



Cleveland Clinic Children's

Pediatric Neuroscience

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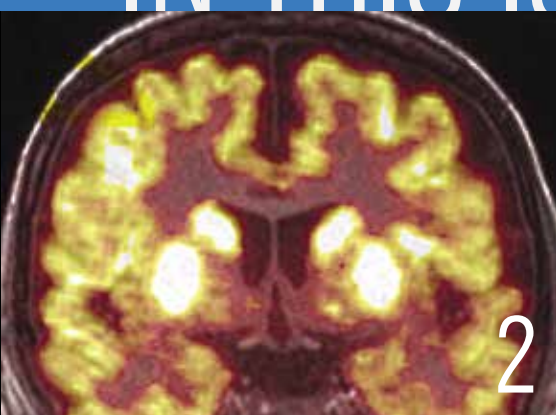
The Squeeze of Chiari Malformation:

Clinicians and Scientists
Collaborate to Understand
Its Cause and Effects

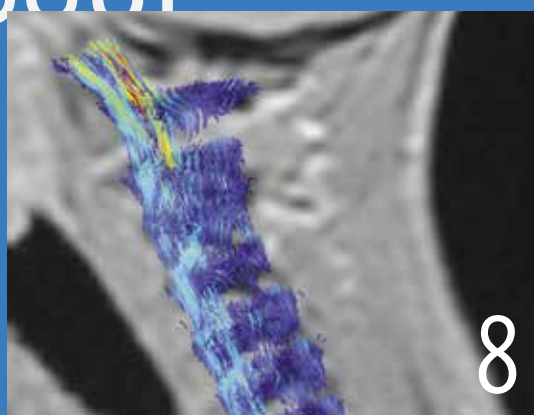
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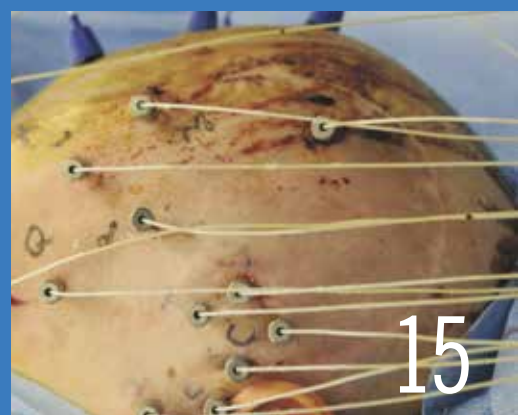
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RESOURCES FOR PHYSICIANS

WELCOME FROM THE EDITORS

The hallmarks of Cleveland Clinic's pediatric neurosciences program are leading-edge treatments and research and a collaborative, multidisciplinary approach to caring for our young patients.

The striking image on *Pediatric Neuroscience Pathways*' cover is a testament to those principles of advanced, integrative medicine.

For years, researchers have worked to better understand the factors that cause Chiari malformation — the descent and compression of the cerebellum at the foramen magnum that produces pain and neurological deficit. Abnormal motion of cerebrospinal fluid (CSF), blood and brain tissue in the constricted cervical-medullary junction is thought to be a significant contributor to the defect.

As you will read on page 8, a multispecialty team of clinicians, radiological physicists, pain specialists, neuroscientists, engineers and psychologists from Cleveland Clinic and the University of Akron is employing novel techniques to visualize what happens in Chiari malformation. One of those methods is computational fluid dynamics, which uses software to model the complex whorls and eddies of CSF in Chiari patients in exquisite and revealing detail, as the cover image shows.

You will find additional evidence throughout this issue of our staff's innovative, wide-ranging research activities and clinical care, which have again brought us the honor of being ranked among the nation's best in pediatric neurology and neurosurgery by *U.S. News & World Report* for 2014-2015. Topics include:

- **Pediatric neuroradiology:** Combined PET-MRI imaging provides novel pediatric diagnostic insights and additional benefits.
- **Pediatric psychiatry and behavioral health:** Authors offer diagnostic and treatment guidance for pediatric aggression, delirium, dyslexia, childhood anxiety disorders, and attention deficit hyperactivity disorder in epileptic patients.
- **Pediatric neurology:** Multidisciplinary management is essential for children with the epileptic encephalopathy and neurodevelopmental disorder known as *CDKL5*-related disease. In addition, we discuss the challenge of diagnosing multiple sclerosis in very young patients.



- **Pediatric epilepsy surgery:** Patients with seizure recurrence after functional/disconnective hemispherectomy need careful evaluation to determine if further surgery is warranted. Also, Cleveland Clinic researchers report on their experience using stereoelectroencephalography to aid decision-making regarding surgical resection in medically refractory pediatric epilepsy patients.
- **Pediatric rehabilitation:** Cleveland Clinic's multidisciplinary Pediatric Pain Rehabilitation Program demonstrates clinically significant improvements in functional quality of life for chronic migraine patients and their families.

Also, we are pleased to announce the appointment of Neil Friedman, MBChB, as the new Director of the Center for Pediatric Neurology in Cleveland Clinic's Neurological Institute. Dr. Friedman has been a staff member in pediatric neurology since 1998. In his new role, he is responsible for the clinical, educational and research activities of the center and its integration with local and regional activity as part of the Neurological Institute, the Pediatric Institute and Cleveland Clinic Children's.

We hope you enjoy this issue of *Pediatric Neuroscience Pathways* and that its articles and "take-home points" summaries provide helpful, actionable information that you can apply in your practice. We welcome your comments. Please contact us if you have questions or if we can assist you in any way.

Elaine Wyllie, MD

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Combining PET and MRI Imaging for a Novel Pediatric Diagnostic Aid

By Stephen Jones, MD, PhD

During the past decade there has been an imaging revolution in the detection of tumors using combined PET-CT scanners. This union synergistically combines the exquisite sensitivity of fluorodeoxyglucose (FDG) PET for hypermetabolic neoplastic tissue with the high spatial anatomic resolution of CT.

This imaging revolution continues with the recent introduction of combined PET-MRI scanners. Since the spatial resolution of PET is relatively poor compared with MRI, a major advantage of the combination is the ability to use MRI's superior spatial resolution to accurately identify corresponding values of PET metabolism changes in selected brain subregions. This is particularly useful in pediatric oncology.

Cleveland Clinic recently acquired a leading-edge PET-MRI unit, which resides in the MRI imaging complex on our main campus.

Simultaneous Scanning Capability

The system utilizes a 3-tesla MRI with a specially developed ring-shaped PET detector inserted in the MRI cowl. The unit is capable of simultaneous scanning, unlike PET-CT, which requires that the imaging acquisitions be obtained sequentially. The time required to obtain a full PET scan easily accommodates a full clinical MRI examination.

Currently our focus is the FDG radiotracer, which is sensitive to tissue metabolic activity; however, in the near future advanced radiotracers will become available.

The image in Figure 1 shows the first pediatric FDG PET-MRI brain examination conducted at Cleveland Clinic, involving a 6-year-old female patient with intractable epilepsy.

This coronal imaging shows a colorized PET image overlaying a colocalized grayscale anatomic T1-weighted MRI image. The combined image comes directly from the scanner; that is, the images do not need to be co-registered by hand afterward, as is the current practice, which introduces non-insignificant errors. The PET-MRI image shows significant hypometabolism involving the left anteromedial temporal lobe and reflects the patient's underlying epileptic disease.

Pediatric Benefits of Combined Scanning

A major benefit of combined PET-MRI scanning for children is the reduced use of sedation. Previously, children who needed both PET and MRI required two separate sedation procedures, each associated with the medical risks of anesthesia and a negative emotional experience. With PET-MRI, both scans can be obtained during a single sedation session. This not only benefits the child and family but is more cost-effective.

The medical benefits of combined PET-MRI scanning for children with neurological disease are multifaceted. As indicated by Figure 1, one advantageous application is for children with focal epilepsy. Children with intracranial or extracranial tumors will also benefit, as will those with inborn errors of metabolism.

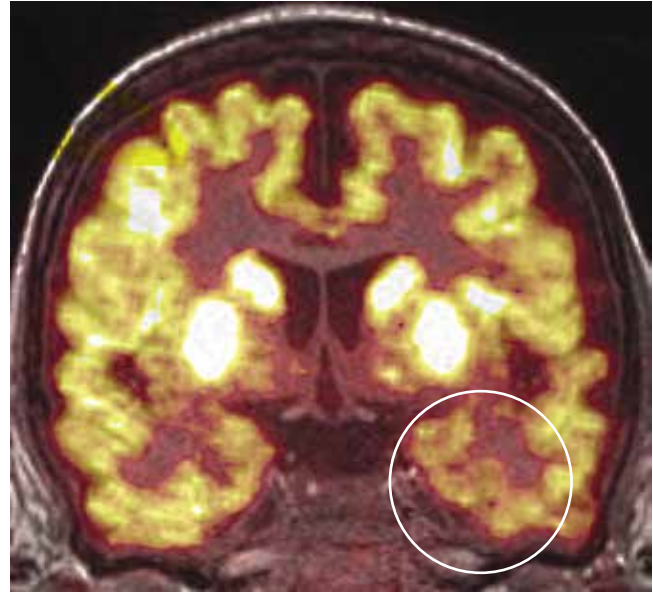


Figure 1. A colorized PET image overlaying a colocalized grayscale anatomic T1-weighted MRI coronal image of a 6-year-old female patient with intractable epilepsy. The white circle is the region of significant hypometabolism involving the left anteromedial temporal lobe and is best appreciated when compared with the same structure on the opposite side.

Dr. Jones is a neuroradiologist and a staff member of Cleveland Clinic's Department of Radiology, the Mellen Center for Multiple Sclerosis and the Epilepsy Center. His specialty interests are advanced and functional neuroimaging. He can be reached at jones19@ccf.org or 216.444.4454.

Cleveland Clinic welcomes the opportunity to partner with you in caring for your patients. For additional information on PET-MRI studies, contact Esbam Vogelius, MD (vogelie@ccf.org or 216.445.5487), for pediatric inquiries and Shetal Shah, MD (shahs2@ccf.org or 216.445.8168), for all other inquiries.

Take-Home Points

- The recent introduction of combined PET-MRI scanning blends MRI's superior spatial resolution with PET's ability to detect changes in the brain's metabolism in selected subregions. This is particularly useful in pediatric oncology and neurological disease.
- The combined system obtains PET and MRI imaging simultaneously, enabling a single sedation session, which is advantageous for pediatric patients.

Multidisciplinary Management of Children with *CDKL5*-related Disease

By Sumit Parikh, MD, and Elia Pestana Knight, MD

Mutations in the cyclin-dependent kinase-like 5 (*CDKL5*) gene lead to a characteristic infant-onset epileptic encephalopathy and neurodevelopmental disorder known as *CDKL5*-related disease.

The initial presentation of the disease in infants (Table 1) includes:

- Early-onset seizures beginning in the first three months of life.
- Seizures that often but not always become refractory to many anti-epileptic drugs.
- Multiple seizure types that can change as the patient gets older.
- Delayed neurocognitive development without a history of regression.
- Other manifestations such as poor social interaction, stereotypic hand movement, severe hypotonia, visual disturbances, feeding difficulties, dysphagia and autonomic changes.
- No specific facial dysmorphic features.

Table 1. Symptoms present in children with *CDKL5*-related disease.

- Early-onset epileptic encephalopathy with a mixture of seizures including infantile spasms, myoclonic seizures and prolonged generalized tonic-clonic seizures.
- Severe early developmental delay
- Absent facial dysmorphic features
- Normal head circumference
- Absent speech/language
- Poor eye contact
- Reduced social interactions
- Visual disturbances
- Severe hypotonia
- Absent or impaired walking
- Hand stereotypies
- Bruxism
- Autonomic dysfunction
- Feeding difficulties and dysphagia
- Poor sleep pattern

Types of Seizures and EEG Patterns

Seizures in patients with *CDKL5*-related disease present as early as the neonatal period. Seizure types may change across the life span of these patients. The initial presentation in almost half of patients includes early-onset infantile spasms with or without other associated seizures. Other associated seizure types include focal motor, tonic, myoclonic, apneic and complex motor with oral automatisms.

As these children become older, a variety of mixed seizures can be seen, including myoclonic, tonic, absence and complex partial seizures. Generalized tonic-clonic seizures are frequent and common. Epileptic spasms persist in some patients. Often seizures are long, lasting more than five minutes. Seizures are often highly refractory to anti-epileptic treatment, but honeymoon periods after the introduction of a new anti-epileptic drug have been described.

No specific EEG pattern has been associated with *CDKL5*-related disease. EEG abnormalities seem to change with age and seizure types. The initial EEG can be interpreted as normal, but a hypsarrhythmia pattern (Figure 1) often becomes a prominent finding once infantile spasms begin (Figure 2). Focal, multifocal, diffuse or generalized sharp waves can also be seen on initial EEGs. Ictal findings are dependent on the seizure type. Abnormalities of the background rhythm are a common finding in these patients and are present in all patients as they become older.

Screening and Etiology

CDKL5-related disease is a dominant X-linked condition that should be considered for any child with an early-onset epileptic encephalopathy, especially when infantile spasms begin prior to 3 months of age. The condition presents in both males and females. The yield of *CDKL5* testing in children with an early-onset epileptic encephalopathy is around 5 percent for males and 14 percent for females. A *CDKL5* gene mutation can be found in as many as 31 percent of females with Rett syndrome-like features and negative *MECP2* test results.

CDKL5-related disease occurs due to mutations in the cyclin-dependent kinase-like 5 gene on the X chromosome. Patients with the condition were only first identified in the early 2000s, and clinical testing became available as of late 2000. Scientific knowledge regarding the disease's pathophysiology is still rudimentary, although we know that the gene is primarily expressed in the brain and expression overlaps that of *MECP2* (the gene involved in Rett syndrome) during neuronal maturation. *CDKL5* and *MECP2* may belong to the same neurodevelopmental pathway.

CDKL5-related disease is a dominant X-linked condition that should be considered for any child with an early-onset epileptic encephalopathy, especially when infantile spasms begin prior to 3 months of age.



Figure 1. Sample of video EEG recording showing hypsarrhythmia. Patient is a 4-year-old male with seizures since age 2½ months, severe neurodevelopmental delay, visual impairment, swallowing dysfunction, gastroesophageal reflux and a gastric tube placed for feeding. Since seizure onset, he has had daily clusters of infantile spasms and tonic seizures that have persisted despite treatment with phenobarbital, rufinamide, topiramate, levetiracetam, valproic acid and the ketogenic diet. He has a confirmed pathogenic mutation in the *CDKL5* gene.



Figure 2. Sample of video EEG recording showing ictal pattern during epileptic spasms in the same patient.

The Importance of a Multidisciplinary Team

The understanding of the clinical phenotype of *CDKL5*-related disease is improving but remains general and incomplete, with notable phenotypic variability. Symptoms include varying degrees of refractory epilepsy and developmental disability. There is notable variability in the severity of the epilepsy and developmental disability from patient to patient. At least one patient without epilepsy has been identified. The natural history of the condition is not yet known. The condition is considered rare but is likely underidentified, and its true incidence is not yet known.

