REVIEW ARTICLE

Allan H. Ropper, M.D., *Editor*

Brain Tumors in Children

Alan R. Cohen, M.D.

From the Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore. Dr. Cohen can be contacted at alan.cohen@jhmi.edu or at Johns Hopkins University School of Medicine, Phipps Bldg., Rm. 556, 600 N. Wolfe St., Baltimore, MD 21287.

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Brain tumors are the most common solid neoplasms and the leading cause of death from cancer in children.[1-3] Tumors of the central nervous system (CNS) account for 20% of childhood cancers and are second only to leukemia in frequency.[4] The average annual age-adjusted incidence of brain tumors in children in the United States is 5.65 cases per 100,000 population, with 0.72 deaths per 100,000 (among children who are newborn to 14 years old).[3]

Recent diagnostic and therapeutic advances have led to improvement in survival and quality of life for many children with CNS cancers. However, the prognosis for many children with brain tumors remains poor, and treatments have long-term sequelae.[2,5] This review highlights recent changes in the classification and management of brain tumors in children. Given the large number of such tumors and the complexity of new classification schemes, only the most common and representative types are discussed here.

Classification of Brain Tumors in Children

The fifth edition of the World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS5), published in 2021, introduced major changes in brain tumor taxonomy, emphasizing molecular diagnostic features.[6] This has created a hybrid nomenclature of molecular biomarkers with conventional classifications based on histologic, ultrastructural, and immunohistochemical features. These changes are extensive and to nonspecialists (and specialists) may seem like simple renaming, but they reflect the trend of assigning diagnostic categories on the basis of genetic features that in many cases drive prognosis and offer potential targets for treatment.

The new system has introduced 22 unique tumor types, many of which include specific molecular alterations. Some names are unwieldy, such as "diffuse pediatric-type high-grade glioma, H3 wild type and IDH wild type" and "desmoplastic myxoid tumor of the pineal region, *SMARCB1* mutant." Molecular profiling is not widely available in developing countries, and even in the United States, exome and genome sequencing can take weeks, and treatment may need to be initiated before the molecular diagnosis is established.[7] There is also a gap between the prospect of understanding the genesis and behavior of brain tumors in children and the application of these new insights to clinical practice. A glossary and broad background information are provided in sections I and II, respectively, of the Supplementary Appendix, available with the full text of this article at NEJM.org.

Gliomas

Pediatric-Type Diffuse, Low-Grade Gliomas

Low-grade gliomas are the most frequent brain tumors of childhood and account for a third of all cases if mixed glioneuronal and neuronal tumors are included (Fig. 1A).[8] This group of tumors is heterogeneous; unlike low-grade gliomas in

adults, low-grade gliomas in children rarely transform into higher-grade tumors.[9] The common IDH1 or IDH2 mutants in low-grade gliomas in adults, which convert to higher-grade tumors, are much less common in tumors in children.[10]

The initial treatment for most low-grade gliomas in children is surgery to establish a tissue diagnosis and achieve maximal safe resection. In a large international study, 5-year progression-free survival for children with low-grade gliomas was 69%, and overall survival was 95%.[11] Risk factors for progression were young age, incomplete resection, fibrillary histologic features, and hypothalamic or chiasmatic location.

Gross total resection of low-grade gliomas in children is often not possible, particularly resection of those located deep in the midline. Many of these tumors are indolent, and observation with surveillance brain imaging is sometimes an option. Radiotherapy is effective for recurrent or residual low-grade gliomas, with 5-year progression-free survival of 71% and overall survival of 93%.[12] Children at risk for tumor progression on the basis of age, anatomical location, and genetic features are often treated with adjuvant chemotherapy because of concern about neurotoxic effects of radiation on the developing brain.[10] Chemotherapeutic agents that have been shown to be effective, either alone or in combination, include vincristine, carboplatin, vinblastine, 6-thioguanine, procarbazine, lomustine, cisplatin, etoposide, and irinotecan.[8,13,14]

