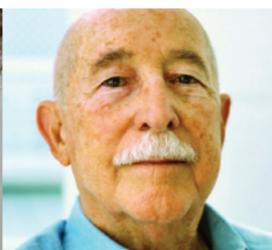


AMERICAN BRAIN TUMOR ASSOCIATION

Medulloblastoma



American
Brain Tumor
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Providing and pursuing answers®

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To learn more about the ABTA, visit www.abta.org.

We gratefully acknowledge Santhosh Upadhyaya, MD, neuro-oncology fellow, and Giles W. Robinson, MD, assistant member, Oncology Department, St. Jude Children's Research Hospital, for their review of this edition of this publication.

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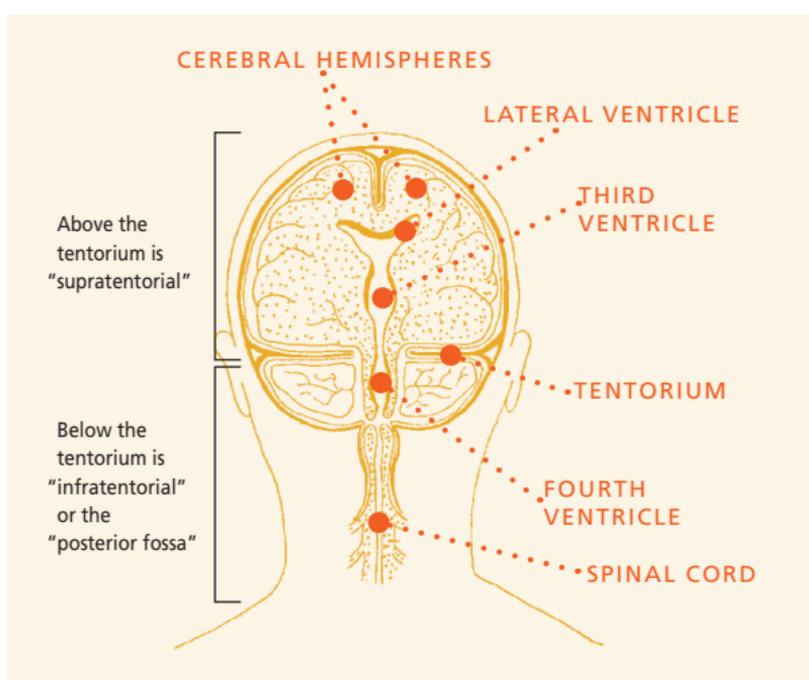
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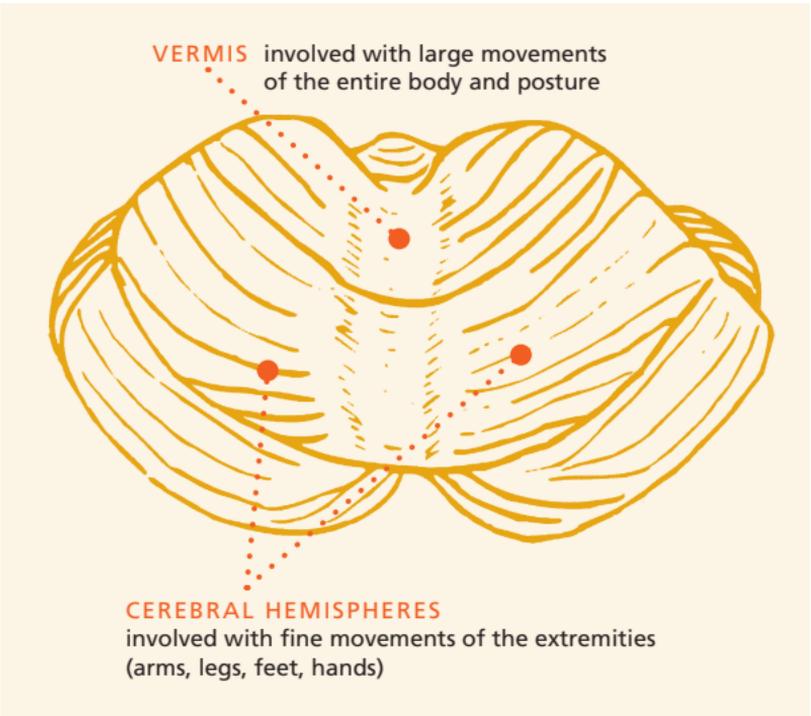
Medulloblastoma

INTRODUCTION

Medulloblastoma is a rapidly-growing tumor of the cerebellum – the lower, rear portion of the brain. Also called the “posterior fossa,” this area controls balance, posture and complex motor functions such as finer hand movements, speech, and swallowing. Tumors located in the cerebellum are referred to as “infratentorial” tumors. That means the tumor is located below the “tentorium,” a thick membrane that separates the larger, cerebral hemispheres of the brain from the cerebellum. In children, medulloblastoma arises most often near the



Tentorium



Cerebellum

vermis, the narrow worm-like bridge that connects the cerebellum's two sides. In adults, this tumor tends to occur in the body of the cerebellum, especially toward the edges.

