Finding New Treatments for High-Grade Pediatric Brain Tumors

Children diagnosed with high-grade brain tumors, including high-grade glioma and medulloblastoma, historically have fared poorly. Over the past 20 years, the prognosis has improved somewhat, particularly for children with medulloblastoma. Despite enhanced treatments for diseases such as childhood leukemia, brain and central nervous system tumors now represent the most common cause of cancer-related death in children. Unfortunately, for children with diffuse intrinsic pontine glioma (DIPG), atypical teratoid rhabdoid tumor (ATRT) and primitive neuroectodermal tumor, the outlook remains bleak.

Researchers at Mayo Clinic in Rochester, Minnesota, are making progress in the laboratory, possibly finding novel ways to treat high-grade gliomas and other brain tumors in children. Over the past decade new information about the molecular diversity of these tumors has emerged, pointing the way toward targeted therapies tailored to tumor subtypes and highlighting differences between pediatric and adult brain tumors. Pediatric high-grade gliomas are often treated like their adult counterparts, despite this new knowledge that pediatric and adult high-grade gliomas represent different biological diseases.

“For example, midline tumors such as DIPG, which occur in the brainstem, have a very specific histone mutation that is different from the histone mutation found in pediatric hemispheric high-grade gliomas, while adult high-grade gliomas do not have these genetic mutations at all,” says David J. Daniels, M.D., Ph.D., a pediatric neurosurgeon at Mayo Clinic’s campus in Minnesota. “Pediatric and adult brain cancers are very different. An adult with a diagnosis of a grade IV glioma has a 14-month life expectancy. We have some long-term survivors of pediatric high-grade gliomas, although children with DIPG still have a poor prognosis similar to adult glioblastoma multiforme.”

“There is plenty of room for hopefulness in pediatric brain cancer,” adds Gesina F. Keating, M.D., a pediatric neuro-oncologist at Mayo Clinic’s campus in Minnesota. “The news that a child has a high-grade brain tumor is always difficult. But I can tell the family that they are at a top medical center with a team of knowledgeable physicians who will see them today and outline a treatment plan.”

Research and compassionate care

At Mayo Clinic, patient consent is sought for obtaining research samples from every biopsy or resection of a brain tumor, including DIPG, medulloblastoma and ATRT. In his research laboratory, Dr. Daniels grows these tumors in cell culture and in mouse xenograft models; he has succeeded in developing more than 20 cell lines or xenografts, including numerous DIPG and medulloblastoma lines.
Groundbreaking research by several groups in 2012 independently discovered the histone mutations that subsequently were shown to drive high-grade gliomas. DIPG tumors, for example, universally harbor an H3K27M histone mutation or equivalent. DIPG is of particular interest in Dr. Daniels’ lab because it is a devastating disease, with a life expectancy after diagnosis of nine to 12 months.

Dr. Daniels’ laboratory is using several different ways to identify therapeutic vulnerabilities in tumors with the H3K27M mutation. One approach is to reverse the effects that this histone mutation has on the epigenome. Another is to screen libraries of chemotherapeutics approved by the Food and Drug Administration, or compounds that are already in clinical testing, and identify compounds that selectively kill tumor cells with this mutation (Figure 1). The researchers hope that testing clinically relevant compounds will result in identifying compounds that can be fast-tracked for approved use in patients.

“We're homing in on some very specific molecular pathways that are critical for tumors with the H3K27M mutation. Knocking out these pathways kills these tumors in vitro,” Dr. Daniels says. Animal models are in development, and Dr. Daniels hopes eventually to move to clinical trials with inhibitors of these pathways.

Alongside this research, Mayo Clinic offers a team approach to clinical care. Expedited referrals and next-day evaluation are available for patients with brain tumors.

“We are able to gather everyone in one room — neurologist, oncologist, surgeon — to discuss the patient’s needs,” Dr. Keating says. “We have nurses, radiation technicians and social workers who provide ongoing support. Our patients feel well looked after.”

After initial treatment, patients have ongoing evaluations through childhood and beyond. “We work with whatever long-term issues arise, whether it’s double vision or diabetes insipidus or sleep disorders,” Dr. Keating says. “Continuity of care is so important. We can seamlessly transition our patients into care from endocrinologists or neuro-ophthalmologists or whatever they need.”

