasound has a high sensitivity in detecting spinal defects. Fetal MRI helps to further characterize spinal abnormalities, including lesion level, presence or absence of a covering membrane, and size of the bony defect. MFM specialists, neonatal neurologists, fetal surgeons and neurosurgeons use MRI findings to assess eligibility for fetal surgery. Recent studies show the potential of fetal MRI in predicting neonatal outcomes in myelomeningocele.

Closed neural tube defects (which usually include meningocele, lipomeningocele, terminal myelocystocele and split cord malformation) are not usually associated with severe functional limitation or structural abnormalities of the CNS. Occasionally, closed neural tube defects may be mistaken for

Fetal MRI has emerged as a robust supplement to ultrasound in the diagnosis of fetal abnormalities. Technical advances and widespread availability continue to expand its role, specifically in cases with incomplete or complex sonographic findings.
more severe open defects. Fetal MRI could aid in diagnosis by identifying the intact covering over the defect.

**A Robust Supplement to Ultrasound**

Fetal MRI has emerged as a robust supplement to ultrasound in the diagnosis of fetal abnormalities. Technical advances and widespread availability continue to expand the role of fetal MRI in fetal neuroimaging, specifically in cases with incomplete or complex sonographic findings.

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**Dr. Udayasankar** is a pediatric radiologist in Cleveland Clinic’s Imaging Institute who focuses on pediatric neuroradiology. He is also Assistant Professor of Radiology in the Cleveland Clinic Lerner College of Medicine. His specialty interests include fetal neuroimaging, epilepsy, and vascular and head and neck imaging. He can be reached at 216.444.9544 or udayasu@ccf.org.

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**SUGGESTED READING**


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**TAKE-HOME POINTS**

- Fetal MRI augments the findings of prenatal ultrasound in the diagnosis of fetal CNS abnormalities. Testing is usually performed after 20 weeks on a 1.5T MRI machine, with no currently known risk to the fetus.
- Cleveland Clinic’s new Special Delivery Unit offers multidisciplinary prenatal care that includes the use of MRI for fetal neuroimaging by pediatric neuroradiologists.
- The most common indications for fetal MRI include fetal ventriculomegaly, agenesis of the corpus callosum, posterior fossa anomalies and spinal dysraphism.
- MRI findings are used to assess eligibility for fetal surgery, most commonly in open neural tube defects.
Identifying Culprit Lesions

A successful surgical strategy in any patient with epilepsy entails identifying the epileptogenic zone that has the potential to be safely resected to obtain seizure freedom without risk of a new postoperative deficit. Challenges of epilepsy surgery in pediatric patients with TSC are more complex, but not insurmountable, in the hands of experienced epilepsy specialists and surgeons working as a team.

The first challenge unique to TSC patients is to identify the culprit lesion (tubers and subcortical dysplasias) in the face of multiple lesions all over the brain. The investigation to find the culprit tuber — and define the epileptogenic zone — begins with a careful history and physical exam and a review of seizures on videos with simultaneous scalp EEG evaluation (video EEG) by an experienced epileptologist. In some patients, the review of previous EEGs may offer crucial clues.

Brain MRI is a critical imaging tool to corroborate findings from the clinical and video EEG evaluation. Brain PET and ictal SPECT, although challenging in children with TSC, sometimes provide useful complementary data in selected children. More recently, studies have found that magnetoencephalography and magnetic source imaging can be useful in identifying the epileptogenic tuber in patients with TSC.

Testing to Inform Surgical Strategy

The second challenge is to determine the safety of resection of the epileptogenic tuber if it is located close to the eloquent region for speech/language, vision, or motor or sensory control. Newer techniques, such as functional MRI and MR tractography, when practical, may help clarify surgical strategy in this situation.

In some cases invasive recordings may be necessary, such as a brain-mapping technique in which subdural grids and depth electrodes are placed to map the seizure onset zone and define its relationship to the area of the eloquent cortex. Such procedures often create a next level of complexity in infants and young children, due to lack of cooperation and electrophysiologically immaturity of the central nervous system. In some instances, invasive recordings can be accomplished in the operating room (intraoperative cortical stimulation and electrocorticography) under the safety of light anesthesia without the requirement of active patient cooperation (Figure 1).

A Multidisciplinary Approach Through a Multispecialty TSC Program

Applying these techniques and creating an individualized plan for each TSC patient requires a team effort by experienced professionals. This is best done at a center where all the facilities and personnel are available under one roof.
At Cleveland Clinic’s Epilepsy Center, a multidisciplinary team of epilepsy professionals works together to perform a comprehensive multimodal evaluation of TSC patients and determine the best plan of care. A team of dedicated pediatric and adult epilepsy specialists, neurosurgeons, neuropsychologists, neuroradiologists, functional neuroimaging experts, and cognitive and behavioral experts meets at a weekly epilepsy management conference, together with health psychologists and bioethicists, to discuss the best individualized plan of care for patients with complex epilepsy.

Patients with TSC often have to deal with involvement of other organs and systems, such as the kidneys, lungs, eyes, skin, heart and gastrointestinal system. This creates a need for intricate decision-making to deliver the most effective epilepsy care that will not result in harm to the other organs or systems. That is why, at our center, an experienced epilepsy treatment team is embedded in an established multispecialty TSC program (Figure 2).

**SUGGESTED READING**


**TAKE-HOME POINTS**

- Early effective treatment of epilepsy is a key factor in improving the lives of children with tuberous sclerosis complex (TSC).
- Epilepsy surgery, despite its unique challenges in TSC, offers hope for seizure freedom.
- Epilepsy treatment in children with TSC is best delivered using a multispecialty approach aimed at individualizing care, like that of the program offered by Cleveland Clinic’s Epilepsy Center.
Hemispherectomy — which involves removal of one hemisphere or, more commonly, disconnection of the hemisphere from the rest of the brain — is an effective treatment option for medically refractory epilepsy due to extensive hemispheric lesions. In a recent study from our center on the longitudinal outcome after hemispherectomy in 170 children (see Suggested Reading), two-thirds of patients were seizure-free at a median follow-up of 5.3 years. Moreover, 80 percent of children in the study either were seizure-free or had major improvement at last follow-up.

Focusing on Function
Apart from seizure outcome, the functional status of these children is a matter of great concern to clinicians and to patients and their families. Before surgery, almost all patients have hemiparesis (with no useful hand function) with or without visual, cognitive or language deficits. Some of these deficits may be expected to worsen in the acute postoperative period. We studied the long-term effect of these deficits on children’s ability to ambulate, speak, read and perform at school, and we presented our findings at the 2012 annual meeting of the Child Neurology Society.

Outcomes After Hemispherectomy
Between 1997 and 2009, 186 patients underwent hemispherectomy at Cleveland Clinic. We were able to collect data on the most recent functional status in 125 patients. Seizure outcome of these patients at a mean follow-up of six years is shown in Figure 1. Ten patients with new postoperative nonepileptic spells were excluded from analysis.

Motor outcomes. As noted in several reports, the majority of children were able to walk on follow-up. In our cohort of 115 children, 92 percent were able to walk independently or with assistance (Figure 2). Of the remaining nine patients, five were 2 to 5 years old, with the potential to eventually attain independent ambulation. Children with bilateral motor deficits (worse on the side concordant with surgery) or bilateral MRI abnormalities (markedly worse on the side of surgery) or seizure recurrence were more likely to have poor motor outcomes. When asked about the strength of arms and legs before and after surgery, 54 percent reported no change and 36.5 percent reported worsening of limb strength postoperatively; a small subgroup of patients (9.5 percent) reported subjective improvement in strength, consistent with previous studies. Decreased spasticity in some patients after hemispherectomy is a common reason for the perceived improvement.

Spoken language and reading ability. Spoken language skills and reading ability outcomes are shown in Figure 2. More than two-thirds of children had spoken language skills sufficient for regular conversation, and nearly half of these children had age-appropriate language abilities. Preoperative language delay, bilateral MRI abnormalities and seizure recurrence were associated with poor language outcomes. Age at seizure onset and left-sided surgery had no significant impact on language outcomes in this cohort. Reading abilities were poor in 59 percent of children, and only 18 percent had age-appropriate reading ability. Two-thirds of patients were in mainstream schools, with the majority requiring some form of additional assistance; only five children were in mainstream schools with no assistance.

TAKE-HOME POINTS
- In Cleveland Clinic’s series of 115 children followed after hemispherectomy, 61 percent were seizure-free since surgery, and a total of 81 percent had favorable outcomes (seizure freedom or > 90 percent seizure reduction).
- 83 percent of patients attained independent walking, and another 9 percent walked with assistance.
- More than two-thirds of patients in our series had satisfactory spoken language skills.
- Postoperative seizure freedom favorably affected functional outcome in all domains studied.
**Figure 1.** Long-term seizure outcome after hemispherectomy in 125 patients. Mean follow-up duration was 6.05 years (± 3.1).

**Figure 2.** Functional status of children after hemispherectomy in ambulation (n = 115), spoken language skills (n = 115) and reading (n = 105). Mean age at follow-up was 12.7 years (± 6.02). For reading ability assessment, children younger than 6 years old were excluded from analysis.

<table>
<thead>
<tr>
<th>AMBULATION</th>
<th>SPOKEN LANGUAGE</th>
<th>READING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walk independently (n = 96, 83%)</td>
<td>Age appropriate (n = 39, 34%)</td>
<td>Age appropriate (n = 19, 18%)</td>
</tr>
<tr>
<td>Few steps with assistance (n = 10, 9%)</td>
<td>Mild impairment (n = 41, 36%)</td>
<td>Few grade levels below (n = 25, 23%)</td>
</tr>
<tr>
<td>Unable to walk (n = 9, 8%)</td>
<td>2- to 3-word phrases only (n = 18, 16%)</td>
<td>Only few words/pictures (n = 27, 25%)</td>
</tr>
<tr>
<td></td>
<td>Few unclear words (n = 8, 7%)</td>
<td>Knows alphabet/numbers (n = 15, 14%)</td>
</tr>
<tr>
<td></td>
<td>Nonverbal (n = 9, 8%)</td>
<td>Cannot read (n = 19, 18%)</td>
</tr>
</tbody>
</table>
Behavior and visual symptoms. Based on parental report, 73 percent of patients had minimal to no behavioral problems. The rest had significant problems in home and school environments. Children with postoperative seizure recurrence were more likely to have behavioral problems. Although visual field defect is expected to be present in every patient, families did not perceive it as a major handicap. Patients were accustomed to the defect and were able to take precautions to avoid major mishaps.

Seizure Freedom Improves Functional Outcomes
Seizure freedom emerged as the single most important predictor of functional outcome. Seizure freedom improved the odds of good outcomes in ambulation, behavior, spoken language and reading skills (Figure 3). There are several possible reasons for this effect:
• Seizure freedom allows the opposite hemisphere to gain new functions
• A reduction in anti-seizure medications in seizure-free patients may have a positive effect on cognition
• Seizure recurrence may be an indirect marker for an abnormal opposite hemisphere
This observation may suggest that hemispherectomy improves functional outcomes by providing seizure freedom. However, our study did not have a control group to definitively support such a conclusion.

Cleveland Clinic Hemispherectomy Program
In the past 15 years, more than 230 hemispheric disconnection surgeries have been performed at Cleveland Clinic. We perform four different techniques/variations in hemispherectomy, which are tailored according to patient characteristics to maximize chances for the best seizure outcome and minimize complications. Our youngest patient to undergo hemispherectomy was 2 months and 10 days old, weighing 5 kg.

A team of experienced and dedicated providers, including pediatric epileptologists, epilepsy neurosurgeons, anesthetists, pediatric critical care specialists and several others, strives to ensure the best possible outcome for these children with catastrophic epilepsy. Our continued efforts are focused on making this procedure safe and effective.

Dr. Moosa is a pediatric epilepsy staff physician in the Epilepsy Center in Cleveland Clinic’s Neurological Institute. His specialty interests include epilepsy surgery, etiology of epilepsy-metabolic disorders, genetic and autoimmune disorders, and the ketogenic diet in epilepsy. He can be reached at 216.636.5469 or naduvia@ccf.org.

Dr. Gupta is Head of the Section of Pediatric Epilepsy in the Epilepsy Center. His specialty interests include surgical and medical treatment of children with epilepsy, epilepsy treatment in neurocutaneous disorders, and intraoperative monitoring and brain mapping for epilepsy surgery. He can be reached at 216.445.7728 or guptaa1@ccf.org.

