Brain tumors are rare diseases of childhood, and are the second leading cause of cancer-related deaths in children under the age of 20. (Leukemia remains the major cause of cancer-related deaths in children.) It is estimated that 3,110 new childhood primary benign and malignant brain tumors were diagnosed in the United States in 2002, including 2,330 brain tumors in children under the age of 15. In the year 2000, over 26,000 children in the United States were living with brain tumors, including over 21,000 children with primary malignant brain tumors.

Pediatric brain tumors are frequently diagnosed before the age of seven, and are slightly more common in boys than in girls. Some types of brain tumors are commonly diagnosed at specific ages: embryonal tumors, primitive neuroectodermal tumors and medulloblastomas between ages 0 and 9; astrocytomas between ages 10 and 14; and pilocytic astrocytomas between ages 15 and 19.

Symptoms of pediatric brain tumors can be very different from the symptoms of adults with brain tumors. Compared to the most frequent adult brain tumors, most common childhood brain tumors have different locations. In addition, many common pediatric brain tumors behave differently than similar tumors in adults and may have a better prognosis. Pediatric brain tumors are often treated differently than those in adults, especially in very young children. In this issue we look at the types of pediatric brain tumors and pediatric arteriovenous malformations.

This issue tries to provide additional guidance on the treatment of neurosurgical radiosurgery with multi-source cobalt 60 instruments, primarily the Gamma Knife®.

Most recurrences of pediatric brain tumors occur within three to five years of initial treatment. Tumors may recur five to ten years after treatment, but this is uncommon among the more malignant tumors.

Recent advances in technology permit improved diagnosis and treatment of pediatric brain tumors. Some treatment methods, such as whole brain radiation therapy, increase survival but may have long-term side effects on young children.

Depending on the type of whole brain radiation treatment, side effects may include a change in overall intelligence, attitude problems, learning disabilities, changes in personality, fatigue, depression and hormonal problems. Some studies have indicated that the developing brain may be less damaged if radiation is delayed until the child is at least three years of age. Whenever possible, more focused treatments utilizing neurosurgical radiosurgery would be used in place of whole brain radiation therapy.

After treatment for a brain tumor many children are able to return to their previous lifestyles. However, long-term specialized rehabilitation or education may be required due to disabilities caused by the tumor and sometimes by the treatment.

The developing brains and bodies of children require particular care and consideration during treatment for brain tumors. Patients who receive advanced treatment from an experienced, multi-disciplinary pediatric health care team often have improved chances of survival and better quality of life.
Stereotactic Radiosurgery

Stereotactic radiosurgery is surgery using radiation as a scalpel. The skull is never opened. Radiosurgery involves the use of precisely directed radiation to create lesions within the brain or to treat tumors or vascular malformations with minimal damage to surrounding structures or tissues. This works by delivering a relatively high dose of radiation in one session to the target with scalpels-like precision. The dose is designed to injure or kill the cells of their supporting blood vessels, while minimizing its effect on surrounding healthy tissue. The radiation distorts the cells’ DNA, causing them to lose the ability to replicate themselves. The safety and clinical effectiveness of this technique has been established since 1968 in over 200,000 treated individuals.

The benefits include: no risks of infection or anesthesia reactions; virtually no pain; reduced costs; and an immediate return to normal activities. Radiosurgery may or may not be appropriate for your condition. It may be used as the primary treatment or recommended in addition to other treatments you may need. Only a treating neurosurgeon can make the evaluation as to whether you can be treated. Some of the most common indications for treatment today are:

- Arteriovenous/vascular malformations
- Meningiomas
- Acoustic neuromas
- Pituitary and pineal tumors
- Metastatic tumors
- Gliial and astrocytoma tumors
- All other malignant & benign tumors
- Trigeminal neuralgia
- Parkinson’s tremors/rigidity
- Functional disorders

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The Role of Neurosurgical Radiosurgery in the Management of Brain Tumors and AVMs in Children

In 1889, the first stereotactic neurosurgery was first introduced in Russia. The goal of this technique is to accurately place lesions or biopsy small areas within the brain surgically. Stereotactic refers to very accurate localization within the brain and is derived from two Greek words: stereos (three-dimensional) and taxis (orderly arrangement). In 1951, Lars Leksell (a neurosurgeon) expanded the concept of stereotactic neurosurgery to radiosurgery, whereby lesions are placed within the brain using precision placement of radiation. True radiosurgery is in the field of neurosurgical treatments and technology. This is a technique whereby a high dose of radiation can be focused with extreme precision by a neurosurgeon on a diseased area within the brain, much the same as a surgical intervention, while minimizing radiation to the surrounding healthy brain.

Extensive research and experience is primarily based on the adult population today. More recently, (in the past 20 years), these neurosurgical technology treatments are being applied to treat a variety of neurologic disorders in children. Children are especially sensitive to the potential side effects of brain irradiation. Thus, the capability of neurosurgical technology to deliver high radiation doses to the diseased area and minimize radiation doses to surrounding normal brain tissue makes this treatment a very attractive option in the pediatric population.

Within the industry, there are several available technologies. The most widely used are the Gamma Knife® and LINAC systems. Each technology has inherent advantages and limitations. We utilize neurosurgical radiosurgery via the Gamma Knife® system, because of the accuracy and safety of this instrument. Gamma Knife® surgery (a photon radiation) has proved to be extremely effective in the pediatric population. Since, the Gamma Knife® machines are the same throughout the world, protocols, dosing, and techniques can be compared and shared with common results. This has led to a wealth of information and research that is shared within the neurosurgeon community. This is not true of LINAC machines that tend to be less accurate and have multiple manufacturers making results and techniques less comparable and harder to repeat.

In some cases, we know that other types of tumors may respond to a different type of radiation more readily. Examples include patients who harbor tumors reported to have an enhanced response to proton beam radiation such as the rare atypical teratoid tumor and chordoma.

The two most common indications for Gamma Knife® surgery in children are to treat brain tumors and arteriovenous malformations (AVMs). In this article, an outline of contemporary management of pediatric brain tumors and AVMs is presented. In addition, neurosurgical radiosurgery is discussed with regard to the unique aspects of this treatment as it pertains to children.