**Medulloblastoma progress**

In addition to his research on glioma treatments, Dr. Daniels is screening medications for effectiveness in treating the molecularly defined subtypes of medulloblastoma. “As clinicians, we are rewriting the way we treat medulloblastoma,” he says. “We used to divide the disease into average risk and high risk. Now we have low, average and high risk. Furthermore, at least four molecular subgroups of medulloblastoma have been identified, including Wnt, SHH, Group 3 and Group 4. We know that children with the Wnt subtype tend to do well. Instead of pounding them with high-dose chemotherapy and radiation and even stem cell transplants, we can back off on their treatment.” Dr. Daniels’ lab is also screening for new drug targets for the Group 3 and 4 tumors, which can be more challenging to treat.

For children with medulloblastoma, proton beam therapy is a new treatment option at Mayo Clinic’s campus in Minnesota. Proton beam therapy targets tumors more precisely than conventional radiation therapy, limiting damage to surrounding tissue (Figure 2).

“Proton beam therapy is yet another step forward,” Dr. Keating says. “The outlook for kids being treated with medulloblastoma is better now than it was even five years ago. Among the 80 percent who survive to five years after diagnosis, most will probably survive another 20 years and beyond.”

To achieve the best results, it is essential that treatment of tumors be tailored to the needs of the developing pediatric nervous system. Historically, about 20 percent of children who undergo medulloblastoma resection developed cerebellar mutism syndrome (CMS), with symptoms including mutism and behavioral and mood changes such as irritability, frequently accompanied by additional neurological signs such as ataxia, flaccid hemiparesis, feeding difficulties and incontinence. The occurrence of CMS can reduce the likelihood of independence as a young adult. Although the cause of CMS isn’t fully understood, it might be linked to surgical approaches that can damage a developing brain.

At Mayo Clinic, preventing this devastating complication is of highest importance. “Pediatric neurosurgeons use several techniques to minimize the occurrence of CMS, such as avoiding the vermis, not violating the cerebral peduncles or deep nuclei,” Dr. Daniels says. “As a large, tertiary center, Mayo Clinic understands how to manage these risks. Over the last five years, our rate of CMS is under 5 percent, and we are embarking on research to further understand this complication.”

Dr. Keating notes that even a teenager with the physical stature of an adult lacks a fully...
developed brain. “Medulloblastoma is a pediatric disease, and it’s important to have a pediatric neurosurgeon,” she says. “We want our patients to be adults who can live independently.

“For all of our pediatric patients with high-grade brain tumors, we are committed to a team approach that combines the best of clinical care and research,” she adds. “Going from lab bench to bedside and back is the only way we can make progress.”

**Clinical Trials of Cannabidiol for Epilepsy**

Dravet syndrome and Lennox-Gastaut syndrome (LGS) are severe childhood-onset epilepsies that are generally refractory to medication. Dravet syndrome begins in the first 18 months of life; LGS is usually diagnosed in children ages 2 to 8. Despite trying multiple medications, children with these conditions often continue to have life-threatening seizures.

Mayo Clinic in Rochester, Minnesota, is participating in multicenter, multinational clinical trials of cannabidiol (CBD) treatment for children with Dravet syndrome and LGS. The double-blind, placebo-controlled trials are the first such studies of CBD in the United States.

“These are very important studies because we have no data on the use of CBD in carefully controlled trial designs. To date, we’ve only had anecdotal evidence in the popular media,” says Elaine C. Wirrell, M.D., a consultant in Pediatric Neurology at Mayo Clinic’s campus in Minnesota.

The medication, Epidiolex, is a pharmacy-grade product composed almost entirely of CBD with minimal tetrahydrocannabinol (THC). “It’s very carefully tested — different from what’s available in medical marijuana shops,” Dr. Wirrell notes.

**Preliminary results**

Children in the studies have been placed on the medication or a placebo for 12 weeks, with both parents and physicians blinded as to whether the child is receiving active or placebo drug. After the initial 12 weeks, all children are given the opportunity to take the active medication, with parents and physicians remaining blinded to what a child received during the study period. At Mayo Clinic, 15 children and two adults with LGS and seven children with Dravet syndrome completed the double-blind, placebo-controlled portion of the trial and are now in the open-label portion.

Multicenter data from the Dravet syndrome study found that seizures were reduced by 39 percent in children treated with CBD versus only 16 percent in the placebo group. “That’s a modest difference, but statistically significant,” Dr. Wirrell says. “CBD is not a cure, but it could potentially be beneficial for children with Dravet syndrome” (Figure).

Multicenter data from the LGS trial is still being analyzed. “Based on what we’re seeing, I suspect CBD could be even more effective for patients with LGS,” Dr. Wirrell says.