Medulloblastoma is the most common of the embryonal tumors – tumors that arise from “embryonal” or “immature” cells at the earliest stages of their development. Its occurrence was first described in 1925 and its prevalence has largely remained unchanged since its initial description. To a neurosurgeon, an embryonal tumor looks like a pinkish or purplish gray mass. Under the microscope, or histologically, classic medulloblastoma tissue has sheets of densely packed, small round cells with large dark centers called nuclei. While this classic pattern is found in the majority, the other notable tissue patterns include desmoplastic nodular medulloblastoma, which contains scattered islands of densely packed tumor cells intermixed with looser, less cellular areas; medulloblastoma with extensive nodularity, which is similar to desmoplastic nodular except with more pronounced nodularity; large-cell medulloblastoma,

HISTOLOGIC TYPES OF MEDULLOBLASTOMA

- Classic Medulloblastoma
- Desmoplastic Nodular Medulloblastoma
- Medulloblastoma with Extensive Nodularity
- Large-Cell Medulloblastoma
- Anaplastic Medulloblastoma
- Melanotic Medulloblastoma
- Medullomyoblastoma

consisting of tumor cells with large round nuclei; and anaplastic medulloblastoma, containing tumor cells with markedly increased proliferation and abnormally shaped nuclei. The anaplastic components often co-exist with large cell components prompting the grouping of such histologic types as Large cell/Anaplastic medulloblastoma.. Two other variants, medullomyoblastoma and melanotic medulloblastoma, are very rare and occur in association with the primary variants described.

These varying “histologic types” are used for grouping and while not ideal predictors of prognosis, these tissue patterns have helped doctors realize that all medulloblastomas are not the same. In fact, these patterns, when combined with new technologically-advanced molecular studies of the disease, now show that medulloblastoma is a term that describes complex collection of tumors rather than a single disease. This collection of tumors are now grouped in to “subgroups” of medulloblastoma and because these subgroups react differently to therapy there is shift in the treatment of medulloblastoma away from a “one therapy fits all” model towards a more subgroup driven therapy. The new hope is that this better understanding and categorizing of the disease will lead to better and more precise therapy.

INCIDENCE

About 400 new patients – primarily children, but also adults – are diagnosed in the US each year, slightly more often in males than females.

Medulloblastoma is relatively rare, accounting for less than 2% of all primary brain tumors (tumors that begin in the brain or on its surface) and 18%-20% of all cancerous pediatric brain tumors. Medulloblastoma is the most common malignant brain tumor in children age four and younger, and the second most common in children ages 5– 14. The median age of diagnosis is seven and more than 70% of all pediatric medulloblastomas are diagnosed in children under age 10. Very few tumors occur in children under age one and around 2/3rd of the patients are males. Medulloblastoma in adults is not common, but does occur. One-fourth of all medulloblastomas diagnosed in the United States are found in adults between the ages of 20– 44. The incidence in adults sharply decreases in frequency after age 45.

CAUSE

Medulloblastomas form because of errors in the machinery of the cell that control the cell's growth and death. Why these errors occur is not understood, however, scientists are making significant progress in understanding what is occurring within these cells that turns a normal brain cell into a growing cancer. Changes have been identified in genes and chromosomes (the cell's DNA blueprints) that may play a role in the development of this tumor. For example, one-half of all pediatric medulloblastomas contain alterations to portions of chromosome 17 while a much smaller proportion of tumors (about 10%) have a solitary deletion of chromosome 6. Similar changes on chromosomes 1, 7, 8, 9, 10q, 11, and 16 may also play

a part and studies are underway to connect these changes with tumor development.

Additional advances are also being made through analyzing specific genes. Although inherited or familial medulloblastoma is extremely rare, there are a few rare, inherited health syndromes that are associated with increased risk for developing this tumor. For instance, a small number of people with Gorlin's syndrome develop medulloblastoma. Gorlin's syndrome is an inherited tendency to develop basal cell carcinoma in combination with other conditions largely due to mutations to a single gene called Patched (abbreviated PTCH1). Similarly, genetic changes in the APC and TP53 genes are involved in two other inherited syndromes, Turcot and Li- Fraumeni. People with these syndromes tend to develop multiple colon polyps and malignant brain tumors.

While these syndromes are inherited the overwhelming majority of medulloblastoma are not.

However, it is through the study of these syndromes that many of the genetic changes in medulloblastoma have been found. For example the PTCH1 gene that is mutated in Gorlin's syndrome has also been found to be mutated in about 10% of medulloblastomas in patients who don't have Gorlin's syndrome. Furthermore research has found PTCH1 to be a key regulatory gene in a cellular growth pathway called the Sonic Hedgehog (SHH) pathway. The absence or dysfunction of this gene impedes the cell's ability to shut the SHH pathway off. When this happens in the cerebellum, the overactive cells cause a medulloblastoma tumor. It is now known that about one-quarter (25%) of patients have a medulloblastoma with an overly active SHH pathway thought to be caused either by acquiring a PTCH1 mutation (like in Gorlin's) or mutations to other genes that activate the SHH pathway. Consequently, this group of SHH pathway activated tumors are now categorized as medulloblastomas belonging to the SHH subgroup.

Similarly, another example of improved understanding of tumors through genetics has been made from the rare association of medulloblastomas with the development of colon polyps and cancers (known as Turcot's syndrome). These patients have inherited mutations in genes designed to control another cellular growth pathway called the "WNT" (pronounced "wint") pathway. Once again the inherited syndrome is exceedingly rare, but research on patient tumors has shown mutations in this pathway occur in about 10%–15% of sporadic (not inherited) medulloblastomas. These medulloblastomas are therefore categorized in the WNT subgroup.

Since the identification of the WNT and the SHH subgroup, 2 more subgroups have been identified. Now based on the current molecular understanding, medulloblastoma is subgrouped into four subgroups; - WNT, SHH, Group 3 and Group 4.

GENETIC VERSUS INHERITED

"Genetic" does not mean "inherited." Genetic changes are those that occur in the DNA, or the inside blueprint, of a cell. No one knows what triggers these changes. Some, but not all, genetic changes can be inherited. Inherited means abnormal genes are passed from one generation to another. Most medulloblastomas do not arise from "inherited" genes. Instead the genetic changes tend to only occur inside the tumor cells, which means that the risk of developing medulloblastoma is not transferred to other family members.

