Craniosynostosis is a common congenital condition, occurring in 1 in 2,500 births. Most of these cases involve the fusion of a single skull suture. Complex or syndromic craniosynostosis involves the fusion of multiple sutures. Although neurological damage can occur in severe cases, most children can have normal cognitive development and achieve good cosmetic results after surgery. Early diagnosis and treatment are key.

At Mayo Clinic in Rochester, Minn., specialists in the Cleft and Craniofacial Clinic treat craniosynostosis ranging from severe syndromes to simple fusions. Every child treated for craniosynostosis is seen by a pediatric neurosurgeon, plastic surgeon and medical geneticist. For patients with syn-
dromic craniosynostosis, oral surgeons, otorhinolaryngologic surgeons, orthodontists, speech pathologists, social workers and psychologists may be consulted.

“We have a very large and comprehensive craniofacial team,” says Nicholas M. Wetjen, M.D., a pediatric neurosurgeon at Mayo in Minnesota. “Not every patient needs all parts of the clinic, but all parts are available.”

Advantages of early referral

Most of the cases seen at Mayo are sagittal craniosynostosis, the most prevalent type. Patients are generally referred by pediatricians after a well-child visit. Although there is no upper age limit for referral, the optimal time is between 1 and 2 months of age. Up to age 6 months, patients with all types of single-suture craniosynostosis — sagittal, metopic, coronal and lambdoid — may be candidates for endoscopic surgery (Figure 3). After that, however, open surgery is generally required.

“Early diagnosis and treatment facilitate the brain’s normal growth and reshaping of the head into the appropriate configuration,” Dr. Wetjen says. “With referral we also can offer the option of endoscopic surgery and make sure patients are receiving care tailored to their needs.”

Both endoscopic and open procedures generally produce very good cosmetic results with low risk of complications. However, compared with an open procedure, endoscopic surgery has a lower rate of complications, requires only a one-night hospital stay and has a patient-transfusion rate of just 10 percent. After endoscopic surgery, children must wear a series of two to three helmets for up to a year. “Each helmet has a significant cost, but the overall cost of endoscopic surgery is still less than open surgery,” Dr. Wetjen notes.

Open surgery lasts two to three hours and requires a three- or four-day hospital stay. Transfusion also is necessary in all open cases, although no helmet is required afterward. “In open surgery, we fix the skull in position with plates and screws that are absorbable. It’s a one-time procedure that requires less follow-up than endoscopic surgery,” Dr. Wetjen says.

For parents whose children qualify for either endoscopic or open surgery, Mayo specialists outline the pros and cons and let the parents decide. “We try to present a balanced view because when the patient presents at a young age, either endoscopic or open surgery can be appropriate,” Dr. Wetjen says.

Virtual surgical planning

Mayo is one of the few centers in the world that offers virtual surgical planning for treatment of craniosynostosis (Figure 1). In virtual surgical planning, high-definition 3-D CT scans of the patient’s skull are sent to a device manufacturer. Engineers at the company consult via Web conference with Dr. Wetjen and Samir Mardini, M.D., a plastic surgeon in Mayo’s Cleft and Craniofacial Clinic. During the meeting the CT data are used to construct a computer-simulated, individualized surgical plan. Based on that virtual surgical plan, patient-specific templates are constructed to guide the Mayo surgeons during the procedure.

“In the past, there has been a standard surgical procedure for sagittal craniosynostosis. These templates allow us to customize the procedure to the individual patient, with a high degree of detail,” Dr. Wetjen says.

Complex or syndromic craniosynostosis

Only 6 percent of craniosynostosis cases involve multiple sutures or are related to a hereditary syndrome. As a major pediatric neurology center, Mayo has experience with these complex and syndromic cases. Multiple surgeries are often required to correct the patient’s head shape.

Treatment for complex or syndromic cranio-
synostosis often involves the use of a distractor—a device placed in the skull for a period of three to four months. The distractor is widened a millimeter a day to separate the skull bones. Over time, new bone grows across the gap. Cosmetic results are generally very good (Figure 2).

Ongoing research
Considerable progress has been made in understanding the genetic causes of syndromic craniosynostosis. But the etiology of about 85 percent of nonsyndromic cases remains unknown. Mayo researchers are analyzing bone removed during craniosynostosis surgery in a genome-wide search for novel genes for the condition.