The International Foundation for *CDKL5* Research (IFCR) is establishing centers of excellence across the country, with each housing a multidisciplinary clinic to improve clinician familiarity with this condition and to provide a standard of care for patients and families. Such centers can better ascertain how the condition unfolds, allowing their researchers to study the natural progression of the disease.

Cleveland Clinic Children's began the third such clinic in the United States in 2014. Patients are evaluated by multiple providers, including dedicated specialists in epilepsy, neurogenetics, genetic counseling, gastroenterology, rehabilitation medicine, orthopaedics, pulmonology, cardiology, ophthalmology, gynecology and physiotherapy. A social worker also is available.

Dr. Parikh is a pediatric neurologist and staff member of Cleveland Clinic's Center for Pediatric Neurology, where he directs the Multidisciplinary CDKL5 Syndrome Clinic and the Neurogenetics, Metabolic and Mitochondrial Disease Program. His specialty interests are the evaluation, diagnosis and treatment of developmental delay, autism, neurodegeneration and metabolic disease. He can be reached at parikhs@ccf.org or 216.444.1944.

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Take-Home Points

- ... Children of either sex with early-onset epileptic encephalopathy, medically refractory seizures and nonregressive neurocognitive delay should be screened for *CDKL5*-related encephalopathy.
- ... Children with *CDKL5*-related encephalopathy have other symptoms including stereotypic hand movement, severe hypotonia, visual disturbances, feeding difficulties, dysphagia and autonomic changes.
- ... Given the variety of symptoms involved, a multidisciplinary team for the care of children with *CDKL5*-related encephalopathy should be considered.

Multiple Sclerosis in the Very Young

By Manikum Moodley, MBChB, FCP, FRCP

Multiple sclerosis (MS) is primarily an autoimmune demyelinating disease of young adulthood with a clinical onset typically occurring between 20 and 40 years of age.

However, it is now being recognized with increasing frequency in children and adolescents. The first descriptions of MS in children were recorded in the early 19th century, but recently improved awareness of this disease and subspecialty training in pediatric MS have allowed early and accurate evaluation and easy access to appropriate comprehensive care.

The youngest age of onset of MS in the medical literature is 2 years but the majority of children are diagnosed in their early teens.¹ In 3 to 5 percent of cases MS onset is before age 16; an onset before 10 years of age is extremely uncommon, with a reported incidence of 0.2 to 0.7 percent.²

Potential for Misdiagnosis

With its protean clinical manifestations and lack of biological markers, MS is easy to misdiagnose in adult patients. In children, correct diagnosis is an even greater problem because MS is uncommon and the various genetic and neurometabolic disorders produce active neurological impairment and white matter changes on MRI that mimic MS.

The burden of MS in the young is substantial. Younger children with MS present with multifocal and sometimes encephalopathic symptoms, making it difficult to distinguish MS from acute disseminated encephalomyelitis (ADEM).³ Children also tend to present with larger and tumefactive lesions, adding to the disease burden. Early-onset MS has an unfavorable outcome with frequent relapses at shorter disease-free intervals.⁴

There are extremely few case reports on the incidence of MS in very young children. Ruggieri et al.^{2,3} in Italy and Duquette et al.⁴ in Canada have published the few case series that have widened our horizon for

further exploration of MS in the very young. Their publications outline the course and unique clinical and radiological features of MS in early childhood and its implications at later ages.

A Case Report

Cleveland Clinic's youngest pediatric patient with MS recently presented to the Pediatric MS and White Matter Disorders Clinic at the age of 2 years 8 months for a second opinion on relapsing-remitting white matter disease, first detected at 2 years 1 month of age.

She had initially presented to another hospital for investigation of an acute onset of ataxia. Her brain MRI revealed extensive demyelinating white matter lesions involving bilateral corona radiata, white matter adjacent to the atria and right frontal horn, bilateral temporal lobes and the subcortical white matter (Figure 1).

Ophthalmologic and cerebrospinal fluid (CSF) studies were normal. She was diagnosed with ADEM and treated with high-dose intravenous methylprednisolone (30mg/kg/day) for three days, followed by an oral steroid taper over six weeks.

She was readmitted with similar symptoms at two and four months after her initial presentation. Her repeat brain MRI revealed new areas of demyelination during each new admission (Figure 2). Her ophthalmologic examination, CSF studies and MRI spine were normal. At both of these presentations she was treated with high-dose intravenous methylprednisolone for three to five days followed by a long oral steroid taper. Her physical examinations at these presentations were normal.

Seven months after the initial presentation, she was seen at the Pediatric MS and White Matter Disorders Clinic for a second opinion on diagnosis and management. Her workup included a repeat MRI brain and spine scan with and without contrast that revealed new foci of acute demyelination (Figure 3); CSF analysis revealed elevated myelin basic protein but negative oligoclonal bands, immunoglobulin index and neuromyelitis optica antibody. Extensive metabolic and thyroid studies were nonrevealing. Her clinical presentation with multiple relapses at two, four and seven months with new radiologic demyelinating lesions validated the diagnosis of MS, but her parents refused disease-modifying therapy.

Early, Accurate Diagnosis Is Essential

Diagnosing MS in the very young is medically and ethically challenging. The patient in the case in point was clinically asymptomatic after her second and third relapses but still demonstrated active demyelinating lesions on subsequent neuroimaging studies of the brain. MS in young children is significantly underdiagnosed, and this has important repercussions for treatment and long-term prognosis.

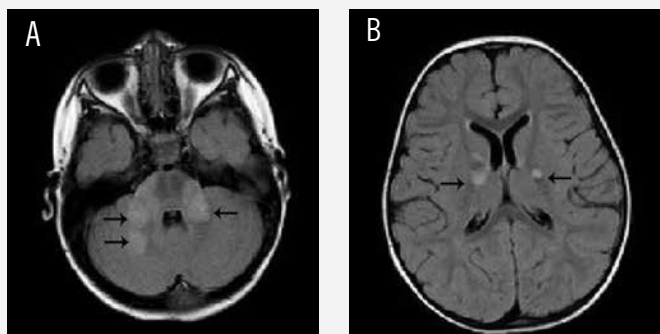


Figure 1. MRI brain (January 2011). T2 FLAIR axial images with black arrows demonstrating (A) Bilateral white matter lesions in the cerebellum, and (B) bilateral white matter lesions in the periventricular regions.

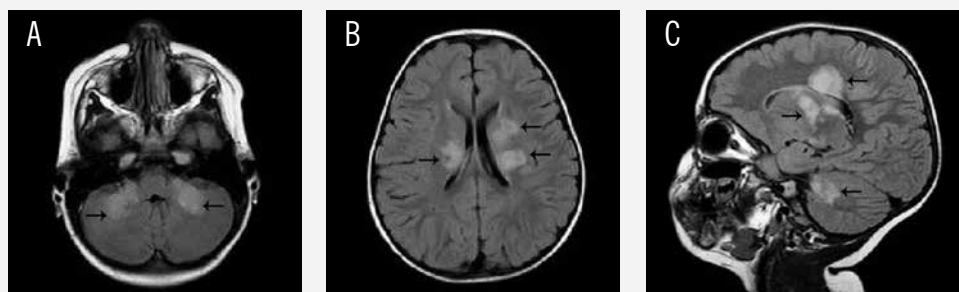


Figure 2. MRI brain (March 2011). T2 FLAIR axial images with black arrows demonstrating (A) Resolving bilateral cerebellar white matter lesions, (B) new white matter lesions in the periventricular regions, and (C) new pericallosal and cerebellar white matter lesions.

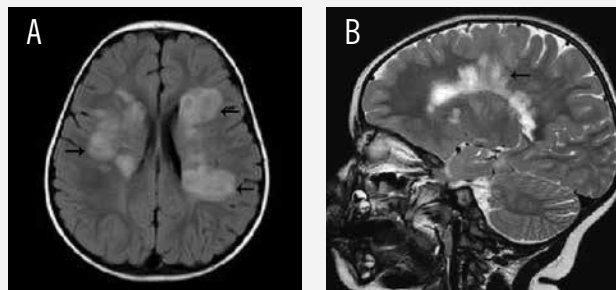


Figure 3. MRI brain (June 2011) T2 FLAIR axial images with black arrows demonstrating (A) extensive burden of demyelinating white matter lesions in the periventricular region, and (B) demyelinating plaques arranged perpendicular to the corpus callosum showing the typical Dawson fingers.

The majority of children initially present with a relapsing-remitting disease course and pose several challenges to the physician. In particular, the initial presenting clinical and radiological features may be difficult to distinguish from those of other congenital and acquired white matter diseases that have a higher prevalence in children than in adults, notably ADEM and metabolic and mitochondrial disorders.

This can lead to difficulties in establishing an early and accurate diagnosis and providing appropriate management.⁵ As there is now robust evidence that children with MS tolerate and may benefit from disease-modifying therapies, it is important to diagnose pediatric MS early and accurately so that the risk of developing major motor disability and cognitive impairment early in life can be significantly reduced.

Dr. Moodley is a neurologist in Cleveland Clinic's Center for Pediatric Neurology. His specialty interests include pediatric multiple sclerosis, ADEM and other white matter disorders; pediatric neuromuscular diseases; neurofibromatosis; neonatal neurology; and pediatric autonomic disorders. He can be reached at moodlem@ccf.org or 216.444.3135.

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Take-Home Points

- Childhood multiple sclerosis (< 16 years of age) is being diagnosed in increasing numbers, with a reported incidence of 3 to 5 percent of all MS cases. Onset before 10 years of age, however, is rare, with an incidence of 0.2 to 0.7 percent of all MS cases.
- The clinical presentation of MS is similar to that for a broad spectrum of congenital and other acquired disorders in childhood. Many pediatricians and neurologists are unaware that MS may occur in the very young, even in infancy, and therefore rarely consider this diagnosis in this population.
- Pediatric MS patients can become significantly disabled very early in life. With the advent of disease-modifying agents, making an early and accurate diagnosis of MS and instituting optimal therapeutic management in young children is critical because of the many implications for their immediate care and long-term prognosis.
- Cleveland Clinic's Pediatric MS and White Matter Disorders Program within the Center for Pediatric Neurology has the knowledge and expertise to distinguish MS from congenital and acquired white matter disorders unique to children, enabling advanced care.

The Squeeze of Chiari Malformation:

CLINICIANS AND SCIENTISTS
COLLABORATE TO UNDERSTAND
ITS CAUSE AND EFFECTS

50 mm

50 mm

Figure 1. Type 1 Chiari malformation and associated spinal cord syrinx in a 7-year-old patient, imaged using T2-weighted sagittal MRI.

COVER STORY

Mark Luciano, MD, PhD; Bryn Martin, PhD; Phil Allen, PhD; and Francis Loth, PhD

In children and adults, Chiari malformation is recognized as a disorder of the cervical-medullary junction that consists of crowding and compression at the foramen magnum (Figure 1).

The current radiographic criterion for the diagnosis of Chiari is cerebellar tonsillar descent below the foramen magnum greater than 3 to 5 mm. Because of the complexity of the region compressed, Chiari may present with a variety of symptoms including headache, cranial nerve dysfunction or extremity deficits. This variable presentation results in a large differential diagnosis and great potential for misdiagnosis.

While Chiari crowding may occur in 1 to 3 percent of the population, symptoms may occur in only 0.06 percent.¹ The poor correlation between the extent of cerebellar crowding and symptoms has led medical scientists to seek other features beyond the static anatomical picture seen on MRI to predict symptoms and guide surgical treatment.

Fluid Motion and Symptoms

Cerebrospinal fluid (CSF), blood and brain tissue all move in the cervical-medullary junction with each heartbeat. Abnormal motion of these fluids and tissues has been suspected to be an important factor contributing to hindbrain descent, compression and ultimately symptoms.

Understanding the effect that abnormal motion has on Chiari symptoms requires a multidisciplinary approach. For this reason, Cleveland Clinic clinicians in pediatric and congenital neurosurgery, radiological physicists and pain specialists are working closely with a team of neuroscientists, engineers and psychologists at the Conquer Chiari Research Center at the University of Akron. This multidisciplinary approach has yielded novel results that have changed our thinking about Chiari diagnosis and treatment and inspired new questions.

The connection between CSF motion and brain tissue damage is not a new idea. The importance of a repetitive “water hammer effect” acting on the cerebellum, brain stem and spinal cord was first postulated in 1965³ by W. James Gardner, MD, Cleveland Clinic’s first Chairman of Neurosurgery. The “Gardner hypothesis” has been greatly debated and has influenced the diagnostic and surgical approach to Chiari for decades.

Novel Imaging Methods

Since that time, novel MRI-based techniques such as 3-D assessment of CSF motion have been developed (Figure 2a).⁴ Researchers have used computational fluid dynamics to model the dynamic nature of CSF in unprecedented detail (Figure 2b) and have shown that Chiari patients exhibit greater CSF flow impedance than do controls.^{2,5}

While decompressive surgery may open the fluid spaces at the foramen magnum, the effect on impedance is variable. Clinicians are now asking if the variable postsurgical course of Chiari sufferers is related to CSF flow impedance or other engineering-based parameters.

Since Dr. Gardner’s time, it has been suspected that cardiac-driven CSF flow and its associated forces act on neural tissues to deform the cerebellum, brain stem and spinal cord. Clinicians have long noted pulsatile movement of the cerebellar tonsils via intraoperative ultrasound imaging.

Using novel phase-contrast MRI-based techniques, our group has observed an increase in neural tissue motion in Chiari patients versus controls and has shown that motion often decreases after surgical decompression (Figure 3). Interestingly, the pattern of cyclic tissue compression and stretching also showed differences for Chiari patients. Understanding the tissue stresses due to the repetitive microstretching of the hindbrain may shed more light on the symptoms and neural tissue damage in Chiari.

Cognitive and Emotional Changes

Finally, although Chiari compromises a region not often associated with influence on higher brain function, recent findings of our multidisciplinary group have suggested there are changes in cognitive and emotional control in some Chiari patients.⁶ While this clinically important change may be due partially to the nonspecific result of chronic pain, there was evidence of cognitive effects that appeared to be independent of pain.

Our team is now investigating the possibility of a Chiari-specific origin of these cognitive effects by examining the association between Chiari brain compression and both fiber injury and abnormal higher brain region function, using diffusion tensor imaging and functional MRI, respectively.

The multidisciplinary collaboration at Cleveland Clinic and the University of Akron has resulted in new ways of quantifying and understanding the underlying pathophysiology of Chiari. Determining how this new information can inform the diagnosis and surgical treatment of pediatric and adult Chiari patients is the priority of this joint venture.

