Medulloblastoma

Types, Causes, Symptoms, Diagnosis, and Treatments

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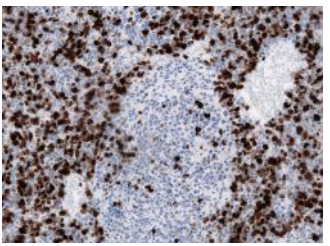
Abstract

Medulloblastoma is a fast-growing, malignant brain tumor predominantly affecting children but can also occur in adults. Originating in the cerebellum, which controls balance and coordination, this tumor poses significant health challenges. This comprehensive guide aims to provide patients, their families, and the general public with an in-depth understanding of medulloblastoma. It covers the tumor's definition, types, risk factors, symptoms, stages, underlying mechanisms, diagnostic procedures, potential complications, treatment options, prognosis, and strategies for living with the condition. Additionally, the article discusses relevant genetic factors and available

medications, including their trade names, to offer a thorough overview of medulloblastoma.

Introduction

Brain tumors present complex challenges due to their location and impact on essential neurological functions. Among these, medulloblastoma stands out as the most common malignant brain tumor in children, accounting for approximately 20% of pediatric central nervous system tumors. This guide explores various aspects of medulloblastoma, offering insights into its nature, progression, and management strategies (1-8).



Medulloblastoma under the microscope. A type of medulloblastoma stained for a molecular marker called MIB1 to test how fast the cells proliferate. More brown means more proliferation. Image Credit: Jensflorian - Own work. https://commons.wikimedia.org/w/index.php?curid=26074967

What is Medulloblastoma?

Medulloblastoma is a malignant, invasive embryonal tumor that arises in the cerebellum, the lower rear part of the brain responsible for coordinating movement and balance. Classified as a grade IV tumor by the World Health Organization, medulloblastomas are highly cellular tumors that tend to spread through the cerebrospinal fluid, often metastasizing to other parts of the brain and spinal cord.

While they can occur at any age, medulloblastomas are most commonly diagnosed in children between 5 and 9 years old.

Medulloblastoma Types

Medulloblastoma is not a single disease but a group of tumors that arise in the cerebellum and differ in their genetic makeup, behavior, and response to treatment. Scientists now classify medulloblastoma into four major molecular subtypes based on gene expression and chromosomal changes.

The WNT-activated medulloblastoma

The WNT-activated subtype is associated with mutations in genes like CTNNB1 and usually has an excellent prognosis due to its favorable response to treatment.

SHH-activated medulloblastoma

SHH-activated medulloblastoma involves the Sonic Hedgehog signaling pathway and is linked to mutations in genes such as PTCH1 and SUFU. Outcomes for this group vary depending on additional genetic alterations and the age of the patient.

Group 3 medulloblastoma

Group 3 medulloblastoma often shows amplification of the MYC gene and tends to be more aggressive, with a higher risk of spreading through the cerebrospinal fluid.

Group 4 medulloblastoma

Group 4 is the most common subtype and is associated with changes in the SNCAIP gene, with an intermediate prognosis. Recognizing these molecular groups helps guide treatment decisions, offering more personalized approaches to therapy and improving long-term outcomes.

Medulloblastoma Causes and Risk Factors

The precise cause of medulloblastoma is not fully understood, but several genetic and environmental risk factors have been identified. Some individuals develop this tumor as part of an inherited cancer syndrome. For example, Gorlin syndrome, caused by mutations in the PTCH1 gene, and Turcot syndrome, involving mutations in the APC gene, are linked to a higher risk of medulloblastoma.

Other children develop the tumor sporadically, meaning there is no family history or known genetic disorder, but mutations arise in critical genes during brain development. These can include alterations in CTNNB1, MYC, and SUFU, among others. Males appear to be slightly more affected than females. Environmental factors have been explored, but so far, no consistent link has been established. The complexity of the genetic landscape suggests that both inherited and acquired mutations contribute to tumor development.

Medulloblastoma in Adults

While the majority of cases occur in children between the ages of three and eight, medulloblastoma can also develop in infants and, more rarely, in adults. In adults, the tumor often presents differently, with a higher likelihood of occurring in the cerebellar hemispheres rather than the midline. Adult cases may be slower growing and are frequently associated with different molecular subtypes, such as SHH-activated, TP53-wildtype tumors. Diagnosis and treatment follow similar protocols to pediatric cases, but adult patients may face distinct challenges in recovery and long-term management.