In a study published in the Feb. 22, 2013, issue of *The Journal of Biological Chemistry*, Mayo researchers showed that the molecular and functional interplay between the RUNX2 and AXIN2 genes controls the rate of cranial suture closure in laboratory animals. The research identifies a key mechanistic pathway for regulating bone development within the skull and thus suggests a potential means of preventing premature cranial suture closure.

Other research at Mayo involves the use of MRI rather than CT scan for diagnosis and treatment of craniosynostosis, strategies for minimizing blood transfusion during surgery, and the use of magnetic resonance elastography as a noninvasive way to measure intracranial pressure.

Dr. Wetjen stresses that the risk of intracranial pressure from simple craniosynostosis is small. “As long as the suture and head shape are fixed, the child’s IQ is likely to end up being just like any other child’s,” he says. As Dr. Wetjen sometimes tells parents, “You can have craniosynostosis and grow up to be a brain surgeon.”

For more information

Figure 3. Scaphocephaly is a relatively common form of craniosynostosis. Premature sagittal suture closure restricts growth in a perpendicular plane, resulting in a narrowing of the head. Compensatory growth occurs forward at the coronal suture and backward at the lambdoid suture, elongating the head. Scaphocephaly can be repaired endoscopically, as can anterior plagiocephaly and trigonocephaly.
Adrenoleukodystrophy: Mayo’s Multidisciplinary Approach

X-linked adrenoleukodystrophy (ALD) is the most common peroxisomal disorder, affecting about 1 in 20,000 males. In ALD, the body’s inability to break down very long-chain fatty acids results in the accumulation of these substances in the myelin sheath. Almost half of males with X-linked ALD develop the cerebral form of the disease, generally during childhood. Progressive white matter destruction occurs with progressive loss of developmental skills as well as spasticity and blindness.

Bone marrow transplantation can arrest progression of the cerebral form of ALD. But the procedure has significant risk and must be performed early in the disease course. New protocols for diagnosis and treatment of children with ALD, aimed at reducing side effects and improving outcomes, are available at Mayo Clinic in Rochester, Minn.

“We hope to halt the condition before the child develops significant neurological problems,” says Deborah L. Renaud, M.D., co-director of the Mayo Clinic Peroxisomal Disorders Program. “We’ve learned that if the bone marrow transplant is done after it is apparent the child has the cerebral form of ALD but before neurological symptoms develop, we can arrest those symptoms. Within three to six months, we usually see a stabilization of the white matter on MRI.”

Unfortunately, many of the children seen at Mayo have progressed too far for transplant eligibility. “These little boys present because of findings detected on an MRI or a CT scan that was done for another reason, or because the boys are experiencing symptoms,” Dr. Renaud says. “These children may present in elementary school with learning difficulties and symptoms similar to attention deficit disorder. But they’ve never had symptoms of ADD before; they were not hyperactive toddlers.”

Early diagnosis and treatment

The Mayo Clinic Peroxisomal Disorders Program offers multidisciplinary care and disease-specific stem cell transplantation for people with X-linked ALD. Patients include presymptomatic boys, boys and men with the cerebral form of ALD (leukodystrophy), and men and women with the adult-onset form of ALD (adrenomyeloneuropathy, or AMN) as well as patients with only adrenal insufficiency.

Although ALD is linked to mutations on the ABCD1 gene, the disease can present differently within the same family. “The most severe form tends to affect males between 3 and 10 years of age,” Dr. Renaud notes.

At Mayo, children of family members with ALD are followed prospectively for signs of neurological symptoms. Presymptomatic boys are evaluated every six months with high-resolution 3 tesla MRI and spectroscopy.

“We believe the MRI may change at least six months before the child has symptoms,” Dr. Renaud says. “With this protocol, we may be able to catch any changes in the MRI sooner, and have a better chance of getting the stem cell transplant done in a timely fashion.”

Detailed neuropsychological testing to detect early changes in attention and learning also is done, along with screening for adrenal insufficiency. Symptoms related to adrenal insufficiency occur separately from neurological symptoms and may appear as early as age 3 months. “Adrenal insufficiency can be life-threatening, especially in children who can’t tell you how badly they feel,” Dr. Renaud says.