Pediatric Brain Tumors

Introduction

It is difficult to think of a more dreaded scenario than when an otherwise healthy child is diagnosed with a brain tumor.

Common Symptoms of Pediatric Brain Tumors

- Vision changes
- Worsening school performance
- History of flu-like symptoms
- Headaches
- Frequent headaches that are:
  - Worse in the morning
  - Associated with nausea or vomiting
- Head tilting to one side
- Increased head size
- Different sized pupils
- Decreased coordination
- Loss of pupils
- Weakness
- Fatigue
- Irritability
- Change in behavior

Continued on page 3
child is diagnosed with a brain tumor. This diagnosis not only impacts the child, but also has far-reaching consequences for family members, friends, and physicians alike—no one escapes the initial shock associated with this diagnosis.

Frequently, there has been little or no apparent warning that the child harbors a brain tumor. The distress of this diagnosis is often compounded by an initial sense of hopelessness that "there is nothing that can be done." Fortunately, in most cases this despair, although understandable, is unfounded. Tremendous advances have been made in the management of pediatric brain tumors over the last decade. In fact, the prognosis for certain pediatric brain tumors is now discussed in terms of "cure" rather than "control" rates.

Incidence
Brain tumors are the most common solid tumors occurring in childhood. Overall, malignancies of the central nervous system (CNS; brain and spinal cord) are second in frequency only to the hematological tumors (leukemias and lymphomas) in children. CNS tumors represent 20% of all childhood malignancies. In contrast, brain tumors represent only 1-2% of all new cancers in adults. Approximately 1800 new cases of pediatric brain tumors are diagnosed per year in the United States, yielding an incidence of brain tumors of 2.5 per 100,000 children under the age of 15.

Of concern is the fact that the incidence of brain tumors in children appears to be increasing. The reasons for this trend are currently the subject of intense research with investigation focusing on genetic, environmental factors or both. In other words, certain individuals may have a genetic predisposition due to an alteration or susceptibility of the cellular DNA (deoxyribonucleic acid—the basic molecular building block of life) to tumor development when exposed to certain environmental factor(s).

Pathogenesis
Pathogenesis means the origin and development of a disease. Genes are composed of DNA and control all aspects of the cell, including growth and proliferation. Genes are the functional unit of how we inherit a trait (like red hair or green eyes), or a tendency to develop a disease (such as diabetes or a cancer). Current views on brain tumor development suggest that there is a central place for a class of genes called oncogenes. Oncogenes are found in the nucleic acid of viruses and tumor cell DNA, and have been shown to be able to transform other cells by gene transfer in the laboratory (in vitro) and in the body (in vivo). Similar genes have been found in normal cells and are called proto-oncogenes. Proto-oncogenes play a role in normal cellular proliferation and differentiation and are activated at regulated times: for example, normal and rapid growth during fetal development. Activation of proto-oncogenes results in the normal formation of a number of proteins necessary for cell growth (such as growth factors and cell receptors) and the formation of new blood vessels. This process is balanced and held in check by a group of genes called regulatory or suppressor genes. It is hypothesized that tumors are formed when there is a genetic imbalance—either an activation of the oncogenes or a deficiency of the tumor suppressor genes—which allows for abnormal cell proliferation.

Abnormal cell proliferation, or tumor development, may be the result of inborn cell defects, inherited mutant genes (defects of the DNA) and/or environmental factors such as cancer-causing chemicals and cancer-causing (oncogenic) viruses and exposure to certain forms of radiation.

Research has been directed at identifying which environmental factors are responsible for brain tumor formation since, at least theoretically, these factors would be easier to control than any inborn genetic defect. Research has focused on electromagnetic field (EMF) exposure because there has been an exponential increase in modern man's exposure to this environmental factor with the proliferation of computer, home appliance and telecommunication technologies. EMF is a form of non-ionizing radiation and is emitted by many modern devices such as cellular phones, electric blankets and electric power lines. To date, the consensus is that there is no relationship between EMF exposure and childhood brain tumors. However, the relationship between ionizing radiation and brain tumors has been well established; a higher incidence of brain tumors has been documented in atomic bomb survivors and those children who underwent cranial irradiation for the treatment of tinea capitis ("low" dose radiation of the head was used on a large scale for the treatment of head lice).

A variety of chemical agents, most notably the N-nitrosamine compounds (NOCs), cause brain tumors in experimental animals. NOCs are ubiquitous in the environment of developed societies and are found in rubber products, cigarette smoke, drinking water and cosmetics. A few studies have suggested that NOCs are responsible for the increase in brain tumors in children of parents who were exposed to second-hand cigarette smoke. Paternal occupation in the aerospace industry, maternal use of certain make-up products during pregnancy, and the use of rubber baby bottle nipples or pacifiers are suggested links to increased brain tumors in children. However, none of these factors has been consistently linked to a higher incidence of brain tumors in children. Other chemical classes that have been implicated in brain tumor formation include polycyclic hydrocarbons, alkylating agents and hydrazines.

Viruses are oncogenic in laboratory situations and may be implicated clinically. Oncogenic viruses include both DNA tumor viruses (SV40, JC papovavirus, adenovirus) and RNA tumor viruses (avian, murine and simian sarcoma virus). An intriguing study of the Connecticut Tumor Registry noted an increase in brain tumors among children who were exposed to SV40 virus contaminated polio vaccine given to pregnant mothers. This finding suggested a causal role for viruses in tumor development. However, a definitive relationship between viral agents and brain tumors has not been found in any large study.

Clearly, genetic factors alone or in combination with environmental influences are involved in tumor formation. However, with the exception of the rare inherited neurocutaneous syndromes (discussed below), no specific familial tendency, genetic abnormality or environmental factor has been consistently demonstrated to be associated with brain tumor development. It is hoped that a better understanding of the role of genes in brain tumor development would increase our knowledge of how environmental exposures thought to be associated with brain cancer might bring about the cellular changes that result in tumor growth.

Conditions Associated with Tumors
Most brain tumors occur with no family history and no apparent cause. However, a minority of CNS tumors are hereditary and recent advances in genetics have enabled localization of the genetic defect that causes some of these tumors. Genetic defects have been identified for retinoblastoma, a rare, malignant tumor of the eye that presents in childhood; neuroblastoma; and the multiple endocrine neoplastic syndromes.

