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Molecular insights and treatment approaches for a common childhood tumor – Medulloblastoma decoded: A review

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ABSTRACT

Introduction: Medulloblastoma is the most common tumor of the central nervous system in children. Advances in medicine have allowed for the identification of molecular subtypes of this tumor, which determine patient prognosis and further therapeutic approaches. *Aim of the study:* This review aims to provide an overview of medulloblastoma, which, due to its frequency, is a significant concern in the pediatric population. Non-specific symptoms can hinder diagnosis and even pose a threat to a child's life, making awareness among parents and clinicians crucial. *Summary of knowledge:* Medulloblastoma is a central nervous system tumor characteristic of childhood, occurring more frequently in boys. Despite being classified as WHO grade IV malignancy, chances of survival are high if detected before metastasis occurs. Symptoms are non-specific and usually result from increased intracranial pressure or mass effect. There is a division of medulloblastoma based on molecular and histological types. The cornerstone of treatment is radical resection, with adjuvant therapies including radiotherapy and chemotherapy. New targeted therapy methods remain under investigation. *Conclusion:* The molecular diagnosis of medulloblastoma subtypes is important for predicting outcomes and choosing the right therapy. Therapeutic approaches based on surgical methods are satisfactory, with high survival rates. New methods of targeted molecular therapy are undergoing continuous research and offer hope for developing treatment methods for this tumor.

Keywords: Brain tumor, neurosurgery, molecular subtypes, pediatric cancer

1. INTRODUCTION

Medulloblastoma (MB) is the most common tumor of the central nervous system in children. It is classified as highly malignant (grade IV according to WHO). However, the survival rate in cases detected before the appearance of metastases is high - even up to 80%. It belongs to the group of embryonal tumors. Due to its location in the posterior cranial fossa, symptoms are often nonspecific, which delays diagnosis (Quinlan and Rizzlo, 2017). The classification of medulloblastomas is based on histological and genetic types and includes types associated with activation of the WNT pathway, SHH, TP53 gene, or none of the above (Cotter and Hawkins, 2022). The current treatment regimen combines surgery, radiotherapy, and chemotherapy. The selection of therapy considers the patient's age, extent of resection, and presence of metastases (Bouffet, 2021).

2. METHODOLOGY

Articles related to the topic were analyzed from January 2006 to March 2024. The PubMed database, Google Scholar, and ScienceDirect were searched. Inclusion criteria are based on the publication date, topic compliance, and keywords. Articles older than ten years old are mainly excluded. To find relevant articles, the phrases: "medulloblastoma", "medulloblastoma molecular therapy", "medulloblastoma treatment", "medulloblastoma epidemiology", and "childhood brain tumors" were used.

3. RESULTS AND DISCUSSION

Epidemiology

Tumors of the central nervous system are the most common solid tumors in children and are associated with the highest mortality rate among all childhood cancers. Supratentorial tumors predominate in the population aged 0 to 3 years and again above the age of 10. Among them, the majority are of embryonal origin. Medulloblastoma, included in this group, is the most common malignant tumor of the central nervous system in children (Udaka and Packer, 2018). It accounts for 30-55% of posterior fossa tumors. The highest incidence occurs in children between 5 and 7 years of age. 75% of cases are diagnosed before the age of 15. Boys are affected twice as often as girls (Greenberg, 2019).

Etiology

Based on the genetic profile, scientists distinguish four types of medulloblastoma: WNT-activated, SHH-activated TP-53 mutant, SHH-activated TP53-wildtype, non-WNT/non-SHH group 3, and non-WNT/non-SHH group 4. The subtypes vary by the types of mutations present, their histological cell structures, and the ages at which they typically develop (Greenberg, 2019). A molecular subtype of the tumor has a more significant impact on the prognosis than its histological type (Millard and De-Braganca, 2016). Among the histological types, we distinguish classic, large cell/anaplastic, desmoplastic/nodular, and extensive nodular (Greenberg, 2019).