WNT medulloblastoma: Identified in in 10-15% of patients. Characteristically, the children with tumors of

this subgroup are school age with the average age being about 10 years old. It is the one subgroup that is slightly more common in females and it is rarely ever seen in children less than 5 years old. These tumors often occupy the fourth ventricle; the fluid filled space in the middle of the posterior fossa. At the cellular level these tumors display an accumulation of a protein termed beta- catenin in the nucleus of the cell and frequently delete one copy of chromosome 6. Accumulation of beta catenin results in activation of the WNT pathway, which appears vital in inducing tumor growth. Patients with WNT subgroup medulloblastoma have an excellent overall outcome with standard therapy of surgery, radiation, and chemotherapy.

SHH medulloblastoma: About 25% of medulloblastomas belong to this subgroup. There is a bimodal (two-peak) age distribution of this disease with young children (< 5yrs old) and adults (> 16 years old) being most common populations to develop this disease. SHH medulloblastomas are primarily located in the body of the cerebellum and often seen lateralizing to the sides of the organ. The SHH pathway is crucial for the normal development of the cerebellum, however, in patients with this subgroup of tumor, there is an unrestrained SHH signaling that results in cancer., The overall survival of patients with this tumor is quite variable and depends heavily on the presence or absence of metastatic disease, the histologic type, and the age at diagnosis.

Group 3 medulloblastoma: These medulloblastomas constitutes about 25% of cases and are most common in young children ranging from 1yr – 10yrs old. These types of tumors are almost never seen in adults. At diagnosis, these are often metastatic (i.e. have already spread to other areas of the brain and spinal cord). Similar to the WNT medulloblastomas the tumor is generally located within the fourth ventricle and may arise from the vermis

of the cerebellum. Under the microscope, the cancer cells of this subgroup are most commonly placed in the large cell/anaplastic histologic subtype but classic histology is also seen. Genetic analysis of the cancer cell, demonstrates more than expected numbers of copies of a growth gene termed MYC although many group 3 medulloblastomas lack this alteration and still behave aggressively. The overall survival of patients with medulloblastomas of this subgroup is the worst among all the molecular subgroups. However, prognosis still varies widely based on presence or absence of metastatic disease and age at diagnosis.

Group 4 medulloblastoma: This is the most common subgroup of medulloblastoma constituting about 35-40% of the cases. These tumors can occur in all ages but are most prevalent in mid-childhood. Similar to Group 3 and WNT subgroup tumors these tumors are located in the fourth ventricle.

While mostly of the classic histology and not-metastatic, more aggressive, anaplastic, and/or metastatic group 4 tumors are seen in about a third of the patients with this disease. Abnormality of the chromosome number 17 is the hallmark of this disease but it is not exclusive to this subgroup. In the absence of metastatic disease, individuals with in this subgroup have a 80% five year survival chance with standard therapy, which drops to about 60% in the presence of metastatic disease.

Though this molecular stratification is distinct from the histological subtype, considerable overlap exists between the two. Primarily, classic histology is most frequently seen in WNT subgroup and Group 4 medulloblastomas, desmoplastic nodular variety and MBEN in the SHH subgroup and the large cell/anaplastic histology in group 3. However this approach is over-simplistic and different histological subtypes are observed within a single molecular subgroup making prediction by

histologic type inaccurate.

The fact that different molecular subgroups have been found to have varied outcome is the most important recent discovery of medulloblastoma. Doctors who study and treat this disease anticipate that subgrouping will become vital to formulating treatment plans for these patients in the future. Still, it is noteworthy to point out that these subgroups are under evaluation and there remains much to be discovered. Groups 3 and 4 are ambiguously named because of the absence of a yet, known pathway causing the development of medulloblastoma in these patients.

Considerable overlapping features occur between these two groups and in the absence of more precisely defining features a non-WNT/non-SHH category is used to combine Group 3 and Group 4 on certain clinical trials. More scientific discovery is expected in the coming years that may alter therapy.

WHAT WE KNOW DOES NOT CAUSE MEDULLOBLASTOMA

While researchers are still sorting out the exact causes of medulloblastoma, several studies have ruled out many environmental factors, including:

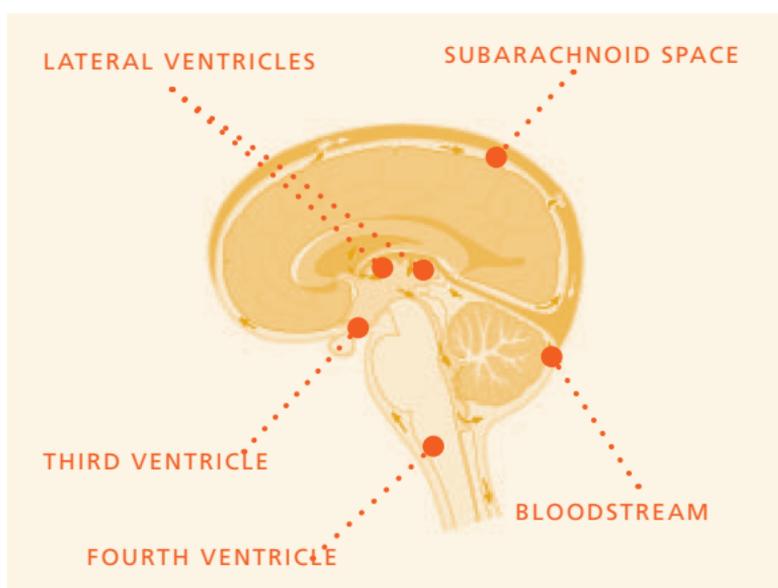
- aspartame or artificial sweeteners.
- smoking, alcohol or diet during pregnancy.