Most familial tumors of the CNS belong to a group of disorders known as the phakomatoses. This term was coined in 1920, and...
describes a number of syndromes that have common characteristics including: hereditary features; affect multiple organ systems, especially the skin, eye and CNS; and demonstration of tumor progression throughout life. The following is a brief description of the phakomatoses.

Neurofibromatosis, the most common phakomatosis, has two distinct forms. Neurofibromatosis affects the growth of nerve tissues and may cause other abnormalities. Type 1 (Von Recklinghausen's) neurofibromatosis is characterized by spinal neurofibromas, plexiform neurofibromas, optic gliomas, meningiomas and intracranial gliomas. There may be associated macrocephaly (large head), seizure disorders and learning disabilities. Skin manifestations include neurofibromas, café au lait spots, and freckling near the armpit; iris hamartomas may be found in the eye. Other manifestations include hemihypertrophy, scoliosis and pheochromocytomas (tumors that secrete epinephrine and norepinephrine). The genetic marker has been found to be located on chromosome 17. Type 2 (bilateral acoustic) neurofibromatosis is characterized by bilateral acoustic neuromas, spinal neurofibromas, meningiomas and gliomas. Skin and eye manifestations include a few neurofibromas and congenital cataracts, respectively. The genetic defect has been located on chromosome number 22.

Tuberous sclerosis is a disorder characterized by brain, skin, heart and kidney abnormalities. Tuberous sclerosis is frequently initially diagnosed by the hallmark cutaneous (skin) lesions of adenoma sebaceum, ash-leaf spots, shagreen patches and fibromas under the nails. Abnormalities of the brain include subependymal astrocytomas, cortical nodules and malignant gliomas. Other features of this syndrome include tooth pit- ting, cardiac rhabdomyomas, seizures, and mental retardation. Von Hippel-Lindau syndrome is characterized by hemangioblastomas of the cerebellum, spinal cord and brain stem. These patients frequently have retinal angiomas as well as angiomas of virtually any other solid organ of the body. In addition, renal cell cancer, pheochromocytomas and cysts of the kidneys, liver and pancreas are characteristic accompanying lesions.

Sturge-Weber is the most frequently found neurocutaneous angiomatosis. These patients can be readily diagnosed by the characteristic facial hemangiomas ("port wine stain"). Typically, the CNS tumor is a parieto-occipital angioma. Often there is associated glaucoma. Other neurocutaneous angiomatosis include Osler-Rendu-Weber syndrome, which has central nervous system angiomas and hemorrhage, and Klippel-Trenaunay-Weber syndrome, characterized by spinal hemangiomas.

It is imperative that CNS tumors be actively excluded, and where necessary treated, in patients with a phakomatosis syndrome. The same is true for their family members.

Unique Features of Pediatric Brain Tumors
Children's Brain Tumors are Different from Adults

Although there are many similarities, brain tumors in children differ from those in adults in several key respects. First, different types of brain tumors are found in children compared with adults. Generally, less aggressive tumors such as low-grade glial tumors, germ cell neoplasms and craniopharyngiomas occur in childhood. Effective treatment of these tumors may result in a cure. For example, some low-grade astrocytomas may be cured by surgery alone, whereas germ cell tumors are sensitive to both chemotherapy and radiation therapy. In contrast, the majority of adult brain tumors are malignant at presentation. The two most common forms of adult brain tumors are high-grade glial tumors and metastatic tumors. Both tend to recur despite treatment. Second, children with brain tumors have an overall better prognosis than their adult counterparts. While 60% of all children with brain tumors can expect to survive into adulthood, the 5-year survival rate of adults with primary brain tumors of all types is approximately 30%. Third, certain presenting clinical features are unique to children. These include growth disturbances, developmental delay and an apparent tolerance of a marked decrease in visual acuity.

Children's Brain Tumors are Different from Other Childhood Tumors

Brain tumors differ from other childhood malignancies in a number of important respects. First, brain tumors in children are a varied group of tumors. This is not surprising when one considers that the developing brain contains many different types of cells—from immature precursor to fully differentiated cells. Any one of these cells (it is estimated that there are 10 billion cells in the brain) may form a tumor. There are more than 40 brain tumor subtypes in children, each with a unique natural history (typical behavior), set of appropriate treatment options and prognosis. Other common tumors of childhood, such as lymphomas and leukemias (tumors of blood elements), sarcomas (soft tissue tumors) and nephromas (kidney tumors) tend to be more homogeneous (of similar cell types). Second, brain tumors tend to recur at the original site or within the central nervous system and thus control at the primary site is most important. Other childhood tumors are more likely to metastasize (spread to other organs) so that treatment must be
Pediatric Radiosurgery...

Continued from page 4

directed throughout the body. Third, brain tissue is essential for normal life and does not regenerate if damaged. Childhood tumors that occur in areas of the body that are not essential for life (for example, a limb) and in tissue that regenerates (for example, the liver) permit aggressive removal of the tumor including a "tumor free" border to ensure that the tumor is completely removed. The critical and non-regenerative nature of brain tissue precludes removal of anything but tumor bearing tissue. "Wide margin" removal of brain tumors is therefore not feasible. Finally, the "blood-brain barrier" protects the brain and spinal cord. This barrier protects the brain and spine from potentially dangerous chemicals that may circulate in the blood. However, it also prevents certain therapeutic drugs from entering the brain, limiting the chemotherapies that can treat brain tumors.

The Pathologic Spectrum of Pediatric Brain Tumors

Brain tumors in children are a heterogeneous group of tumors. This is not surprising when one considers that the cellular content of the brain is not homogeneous and is comprised of many different cell types. Every cell in the brain has the potential to form a tumor. This applies to primitive precursor cells as well as cells found in the mature, fully developed brain. Given that precursor cells are more abundant during fetal development and early infancy, tumors that arise from these cells are more frequently encountered in young children less than two years of age. These tumors include primitive neuroectodermal tumors, malignant teratomas and primitive mesenchymal tumors. Thus, the pathologic spectrum of brain tumors varies by age. In the extremes of childhood (young infants and older adolescents), cerebral tumors are more common than cerebellar tumors. However, overall, children are more apt to develop cerebellar tumors than adults.