Dr. Bingaman is Vice Chairman of Cleveland Clinic’s Neurological Institute and Head of the Section of Epilepsy Surgery. His specialty interests include epilepsy surgery in children and adults and complex spine disorders. He can be reached at 216.444.5670 or bingamb@ccf.org.
Figure 3. Effects of Seizure-Free Status on Functional Outcome Measures

<table>
<thead>
<tr>
<th>Ambulation and Seizure Outcome (n = 115)</th>
<th>Behavior and Seizure Outcome (n = 115)</th>
<th>Spoken Language and Seizure Outcome (n = 115)</th>
<th>Reading and Seizure Outcome (n = 105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure-free (n = 70)</td>
<td>Seizure recurrence (n = 45)</td>
<td>Seizure-free (n = 70)</td>
<td>Seizure recurrence (n = 45)</td>
</tr>
<tr>
<td>Unable to walk</td>
<td>Walk with assistance</td>
<td>Independent walking</td>
<td>Poor</td>
</tr>
<tr>
<td>Seizure-free (n = 70)</td>
<td>Seizure recurrence (n = 45)</td>
<td>Seizure-free (n = 70)</td>
<td>Seizure recurrence (n = 45)</td>
</tr>
<tr>
<td>Seizure recurrence (n = 45)</td>
<td>Seizure recurrence (n = 45)</td>
<td>Seizure-free (n = 70)</td>
<td>Seizure recurrence (n = 45)</td>
</tr>
</tbody>
</table>

Figure 3. Data illustrate positive effects of seizure-free status on functional outcome measures following hemispherectomy. Numbers along the y-axes indicate number of patients.

SUGGESTED READING


PEDIATRIC EPILEPSY

A recent survey of institutions in the United States and Canada demonstrated that very few institutions have clinical pathways addressing cEEG use, and fewer still are able to offer this service with administration by certified EEG technicians. The majority of institutions limit such monitoring to critically sick patients, and they do not truly provide cEEG monitoring but rather continuously acquire data and periodically interpret the tracings.

Our experience at Cleveland Clinic suggests that relatively short cEEG monitoring (two days or less) allows for efficient detection of abnormal findings, with abnormal findings identified about two-thirds of the time. These trends have remained consistent since the start of our cEEG service.

An Underutilized Tool

Conventional use of continuous EEG monitoring has long been carried out in dedicated pediatric epilepsy monitoring units. Use of bedside cEEG monitoring is also valuable in other hospitalized patients, where it serves as a surrogate marker for monitoring brain function. For instance, in patients with an alteration in mental status, cEEG is critical in detecting nonconvulsive seizures. In other situations, cEEG helps to evaluate predisposition for future seizures and to accurately differentiate epileptic from nonepileptic paroxysmal events. The capability of cEEG to detect these and many other abnormalities has a significant bearing on patient management and prognosis.

Despite obvious benefits, cEEG is an underutilized tool in pediatric medicine due to its heavy dependence on technical, monetary and personnel resources. Recent data suggest there is a substantial gap between the clinical need and available resources. Clinical practices vary, and a consistent pathway of offering cEEG, including guidelines for clinical indications, is lacking.

Making cEEG a Priority

We have implemented significant changes during the past five years that have made state-of-the-art cEEG service possible for pediatric patients. These changes include:

- More thoughtfully allocating Epilepsy Center resources (EEG technicians, EEG machines)
- Establishing real-time monitoring capabilities within a central EEG monitoring unit
- Dedicating staff for timely interpretation of studies

Physicians within the Epilepsy Center have worked closely with the Center for Pediatric Neurology and other inpatient pediatric providers to offer cEEG service for carefully selected pediatric patients anywhere in the hospital. Continuous brain monitoring and interpretation optimize the care of sick patients and provide necessary information to help counsel families about future prognosis.

Our Experience: Monitoring for Timely Intervention

A review of pediatric (patients < 18 years) bedside cEEGs performed at our institution between January 2009 and July 2010 found that 377 studies were done in children on general pediatric floors and in pediatric and neonatal ICUs. The reasons for requesting cEEG were as follows:

- Evaluation of events concerning for seizures (41 percent)
- Previous seizures (28 percent)
- Screening for nonconvulsive seizures (14 percent)
- Altered mental state (12 percent)
- Ongoing status epilepticus (3 percent)
- Hypoxic ischemic encephalopathy cooling protocol, congenital heart disease and other reasons (2 percent)
Most (60 percent) of the cEEG studies showed abnormalities and demonstrated evidence of focal or generalized slowing, seizures, sharp waves or background suppression. In the cEEG studies demonstrating seizures, more than 40 percent of recorded seizures had no clinical signs, which underscores the importance of brain monitoring for timely intervention in treating silent seizures.

A more recent review found that 671 cEEG studies were performed over the past three calendar years (2010 through 2012) in patients ranging from neonates to adolescents. As detailed in Figure 1, infants and toddlers were the most frequently studied group (57 percent across all three years), followed by adolescents (21 percent), young children (13 percent) and neonates (8 percent). As detailed in Figure 2, the majority of studies were up to two days in duration (77 percent across all three years), a small proportion spanned two to five days (16 percent), and rarely were studies carried out beyond five days (7 percent).

As shown in Figure 3, the yield of cEEG studies in detecting abnormalities continues to remain high, with less than one-third of the studies (30 percent across all three years) classified as normal or only mildly abnormal. More than half of the studied patients (56 percent) were classified as having the highest degree of EEG abnormality (Abnormal III), which is followed by adolescents (21 percent), young children (13 percent) and neonates (8 percent).
reserved for patients with severe encephalopathy, structural lesions or epileptic activity. The remaining studies (14 percent) showed a moderately abnormal EEG.

A Collaborative Effort

Over the past few years, the pediatric cEEG program has become integral to patient care at Cleveland Clinic. It is a collaborative effort among pediatric care providers, including hospitalists, pediatric intensivists, pediatric neurologists, neonatologists and pediatric epilepsy teams.

We aim to maintain judicious utilization of this intensive and expensive procedure. Robust patient selection criteria and collaboration across these pediatric specialty areas, including the Epilepsy Center, are cornerstones of this effort.

Dr. Lachhwani is a pediatric epileptologist in the Epilepsy Center within Cleveland Clinic’s Neurological Institute. His clinical interests lie in treating children with medically refractory epilepsy, functional neuroimaging, pediatric epilepsy surgery, and ICU monitoring of neonates and children. He can be reached at 216.445.9818 or lachhwd@ccf.org.

Dr. Lachhwani thanks Mr. Terrence Lesko, Dr. Richard Burgess, Mr. Greg Wooledge and Mr. Zhe Piao for their assistance with data gathering.

REFERENCES


TAKE-HOME POINTS

• A recent survey of U.S. and Canadian institutions found that very few have clinical pathways addressing cEEG use, and fewer still are able to offer this service with administration by certified EEG technicians.

• Cleveland Clinic is one of the only centers in the country providing continuous technologist review of EEG tracings backed with interpretation by physician specialists in EEG and epilepsy.

• Experience at Cleveland Clinic suggests that relatively short cEEG monitoring (two days or less) allows for efficient detection of abnormal findings, with abnormal findings identified about two-thirds of the time.
At Cleveland Clinic’s Neurological Institute, an innovative database known as the Knowledge Program© (clevelandclinic.org/knowledgeprogram) allows treating physicians to identify depression and other neuropsychiatric comorbidities in children with epilepsy and to track major epilepsy outcomes. Future directions include the tailoring of the program to identify comorbidities that are present in preschool children with epilepsy.

Children with epilepsy are affected by neurocognitive, psychiatric, medical and social comorbidities. The association of epilepsy with learning disabilities, cognitive problems, low IQ and cerebral palsy has been well recognized for many years. Therefore, screening for and diagnosis of these conditions in children with epilepsy have been early and very consistent.

Now, clinicians are recognizing a growing need to screen for other important neuropsychiatric comorbidities that sometimes have been neglected despite the obvious association with epilepsy. Cleveland Clinic’s Knowledge Program is an example of an innovative, high-tech tool that can facilitate this type of monitoring.

Commonly Asked Questions
What follows are some common questions about screening children with epilepsy for neuropsychiatric comorbidities.

Why screen for neuropsychiatric comorbidities? There is a bidirectional relationship between epilepsy and neuropsychiatric comorbidities. The existence of comorbidities affects our selection of anti-epileptic treatment. Also, the effects of anti-epileptic medication can cause, or worsen, some comorbidities.

Children with epilepsy often have unmet needs for medical and mental health along with poor coordination of care. Therefore, screening and early identification of these comorbidities can lead to more comprehensive care delivery.

Which children are at greatest risk for neuropsychiatric comorbidities? Certain biological, social and treatment-related factors increase the risk for comorbidities in children with epilepsy:

- Biological factors — younger age at seizure onset, history of cognitive impairment, temporal or frontal lobe epilepsies and refractory seizures
- Social factors — lower socioeconomic status, lower parental education level and poorer family function
- Treatment-related factors — longer period of treatment with anti-epileptic medications and polytherapy

Which neuropsychiatric comorbidities should be screened for in children with epilepsy? A number of neuropsychiatric comorbidities can be found in children with epilepsy, including autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), depression and anxiety. Information relevant to these conditions in children with epilepsy is found in Table 1.

The age at onset of these comorbidities in children can vary, so any screening program needs to take this variable into account.

ASD. Initial ASD symptoms are present in the toddler years. The diagnosis of ASD often is not made until age 2 or 3 years, after the symptoms are recognized. The average age at diagnosis of
Table 1. Neuropsychiatric Comorbidities in Children with Epilepsy

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Relevant Data in Children with Epilepsy</th>
<th>Screening Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism spectrum disorder (ASD)</td>
<td>Prevalence of ASD is 60 to 70 per 10,000 Frequency of epilepsy in children with ASD is 4% to 46% Age at seizure onset for children with ASD is bimodal (0 to 5 years and 10 to 15 years) Epilepsy is persistent to adulthood in patients with autism Risk factors for epilepsy in ASD are severe mental retardation and additional neurological disorders Seizures are more prevalent in females than males with ASD 15% of children with infantile spasm are diagnosed with ASD 70% of children with spasms due to tuberous sclerosis have ASD Seizure type in ASD depends on age at onset of epilepsy: In patients 9 years or younger, the most common type is complex partial simple; in those 10 or older, almost half of seizures are generalized tonic-clonic</td>
<td>Modified Checklist for Autism in Toddlers (M-CHAT)</td>
</tr>
<tr>
<td>Attention deficit hyperactivity disorder (ADHD)</td>
<td>ADHD affects 5% to 7% of the general population 20% to 42% of children with epilepsy have ADHD ADHD equally affects boys and girls with epilepsy Children with epilepsy have a higher incidence of ADHD relative to their healthy siblings Rate of ADHD is: • 15.8% for children with early seizure onset • 8.1% for children with recent seizure onset ADHD is more prevalent in children with new-onset epilepsy (31%) than in healthy controls. Epilepsies associated with ADHD are lesional or nonlesional frontal lobe epilepsy, childhood absence epilepsy, rolandic epilepsy and electrographic status epilepticus of sleep. EEG abnormalities in children with ADHD: • 5% to 60% of children with ADHD have EEG abnormalities vs. 3.5% of healthy children • 5.6% of children with ADHD have rolandic spikes on EEG vs. 2.4% of healthy children • 14% of children with ADHD and EEG abnormalities develop seizures</td>
<td>Distractibility, hyperactivity and impulsivity in two settings</td>
</tr>
<tr>
<td>Depression</td>
<td>Prevalence is 23% to 26% of children with epilepsy Suicidal ideation is present in 20% of children with epilepsy and depression Children in different age groups present with differing symptoms: • Childhood: irritability, anger, academic decline, agitation, anxiety, phobias, regressing behavior, separation anxiety, somatic symptoms • Adolescence: psychomotor retardation, anhedonia, hypersomnia, hopelessness, weight changes, drug abuse</td>
<td>PHQ-2 and PHQ-9</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Prevalence of anxiety is 15% to 20% of children with epilepsy Anxiety disorder includes panic disorder, obsessive-compulsive disorder, generalized anxiety disorder, social phobia and separation anxiety disorder Risk factors: • Epilepsy-related: uncertainty, misinformation, stigma • Patient factors: teenagers, depression, low self-esteem, peer relationships, academic achievements • Parental factors: reaction to seizures, lack of support</td>
<td>Revised Children's Manifest Anxiety Scale State-Trait Anxiety Inventory for Children Screen for Child Anxiety Related Emotional Disorders</td>
</tr>
</tbody>
</table>
ASD is about 6 years. Screening for ASD needs to target toddlers and preschool children.