SYMPTOMS

The recognition of the presence of a brain tumor is often difficult for a parent or caregiver, and even in some instances to the primary care physician. The early “flu-like” signs of this tumor – lethargy, irritability and loss of appetite – are often so non-specific that the disease first goes unnoticed. In infants, increased head size and irritability may be the first symptoms. Older children and adults may experience headaches and vomiting

upon awakening. Typically, the person feels better after vomiting and as the day goes on. As the pressure in the brain increases due to a growing tumor or blocked fluid passages, the headaches, vomiting and drowsiness may increase. Headache severe enough to awake an individual from his or her sleep should raise concern as should persistent headache or symptoms that are not improving over time.

Other symptoms depend on the nerves and brain structures affected by the tumor. Since medulloblastomas appear in the cerebellum, the



Cerebrospinal fluid flow

center of balance and movement, problems with dizziness and coordination are common. Tumors growing close to the brain's fourth ventricle may expand into that cavity, blocking the normal flow of cerebrospinal fluid. This can result in hydrocephalus – the buildup of cerebrospinal fluid within the cavities of the brain. The pressure of this buildup triggers the tumor's characteristic symptoms: morning headaches, nausea, vomiting and lethargy.

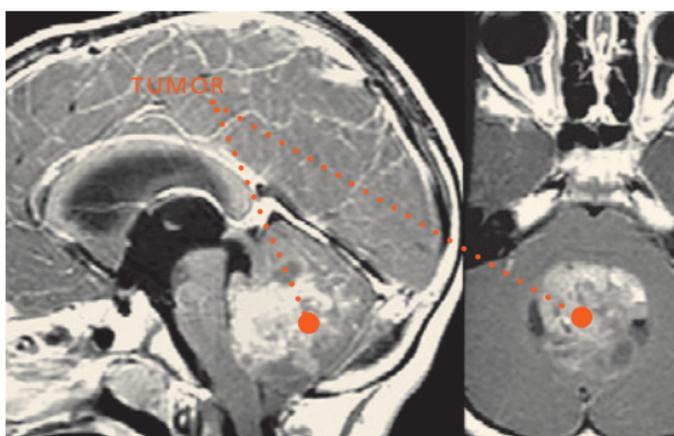
Children with this tumor may exhibit a clumsy, staggered walking pattern. They may also complain

of visual problems; diplopia (double vision), nystagmus (involuntary jerky movements of the eyes) or esotropia (inward turning of one eye) can occur. While seizures are not common with medulloblastoma, other symptoms such as mild neck stiffness and a tilt of the head may occur.

In infants, symptoms can be more subtle and include intermittent vomiting, failure to thrive, weight loss, an enlarging head with or without a bulging of the soft spot of the head (fontanel), and inability to raise the eyes upward (the so-called “sun-setting” sign).

DIAGNOSIS

Obtaining a symptom history and performing a neurological examination will be your doctor’s first steps in making a diagnosis. Magnetic resonance imaging (MRI), done both with and without contrast dye, is then used to identify the presence of a tumor in the brain. The contrast dye is given intravenously (into the vein) to improve visualization of the tumor on the scan.



Enhanced MRI of a child with a medulloblastoma

By concentrating in abnormal tissue, the dye makes a tumor appear much brighter than other areas. MRI technology is not X-rays or radiation. Instead, this technique uses magnetic energy to create a picture of the movement of hydrogen atoms within the brain.

Before having an MRI, let your doctor know if you have any allergies to contrast dyes. In addition, alert the MRI technician if you have a metallic implant: a cardiac monitor, pacemaker, metallic stent, metal surgical clips and/or tattoo containing metallic dyes.

If a tumor suspected of being a medulloblastoma is identified, an MRI of the entire spine and a lumbar puncture will be done to determine if the tumor has spread to the spinal cord or in the fluid around the spinal cord.

While scans provide important and intricate details, microscopic examination of tissue obtained during a surgical procedure, such as a biopsy or tumor removal, is required to confirm the diagnosis. The pathologist, a doctor who specializes in studying tissue samples, will be looking for cell patterns that identify the tumor type and performing tests to place the tumor into subgroups. A pathology report usually takes a couple of days to a week to be completed. The report is sent to your neurosurgeon, and the results then shared with you.

TREATMENT

If the tumor is determined to be a medulloblastoma, current treatment consists of surgically removing as much tumor as possible, followed by craniospinal (brain and spine) radiation and/or chemotherapy. Your doctor will suggest a treatment plan based on factors that indicate the risk of tumor recurrence. To determine risk, doctors look at the age of the patient; the amount of tumor remaining following surgery; and the amount of metastases, or tumor spread (also called M stage).

For children, the presence of any one of the following features constitutes “high risk” disease-

1. Age less than 3 years at diagnosis
2. The amount of tumor remaining following surgery is more than 1.5cm² in volume as defined either on a post-operative MRI scan or by the surgeon's assessment
3. If there is evidence of distant spread of the tumor (presence of M+ disease)

In the absence of all of these features, the child will be categorized as having “average risk” disease.

For adults, risk is generally determined by the amount of remaining tumor, and the presence or absence of tumor spread.