Aida N. Lteif, M.D., chair of Pediatric Endocrinology and Metabolism, is an expert in adrenal insufficiency and a critical part of Mayo’s multidisciplinary treatment team. Other clinicians include neurologists, neuroradiologists, ophthalmologists, neuropsychologists, endocrinologists and bone marrow transplant specialists. Patients generally can see all of these specialists as needed in a single visit over several days.

Stem cell transplantation

Children who qualify for stem cell transplantation are treated according to a protocol developed by Dr. Renaud and Shakila P. Khan, M.D., co-director of the Peroxisomal Disorders Program and Mayo’s principal investigator for the multi-institutional Pediatric Blood and Marrow Transplant Consortium. Dr. Renaud and Dr. Khan did an extensive literature review of bone marrow transplant protocols, many of which were designed to treat leukemia. “But in treating ALD, we’re not killing a cancer. We’re just trying to inject cells that produce the ALD protein,” Dr. Renaud says.

The new Mayo protocol is reduced intensity, eliminating components that aren’t necessary for treating ALD and that pose risks to children. Although bone marrow transplant carries risk at any age, it is particularly risky in young children. Morbidities include infection, bleeding, anemia
Niemann-Pick disease type C (NPC) is a rare, inherited neurodegenerative disorder caused by an intracellular lipid-trafficking defect. Although the disease can present at any age — from before birth to late middle age — about half of those affected have signs and symptoms before age 10. While NPC is a progressive disease, early diagnosis and treatment can improve quality and duration of life.

Mayo Clinic in Rochester, Minn., is one of the few centers in the world with experience diagnosing and treating patients with NPC. In collaboration with the National Institutes of Health (NIH), Mayo also is at the forefront of research into the genetics of the disease as well as efforts to improve patient care.

"Even though we don’t have a disease-modifying therapy, quality of life and survival have improved for these patients over the last quarter century," says Marc C. Patterson, M.D., chair of Child and Adolescent Neurology at Mayo in Minnesota. "There is no known cure, but we can treat patients. The sooner we are able to diagnose and start treatment, the better the outcome."

NPC results from mutations in the NPC1 or NPC2 genes, which encode proteins involved in the movement of lipids within cells. The malfunctioning proteins cause lipids to accumulate in cells — free cholesterol in peripheral tissues (Figure) and gangliosides in neurons.

The disease can present in utero, with ultrasound examination detecting an enlarged liver and spleen and fluid in the fetal abdomen. Infants may present with profound jaundice or liver failure. These early cases are often fatal.

Beyond infancy, NPC is predominantly a neurological disease. Younger children may present with developmental delays and low muscle tone. Older children are more likely to have problems with gait, balance, coordination, dystonia, spasticity, speech, swallowing and cognitive impairment, all of which worsen over time. Teenagers and adults often present with those problems as well as psychiatric symptoms or early-onset dementia.

**Characteristic early sign**

Dr. Patterson notes that one of the most important early signs of NPC is problems with vertical supranuclear gaze. “It can be very subtle at first and is almost always missed,” he says. “But children who are having difficulty with rapid vertical eye movement may blink, then jerk their heads up or down to generate a reflex to move their eyes vertically. In our experience, vertical supranuclear gaze is the first neurological sign of Niemann-Pick C. Examining for it gives the best chance of diagnosing the disease early.”

In addition, about one-third to one-half of patients have seizures that can be difficult to control. Up to a third of that group can have gelastic cataplexy, a sudden loss of muscle tone triggered by feeling amused. “In severe cases, if anything amuses these children, they collapse to the floor,” Dr. Patterson says. “It can be quite disabling.”

A definitive diagnosis of NPC requires biochemical analysis of a skin biopsy. Mayo has one of the few labs in the U.S. capable of performing this test. The Mayo lab can also analyze blood samples to look for mutations on

**Figure.** Skin fibroblasts stained with filipin, which binds strongly to free cholesterol. On the left, fibroblasts from a control subject showing only faint staining. On the right, bright staining indicates accumulation of cholesterol in the lysosomes of nuclear pore complexes.
Medulloblastomas are the most common pediatric brain malignancy and the most common cause of cancer death in children. Glioblastoma multiforme is an aggressive brain tumor that has a median survival of about 14 months. Current treatments for these cancers, which combine surgery, chemotherapy and radiation, are especially challenging for younger patients.