**ADHD** is the most common disorder in preschool- and school-age children with epilepsy. According to the DSM-IV, the diagnosis of ADHD is made when there are six out of nine behavioral and functional symptoms of inattention, hyperactivity and impulsivity, with onset before age 7 years and more than six months’ duration of symptoms. Treatment of ADHD today offers a variety of options and selection of medications.

*Depression and anxiety* affect at least one-third of school-age children and teenagers with epilepsy. There are well-established standardized screening tests for depression and anxiety in children (see Table 1). The selection of one screening tool over another depends on the time frame available for the screening and validation characteristics of the tool.

**The Importance of Multidisciplinary Care**

One cannot overstate the importance of a multidisciplinary team in the identification, diagnosis and management of neuropsychiatric comorbidities in children with epilepsy. Multidisciplinary teams vary from institution to institution, but ideally they should include specialized nurse practitioners and clinical nurses, pediatricians, behavioral specialists, pediatric neurologists and epileptologists, and child psychiatrists.

At Cleveland Clinic, children with epilepsy and their families receive diagnosis and management not only from our pediatric epilepsy specialists, but also from epilepsy specialized social workers, medical ethicists, clinical nurses, nurse practitioners, child psychologists and child psychiatrists. A vast network of physicians facilitates easy referral to pediatricians and behavioral pediatricians at our main campus and community sites within the region.

**SUGGESTED READING**


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Clinicians are recognizing a growing need to screen for other important neuropsychiatric comorbidities that sometimes have been neglected despite their obvious association with epilepsy.
Rasmussen Encephalitis: An Update on Surgical Treatments and Autoimmune Therapies

By Ahsan N.V. Moosa, MD

Cleveland Clinic has long offered hemispherectomy for severe epilepsy associated with Rasmussen encephalitis (RE). Now, our pediatric epilepsy and immunology specialists are teaming up to offer immune modulatory therapy to help children with RE who are not favorable candidates for surgery.

Rasmussen Encephalitis at a Glance

RE is a unique inflammatory disorder of the brain that leads to progressive destruction of one hemisphere. Typical manifestations include drug-resistant epilepsy, progressive hemiparesis and cognitive/language deficits.

The precise etiology of RE remains unknown, but immune-mediated injury is considered central in the pathogenesis. Current evidence suggests neuronal and astrocyte injury mediated by granzyme B-expressing T cells. Similarities in the histopathological changes between RE and viral encephalitis have long suggested possible viral infection as an initiating event, leading to an inflammatory cascade over the entire hemisphere. This hypothesis remains viable, but no specific viruses have been found to date.

RE typically affects children between 5 and 7 years of age. Patients often present with motor seizures that quickly become medically refractory; many patients also develop epilepsia partialis continua. Over several months, motor and cognitive deficits due to hemispheric injury ensue (Figure 1). The periorolandic cortex appears to be at the epicenter of the disease process, thus explaining motor seizures and hemiparesis.

RE sometimes presents with atypical features, as noted in Figure 2. Atypical features may occur in various forms, as follows:

- Younger age (often associated with more rapid progression, and occasionally involving both hemispheres)
- Older age (frequently slow progression and localized disease)
- Location of brain injury outside the periorolandic region (e.g., temporal lobe, basal ganglia involvement)
- Atypical clinical features (infrequent or no seizures, early hemiparesis or no hemiparesis)
- Dual pathology (10 percent of patients have additional pathology such as dysplasia)

Treatment Options for Seizure Freedom

Treatment options in children with RE are outlined in Figure 3. Hemispherectomy or some form of hemispheric disconnection is the most effective treatment leading to seizure freedom. Though several variations of hemispherectomy are available, all procedures aim to disconnect the diseased hemisphere from the opposite hemisphere and the brain stem. In our recent study at Cleveland Clinic examining longitudinal outcomes of 170 children after hemispherectomy (see Suggested Reading), 71 percent of 21 patients with RE were seizure-free on long-term follow-up.

No anti-epileptic drug is particularly effective in RE. Surgery is undertaken when there is no additional risk of neurological deficits after hemispherectomy. In an ideal candidate, hemispheric disconnection offers maximal chances for seizure freedom without the risk of additional neurological deficits.

In practice, surgery is usually considered when patients lose hand function on the affected side. Rarely, some patients with life-threatening recurrent status epilepticus may be subjected to hemispherectomy even in the absence of hemiparesis. Focal cortical resections have not been found to be of benefit in RE.

Figure 1. Typical Natural Course of RE

**Prodromal stage**

- Motor seizures
- Median 0 months (0-7 mo)
- Onset: 5-7 years

**Acute/“active” stage**

- Frequent seizures
- Progressive hemiplegia
- Hemianopia
- Aphasia
- Few months to a year

**Residual stage**

- End-stage hemispheric failure
- Variable

**EPC = epilepsia partialis continua.**

Figure 1. Natural course of Rasmussen encephalitis (RE) in a typical patient. EPC = epilepsia partialis continua.
Immunotherapy Effect: Modest at Best

The presence of inflammatory changes on pathology and early reports of an association with the Glut3 receptor antibody prompted clinicians and researchers to try various forms of immunotherapy. Autoimmune disorders may be viewed as “autoimmune errors” committed by the host’s immune system. Recovery from autoimmune disorders depends on the host’s ability to correct its own error. In some autoimmune disorders, this occurs in a few weeks — and in others, a few years. Immune therapy reduces ongoing injury when the organs self-correct the autoimmune error.

As a general rule, in most autoimmune disorders, immunosuppression reduces injury by inflammation but has a minor role in reversing the primary disease process itself. Injury to the brain, unlike other organs, is frequently irreversible, resulting in debilitating neurological deficits. For this reason, every attempt should be made to preserve function in patients who are not candidates for hemispherectomy.

The effect of immunotherapy on the course of RE is still modest at best. The goal of “no seizures and no progression of disease” by immunotherapy remains elusive. Initial reports of steroid use (pulse intravenous steroids followed by oral steroids) have revealed only short-term improvement with no benefits in long-term outcomes. Side effects related to long-term use of steroids further compromised any benefits.

Currently, most centers use intermittent intravenous immunoglobulin (IVIg) or continuous tacrolimus as long-term immune therapy. A recent trial of IVIg vs. tacrolimus in RE showed a decrease in progression of neurological deficits in some patients, but there was little effect on epilepsy.

In short, immunotherapy may delay the onset of neurological deficits, but it does not reduce seizure burden. This may at times
Immunotherapy may delay the onset of neurological deficits, but it does not reduce seizure burden. Nevertheless, it remains an option to be considered in patients at risk for major deficits after surgery.

lead to a protracted course of continued seizures (prolonged active stage) without hemiparesis, making surgery undesirable. Nevertheless, immunotherapy remains an option and should be considered in patients at risk for major deficit(s) after surgery.

The combination of immunotherapy agents (e.g., IVIg and tacrolimus) and newer biologicals used in other autoimmune diseases may be considered for trials in RE. Rare patients who have fairly well-controlled seizures without clinical evidence of progression may be observed with anti-epileptic drugs alone.

**Bottom Line**

Hemispherectomy remains the best available treatment for intractable epilepsy due to RE. Further research on pathogenesis and treatment may guide us toward the elusive goal of “no seizures and no progression of disease” without surgery.

Dr. Moosa is a pediatric epilepsy staff physician in the Epilepsy Center in Cleveland Clinic’s Neurological Institute. His specialty interests include epilepsy surgery, etiology of epilepsy-metabolic disorders, genetic and autoimmune disorders, and the ketogenic diet in epilepsy. He can be reached at 216.636.5469 or naduvia@ccf.org.

**TAKE-HOME POINTS**

- Hemispherectomy remains the best option for seizure control in Rasmussen encephalitis (RE) patients not at risk for new postoperative deficits.
- Pediatric epilepsy and immunology specialists at Cleveland Clinic are teaming up to offer immune modulatory therapy to help children with RE who are not favorable candidates for surgery.
- Commonly used immune/anti-inflammatory therapy includes steroids (IV pulse + oral), intravenous immunoglobulin, tacrolimus or a combination of these.
- The scope of immune/anti-inflammatory therapy is limited to slowing disease progression.

**SUGGESTED READING**


Seizure Outcome in SEEG-Guided Resections in Children and Adolescents with Difficult-to-Localize Refractory Focal Epilepsy

By Jorge Gonzalez-Martinez, MD, PhD; Elaine Wyllie, MD; and Deepak Lachhwani, MD

In the United States, subdural grids and strips are the most common invasive method used in pediatric epileptic patients who need extra-operative invasive monitoring procedures. Despite the high spatial resolution provided by the subdural methodology, which allows for accurate mapping of superficial cortical areas, relatively deep epileptic foci cannot be localized with adequate spatial and temporal resolution. In addition, subdural grids require relatively large craniotomies and are, in general, limited to exploration of one hemisphere, which are important limiting factors in the pediatric population.

In Search of a Better Way

In the face of these relative limitations, we explored alternative/complementary methods for invasive monitoring, revisiting the concepts and techniques of the stereoelectroencephalography (SEEG) methodology and applying it to a selected group of pediatric patients with difficult-to-localize epilepsy.

We consecutively studied all pediatric patients (younger than 21 years) with the diagnosis of medically refractory focal epilepsy who underwent SEEG implantation at Cleveland Clinic’s Epilepsy Center between August 2009 and March 2012. All surgeries were part of standard patient care, and no procedures were performed for research purposes. Postoperative clinical data were collected by patient interview, during regularly scheduled clinic visits or by telephone.

Postoperative seizure outcome was classified according to the Engel Epilepsy Surgery Outcome Scale. All adverse events within 30 days after SEEG implantations were counted as complications. The study was approved by Cleveland Clinic’s Institutional Review Board.

Results: SEEG-Guided Resections

The hypothetical epileptogenic zone (EZ) was localized in 26 of 30 patients (86.6 percent). Of these patients, 18 (69.2 percent) underwent resection (Table 1). Reasons for not undergoing resection despite localization of the hypothetical EZ included failure in localizing the EZ (n = 4); multifocal EZ (n = 4); EZ localization in eloquent cortex, preventing resection (n = 3); and improvement of seizures after implantation (n = 1).

The total number of implanted electrodes was 402 (average of 13.4 electrodes per patient). Each patient underwent two or three surgical procedures (12 and 18 patients, respectively), which included SEEG implantations, SEEG electrode removals and SEEG-guided resections. In total, 78 procedures were performed.

Among the 18 patients who underwent surgical resections, preoperative MRIs were nonlesional in 11 patients (61.1 percent). Eleven patients (61.1 percent) had resections on the right side, and seven (38.9 percent) on the left side. Temporal lobe resections were performed in five patients (27.7 percent), unilobar extratemporal resections were done in five (27.7 percent) and multilobar resections were performed in eight (44.4 percent).

In the SEEG implantation series, no child experienced serious or permanent morbidity. One patient developed a small and asymptomatic intraparenchymal hematoma, which required no surgical intervention or prolonged hospital stay. The complication rate was 3.3 percent. The rate of hemorrhagic complications per implanted electrode was 0.2 percent. The average estimated blood loss per SEEG implantation procedure was 5 cc. The average hospital stay for the SEEG implantations was 9.7 days.

TAKE-HOME POINTS

- A recent study at Cleveland Clinic explored use of stereoelectroencephalography (SEEG) in guiding resections in a selected group of pediatric patients with difficult-to-localize epilepsy.
- The hypothetical epileptogenic zone was localized in 86.6 percent of patients, of whom 69.2 percent underwent resection.
- In the SEEG implantation series, no child experienced serious or permanent morbidity.
- The SEEG method, when individualized through careful and meticulous analysis, is a safe and efficient option for pediatric patients who present with clinical features of medically intractable focal epilepsy in the setting of nonlocalizable scalp EEG recordings and with nonlesional MRIs.
Results: Seizure Outcomes and Pathology

The mean follow-up after SEEG-guided resections was 21.9 months (range, 8 to 43). Of the 18 patients who underwent resection, 10 (55.6 percent) were seizure-free at last follow-up (Engel class I) and five (27.7 percent) experienced seizure improvement (classes II and III). Regrettably, three patients (16.6 percent) had no improvement in seizures following resection (class IV).

Figure 1 presents illustrative images from one of the patients who achieved seizure freedom.

Surgical pathology from resected specimens showed mild forms of cortical dysplasia in 13 patients (72.2 percent); three patients (16.6 percent) had unspecific findings as gliosis; one patient had encephalomalacia; and one patient had hippocampus changes consistent with mesial temporal sclerosis. Among the three patients with no seizure improvement, histopathology showed gliosis in two and a mild form of cortical dysplasia in the remaining patient (Table 1).