Risk factors

Environmental factors influencing the occurrence of medulloblastoma are not known. Only the role of genetic factors has been proven, including those related to mutations in developmental signaling pathways. These mutations often occur in congenital diseases such as Gorlin syndrome, Li-Fraumeni syndrome, or Fanconi anemia. The exact risk associated with inherited mutations in medulloblastoma remains unclear. However, individuals carrying mutations in SUFU and TP53 or biallelic mutations in BRCA2 and PALB2, are believed to face a heightened risk of MB. Researchers think the risk level is based on various factors including the specific type of mutation and the presence of genetic, epigenetic, and environmental factors (Northcott et al., 2019). In a study of 1,022 patients, 5.9% of medulloblastomas showed pathogenic germline variants in APC, BRCA2, PALB2, PTCH1, SUFU, and TP53 (Waszak et al., 2018). Mutations in the TP53 gene occur in 24% of children aged 5-14 years diagnosed with SHH-MB, while mutations in the SUFU gene in the same type of MB occur in 21% of children aged 0-3 years (Northcott et al., 2019).

Classification

Experts classify medulloblastoma into molecular and histological subtypes based on specific mutations and cellular architecture.

*Molecular classification**WNT subgroup*

WNT-medulloblastoma represents approximately 10% of all MB cases. It typically emerges after the age of 4, with a relatively even distribution between males and females. At diagnosis, WNT-MB tumors are rarely metastatic, and the prognosis for patients under 16 years old is highly favorable, with over 95% surviving beyond five years. However, adults diagnosed with WNT-MB may have a less positive outcome (Udaka and Packer, 2018; Northcott et al., 2019). This type of MB is typically found near the brainstem and the fourth ventricle. Histologically, it originates from progenitor cells from the lower rhombic lip. Receptors from the WNT family are responsible for controlling the cell cycle and embryogenesis. They first appeared in the etiology of Turcot syndrome, which is associated with an increased risk of MB.

The syndrome is attributed to mutations in the APC gene, which plays a role in inhibiting the WNT pathway. However, the most common mutation in this pathway is in the CTNNB1 gene, encoding β -catenin (Udaka and Packer, 2018). This mutation leads to the blocking of β -catenin degradation and its accumulation in the cell nucleus, resulting in a change in phenotype. Mutations in β -catenin associated with positive immunophenotyping of the cell nucleus contribute to increased patient survival (Geron et al., 2018). WNT-activated MB is characterized by a tendency to bleed, partially due to the poorly formed blood-brain barrier (Orr, 2020). Mutated β -catenin generates paracrine signals, causing vascular fenestration and, consequently, accumulation of drugs within the tumor.

Because of this process, the WNT subtype responds better to treatment than other types (Phoenix et al., 2016). Other genes mutated in this type of MB include TP53, SMARCA4, KMT2D, and DDX3X. TP53 mutations in WNT-MB are not associated with a worse prognosis, unlike their occurrence in the SHH-activated type (Orr, 2020). Most recent studies demonstrate the role of LEF-1 immunostaining in diagnosing this type of MB. Nuclear staining of LEF1 is easier to interpret than β -catenin and allows for positive results even in cases where β -catenin is negative. Therefore, this staining is recommended as routine in the diagnostic process (Aboubakr et al., 2024).

SHH subgroup

Sonic Hedgehog (SHH) MB constitutes roughly 30% of all cases and is most common in infants and adults (Table 1). SHH-MB is the most prevalent molecular subgroup among adult patients, constituting around 60% of all diagnosed cases. This subtype mainly originates in the cerebellar hemisphere, although it can also occur in the cerebellar vermis (Orr, 2020). Recent molecular studies classify SHH medulloblastomas into at least three variations in infants, children, and adults. This classification highlights the considerable heterogeneity within SHH tumors, characterized by a diverse array of genetic aberrations that distinguish them from one another (Udaka and Packer, 2018). SUFU mutations are observed in 21% of children under three years old (Northcott et al., 2019).

Germinal mutations in the TP53 gene typically occur in older children between the ages of 8 and 17 (Udaka and Packer, 2018). This mutation is associated with a worse prognosis, most commonly with the histological type of large cell/anaplastic (LCA) (Orr, 2020). In adults, the most somatic mutations are found in the TERT promoter. Other genes found to be responsible for the development of SHH-MB are SMO, GLI2, and MYCN. SHH medulloblastoma possibly originates from various cell types, including granule neuron precursor cells in the external granule layer, neural stem cells in the subventricular zone, or progenitor cells in the brainstem. However, recent findings indicate that infant SHH medulloblastomas might have a distinct cellular origin compared to those occurring in childhood or adulthood (Udaka and Packer, 2018).