Different areas of the brain have unique functions, which is largely due to the cellular make-up of that specific area. Thus tumors derived from a particular cell line are more likely to be found in certain areas of the brain. This regional distribution of brain tumors is illustrated in Figure 1. The common brain tumors encountered in childhood include medulloblastoma (25%), low-grade cerebral astrocytoma (23%), cerebellar astrocytoma (13%), high-grade astrocytoma (11%), brain stem glioma (10%) and ependymoma (9%).

Benign and Malignant Pediatric Brain Tumors

Confusion often occurs regarding the terminology "benign" and "malignant" when applied to brain tumors. In most tissues, other than the brain, a benign tumor is one that remains localized, grows more slowly, and has a better prognosis; a malignant tumor invades adjacent tissue and/or metastasizes (spreads to distant tissue), responds poorly to treatment and has an unfavorable prognosis. Most malignant non-CNS tumors are fatal because of metastases to the brain. Therefore, the terms "benign" (low grade) and "malignant" (high grade) are relative terms in the context of brain tumors and are used to describe relative degrees of aggressiveness, cellular differentiation and prognosis. Unlike benign tumors in tissues other than the brain, low grade brain tumors, despite a slow growth pattern, may be potentially lethal because of a critical location near vital brain structures. A benign brain or malignant tumor may "push" on other healthy areas of the brain causing problems with reduced eyesight, seizures, weakness in the arms or legs, and personality problems along with other problems. It may be these symptoms which guide pediatricians to rule out a brain tumor with proper scanning. On the other hand, some malignant tumors such as medulloblastomas may be cured with a combination of surgery, irradiation and chemotherapy.

Clinical Presentation

One of the most challenging aspects of the management of pediatric brain tumors is to recognize as early as possible that a child has a brain tumor. Most commonly, the primary care physician is first consulted about the presenting signs and symptoms. Unfortunately, the "typical" clinical presentation of a brain tumor in a child (progressively worsening headaches, early morning vomiting and difficulty walking) occurs in the minority of cases. In the majority of cases, the presenting features are less obvious. Alterations in personality are often the first sign of the brain tumor in children, irrespective of its location. Many months prior to tumor diagnosis, the child may become irritable, hyperactive, forgetful, or perform poorly academically. The causes of these behavior changes are not known. The presentation of brain tumors in children depends on a number of factors including the age of the child, tumor location within the brain, rate of tumor growth, and associated raised pressure within the brain. The two most common patterns of clinical presentation of brain tumors are signs and symptoms of raised intracranial pressure (ICP) and focal (specific or localized) neurological signs.

Intracranial Pressure (ICP)

Raised ICP, also known as intracranial hypertension, occurs when the pressure within the head is increased above normal levels. Raised ICP may be due to large tumor size (mass effect), swelling of the surrounding brain (peritumoral edema) and/or associated hydrocephalus, which is usually of the obstructive form. Hydrocephalus typically occurs when the tumor obstructs the normal cerebrospinal fluid (CSF) pathways within the brain, resulting in a "damming up" of the fluid within the brain. The manifestations of raised ICP vary by age.

In infants, raised ICP is characterized by irritability, feeding difficulties, progressive macrocephaly (large head), a bulging fontanelle ("soft spot"), spreading apart of the skull bones (spaying of the sutures) and engorgement of scalp and retinal veins. It is important to remember that in infants, separation of the skull bones and bulging of the fontanelle may decompress the contents of the skull so that other features of raised ICP are minimized. Not infrequently, the only clinical finding in an infant with raised ICP is an increase in the head circumference across percentiles on standard growth charts (progressive macrocephaly). Although the skull bones continue to fuse throughout early childhood, the cranium is functionally fused by approximately two years of age. Therefore, older children with raised ICP rarely present with macrocephaly. Rather, the typical manifestations in older children are progressively worsening headaches, nausea and vomiting, and diplopia (double vision). The headache is often described as dull and steady, exacerbated by coughing or sneezing. It is classically associated with early morning vomiting which provides temporary relief. Children with brain tumors may vomit for other reasons. For example, a tumor within the fourth ventricle may irritate the vomiting center (area postrema) which is located in the adjacent brainstem. This may occur without raised ICP. Often, a child who presents with persistent vomiting undergoes a gastrointestinal workup. A negative gastrointestinal workup should raise the suspicion that a brain tumor may be present.

Papilledema, a swelling of the optic nerve head as it terminates in the retina, is a cardinal finding of raised ICP. It is due to transmission of increased pressure to the eyes through the optic nerve sheaths. Late signs of raised ICP include lethargy progressing to coma, bradycardia, pulse irregularities, and hypertension.
Two AVMs Do Not Slow Dee Down

"Dee loves to draw," says Demetrius's mother, Michelle. Dee drew the sketch of himself that accompanies this story. "He went to art camp," she says, "and they took a picture of him and he had to draw it. He won second place!" Dee prefers drawing in black and white. "He doesn't like color when he draws," his mother says.

Dee has two arteriovenous malformations (AVMs) in the motor skills area of his brain. The family learned about these tangles of blood vessels during a procedure routinely performed on children with sickle cell anemia, which he has. "The hematology department was doing a routine MRI and found the AVMs," Michelle says.

Sickle cell anemia refers to a group of inherited red blood cell disorders. In these disorders, red blood cells are not round like normal red blood cells but are "sickle" or crescent shaped. These "sickled" red blood cells are harder and stickier than normal red blood cells, and can obstruct blood flow or break apart, resulting in pain and sometimes anemia.

"He doesn't get sick that often," says Dee's mother of his sickle cell anemia, "but when he gets sick, he gets sick. He actually has growing pain," she adds. "His limbs ache in the cold weather."

Before the AVMs were discovered, Michelle observed some changes in Dee. "He's always been kind of active, playing around, talking," she recalls. "Then he got listless and didn't have any energy. I noticed changes in his personality."

"Before they found the AVMs he hardly watched television," she states. "I thought maybe he was just tired, or maybe he did too much during the day." Dee could have a sickle cell pain crisis due to overexertion, or dehydration in the summer months.

"Then they told me what they had found," she says of the AVMs visualized on the MRI. "When we first found out, Dee wasn't too terribly scared," says Michelle. "But he was scared from the arteriograms, and we had to comfort him."