Medulloblastoma Symptoms

The symptoms of medulloblastoma usually arise because the tumor grows in the cerebellum and can block the flow of cerebrospinal fluid, increasing pressure within the skull. One of the most common symptoms is headache, which often occurs in the morning and may be accompanied by nausea or vomiting due to increased intracranial pressure.

As the cerebellum controls balance and coordination, children may develop unsteady walking, clumsiness, or difficulty with fine motor tasks like writing or using utensils. Some may experience double vision, blurred vision, or eye movement abnormalities if the tumor compresses cranial nerves. Irritability, personality changes, or a noticeable decline in school performance may also be observed. In infants, signs can include increased head size or bulging of the soft spot on the skull. These symptoms can develop gradually but may worsen quickly if the tumor grows rapidly or causes a blockage in cerebrospinal fluid circulation, making early medical attention critical.

Medulloblastoma Stages

Unlike cancers such as breast or colon cancer, medulloblastoma is not classified using traditional staging systems based on tumor size and lymph node involvement. Instead, doctors use risk categories to guide treatment and predict outcomes. Patients are generally placed into two groups: standard-risk or high-risk.

Standard-risk medulloblastoma

Standard-risk medulloblastoma typically refers to tumors that have been mostly or completely removed with no evidence of spread through the brain or spine, and without aggressive genetic features.

High-risk medulloblastoma

High-risk cases include those where the tumor has spread to other areas of the central nervous system, was not fully removed during surgery, or shows unfavorable molecular characteristics such as MYC amplification. Age is another factor in classification, with children under three often placed in a higher risk category because their brains are more sensitive to radiation, making treatment more challenging.

M0-M4

In addition to standard- and high-risk categories, medulloblastoma is further classified using the M-staging system, which describes how far the tumor has spread through the central nervous system. The M0–M4 classification is used after surgery to determine whether and how far the medulloblastoma has spread within the central nervous system. This staging is based on brain and spine MRI scans and cerebrospinal fluid (CSF) analysis, typically performed 10 to 14 days after surgery to allow any blood from the operation to clear. M0 means no spread is detected beyond the original tumor site. M1 indicates cancer cells are found in the CSF. M2 and M3 reflect increasing levels of visible metastatic spread to the brain (M2) or spine (M3), while M4 signifies spread beyond the central nervous system. This classification helps refine risk assessment and guides further treatment decisions.

Medulloblastoma Pathology

Medulloblastoma originates from primitive neural cells in the cerebellum that fail to stop dividing when they should, leading to the formation of a malignant tumor. The process is driven by disruptions in key signaling pathways that regulate normal brain development.

In WNT-activated medulloblastoma, mutations in the CTNNB1 gene lead to the stabilization of beta-catenin, a protein involved in cell proliferation and differentiation.

SHH-activated tumors result from alterations in the Sonic Hedgehog pathway, often involving the PTCH1, SUFU, or SMO genes, which are responsible for controlling cell growth in the developing brain.

Group 3 tumors often exhibit amplification of the MYC oncogene, which drives rapid cell division and contributes to their aggressive nature.
Group 4 tumors involve changes in chromatin remodeling genes and often show a duplication of chromosome 17q. These genetic disruptions lead to uncontrolled growth and the ability to invade nearby brain structures and spread through cerebrospinal fluid.

Medulloblastoma Diagnosis

Diagnosing medulloblastoma begins with a thorough medical history and neurological examination to assess symptoms and identify any abnormalities in movement, coordination, or vision.

Imaging tests are essential for visualizing the tumor. Magnetic resonance imaging, or MRI, of the brain and spine is the gold standard for detecting the presence, size, and location of the tumor, and also helps evaluate whether it has spread through the cerebrospinal fluid. Sometimes, an MRI of the spine is done separately to check for drop metastases, which are small clusters of tumor cells that may settle along the spinal cord. A lumbar puncture is often performed after surgery to collect cerebrospinal fluid and examine it for cancer cells, confirming whether the tumor has spread.

Definitive diagnosis comes from examining tumor tissue obtained during surgical resection. Pathologists look at the tumor under a microscope and perform molecular tests to identify the specific subtype based on genetic and protein markers. This information is vital for determining risk level and choosing the most appropriate treatment strategy.

Medulloblastoma Complications

Medulloblastoma and its treatment can lead to several physical, neurological, and psychological complications. The tumor itself, due to its location in the cerebellum, can cause long-term balance issues, coordination problems, and persistent headaches. If the tumor obstructs the flow of cerebrospinal fluid, it can lead to hydrocephalus, a condition that increases pressure inside the skull and may require the surgical placement of a shunt.

