Team Approach for Optimal Tumor Care

Mayo Clinic has the breadth of expertise to quickly assemble a pediatric care team for children with brain tumors. This multidisciplinary approach typically includes pediatric specialists in neurology, hematology-oncology, radiation oncology and neurosurgery.

“We often see these patients within a day of their referral to Mayo Clinic,” says David J. Daniels, M.D., Ph.D., a pediatric neurosurgeon at Mayo Clinic in Rochester, Minnesota. “We do the necessary scans and meet as a group to come up with the optimal treatment plan — we don’t make decisions individually. Our integrated team is able to mobilize rapidly to provide that expertise.”

As a high-volume center with deep neurological and neurosurgical expertise, Mayo Clinic has experience with the most challenging benign and cancerous brain tumors in children (Figure 1). Dr. Daniels and his team treat patients with tumors located in difficult areas of the brain, including the third and fourth ventricle, skull base and eloquent areas such as speech and motor. Awake craniotomies are occasionally performed in carefully selected pediatric patients to resect lesions near speech centers. An awake craniotomy allows for safe maximal tumor resection while preserving functional tissue.

“The patient we would consider for an awake procedure is older — 14 to 18 years old — and we are very selective in terms of the patient’s anxiety with an awake procedure,” Dr. Daniels says. “Mayo has a long history of performing awake craniotomies in adults, so we have anesthesiologists and other specialists who can support our work in these selected pediatric patients.”

For all pediatric brain tumor surgeries, Mayo Clinic employs state-of-the-art imaging. Functional MRI is used to map speech, motor and sensory pathways before surgery. Advanced intraoperative monitoring, including sensory cortex neuromonitoring and intraoperative MRI, also is routinely used.

“Intraoperative MRI allows us to be very specific in our tumor resection,” Dr. Daniels says. “If any residual tumor is seen on intraoperative MRI, we can resect it right away rather than waiting to get an MRI and going back into surgery the next day.”

Developing novel therapies for H3K27M tumors

At Mayo Clinic, every pediatric brain tumor with sufficient tissue available is saved for research purposes, with some of the tissue going to the Pediatric Brain Tumor Laboratory, led by Dr.
Daniels. The tumors are grown in cell culture, transferred to mouse models and treated with experimental drugs. In an effort to identify potential for rapid clinical translation, the lab has screened thousands of promising drugs in numerous cancer cell lines and uncovered important signaling pathways in these tumors.

About 60 cell lines have been developed, including H3K27M-mutant diffuse midline glioma tumors. Patients with H3K27M-mutant gliomas, formerly classified as diffuse intrinsic pontine gliomas, have a life expectancy of nine to 12 months after diagnosis in patients.

A key focus of the lab’s investigation of possible treatments for this devastating disease is signal transducer and activator of transcription 3 (STAT3) proteins. “This transcription factor appears to be very integral for the H3K27M-mutant tumor to grow and survive,” Dr. Daniels says. “When we treat lab mice with STAT3 inhibitors or knock this pathway out genetically, we’re able to decrease the tumor size and extend life expectancy in these models.”

Dr. Daniels is proposing a phase 1 clinical trial of a STAT3 inhibitor that has worked effectively in the lab’s mouse models (Figure 2). The lab has also synthesized and patented other novel drugs and found them to be potent inhibitors of the STAT3 pathway.

In addition to the STAT3 pathway, the lab is investigating ways to reverse the effects of this histone mutation on the epigenome. That work led the researchers to discover another class of compounds, the Aurora kinase inhibitors, as potential therapeutic targets. Experimental therapies focused on that pathway have succeeded in reducing the size of tumors grown in mouse flanks; experiments on cranial tumors in mice are underway. The lab’s findings support the hypothesis that Aurora kinases are critical for epigenetic reprogramming in H3K27M tumor cells and represent a targeted approach for treating tumors with this mutation.

“As with the STAT3 pathway, we have found not just a therapy that seems to work but also a mechanism that explains why certain therapies might work against the H3K27M mutation,” Dr. Daniels says. He hopes to propose a clinical trial of a drug targeting Aurora kinases in the next couple of years.

In conjunction with Mayo Clinic’s Center for Immunology and Immune Therapies, the Pediatric Brain Tumor Laboratory is also exploring oncolytic viruses and chimeric antigen receptor (CAR)-T cell therapy for H3K27M-mutant tumors.