Multiagent chemotherapy has been evaluated in a trial comparing carboplatin and vincristine with 6-thioguanine, procarbazine, lomustine, and vincristine. Event-free survival was similar in the two chemotherapy groups and was similar or superior to event-free survival with radiotherapy.[15] Tumors in both chemotherapy groups progressed within 5 years, but the four-agent regimen was associated with greater toxic effects. The role of the alkylating agent temozolomide is less clear in low-grade gliomas in children than in gliomas in adults, for which it is widely used.[8] The drug stabilized disease in children with recurrent low-grade gliomas in a phase 2 trial, although progression-free survival was only 17% at 4 years, and 70% of the patients required other treatments after temozolomide.[16] In another phase 2 trial involving children with recurrent low-grade gliomas, temozolomide was ineffective.[17]

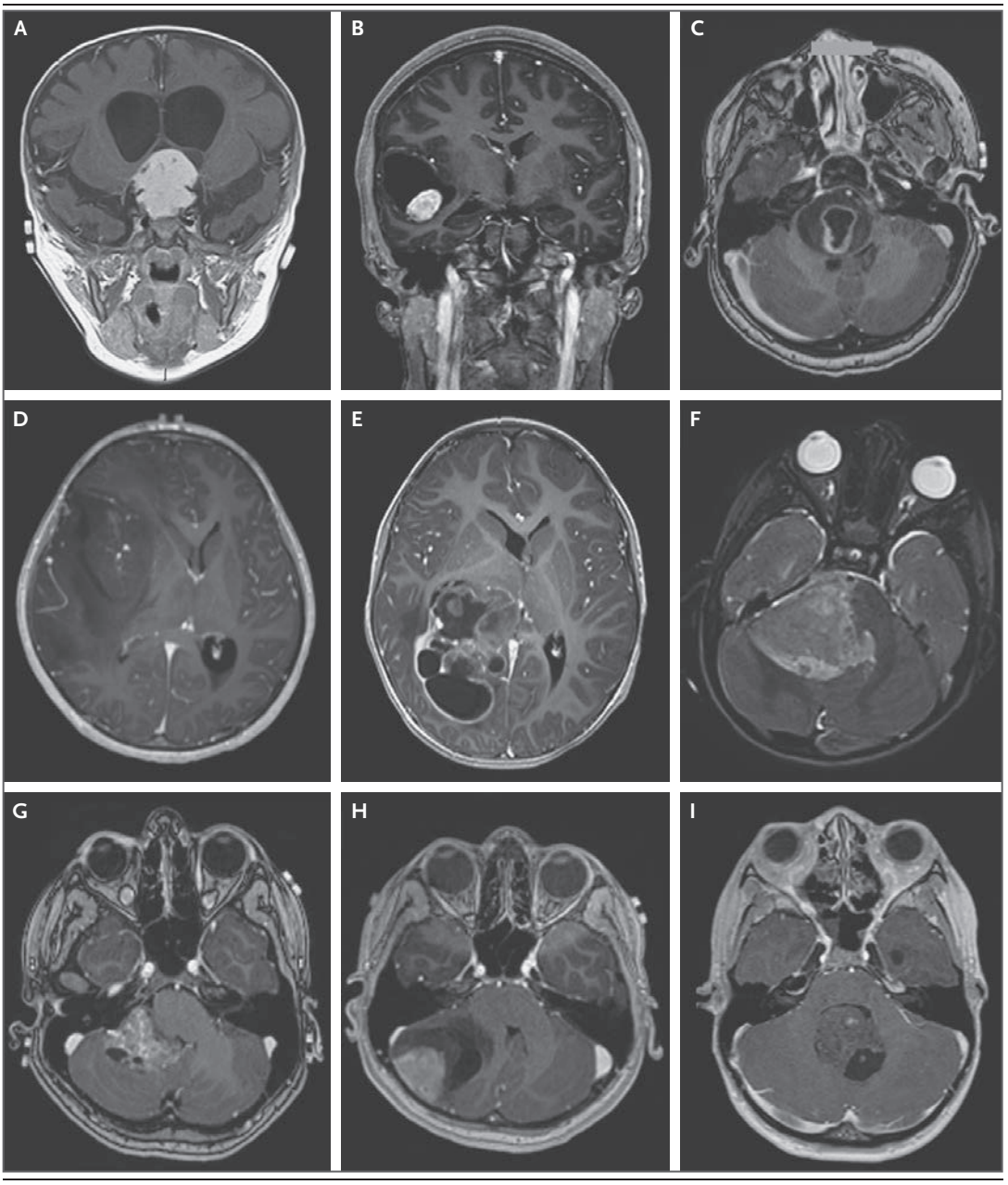
Molecular alterations have been targeted with the use of drugs that may be more effective and less toxic than conventional chemotherapy.[18] Alterations in the downstream signaling pathway of the rat sarcoma virus–mitogen-activated protein kinase (MAPK) pathway have generated considerable attention. This pathway sends information from the cell surface to modulate gene expression for several cellular functions, including growth. Most low-grade gliomas have one or more alterations in the MAPK pathway, including mutation or fusion of the *BRAF* oncogene (Table 1), *NF1* mutation, fibroblast growth factor receptor 1 mutation, and neurotrophic tyrosine receptor kinase (*NTRK*) family fusions.[19,20]