Regarding the histologic types, the desmoplastic/nodular (DN) variant is the most frequently observed, accounting for slightly over 50% of cases (Orr, 2020). The SHH signaling pathway is essential in cell proliferation and differentiation (Udaka and Packer, 2018). In SHH-MB, transcriptional programs of the SHH pathway are activated and mutations often occur in its genes. Medulloblastomas characterized by SHH activation and wild-type TP53 status are typically linked with intermediate-risk disease, boasting a 5-year overall survival rate of approximately 76%. Conversely, TP53 mutations signify particularly high-risk clinical disease, marked by a dismal prognosis with only 41% survival at five years (Orr, 2020; Cambruzzi, 2018).

In Sonic Hedgehog-driven medulloblastoma, research has demonstrated that the activation of WNT signaling can suppress tumor growth through two distinct mechanisms: Beta-catenin-dependent or -independent inhibition of SHH signaling (Zinke et al., 2015). This type of MB has an intact blood-brain barrier, which hinders the penetration of chemotherapy drugs into the tumor mass and makes it resistant to treatment. Vincristine, commonly used in MB therapy due to its high molecular weight and high affinity with serum, penetrates very poorly through the intact blood-brain barrier. In vivo studies have demonstrated the resistance of SHH-MB to

vincristine, and reducing its cumulative dose had no impact on survival length. This explains the ineffectiveness of vincristine therapy in this type of MB (Phoenix et al., 2016).

Group 3

Medulloblastomas from this group account for 20% of all cases and 45% of cases in infants. They are typical in children, occurring extremely rarely in adults. Both group 3 and group 4 show a tendency to early metastasis formation and have a much worse prognosis than WNT- and SHH-activated MBs. The survival rate for patients with MB-G3 is lower than 60%. The most commonly presented histological type is classic, although cases of LCA occur. Molecularly, in G3 and G4, activation of the GFI1 and GFI1B loci occurs, while amplification of the MYC gene is characteristic of G3. The role of transforming growth factor β (TGF β) found in 20% of patients is also considered in the pathogenesis of MB G3 (Udaka and Packer, 2018; Orr, 2020; Juraschka and Taylor, 2019).

Group 4

G4 accounts for 40% of all MBs. It typically affects older children and adults. MBs from this group show a more significant disproportion in occurrence between genders than other types: They affect boys three times more often than girls. Although the G4 group is the most common, it is the least molecularly understood. The classic histological type predominates. Characteristic is the amplification of the MYCN gene (Udaka and Packer, 2018; Orr, 2020). Chromosomal instability may also occur, including the formation of the high-risk isochromosome 17q subtype, where the ten-year survival rate reaches 36%. Loss of part of chromosome 11 is a low-risk subtype, with a ten-year survival rate of 72% (Juraschka and Taylor, 2019).

Table 1 Latest discoveries based on the type of MB

Type of medulloblastoma	Mutations	Latest discoveries
WNT-MB	CTNNB1, TP53, SMARCA4, KMT2D, DDX3X	LEF-1 staining role in diagnosis
SHH-MB	TP53, SUFU, TERT promoter, SMO, GLI2, MYCN	Small-molecule inhibitors in targeted treatment; intact blood-brain barrier makes it resistant to chemotherapy
Group 3	GFI1, GFI1B, MYC	TGF β role in pathogenesis; observed relapses after radiation-sparing treatment approach
Group 4	MYCN, isochromosome 17q, loss of part of chromosome 11	Observed relapses after radiation-sparing treatment approach

Histological classification

Three main histological types of MB are distinguished: classic, large cell/anaplastic (LCA), and desmoplastic/nodular (DN). All types are considered grade IV by WHO (Greenberg, 2019).

Classic variant

It is the most commonly encountered variant, accounting for 72% of MB cases. It contains round-shaped cells of normal size and lacks excessive mitotic activity. Homer-Wright rosettes are observed (Millard and De-Braganca, 2016; Orr, 2020). This histological variant is found in each molecular type (Greenberg, 2019).