The AVMs were discovered three years ago in May, when Dee was nine years old. "They referred us to neurology," Michelle says. "The doctor recommended a surgery where they would cut him ear to ear and pull his face back."

"We decided that the surgery was not an option! I gave Dee the option also, and he didn't like the idea of having surgery and being cut on," Michelle says. "It's just hard seeing your children like that." Dee was then referred to Dr. Reisner.

Dee had Gamma Knife® surgery on both AVMs with Dr. Reisner, at Scottish Rite Children's Medical Center in Atlanta, Georgia. "He was going to treat them one at a time but he did both at once," Michelle says.

When asked about the Gamma Knife®, Dee says, "It was nice."

"I think I was the one that was more emotional," his mother adds. "He came home the day after the Gamma Knife®," Michelle recalls. "Two days after that he was himself again—he was worried about his hair coming out." After the radiosurgery, Dee's hair came out in one area. "It's a little indented on his skull where the radiation went in," his mother adds.

Following radiosurgery, Dr. Reisner ordered an MRI to check for fluid buildup in the area of the AVMs. "We have to wait one or two years for them to shrink," Dee's mother reports. "Dr. Reisner is planning on doing an angiogram this summer."

"We found out about his sickle cell three days after he was born," Michelle says. Both Dee's parents have sickle cell trait, as does his brother. "From infancy to first or second grade, he took folic acid and antibiotics every day. Now he just takes folic acid every day."

Folic acid promotes formation of new red blood cells. Children with sickle cell anemia often take daily antibiotics to prevent serious infection.

"I can't stress how glad I am they found the AVMs," Michelle says. "A lot of kids with sickle cell anemia have stroke after stroke. I guess they did the MRI to see if he was a candidate for a stroke later down the line."

Now 12 years old, Dee is finishing seventh grade. "He's in the band and plays alto sax," his mother reports. "He's really good. His teacher picked him to represent the school at a competition."

Michelle and Christopher, Dee's father, both work for the U.S. Postal Service. "Dee and his dad go on trails and ride bikes," she says. "He likes riding his bike. They fish a lot, too."

Dee has an older brother, Christopher, who is 19 years old. "He wants to go into the Air Force Reserves," his mother says. Rounding out the family are two dachshund mixes named Toby and Ingrid.

"I'm really and truly glad that we went the Gamma Knife® way," Michelle says. "I just thought it was so amazing. I don't regret one minute of it."

For additional stories on children and tumors or AVMs, go to www.IRSA.org and search under publications.
(Cushing reflex). Initially, hyperventilation is noted which pro-
gresses to ataxic, irregular breathing as a premorbid finding.

**Focal Deficits**

As the term implies, focal deficits are specific, localized neurolog-
ictic disturbances due to a disruption of function of a (focal) part of
the brain. For example, movement of one side of the body is initi-
ated in the cerebral cortex of the frontal lobe on the opposite side.
A tumor in this location may cause weakness of the opposite arm
or leg. Other common focal deficits involve the sensory, visual and
speech pathways. Seizures are a common manifestation of brain
tumors and often focal, i.e., causing movements of part of the body
on one side only. In other cases the seizures are generalized and
cause tonic-clonic (jerking) movements of both sides as well as a
loss of consciousness.

The brain is often described anatomically in two parts: a larger top
part (cerebrum) lies above a large fibrous shelf (the tentorium), and
a smaller bottom part (cerebellum) lies below the tentorium. Thus,
cerebral and cerebellar tumors are referred to as supratentorial and
infratentorial tumors, respectively.

Supratentorial tumors may be associated with signs and symptoms
of raised ICP, but more commonly present with focal findings such as
long tract signs (weakness or paralysis), hemianopia (a large
"blind spot" on one side) and complex seizures, particularly if the
temporal lobe is involved. Infratentorial tumors generally present
with signs and symptoms of raised ICP due to obstructive hydro-
cephalus with associated cerebellar findings such as ataxia, motor
ingcoordination and speech slurring. Another sign of a cerebellar
tumor is nystagmus (rapid involuntary eye movement). Unilateral
cerebellar tumors cause horizontal nystagmus, which is exacerbated
by looking towards the side of the tumor. Tumors located in the
cerebellar vermis or fourth ventricle produce nystagmus in all direc-
tions of gaze. Brain stem tumors present horizontal, vertical or rota-
tory nystagmus.

A disturbance of vision is another frequent manifestation of pedi-
atriic brain tumors because children are especially prone to develop
tumors of the optic nerves and tracts. Adults are exquisitely sensi-
tive to minor changes in visual acuity and fields and any alteration
usually prompts the seeking of medical attention. It is worth stress-
ing that children may tolerate major visual loss, even near blind-
ness, without complaint. On occasion, it is a parent or teacher who
notices that the child is getting progressively clumsier, has reading
difficulties or falls frequently. The stumbling and imbalance is not
due to any problem with the "motor" system, but in fact is due to
decreased vision.

Double vision (diplopia) is a common symptom of a posterior
fossa (infratentorial) tumor. Some children compensate by tilting
the head in an attempt to align the images. Head tilting and rigid-
ty at the base of the neck are also indicative of cervicomedullary
compression, which may be seen with an upper spinal cord tumor or
cerebellar tumor.

**Other Presenting Features**

An unusual form of presentation of pediatric brain tumors is the
diencephalic syndrome. This syndrome is unique to children and is
characterized by a hyperalert state, increased activity and appetite,
and almost complete absence of subcutaneous tissues. These chil-
dren appear very thin. This syndrome is commonly seen with
hypothalamic tumors. Hypothalamic tumors may also manifest
with endocrinopathies, which are disturbances of hormone produc-
tion controlled by the brain. Endocrinopathies are either due to too
much (hypersecretory) or too little (hyposecretory) hormone pro-
duction. In the case of hypothalamic tumors, the disturbance is
most often hyposecretory (e.g., growth hormone insufficiency).
Pituitary tumors often manifest with hypersecretory states, which
result in an oversupply of one of a variety of hormones. Examples
of this include the amonorrhoea-galactorrhoea syndrome (increased
prolactin), acromegaly (increased growth hormone),
and Cushing's syndrome (increased adrenocorticotrophic hor-
none).