An Additional Opportunity for Seizure Freedom

We conclude that the SEEG method, when individualized through careful and meticulous analysis, is a safe and efficient option for pediatric patients who present with clinical features of medically intractable focal epilepsy in the setting of nonlocalizable scalp EEG recordings and with nonlesional MRIs.

In performing SEEG in this highly selected group, we were able to partially overcome the relative limitations of the current standard methods of invasive monitoring. This approach offers an additional opportunity for seizure freedom without safety compromises in clinically challenging cases — an opportunity likely not possible with other methods of extra-operative invasive monitoring.

Dr. Gonzalez-Martinez is a neurosurgeon specializing in pediatric epilepsy surgery and pediatric brain tumors. He is an associate staff member in Cleveland Clinic’s Epilepsy Center and the Departments of Neurological Surgery and Biomedical Engineering. His interests include epilepsy and epilepsy surgery in children and adolescents. He can be reached at 216.636.5860 or gonza1@ccf.org.

Dr. Wyllie is a professor and pediatric epileptologist in Cleveland Clinic’s Epilepsy Center. Her clinical and research interests include pediatric epilepsy, EEG, anti-epileptic medications and epilepsy surgery. She can be reached at 216.636.5860 or wyllie@ccf.org.

Dr. Lachhwani is a 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 lachhd@ccf.org.

Table 1. SEEG-Guided Resections at Cleveland Clinic

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (Yr)</th>
<th>Gender</th>
<th>Resection Type</th>
<th>Seizure Outcome (Engel Scale)</th>
<th>Pathology</th>
<th>Complications (Resections)</th>
<th>Follow-Up (Mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>F</td>
<td>LT</td>
<td>I</td>
<td>Hippocampus sclerosis</td>
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<td>15</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>M</td>
<td>LT</td>
<td>I</td>
<td>CDI</td>
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<td>8</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>M</td>
<td>LF</td>
<td>III</td>
<td>CDI</td>
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</tr>
<tr>
<td>9</td>
<td>16</td>
<td>M</td>
<td>RF</td>
<td>I</td>
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<tr>
<td>10</td>
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<td>RT</td>
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</tr>
<tr>
<td>11</td>
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<td>RFTI</td>
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<td>13</td>
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<td>RFT</td>
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<td>M</td>
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<tr>
<td>17</td>
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<td>LT</td>
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<td>None</td>
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<tr>
<td>18</td>
<td>6</td>
<td>M</td>
<td>RFTI</td>
<td>I</td>
<td>CDI</td>
<td>R IC infarct</td>
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</tr>
<tr>
<td>19</td>
<td>14</td>
<td>M</td>
<td>RFI</td>
<td>I</td>
<td>Gliosis</td>
<td>None</td>
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</tr>
<tr>
<td>20</td>
<td>20</td>
<td>M</td>
<td>RC</td>
<td>IV</td>
<td>Gliosis</td>
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<td>23</td>
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<td>CDI</td>
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<tr>
<td>30</td>
<td>9</td>
<td>F</td>
<td>RT</td>
<td>I</td>
<td>CDI</td>
<td>CSF leakage</td>
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</tr>
</tbody>
</table>

L = left; R = right; T = temporal; F = frontal; I = insula; C = cingulate gyrus; P = parietal; CDI = cortical dysplasia type I; IC = internal capsule
SUGGESTED READING


Figure 1. Illustrative case of a 14-year-old male with medically intractable focal epilepsy for 12 years (patient 19 in Table 1). Multiple scalp EEGs showed multifocal epileptic discharges (temporal, frontal and parietal) on the right. MRI was considered nonlesional. (A) Ictal SPECT showing increased blood flow in the right frontal opercular and insular regions. (B) MEG scans showing dipoles located in the right frontal opercular areas. (C) SEEG implantation and co-registration with preoperative MRI demonstrating right frontal, perisylvian, insular, temporal and parietal SEEG implantation. On the bottom, SEEG ictal recordings demonstrate ictal onset in the R electrodes, in contacts located in the superior insula and frontal opercular areas. (D) Postoperative MRI after SEEG-guided resection focused on the right superior insula and frontal opercular area. The patient has been seizure-free for 12 months.
Augmentative and Alternative Communication Strategies for Children with Angelman Syndrome

By Jackie Kears, CCC-SLP, and Douglas Henry, MD

Cleveland Clinic’s experts in pediatric speech and language pathology are using cutting-edge technology to improve communication skills for children with Angelman syndrome and other neurological disorders. Through the use of augmentative and alternative communication strategies, speech-language pathologists work to shorten the gap between a child’s receptive and expressive language skills.

An Approach Well Suited to Angelman Syndrome

Augmentative and alternative communication (AAC) refers to a set of procedures that seek to improve, temporarily or permanently, the communication skills of those who have minimal to no functional speech and/or writing. AAC can use both unaided (manual signs, gestures, finger spelling, eye gaze) and aided (picture communication symbols, voice output communication aids) forms of communication. While all speech-language pathologists generally have some cursory knowledge of AAC, not all therapists specialize in this area of communication.

At Cleveland Clinic, AAC has been especially rewarding for children with Angelman syndrome. This disorder is caused by a disruption in chromosome 15, with the most common disruption caused by a large deletion of the maternal chromosome. Despite several differences in gene mutation, some characteristics are present in all cases of Angelman syndrome. In addition to severe developmental delays, Angelman syndrome is characterized by a movement or balance disorder, ataxia, which can vary from mild to severe. Affected children demonstrate an apparent happy demeanor and hypermotoric behavior.

Children with Angelman syndrome have severe to profound communication impairments. Receptive language is typically more advanced than expressive language. Verbal speech is extremely limited, so all children with Angelman syndrome are excellent candidates for AAC.

Early Intervention Critical

Children with Angelman syndrome vary greatly in the types of AAC they use, often using more than one mode of communication. It has been observed that early communication milestones include the use of eye gaze, facial expression and body posturing. While these behaviors are unintentional initially, it is crucial for early intervention services to train caregivers to interpret these unintentional actions. Only then will these unintentional acts be shaped into more conventional forms of communication.

A common example of language shaping can be seen with infants, who go through a period of reduplicated babbling. A typical child may spontaneously babble an approximation of “mama” or “dada.” This is not intentional at first. A caregiver, on hearing the child use that approximation, will say, “That’s right! You said ‘mama/dada’…that’s me!” Shortly after receiving this consistent praise and attention, the child begins to use “mama” and “dada” purposefully.

While the child was initially demonstrating early, unintentional communication acts, it is really the caregiver who provides the necessary supports and encouragement to shape those unintentional acts into true communication. Similarly, this strategy is often used for children with complex communication needs.

Gestural communication is another strong skill in children with Angelman syndrome. Initially, these gestures may begin by physical contact. For example, a child may push away an unwanted object or take a caregiver’s hand to lead him or her toward a desired object. The 2002 article by Stephen Calculator (see Suggested Reading) provides an excellent

TAKE-HOME POINTS

- Children with Angelman syndrome have significant communication deficits but demonstrate a gap between their receptive and expressive language skills.
- Augmentative and alternative communication (AAC) strategies can use both nonaided and aided forms of communication to help children communicate their wants and needs and to interact with others.
- Not all speech-language pathologists specialize in AAC, so consultations/referrals may be warranted.
- The Technology Resource Center at Cleveland Clinic Children’s Hospital for Rehabilitation provides evaluations for children with Angelman syndrome or other complex communication needs to help them reach their full potential.
therapeutic technique for creating enhanced natural gestures for children with severe communication impairments, including Angelman syndrome.

In addition to nonaided forms of AAC, aided AAC techniques have also proven quite successful in children with Angelman syndrome. These methods may include use of single pictures, communication books/boards or voice output communication aids (VOCAs). A wide range of VOCAs are available on the market today, from simple single-message communicators to dynamic display communication aids (see Figures 1 to 3). iPad® devices with apps such as Proloquo2Go®, TouchChat™ or LAMP Words for Life™ also may be suitable communication aids for children with Angelman syndrome.

Team-Based Approach to Care

The Technology Resource Center at Cleveland Clinic Children’s Hospital for Rehabilitation helps all children whose ability to communicate has been hurt by injury, chronic illness or congenital issues. The therapists at the Technology Resource Center help children interact with others by teaching AAC.

Every child is first seen by a speech-language pathologist who specializes in AAC. The therapist may consult with occupational therapists, physical therapists and physicians to help evaluate a child’s strengths and barriers. Parents, teachers and other professionals already involved with the child are important members of the team and participate in planning and decisions.

Based on team recommendations, a communication plan is developed. If a child needs specialized equipment, Technology Resource Center staff will help families find it. The staff not only prescribes communication devices but also teaches patients, family members and other members of a child’s care team how to use them.

Ms. Kearns is a senior speech-language pathologist and Coordinator of the Technology Resource Center at Cleveland Clinic Children’s Hospital for Rehabilitation. She works with children with a variety of complex communication needs. She can be reached at 216.448.6157 or kearnsj@ccf.org.

Dr. Henry is Director of Developmental Pediatrics and Physical Medicine and Rehabilitation at Cleveland Clinic Children’s. He can be reached at 216.448.6179 or henryd@ccf.org.

SUGGESTED READING


Figure 1. Pragmatic Organization Dynamic Display (PODD) communication books.

Figure 2. DynaVox Xpress™ voice output communication aid.

Figure 3. iPad with Proloquo2Go application software.
Electroconvulsive Therapy: Underutilized Modality Can Be Safe, Effective for Severe Mood Disorders in Adolescents

By Joseph Austerman, DO

Electroconvulsive therapy (ECT) is a highly effective treatment modality for multiple psychiatric and medical illnesses. Although commonly used in adults, this therapy is significantly underutilized in the adolescent population. Cleveland Clinic is the only medical center in Northeast Ohio offering ECT for pediatric patients. The therapy is administered here by a team of child and adolescent psychiatrists who are accredited in its use.

Effective use of ECT has been demonstrated in adolescents since 1942. Yet despite the longevity of its use and endorsement by the American Academy of Child and Adolescent Psychiatry, ECT remains highly stigmatized and misunderstood.

ECT Knowledge Gaps Persist

Even mental health professionals have knowledge gaps about the use of ECT. In a survey of child psychiatrists and psychologists, 53.8 percent reported their knowledge about ECT to be minimal, 75 percent said they lacked confidence in giving a second opinion about the treatment modality and 70 percent regarded it as a treatment of last resort. In a survey of 113 hospitals in Australia, among 7,469 patients who received ECT, only 0.2 percent were younger than 18 years.

Determining Appropriate Indications

The adult population is referred for ECT most often for mood disorders, while adolescents are referred most often for schizophrenia or schizoaffective disorders. This contrasts with findings that the adolescent population responds to ECT as well as, or even better than, the adult population for mood disorders and psychosis, while experiencing fewer or the same degree of side effects. Substantial empirical evidence supports the benefit of ECT in adolescents in severe, persistent mood disorders, psychosis or catatonia. There also are multiple reports demonstrating benefits for self-injurious behavior in autistic spectrum disorders and Tourette syndrome.

As with adults, ECT should be considered in adolescents when there are severe, persistent and significantly disabling symptoms. Unless there is an urgent need, such as the refusal to eat or drink, severe suicidality, uncontrollable mania or florid psychosis, ECT should be considered only after usual treatment modalities have failed. There should be at least two adequate trials of appropriate psychopharmacologic agents accompanied by other appropriate treatment modalities such as psychotherapy.

Best Practices When Administering ECT

Adolescent patients should undergo a full psychiatric and medical evaluation in a standardized fashion when ECT is being considered (Table 1). Collateral information should be obtained.