Clobazam dosage often needs to be reduced when CBD is added. “But otherwise, CBD doesn’t react with a lot of other medications. It’s pretty well-tolerated, although some of the kids at higher doses can get a little bit of sleepiness, and we’ve had to reduce the dose for some kids who had loose stools,” Dr. Wirrell says.

If approved by the Food and Drug Administration, Epidiolex could provide a treatment option for children with devastating disease. “Kids with Dravet syndrome have recurring bouts of status epilepticus,” Dr. Wirrell says. “In

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**Figure.** On the left, electroencephalography (EEG) of a patient in the cannabidiol (CBD) study shows frequent spikes indicating seizure activity before beginning treatment with CBD. On the right, EEG in the same patient shows no evident spikes after beginning treatment with CBD.
addition, the frequency of seizures takes a toll on children’s development. As time goes on, it becomes clear that these kids aren’t keeping up with their peers, and many have severe behavioral issues. These aren’t kids who respond to surgery, so we don’t have that option for them.

“We need to do safe and scientific studies of CBD, and get good evidence for both safety and efficacy,” she adds. “That’s what families deserve.”

Elucidating Lysosomal Diseases

Lysosomal diseases comprise a family of inherited metabolic disorders that generally involve progressive neurological manifestations and that primarily affect children. Although individually rare, collectively the diseases are not uncommon. Symptoms vary greatly among the specific disorders, and can be mild or severe. Neurological symptoms can include developmental delay, movement disorders and seizures. Other symptoms might affect the orthopedic, gastrointestinal, dermatological, cardiac and ophthalmologic systems. Although most of these diseases were described in the 20th century, their natural histories are not yet fully understood.

Through the generosity of a benefactor, Mayo Clinic in Rochester, Minnesota, is launching a research initiative aimed at learning more about lysosomal diseases and possible new treatments. A uniform program is being put in place to obtain consent and biosamples from every patient seen at Mayo Clinic with a suspected lysosomal disease. Through gaining more genetic samples, Mayo Clinic researchers expect to learn more about the prognosis for patients with specific lysosomal diseases and to enhance the design of future studies.

“We now have an opportunity to build on our strengths and to more readily offer our patients the opportunity to be continuing partners in research,” says Marc C. Patterson, M.D., chair of Child and Adolescent Neurology at Mayo Clinic’s campus in Minnesota. “We’re at a very exciting time for lysosomal disorders.”

Breaking the brick wall

In collaboration with the National Institutes of Health (NIH), Mayo Clinic has been at the forefront of research into the genetics of lysosomal storage diseases as well as efforts to improve patient care. Dr. Patterson has researched these disorders for 25 years, and was part of an NIH team that in 1997 identified a genetic mutation that causes Niemann-Pick disease type C (NPC). Mayo Clinic researchers currently are conducting next-generation sequencing of the genes of people with a lysosomal disease.

“With the power of next-generation sequencing, we can often get to a diagnosis more rapidly. We have one of the world’s best biochemical genetics labs here to support our clinical diagnoses and investigate the significance of mutations,” Dr. Patterson says. “One of the challenges is that next-generation sequencing is finding many more variants of undetermined significance. This is often a barrier to diagnosis.”

Figure 1. MRI scans of a teenage girl who presented with severe, abrupt behavioral changes and who subsequently had a diagnosis of metachromatic leukodystrophy. A. and B. Axial images at the level of the eyes and above the eyes show bright (white) signal bilaterally, which is typical of a lysosomal disorder. C. Axial image of the brain high in the skull shows — in addition to bright signal bilaterally — faint horizontal dark lines known as tigroid appearance, which is also typical of a lysosomal disorder.
sometimes a brick wall that we come up against.”

Mayo Clinic scientists are using clustered regularly interspaced short palindromic repeats (CRISPR) technology to make targeted mutations in flies. “That allows us to have a very rapid turn-around and see if a mutation of undetermined significance will produce a phenotype in that animal model,” Dr. Patterson says.

The current lack of data on lysosomal diseases inhibits studies of potential treatments. “It’s difficult for us to design studies with meaningful outcomes,” Dr. Patterson says. “Natural history and treatment go hand in hand.”

Because lysosomal diseases typically progress over decades, researchers must go beyond identifying clinical features of the disorders and find biochemical, imaging or electrical biomarkers that can serve as study endpoints. Mayo Clinic’s multidisciplinary approach promotes collaboration among neurologists, medical geneticists and other specialists who treat people with lysosomal diseases.