“M stage” is a medical way of indicating the degree of metastasis (tumor spread), if any. M0 means no evidence of metastasis has been found – the tumor appears to be limited to the area in which it grew. M1 means there are tumor cells in the spinal fluid. M2 means the tumor has spread within the brain. M3 means the tumor has spread into the spine. M4 means tumor spread away from the brain or spine (for example, in the rare situation in which the medulloblastoma spread to the chest or bones).

The present staging system for medulloblastoma is of major importance. However, molecular changes are also being studied to determine if the additional molecular information might help to predict the chances of recurrence or spread. Current clinical trials are evaluating if treatment tailored to the additional information of the histologic type and the subgroup of the tumor will help improve therapy.

SURGERY

Removing as much tumor as possible is an important step in treating medulloblastoma. The neurosurgeon has three goals for the surgery: to relieve cerebrospinal fluid buildup caused by tumor or swelling; to confirm the diagnosis by

obtaining a tissue sample; and to remove as much tumor as possible while causing minimal, or no, neurological damage. Several studies have shown the best chance for long-term tumor control is when almost all of the medulloblastoma visible to the neurosurgeon's eye is removed safely.

Many technologically advanced surgical tools are now available. MRI scanning combined with computer-aided navigation tools help the neurosurgeon map the exact tumor location before the operation, and track its removal during the procedure. High powered microscopes provide visual enhancement. Ultrasound and gentle suction devices are used to remove tumor during the actual procedure. These techniques assist the surgeon in navigating around adjacent healthy structures.

While the goal is to remove all of the tumor, some medulloblastomas cannot be removed completely.

In one-third of patients, the tumor grows into the brain stem, making total removal difficult because of potential neurological damage. If the tumor cannot be totally removed, an operation to resect most of the tumor may still be done to reduce the mass and confirm the diagnosis.

Glucocorticosteroids (decadron, dexamethasone) are drugs used before and after surgery to reduce swelling around the tumor. Occasionally, a ventriculostomy (an external drainage device) may be placed to divert excess cerebrospinal fluid from the brain. A permanent shunt, a long catheter-like tube that drains fluid from the brain to the abdomen, is sometimes necessary. In many cases, however, removing the tumor opens the cerebrospinal pathways, which restores both normal fluid flow and pressure. It also eliminates the need for a shunt or drainage device.

Within days following surgery, an MRI will be done

to visualize the amount of remaining tumor. (If an MRI scanner is available in the operating room, the scan may be done during surgery.) The amount of “residual” or remaining tumor will be a strong factor in determining further treatment.

RADIATION

Following surgery, medulloblastoma is usually treated with radiation therapy. It is an important “next-step” because microscopic tumor cells remain in the surrounding brain tissue even after surgery has successfully removed the entire visible tumor. Since these remaining cells can lead to tumor regrowth and spread, the goal of radiation therapy is to destroy the leftover cells.

Doctors consider several factors in planning radiation therapy: the age of the patient, the location of the tumor, the amount of remaining tumor and any tumor spread. Since radiating the brain and central nervous system can be damaging to a developing brain, radiation therapy is usually delayed in children under age three. Initial treatment for these young children includes surgery followed by chemotherapy to control the tumor. Radiation may be delivered later, if needed.

Radiation therapy given to the brain and spine is called “craniospinal irradiation” (CSI). This form of radiation is given five days a week for about six weeks. A “boost” is given to the resection cavity and the surrounding rim. This is the region most at-risk for tumor re-growth because it housed the original tumor. An additional boost may be given to areas of tumor spread. Age and risk factors determine the total doses of radiation given to each area.

While radiation therapy has proven effective for most medulloblastoma, scientists are still looking for new ways to lower the potential side effects of this treatment.

Clinical trials are underway looking at outcomes with reduced dose of CSI in children with average risk disease and who are between 3-7 years of age. Children in this age group are highly vulnerable to the neuro-cognitive effects of radiation (see side effect section below) and reducing their exposure to dose of CSI could be beneficial, provided that this reduction in dose does not change the outcome of the therapy.

Radiation techniques have been evolving with advances in technology and each advancement aims to reduce the amount of collateral damage experienced by normal structures with this therapy. Focused radiation, also called stereotactic radiation therapy (SRT), aims converged beams of radiation directly at the tumor.

Conformal radiation allows doctors to shape the radiation beams to match the tumor's contour. Clinically delivered proton beam radiation therapy (PBRT) is the most recent development. While conventional radiotherapy uses photons to deliver the dose of radiation to the tumor tissue this technique uses a different particle called a proton. The proposed advantage of PBRT is the reduced amount of radiation received by the normal tissues surrounding the treated area.

Consequently, use of protons could potentially reduce the exposure of the brain, spine, heart, lungs, thyroid and gonads to radiation. This reduced area of radiation will hopefully reduce the side effects. While this potential for lower toxicity is very appealing, especially in growing children, this technique still needs to be rigorously evaluated in clinical trials to make sure that it remains as effective as conventional techniques. It is also noteworthy to point out that since CSI remains an important part of medulloblastoma therapy, the exposure of the brain and spine of patients with medulloblastoma

to radiation will still be substantial regardless of the radiation technique used. The availability of PBRT is currently restricted to locations where it is available but more centers are being developed around the country.

Your radiation oncologist, a doctor specially trained in the use of radiation therapy, can talk with you about the best method of radiating your or your child's tumor.

CHEMOTHERAPY

Chemotherapy is the use of powerful chemicals, or drugs, to kill cancer cells. For the most part these drugs kill the fast growing cells over slow growing ones and since cancer cells are rapidly growing, they are particularly vulnerable.

For children with medulloblastoma, chemotherapy is used to kill the medulloblastoma cells that remain after surgery and/or radiation. In doing so chemotherapy reduces the risk of tumor cells spreading through the spinal fluid and the risk of the tumor returning. Most studies suggest, both adults and children with medulloblastoma fare better with chemotherapy than without.