To develop more-effective therapies for pediatric brain tumors, researchers at Mayo Clinic in Rochester, Minn., are designing novel drugs aimed at inhibiting the STAT3 signaling pathway. STAT3 is a key signaling molecule in several cancers including medulloblastoma and glioblastoma, affecting tumor-cell proliferation, growth and apoptosis.

“If we can develop therapies that inhibit signaling pathways, we might eventually be able to treat these high-risk tumors with resection and the drug,” says David J. Daniels, M.D., Ph.D., a neurosurgeon and research chemist at Mayo Clinic in Minnesota. “We typically hammer these kids hard with radiation and chemotherapy, and they pay a price for that neurocognitively.”

Mayo researchers have synthesized several compounds that kill medulloblastoma and glioblastoma tumor cells in vitro. Dr. Daniels is currently testing the compounds in mouse models at St. Jude Children’s Research Hospital, where he is completing a clinical-research fellowship. The compounds are also being tested in an adult glioblastoma mouse model at Mayo in Minnesota.

Rational design
Rather than screening millions of compounds for potential therapeutic use, Dr. Daniels uses a rational design process aimed at a specific target. “We started with a 3-D model for STAT3, then did a computer screening for compounds that can bind to it,” Dr. Daniels explains. “Then we went to the lab and made the drugs by synthesis.”

The central structure of the compounds being tested is based on celecoxib, a rheumatoid arthritis medication approved by the Food and Drug Administration (FDA). “Based on computer modeling, that compound was predicted to bind into STAT3,” Dr. Daniels says. “We essentially ‘de-engineered’ that molecule and modified it to fit into the STAT3 pocket better” (Figure).

This unique, structure-based approach modifies an FDA-approved drug to select a new target. “Our hypothesis is that small changes can be made to the drug structure that can profoundly affect target binding but have minimal effect on pharmacokinetic properties and toxicity,” Dr. Daniels says.

Mayo researchers hope to conduct clinical trials of the compounds and, eventually, to investigate inhibitors for other pathways. “We’re starting to learn that STAT3 is just one pathway for medulloblastomas. If we know which pathways the various subtypes of medulloblastoma are using, we can develop therapies aimed at these specific pathways. The goal is to learn as much as we can about these high-risk tumors and then develop novel drugs for those specific types.”
Research Highlights in Pediatric Neurology and Neurosurgery

Research in childhood epilepsy

Research in pediatric sleep medicine

Research in neurometabolic diseases

Research in multiple sclerosis

Research in immunoproliferative disorders

Congratulations to Marc C. Patterson, M.D., named editor of the *Journal of Child Neurology*, and to Deborah L. Renaud, M.D., newly certified by the American Board of Medical Genetics in Medical Biochemical Genetics.
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 Opportunities

2014 courses

March
Mayo Clinic EEG, EMG and Neurophysiology in Clinical Practice
March 2-7, 2014
Mayo Clinic, Education Center, Phoenix

Tackling Problematic Chronic Rhinosinusitis: A Conclave of Global Experts
March 27-29, 2014
Mayo Clinic, Education Center, Phoenix

April
Southwest Laryngology and Voice Rehabilitation Conference
April 4-5, 2014
Mayo Clinic, Education Center, Phoenix

May
Neurorehabilitation Summit
May 19-20, 2014
DoubleTree, Rochester, Minn.

September
Neuro-Ophthalmology in Clinical Practice
Sept. 19-21, 2014
Orlando, Fla.

Stroke and Cerebrovascular Reviews
Sept. 25-28, 2014
Amelia Island, Fla.

October
Practical Clinical Neurology for the Primary Care Physician
Oct. 20-23, 2014
Orlando, Fla.

November
Parkinson's Disease & Other Movement Disorders for the Practitioner — 2014
Nov. 7-8, 2014
Mayo Clinic, Education Center, Phoenix

Neuroradiology: Practice to Innovation
Nov. 10-14, 2014
The Ritz-Carlton, Dove Mountain, Marana, Ariz.

2015 courses

February
Update in EEG, EMG and Clinical Neurophysiology
Feb. 22-28, 2015
Amelia Island, Fla.

September
Stroke and Cerebrovascular Reviews
Sept. 24-27, 2015
Amelia Island, Fla.

Information and registration

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Contact Us

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

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Resources

MayoClinic.org/medicalprofs

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