“By understanding how the H3K27M histone mutation contributes to therapeutic vulnerabilities in tumor cells, we hope to develop new treatment paradigms for children with this devastating disease,” Dr. Daniels says.

Advances in Pediatric Refractory Epilepsy

Children with epilepsy are benefiting from Mayo Clinic’s recent advances in the diagnosis and treatment of the disease. Mayo’s routine clinical use of a unique imaging protocol is improving detection of focal cortical dysplasia. In addition, Mayo Clinic researchers are working to develop biomarkers for antibody-negative neuroinflammation causing epilepsy and cognitive impairment.
Enhanced diagnosis of focal cortical dysplasia

Mayo Clinic is one of the few centers that routinely offers morphometric MRI analysis to detect focal cortical dysplasia in children (Figure). The quantitative analysis, with voxel-by-voxel comparisons between patient MRIs and a normative pediatric sample, can detect the subtle signs of focal cortical dysplasia and guide decisions about surgical treatment.

“Many of these patients start having seizures during the first decade of life. Their families are told that the MRIs are normal, so if a child is failing medications, nothing can be done. Our testing can show that perhaps there is a surgical option,” says Lily C. Wong-Kisiel, M.D., a pediatric epileptologist at Mayo Clinic in Rochester, Minnesota.

Even with high-tesla MRI, evidence of focal cortical dysplasia is often subtle, as it tends to occur in the gradient between the brain’s cortical surface and white matter. Double inversion recovery MRI, which suppresses the white matter signal, can help with detection. “But even then, focal cortical dysplasia can be easily missed,” Dr. Wong-Kisiel says.

The use of a normative pediatric database is key to Mayo Clinic’s morphometric MRI analysis. “It’s unusual to have that normative database in a pediatric population. Assembling it took some time,” Dr. Wong-Kisiel says. “But comparing the patient’s information to those statistical population norms enhances the radiological detection. As a result, we’re picking up additional cases of focal cortical dysplasia.”

In a study published in the February 2018 issue of Epilepsy Research, Dr. Wong-Kisiel and colleagues described the enhanced sensitivity of the quantitative MRI analysis compared with visual analysis. The version of the test now in routine clinical use at Mayo was developed by Mayo Clinic’s Center for Innovation.

Dr. Wong-Kisiel notes that only 30 to 40 percent of children with MRI-negative epilepsy achieve seizure-free outcomes after surgery, versus 60 to 80 percent of children with a visible MRI finding. “If there’s a visual target, we can talk to families about the higher likelihood of successful surgery,” she says.

Antibody-negative inflammatory seizures

Mayo Clinic researchers are investigating epileptic encephalopathies in children that appear to be caused by neuroinflammation in the absence of antibodies. Patients with this type of seizure disorder can present with signs and symptoms similar to those seen with autoimmune epilepsy.

“A child who previously was doing well and then has an epileptic encephalopathy of unclear etiology, with an explosive onset and deterioration cognitively, could very well have an inflammatory-mediated disease process even...”

Figure. Sagittal and axial images illustrate Mayo Clinic’s use of morphometric MRI analysis for focal cortical dysplasia. A and D. Evidence of focal cortical dysplasia doesn’t appear in MRIs. B and E. Morphometric MRI analysis indicates focal cortical dysplasia at the crosshair. C and F. Resected areas are visible. Images courtesy of Benjamin Brinkmann, Ph.D.
when autoantibodies are not identified, “says Eric T. Payne, M.D., M.P.H., a pediatric epileptologist at Mayo Clinic’s campus in Minnesota.

Dr. Payne is working with Charles L. Howe, Ph.D., director of Mayo’s Translational Neuroimmunology Laboratory, to find biomarkers for these antibody-negative inflammatory seizures. Blood and cerebral spinal fluid samples from 20 patients have been analyzed.

“We’ve found that certain inflammatory systems, such as the cytokine interleukin-1 system, are significantly elevated in some of these samples,” Dr. Payne says. “It looks as though some of these children are unable to produce functional IL-1 antagonist. That’s very interesting because there are IL-1 antagonist therapies, including anakinra, available for use.”