Because different drugs are effective during different phases of a cell's life cycle, a combination of drugs may be given. The combination increases the likelihood of more tumor cells being destroyed and reduces the chances of a tumor cell becoming resistant to a particular drug.

Chemotherapy is now a standard part of treatment for many children with medulloblastoma. Most children are treated in clinical trials. Clinical trials offer a formal way to test new therapies against existing therapies to learn which is better at improving outcome and also at reducing the adverse effects. Chemotherapy drugs are administered in cycles, with each cycle varying between

3-4 weeks. This routine allows time for the body to recover from the potential adverse effects of the chemotherapy drugs, which are usually administered at the beginning of each cycle. The duration and number of cycles of chemotherapy to be administered is dependent on the extent of the disease and could vary from four to nine cycles.

In children at average-risk of recurrence, (>3 years old, <1.5cm² residual disease and no distant spread of the disease) current studies are exploring the use of chemotherapy as a way to reduce the total amount of craniospinal radiation. Chemotherapy is generally administered following the completion of the CSI, though in some instances certain drugs may be given concomitantly with radiotherapy. There are several chemotherapy plans in use, but most focus on a combination of vincristine, cisplatin, carboplatin, cyclophosphamide and/or lomustine.

For children at high-risk of recurrence, the drugs vincristine, cisplatin and cyclophosphamide tend to be the main focus, but others are being tested in clinical trials. Researchers are also looking at the use of chemotherapy during radiation to enhance the effect of the radiation on this disease.

For infants and children under the age of three, chemotherapy is used to delay or even eliminate the need for radiation therapy. In fact, in these young children with SHH subgroup disease, when the tumor is of the nodular-desmoplastic type and has not metastasized, chemotherapy treatment alone after surgery is proving to be an effective way to treat.

Unfortunately for those young children in whom the disease has spread or the type is aggressive, survival outcome remains poor. A variety of studies are underway to attempt to establish a better way to rid

these children of this disease. Studies are also evaluating the efficacy and safety of utilizing local radiation therapy (radiation therapy only to the primary tumor site) after chemotherapy in infants whose initial disease was not metastatic.

There is also interest in delivering chemotherapy directly into the cerebrospinal fluid (either “intrathecally” – into the lumbar spine by spinal taps, or “intraventricularly” – into the ventricular fluids of the brain via an Ommaya reservoir).

This is being done in attempts to deliver high doses of therapy to the coating regions of the brain to reduce disease relapse in these areas. Although this modality of treatment provides high concentration of the drug at the site of the tumor, it unfortunately also exposes the normal brain to these higher concentrations with a potential to cause more adverse effects.

New drugs for medulloblastoma are being evaluated and are under consideration, but their effectiveness remains under investigation and these are generally reserved for patients where the disease has returned after conventional therapy has failed to provide a long term cure.

It is important to note that these types of treatments need to go through rigorous testing before they become accepted as therapy. This is because the side effects of these drugs are not yet well known and may well be harmful.

The discovery of the molecular pathways involved in the development of medulloblastoma and consequent subgrouping of medulloblastoma, has opened up a potentially useful way of treatment by using drugs that could specifically target these pathways.

Clinical trials using drugs that block the SHH pathway, like Vismodegib and Sonidegib, have shown short lived but promising preliminary results in patients who have had a relapse of their disease. They are now being tested on a larger scale, to determine if these drugs could be incorporated as a part of the chemotherapy regimen being used to treat patients at their initial diagnosis.

Another example of more personalized medicine is the attempt to reduce the dose of CSI in patients with WNT subgroup medulloblastoma who have localized disease. These patients have excellent outcomes and reducing the treatment related toxicities while maintaining the excellent outcome is now becoming a priority.

Group 3 and 4 medulloblastomas remain a challenge especially in their most aggressive and metastatic form. While no specific target has been identified in these medulloblastoma much laboratory work and early phase clinical trials are exploring the use of new agents in this disease.

Although large scale studies have not been done, some smaller studies indicate adult tumors may likewise respond to some of the above combinations and efforts are underway to generate clinical trials in adults to establish a consensus on the treatment of this disease.

Research continues to define the best type and method of delivery of chemotherapy, to determine the best tolerated and most effective drugs, and to identify new drugs targeted to specific genetic changes found in medulloblastomas. Your doctor will outline a treatment plan based on current studies, your (or your child's) age, the amount of remaining tumor and the risk of the tumor recurring.

SIDE EFFECTS

Despite its impact on increasing survival, the treatment can cause significant side effects. Your health care team can speak with you about the potential side effects of your or your child's personalized treatment plan, and help you weigh the risks against the benefits. Some of the more common effects are discussed here.

In a recent study, about 25% of children undergoing surgery for their tumor developed delayed onset (usually 6–24 hours after awakening) loss of speech which was often associated with decreased muscle tone, unsteadiness, emotional lability and irritability. This syndrome, called “posterior fossa mutism syndrome” or “cerebellar mutism,” seems to occur predominantly after surgery in children with medulloblastoma, and has not been clearly related to tumor size or surgical approach.

Many of these children recover, but the study noted that some children still have significant neurological problems – such as abnormal speech and unsteadiness – years after surgery.

If mutism occurs, a speech pathologist can help outline a temporary communication plan for your child, and help initiate a rehabilitation evaluation. The rehab team can plan a program specialized to your child's needs and strengths. Visit www.abta.org to learn more about rehabilitation options.