Table 1. Recommended Assessment Protocol in Adolescents with Depression

<table>
<thead>
<tr>
<th>Steps</th>
<th>Actions/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient selection</td>
<td>Symptoms are severe and persistent</td>
</tr>
<tr>
<td></td>
<td>Failed at least two adequate antidepressant trials accompanied by other</td>
</tr>
<tr>
<td></td>
<td>appropriate treatment modalities such as psychotherapy</td>
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<tr>
<td></td>
<td>Active suicidality, florid psychosis or life-threatening symptoms such as</td>
</tr>
<tr>
<td></td>
<td>refusal to eat</td>
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<tr>
<td>Psychiatric assessment</td>
<td>Detailed clinical interview incorporating past treatments</td>
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<tr>
<td></td>
<td>Reliable rating instruments administered</td>
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<tr>
<td></td>
<td>Second opinion obtained by a psychiatrist knowledgeable about ECT who is</td>
</tr>
<tr>
<td></td>
<td>not treating the patient</td>
</tr>
<tr>
<td></td>
<td>Cognitive and memory assessment</td>
</tr>
<tr>
<td>Medical assessment</td>
<td>Complete physical assessment</td>
</tr>
<tr>
<td></td>
<td>Laboratory data:</td>
</tr>
<tr>
<td></td>
<td>- CBC with differential</td>
</tr>
<tr>
<td></td>
<td>- Thyroid function test</td>
</tr>
<tr>
<td></td>
<td>- Liver function test</td>
</tr>
<tr>
<td></td>
<td>- Urinalysis and toxicology</td>
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<tr>
<td></td>
<td>Imaging:</td>
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<tr>
<td></td>
<td>- ECG</td>
</tr>
<tr>
<td></td>
<td>- EEG</td>
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<tr>
<td></td>
<td>- CT</td>
</tr>
<tr>
<td>Anesthesia preoperative assessment</td>
<td></td>
</tr>
<tr>
<td>Consent</td>
<td>Complete explanation of the procedure, risks, benefits</td>
</tr>
<tr>
<td></td>
<td>and alternative treatments to both the patient and parent/guardian</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Monitor patients during and after treatment until fully recovered from</td>
</tr>
<tr>
<td></td>
<td>anesthesia</td>
</tr>
<tr>
<td></td>
<td>Monitoring should continue for at least 24 hours after the procedure</td>
</tr>
<tr>
<td></td>
<td>Cognitive assessment prior to acute ECT series, immediately after the acute</td>
</tr>
<tr>
<td></td>
<td>series and three to six months after the acute series</td>
</tr>
</tbody>
</table>

Source: Based on recommendations in Ghaziuddin et al
from parents and treatment providers. Target symptoms should be assessed using reliable rating instruments.

Before ECT is administered, a comprehensive physical should be done that includes a complete blood count, differential white blood cell count, thyroid function test, liver function test, urinalysis and toxicology screen, ECG and brain CT. A serum urine pregnancy test should be obtained for females. Also, it is recommended that adolescents undergoing ECT have a memory assessment before treatment. Permission must be obtained from the parent/guardian and assent obtained from the child.

When considering ECT, every patient should receive an independent evaluation from a psychiatrist who is knowledgeable about ECT and not directly responsible for treatment of the patient. While supportive treatment of adolescents should continue during the course of ECT whenever possible, ECT should be administered without concurrent medications, as some psychotropic medications may affect the quality of ECT or confer a neurocognitive risk with the concurrent use of ECT.2

Low Incidence of Side Effects

There are no absolute contraindications to the use of ECT; however, tumors of the CNS associated with increased cerebrospinal fluid pressure, active chest infection or recent myocardial infarction are considered relative contraindications.

A few side effects are associated with the use of ECT, the most common of which are transient: headaches, delirium lasting less than one hour post-procedure, hypomanic symptoms and memory loss. Cognitive effects associated with ECT are comparable to those in adults, and there are no data to support long-term cognitive effects.

One rare side effect may include tardive seizures arising in the first 20 to 48 hours after ECT is administered. This effect was seen more often in those patients experiencing a prolonged seizure (> 180 seconds).

Fatality is rare, with an overall fatality rate similar to that in adults (0.2 per 10,000). The risk of anesthesia and complications is believed to be no greater than 1.1 per 10,000 incidents, which is cited as comparable to adults.2

Good Remission Rates in Unipolar Depression

ECT in adolescents is most beneficial for the treatment of severe mood symptoms, acute suicidality, catatonia and psychosis.

Some studies report a remission rate of approximately 60 percent for treatment of refractory unipolar depression.3 Although ECT is commonly misunderstood and stigmatized, it is a valid, safe and effective treatment modality for adolescents suffering from mood or psychotic symptoms and should be considered as a rational treatment option.

Dr. Austerman is a staff physician in Cleveland Clinic’s Center for Pediatric Behavioral Health and Department of Psychiatry and Psychology. He specializes in the acute care of medically ill children who require hospitalization for physical illnesses. He can be reached at 216.445.7656 or austerj@ccf.org.

REFERENCES

Childhood Emotional Trauma Closely Linked to Psychopathology and Chronic Illness in Adulthood

By Tatiana Falcone, MD

The adverse consequences of childhood trauma not only impact children's lives in the near term but also can have severe long-term impact on their future lives as adults. Several studies have demonstrated that patients exposed to trauma-induced stress in their first eight years of life are more likely to develop mood disorders, psychotic disorders and post-traumatic stress disorder (PTSD) than are children not exposed to trauma.

At Cleveland Clinic, we are studying the link between childhood trauma, inflammatory markers and development of psychiatric disorders in children, as well as how effective interventions during critical periods of development can potentially alter the course of psychiatric disorders.

The problem is widespread: 3 million cases of childhood trauma are reported in the United States each year, according to the U.S. Department of Health and Human Services. In 2009, about 1 million of these cases were substantiated; of those cases, 1,770 resulted in death of a child secondary to the maltreatment. Statistically, this means that an average of five children per day are victims of fatal maltreatment. Approximately 80 percent of the cases were reported in children under age 4. Retrospective studies in the adult population evaluating the rate of trauma exposure during childhood estimate the rate to be as high as 25 to 45 percent.

Increased Risk for Psychopathology
There is an important link between trauma in childhood and the development of psychopathology. Traumatic experiences in childhood have been identified as a particularly strong risk factor for:
- Mood disorders
- Anxiety disorders (including PTSD, generalized anxiety disorder and phobias)
- Psychotic disorders
- Schizophrenia, personality disorders, substance abuse and eating disorders

There is also an increased incidence of traumatic experiences in childhood among individuals who attempt suicide. The severity of the trauma, as measured by patients' total Adverse Childhood Experiences score, is positively correlated with suicide attempts during childhood or adolescence and has been found to have a strong graded relationship with the severity of the trauma exposure.

Moreover, childhood trauma severely impacts the clinical course of multiple psychiatric disorders. Remission from depression and anxiety symptoms is less likely in patients with a history of trauma during childhood. Childhood trauma is also associated with chronicity in patients with depression and anxiety, and it was a predictor of treatment resistance in two mood disorder studies. Patients with childhood trauma also tend to have earlier onset of major depressive disorder and much higher levels of comorbidity.

Linkage to Chronic Illness
During the past few decades, researchers have demonstrated how trauma early in life can strongly impact and potentially trigger the development of chronic illness. Victims of child abuse are more susceptible to developing (in addition to mental illness) allergies and asthma, autoimmune disorders, osteoarthritis, cardiovascular disease and metabolic disorders.

Several specific characteristics occur more frequently in victims of childhood abuse and might influence the development of chronic illness; these include poor sleep quality, elevated perceived stress, high body weight and small social networks. These factors all have been demonstrated to increase

TAKE-HOME POINTS
- Individuals who experience trauma early in life are more likely to develop mental health issues. The greater the exposure, duration, frequency and severity of childhood trauma, the more likely individuals are to experience depression and other psychiatric comorbidities.
- Children who experience chronic and severe trauma early in life are at high risk for poor health outcomes in adulthood, including cardiovascular disease, cancer, asthma and depression.
- Early traumatic events severely affect the brain, the heart and the immune system. Effective interventions to reduce childhood trauma can improve outcomes.
inflammation in victims of childhood abuse compared with nonvictims. These patients may be at risk of dying younger secondary to the chronic effects of inflammation.

**Blood-Brain Barrier Disruption**

Advances in neuroscience, genetics and biomarker studies are changing how we view the impact of adversity.

When an individual feels threatened, the human body activates different biological pathways designed to protect the individual from events that may threaten survival (Figure 1). The initial sympathetic response — “the fight or flight” reaction — produces increased levels of adrenaline and noradrenaline that cause an increased heart rate, peripheral vasoconstriction and massive energy mobilization.

The hypothalamus-pituitary-adrenal axis, one of the central stress response systems, provides a protracted response, triggering secretion of corticotropin-releasing hormone. Studies have demonstrated that corticotropin-releasing hormone has pro-inflammatory properties that can regulate blood-brain barrier (BBB) leakage. Animal models of early stress in rats have been shown to induce BBB breakdown. Several animal models of PTSD have demonstrated how rats confronted with a traumatic event have increased values of the BBB disruption biomarker S100B.

**Intervening with Continued Vigilance and Research**

Practically speaking, effective interventions to reduce rates of trauma in children can improve outcomes. Pediatric specialists, generalists and psychiatrists are in a unique position to help youth improve their quality of life as adults by helping identify children at risk. At Cleveland Clinic, our research continues on the long-term impact of childhood abuse in youth and on the relationship between childhood trauma and development of psychiatric disorders.

*Suggested Reading*


Quality of Life in Youth with Epilepsy: More than Seizure Control

By Tatiana Falcone, MD, and Sarah O'Connor

Epilepsy is a chronic life-altering disease with episodic, recurring and unpredictable symptoms. It is associated with increased risk for a number of psychosocial problems, yet treatment has focused primarily on seizure control.

Studies have found that psychiatric diagnoses in patients with epilepsy are poorly addressed. Sixty percent of children with epilepsy fit DSM-IV criteria for a psychiatric diagnosis, yet less than 33 percent of them are receiving psychiatric services.

Cleveland Clinic Study in 1,500+ Patients

We conducted a study (see “Study Methodology” sidebar) of more than 1,500 pediatric outpatients diagnosed with epilepsy at Cleveland Clinic over a 2.5-year period to examine the relationship between quality-of-life (QOL) ratings and the following domains: inattentiveness, ability to think and remember, neurological and physical limitations, and epilepsy.

The study found a negative correlation between QOL and total Impact of Childhood Neurologic Disability Scale (ICNDS) scores (see “Key Study Findings” sidebar and Figure 1). Individual subscores demonstrated similar correlations between QOL and ICNDS subscores. Higher scores reported for the impact of epilepsy, cognition, behavior and neurological/physical limitations were significantly correlated with lower QOL ratings.

These results indicate that the greater the impact of each domain on the child’s social relationships, school performance and self-esteem, the worse the reported QOL.

More to QOL than Seizure Control

Our data support the conclusions reached by others that illness-associated symptoms of seizure frequency and severity are not the only symptoms associated with decreased QOL in youth with epilepsy. Psychosocial factors, such as the ability to focus attention, are significantly associated with reduced QOL. For instance, children with epilepsy have been shown to be at increased risk for attention deficit hyperactivity disorder (ADHD) and behavioral problems.

Clinical reasoning has focused on the idea that treatment of the epilepsy, with the goal of freedom from seizures, improves QOL in youth with epilepsy. Yet attaining this goal does not address the other issues, such as behavior and cognition, that also impact QOL. Broadening the treatment focus by addressing psychosocial factors and comorbid conditions may help improve QOL for children with epilepsy.

Future Research Needs

No double-blind, placebo-controlled trial has addressed the question of which stimulant therapy is best for children with epilepsy and ADHD. There is clearly a need to conduct research focused on treatment of children with epilepsy and other psychiatric conditions, especially ADHD.

Although our study profiled here cannot show a causal relationship between psychosocial domains and reduced QOL, it points to an increasing need to address epilepsy-associated comorbid conditions when treating children with epilepsy.

Dr. Falcone is a child and adolescent psychiatrist in Cleveland Clinic’s Neurological Institute, where she is also a staff member in the Epilepsy Center. She is the project director for Cleveland Clinic’s Project COPE (Collaboration for Outreach and Prevention Education) for children with epilepsy. She also is implementing Project Stand Up to help youth with special healthcare needs in Ohio and seven other states. Her interests...
include psychiatric comorbidities faced by pediatric patients with epilepsy, biomarkers in child psychiatry, and suicide prevention in children and adolescents. She can be reached at 216.444.7459 or falcon1@ccf.org.

Ms. O’Connor is a fourth-year medical student.

SUGGESTED READING


Key Study Findings

Inattention, neurological/physical limitations, ability to think and epilepsy were each significantly associated with reduced QOL ratings for children with epilepsy (adjusted \( P < .05 \)).

Bland-Altman analysis of the differences in ICNDS subscores for attentiveness, other neurological limitations and ability to think compared with the ICNDS score for epilepsy indicated a significant bias between the ICNDS scores for attentiveness and other neurological limitations when contrasted with the ICNDS score for epilepsy.

Seizure severity and seizure frequency were associated with reduced QOL (\( P < .005 \)), whereas higher numbers of friends (\( P < .0005 \)) and hours of activity (\( P < .005 \)) were positively associated with QOL.

TAKE-HOME POINTS

• Psychiatric diagnoses in patients with epilepsy are poorly addressed: 60 percent of children with epilepsy fit DSM-IV criteria for a psychiatric diagnosis, yet less than 33 percent of them receive psychiatric services.