Somatic alterations of *BRAF* or germline alterations of *NF1* have been found that may play a role in tumorigenesis.[9] Some low-grade gliomas have alterations in *BRAF*, which encodes a serine–threonine kinase protein (BRAF), a downstream regulator of the MAPK pathway. Two common *BRAF* alterations are a point mutation in the *BRAF* V600E oncogene and fusion of *BRAF* and another large gene of unknown function, *KIAA1549* (Table 1).[21,22]

BRAF inhibitors (dabrafenib) and downstream MEK inhibitors (trametinib and selumetinib) are under investigation.[2,7] Children with *BRAF*-mutated low-grade gliomas, particularly those associated with homozygous deletion of the tumor-suppressor gene *CDKN2A*, have a poor response to conventional chemoradiation therapy.[22,23] *BRAF* inhibition, however, has led to initial and durable responses,[22] and selumetinib was effective in a phase 2 trial involving children with *BRAF*-aberrant or *NF1*-associated low-grade gliomas that were recurrent, progressive, or refractory to treatment.[24] These findings have prompted phase 3 trials comparing selumetinib with standard chemotherapy for newly diagnosed low-grade gliomas.

PILOCYTIC ASTROCYTOMAS

The most common astrocytomas of childhood are pilocytic astrocytomas, which account for about 20% of brain tumors in children, adolescents, and young adults (<20 years of age) (Fig. 1B).[8,25-27] They are generally slow-growing and circumscribed, with 10-year survival exceeding 90%.[26,28] Most of these tumors are located in the cerebellum and suprasellar region, but they can appear elsewhere. Although pilocytic astrocytomas rarely undergo malignant transformation and generally have a favorable prognosis,



20% have a poor outcome, with local recurrence or dissemination.[18,25] The *KIAA1549–BRAF* fusion occurs in 80 to 90% of pilocytic astrocytomas, particularly those in the posterior fossa, and may be associated with increased overall survival.[19,25,29] Other genetically driven gliomas are discussed in section III of the Supplementary Appendix.

PEDIATRIC-TYPE DIFFUSE, HIGH-GRADE GLIOMAS

Pediatric-type high-grade gliomas account for 10% of brain tumors in children and have a poor prognosis (Table 2).[30] Despite surgery and adjuvant therapy, 70 to 90% of affected children die within 2 years after diagnosis.[31] The term "glioblastoma multiforme," the most common primary malignant brain tumor in adults, has been reclassified in the WHO CNS5, with an emphasis on molecular markers. The new classification defines glioblastoma narrowly as a diffuse, IDH wild-type astrocytic glioma in adults with specific histologic or molecular alterations. As a result, the term "glioblastoma" has been removed from the lexicon of neoplasms in children.[6]

An advance in understanding high-grade glio-

Figure 1 (facing page). T1-Weighted, Contrast-Enhanced Magnetic Resonance Imaging (MRI) Scans of Representative Brain Tumors of Childhood.