“One of our important collaborations will be with our radiologists,” Dr. Patterson says. “They have developed exciting techniques such as elastography, which will allow us to determine if lysosomal storage stiffens the brain.”

Improving diagnosis and treatment

The mainstay treatment in lysosomal disorders is enzyme-replacement therapy, which doesn’t enter the nervous system and thus can improve systemic manifestations of the diseases but not underlying neurological disease. As a result of the lysosomal initiative, Mayo Clinic will enhance its efforts to find small molecules that can be active in the nervous system to prevent accumulation of substrate in lysosomes.

A diagnosis of lysosomal disease can be overlooked, particularly in teenagers and young adults where the symptoms might be subtle. “As with many genetic disorders, lysosomal disease has with very rare exceptions been recognized first in its really severe childhood forms,” Dr. Patterson says. “But there’s no question there’s a hidden pool of patients who have been diagnosed, for example, with atypical early-onset dementias or who have psychiatric presentations that are treatment resistant.”

He cites a patient who, as a teenage girl in an old order religious community, abruptly refused to do chores and exhibited other behavioral changes (Figure 1). “She had a metachromatic leukodystrophy, which presents as schizophrenia,” Dr. Patterson says.

Clues to diagnosis of lysosomal disorder include:
• Progressive cognitive problems, such as developmental regression in a child or dementia in a young adult
• Enlargement of the liver or spleen
• Characteristic facial features, particularly in people with a mucopolysaccharidosis (Figure 2)
• Cataracts, sensitivity to light or abnormal eye movements
• Hearing problems
• Myoclonus, dystonia or seizures

“If you have an unexplained constellation of neurological findings with or without systemic changes in the skin, viscera, heart or bones, think about a lysosomal disease as a possibility,” Dr. Patterson says. “At Mayo Clinic we have a tremendous opportunity, thanks to the generosity of our benefactor, to develop new approaches to diagnosing and treating lysosomal diseases, and to create awareness.”

Complex Craniocervical Junction Anomalies

The musculoskeletal configuration of the craniocervical junction is highly complex. Congenital or acquired anomalies in the interface between the skull and cervical spine can not only cause headache, neck pain and joint instability but also lead to neurological deficits that affect swallowing and breathing, and cause weakness and spasticity.

Neurosurgeons at Mayo Clinic in Rochester, Minnesota, have experience treating these complex cases in children as young as infants. A number of these cases involve children who have developed new problems after previous surgeries. A sizable number also involve children with genetic syndromes that correlate with atlantoaxial and occipital cervical instability, such as Down syndrome. Other cases arise from high-energy trauma, generally falls or motor vehicle accidents.

“Because of the complex anatomy in the craniocervical junction, children can present with a variety of physical symptoms and findings,” says Nicholas M. Wetjen, M.D., a pediatric neurosurgeon at Mayo Clinic’s campus in Minnesota. “Our primary goal is to reverse or prevent any neurological problems by decompressing the brainstem and spinal cord while realigning the bones on the spine and stabilizing the joints.”

Mayo Clinic’s interdisciplinary approach ensures that children with craniocervical junction anomalies see not only a pediatric neurosurgeon but also specialists in neurology, otolaryngology, sleep medicine and occupational therapy, as needed. “Our patients have a comprehensive...”

Figure 2. Photograph of a boy with mucopolysaccharidosis shows full lips, puffy tissues around the eyes and use of a hearing aid — all suggestive of the diagnosis.
evaluation within a relatively short time frame, with very good communication between all the specialists,” Dr. Wetjen says.

3-D printing to model anatomy
One of the challenges of treating craniocervical junction anomalies in children is obtaining clear imaging to guide surgery. At Mayo Clinic, models of a patient’s individual anatomy are generated by 3-D printers (Figure), based on extensive imaging of the patient through MRIs and CT scans.

“It can be difficult to make sense of this complex anatomy just on serial imaging or even with 3-D reconstruction of the imaging on a video screen,” Dr. Wetjen says. “But printing a 3-D model helps us grasp the relationships within the anatomy, to see the limits on where we can decompress, and the size of the bones where we might want to insert instrumentation.”

The 3-D-printed models, developed by Mayo Clinic radiologists and neurologists, provide essential information for treating young patients. “We don’t have much biomechanical data of this region of the spine for kids,” Dr. Wetjen notes. “We don’t have cadaver studies of how children’s bones move with one another.”