Last, it should be stressed that examination of the skin and eyes is
an essential part of the evaluation of a child with a suspected brain
tumor. The child may have classic cutaneous or ophthalmic mark-
ers of a phakomatosis, which increases the possibility that he or she
may have an associated brain tumor. Classic examples are the typ-
ical "butterfly" facial adenoma sebaceum of tuberous sclerosis,
café au lait spots of neurofibromatosis and retinal angiomas asso-
ciated with von Hippel-Lindau syndrome.

**Initial Management and Overview of Treatment Options**

Most commonly, the brain tumor is suspected by a primary care
physician who orders an imaging study, which confirms the diag-
nosis. Referral is typically made to a pediatric neurosurgeon. As

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**Definitions**

- **CNS**: Central nervous system.
- **Diplopia**: Double vision.
- **Macrocephaly**: An abnormally large head.
- **Neurofibromatosis**: A genetic nervous system disorder affecting the growth and development of nerve tissues, including the growth of tumors on nerves.
- **Nystagmus**: Rapid, repetitious involuntary eye movements.
- **Oncogene**: A gene altered by mutation that contributes to tumor formation.
- **Oncogenic**: Cancer-causing.
- **Phakomatoses**: A group of disorders with common characteristics, including tumors of the skin, eye and nervous system.
- **Pheochromocytomas**: Tumors that secrete epinephrine and norepinephrine.
- **Proto-oncogene**: A normal gene which can become an oncogene, if it is altered by mutation.
- **Tuberous sclerosis**: A disorder characterized by brain, skin, heart and kidney abnormalities, including tumors on the skin and affected organs.

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discussed, it is imperative that a diagnosis be established because pediatric brain tumors are a heterogeneous group of tumors, each of which has a different natural history, treatment protocol and prognosis. Therefore, in almost all cases, the patient will undergo surgery with the dual goals of obtaining a tissue sample to establish a pathological diagnosis and to debulk (remove) the tumor, if appropriate. Exceptions do occur. These would include a child with an obviously malignant infiltrating brain stem tumor or a child with a benign tumor of a visual pathway. There is no role for surgery in these cases, unless hydrocephalus is present. Hydrocephalus is treated with either a ventriculostomy or shunt placement.

In my personal practice, once the pathological diagnosis has been established, the patient is referred to a center that specializes in pediatric neuro-oncology, such as the brain tumor clinic at Children's Healthcare of Atlanta at Scottish Rite Hospital. A multidisciplinary approach is employed with evaluation by a panel of subspecialists, including a pediatric neurosurgeon, neuro-oncologist, radiation therapist, endocrinologist, radiologist, ophthalmologist, dietician, physiotherapist, psychologist and social worker. The multidisciplinary approach is invaluable in that it not only offers convenience to patients by allowing them to be seen by numerous physicians at one time, but it also allows for rigorous debate among the various subspecialists as to what is the most appropriate treatment option. Further, this approach allows us to address all the needs of the patient and family, rather than only issues related to the tumor in isolation. All aspects of the child's physical, emotional and social well-being are addressed. We believe that this approach not only allows for more effective tumor treatment and monitoring, but also more compassionate care to the patient and family.

Post-operatively, the multidisciplinary brain tumor team evaluates the child's neurologic status, pre- and postoperative radiographs and tumor pathology. All treatment options, including simple tumor surveillance with serial scans, further surgery, chemotherapy and/or Gamma Knife® surgery are considered. We typically enroll children in treatment protocols under the auspices of the Children's Cancer Group (CCG), a national consortium of experts that addresses issues of brain tumors in children.

The indications for post-operative treatment are largely based on the tumor pathology. Other factors include the patient's age, the degree of resection (how much tumor was removed) and any associated condition (such as neurofibromatosis).

Low Grade Tumors
Total resection of a low-grade tumor should be the surgical goal. However, tumors in certain locations within the brain make this goal unobtainable. For example, tumors within the basal ganglia or brain stem are not resectable without significant morbidity (complications). These tumors may be excellent candidates for Gamma Knife® surgery. In some cases of benign brain tumors, an expectant policy of observation (“watch” with repeated scans only—with no treatment) may be appropriate. These patients are usually followed with serial scans and subjected to surgery only if they become symptomatic or there is an increase in tumor size.

Increasingly, the approach to children with brain tumors is tempered by the natural history of the malignancy and the effectiveness and side effects of treatment options. For example, optic pathway tumors and hypothalamic tumors are known to be associated with a slow growth potential. Current management is that children with such tumors are not treated until they become symptomatic or there is evidence of growth on neuro-imaging studies. In the case of optic pathway tumors, treatment is considered upon visual loss or when growth is seen on imaging studies (usually MRI).

For patients with low-grade astrocytomas, the current management is debulking surgery (if possible) with no adjuvant treatment. Adjuvant chemotherapy or radiation therapy is reserved for recurrence (regrowth). If recurrence is localized and in an area of the brain that precludes a safe resection, Gamma Knife® surgery is an option. We have been encouraged with the results of Gamma Knife® surgery in the treatment of recurrent ependymomas. Survival is improved with radiosurgery in cases of both residual and recurrent ependymomas.

The area where radiosurgery is not generally applicable in young children is the region of the optic nerves and optic chiasm. Astrocytic tumors grow directly within these critical structures and cannot be excluded from the treatment volume during radiosurgery treatment. However, other intra- and parasellar (in the area of the pituitary gland) tumors, including pituitary tumors, are amenable to Gamma Knife® surgery if there is an appropriate distance between the tumor and the optic pathways. Proximity to the optic pathway is often the rate limiting factor in this location. Residual or recurrent craniopharyngiomas (benign tumors near the pituitary stalk), particularly intrasellar recurrences, may be treated with Gamma Knife® surgery. With pituitary tumors, results similar to those seen in adults are expected in children. Pituitary tumors that are not cured by surgery or medical management are potential candidates for Gamma Knife®.