Understandably, parents and adult patients often express concern about the effects of radiation therapy. In the short-term, fatigue, lack of appetite, nausea, sore throat, difficulty swallowing and hair loss in the path of the radiation beams are the most common acute effects of this treatment. Adults seem to experience these temporary, short-term effects to a greater degree than children.

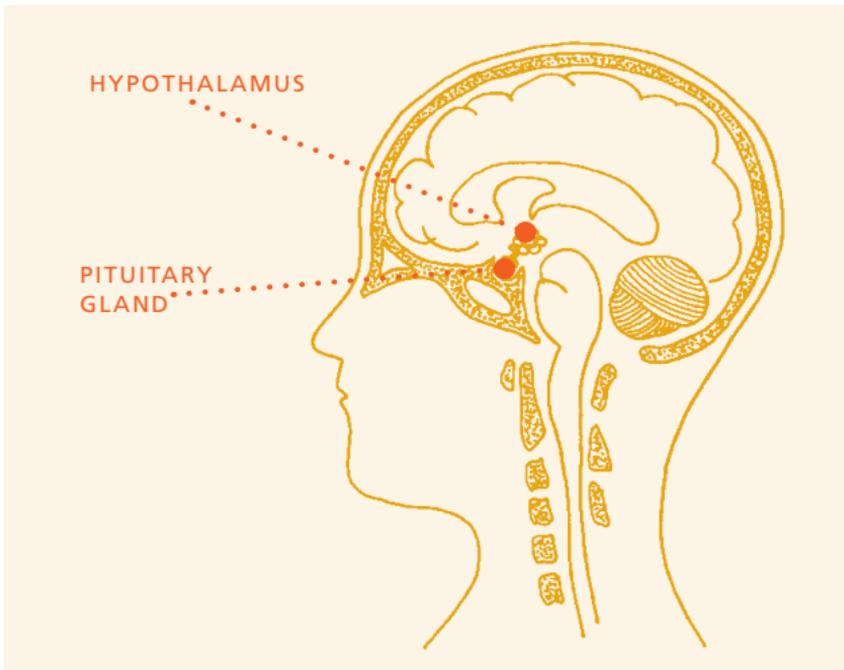
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Children appear to experience greater intensity of the long-term effects. Radiation may trigger a decrease in IQ or intellectual ability, accompanied by learning disabilities, attention deficit and memory loss. The younger the child during treatment, the greater the potential subsequent learning challenges. Infants and children less than 3 years of age are particularly vulnerable because the brain is maturing rapidly during this time. For any age group, however, the radiation oncologist will be able to talk with you about what you can expect based on age and the planned dose of radiation.

Radiation can also have long-term effects on the hypothalamus and pituitary gland, both of which regulate important hormones for bodily function and growth.

Since these structures are directly in the pathway of the radiation beam, their normal function may be disturbed by the treatment. As a consequence, patients can have problems with obesity and hypothyroidism (thyroid deficiency). They also can suffer from short stature and scoliosis (curvature of the spine) if the spinal cord is irradiated. Patients should be evaluated carefully for hypothalamic or pituitary dysfunction and receive replacement



Hypothalamus and pituitary gland

therapy. Studies have not shown that children treated with growth hormone replacement are at a higher risk for tumor recurrence.

Hearing loss may accompany the use of the drug cisplatin in children. Because this drug has an important role in treating childhood medulloblastoma, scientists are testing “protective” drugs, such as sodium thiosulfate (STS) and amifostine, that may be able to defend a child’s hearing mechanisms from cisplatin. Hearing may also be affected if radiation beams pass near the ears; an audiologist (hearing specialist) can be of help in diagnosing and treating this effect. Research is also underway to see if there are genetic ways to determine the susceptibility of a child to hearing loss with treatment.

The short-term effects of chemotherapy are similar to those of radiation: hair loss, nausea, vomiting, fatigue and weakness. However, chemotherapy can also lead to reduced blood counts and kidney problems. Long-term effects of chemotherapy also remain a concern and early heart, lung, kidney disease are seen in surviving patients. Furthermore as patients live longer, there’s the

added danger in the future of secondary malignancies (cancers), such as leukemia.

Doctors continue to study the long-term effects of both radiation and chemotherapy in hopes of developing new agents and combinations of agents that are more effective and less toxic. Discoveries continue to emerge about the molecular mechanisms used by tumor cells to evade the body's normal growth controls, and the methods by which tumor cells move through the brain or spine.

FOLLOW-UP

MRI scanning of the brain will be done every two to three months and spinal MRI every four to six months for the first two years following surgery. The scans help determine the effectiveness of treatment, and are used to monitor for early evidence of a recurrence. Scans will be conducted less frequently thereafter, unless specific symptoms develop that might indicate further growth. Long-term follow-up is crucial for patients with medulloblastoma as it allows medical staff to continue to assess the impact of specific treatment, ultimately helping future patients. Your doctor will determine the appropriate schedule.

Your doctor also may refer you to one or more specialists, including an endocrinologist (a physician specially trained in treating growth or hormone imbalances), an oncologist (a physician trained in treating cancer, particularly with chemotherapy drugs), and/or a neuropsychologist (a mental health professional with expertise in assessing and treating problems of psychological functions and behavior as it relates to the brain and central nervous system).

In children, cognitive difficulties may not surface until they try to complete class work, tests and homework. These challenges – in addition to the very real fear of

being perceived as different from classmates following a brain tumor diagnosis – can make the return to school difficult. It is very important for parents, teachers and classmates to understand and accept the special needs of a child or teen recovering from a brain tumor. Children should receive early aggressive learning support, and should be carefully evaluated for long-term cognitive problems.