In an article published in the December 2016 issue of *Annals of Neurology*, Dr. Payne and colleagues described the first reported use of anakinra to treat a child with superrefractory status epilepticus secondary to febrile infection-related epilepsy syndrome (FIRES). The patient, who presented at Mayo Clinic at age 32 months, has tolerated treatment with anakinra for more than 12 months. She experiences rare focal seizures but exceeds her pre-illness developmental and cognitive levels.

“Prior to this girl, every patient I had seen with FIRES either died or experienced devastating disabilities, including an inability to walk or talk,” Dr. Payne says. “Since our study was published, we get monthly emails from doctors asking us about similar patients they’ve seen. Some of the patient samples we’re analyzing have come from these other centers.”

Dr. Payne notes that inflammatory-mediated epilepsy ranges in severity, and the etiology likely involves a number of possible pathways. “FIRES itself might have a heterogeneous etiology,” he says. “Although the patient described in our published case report lacked the ability to form functional IL-1 antagonist, we don’t know that’s the case for everyone with FIRES.”

Dr. Payne hopes that further exploration yields information that can be incorporated into standard diagnosis and treatment of status epilepticus. “Why is it that one child might have a seizure that stops after two minutes, another kid’s seizures will stop with a bit of medicine and other kids go on to be refractory to medication? Maybe there’s an inflammatory process that we haven’t yet factored in,” he says.

*For more information*


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**Who’s New, What’s New**

Edward S. Ahn, M.D., recently joined the Department of Neurological Surgery at Mayo Clinic in Rochester, Minnesota. As a pediatric neurosurgeon, he specializes in syndromic and nonsyndromic craniofacial disorders, minimally invasive surgery for hydrocephalus and brain tumors, and vascular disorders, including arteriovenous malformations and moyamoya disease. Learn more about Dr. Ahn and Mayo Clinic’s approach to pediatric neurosurgery. [http://medprofvideos.mayoclinic.org/neurosurgery](http://medprofvideos.mayoclinic.org/neurosurgery)
Minimally Invasive Surgery for Craniosynostosis

Mayo Clinic has enhanced its capability to offer minimally invasive surgery for craniosynostosis, even for babies with multiple sutures or syndromic conditions. “The long-term results we’re seeing from minimally invasive surgery are as good if not better than from open surgery,” says Edward S. Ahn, M.D., a pediatric neurosurgeon at Mayo Clinic in Rochester, Minnesota. “We’re able to achieve the same results but with smaller incisions and shorter hospital stays for infants.

“The less invasive procedure can be performed early,” he adds. “With traditional open surgery, we’ve typically waited until at least 6 months of age before performing the procedure so that the baby will be larger and better able to tolerate major surgery. But the earlier surgery is performed, the better the results in general.”

For optimal results, minimally invasive surgery for craniosynostosis should be performed before age 3 months. “However, there are circumstances — such as if the abnormality is milder — that allow us to do minimally invasive surgery successfully even for slightly older children,” Dr. Ahn says.

Open craniosynostosis surgery takes several hours. “Afterward, we monitor the babies, usually in the ICU, for at least one night and then in the hospital for several more days because of the invasiveness of the procedure and the risk of blood loss,” Dr. Ahn says. “With the less invasive procedure, we’ve been happy to have the babies monitored just overnight in a regular unit and go home the next day.”

Single surgery for children with syndromic conditions

Mayo Clinic treats about 400 babies with craniosynostosis or other craniofacial disorders each year. Minimally invasive surgery can be effective even for children with syndromic craniosynostosis. Typically, those patients — who account for 8 to 24 percent of all children with craniosynostosis — have had open surgery. Among the limited number who have had an endoscopic procedure, many have needed subsequent calvarial remodeling.

But in a study published in the July 2017 issue of *Journal of Neurosurgery: Pediatrics*, Dr. Ahn and colleagues found that early endoscopic suturectomy followed by helmet therapy is sufficient to treat about half the children with syndromic craniosynostosis.

Figure. Illustration depicts the surgical technique for single incision endoscope-assisted sagittal strip craniectomy. The upper panel shows the elongated skull shape that results from sagittal synostosis. The lower panel shows the removal of the abnormal skull shape with the aid of a molding helmet.
“Although the chance of needing repeat surgery is higher in children with syndromic craniosynostosis than in babies with the non-syndromic condition, some can be treated with just that single endoscopic procedure,” Dr. Ahn says. “Even if subsequent open surgery is needed, the early endoscopic procedure might allow time for the brain and skull to grow and develop, delaying the need for open remodeling until the child is older and can better tolerate the procedure.”