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Children with type I neurofibromatosis and especially type II neurofibromatosis are excellent candidates for radiosurgery. Neurofibromatosis type II is associated with bilateral acoustic neuromas and intracranial meningiomas. The chance for deafness in bilateral acoustic neuromas is very high. Treatment with Gamma Knife® in these cases has achieved 90% or greater tumor control rates, with better hearing and facial nerve preservation than with standard surgical resection. Meningiomas tend to occur along the skull base and as in adults, the cavernous sinus is a frequent site. Surgical resection of cavernous sinus tumors is likely to impart significant cranial nerve defects, and complete removal of the tumor is unusual. Even with the most careful microsurgical technique, complications such as cranial nerve deficit or vascular flow injury are significant. External beam fractionated radiation treatments, even with advanced planning programs, are likely to deliver a significant dose to the temporal lobes with potential for memory and development of moyamoya phenomenon, a condition of slow constriction of skull base arteries. Many of these complications are obviated by employing stereotactic radiosurgical techniques. Thus, young patients with neurofibromatosis type II should be evaluated for Gamma Knife® radiosurgery as a primary treatment at the time of diagnosis and when a new tumor develops.

Similarly, patients with other hereditary neurocutaneous disorders (described above) should be evaluated for radiosurgery. Patients with tuberous sclerosis develop giant cell astrocytomas within the ventricular system. The pathology of these tumors is rarely in question and a biopsy is not beneficial. Radiosurgery is highly effective for this vascular benign tumor and no invasive surgery may be required. Patients with von Hippel-Lindau disorder are prone to develop multiple highly vascular tumors called hemangioblastomas. Careful radiosurgery with Gamma Knife® can control the majority of these tumors without microsurgery or the need for external beam radiation or embolization procedures.

High Grade Tumors
High grade (malignant) tumors such as glioblastomas, primitive neuroectodermal tumors and ependymomas represent a daunting challenge and may necessitate multiple forms of treatments. Increasingly, untoward side effects have been documented in patients treated with aggressive radiation and chemotherapy protocols. These side effects consist of leukoencephalopathy (changes in the brain's white matter), dementia, learning disabilities, secondary induced tumors, and vascular and endocrine pathologies. The major complication rate may be as high as 50% in patients treated with aggressive protocols. Newer treatments are being sought to increase the sensitivity of the agents and circumvent some of the side effects. Given the potentially devastating complications associated with brain and spinal irradiation in young children, chemotherapy alone is being used with increasing frequency in infants less than three years of age with malignant brain tumors.

For tumors that do not respond to standard treatment, "novel" radiation approaches consisting of neurosurgical radiosurgery, hyperfractionation and brachytherapy (radioactive materials placed in direct contact with the tumor) are increasingly applied. In children, primitive neuroectodermal tumors such as medulloblastoma, ependymoblastoma and pineoblastoma are common. Although they have a propensity to disseminate within the spinal fluid spaces, the main site of treatment failure is the primary tumor site. Protocols using radiosurgery boosts to the primary site are under evaluation. For the present, radiosurgery has been reserved for the treatment of local recurrences in high grade brain tumors. Generally, Gamma Knife® surgery as the primary treatment for these tumors is not an option, but it has promise as an adjunct to surgery, multi-session (fractionated) external beam radiation treatments and chemotherapy in these patients.

The treatment of brain tumors in children is rarely complete after any single treatment. These children require constant surveillance, not only of the tumor, but also for side effects of treatment, psychological manifestations of the tumor and disease, and schooling and psychological issues of adolescence. The multidisciplinary brain tumor clinic is an excellent forum to evaluate and monitor these potential problems and intervene when necessary.

Cerebral vascular malformations include a wide variety of structural abnormalities of the brain and spinal cord. They are best described as a region of abnormal tangles of blood vessels. The widespread utilization of magnetic resonance imaging over the last two decades has given us a better understanding of the epidemiology and natural history of vascular malformations of the brain. Distinct entities in this group include AVMs, cavernous malformations and venous angiomata. These lesions are usually of congenital origin and have a natural history typified by recurrent intracranial hemorrhages or progressive cerebral ischemia. Of the three types, AVMs have the most sinister clinical course and prognosis. AVMs are a compact collection of abnormal arteries that drain directly into large veins with no intervening capillary bed. AVMs "recruit" surrounding vessels, enlarge with time and subsequently become symptomatic by mass effect, unassociated with hemorrhage. Absence of normal functioning metarterioles and capillary beds allows a rapid, low resistance arterial to venous shunt to develop. Because of rapid flow, there is a tendency for aneurysm formation on feeding arteries and intimal changes in draining veins, which result in venous stenosis or occlusion. In addition to these characteristics, the fact that these vessels are thin-walled account for the tendency of AVMs to hemorrhage. AVMs account for approximately 20% of cerebrovascular events in children less than 15 years of age. AVMs typically hemorrhage into the surrounding brain substance but can also cause subarachnoid hemorrhages.

 Typically, AVMs present in an abrupt fashion. Features include sudden onset of severe headaches, seizures, focal neurologic deficits and raised ICP (as discussed with brain tumors). Approximately 20% of AVMs are symptomatic in childhood. On occasion, they are diagnosed incidentally before they become symptomatic (for example, when a head CT or MRI is obtained following a head injury). Mortality resulting from initial ruptures is approximately 10% and increases with each bleeding episode. Although the natural history is becoming more clearly defined with modern imaging techniques, it is not completely known. However, it appears that the risk of rebleeding is 2-3% per year. Most studies suggest the risk of rebleed in children with AVMs is significantly greater than in adults. Additionally, brain stem AVMs carry a high morbidity and mortality in children.

Thus, there is little doubt that most AVMs should be treated. However, there is considerable controversy over the most appropriate treatment option. The major treatment options are embolization, surgical resection and radiation. All have inherent advantages and disadvantages. In all cases, the treatment must be individualized for the patient. Typically, if the AVM lends itself to surgical resection (by size and location) we recommend surgery as the primary option.
Gamma Knife® surgery, either alone or occasionally after interventional radiology (embolization) techniques, is a very attractive option in children with AVMs. The irradiated AVM undergoes a slow obliteration over approximately one to three years after the treatment. This obliteration is the result of radiation-induced changes to the vessel wall, especially a thick proliferation of endothelial cells of the vessel wall. This process continues until the interior of the vessel narrows so much that there is no blood flow through the AVM (i.e., it is cured).