The MRI scans show the heterogeneity of brain tumors in children in terms of location, size, enhancement, and internal structure. The coronal scan in Panel A shows a suprasellar *BRAF* V600E–mutated, low-grade glioma. The coronal scan in Panel B shows a cystic and solid pilocytic astrocytoma in the right temporal lobe. In Panel C, an axial scan shows a swollen pons with ring-enhancing, right paracentral diffuse midline glioma, H3K27-altered. The axial scan in Panel D shows a large, infiltrative, slightly enhancing, diffuse, pediatric-type high-grade glioma in the right hemisphere, H3 wild type and IDH wild type. In Panel E, an axial scan shows a large, heterogeneously enhancing, *ZFTA* fusion–positive supratentorial ependymoma in the right parietal lobe. In Panel F, an axial scan shows a heterogeneously enhancing, right infratentorial posterior fossa A (PFA) tumor compressing the brain stem; H3K27 methylation was absent, which is characteristic of PFA tumors. The axial scan in Panel G shows an enhancing wingless/integrated (WNT)–activated medulloblastoma in the right cerebellopontine angle. In Panel H, an axial scan shows a cystic and solid, heterogeneously enhancing sonic hedgehog (SHH)–activated medulloblastoma, *TP53* wild type, in the posterolateral right cerebellar hemisphere. The axial scan in Panel I shows a cystic and solid, slightly enhancing, midline non-WNT, non-SHH medulloblastoma in the fourth ventricle.

Table 1. *BRAF* Oncogene Alterations in Low-Grade Gliomas in Children.

Variable	Mutation	Fusion
Gene	*BRAF* V600E	*KIAA1549–BRAF*
Alteration	Point mutation	Truncated tandem fusion
Gene locus	7q34	7q34
Tumors affected	Low-grade glioma, pleomorphic xanthoastrocytoma, ganglioglioma (less commonly, pilocytic astrocytoma)	Pilocytic astrocytoma
Frequency	15–20% of low-grade gliomas, second most common mutation after neurofibromatosis type 1	80% of pilocytic astrocytomas
Tumor location	More often supratentorial	More often infratentorial
Prognosis	Predicts poor response to standard chemoradiation therapy*	Generally favorable
Targeted inhibition	Response in early trials	Response in early trials

* The response is poor particularly when the *BRAF* mutation occurs with homozygous deletion of the tumor-suppressor gene *CDKN2A*.

mas has been the identification of driver mutations in the chromatin-remodeling gene family, histone *H3*.[32,33] In patients with diffuse midline or hemispheric gliomas, somatic mutations in the tail of H3 decrease methylation and block glial differentiation, promoting gliomagenesis.[34]

Four subtypes of gliomas have been identified. The diffuse midline glioma is a particularly lethal tumor that affects young children and is unresectable. A new term, "H3K27-altered," has been substituted for the prior term, "H3K27M-mutant," since additional molecular changes have been identified.[6] H3K27-altered tumors include the previously named diffuse intrinsic pontine glioma, along with aggressive gliomas involving the thalamus and other midline structures. Methylation studies of diffuse midline gliomas have identified an oncogenic histone missense point mutation in histone H3.[35,36] These tumors are associated with worse survival than wild-type counterparts (Fig. 1C).[37] The H3K27