Desmoplastic/nodular variant (DN)

The DN variant contains neurocytoid differentiation nodules with intermediate embryonal elements in its structure. This type of MB tends to deposit collagen fibers around the cells but not near the differentiation nodules. They are detected by reticulin deposition. Some tumors in histological images show only nodules or desmoplasia (Orr, 2020). The DN variant occurs in the molecular type of SHH-activated MB, so it is essential to recognize it and implement appropriate therapy for this type (Greenberg, 2019; Orr, 2020). A separate variant of DN-MB is medulloblastoma with extensive nodularity (MBEN), occurring in newborns. The nodules have irregular shapes and often merge, creating a typical “stream” pattern (Orr, 2020).

Large cell/anaplastic variant (LCA)

This group combines two formerly distinct variants - large cell and anaplastic. The large cell type consists of large, round cells with prominent nuclei. Anaplastic features often occur, such as increased mitotic activity and apoptosis, but with no obvious pleomorphism. Anaplasia is described as increased cell size, cytological pleomorphism, nuclear shape change, mitotic activity, and the presence of apoptotic bodies (Orr, 2020). The occurrence of this variant among WNT-activated and G4 MBs is sporadic, but its presence in the SHH-TP53 mutant type and G3 makes an MB high-risk (Greenberg, 2019).

Symptoms

The symptoms are nonspecific, and children often cannot accurately describe them due to their age, which complicates the diagnostic process. The most common symptoms include increased intracranial pressure and tumor compression, such as headaches, clumsiness, fatigue, nausea, and morning vomiting. In younger children, developmental regression may occur. In older children, concentration weakness and school problems may appear. Due to the location of MB, most commonly in the cerebellum, more specific cerebellar symptoms may also be present: Ataxia, handwriting problems, strabismus, and nystagmus. Sometimes, there is a total loss of vision and neck stiffness.

Symptoms may quickly escalate from initially intermittent to moderate or severe. In infants, symptoms of increased intracranial pressure may not be obvious because compensation occurs by increasing head circumference - macrocephaly may be visible. In cases of metastasis to the spinal cord, the patient may complain of back pain, gait disturbances, and rarely - neurogenic bladder. Consciousness impairment was associated with metastatic processes (Northcott et al., 2019; Vinchon and Leblond, 2021). The manifestation in adults is similar: increased intracranial pressure and ataxia occur (Ciccarino et al., 2012; Eibl et al., 2021).

Diagnosis

The diagnosis of medulloblastoma relies on clinical symptoms, imaging studies, cerebrospinal fluid (CSF) cytology, and a combined assessment of histopathology and molecular analysis (Northcott et al., 2019). MB is a posterior fossa tumor typically localized in the cerebellum or the walls of the fourth ventricle in the midline. Extracranial location is infrequent but possible (Singh et al., 2021). Recent reports indicate the possibility of ectopic MB foci in the pineal region, showing affiliation with the WNT-activated molecular group (Tauziède-Espariat et al., 2023). Different tumor locations are indicated depending on the molecular type. WNT-MBs localize along the cerebellar peduncle/cerebellopontine angle, SHH-MBs in the cerebellar hemispheres, and G3 with G4 predominated within the midline fourth ventricle (Perreault et al., 2014).

Typically, after the onset of clinical symptoms, the patient undergoes imaging studies. If the patient's condition is severe, non-contrast CT is advised, while MRI is the method of choice. In the T1 sequence, the tumor is hypointense and enhances after contrast administration. An exception is group 4 tumors, which do not enhance, and group 3 tumors, whose outlines are blurred (Szalontay and Khakoo, 2020). In the T2 sequence, images are more diverse, and the tumor mass may be hypointense, isointense, or hyperintense. Due to their high cellularity, MBs give a hyperintense image in 80% of cases in the DWI sequence (Dangouloff-Ros et al., 2021). Infrared spectroscopy can also be used as an additional diagnostic tool, although it does not allow differentiation of MB molecular types (Łach et al., 2023). During the differential diagnosis, atypical teratoid/rhabdoid tumor (AT/RT), embryonal tumor with multilayered rosettes, and non-embryonal tumors of the posterior fossa such as ependymoma or ganglioglioma are considered (Cassia et al., 2018).

Treatment

A new risk stratification system is introduced for medulloblastoma patients aged 3 to 17. It incorporates subgroup status and specific genetic and cytogenetic abnormalities to better forecast outcomes. This system categorizes patients into four risk groups: Low risk (with over 90% survival rate), standard risk (with a survival rate between 75% and 90%), high risk (with a survival rate between 50% and 75%), and very high risk (with a survival rate below 50%) (Juraschka and Taylor, 2019). Identifying subtype-specific molecular drivers and pathways presents new therapeutic targets, potentially leading to subtype-specific treatment approaches (Suk et al., 2022).