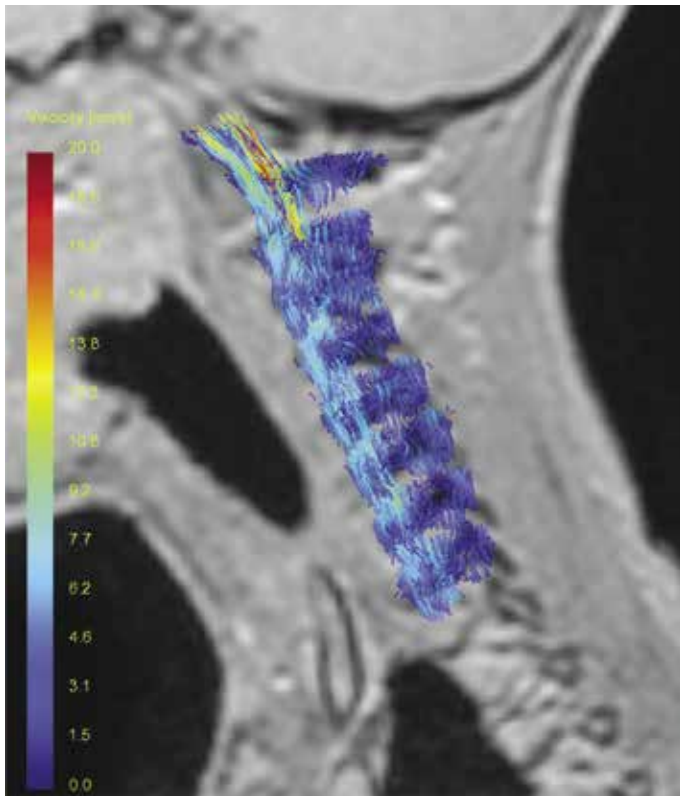


Figure 2a. 3-D measurement of CSF flow velocities by 4-D phase-contrast MRI⁴ in a 5-year-old Chiari patient with mild tonsillar descent, showing regions of elevated CSF flow velocities on the anterior side of the spinal cord from the pontine cistern (image courtesy of Alexander Bunck, MD).

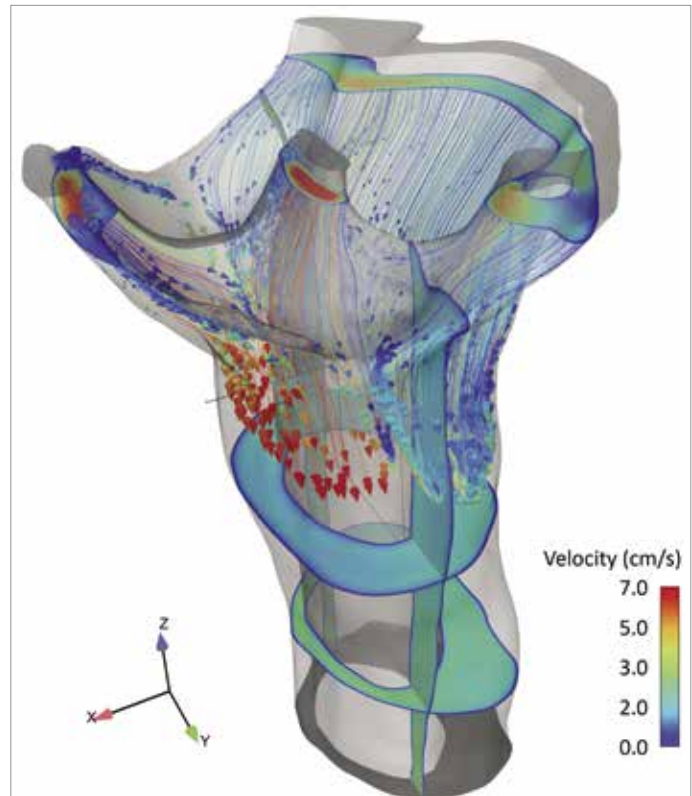


Figure 2b. Subject-specific computational fluid dynamics simulation of CSF motion based on *in vivo* MRI measurements from an adult-age Chiari patient with mild tonsillar descent below the foramen magnum⁷ (figure left = posterior CSF space, right = anterior; arrows show direction and magnitude of velocity streamlines). (Image courtesy of Soroush Pahlavian, MS.)

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Researchers have used computational fluid dynamics to model the dynamic nature of cerebrospinal fluid in unprecedented detail and have shown that Chiari patients exhibit greater flow impedance than do controls.

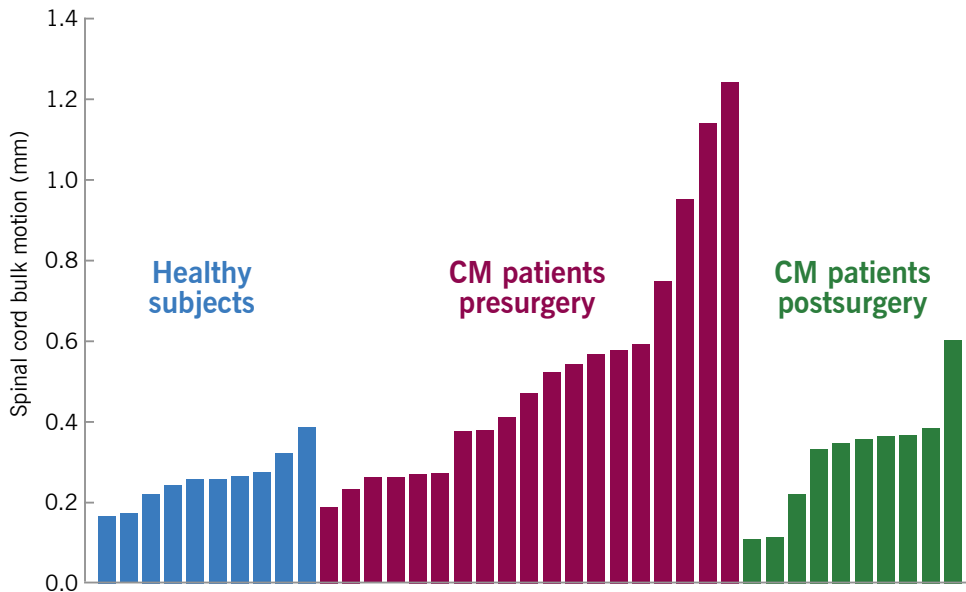


Figure 3. Quantification of spinal cord bulk motion at the foramen magnum using phase-contrast MRI, showing greater motion in Chiari (CM) patients than in healthy subjects, and that motion decreased following surgery.

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Dr. Allen is a professor of psychology at the University of Akron. His specialty interest in Chiari malformation type I concerns how cognition and emotion are related to the systems neuroscience of this disorder.

Dr. Loth is a professor and holds the F. Theodore Harrington Endowed Chair in the Department of Mechanical Engineering at the University of Akron. He also is executive director of the Conquer Chiari Research Center. His specialty interest is the simulation and measurement of blood and cerebrospinal fluid dynamics.

Take-Home Points

- Chiari malformation is a craniospinal deformity that has been defined based on descent of the cerebellar tonsils 3 to 5 mm below the foramen magnum and presents clinically with symptoms due to cervical-medullary compression.
- There is a poor correlation between the severity of anatomical crowding seen on standard MRIs and the occurrence of symptoms. Incidental findings of people with 3 to 5 mm of tonsillar descent without any symptoms are common. Only a minority of patients with cerebellar tonsillar descent may actually have symptoms.
- A significant factor in the pathophysiology of Chiari malformation may be the movement of the cerebrospinal fluid and brain tissue during the cardiac cycle. CSF and brain dynamics are altered in Chiari and can normalize with surgical decompression.
- New methods of quantifying the pulsatile movements at the cervical-medullary junction as well as nerve fiber connectivity, intactness and cognitive function may provide a greater understanding of the root causes of Chiari, symptoms and the best treatment.

Role of Reoperation in Children with Postoperative Seizure Recurrence After Functional/Disconnective Hemispherectomy

By Ahsan N.V. Moosa, MD, and William E. Bingaman, MD

Functional hemispherectomy (FH) is an effective treatment option for selected children with medically refractory epilepsy due to multilobar/hemispheric epileptogenic lesions.

Seizure recurrence despite FH poses special challenges. Does this seizure recurrence indicate independent epileptogenicity in the other hemisphere? What if the seizures are still coming from the operated hemisphere due to incomplete disconnection? Here we briefly review our experience with this special group of children.

Evolution of Functional Hemispherectomy

Anatomic hemispherectomy that involves removal of the entire affected hemisphere, leaving the basal ganglia and thalamus intact, proved useful for seizure control in patients with large hemispheric lesions and pre-existing hemiplegia. In the 1960s and '70s, reports of delayed worsening with hydrocephalus and superficial siderosis of the central nervous system after anatomic hemispherectomy dictated the newer modifications of this procedure. Minimizing tissue resection and leaving residual disconnected brain tissue inside the cranial cavity was proposed to reduce the chance for repeated microhemorrhages, thus reducing the risk of such delayed worsening.

Over time, the amount of tissue resected was reduced significantly, leading to various methods of functional (also called disconnective) hemispherectomy; some techniques with very minimal tissue removal are referred to as hemispherotomy. However, such disconnective procedures with minimal tissue resection have one limitation: risk of incomplete disconnection and continued seizures from the same hemisphere.

Outcome After Hemispherectomy and Reasons for Seizure Recurrence

We recently reported the longitudinal seizure-free rates after hemispherectomy in a series of 170 children. Nearly two-thirds of patients were seizure-free at a median follow-up of 5.3 years, and 80 percent of children were either seizure-free or had major improvement at last examination.

Let us focus our discussion on the patients who had seizure recurrence. Seizure recurrence after FH indicates two possibilities: seizures arising from the opposite hemisphere due to independent epileptogenicity, or seizures arising from the operated hemisphere as a result of incomplete disconnection. The latter situation can be corrected by repeat surgery to ensure complete hemispherectomy. Hence, all patients with seizure recurrence after functional hemispherectomy should be carefully evaluated to determine whether further surgery would be of benefit.

Challenges in Interpreting EEG and MRI Studies After Functional Hemispherectomy

Interpretation of EEG and video EEG studies in patients after functional hemispherectomy poses unique challenges. It is not uncommon to see patterns such as periodic lateralized epileptiform discharges (PLEDs) and EEG seizures (without clinical signs) in the operated hemisphere in patients who are completely seizure-free after functional hemispherectomy (Figure 1). These patterns are known to occur in the disconnected residual brain tissue and do not indicate active epilepsy in a patient who is clinically seizure-free. In patients with seizure recurrence, it may be difficult to determine the significance of such patterns.

However, EEG seizures in the operated hemisphere along with clinical ictal manifestations unequivocally prove incomplete disconnection; a similar conclusion can be made if the seizures are noted on EEG to spread from the operated side to the other hemisphere.

On the contrary, apparent ictal EEG patterns on the nonoperated hemisphere (without any ictal onset from the operated hemisphere) indicate two possibilities: independent epileptogenicity in the opposite hemisphere or seizure spread from the operated hemisphere. It is possible that residual tissue on the disconnected hemisphere may not generate robust ictal rhythms but is sufficient to generate seizures and spread through residual connections to the opposite hemisphere, as shown in the case depicted in Figure 2. In such cases, the “normal” hemisphere is part of the symptomatogenic zone, but the ictal onset could still be in the operated hemisphere.

The completeness of disconnection is also assessed by brain MRI. Interhemispheric disconnections are relatively easy to confirm, but subcortical disconnections are difficult to assess, especially when the tissue resection is minimal. Some authors believe that diffusion tensor imaging may be useful, but there are no published studies to support this.

If incomplete disconnection is obvious on MRI, then proceeding with further surgery to ensure complete disconnection should be considered. However, in our experience, both video EEG and MRI may be unhelpful and may be potentially misleading, and the only way to ensure complete hemispherectomy would be to perform repeat surgery with additional tissue resection and, not infrequently, anatomical hemispherectomy. It appears that past instances of delayed worsening after anatomic hemispherectomy were mostly caused by delay in detection of hydrocephalus in the pre-CT era.

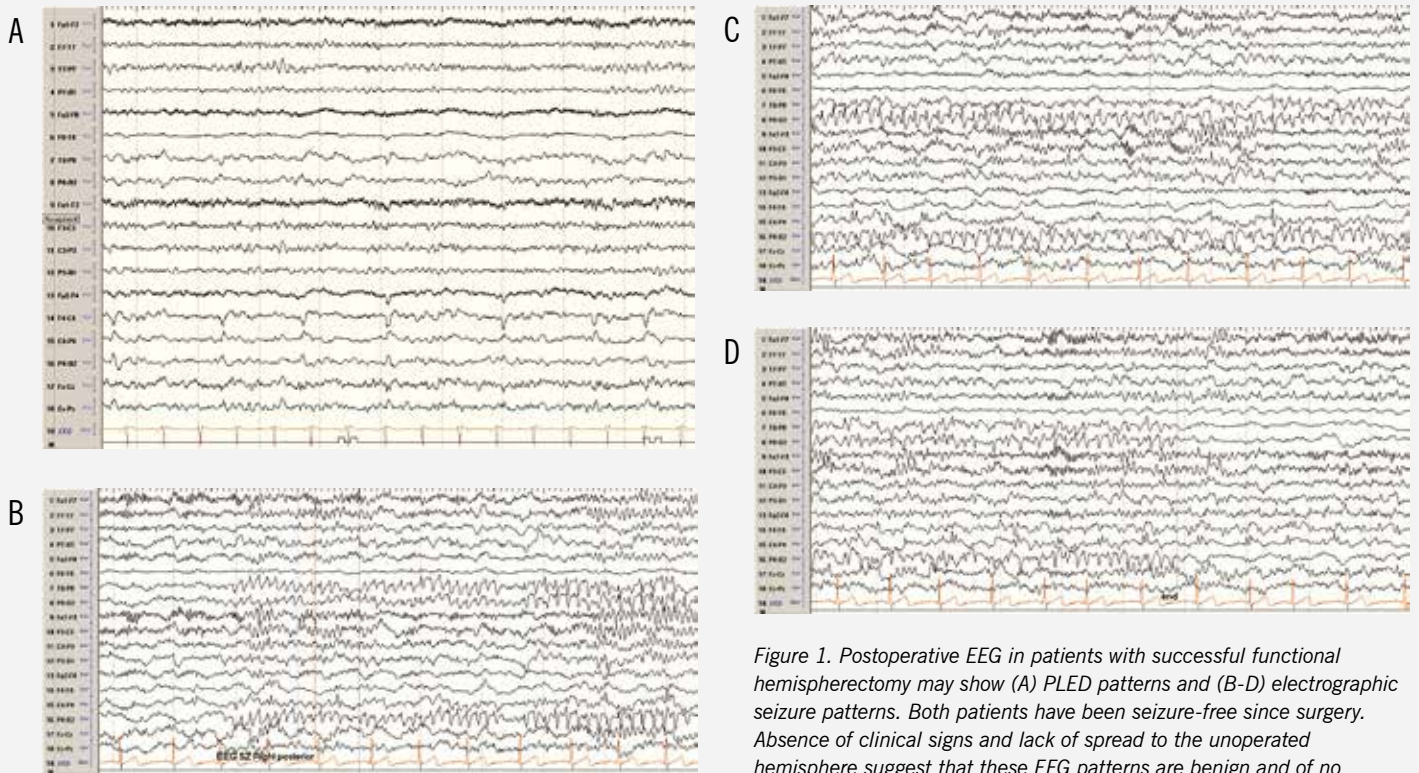


Figure 1. Postoperative EEG in patients with successful functional hemispherectomy may show (A) PLED patterns and (B-D) electrographic seizure patterns. Both patients have been seizure-free since surgery. Absence of clinical signs and lack of spread to the unoperated hemisphere suggest that these EEG patterns are benign and of no clinical significance in a patient who is seizure-free after functional hemispherectomy.