Table 2. Pediatric-Type Diffuse, High-Grade Gliomas.*

Variable	Midline Gliomas	Hemispheric Gliomas	H3 and IDH Wild-Type Gliomas
Histone status	H3K27-altered in about 90% of cases	H3G34-mutant in about 20% of cases	—
Median age of patient (yr)	5–10	14	10
Location	Midline, thalamus	Cerebral hemispheres	Mostly supratentorial
Other genomic alterations	*TP53* mutation, *ACVR1* mutation, *PDGFRA* mutation	*TP53* mutation, *ATRX* mutation, MGMT promoter methylation	*TP53* mutation
Prognosis (median overall survival)†	Very poor (<1 yr)	Poor (1–2 yr)	*MYCN* amplification: very poor (14 mo) *PDGFRA* amplification: poor (21 mo) *EGFR* amplification: intermediate (44 mo)

* ACVR1 denotes activin A receptor type 1, ATRX α-thalassemia X-linked, EGFR epidermal growth factor receptor, TP53 tumor protein 53, MGMT O^6-methylguanine–DNA methyltransferase, MYCN v-myc avian myelocytomatosis viral oncogene neuroblastoma–derived homologue, and PDGFRA platelet-derived growth factor receptor α.
† There are three prognostic subgroups for H3 and IDH wild-type gliomas.

alteration is more predictive of prognosis than is histologic grading.[35]

The H3K27 alteration appears to be specific for diffuse midline high-grade gliomas in children.[38] A second subtype, diffuse hemispheric glioma, H3G34-mutant, arises in the cerebral hemispheres in older children and young adults.[35,39,40] This tumor is associated with other genetic alterations, including α-thalassemia X-linked (*ATRX*) and TP53 tumor protein 53 (*TP53*) mutations and O^6-methylguanine–DNA methyltransferase (MGMT) promoter methylation.[8] Histone mutations have been identified in more than 80% of midline high-grade gliomas and in more than 40% of those in the cerebral hemispheres, predominantly in children.[32,41]

A third subtype is diffuse pediatric-type high-grade glioma, H3 wild type and IDH wild type (Fig. 1D). This is an aggressive tumor, usually found in the cerebral hemispheres, with a poor prognosis.[42] The fourth subtype, a clinically distinct neoplasm in newborns and infants, is the infant-type hemispheric glioma, which often harbors receptor tyrosine kinase gene fusions, including *ALK*, *NTRK1/2/3*, *ROS1*, and *MET4*. These kinase alterations are potentially targetable, and preliminary studies suggest an improved outcome for patients with kinase fusion–positive tumors.[41,43,44]

Standard adjuvant treatment is focal palliative irradiation, but long-term survival is poor, with no appreciable improvement in outcome during the past 50 years. The 3-year event-free survival and overall survival rates for children with high-grade gliomas are 10% and 20%, respectively.[45] The outcome for diffuse midline gliomas of the pons is abysmal, with a median survival of 4 months in the absence of radiotherapy and only 8 to 11 months with radiotherapy.[46]

Targeted therapy driven by mutations has thus far not had substantial effect, but it has only recently been introduced into clinical practice. In general, chemotherapy has had only limited effectiveness in the treatment of high-grade gliomas in children. In adults with high-grade gliomas, temozolomide has improved event-free and overall survival, as compared with radiotherapy alone.[45] This has not been the case for children. In a phase 2 study, temozolomide failed to improve the outcome for children with newly diagnosed high-grade gliomas. However, overexpression of MGMT adversely affected survival, which may have caused the lack of response to temozolomide.[47] In an effort to overcome presumed MGMT-mediated resistance, a phase 2 study added lomustine to temozolomide in a dual-alkylator regimen to deplete MGMT and resulted in better event-free and overall survival, as compared with temozolomide alone.[48]

The H3K27 mutant has been targeted with the use of the histone deacetylase (HDAC) inhibitors. For example, panobinostat, used to treat multiple myeloma, has shown efficacy in vitro and in orthotopic xenograft murine models of infiltrative gliomas and is being evaluated in clinical trials.[2,49] Fimepinostat, a pan-HDAC and PI3K inhibitor, is under investigation in a phase 1 trial involving patients with high-grade gliomas and those with recurrent medulloblastomas. Other treatments under investigation include immune checkpoint inhibitors, chimeric antigen receptor T-cell therapy, cancer vaccines, and oncolytic virotherapy.