The disadvantage of radiosurgery (compared to surgical excision) is that rebleeding may occur during this time. Further, the child is exposed to radiation which, although focused on a limited area of the brain, may have life-long inherent risks. The advantages of radiosurgery include a slow, steady adaptation of the cerebral circulation to the incremental reduction of blood flow through the AVM. A rapid, abrupt decrease in flow through the AVM (as may occur with surgical excision) can result in swelling of the surrounding brain—a phenomenon known as “perfusion pressure breakthrough.” Additional advantages of radiosurgery are the avoidance of conventional surgery and its attendant potential complications. Typically, radiosurgery allows a rapid return to most school and sport activities.

Radiosurgery success is inversely related to the size of the AVM. The usual time to resolution and occlusion in adults is two to three years for AVMs that are approximately 3 cm in average diameter. Children tend to have a shorter time to obliteration of the AVM after radiosurgery than adults. It is not unusual to see a child’s AVM disappear in less than one year following radiosurgery. For lesions 3 cm or less, the rate of complete occlusion approaches 80% with less than 1% mortality and less than 3% morbidity. For larger AVMs, combination treatment is an option. These lesions are treated with a combination of surgery, embolization, and/or Gamma Knife radiosurgery. Staged Gamma Knife® surgery, spaced three to six months apart, is also an option for larger AVMs not suitable for surgery.

Regardless of the treatment, it is usually necessary to confirm complete obliteration (cure) with angiography. In children, this is usually done three years after Gamma Knife® surgery.

On rare occasions other forms of vascular malformations may require radiosurgery. Cavernous malformations are usually treated with surgical resection if located near the brain surface. If a cavernous malformation is located in an area of the brain that does not allow safe surgical resection, Gamma Knife® surgery should be considered.

### Unique Aspects of Radiosurgery in Children

Although there are many similarities, stereotactic irradiation in children differs from that in the adult population in a number of important respects. First, the pathologies encountered are different (as highlighted in the foregoing section on brain tumors). Thus the treatment options, including the indications for Gamma Knife®, vary. Second, children have a higher sensitivity of brain tissue to ionizing radiation. This is especially true for children three years of age. Whole brain irradiation (as opposed to radiosurgery) can have devastating consequences for the developing brain of an infant. Although these effects are limited by focal radiation as delivered by stereotactic irradiation, these issues must be taken into consideration while formulating a treatment decision or plan. Third, in children less than 24 months old, a lack of skull thickness complicates the fixation of a stereotactic localization frame to the skull. It is the placement and maintenance of the localizing frame to the skull that is important to achieve and maintain accurate intracranial targeting (the targeting error with Gamma Knife® stereotaxis is less than 1 mm). For obvious reasons, a thin skull of a child under two years is problematic. An inappropriately applied head frame pin may easily penetrate the skull. To avoid this complication, we have developed a special torque wrench that allows accurate measurement of torque force applied to a child’s skull during head frame placement. Another potential complication of a child’s thin skull is that it is deformable. This may result in a loss of precision which would be unacceptable for radiosurgery treatment. Despite these issues, we have treated infants less than two years of age with Gamma Knife® surgery without compromising precision or skull penetration. Fourth, the integral radiation dose to the body of small children may preclude safe administration.

In younger children (2-10 years of age), precision is maintained by using special posts of the head frame that are tailored to the curve of a small child’s head. Often, longer pins are used because of their small head circumference, making placement of the frame more critical than in adolescents and adults. Because of the need to use long pins, special care must be used when moving the child during the procedure.

Most adult patients have Gamma Knife® surgery under local anes-
Commentary: Pediatric Brain Tumors and the Role of Neurosurgical Radiosurgery

Dr. Reisner has provided a detailed summary of the challenges and opportunities in the management of childhood brain tumors. In this comprehensive essay, the reader will find a great deal of information about the current diagnosis, genetic relationships, outcomes, and potential roles of a variety of treatment options. We have found Gamma Knife surgery (neurosurgical radiosurgery) to be a very valuable management strategy for carefully selected patients with newly diagnosed pediatric arteriovenous malformations and brain tumors. It is especially valuable as a primary management strategy to eradicate deep-seated arteriovenous malformations, many of which respond more completely and faster than do comparable size AVMs in adults. The reasons for this are clear, but the pediatric AVM seems to be more radio-responsive than the adult AVM. In addition, of course, pediatric patients have the opportunity to recover much better because of the residual plasticity of the developing nervous system. Another very successful application for Gamma Knife surgery is the treatment of residual pilocytic astrocytomas. Many such tumors simply melt away after radiosurgery; we have follow-up studies that extend for more than 17 years and confirm long-term tumor growth control. As part of an adjunct management for other glial neoplasms, ependymomas, and occasional medulloblastomas, radiosurgery has a distinct role. Because it is able to provide a focused radiation ablative technique (without the risks of adverse radiation consequences when administered to wider areas of the brain), radiosurgery is a particularly attractive option in the developing nervous system.

We have been reluctant to consider patients for treatment younger than two years of age, primarily because of the inability to shield the rest of the body from scattered irradiation delivered to the target area. In small children, the body, itself, is much closer to the radiation sources, and the thyroid and gonad dose must be considered. In certain cases, radiosurgery may well be indicated, primarily because of the lack of other effective management options.

We do use general anesthesia in the majority of children younger than 12. Occasionally, a very mature 10-year-old may have intravenous sedation alone with satisfactory results. The development of a comprehensive anesthesia team, who are especially challenged by the need to move patients between imaging sites and the Gamma Knife surgery, represents a particular hurdle in the pediatric population. Tumors on or about the fourth ventricle are more likely to be associated with postoperative nausea. It is for this reason that we usually admit our patients for one night after the procedure. On the other hand, children often snap back from general anesthesia very quickly and are often in the playroom later the same day.

Dr. Reisner gives a cogent and detailed summary of the status of pediatric brain tumors and the potential role of Gamma Knife surgery. Hopefully, the readership will be able to glean certain components of this that may help them understand both the challenges and opportunities available to surgeons who treat pediatric tumors and vascular malformations.

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The International RadioSurgery Association is an independent organization dedicated to providing information to patients, physicians, insurers, and government agencies through education about radiosurgery treatment and its availability.

The Association is instrumental in promoting the development of evidenced based guidelines that have appropriate recommendations for radiosurgery treatment options. Currently, IRSA receives over 400,000 inquiries annually.

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