Reoperative Hemispherectomy at Cleveland Clinic

In our published series of 170 children who had hemispherectomy, 26 had a history of various forms of disconnective hemispherectomy. One-third of this cohort became seizure-free after further surgery, most commonly anatomic hemispherectomy.

In another series of 36 children who had reoperative hemispherectomy at Cleveland Clinic, two-thirds had major improvement (seizure-free or more than 90 percent reduction in seizures). Children with a malformation had a poor outcome, but the presence of structural

abnormalities in the other hemisphere on MRI did not affect the outcome. In another hemispherectomy series, 7 of 14 who had reoperation were seizure-free. The type of second surgery is not described in this study.

In conclusion, seizure recurrence after functional/disconnective hemispherectomy warrants careful re-evaluation. Incomplete disconnection may be the primary reason in one-third of cases, and these children can potentially achieve seizure freedom after reoperation to ensure effective hemispherectomy; another one-third may have substantial seizure reduction.

All patients with seizure recurrence after functional hemispherectomy should be carefully evaluated to determine whether further surgery would be of benefit.

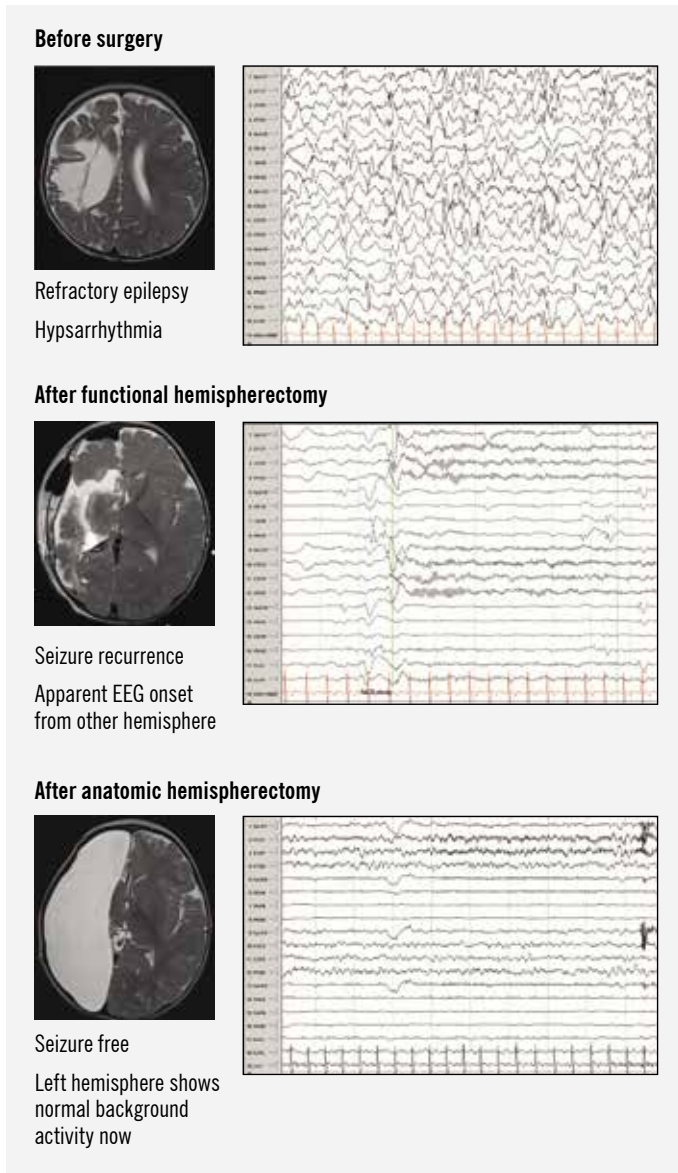


Figure 2. Illustrative case to highlight the misleading postoperative EEG after functional hemispherectomy. A 2-year-old boy presented with spasms and generalized tonic seizures. EEG showed generalized hypsarrhythmia, and MRI brain scan showed encephalomalacia due to remote right middle cerebral artery ischemia. Patient had recurrence of postoperative seizures soon after functional hemispherectomy. EEG showed ictal patterns on the unoperated hemisphere. Patient became completely seizure-free after conversion to anatomic hemispherectomy. EEG at six months after surgery showed normal background in the opposite hemisphere and diffuse attenuation over the right hemisphere, as expected after anatomic hemispherectomy.

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Take-Home Points

- Nearly one-third of patients with seizure recurrence after functional/disconnective hemispherectomy procedures may have persistent seizures due to incomplete disconnection. These patients require careful evaluation to determine whether further surgery to ensure complete disconnection could be of benefit.
- Interpretation of the EEG and video EEG after functional hemispherectomy poses unique challenges. Apparent ictal patterns from the "normal" hemisphere may represent spread patterns due to incomplete disconnection. Conversely, overt EEG seizures without clinical signs in the operated hemisphere may not be clinically relevant in a patient who is seizure-free.

SEEG in Pediatric Patients: Ongoing Lessons

By Deepak Lachhwani, MD, and Jorgé Gonzalez-Martinez, MD, PhD

Stereoelectroencephalography (SEEG) is a methodology for exploring surgical resection strategy in medically refractory patients suspected to have focal epilepsy. SEEG involves the temporary surgical implantation of electrodes that enable simultaneous recording of electrical activity from many parts of the brain at high temporal resolution (~1 ms), which is used to identify the epileptogenic zone.

SEEG involves relatively minimal risk of morbidity and mortality, and its results have aided the planning of surgical resection in appropriate candidates and the decision to avoid resection in patients deemed to have a poor prognosis.

Cleveland Clinic's SEEG Experience

Our institution has seen a steady growth and acceptance of this methodology based on some distinct merits of SEEG compared with other methods of invasive evaluation, such as subdural grids.

In our recently published series¹ of 28 pediatric patients who underwent SEEG evaluation, 18 of 28 were able to undergo resection, 13 of 18 had improvement in their seizure control and 5 of 18 were seizure-free. Careful review of patient profiles highlighted that SEEG-related advantages are especially relevant in young patients such as BB.

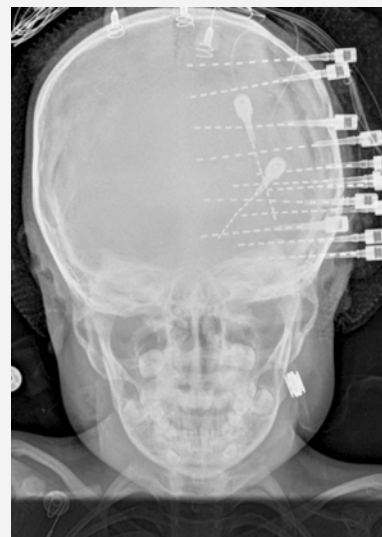
By the age of 2 years 5 months, BB had failed multiple seizure medications and the first attempt at tailored resection (guided by subdural grids) of the presumed seizure focus in her left frontal lobe. Frequent and intense daily seizures caused a significant impairment in her quality of life.

The family arrived at our institution for a second opinion, and we recommended SEEG as the methodology of choice to explore surgical treatment options. At the age of 3 years 4 months, BB became the youngest of our patients to undergo successful SEEG implantation, followed by resection within six weeks. Since surgery, she has remained seizure-free for more than 18 months.

SEEG's Advantages

Our experience with SEEG has provided these insights:

- **SEEG is effective.** Invasive recordings are intended for the very specific result of identifying or excluding surgical candidacy. In epilepsy patients with difficult-to-localize epilepsy, sometimes it is necessary to sample widely separated candidate areas within one hemisphere (e.g., the frontal and occipital lobes) or to exclude potential bihemispheric epileptogenicity before offering a tailored resection. SEEG allowed us to offer resection to 64 percent of the patients (18 of 28); poor surgical candidacy was confirmed for the remaining patients due to nonlocalizable or multifocal ictal onset or location of the epileptogenic zone within the eloquent cortex. SEEG allowed us to strategically sample and evaluate depths of cortical gyri and widely separated and even bilateral regions with the help of small burr holes.



Figures 1 and 2. Patient BB at 3 years 4 months of age. Operating room photos show implanted SEEG electrodes (left) and a skull X-ray (right) demonstrating positioning of SEEG electrodes.

Our ongoing experience weighs strongly in favor of stereoelectroencephalography as a safe and effective methodology for identifying young candidates suitable for surgical treatment of refractory epilepsy.

- **SEEG is efficient.** Exploring surgical candidacy with SEEG methodology does not require a craniotomy. Electrodes are placed by robotic technology with the help of stereoscopic guidance in an angiography suite. This process is completed within two to three hours. Compared to a craniotomy carried out in an operating theater — requiring more than six hours and deployment of many more resources — SEEG stands out as an efficient procedure.
- **SEEG has reduced morbidity.** Subdural grid electrode placement requires exposure of the brain surface using a large craniotomy. Placement of SEEG electrodes is performed through small burr holes. Obviating the need for craniotomy reduces blood loss and pain. Young patients are less likely to need aggressive pain control and 24 to 36 hours of recovery in the ICU before transfer to the monitoring unit to initiate seizure recording. These aspects make SEEG a less morbid procedure.
- **SEEG is safe.** Only one of the patients in our series experienced complications related to lead implantation, monitoring or lead removal. This was in the form of a cerebrospinal fluid leak that was successfully treated. There were no other serious morbidity or mortality issues.
- **SEEG delays time to resection, allowing for a more thoughtful informed consent process.** In the typical course of invasive evaluation with subdural grids, the patient undergoes a craniotomy for implantation of electrodes based on the preoperative hypothesis of seizure foci. After a variable delay of seven to 10 days during which seizures and cortical mapping data are analyzed, the patient undergoes a second craniotomy for removal of electrodes and resection of the proposed epileptogenic zone. SEEG does not involve a craniotomy at the time of electrode implantation or explantation. The implantation is carried out via small burr holes based on preplanned strategy, and explantation involves a sterile pullout of these electrodes. Resection of the proposed epileptogenic zone is carried out after a minimum delay of six weeks postimplantation to allow the brain to heal from the procedure and to minimize infection risk. The delay to surgery may be perceived as a disadvantage, but the chance to evaluate gathered data without the rush to proceed to resection at the time of a second craniotomy is a definite upside. Moreover, the postimplantation period allows additional time for a more detailed and thoughtful informed consent process, with no time limitations. Patients can return home and then decide regarding surgical intervention.

In conclusion, our ongoing experience weighs strongly in favor of SEEG as a safe and effective methodology for identifying young candidates suitable for surgical treatment of refractory epilepsy.

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Take-Home Points

- Stereoelectroencephalography (SEEG) uses temporarily implanted electrodes to perform simultaneous, multisite, high-resolution recording of electrical activity in medically refractory epilepsy patients, aiding in decision-making regarding surgical resection.
- Cleveland Clinic's experience with SEEG in pediatric patients has shown SEEG to be safe, efficient and effective at identifying resection candidates while reducing patient pain and morbidity compared with subdural grid electrode placement and craniotomy.

The Use and Monitoring of Second-Generation Antipsychotic Medications in Children and Adolescents Displaying Aggression

By Joseph M. Austerman, DO

Beginning in the 1970s, first-generation antipsychotic medication showed efficacy in children and adolescents suffering from various symptoms and disorders including psychotic disorders, pervasive developmental disorders, bipolar affective disorders, Tourette syndrome and other tic disorders.

Included in off-label use was the treatment of disruptive behavioral disorders including conduct disorder, oppositional defiant disorder (ODD), attention deficit hyperactivity disorder (ADHD) with aggression, and disruptive behavior disorder not otherwise specified.

SGA Introduction Spurs Use for Disruptive Behavior

Since the advent of second-generation antipsychotic (SGA) medications, there has been a significant increase in usage of these medications for treatment of pediatric mental illnesses not associated with pediatric psychosis. According to U.S. and European data for children and adolescents, these medications are primarily not used for treatment of psychiatric disorders but instead for disruptive behavior disorders, mood disorders and pervasive developmental disorders with intellectual disabilities.

Even more recently, there has been a significant increase in medication use observed in very young (2- to 5-year-old) children. From 1999 to 2001 versus 2007, in a cohort of more than 400,000 very young children, the annualized rate of antipsychotic use per 1,000 children increased from 0.78 to 1.59.¹⁻³

These children were mainly affected by pervasive developmental disorder or mental retardation, ADHD or other types of disruptive behavior disorders.

Current Research Findings Are Limited

However, knowledge is limited about how children without an autism spectrum disorder or intellectual disability who display aggression respond to and tolerate SGAs.

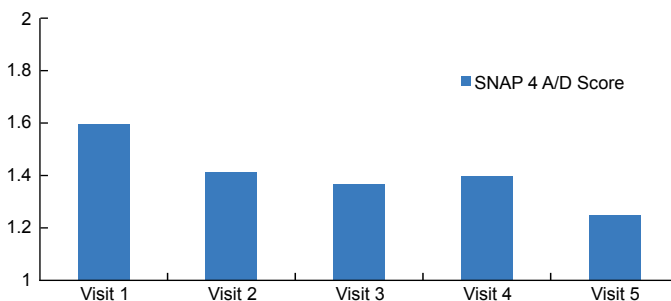


Figure 1. SNAP-IV scores from a series of office visits show a positive effect — less severe and less frequent aggressive episodes — with the use of SGAs in patients with ADHD, ODD, conduct disorder, disruptive behavior disorder or intermittent explosive disorder.

To date there are only 32 papers analyzing the efficacy and/or tolerability of SGAs without adjunctive agents in children and adolescents younger than 18: eight studies involved patients with mania/bipolar disorders, 12 involved patients with autism spectrum disorder showing irritability/behavioral symptoms, seven involved patients with conduct disorder/disruptive behavior disorder and five involved patients with Tourette syndrome. There are no double-blind studies comparing the different SGAs for these disorders.

SGAs and Aggression

One common feature targeted with SGAs is aggression. We define aggression as any hostile or violent behavior or attitude directed at oneself or others. Aggression can be an outcome of multiple etiologies including:

- Psychosis
- Mood disorders
- Anxiety
- Externalizing disorders (ADHD, ODD, conduct disorder)
- Intellectual disability
- Disrupted developmental attachment
- Trauma
- Use of illicit substances

Aggression may also result from medical illnesses or environmental stresses.

When managing aggression, investigation of etiology is critical and can help guide treatment. A comprehensive multidisciplinary approach including behavioral management, school interventions and parental training should always be the foundation for managing aggression. At times, medications may be appropriate and beneficial. However, there are no clear guidelines for when to use SGAs for aggression associated with psychiatric illness outside of autism spectrum disorders.

To help better determine the utility of SGAs for use in aggression, we retrospectively reviewed treatment outcomes in children and adolescents suffering from an externalizing disorder. We tracked symptom severity using a parental rating instrument, the Swanson, Nolan and Pelham-IV Questionnaire (SNAP-IV). It has been well-validated and, in addition to measuring core features of ADHD, has a specific subscale for aggression and defiance.