Another challenge is balancing the risks and benefits of surgery in very young patients. “If a baby has a complex craniocervical junction anomaly with pending severe neurological problems, we might do surgery to get decompression and immobilization,” Dr. Wetjen says. “Sometimes, custom-made braces can be used to hold the cranium and spine in position. But if the baby is not really active or mobile yet and the child is asymptomatic, we might wait to see how the deformity changes with bone growth.”

The limited mobility that can result from fusing bones is another consideration. “We’d like to preserve neck rotation, flexion and extension,” Dr. Wetjen says. “The risks of treatment have to be weighed against the risk of instability.”

Research at Mayo Clinic is shedding further light on the most appropriate surgical approaches to the pediatric craniocervical junction. In a study published in the April 2016 issue of *Journal of Neurosurgery: Spine*, Mayo Clinic researchers found that the relationship between C2 and the hard palate varies significantly with sex and age. Specifically, the distance from the base of C2 to the hard palate was found to be shorter in females than in males, and shorter in the early and late decades of life compared with the middle decades. The findings have relevance in determining optimal surgical approaches to the anterior craniocervical junction.

“For some kids with congenital anomalies that push the anterior spine into the brainstem, we’re not able to decompress or to use traction to achieve realignment. We then consider approaching through the nose or mouth to remove the portion of bone that is pressing on the spinal cord. The position of the hard palate relative to C2 helps determine whether we have enough space for that approach,” Dr. Wetjen says.

“Balancing the risks involved in treating craniocervical junction anomalies can be very complicated,” he adds. “The anatomy in this area is unique in every patient.”

For more information
Research in Childhood Epilepsy

Research in Pediatric Sleep Medicine

Research in Multiple Sclerosis

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Research in Pediatric Headaches
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

Education 2016-2017 Neurology and Neurologic Surgery Continuing Medical Education Programs

2016 courses

**September-October**
- Emergency Neurological Life Support (ENLS) 2016
  - Sept. 28, 2016
  - The Ritz-Carton, Amelia Island, Fla.
- Mayo Clinic 8th Annual Stroke and Cerebrovascular Disease Review 2016
  - Sept. 29-Oct. 1, 2016
  - The Ritz-Carton, Amelia Island, Fla.
- Transcranial Doppler Hands-on Workshop
  - Oct. 1, 2016
  - The Ritz-Carton, Amelia Island, Fla.
- Microvascular Surgery Skills Training
  - Oct. 3-7, 2016
  - Mayo Clinic, Rochester, Minn.

**November**
- Epilepsy and EEG in Clinical Practice 2016
  - Nov. 10-12, 2016
  - Hard Rock Hotel Universal, Orlando, Fla.
- Parkinson’s Disease and Other Movement Disorders Conference — 2016
  - Nov. 11-12, 2016
  - Mayo Clinic Education Center, Phoenix

**December**
- Practical Clinical Case-Oriented Neuro-Ophthalmology 2016
  - Dec. 8-10, 2016
  - The Venetian, Las Vegas

2017 courses

**January**
- Mayo Clinic Radiation Oncology: Current Practice and Future Direction 2017
  - Jan. 9-13, 2017
  - The Fairmont Kea Lani, Maui, Hawaii

11th Mayo Clinic Medical and Surgical Spine Course: Comprehensive Surgical Spine Update 2017
- Jan. 13-14, 2017
- Mayo Clinic Education Center, Phoenix

**January-February**
- Electromyography (EMG), Electroencephalography (EEG), and Neurophysiology in Clinical Practice 2017
  - Jan. 29-Feb. 4, 2017
  - The Ritz-Carton, Amelia Island, Fla.

**February**
- Multiple Sclerosis and Autoimmune Neurology Update 2017
  - Feb. 10-11, 2017
  - Mayo Clinic Education Center, Phoenix

**March**
- Healing & Re-engineering Minds and Bodies: Ethical Challenges in Neurology, Disabilities and Technology Assessment 2017
  - March 29-31, 2017
  - Mayo Clinic, Rochester, Minn.

**April**
- Advances in Brachial Plexus Reconstruction: A Surgical Skills Course 2017
  - April 13-15, 2017
  - Mayo Clinic, Rochester, Minn.

Contact Us
Mayo Clinic welcomes inquiries and referrals, and a request to a specific physician is not required to refer a patient.

**Phoenix/Scottsdale, Arizona**
- 866-629-6362 (toll-free)

**Jacksonville, Florida**
- 800-634-1417 (toll-free)

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Resources
MayoClinic.org/medicalprofs
Clinical trials, CME, Grand Rounds, scientific videos and online referrals

Explored 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
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