To minimize blood loss during endoscopic craniosynostosis surgery, Dr. Ahn uses an ultrasonic device to remove bone. “That instrument minimizes bleeding from the bone,” he notes.

For babies with sagittal synostosis, Dr. Ahn has experience performing endoscopic suturectomy with a single incision (Figure). As described in the January 2017 issue of Child’s Nervous System, the novel technique decreases blood loss associated with the traditional two-incision procedure while allowing for excellent clinical outcomes. The average operative time for the procedures among cases studied was 87 minutes.


For more information

“Endoscopic incisions are small. But perfecting our technique to eliminate one of those incisions has made the endoscopic procedure even less invasive,” Dr. Ahn says.

Helmet therapy after endoscopic surgery has historically lasted as long as a year to 18 months. “We’re studying the optimal time for helmet use, to try to minimize it if possible,” Dr. Ahn says. “The need for helmet use is probably not as long as we’ve generally done. I would estimate that the ideal time for most of our patients is six to eight months. For all of our patients with craniosynostosis, we’re trying to be smarter and less invasive.”

Pediatric Care in Arizona and Florida

Mayo Clinic is collaborating with local hospitals to provide certain pediatric neurological and neurosurgical services at its campuses in Phoenix/Scottsdale, Arizona, and Jacksonville, Florida. The collaboration offers pediatric patients in those regions access to Mayo Clinic’s expertise in those specialties.

In Arizona, Mayo’s collaboration with Phoenix Children’s Hospital focuses on spinal surgery. Many of the cases involve complex reconstructive surgery for children and adolescents with scoliosis, or revision surgery for patients who had spinal operations elsewhere.

“We’re now able to care for these patients here, rather than referring them to another center,” says Jamal McClendon Jr., M.D., a neurosurgeon at Mayo’s campus in Arizona.

Decisions about whether a particular patient’s surgery is performed at Mayo or Phoenix Children’s Hospital depend mostly on the patient’s age. “If we see a 12-year-old who has a spinal deformity or progressive curvature of the spine, we often facilitate that patient’s surgery at Phoenix Children’s. But a 20-year-old who has had previous fusion or scoliosis surgery and requires more surgery might have that at Mayo Clinic,” Dr. McClendon says.

The collaboration continues with post-surgical care. “Our work with Phoenix Children’s allows for joint follow-up and a seamless transition between both institutions,” Dr. McClendon says. “We have created an environment where patients receive the level of dedication and care necessary to see their conditions through from childhood into the adult years.”

In Florida, Mayo’s collaboration with Wolfson Children’s Hospital offers a similar advantage. “We have a relationship so that children initially treated at Wolfson Children’s can transition their care to Mayo,” says Selby G. Chen, M.D., a neurosurgeon at Mayo’s campus in Florida.

The collaboration in Florida focuses on tumors, with neurosurgeons from Wolfson Children’s Hospital consulting Mayo Clinic specialists about cases. “We can provide multidisciplinary discussions with our radiation oncologists, medical oncologists and neurosurgeons,” Dr. Chen says. In addition, Mayo’s fourth-year residents at the Florida campus are able to do a four-month rotation in pediatric neurosurgery at Wolfson Children’s Hospital.

All Mayo Clinic campuses have subspecialized expertise, including spinal surgeons with training in complex spinal deformities. “For all our patients we offer a level of attention to detail that is difficult to find elsewhere,” Dr. McClendon says. “Although pediatric cases can be highly complex, we and our collaborating institutions have the resources to treat them.”