Surgical removal of the tumor, while essential, may cause injury to healthy brain tissue, leading to speech and movement difficulties. Radiation therapy, especially in children under three, can impact brain development, resulting in cognitive delays and learning disabilities. Hormonal imbalances are another potential complication, particularly when radiation affects the pituitary gland. Survivors may experience growth problems, early or delayed puberty, and thyroid dysfunction.

Chemotherapy, commonly used in high-risk or metastatic cases, can weaken the immune system, increase infection risk, and lead to fatigue, nausea, and hearing loss. Some patients may also experience psychological effects, such as depression or anxiety, which can impact their social and emotional well-being. Long-term follow-up care is critical to monitor and manage these complications over time.

Medulloblastoma Treatment

The treatment plan for medulloblastoma depends on the patient's age, the tumor subtype, the extent of the disease, and whether it has spread. Treatment typically begins with surgery to remove as much of the tumor as possible. Complete surgical resection is the goal, but even partial removal can relieve pressure and improve symptoms.

After surgery, most patients receive radiation therapy. For children older than three, craniospinal irradiation is standard, targeting the brain and spinal cord to eliminate microscopic tumor cells. In very young children, radiation may be delayed or avoided to prevent severe developmental issues. Instead, high-dose chemotherapy may be used to reduce tumor size and delay the need for radiation.

Chemotherapy plays a key role in treating both standard-risk and high-risk medulloblastoma. Common drugs include vincristine, cisplatin, and cyclophosphamide. These drugs are often used in combination and given in multiple cycles. In some cases, newer targeted therapies are considered, particularly when specific genetic mutations are identified. For example, vismodegib (Erivedge) targets the SHH pathway and has been studied in SHH-activated medulloblastomas.

Supportive care is vital during treatment to manage side effects and maintain quality of life. This includes medications for nausea, therapies for cognitive support, and rehabilitation services for motor function recovery. The treatment journey can be long and challenging, but advancements in therapy have led to better outcomes and improved survival rates in recent years.

Medulloblastoma Prognosis

The outlook for individuals with medulloblastoma has improved significantly due to advances in treatment and better understanding of the disease. Prognosis depends on several factors, including the molecular subtype, the extent of tumor removal during surgery, age at diagnosis, and whether the cancer has spread at the time of detection.

Patients with WNT-activated tumors generally have the best prognosis, with survival rates exceeding 90 percent with standard therapy. SHH-activated tumors have intermediate outcomes, which vary depending on additional genetic markers. Group 3 tumors, especially those with MYC amplification, are associated with a poorer prognosis due to their aggressive nature and higher likelihood of spreading. Group 4 tumors fall in between and account for the largest number of cases.

Younger children, especially those under three years of age, tend to have more challenging outcomes due to limitations in using full-dose radiation therapy. However, risk-adapted treatment strategies and tailored protocols are helping improve outcomes in this population.

Long-term survivors of medulloblastoma may experience late effects of treatment, such as cognitive delays, hearing loss, hormonal imbalances, and psychosocial challenges. Continued research is helping identify ways to reduce these effects while maintaining high cure rates.

Living with Medulloblastoma

Living with medulloblastoma, whether during active treatment or after remission, involves navigating a range of physical, emotional, and social challenges. For children, school reintegration can be difficult due to learning

difficulties or changes in concentration and memory. Cognitive rehabilitation and individualized education plans are often necessary to help them succeed academically. Physical therapy may be needed to address balance or coordination problems resulting from the tumor or its treatment.

Support from family, friends, and healthcare professionals is critical. Parents and caregivers often carry a heavy emotional burden and may benefit from counseling or peer support groups. Mental health care for both patients and caregivers should be part of the overall treatment plan to address anxiety, depression, or post-traumatic stress.

Regular medical follow-ups are essential for monitoring recurrence, managing side effects, and supporting developmental milestones. Survivorship programs, often offered by pediatric cancer centers, provide coordinated care that includes neurocognitive evaluations, endocrinology assessments, and social work services.

Conclusion

Medulloblastoma is a serious but increasingly treatable form of brain cancer, particularly in children. Through early detection, precise diagnosis, and targeted treatment strategies, outcomes have improved dramatically over the past few decades. The classification of medulloblastoma into genetic subtypes has allowed for more personalized and effective therapies, reducing unnecessary treatment and minimizing long-term side effects. While the journey through medulloblastoma can be long and complex, advances in medicine, supportive care, and rehabilitation offer hope for a better quality of life and long-term survival.

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