Patients included in the analysis were diagnosed with ADHD, ODD, conduct disorder, disruptive behavior disorder or intermittent explosive disorder, based on DSM-IV-TR criteria. A minimum of six office visits with completed SNAP-IV scales for a one-year period were required for inclusion in the data analysis. Patients with a diagnosis of any autism spectrum disorder were excluded. A total of 236 patients were enrolled in this outcomes study.

Results were similar for all SGAs studied (risperidone, aripiprazole, quetiapine, ziprasidone, olanzapine) and are displayed in Figure 1. They showed a positive effect — less severe and less frequent aggressive episodes — with the use of SGAs targeting aggression. Caution is recommended, however, in interpreting these results as this was a retrospective naturalistic outcomes study. Prospective randomized placebo-controlled studies are needed to further clarify the utility of these medications.

Prescribing and Monitoring

SGAs should be used only after other treatment lines have failed or if specific psychiatric etiologies are contributing to the aggression. When using SGAs, a conservative approach starting with low dosages and slow titration is recommended. Our outcomes did not reveal a significant difference in efficacy among the medications used.

Both short- and long-term potential side effects from SGA use are well-described in the pediatric and adult literature. It is important to track potential side effect profiles and clinical efficacy when using these medications in the pediatric population.

Potential side effects include the risk of metabolic syndrome, movement disorders and specific hormonal changes. Common reactions include sedation, weight gain, dry mouth, constipation, increased salivation, orthostatic hypotension, akathisia and photosensitivity.

Efficacy and adverse reactions should be monitored prior to initiation and at every visit. Prior to starting an SGA, baseline weight, body mass index (BMI) and waist circumference should be obtained. Baseline laboratory data should include complete blood count/differential, liver function test (LFT), basic metabolic panel, lipid profile and fasting blood sugar. On physical exam, a baseline Abnormal Involuntary Movement Scale (AIMS) examination should be performed.

After starting the medication, the patient should return monthly for the first three months for weight, BMI, AIMS, blood pressure and waist circumference measurements. Fasting glucose and lipid panel should be monitored at the third, sixth and 12th month visits, then annually. CBC, prolactin level, amylase and LFT should be monitored once in the first month, then annually.

Once efficacy is achieved and the patient is tolerating the medication, the provider should enter the patient into the maintenance phase of treatment. There is no SGA research dictating how long a patient should remain on these medications. We recommend that after a patient has remained in remission from severe aggression for one year, an attempt at weaning him or her from and then discontinuing the SGA should be undertaken. The physician should discuss these guidelines and the limitations of SGA research with the patient and family prior to treatment initiation.

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Take-Home Points

- Aggression is a symptom with multiple potential etiologies.
- Antipsychotic medications can be a viable and efficacious treatment option for pediatric aggression.
- The use of medications should only occur within a comprehensive multidisciplinary approach that includes behavioral management, school interventions and parental training.
- SGAs have a significant side-effect profile, and regular monitoring should include patient reports of side effects, a physical exam and laboratory monitoring.

Delirium in Pediatric Patients

By Mariela Herrera, MD, and Tatiana Falcone, MD

Delirium is a brain dysfunction defined as a disturbance in attention and awareness with an acute onset and a fluctuating course, associated with alterations in cognition. Patients develop delirium as a direct physiological consequence of another medical condition, or due to substance intoxication or withdrawal. Emergence delirium follows emergence from anesthesia.

The prevalence of pediatric delirium (PD) in critically ill children varies between 4.5 and 28 percent. In one study, it constituted 10 percent of all inpatient referrals for a child and adolescent psychiatry consult and between 17 and 66 percent of psychiatry referrals from pediatric intensive care units (PICUs).

Behaviors associated with PD include auto-extubation, pulling out intravenous lines and climbing out of bed, all of which can impair a patient's recovery. Research shows that delirium may prolong PICU stay by 2.4 days, with a cost increase of 1.5 percent. It is a traumatic experience for family and caregivers and can lead to post-traumatic stress disorder in the patient due to unrecognized delirious experiences.

PD is associated with high mortality rates, from 12.5 to 29 percent, but it is unclear if this association is independent of other factors. Disturbed perceptual-motor performance and electroencephalogram abnormalities after resolution of clinical PD have been reported.

A Multifactorial Syndrome

Various proposed hypotheses for the etiology of delirium suggest that the contributing factors are complementary and act together to precipitate the neurobehavioral syndrome. These hypotheses are based on constructs of neuroinflammation, neuronal aging, oxidative stress, neurotransmitter alterations, neuroendocrine dysfunction, diurnal or melatonin dysregulation, and network disconnectivity.

Delirium is a multifactorial syndrome in which predisposing factors interact with precipitant factors. The greater the number of predisposing factors, the fewer precipitating factors are needed for delirium to occur. Different risk factors for PD are shown in Figure 1.

Delirium is classified according to the motor level of activity in hyperactive, hypoactive and mixed subtypes. The presentation of PD is similar to that observed in adults, with symptoms of sleep-wake disturbances, disorientation and inattention. Features more frequently or uniquely reported in PD and that are specifically related to the developmental stage of the child include purposeless actions, labile affect, unexplained lethargy, inconsolability, changes in the quality of parent-child interaction, developmental regression with transient loss of previously acquired skills, and signs of autonomic dysregulation.

Screening to Detect Delirium

Delirium, especially the hypoactive form, is often underrecognized and undertreated. Routine screening is recommended for patients at high risk, such as those admitted to the PICU or those with neurological

Figure 1. Predisposing and precipitating risk factors for pediatric delirium.

Predisposing Factors	Precipitating Factors
Young age	Infections
Pre-existing progressive cognitive impairment	Metabolic disturbances
Mental retardation	Traumatic brain injury
Pre-existing emotional and behavioral problems	Hypoxia
Severity of physical illness and longer hospital stay	Medication toxicity
Anxiety or absence of caregiver	Post-transplant
	Postoperative
	Stroke
	Confusional migraine
	Cerebral SLE
	Inflammatory encephalopathy
	HIV/AIDS
	Extensive burn injuries
	High fever
	Various cancers
	Multiple sclerosis
	Thiamine deficiency
	Withdrawal syndromes
	Intoxication with drugs or abuse
	Paraneoplastic limbic encephalitis
	Nonconclusive status epilepticus
	Cardiac failure

SLE: systemic lupus erythematosus, HIV: human immunodeficiency virus, AIDS: acquired immune deficiency syndrome

disorders. The assessment should start with a sedation scale, such as the Richmond Agitation Sedation Scale, to determine whether the patient can be evaluated.

Scales that have been validated in children for the diagnosis of PD include the Delirium Rating Scale, the Pediatric Confusion Assessment Method for the ICU (for critically ill children chronologically and developmentally at least 5 years of age both on and off mechanical ventilation) and the Cornell Assessment of Pediatric Delirium (for children ages 0 to 21 years; can also detect the hypoactive form).

Pediatric delirium, especially the hypoactive form, is often underrecognized and undertreated.

Table 1. Nonpharmacological and pharmacological approaches for pediatric delirium.

NON PHARMACOLOGICAL STRATEGIES		
Support and orientation		
Constant presence of parents in the room; presence of familiar objects, photographs, music, favorite toys, people who can reassure and orient the patient, age-appropriate clocks, calendars or signs		
Avoidance of frequent staff changes		
Frequent and repeated reassurance		
Education for the staff, parents and, if applicable, the patient about delirium		
Sleep promotion		
Protocols for optimization of noise and light exposure, use of earplugs and eye mask, private room, relaxation		
Mobilization		
Avoid immobilization and use of physical restraints.		
Ensure adequate hydration, nutrition, oxygenation, regular bowel function and correction of electrolyte imbalance		
Infection		
Implementation of infection-control procedures; avoidance of unnecessary catheterization		
Considerations about analgesia and sedation		
Optimization of pain management and sedation with a daily, individualized goal-defined plan		
Consideration of withdrawal after high dose/long duration of sedation with opiates or benzodiazepines		
Considerations about medications		
Frequent review of type and number of medications with limitation of the total number of drugs		
Avoidance or cautious use of hypnotics, benzodiazepines, anticholinergic drugs and opiates		
PHARMACOLOGICAL MANAGEMENT		
Antipsychotics (symptomatic management of aggression, agitation or behavior that threatens safety and/or recovery)		
Atypical antipsychotics		
Risperidone ^{†*} : starting dose 0.1 to 0.2 mg per dose PO (infants) or 0.5-2.5 mg/day divided in 2 or 4 doses (5-16 y/o) Average daily dose 0.2-2.0 mg/24 hours Maximum doses: 1 mg/day (weight < 20 kg), 2.5 mg/day (20-45 kg), 3 mg/day (> 45 kg) Doses > 6 mg associated with increased risk of EPS	Olanzapine [‡] : starting dose 4 mg and average daily dose 10 mg in one retrospective study	Quetiapine: starting dose 30 mg and average daily dose 56 mg in one retrospective study
Typical Antipsychotics		
Haloperidol ^{†*} : loading dose 0.05 mg IV in 30 minutes (3.5-10 kg weight and ages 0-1 y/o), or up to 0.25 mg IV in 30 minutes (weight > 15 kg and older than 3 y/o); maintenance dose 0.05 to 0.5 mg/kg/24 hours in divided doses Maximum dose: 5 mg in 24 hours Side effects (acute dystonia, EPS, hyperpyrexia, prolongation of QT interval in EKG and hypotension) limit its use		
Sleeping aid		
Melatonin [*] (promotion of regular sleep cycle): dose between 0.5 mg and 10 mg QHS		

EPS = extrapyramidal symptoms *Oral solution available †Orally disintegrating tablet available ‡Parenteral form available

The Pediatric Anesthesia Emergence Delirium Scale and the Post-anesthetic Behavior Scale are specifically designed to detect emergence delirium.

The gold standard for diagnosis of PD is assessment by a child and adolescent psychiatrist based on DSM-5 criteria.

Nonpharmacological and Pharmacological Treatment

Treatment of delirium is achieved by promptly identifying and treating the underlying cause, which leads to resolution of symptoms. Infections and drug withdrawal are the most frequent causes of PD. Nonpharmacological and pharmacological approaches might be helpful for symptom management (Table 1).

Nonpharmacological strategies are focused on increasing support and orientation and mitigating modifiable risk factors.

The interplay among sedation, sleep, pain and delirium should be considered in the daily assessment of and goals for the patient. Regulation of sleep-wake homeostasis is essential and can be achieved with nonpharmacological and, if needed, pharmacological strategies such as the use of melatonin. Current medications administered should be reviewed, and avoiding or weaning the patient off benzodiazepines and other medications known to increase delirium risk is recommended.

Pharmacological interventions are indicated if the patient is distressed by the PD or is becoming dangerous because of his or her lack of cooperation with care. The research on pharmacological approaches to PD is scarce; recommendations mostly come from adult delirium and pediatric anesthesia literature. Currently there are no FDA-approved medications for delirium in either adult or pediatric populations.

Antipsychotics, both typical and atypical, have been used with some success (Table 1). In two retrospective reports the use of olanzapine and risperidone in infants (< 3 years old) with delirium, and the use of olanzapine, quetiapine and risperidone in children and adolescents with delirium, were effective, without significant adverse effects. However, the retrospective design and lack of control group in both studies limit the interpretation of the results.

Benzodiazepine use is indicated only for PD resulting from sedative or hypnotic withdrawal, or as an adjunct to antipsychotics for persistent agitation and insomnia. Emergence delirium might be reduced with the use of dexmedetomidine, ketamine, clonidine or propofol, but more research is needed to confirm these findings.

Dr. Herrera is a child and adolescent psychiatry fellow at Cleveland Clinic. She participated with Cleveland Clinic's Delirium Task Force in the development of an institutional care path to standardize the detection, prevention and management of delirium. She can be reached at herrerm@ccf.org or 216.445.8267.

Dr. Falcone is a child and adolescent psychiatrist at Cleveland Clinic and Assistant Professor of Medicine at Cleveland Clinic Lerner College of Medicine. She is the Principal Investigator for Project CARE (Coordination, Access, Resources, Education) 4 Epilepsy, a three-year Health Resources and Services Administration grant to enhance services, including mental health services, for children with epilepsy. She can be reached at falcont1@ccf.org or 216.444.7459.

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Take-Home Points

- Pediatric delirium is a multifactorial brain dysfunction often under-recognized and with potential negative outcomes.
- Pediatric hospital providers should routinely monitor their patients for delirium with the use of validated tools, especially those patients at higher risk while undergoing treatment in the PICU, surgical services or pediatric neurology services.
- Due to the interplay among sedation, pain, sleep disruption and delirium in the intensive care unit, all these factors should be assessed daily with appropriate scales, and daily goals should be identified and achieved.
- Treatment of delirium is achieved by identifying and treating the underlying cause. Nonpharmacological and pharmacological interventions can help manage symptoms and decrease distress for the patient, family and healthcare providers.

A Systematic Review of Treatment in Children with ADHD and Epilepsy

By Tatiana Falcone, MD, and Diana Lorenzo, MD

Attention deficit hyperactivity disorder (ADHD) is the most common comorbidity in pediatric epilepsy. For children with ADHD but without epilepsy, some studies have established the short-term therapeutic benefit of medication, primarily stimulants.

However, parents and providers may be reluctant to treat children with epilepsy and ADHD using stimulant medications out of concern that stimulants may precipitate seizures. Several studies in children with well-controlled seizures and ADHD suggest there is no seizure frequency increase with stimulant treatment. But most of those studies excluded children with poorly controlled seizures. Therefore, whether it is safe to use stimulant medication in children with uncontrolled epilepsy and ADHD continues to be an important unanswered question.

Methylphenidate (MPH) is an effective treatment for symptoms of ADHD in children without epilepsy.^{1,2}

Several studies have demonstrated that MPH reduces the symptoms of ADHD in children with epilepsy (CWE). However, these open trials⁴⁻⁶ and placebo-controlled studies^{7,8} have evaluated only CWE patients with well-controlled seizures. Table 1 summarizes studies, other than case report studies, conducted to date on MPH treatment of ADHD in CWE.