• A Cleveland Clinic study of more than 1,500 pediatric outpatients diagnosed with epilepsy over a 2.5-year period examined the relation between QOL and inattentiveness, ability to think and remember, neurological and physical limitations, and epilepsy.

• The study found that the greater the impact of each domain on the child’s social relationships, school performance and self-esteem, the worse the reported QOL.

• Broadening the treatment focus to address psychosocial factors and comorbid conditions may help improve QOL for children with epilepsy.
Best Practices: Managing Sports-Related Concussion in Children and Adolescents

By A.D. Rothner, MD

Up to 3.8 million recreation- and sports-related concussions occur each year in the United States, with a large share occurring in children and adolescents. At Cleveland Clinic, children and adolescents with sports-related concussion are treated by general pediatricians/family practitioners, sports medicine doctors and pediatric neurologists. While about 90 percent of symptoms associated with concussions resolve within two weeks, when signs and symptoms persist beyond six weeks, patients should be referred for further evaluation by a pediatric neurologist.

The neurologist’s role in treating the concussed patient goes much deeper than simply ordering neurological testing. At Cleveland Clinic, we take a holistic approach that includes not only diagnosis and treatment but also education, prevention and treatment of underlying issues related to persistent headache that may come to the fore following an acute injury.

Best Practices in Education, Communication

Our experience in treating pediatric patients with sports-related concussion has yielded some best practices in education and communication that are essential to effective management:

- **Emphasize patient/parent education**: Patients and parents/guardians should receive educational literature about concussion and return to play. While face-to-face education certainly is important, often patients and parents are so anxious during a medical appointment that they are unable to remember important details afterward. Having materials in hand will reinforce key messages.

  The American Academy of Pediatrics has helpful information available on its healthychildren.org website, and the American Academy of Neurology’s Sports Concussion Toolkit at aan.com/concussion is an excellent resource.

- **Provide confident reassurance**: Once neurological testing is done and tests appear normal, it is important to reassure parents: “Mrs. Jones, this might seem frightening right now, but your child will get better. He is showing zero neurological symptoms. He isn’t having seizures and hasn’t lost any vision, he isn’t weak on one side, and his neurological exam and CT scan are normal.”

  Parents want to know that nothing scary is going on from a neurological standpoint. It’s important that the information be conveyed as authoritatively and definitively as possible.

- **Address any underlying stress, whether previously present or caused by the incident**: In addition to parents’ concerns, often there are hidden stresses affecting the patient that need to be addressed. For example, a 17-year-old football player may have hidden fears of another concussion and may no longer want to play, but he may be afraid to tell his teammates because he is a star player. We frequently refer to adolescent psychologists in situations such as this.

Avoiding a Second Injury

Numerous studies have found that a pediatric patient who experiences a concussion is statistically more likely to have a second one. The pediatric neurologist plays a pivotal role in educating parents and patients about the importance of prevention, especially if symptoms from the first concussion have not yet resolved.

Much debate surrounds the idea of cognitive rest. We generally recommend that children/adolescents can start...
physical activity as tolerated but certainly no contact sports if they still have symptoms of concussion. If physical activity makes symptoms worse, follow-up with the neurologist is indicated.

The strict guideline for return to play is no contact sports when symptoms persist (with one exception: see "Chronic Daily Headaches" section below). Pediatric patients who have experienced a single concussion are usually able to return to play using appropriate precautions once signs and symptoms of the concussion have resolved. It’s important for parents to ensure via the school or sports organization that athletes have adequate supervision and physical conditioning; that they are properly trained in maneuvers such as tackling; and that they have appropriate, properly fitted equipment.

If the child/adolescent is injured again, he or she should immediately be removed from play until cleared by a healthcare professional familiar with concussions. In addition, technology such as the Cleveland Clinic Concussion App for the iPad (see sidebar) can be useful in assessing athletes at baseline and following an injury.

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Cleveland Clinic Concussion App Brings Objective Assessment to the Sidelines for Student Athletes

By Jay L. Alberts, PhD, and Terra Blatnik, MD

Cleveland Clinic has developed a proprietary concussion application (app) for Apple’s iPad® 2 that could change the trajectory of concussion care in young athletes by enabling objective, affordable point-of-care assessment of symptoms associated with concussion. The app provides this information to clinicians in a meaningful manner on a portable device that allows for interaction with the data.

**How It Works**

The Cleveland Clinic Concussion (C3) App was designed for the iPad 2 due to the device’s built-in gyroscope and accelerometer to measure motion and acceleration. The C3 App works by collecting position and time-series data, along with linear and angular acceleration data, to assess balance and concussion symptoms while an athlete performs clinical balance tests with an iPad attached to the waist (Figure 1). The functions assessed by the app also include those evaluated through trail-making tests performed with a stylus.

After baseline data are collected, the C3 App can be deployed in the locker room or on the sidelines for immediate concussion assessment if the athlete sustains a head injury. The app analyzes data to provide objective and specific measures of cognitive and motor function as well as balance and postural stability at baseline and post-injury. The 15-minute test gathers data on an athlete’s information processing, reaction times, working memory, dynamic visual acuity, postural stability and visual memory. Test results immediately after a possible concussive injury during play can be compared with the athlete’s baseline results, improving the chances of an accurate diagnosis.

The app also provides a comprehensive, systematic questionnaire about the incident and initial symptoms, which the certified athletic trainer or other on-site provider completes for
Return-to-play legislation has now been enacted in more than 40 states and serves as a good first-line safeguard, but it relies heavily on the judgment of referees, coaches and trainers. It’s important to emphasize to parents and patients that they should err on the side of caution. If an injury occurs, removal from play for assessment is indicated.

Few conclusive studies have been done on why children and adolescents are more prone to concussions if they have already had one. Theories include environmental factors and/or genetic predisposition. For patients who play high-contact sports and have had multiple concussions, we sometimes discuss considering other sports, such as golf or tennis, with less risk of recurrent head injury.

The incidence of concussions appears to be increasing in athletes younger than 13 years old, in whom data on the potential long-term effects of concussion are more limited.

We are particularly cautious in recommendations for athletes younger than 13 years, because the incidence of concussions appears to be increasing in this age group and we do not have as much data regarding potential long-term effects as we do in older age groups.

**Chronic Daily Headaches**

There is one exception to the guideline about return to play when symptoms persist: If a patient is seen six weeks after a concussion and the only persistent neurological symptom is chronic daily headaches that do not worsen with activity, return to play may be possible, especially for noncontact sports such as cross-country running.

Integration into the electronic medical record, providing valuable details for later use by a treating physician.

When a concussion has occurred, reassessments with the app are performed frequently to monitor recovery. Studies of functional return following concussion are facilitated by a method of data visualization we call the “Performance Polygon” (Figure 2).

**Initial Rollout and Next Steps**

In 2012, Cleveland Clinic certified athletic trainers used the C3 App to conduct baseline assessments in nearly 6,000 students who play contact sports from 56 high schools and three colleges in Northeast Ohio. A 2.0 version of the app — which is a bit faster and more user-friendly — has since been rolled out, and another 6,000 to 7,000 baseline evaluations are underway in 2013.

Demand for the C3 App’s capabilities has been fueled by passage of legislation in more than 40 states regarding return to play for student athletes, including Ohio’s Return to Play Law, which was enacted earlier this year.

In keeping with that demand, we aim to explore broader deployment of the C3 App for coordinated use by schools and hospitals across the country, through iComet Technologies, a spin-off company under Cleveland Clinic Innovations. Ideally,
When headaches persist beyond six weeks post-concussion, the child/adolescent should be treated separately for chronic daily headaches (see related article on page 38). At this point, in the absence of other signs and symptoms of concussion, the persistent headaches have taken on a life of their own and typically have nothing to do with the injury even if that’s how they started. Successful treatment of chronic daily headaches addresses underlying comorbidities. In addition, the pediatric neurologist should counsel the parents and patient on avoiding excessive school absence, returning to normal school function and avoiding overuse of over-the-counter medication.

Comprehensive Care

Comprehensive neurological care that includes focused education, prevention and treatment of comorbidities results in better patient outcomes — and more satisfied patients and parents.

Dr. Rothner is Chairman Emeritus of the Section of Child Neurology and Director of the Pediatric/Adolescent Headache Program. He can be reached at 216.444.5514 or rothned@ccf.org.

Comprehensive Care

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Dr. Alberts is Director of Cleveland Clinic’s Concussion Center and led the development of the C3 App. He can be reached at 216.445.3222 or albertj@ccf.org.

Dr. Blatnik is a pediatrician in Cleveland Clinic Children’s Department of Community Pediatrics who focuses on sports medicine and general pediatrics. She can be reached at 330.888.4000 or blatnit@ccf.org.

Figure 2. Studies of functional return following concussion are facilitated by a method of data visualization we call the “Performance Polygon.” It plots an athlete’s scores in nine performance domains on the first post-concussion C3 App assessment and periodically thereafter to allow easy visual monitoring of recovery to baseline levels (outer trace) over time.
Chronic Daily Headache at a Glance

Chronic daily headache (CDH) is diagnosed when headaches occur more than 15 days per month and last at least four hours per day. The frequency of CDH is 4 percent in adults, 2.4 percent in adolescent females and 0.8 percent in adolescent males.

At Cleveland Clinic, 30 percent of new consultations for adolescent headaches are due to CDH. CDH can consist of:

- Tension-type headache
- A combination of tension-type headache and migraine (also known as chronic migraine/transformed migraine)
- New-onset daily persistent headache, in which the patient has not had previous headache and within 24 to 72 hours develops a persistent daily headache

Consultations involve a thorough history, general physical and detailed neurological exam. Common comorbidities are noted in Table 1. Laboratory tests, MRI and EEG are usually normal. Patients with refractory headache also may be seen by other specialists (Table 2).

Excessive School Absences

Excessive school absences are noted in patients with refractory headache. A red flag is when more than 10 to 15 days of school are missed secondary to headache. Sometimes children who would miss a large number of school days due to headache in traditional settings are home-schooled or cyber-schooled instead; they should still be included in this category.

Excessive school absences, which occur in up to 20 percent of adolescents with CDH, are a marker of risk for psychological morbidity. Excessive absences from school or work are more common in adolescents than in pre-teens, in women than in men, and in CDH than in migraine. CDH is the most difficult headache to remediate.

Medication Overuse, Sleep Disruption

Medication overuse in adults with refractory headache often includes barbiturates and narcotics. In adolescents, overused medications include NSAIDs, acetaminophen, and over-the-counter (OTC) combinations containing aspirin and caffeine.

Using medications three days per week for longer than six weeks can cause medication overuse (rebound) headache. Complications of OTC medication overuse can include gastric irritation, GI bleeding, and hepatic and renal dysfunction.

Abnormal sleep hygiene perpetuates CDH. Problems include insomnia, multiple nocturnal awakenings, delayed sleep cycle and snoring with sleep apnea.
Treatment Protocol: Best Practices

Treatment of CDH takes weeks to months. Effective intervention requires a multidisciplinary approach (Table 2), and treatment is multifaceted:

**Education of patients and parents/guardians is critical, and handouts are helpful.** Patients and parents/guardians need to be reassured that a structural abnormality is not present once that possibility has been ruled out.

**The role that stress can play in headaches needs to be discussed.** Issues that may need to be addressed include family, friends and school, including extracurricular activities and bullying. The role of counseling should be discussed. The book *Conquering Your Child’s Chronic Pain* (see Suggested Reading) can serve as an excellent resource to guide parents/guardians in helping children with CDH.

**Lifestyle issues follow.** Eight hours of restorative sleep are needed. Adequate hydration, consisting of at least four to six 8-ounce glasses of water daily, is critical. Breakfast should not be skipped. An exercise program is initiated, as these patients typically are deconditioned.

**Return to school full time is a must.** In some patients, this is done gradually. A multidisciplinary approach involves patients, physicians, school personnel, parents/guardians, counselors and other therapists (Table 2). School should not be missed, as school absences perpetuate CDH.

**Medication overuse, which occurs in up to 20 percent of patients with CDH, should be addressed.** In adolescents, OTC medications are frequently used without parental knowledge. Medication overuse can cause transformation from episodic to chronic headaches. Risks of medication overuse are discussed with patients and parents/guardians. Medications may be tapered or stopped “cold turkey.” Bridging this period with rescue and preventive medications is helpful. OTC medications should be used two days per week or less to avoid medication overuse headache.