Surgery

The primary treatment is tumor mass resection according to the golden rule of maximal safe resection. Studies have shown increased survival among patients undergoing gross total resection compared to subtotal resection. However, potential postoperative neurological complications have to be considered, and therefore, if necessary, leaving residual tumor mass is permissible. An important aspect is obtaining an adequate amount of tissue for histopathological and molecular examination, allowing for the assessment of tumor type and potential changes in the treatment pathway. One of the postoperative complications may be posterior fossa syndrome (Greenberg, 2019).

Posterior fossa syndrome, or cerebellar mutism, can occur in up to 25% of patients following the resection of midline cerebellar tumors. The development of posterior fossa syndrome (PFS) is likely influenced by multiple factors, with direct surgical injury being a significant contributor. Thermal damage, alongside mechanical injury to the proximal segment of the dentatohalamocortical (DTC) pathway, plays an essential role in the pathogenesis of PFS. Brainstem invasion is the only known preoperative risk factor associated with cerebellar mutism syndrome (Robertson et al., 2006; Avula et al., 2015).

Radiation therapy

The child's age is a limitation of radiotherapy. After surgery, children over three years old undergo craniospinal radiation with a boost to the tumor site, followed by chemotherapy. Younger children receive intensive chemotherapy alone (Jackson and Packer, 2023). A radiation-sparing approach has demonstrated good outcomes in the SHH-MB but hasn't shown the same effectiveness in groups 3 and 4. In these latter groups, relapses have been observed frequently (Ronsley et al., 2023).

Chemotherapy and modern methods of systemic therapy

In children aged over 3–5 years old who are deemed suitable for radiotherapy and have undergone near-total or gross total resection with no metastases, the standard of care involves a chemotherapy protocol. This regimen typically begins with weekly vincristine alongside radiotherapy, followed by eight cycles of another drug. Depending on the country, it can be cisplatin, vincristine, cyclophosphamide, and lomustine, Juraschka and Taylor, (2019) or etoposide, carboplatin, ifosfamide, and high-dose methotrexate (Mushtaq et al., 2023). However, the identification of four distinct subgroups of MB in the last decades has been a significant breakthrough, paving the way for developing novel clinical trials tailored to the molecular characteristics of each subgroup (Mushtaq et al., 2023). For example, current therapies for SHH medulloblastoma have aimed to target various aspects of the SHH signaling pathway. The inhibition of upstream targets using small-molecule inhibitors (erismodegi, sonidegib, and vismodegib) is one of the new methods.

Unfortunately, outcomes have been more favorable in adults compared to children. Downstream target inhibition has also demonstrated activity in preclinical models. However, the diverse heterogeneity of SHH tumors, characterized by multiple mutations and resistance mechanisms, presents a challenge in selecting appropriate therapy (Udaka and Packer, 2018; Samkari et al., 2015). Considerable efforts are dedicated to developing therapeutic agents that target the WNT pathway, with many undergoing investigations in preclinical and clinical trials for their potential as antitumor therapies. Despite these efforts, it remains uncertain whether modulating the WNT signaling cascade can yield substantial clinical benefits, as no WNT modulators have yet received approval as antitumor agents (Wen and Hadden, 2021). Another modern therapy strategy involves targeting the epigenetic processes associated with the development of MB. This treatment selectively affects cancer cells without damaging healthy tissues, which is a significant advantage (Strejcek et al., 2021).

4. CONCLUSION

Medulloblastoma is the most common malignant brain tumor in children, typically occurring in the cerebellum. Symptoms are often nonspecific, including headaches, nausea, vomiting, and problems with coordination. Diagnosis involves a combination of imaging studies, cerebrospinal fluid analysis, and histopathological examination. Treatment typically involves surgical resection followed by radiation therapy and chemotherapy. Recent advancements in molecular profiling have led to the identification of distinct subtypes, allowing for more targeted and personalized treatment approaches. Medulloblastoma remains a challenging disease despite advancements in therapy, highlighting the need for ongoing research and innovation in treatment strategies.

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The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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