Feldman et al. reported that MPH improved ADHD symptoms in 7 of 10 children on the Teacher Behavior Rating Scale with no MPH-associated epileptiform changes or side effects.⁷ Gross-Tsur et al. demonstrated

improvement of ADHD symptoms in 70 percent of patients. These authors reported no change in seizure frequency and concluded that MPH was safe and effective for seizure-free CWE. However, there were not enough subjects with active seizures in this study to actually determine the safety of MPH with respect to seizure frequency.⁴

Gucuyener et al. reported a beneficial effect of MPH and no change in seizure frequency from baseline. However, five patients on multiple anti-epileptic drugs (suggesting poor seizure control) had seizures during the study. This paper did not specify the percentage of improvement of patients' ADHD symptoms while taking MPH or the types of side effects, although they were described as mild and transient.⁵

Gonzalez-Heydrich et al.'s crossover design in 33 subjects taking osmotic-release oral system (OROS) MPH found "robust" evidence that patients' ADHD symptoms improved. However, patients' daily seizure risk increased with increasing doses of OROS-MPH, suggesting a potential safety concern. The study revealed no serious adverse events; the most frequently reported were seizures, mainly in subjects on higher doses, and emotional lability.⁸

In contrast to the above studies, the 24 subjects in the Koneski et al. open label study had experienced at least two seizures within the previous six months. These authors reported an overall improvement in ADHD symptoms in 70.8 percent of the study's patients, with no increase in seizure frequency in 91.6 percent of patients.⁶

Nonstimulant Medication Treatment

- A 12-week prospective trial of atomoxetine (ATX), a norepinephrine reuptake inhibitor, in 17 children and adolescents with epilepsy showed significant improvement of ADHD symptoms. Side effects were sedation, loss of appetite and nausea. One patient had an increase in the number of seizures.¹⁰
- A retrospective study examined 25 epilepsy patients with stimulant-resistant ADHD treated with ATX. None of the patients' seizures worsened. Seventeen patients discontinued ATX due to inadequate response, increased irritability, emerging psychotic-like symptoms, decreased appetite and tremors.³
- The antidepressant bupropion is contraindicated in the treatment of CWE since it is the only medication used in ADHD treatment with a well-documented risk of seizures.⁸
- Clonidine and guanfacine, both sympatholytic medications, are used to treat ADHD, but we are not aware of any prospective, controlled trials of clonidine or guanfacine in children with ADHD and epilepsy.

On the basis of the research we reviewed, there is evidence that MPH can provide safe, effective treatment of ADHD in children with well-controlled epilepsy. Initial doses should be low and short-acting and should be accompanied by close monitoring for seizures.

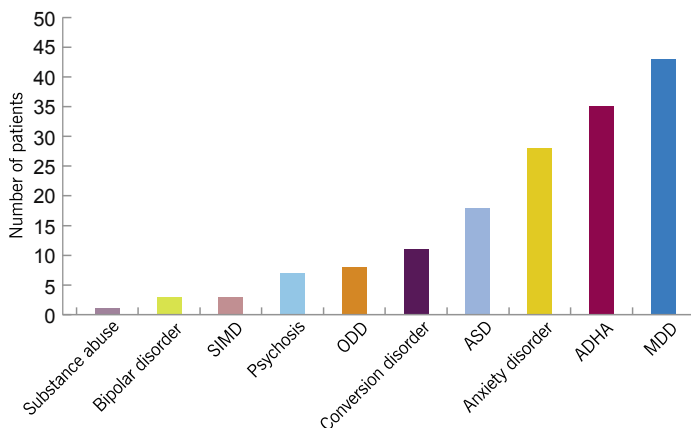


Figure 1. Psychiatric comorbidities in children and adolescents with epilepsy. In a retrospective study of 116 children 18 years old and younger who were screened in the pediatric epilepsy monitoring unit, ADHD was the second most frequent comorbidity in youths with epilepsy. SIMD = substance-induced mood disorder; ODD = oppositional defiant disorder; ASD = autism spectrum disorder; MDD = major depressive disorder. (Falcone T, Klaas P, Kotagal P. Psychiatric comorbidities in children and adolescents undergoing epilepsy surgery. Presented at the 2009 American Epilepsy Society annual meeting.)

Table 1. Prospective studies of MPH in children with epilepsy.

Study	Design	Population, Age, Seizures	N, Dose (mg/kg/day)	Effect of MPH on Seizures	Effect of MPH on ADHD
Feldman et al. 1989 ⁷	Safety/efficacy 4-week double-blind placebo-controlled crossover	CWE/ADHD, age 6-10, no seizures in last 3 months	10, 0.3	No changes in epileptiform activity	Statistically significant improvement in 7/10 children: Hyperactivity 40%; Inattention 30%
Gross-Tsur et al. 1997 ⁴	Safety/efficacy 8-week open-label observation	CWE/ADHD, age 6.4-14.6	30, 0.3	25 seizure-free had no change in seizure pattern; 3/5 children with seizures: increase of 1.8 seizures/week	MPH effect of 70% parent reported on CBCL; increased speed on Continuous Performance Test
Gucuyener et al. 2003 ⁵	Safety/efficacy 12-month open label	CWE/ADHD, age 6-16, EEG abnormalities and/or active seizures	119, 0.3-1 (57 w/ active seizures; 62 w/ EEG abnormalities)	Beneficial effect in EEG group; no seizure change from baseline in 52 on 1 AED, but increased in 5 on > 1 AED	Significant improvement between baseline and end-of-study by Connors scores in both groups
Gonzalez-Heydrich et al. 2010 ⁸	Safety/efficacy pilot randomized control trial of OROS MPH 1, 2, or 3 weeks	CWE/ADHD, age 6-17, seizure free for 1 month, but no more than 5 years	33, 0.3-2 3 dosage groups (18, 36, 54 mg) adapted for subject	Greater seizure hazard in patients on higher mg/kg dose	Response % MPH/placebo: 18 mg: 41/7 36 mg: 54/6 54 mg: 75/6 SNAP-IV
Koneski et al. 2011 ⁶	Safety/efficacy 6-month open label	CWE/ADHD, age 7-16, at least two seizures in last six months	24, < 25 mg per dose; max 60 per day	91.6% had no increase in seizures	70.8% improved; 20.8% no change; 8.3% worse on SNAP-IV

AED = anti-epileptic drug; CBCL = Child Behavior Checklist; SNAP-IV = Swanson, Nolan and Pelham-IV Teacher and Parent Rating Scale

Dr. Falcone is a child and adolescent psychiatrist at Cleveland Clinic and Assistant Professor of Medicine at Cleveland Clinic Lerner College of Medicine. She is the Principal Investigator for Project CARE (Coordination, Access, Resources, Education) 4 Epilepsy, a three-year Health Resources and Services Administration grant to enhance services, including mental health services, for children with epilepsy. She can be reached at falcont1@ccf.org or 216.444.7459.

Dr. Lorenzo is a psychiatry resident at Cleveland Clinic. She received her medical degree from Instituto Universitario de Ciencias de La Salud in Buenos Aires, Argentina. She can be reached at lorenzd@ccf.org or 216.444.0463.

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Take-Home Points

- ... ADHD is the most common comorbidity in children with epilepsy.
- ... All of the open-label studies reviewed herein used MPH for treatment of ADHD in children with epilepsy.
- ... There is evidence that in children with well-controlled epilepsy, MPH is an effective and safe treatment.
- ... Start with short-acting, low-dose MPH, with close monitoring for seizures.

Collaborative Childhood Anxiety Disorder Treatment

By Amy L. Lee, PhD, and Joseph M. Austerman, DO

Anxiety disorders involve excessive fear or worry about possible future threats, associated physiologic arousal and related behavioral disturbances.

Children with anxiety disorders often display emotional distress including crying, tantrums or extreme emotional outbursts. They may also engage in pervasive avoidance and vigilance behaviors. In addition, children experience physical symptoms including muscle tension, abdominal pain or sleep disturbance. These children typically hold a variety of mistaken beliefs or cognitions associated with their anxiety.

Common anxiety disorders exhibited in childhood and adolescence include separation anxiety disorder, selective mutism, phobias, generalized anxiety disorder and panic disorder.

High Prevalence and Physical and Functional Impacts

Anxiety disorders are widely recognized as the most common mental health problem experienced by children and adolescents. The prevalence of anxiety disorders among those younger than 18 years is estimated to be between 5.7 and 12.8 percent, which is a larger proportion than for attention deficit hyperactivity disorder or mood disorders. Anxiety disorders also tend to be chronic and when left untreated can lead to increased risk for adult psychiatric disorders.

Childhood anxiety disorders are often associated with school absenteeism and poor or lower than expected academic performance. Anxiety in children can lead to avoidance of activities associated with improved physical and mental health, such as exercise, play and social activity.

Anxiety disorders are also associated with physical complaints such as recurrent abdominal pain, nausea, limb pain, shortness of breath and headache. Due to the ambiguity of such symptoms, children may be subjected to potentially unnecessary medical tests and physician visits. Among children with medical illnesses such as asthma or gastrointestinal illnesses, anxiety symptoms may go untreated or unnoticed, leading to increased distress and decreased functioning. The complex relationship between anxiety and physical symptoms often leads to more healthcare utilization and a pattern of less than optimal symptom management.

Collaborative Treatment and Parent Training

Effective treatments for anxiety disorders combine cognitive behavioral therapies (CBT), parent training and medication. At Cleveland Clinic, we are developing collaborative treatments that teach children and youth how to manage their anxiety symptoms while instructing parents to support and participate in treatment goals.

With the benefit of electronic medical records, treatment goals are easily shared with key pediatric providers, allowing for complementary therapies and collaboration. For example, pediatricians, child psychologists and child psychiatrists can work together to positively reinforce a patient's progress in managing fears or physical symptoms while also managing medical or medication aspects of treatment.

As one example, a brief group CBT protocol has been developed for initiating and reinforcing CBT for pediatric anxiety disorders. The four- to five-week program uses a didactic, child-centered approach in teaching the basic skills of CBT for anxiety — for example, body calming, thought changing and behavioral practice. Each skill set is taught in weekly modules, with practice during group therapy sessions and weekly homework practice. Children are taught the relationship between body, mind and behavior in the first session and participate in reviews at each subsequent session as new anxiety management skills are added (Figure 1).

For example, one module teaches children to change anxious thought patterns to more neutral or positive ones. Engaging materials are used to teach children the nature of common thinking errors associated with anxiety. These thinking errors are referred to as “worry thoughts.”

Using a gamelike sorting task, children learn to differentiate worry thoughts — for example, “What if that dog chases me?” — from neutral thoughts — for example, “Some dogs are nice.” Children also learn to replace worry thoughts with “worry erasers,” and are given examples for homework practice (Figure 2).

The skills learned in group therapy are reviewed with parents each week. The parenting skills reviewed include methods for practicing with children at home, common parenting challenges and methods for responding to anxiety symptoms as they emerge. Parents are also involved in the weekly homework practice assigned to their child.

Medications

When administered in conjunction with psychotherapeutic modalities, psychopharmacologic options have shown benefit for pediatric anxiety disorders. Currently, selective serotonin reuptake inhibitors (SSRIs) are considered the first-line psychopharmacologic treatment for pediatric anxiety disorders. It is generally thought that the response rate is similar for all SSRI medications. Several randomized placebo-controlled trials have demonstrated the efficacy of these medications over placebo. Other studies have shown that the combination of SSRIs and CBT provides superior anxiety control over medications or CBT alone. SSRIs are generally well-tolerated, but common side effects and the FDA package insert warning should be carefully reviewed with parents and patients.

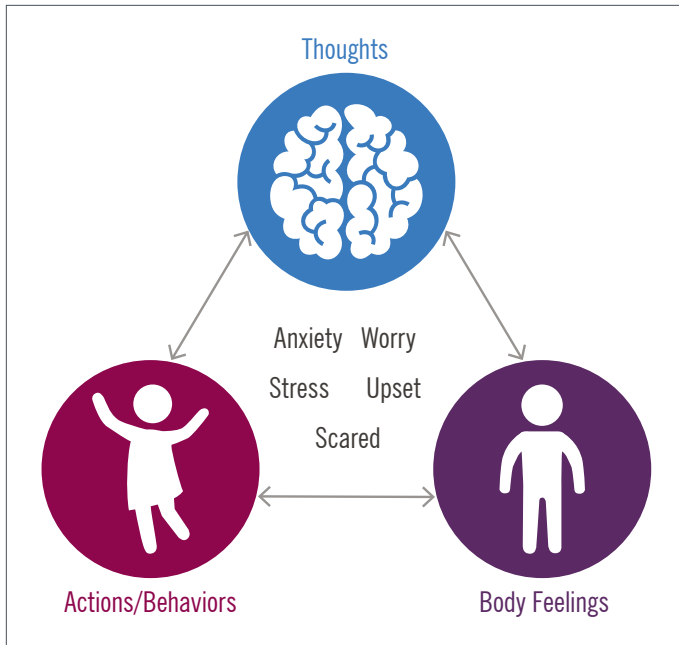


Figure 1. Anxiety cycle.

Worry Thought	Worry Eraser
"What if something bad happens?"	"I am safe."
"If I can't fall asleep, I will be awake all night."	"It will be OK. Take deep breaths."

Figure 2. Examples of anxious thinking and replacement thoughts.

The use of benzodiazepines is not supported in the pediatric literature. Several older studies show conflicting results regarding efficacy, and there is an increased risk of benzodiazepine addiction as well as behavioral disinhibition associated with their use.

Older medications such as clomipramine or imipramine have shown efficacy in pediatric anxiety disorders, but due to complications in their use — such as the need for cardiac monitoring, increased side effect profile and toxicity potential — these medications have been relegated to use in treatment-refractory moderate to severe anxiety.

Dr. Lee is a pediatric psychologist with Cleveland Clinic Children's. Her specialty interest is the diagnosis and treatment of childhood anxiety disorders as well as frequently co-occurring disorders such as ADHD, autism spectrum disorder and behavioral disorders. She can be reached at leea1@ccf.org or 440.835.1445.

Dr. Austerman is a staff physician in Cleveland Clinic's Center for Pediatric Behavioral Health and Section Head of Child and Adolescent Psychiatry. His specialty interest is the acute care of children and adolescents with psychiatric disorders. He can be reached at austerj@ccf.org or 216.445.7656.

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Take-Home Points

- Anxiety disorders are the most common mental health problem in childhood and adolescence.
- Cleveland Clinic offers integrated treatment for pediatric anxiety disorders, including cognitive behavioral therapy, parent training and medication treatment.
- Providers are able to communicate in real time with the benefit of electronic medical records, providing patients and families with coordinated and efficient care to reduce the impact of anxiety disorders on a child's functioning.

Making the Elusive Diagnosis of Dyslexia

By Katherine Lamparyk, PsyD

It is not uncommon for dyslexic patients to present with a myriad of previous psychological and educational testing and evaluations but no clear diagnosis. Parents are often confused about the meaning of the testing results and, more important, about what interventions and other recommendations will be effective.

The confusion surrounding dyslexia is complicated by its diagnosis not falling under the scope of a single field. While it is considered a medical diagnosis, physicians are not routinely trained in the psychological testing required to make the diagnosis. The educational system is equipped to conduct such testing, but it is not focused on diagnostic classifications.

Similarly, until the release of *Diagnostic and Statistical Manual of Mental Disorders-5* (DSM-5) in 2013, dyslexia was not included as a possible diagnostic classification to be made by psychologists. Instead, the diagnosis of reading disorder by psychologists and the classification of specific learning disability from the academic setting were utilized, resulting in confusion and likely unnecessary testing.

Defining Dyslexia

The term dyslexia, or more specifically developmental dyslexia, is used to describe a key set of strengths and weaknesses related to an individual's ability to read. It is characterized by difficulties in the areas of phonological processing and decoding skills, despite strengths in other areas of verbal processing and oral language abilities.