**Therapeutic medication includes rescue and/or prevention.** Rescue should be used two days per week or less. At the onset of a “bad” headache, rest and a cold compress are used. Ondansetron, diphenhydramine and 10 mg/kg of an NSAID are given. Two hours later, if symptoms persist, diphenhydramine and 15 mg/kg of acetaminophen are given. If this regimen fails

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**Table 3. Preventive Medicine and Therapies**

<table>
<thead>
<tr>
<th>Cyproheptadine</th>
<th>Alternative approaches</th>
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<tbody>
<tr>
<td>Amitriptyline</td>
<td>Magnesium</td>
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<tr>
<td>Topiramate</td>
<td>Riboflavin</td>
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<tr>
<td>Gabapentin</td>
<td>Coenzyme Q10</td>
</tr>
<tr>
<td>Other</td>
<td>Butterbur root</td>
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<tr>
<td>Valproate</td>
<td>Feverfew</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Biofeedback</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Acupuncture</td>
</tr>
<tr>
<td>Botox</td>
<td>Physical therapy</td>
</tr>
<tr>
<td>Nerve blocks</td>
<td>Yoga</td>
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<tr>
<td></td>
<td>Massage</td>
</tr>
<tr>
<td></td>
<td>Hypnosis</td>
</tr>
</tbody>
</table>

**Table 4. Dietary Categories to Be Eliminated**

<table>
<thead>
<tr>
<th>Foods suspected by parent or child to precipitate headaches</th>
<th>Aged cheese (tyramine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>Monosodium glutamate</td>
</tr>
<tr>
<td>Chocolate</td>
<td>(look for hidden sources such as ramen noodles and snack chips)</td>
</tr>
</tbody>
</table>
Preventive medications are helpful when patients are experiencing at least three days of headache per week or when rescue medications are not helpful. We try to match the medication with the patient’s individual needs.

Table 5. Pain Ratings and School/Work Absences Among Participants in Cleveland Clinic’s Pediatric Pain Rehabilitation Program

<table>
<thead>
<tr>
<th></th>
<th>School Days Missed Per Week</th>
<th>Parental Workdays Missed Per Week</th>
<th>Hospitalization Days Per Month</th>
<th>Pain Ratings (0-10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission</td>
<td>3.32</td>
<td>2.51</td>
<td>2.47</td>
<td>6.76</td>
</tr>
<tr>
<td>Two years post-discharge</td>
<td>0.22</td>
<td>0.16</td>
<td>0.13</td>
<td>3.79</td>
</tr>
<tr>
<td>Three years post-discharge</td>
<td>0.32</td>
<td>0.00</td>
<td>0.31</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Reprinted from Banez GA, Pediatric Neuroscience Pathways, 2012-2013 (see Suggested Reading).

on three occasions, we add a triptan at onset and two hours later. If this fails and/or there are three or more headaches per week, we consider preventive medication (Table 3).

Preventive medications are helpful when patients are experiencing at least three days of headache per week or when rescue medications as described above are not helpful. We try to match the medication with the patient’s individual needs. If patients have trouble falling asleep, for example, we use cyproheptadine or amitriptyline. If patients are normal weight or underweight, we prescribe a medication that may cause some weight gain, such as cyproheptadine or amitriptyline. If patients are obese, we use topiramate, which may help in weight reduction. If anxiety and/or depression are present, amitriptyline may be the most useful. We always begin with very low dosages and very slowly increase them to tolerance and benefit.

The role of diet is controversial, but the parents and children with whom we work have found dietary interventions to be quite valuable (Table 4).

Inpatient Therapy
At Cleveland Clinic, patients with refractory CDH who do not respond to outpatient treatment are referred to our multidisciplinary three-week inpatient Pediatric Pain Rehabilitation Program, which has been accredited by the Commission on Accreditation of Rehabilitation Facilities (CARF). This program
provides an effective model of care that focuses on independent functioning, improved coping, self-efficacy, and reduction of excessive school absences and medication overuse.

For patients who undergo treatment in Cleveland Clinic’s Pediatric Pain Rehabilitation Program, improvement in real-world indices of functioning have been shown at 24 to 36 months, including significant reductions in school days missed and parental workdays missed (Table 5).

Dr. Rothner is Chairman Emeritus of the Section of Child Neurology at Cleveland Clinic, where he has been a member of the faculty of the Departments of Pediatrics and Neurology since 1973. He is Director of the Pediatric/Adolescent Headache Program. He can be reached at 216.444.5514 or rothned@ccf.org.

SUGGESTED READING


TAKE-HOME POINTS

• Chronic daily headache (CDH) in adolescents is a significant medical/family problem.
• Over-the-counter medication overuse, which occurs frequently, can perpetuate the cycle of CDH and should be avoided.
• Excessive school absences are a marker for significant psychological issues. Return to school full time is essential.
• Cleveland Clinic’s treatment protocol takes a multidisciplinary approach that includes patients, physicians, parents/guardians, school personnel, counselors and other therapists.
Early Intensive Behavioral Intervention for Autism Spectrum Disorders
Results in Mainstream Educational Placements

By Thomas W. Frazier II, PhD

The Early Childhood Program within Cleveland Clinic Children’s Center for Autism provides intensive applied behavior analysis services to children 18 months to 6 years old. These services allow a majority of children who exit the program to transition to a less intensive educational placement.

The Early Childhood Program, which is also part of the Cleveland Clinic Lerner School for Autism for school-age children, provides early, intensive behavioral intervention year-round to young children who are diagnosed with autism spectrum disorders. Children receive 30 or more hours per week of intervention through partnership between the education team and the parents/guardians.

Utilizing the science of applied behavior analysis and child development principles, an individualized curriculum is designed to teach communication, social interaction, play, and a range of functional and adaptive skills.

Improving Mainstream Placements
Since the program opened in 2002, 101 students have graduated. The majority of children who have exited the Early Childhood Program over the past decade have moved on to mainstream placements with minimal or no educational supports needed (39 percent) or to less intensive special education placements (26 percent) that do not require intensive behavioral intervention (Figure 1). A minority of students (35 percent) continue to need intensive behavioral intervention.

As a comparison, previous studies of intensive behavioral intervention programs for preschoolers have found rates of minimal-support placements of approximately 30 percent.

Over the past five years, an increasing percentage of preschoolers have exited to settings where intensive behavioral intervention is no longer required for student success (Figure 2). These placements include mainstream classrooms without any additional support or with either pullout intervention (for example, individualized instruction in mathematics or reading) or an aide providing behavioral and academic support as necessary. Higher baseline language scores and increases in language scores after six months of intervention nearly perfectly predicted minimal-support placement at exit.

Figure 1. Early Childhood Program Placement Outcomes

Figure 2. Percentage of Students in Early Childhood Program Exiting to Less Intensive Placement

Figure 1. Cumulative Early Childhood Program placement outcomes, 2002 to 2012 (N = 101), show that a majority of graduates exited to less intensive educational placements that did not require intensive behavioral intervention.

Figure 2. A steady increase has been observed in the percentage of Early Childhood Program students who exit to educational placements where intensive behavioral intervention is no longer required for student success.
Early Intervention Reduces Costs

These findings indicate that young children with autism who attend the Early Childhood Program experience substantial improvements in their ability to function independently, resulting in decreased resource utilization and cost to the public education system.

Dr. Frazier is a staff psychologist in Cleveland Clinic’s Center for Pediatric Behavioral Health and Center for Autism. His research interests include studies to better understand autism symptoms and diagnosis, identification of autism traits in unaffected relatives and brain imaging studies of autism. He can be reached at 216.448.6440 or fraziet2@ccf.org.

TAKE-HOME POINTS

- Outcomes from the Cleveland Clinic Center for Autism’s Early Childhood Program indicate that young children with autism who attend the program experience substantial improvements in their ability to function independently in their future educational placements.
- Over the past five years, an increasing percentage of preschoolers have exited to classroom placements where intensive behavioral intervention is no longer required for student success.
- Better language at program entry and larger gains in language early in treatment nearly perfectly predicted more favorable placement at exit.

SUGGESTED READING


Cleveland Clinic to Host 2014 International Pediatric Epilepsy Surgery Symposium

Conference to focus on emerging surgical treatments and pathology-driven approaches

Pediatric epilepsy and neurology specialists from around the world will converge in Cleveland, Ohio, from Oct. 5 to 11, 2014, for the Cleveland Clinic-hosted International Pediatric Epilepsy Surgery Symposium.

The conference, the first of its size and caliber on this topic in more than a decade, will focus on cutting-edge and emerging treatments for difficult-to-treat pediatric epilepsy, with a focus on surgery and pathology-driven approaches.

Unique Opportunity

“There aren’t many opportunities like this for specialists who treat complex epilepsy in children,” says Ajay Gupta, MD, Head of Pediatric Epilepsy at Cleveland Clinic, who is serving as a co-chair of the symposium along with other Cleveland Clinic specialists. “National and international experts in pediatric epilepsy surgery will be highlighting innovative treatments and research, with a focus on cutting-edge technology and new developments.”

Focus on Engaged Learning

The CME-certified symposium will include lectures, interactive sessions, workshops, poster presentations and real-time, hands-on training in surgical techniques (simulation lab training, mock specimens).

The agenda will focus on:
• Pathology-driven approaches to pediatric epilepsy surgery
• How to improve pediatric epilepsy outcomes through surgical treatment
• Novel surgical techniques, strategies and testing paradigms

“We will be assembling a multispecialty faculty — including neurosurgeons, neurologists, epileptologists, imaging specialists and pathologists — who are experts in the fields of epilepsy treatment for a variety of conditions such as cortical dysplasia, malformations in the brain, genetic conditions such as tuberous sclerosis, and conditions due to infection or head trauma,” says Dr. Gupta.

He adds, “These interactive discussions will center on what we have done, what we have learned and what the future holds for children with difficult-to-treat epilepsy.”

Symposium at a Glance

**WHAT:** International Pediatric Epilepsy Surgery Symposium

**WHEN:** Oct. 5-11, 2014

**WHERE:** Cleveland, Ohio, United States

**HOST:** Cleveland Clinic’s Epilepsy Center, Neurological Institute

**CME:** Continuing medical education credit will be available

**REGISTRATION WILL OPEN:** Spring/summer 2014 — details to be announced

**FOR MORE INFORMATION:** Contact Marty Tobin at 216.445.3449 or tobinm@ccf.org

Call for Abstracts and Posters

If you are interested in submitting an abstract or poster for Cleveland Clinic’s 2014 International Pediatric Epilepsy Surgery Symposium, please contact Marty Tobin at 216.445.3449 or tobinm@ccf.org. The submission process will be opened in spring/summer 2014.
Pediatric Neurology

Kerry Levin, MD  
*Interim Director, Center for Pediatric Neurology*
Specialty interests: Clinical trials, EMG, general and neuromuscular neurology, immune-mediated neuropathies, metabolic myopathies, neuromuscular disorders, peripheral neuropathy  
216.444.5551

Neil Friedman, MBChB  
Specialty interests: Pediatric neuromuscular disease, pediatric stroke and cerebrovascular disease, neurocardiology, fetal and neonatal neurology  
216.444.6772

Gary Hsich, MD  
Specialty interests: General pediatric neurology, genetic metabolic disorders, leukodystrophies, lysosomal storage disorders, headache  
216.444.4899

Irwin Jacobs, MD  
Specialty interests: Neuromuscular disorders, general child neurology including epilepsy, headache, tics and ADHD  
216.476.7600

Sudeshna Mitra, MD  
Specialty interests: Pediatric neurology, neuromuscular disorders  
216.444.1844

Manikum Moodley, MBChB, FCP, FRCP  
Specialty interests: Pediatric multiple sclerosis and white matter disorders, pediatric neuromuscular diseases, neurofibromatosis, neonatal neurology, pediatric autonomic disorders  
216.444.3135

Sumit Parikh, MD  
Specialty interests: Child neurology, neurometabolism, neurogenetics, mitochondrial disease  
216.444.1994

A. David Rothner, MD  
Specialty interests: Pediatric headache, pediatric neurology, neurofibromatosis  
216.444.5514

Pediatric Neurosurgery

Mark Luciano, MD, PhD  
*Director, Pediatric Neurosurgery*
Specialty interests: Pediatric neurosurgery, neuroendoscopy, hydrocephalus, adult and pediatric brain and spinal cord tumors, Chiari malformation, craniofacial surgery, spasticity  
216.444.5747

Stephen Dombrowski, PhD  
Specialty interests: Pediatric neuro-oncology research, hydrocephalus research, neurohydrodynamics, cerebral blood flow and autoregulation  
216.444.9923
Kambiz Kamian, MD
Specialty interests: Pediatric neurosurgery, brain tumors, hydrocephalus, congenital spine and brain malformation, skull base tumors, pediatric spine surgery
216.529.7110