For both adults and children, neuropsychological testing before treatment can serve as a baseline for follow-up evaluations; and, post-treatment rehabilitation and special education programs can help patients to regain or better manage lost cognitive skills. Rehabilitation exercises may include computer programs designed to improve visual-perceptual skills (the ability to correctly interpret what we see), reaction time, memory and attention. A large chalk board or a practice grocery store shelf can be used to practice visual scanning and visual attention skills. Workbooks and puzzle books can help with reasoning, mathematical, memory and visual-perception skills. In addition, strategies, compensatory techniques and other brain “tools” can help patients to cope or compensate for memory, attention, problem solving, organization and impulsivity difficulties.

RECURRENCE

Tumors recur when all the tumor cells cannot be removed by surgery or killed by other treatments. In children, medulloblastoma tends to “seed” or drop tumor cells into the spinal fluid. These cells can give rise to tumor growth in the spine. This type of spread may or may not be accompanied by tumor regrowth in the cerebellum. In adults, the tumor tends to first re-grow in the cerebellum. On occasions, the tumor may spread elsewhere in, and outside, of the central nervous system.

Recurrent medulloblastoma is treated aggressively with repeated surgery, re-irradiation if possible, and

chemotherapy. Patients who previously received chemotherapy can be given different drugs for the recurrence, and a clinical trial investigating new therapies may be considered.

PROGNOSIS

How well a patient responds to treatment is affected in general by their age at the time of diagnosis; the size and extent of the tumor; the amount of mass that can be removed safely; and the level of metastatic disease (the M stage).

With the molecular subgrouping information that is now available, it is becoming clear that patients with certain subgroups of medulloblastoma have a better long term outcome in comparison to the others.

Overall, the Central Brain Tumor Registry of the United States reports about 57%–60% of adults (age 20+) with medulloblastoma are alive at five years following diagnosis, and 44% at 10 years. It is important to realize these statistics do not reflect differences in outcome between low risk and high risks groups (since high risk groups may not do as well), differences in patient characteristics, nor differences between patient responses to treatment. And “10 year survival” means the patients were followed for only 10 years; we do not know how well they did beyond that length of time.

With current therapies, about 80% of children with non metastatic medulloblastoma can be expected to be alive and free of disease five years from diagnosis.

The survival percentage is even more impressive for patients with WNT subgroup of medulloblastoma with over 90% of the patients with non-metastatic disease alive after 5 years from diagnosis.

Even in those children with high-risk disease, effective

therapy is possible and results in long-term disease control in as high as 60%– 65% of patients.

While the presence of metastatic disease clearly decreases overall survival, researchers are still studying the reasons for metastatic disease being more common in certain molecular subtypes of medulloblastoma. This is especially true of Group 3 medulloblastoma, which has a ~45% of likelihood of having metastatic disease at diagnosis. Patients with this subgroup of medulloblastoma have the worse outcome with a 5 year survival chance of about 55% in children.

Outcome for infants is poorer, but for those infants with localized disease at the time of diagnosis, survival rates are better. The heterogeneity of medulloblastoma is further highlighted in the case of infants with nodular desmoplastic histology and SHH activation who have been found to have a good prognosis with reports of these patients having been cured only with chemotherapy and being able to avoid radiation altogether.

Take the opportunity to speak with the healthcare team treating you or your child to learn how these statistics apply to your individual situation.

CHALLENGES AND FUTURE DIRECTIONS

The wealth of knowledge created by the molecular subgrouping of medulloblastoma has raised a lot of hope for understanding how medulloblastoma develops. In addition, the subgroups offer doctors the opportunity to tailor therapy to different subgroups. Reduced dose therapy can be given to those that are predicted to do well but who are vulnerable to severe treatment related side effects. Specific targeted agents can be developed to replace or reduce current conventional therapy.

Populations with very aggressive forms of the disease can be offered newer therapies more rapidly when different therapy appears needed. These changes are expected

to bring about significant improvements in survival and quality of life after therapy. Clinical trials are looking at doing this by studying reduced intensity treatment, targeted therapies, and the benefits of proton radiation as compared to conventional radiation treatment. Together the medical community, the scientific community, supporting organizations, the patients and their families are building on past successes towards a better cure for all persons diagnosed with medullblastoma.

THE ABTA IS HERE FOR YOU

You don't have to go through this journey alone. The American Brain Tumor Association is here to help.

Visit us at www.abta.org to find additional brochures, read about research and treatment updates, connect with a support community, join a local event and more.

We can help you better understand brain tumors, treatment options, and support resources. Our team of health care professionals are available via email at abtacares@abta.org or via our toll-free CareLine at 800-886-ABTA (2282).

NOTES/QUESTIONS

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AMERICAN BRAIN TUMOR ASSOCIATION PUBLICATIONS AND SERVICES

CARE & SUPPORT

CareLine: 800-886-ABTA (2282)

Email: abtacares@abta.org

PUBLICATIONS

About Brain Tumors: A Primer for Patients and Caregivers

Tumor Types:

Ependymoma

Glioblastoma and Malignant Astrocytoma

Medulloblastoma

Meningioma

Metastatic Brain Tumors

Oligodendroglioma and Oligoastrocytoma

Pituitary Tumors

Treatments:

Chemotherapy

Clinical Trials

Conventional Radiation Therapy

Proton Therapy

Stereotactic Radiosurgery*

Steroids

All publications are available for download in Spanish.

*(exception is marked *)*

CLINICAL TRIALS

TrialConnect®: www.abtatrialconnect.org or 877-769-4833

*More brain tumor resources and information
are available at www.abta.org.*

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Email: abtacares@abta.org

Website: www.abta.org

*To find out how you can get
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