Phonological processing deficits can be demonstrated with difficulties in rhyming, making sound substitutions in words and sounding out pseudowords. These difficulties result in poor decoding abilities, which are often measured by single-word pronunciation and reading fluency.

Despite these difficulties, dyslexic children and adults will have intact oral language abilities in other areas such as vocabulary and oral comprehension. Reading comprehension abilities are also often intact, unless the decoding skills are so poor that they distract from the child's ability to derive meaning from the words he or she is attempting to pronounce.

Alternative Terminology

The education system focuses on qualifying students for special education services based on the federal requirements of the Individuals with Disabilities Education Act and the standards set by individual states.

Following a parent's or school's request, students are evaluated for eligibility for an Individualized Education Program and may be eligible under many potential categories, including specific learning disability.

This is a broad category to describe students struggling to meet the state's grade-level standards in one or more of many academic areas including reading fluency, reading comprehension, mathematics,

written expression or oral expression. While the school system's testing is often the same as a psychologist would administer, the child and parent do not receive a diagnosis more specific than specific learning disability. This usually provides little additional guidance regarding outside treatment options, understanding and prognosis.

Though psychologists are able to administer and interpret the same tests, they have often been hesitant to diagnose dyslexia, as it was not specifically listed in the *Diagnostic and Statistical Manual of Mental Disorders* until the latest edition.

Previously, the appropriate psychological diagnosis would have been reading disorder, although this term has been confusing for many families and does not differentiate between difficulties with reading comprehension versus decoding skills. DSM-5 specifies under the new term "specific learning disorder" (SLD) that "dyslexia is an alternative term used to refer to a pattern of learning difficulties characterized by problems with accurate or fluent word recognition, poor decoding, and poor spelling abilities" and indicates that it can be appropriate to list this term alongside the SLD diagnosis.

Diagnosing Dyslexia

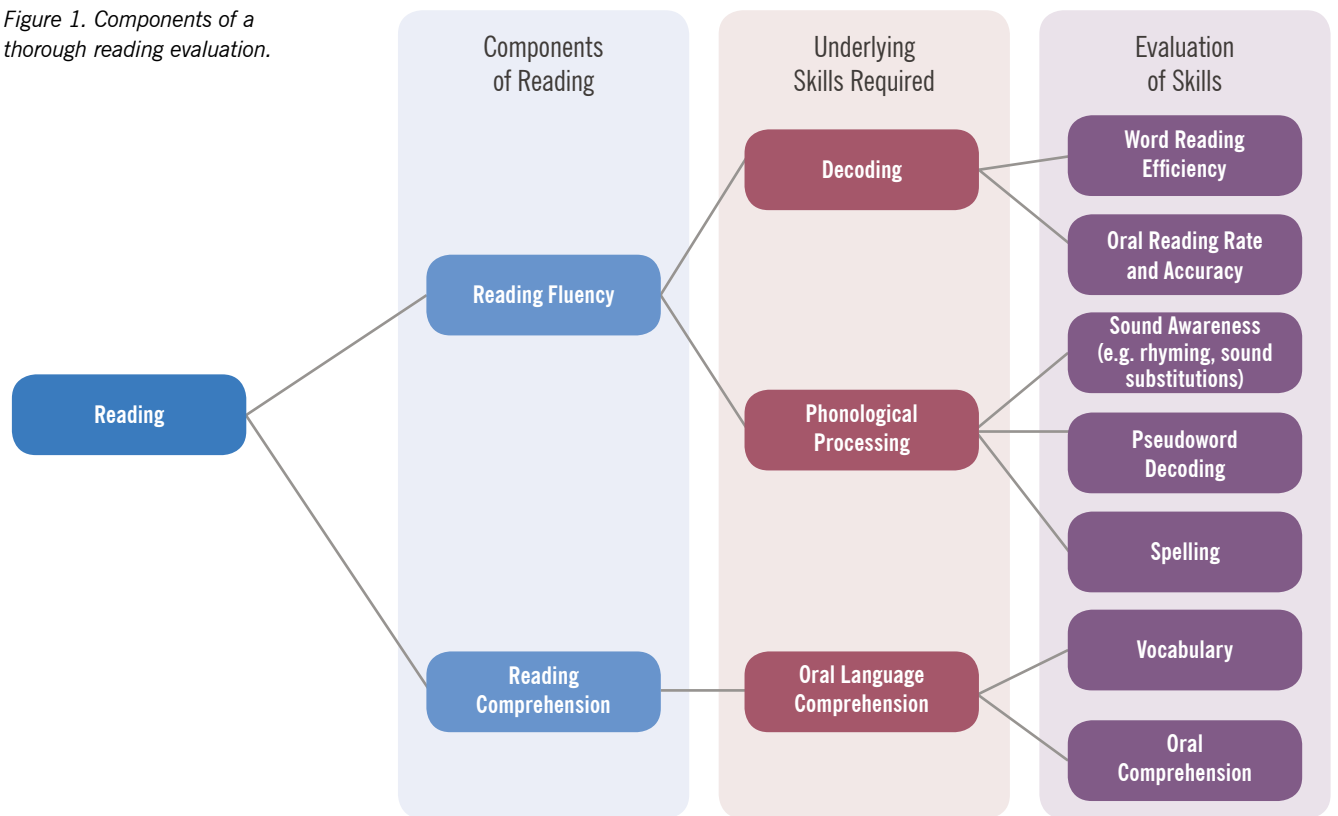
At Cleveland Clinic's Learning Evaluation and Consultation Clinic, we do not shy away from the specific diagnosis of dyslexia. Children, adolescents and even some adults undergo a comprehensive but targeted evaluation.

Testing includes intellectual ability — both verbal and nonverbal reasoning capacity — and various academic skills. We pay particular attention to the discrepancies between phonological processing and other oral language skills, and between reading fluency and reading comprehension compared with oral fluency and comprehension.

If recent testing has been completed through the child's school system, this can be reviewed in place of repeating similar tests. We provide a specific diagnosis and tailored treatment recommendations to each family and discuss them in depth. This enables the family to better advocate for their child, seek appropriate resources and develop a specific treatment plan.

Dr. Lamparyk is a pediatric psychologist and an associate staff member in Cleveland Clinic's Center for Pediatric Behavioral Health. Her specialty interests include the diagnosis and management of developmental dyslexia, identifying neurodevelopmental disorders in children with superior intellect and treating functional gastrointestinal disorders. She can be reached at lampark@ccf.org or 216.445.7574.

Figure 1. Components of a thorough reading evaluation.



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Take-Home Points

- Developmental dyslexia represents a specific pattern of academic weaknesses, yet its diagnosis is confused by numerous alternative terminologies of various disciplines.
- Academic settings focus on qualification criteria rather than specific diagnoses, which can leave families with little direction outside the school system.
- The diagnosis of dyslexia can be made by using a detailed history along with the administration and interpretation of current psycho-educational testing or review of recent testing conducted by other trained professionals.

Working with the Web: Understanding the Social Media Galaxy

By Charles Brown, DO, and Tatiana Falcone, MD

The Internet has blossomed into an integral part of society.

As an outgrowth of the Internet and the World Wide Web, social networking sites (SNS) serve as platforms to establish and maintain personal interactions. It is important that pediatric practitioners stay current about the different SNS our patients use.

The ever-changing nature of the online world makes it difficult to stay up to date regarding what SNS patients may be utilizing (Figure 1). In some instances, by the time we become aware of a site, its usage may have shifted, as with the case of Facebook's declining adolescent usage.⁶ Of the numerous sites and applications, Figure 2 shows some of the more noteworthy.

The Web has altered the way we look at relationships and psychological and psychosocial development. Use of SNS has been credited with helping adolescents:

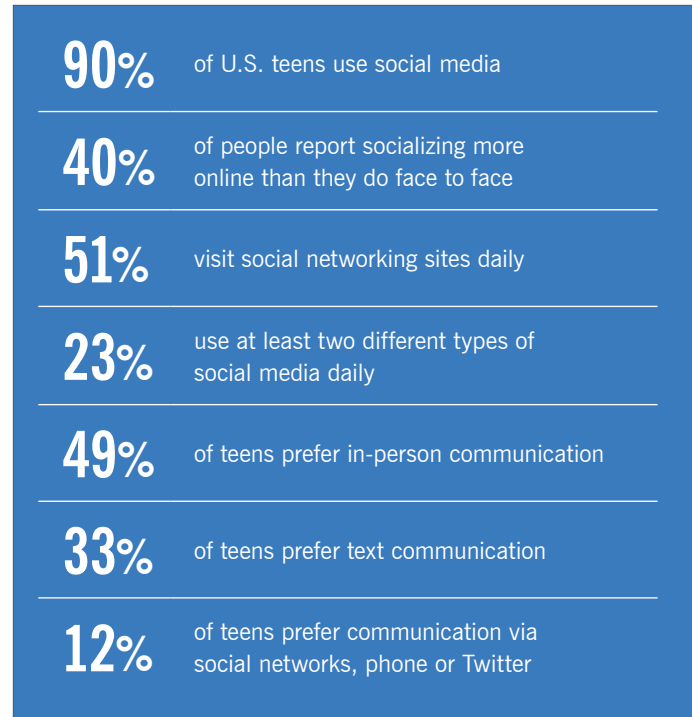
- Foster their identity and social skills
- Form new relationships and maintain established ones
- Enhance their sense of community and collective creativity
- Develop their ideas through exposure to different forms of shared media
- Expand their exposure to individuals with shared interests⁵

Studies have evaluated how SNS impact social interaction. For instance, individuals with higher early adolescent positivity went on to have more friends in their online networks as adults.³ Also, a review of online profiles by blinded raters provided accurate assessments of individuals' levels of extroversion, conscientiousness, openness and agreeableness.¹

Additionally, a person's positive and honest portrayal of him- or herself online has a positive relationship with the individual's perceived support and social well-being.⁸ Steinfeld et al. found that people with more social connections are more likely to engage in positive behaviors, and that adolescents with low self-esteem could potentially benefit from social support via social networking sites.⁷ Moreno et al. explored Facebook friendships and reported that people with fewer than 300 friends could get positive support when posting negative comments, but people with more than 1,000 friends could get negative remarks when posting self-deprecating comments.⁴

The rapid changes in the social media landscape warrant continued evaluation of previous findings. For example, Kraut et al. discussed how Internet use was associated with loneliness and stress; however, other studies were unable to replicate this finding. The same group, in a later study that followed the sample for a longer period of time, found no relationship between Internet use and depression.

Figure 1. Teen social network sites fast facts.



Adapted from http://big.assets.huffingtonpost.com/socialmedia_infographic_062612_950px.jpeg

Individuals have been utilizing the Internet not just to create new social connections, but to learn about disorders and diseases that they or loved ones may be experiencing and to find support to address them.

Practitioners should be aware that online forums have also been created to provide negative support. A quick search reveals that pro-substance abuse ("Erowid"), pro-eating disorder ("Pro-ana"), pro-suicide and pro-self-harm sites exist and these must be considered when exploring a patient's online usage and behaviors. Asking parents about their child's social media use is important and necessary.

Bullying is an unfortunate frequent source of stress for many children and teens. There is a strong relationship between bullying, cyberbullying and suicide. Studies have reported that as many as 90 percent of social media-using teens have witnessed and ignored mean behavior online, while 20 percent of surveyed teens said that their peers are mostly unkind to each other online.²

Figure 2. Popular social networking sites (SNS) and applications, and potential concerns.

Site	Intended Use	Keys for Providers and Parents
Facebook	Has > 1 billion users	Privacy setting changes can default to public view.
Twitter	Microblogging site with > 500 million users	All information posted is publicly accessible.
Instagram	Social network and media-sharing site with > 100 million users	Posted content can be sold to businesses for use by Instagram.
Tumblr	Personal blogging site with > 108 million blogs	2-4% of site material is pornographic in nature and allowed by Tumblr policy.
Vine	6-second video clips	Minimum user age was raised to 17 due to policy allowing pornographic material.
Snapchat	Private mobile individual/group chat with media exchange site (i.e., photos, videos and text)	Popular for sexting because users believed items were deleted after 10 seconds (items actually are archived on recipients' devices).
Kik	Private individual/Group chat with media exchange site (i.e. Photos, videos, and text)	Mobile message and content activity not accessible by phone data providers.
4chan	Photoboard/media site	All postings are anonymous. Utilized by various hackers and hacking groups.

Dr. Brown recently completed a child and adolescent psychiatry fellowship at Cleveland Clinic.

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Take-Home Points

- Internet and social networking site usage should be assessed routinely as part of the regular well-child visit.
- There is an important relationship between bullying, cyberbullying and suicide; unless bullying is systematically assessed, adolescents are unlikely to report it.
- Questions regarding your patient's SNS usage, the nature of their online relationships, the types of online support they're seeking/ receiving and their potential experience with online victimization are all worth exploring.

Outcomes of an Interdisciplinary Pediatric Pain Rehabilitation Program for Children with Chronic Migraine and Headache

By Ethan Benore, PhD; Gerard Banez, PhD; and David Rothner, MD

Headache is a widespread health condition for children, with an estimated prevalence rate of 58 percent.¹

Headache and migraine also present with significant morbidity in terms of anxiety, depression and impairment in daily life.² These children struggle with regular school attendance, peer interactions, and participation in athletics, extracurricular and personal/family activities. Outcomes are often worse for those with chronic headache or chronic migraine.^{3,4}

When children suffer, parents and family are also affected, with work-life interference and parental anxiety and depression. At Cleveland Clinic, we evaluate approximately 350 children each year with a diagnosis of chronic migraine headache. Approximately 20 are treated each year in our Pediatric Pain Rehabilitation Program, an intensive multidisciplinary program designed to improve the functional quality of life for children and their families.

Several studies have examined the utility of rehabilitation for children with chronic pain and functional disability.⁵⁻⁷ Often, children with chronic migraine are treated in groups along with children who have other types of chronic pain, such as complex regional pain syndrome, fibromyalgia and recurrent abdominal pain. Rehabilitation seems most appropriate for severely affected children with pediatric headache who have not responded well to outpatient therapies and medications and require a multidisciplinary setting that can address medical, psychological, environmental and lifestyle factors concurrently and intensively.^{8,9} A recent review found that children with chronic migraine reported less pain and improved mood following pediatric rehabilitation.¹⁰

Cleveland Clinic's Pain Rehab Approach

At Cleveland Clinic, the Pediatric Pain Rehabilitation Program is an interprofessional (i.e., multidisciplinary) program that supports children with chronic migraine by increasing strength and endurance, helping them return to daily life activities and teaching them appropriate self-directed coping and pain management skills. We are currently the nation's only Commission on Accreditation of Rehabilitation Facilities-accredited pediatric specialty interdisciplinary pain rehabilitation program.

Children are typically enrolled in a three-week program — two weeks of inpatient care and one of daytime hospital care. The program blends rehabilitation therapies (physical, occupational and recreational), psychological services, medical subspecialty care, alternative therapies (aromatherapy, acupuncture, biofeedback and Reiki), and school. On average, patients spend seven to eight hours in treatment each day, with services scheduled hourly from 8 a.m. to 5 p.m.