Erin Murphy, MD
Specialty interests: Radiation oncology, adult brain tumors, pediatric brain tumors, Gamma Knife radiosurgery®, sarcoma, late effects, neurocognitive outcomes, quality of life
216.445.4895

Violette Recinos, MD
Specialty interests: Pediatric neurosurgery, adult and pediatric brain and spinal cord tumors, Chiari malformation, craniofacial surgery, pediatric hydrocephalus and neuroendoscopy, pediatric spina bifida and tethered cord
216.444.4549

Tanya Tekautz, MD
Specialty interests: Brain tumors in infants, children and young adults; the treatment of progressive/recurrent glioma; atypical teratoid/rhabdoid tumors; school and/or work re-entry and cognitive retraining for children and young adults with brain tumors
216.444.9532

Pediatric Neurosurgery
Epilepsy Surgery
William Bingaman, MD
Vice Chairman, Clinical Areas, Neurological Institute
Specialty interests: Epilepsy surgery, complex spinal disorders
216.444.9058

Jorge Gonzalez-Martinez, MD, PhD
Specialty interests: Epilepsy surgery, general neurosurgery, stereoelectroencephalography (SEEG)
216.445.4425

Pediatric Epilepsy
Ajay Gupta, MD
Section Head, Pediatric Epilepsy
Specialty interests: Epilepsy and epilepsy surgery in children and adolescents, tuberous sclerosis, brain malformations causing epilepsy, intraoperative brain mapping, neurophysiology
216.445.7728

William Bingaman, MD
Vice Chairman, Clinical Areas, Neurological Institute
Specialty interests: Epilepsy surgery, complex spinal disorders
216.444.9058
Tatiana Falcone, MD  
Specialty interests: First-episode psychosis, epilepsy, the role of inflammation in schizophrenia, research and education, child psychiatry, consultation-liaison psychiatry  
216.444.7459

Deepak Lachhwani, MBBS, MD  
Specialty interests: Pediatric epilepsy; EEG; outcomes following epilepsy surgery; surgical treatment of refractory epilepsy due to cortical malfunctions, Rasmussen syndrome, tuberous sclerosis and other causes  
216.445.9818

Jorge Gonzalez-Martinez, MD, PhD  
Specialty interests: Epilepsy surgery, general neurosurgery, stereoelectroencephalography (SEEG)  
216.445.4425

Ahsan Moosa Naduvil Valappil, MD  
Specialty interests: Medical and surgical treatment of epilepsy, hemispheric epilepsy syndrome and hemispherectomy/hemispherotomy, ketogenic diet therapy, genetic and metabolic causes of epilepsy, Rasmussen encephalitis, autoimmune epilepsy, video EEG monitoring, invasive EEG monitoring  
216.445.6746

Jennifer W. Haut, PhD, ABPP-CN  
Specialty interests: Pediatric neuropsychology  
216.444.2454

Elia Pestana Knight, MD  
Specialty interests: Epileptic encephalopathy, pediatric epilepsy syndromes and comorbidities, quality of life in children with epilepsy, pediatric epilepsy surgery, neonatal EEG  
216.445.6739

Patricia Klaas, PhD  
Specialty interests: Pediatric neuropsychology, neurodevelopmental disorders, epilepsy, epilepsy surgery, head injury  
216.444.2450

Elaine Wyllie, MD  
Specialty interests: Pediatric epilepsy, EEG, epilepsy surgery, brain malformations and early brain injuries causing epilepsy  
216.444.2095

Prakash Kotagal, MD  
Specialty interests: Pediatric epilepsy and epilepsy surgery, pediatric sleep disorders  
216.444.9083
Pediatric Psychiatry

Manish Aggarwal, MD
Specialty interests: Inpatient psychiatry, acute stabilization of mood disorders, psychotic disorders
216.476.6958

Joseph M. Austerman, DO
Specialty interests: Pediatric and adult ADHD, children and adolescents with comorbid physical and mental illness, eating disorders, pediatric anxiety disorders, acute care psychiatry
216.445.7656

Tatiana Falcone, MD
Specialty interests: First-episode psychosis, epilepsy, the role of inflammation in schizophrenia, research and education, child psychiatry, consultation-liaison psychiatry
216.444.7459

Kathleen Quinn, MD
Specialty interests: ADHD, anxiety disorders and autistic spectrum disorders, residency and medical school education
216.444.5950

Barry Simon, DO
Specialty interests: Crisis management and inpatient psychiatry
216.445.1954

Mackenzie Varkula, DO
Specialty interests: Inpatient child and adolescent psychiatry
216.476.6958

Molly Wimbiscus, MD
Specialty interests: Child and adolescent psychiatry, community psychiatry, medical humanities
216.444.8674

Pediatric Neuropsychology

Jennifer W. Haut, PhD, ABPP-CN
Specialty interests: Pediatric neuropsychology
216.444.2454

Patricia Klaas, PhD
Specialty interests: Pediatric neuropsychology, neurodevelopmental disorders, epilepsy, epilepsy surgery, head injury
216.444.2450
Pediatric Behavioral Health

**Michael Manos, PhD**  
*Head, Center for Pediatric Behavioral Health*

Specialty interests: ADHD in children and adults, parent guidance and training, summer treatment program, social skills training, medication monitoring clinic  
216.445.7574

**Gerard A. Banez, PhD**  
*Program Director, Pediatric Pain Rehabilitation*

Specialty interests: Chronic pain/functional disability, pediatric functional gastrointestinal disorders, elimination disorders  
216.448.6253

**Ethan Benore, PhD, BCB, ABPP**

Specialty interests: Headache, chronic pain, biofeedback, sleep disorders  
216.448.6253

**Cara Cuddy, PhD**

Specialty interests: Elimination disorders (toileting), headaches, feeding disorders  
216.448.6024

**Wendy Cunningham, PsyD**

Specialty interests: Adjustment disorders, anorexia, anxiety disorders, depression, emotional and behavioral problems in children and adolescents, parenting support, pediatric stress  
440.878.2500

**Kristen Eastman, PsyD**

Specialty interests: General child psychology (anxiety, depression, OCD, ADHD and evaluation of developmental concerns), social anxiety, selective mutism  
440.835.1445

**Kate Eshleman, PsyD**

Specialty interests: Tic disorders (Tourette syndrome, HRT treatment); developmental, behavioral and emotional concerns associated with chronic physical health problems  
216.444.9323

**Thomas Frazier II, PhD**

Specialty interests: ADHD in children and adults, autism spectrum disorder in children 4 years and older, parent guidance and training, bipolar disorder  
216.448.6440

**Catherine Gaw, PsyD**

Specialty interests: Anxiety/OCD/panic, depression, autism spectrum disorders, loss and bereavement, divorce, family therapy  
440.516.8690

**Vanessa K. Jensen, PsyD**

Specialty interests: Diagnostic evaluation, psychological testing/assessment and consultation, infant to age 18; focused primarily on autism and related disorders (Asperger syndrome, PDD)  
440.516.8690
**Eileen Kennedy, PhD**
Specialty interests: Depression, anxiety disorders, emotional and behavioral difficulties in young children, adjustment disorders, Fit Youth program (group obesity treatment)
216.986.4000

**Kathleen Laing, PhD**
Specialty interests: Trichotillomania, anxiety disorders, depression, emotional and behavioral difficulties in young children, adjustment disorders, headache, abdominal pain, chronic illness
440.519.3003

**Katherine Lamparyk, PsyD**
Specialty interests: Pediatric behavioral health
216.448.6253

**Amy Lee, PhD**
Specialty interests: New evaluations, ADHD, behavioral problems in young children, behavior disorders, depression, autism spectrum disorders, somatization disorders
440.835.1445

**Beth Anne Martin, PhD**
Specialty interests: Pervasive developmental disorders (evaluation and treatment), anxiety disorders (OCD), behavior disorders, ADHD, toileting control
440.519.3003

**Ted Raddell, PhD**
Specialty interests: Trauma recovery, depression/anxiety conditions, grief recovery, stress management, marital therapy, health psychology/behavioral medicine, codependency
216.839.3900

**Pamela Senders, PhD**
Specialty interests: Pediatric inpatient rehabilitation, traumatic brain injury, psychoeducational evaluation of learning and school problems, school re-entry, chronic pain, fibromyalgia, dialysis
216.448.6282

**Sandra Sommers, PhD**
Consulting Staff
Specialty interests: General pediatric and adult psychology, psychoeducational evaluation of learning and school problems, anxiety disorder spectrum (anxiety, OCD, panic attacks)
216.986.4000

**Leslie Speer, PhD**
Specialty interests: Evaluations of autism spectrum disorders (autistic disorder, Asperger disorder and pervasive developmental disorder, not otherwise specified), treatment of autism spectrum disorders, consultations regarding educational placements and services (e.g., special education, IEP, 504 accommodations), behavior management
216.448.6440
Developmental and Rehabilitative Pediatrics

Douglas Henry, MD  
Director, Center for Developmental and Rehabilitative Pediatrics  
Specialty interests: Spasticity management, chronic pain disorders  
216.448.6179

Roberta Bauer, MD  
Specialty interests: Developmental pediatrics, autism, aversive feeding disorders  
216.448.6196

Jeffrey Bolek, PhD  
Specialty interests: Biofeedback, motor control in rehabilitation  
216.448.6362

Carol Delahunty, MD  
Specialty interests: Developmental pediatrics, autism, fragile X syndrome, pharmacologic management of behavior problems  
440.878.2500

Benjamin Katholi, MD  
Specialty interests: Spinal cord injuries, cerebral palsy, wheelchair evaluations, spasticity management, nerve blocks, spina bifida, amputee care, neuromuscular disorders, acupuncture  
216.448.6179

Virmarie Quinones-Pagan, MD  
Specialty interests: Traumatic brain injury, spinal cord injury, rheumatologic and musculoskeletal disorders, torticollis, plagiocephaly, spina bifida, gait abnormalities, limb deficiencies, spasticity management, spine disorders, neuromuscular diseases  
216.448.6179

Pediatric Sleep Disorders

Jyoti Krishna, MD  
Section Head, Pediatric Sleep Disorders  
Specialty interests: Pediatric sleep disorders including snoring, sleep apnea, excessive daytime sleepiness, parasomnias, behavioral insomnia and circadian rhythm disorders  
216.445.8308

Sally Ibrahim, MD  
Specialty interests: Pediatric and adult sleep apnea, restless legs syndrome, circadian disorders, parasomnias, insomnia, narcolepsy, disorders of excessive sleepiness  
216.444.7719
Pediatric Radiologists and Neuroradiologists

**Paul Ruggieri, MD**  
*Director, Center for Neuroimaging*  
Specialty interests: Pediatric neuroradiology and advanced epilepsy neuroimaging  
216.445.7035

**Ramin Hamidi, DO**  
Specialty interests: Pediatric neuroradiology  
216.448.0212

**Stephen Jones, MD, PhD**  
Specialty interests: Pediatric neuroradiology, advanced epilepsy neuroimaging  
216.444.4454

**Doksu Moon, MD**  
Specialty interests: Pediatric neuroradiology, advanced epilepsy neuroimaging  
216.444.0988

**Stuart Morrison, MD**  
Specialty interests: Pediatric radiology, pediatric brain and spinal MRI and ultrasound  
216.445.2983

**Ellen Park, MD**  
Specialty interests: Pediatric radiology, pediatric brain and spinal MRI and ultrasound  
216.445.4236

**Unni Udayasankar, MD**  
Specialty interests: Pediatric radiology, pediatric neuroradiology  
216.445.0441

**Neil Vachhani, MD**  
Specialty interests: Pediatric radiology, pediatric brain and spinal MRI and ultrasound  
216.444.4778
Pediatric Neuroscience Pathways

Elaine Wyllie, MD, Medical Co-Editor
Mark Luciano, MD, PhD, Medical Co-Editor
Glenn Campbell, Managing Editor
Tara Stultz, Copyeditor
Anne Drago, Art Director
A.M. Design Group, Inc., Graphic Design

For address changes or more information about Cleveland Clinic Children’s or the Neurological Institute, please contact:
Cleveland Clinic
9500 Euclid Ave./AC311
Cleveland, OH 44195
216.448.0336
CCNI@ccf.org

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Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, more than 3,000 physicians and researchers represent 120 medical specialties and subspecialties. We are a nonprofit academic medical center with a main campus, eight community hospitals, more than 75 northern Ohio outpatient locations (including 16 full-service family health centers), Cleveland Clinic Florida, Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Cleveland Clinic Canada, Sheikh Khalifa Medical City and Cleveland Clinic Abu Dhabi.

In 2013, 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 in heart care for the 19th consecutive year.