Research Highlights in Neurology and Neurosurgery

Updated Diagnostic Recommendations for Niemann-Pick Disease
Niemann-Pick disease type C (NP-C) is a rare neurovisceral lysosomal disorder that may be more prevalent than previously thought. An international committee led by a Mayo Clinic neurologist has updated recommendations for detecting and diagnosing the disease. Previous recommendations focused on identifying individual patients with a high clinical suspicion of NP-C. Utilizing recent advances in NP-C screening and diagnostic technologies, most diagnoses can now be confirmed by combination biomarker and genetic analysis techniques. The updated recommendations include those technologies as first-line diagnostic techniques. Filipin staining may facilitate diagnosis in uncertain cases. In addition, the new recommendations update and simplify the NP-C diagnostic algorithm. These updated clinical guidelines provide recommendations for psychiatrists, neuro-ophtalmologists and radiologists, as well as recommendations on screening within specific cohorts of at-risk patients. Currently, diagnosis of NP-C is often delayed. The committee issuing the new guidelines notes that all undiagnosed patients with any manifestation of NP-C should be referred to regional or national centers specializing in inherited metabolic disorders and that facilitating the identification of patients may ultimately improve outcomes. (Patterson MC, et al. Recommendations for the detection and diagnosis of Niemann-Pick disease type C: An update. Neurology: Clinical Practice. 2017;7:499.)

Cognitive and Social Outcomes of Epileptic Encephalopathies
Epileptic encephalopathies are disorders in which seizures of frequent interictal discharges exacerbate neurocognitive dysfunction beyond what would be expected on the basis of underlying etiology. However, many underlying causes of epileptic encephalopathy also result in neurocognitive deficits, and it can be challenging to discern to what extent these deficits can be improved with better seizure control. In addition, as seizures in these conditions are typically refractory, children are often exposed to high doses of multiple anti-epileptic drugs, further exacerbating these comorbidities. In a review, Mayo Clinic pediatric epileptologists summarize the neurocognitive and social outcomes in children with various epileptic encephalopathies. These seizure conditions are often associated with intellectual disability, learning problems, attention-deficit/hyperactivity disorder and autism spectrum disorder. Among other points, the researchers note the following:
- Intellectual disability and learning disorders should be recognized early, preferably through formal neuropsychometric testing, to allow for adequate academic support.
- Attention-deficit/hyperactivity disorder is underrecognized in children with epilepsy, and there is often hesitancy to treat these children with psychostimulants — although there is no evidence to support seizure exacerbation due to these agents.
- Optimizing seizure control in a timely manner is essential to maximize neurocognitive outcome. However, anti-seizure medications can be associated with sedation and cognitive slowing, which may worsen the encephalopathy. It is essential to strike a balance between controlling seizures and overmedicating.
- Proper identification of epilepsy syndrome is crucial, as some epileptic encephalopathies can be exacerbated by specific medications. (Nickels KC, et al. Cognitive and social outcomes of epileptic encephalopathies. Seminars in Pediatric Neurology. 2018;24:264.)

Investigating Congenital Myasthenic Syndromes
Congenital myasthenic syndromes (CMSs) are heterogeneous disorders in which one or more specific mechanisms impair the safety margin of neuromuscular transmission. Since the advent of next-generation sequencing methods, the discovery of novel CMS targets and phenotypes has proceeded at an accelerating rate. In a review, Mayo Clinic researchers describe the current classifications of CMSs. The 358 CMS kinships investigated at Mayo Clinic to date are grouped according to:
- Anatomic location of the disease protein
- Defects in glycosylation of proteins required for neuromuscular transmission
- Defects in the development and maintenance of the neuromuscular junction
- Miscellaneous other syndromes that compromise the safety margin of neuromuscular transmission
The researchers also describe their findings in five of the CMS targets identified at Mayo Clinic in the past five years: LRP4-related protein 4 myasthenia, PREPL deficiency-related myasthenia, presynaptic exocytosis-related myasthenias, SNAP25B myasthenia and Munc13-1 myasthenia. Increased understanding of the diverse targets and molecular mechanisms of CMSs has come from structural, electrophysiologic and cytochemical investigations of the neuromuscular junctions of affected patients and from analyzing the effects of the mutant proteins engineered into heterologous cells. The researchers predict that additional CMSs await discovery. (Engel AG, et al. The unfolding landscape of the congenital myasthenic syndromes. Annals of the New York Academy of Sciences. 2018;1413:25.)

To read more about Mayo Clinic neurosciences research and patient care, visit http://www.mayoclinic.org/medical-professionals.
Expedited Patient Referrals to Mayo Clinic Departments of Neurology and Neurologic Surgery

While Mayo Clinic welcomes appointment requests for all neurologic and neurosurgical conditions, patients with the following conditions are offered expedited appointments:

1. Cerebral aneurysms
2. Cerebral or spinal arteriovenous malformations
3. Brain, spinal cord or peripheral nerve tumors
4. Epilepsy with indications for surgery
5. Carotid disease