Rehabilitation therapy occurs in group settings and individually, using both land and aquatic forms of therapy three hours per day. Patients receive an average of three individual/family psychological treatment sessions per week and participate in a cognitive-behavioral skills training group three times per week. They participate in a school program one to two hours each day and in recreation or music therapy groups at least one hour daily. Since children are part of a family unit, parents are also involved in a separate part of the program focused on parent support and parent wellness, and parents and siblings participate in recreational therapy.

Significant Improvements in Chronic Headache and Migraine Pain

Here we present outcomes for 111 children with chronic migraine or headache who were treated in our program during the past seven years. These children reported headache lasting three years on average prior to enrolling in our program.

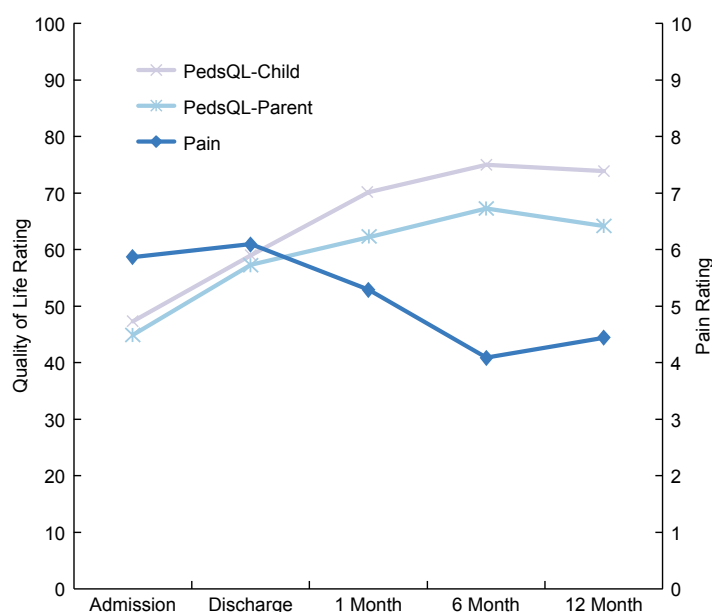


Figure 1. Self-reported headache pain rating (0-10) and child quality of life (0-100) as rated by PedsQL™ child and parent proxy report.¹³

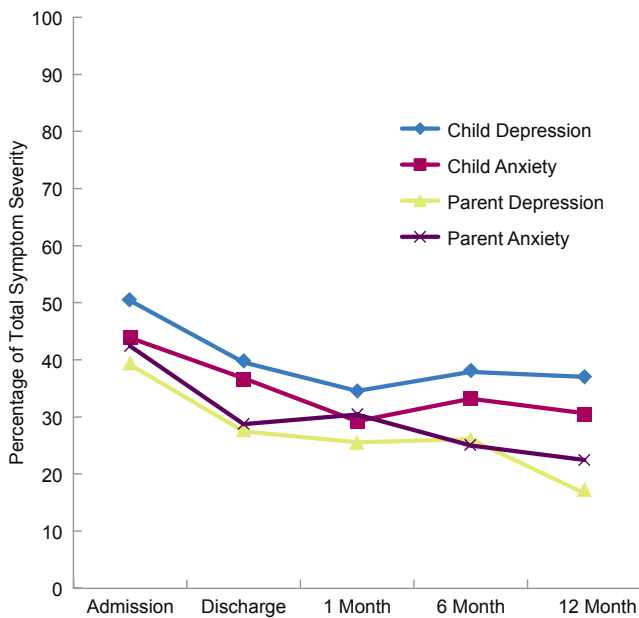


Figure 2. Raw score of symptoms of parent depression and anxiety, rated on the Bath Adolescent Pain-Parental Impact Questionnaire.¹⁴ Raw score of symptoms of child depression and anxiety, rated on the Bath Adolescent Pain Questionnaire.¹⁵ Scores reported as percentage of total symptom severity.

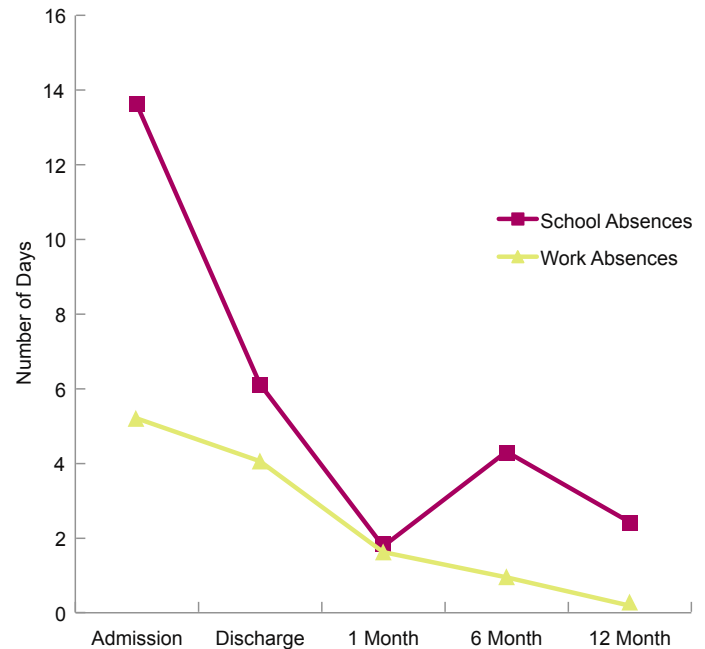


Figure 3. Rates of child absences from school (per month) and parent absences from work (per month) related to pediatric chronic headache or migraine.

To date, our program has demonstrated clinically significant changes in the lives of our patients and families. As shown in Figure 1, children and parents both report a sharp improvement in the child's quality of life, which continues as long as a year after discharge. Scores at 12 months are close to a previously reported average for "healthy children" (Cleveland Clinic child report = 73.9; healthy child report = 83.84. Cleveland Clinic parent-proxy report = 64.2; healthy child parent-proxy report = 82.7).¹¹

Interestingly, though not unexpectedly, pain level is reduced but not eliminated during a one-year time period (Figure 1). This is consistent with our program's philosophy and the findings in related literature — that the primary goal for treating chronic pain in these families is to increase independent functioning despite pain. At each time point, between 4 and 11 percent of children reported no pain that day.

Given the link between pain and emotional functioning, we also report notable decreases in both anxiety and depressed mood in children and their parents following the program (Figure 2). Scores are reported as a percentage of total symptom severity for these scales. This result

underscores the link between emotional and physical functioning in these patients, providing further support for an interdisciplinary program that addresses the full gamut of a child's well-being.

Reductions in Absenteeism

Finally, outcomes from our program translate into reduced school and work absences related to the child's headache (Figure 3). When children are physically conditioned and learn coping skills to maintain high levels of functioning despite the presence of headache, they are less likely to miss school (due to headache or doctor appointments). In turn, their parents can return to a regular workweek. These outcomes are a marker for the impact of chronic pain and the benefit of intensive multidisciplinary rehabilitation.¹²

Pediatric chronic headache or migraine presents a serious problem for a child's well-being and profoundly impacts the family as well. Cleveland Clinic's Pediatric Pain Rehabilitation Program is measurably improving the lives of these children, and our updated findings provide hope for them and their families.

Pediatric chronic headache or migraine presents a serious problem for a child's well-being and profoundly impacts the family as well.

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Take-Home Points

- In addition to pain, chronic headaches and migraines in pediatric patients cause significant morbidity in terms of anxiety, depression and impairment of daily life activities.
- Cleveland Clinic's multidisciplinary Pediatric Pain Rehabilitation Program works with chronic migraine patients and families to increase strength and endurance, assist a return to daily activities, and use self-directed coping and pain-management skills.
- An outcomes review shows clinically significant changes in the lives of the program's patients and families, including reduced pain, improved quality of life and reduced absenteeism.

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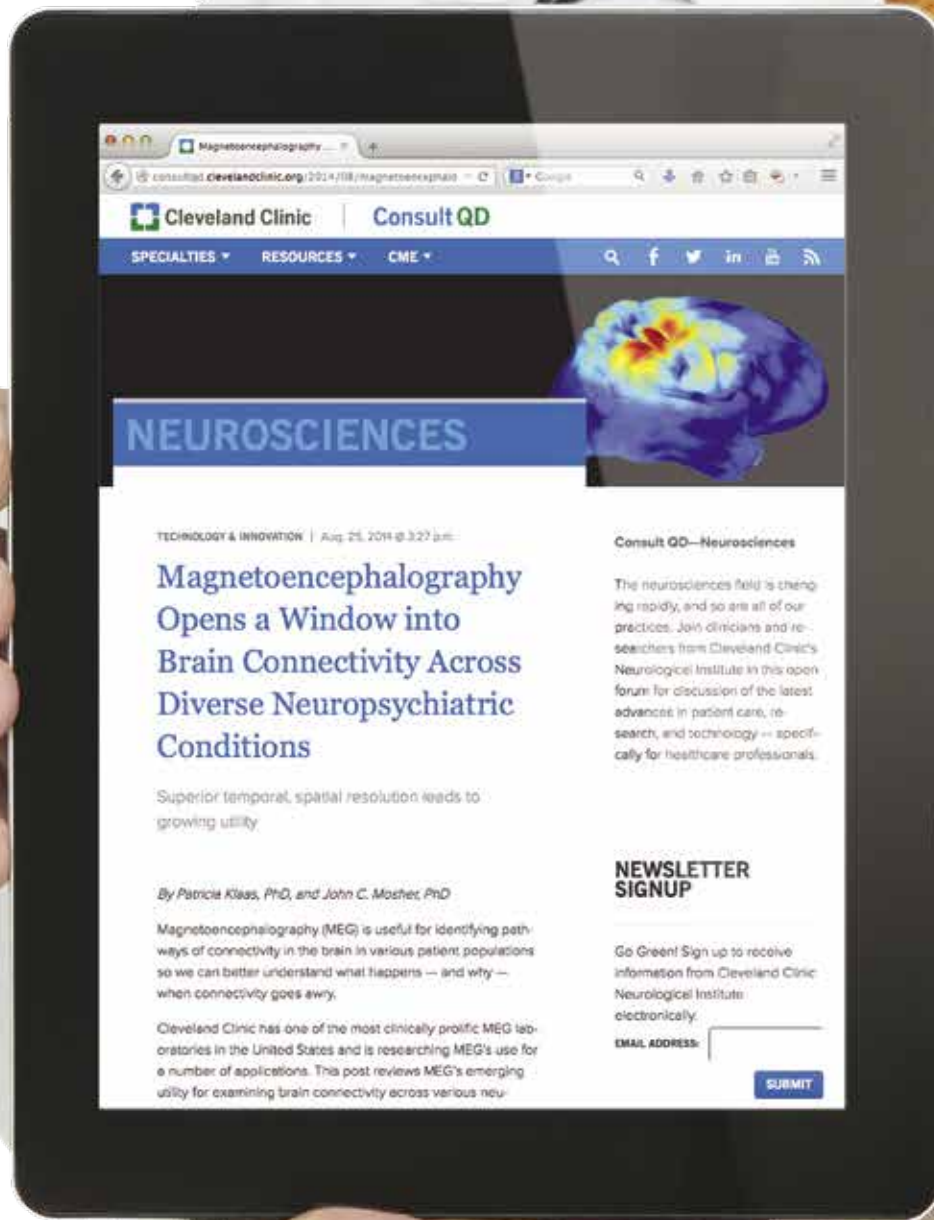
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By Toby Cosgrove, MD,
CEO and President, Cleveland Clinic

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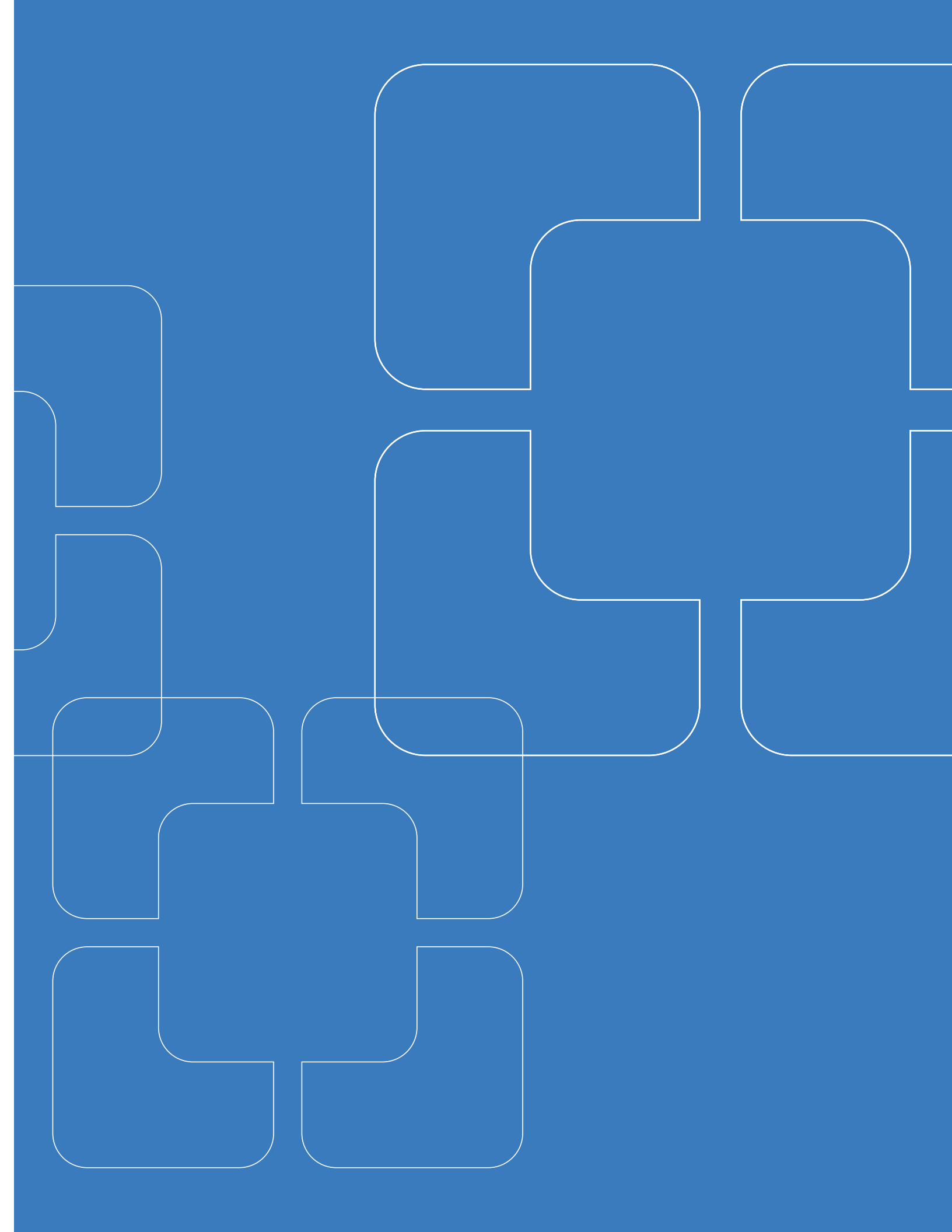
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