EPENDYMAL TUMORS

Ependymomas are the third most common brain tumors of childhood, after gliomas and medulloblastomas, accounting for 5 to 10% of CNS neoplasms in children; 90% are intracranial, with most arising in the posterior fossa, and the remainder are spinal.[50,51] Ependymal tumors are a heterogeneous group, classified on the basis of histologic characteristics, molecular features, and location, with at least nine molecular subtypes.[6,52] The former WHO histologic classification did not correlate well with prognosis and has been modified. Ependymomas are still classified as grade 1, 2, or 3 according to the degree of anaplasia. The rare subependymoma is grade 1. The myxopapillary ependymoma, once considered grade 1, is now classified as grade 2, since the likelihood of recurrence is thought to be similar to that of conventional spinal ependymomas.[6] Emphasis has been placed on molecular aberrations, and the term "anaplastic ependymoma" is no longer listed.

Grade 2 and 3 ependymomas are supratentorial or infratentorial in location (Table 3). Supratentorial ependymomas are categorized on the basis of two oncogenic molecular fusions. The *C11orf95–RELA* fusion occurs in 70% of cases, causing constitutive activation of the nuclear fac-

Table 3. Ependymomas in Children.

Variable	Supratentorial		Infratentorial	
	ZFTA Fusion–Positive	*YAP1* Fusion–Positive	Posterior Fossa A	Posterior Fossa B
Frequency (%)	70	30	90	10
Median age of patient (yr)	8	1	3	20
Sex predominance	Female	Male	Female	Female
Location	Cerebral hemisphere	Cerebral hemisphere	Lateral	Midline
Molecular alteration	*ZFTA* fusion, chromothripsis*	*YAP1–MAMLD1* fusion	H3K27 trimethylation: low	H3K27 trimethylation: high
Prognosis†	Usually poor	Usually good	Usually poor	Usually good

* The *ZFTA* gene was previously called *C11orf95*. Chromothripsis refers to catastrophic chromosomal shattering and rearrangement at chromosome 11.

† In the Children's Oncology Group trial ACNS0121,[54] significant differences in prognosis were not found between *ZFTA* fusion–positive cases and *YAP1* fusion–positive cases or between posterior fossa A cases and posterior fossa B cases treated with conformal radiotherapy.

tor κB signaling pathway[52] (Fig. 1E). The new designation of the *C11orf95* gene is *ZFTA*; *ZFTA* may fuse with more ligands than just *RELA*.[6] The other fusion involves *YAP1*. As compared with the *YAP1* fusion, the newly named *ZFTA* fusion has been reported to outperform histologic classification in predicting clinical course, conferring a worse prognosis.[53] However, patients with the *ZFTA* fusion who received conformal radiotherapy (with beams matched to the shape of the tumor) did not have a uniformly poor outcome, suggesting that the clinical significance of this fusion remains unclear.[52,54]

Posterior fossa ependymomas are subdivided on the basis of methylomic profiling into the two most common subtypes: PFA and PFB ependymomas. The former occur predominantly in infants, are located laterally, and have a worse prognosis than PFB ependymomas. PFA tumors have a relative loss of the H3K27 trimethylation epigenetic marker as compared with PFB tumors.[52,55] The PFB subtype occurs in older children and generally has a better prognosis (Fig. 1F).[56] However, prognostic value was not found when children in PFA and PFB groups received conformal radiotherapy.[54]

Children with nonmetastatic ependymomas are initially treated with maximal safe resection, followed by focal conformal irradiation, except for infants.[2,50,53] A role for chemotherapy has not been established but is under investigation. Despite advances in surgery and radiotherapy, the long-term outcome for childhood ependymomas remains poor, with 10-year rates of overall and progression-free survival of 50% and 30%, respectively.[50]

CNS EMBRYONAL TUMORS

Embryonal tumors are also a heterogeneous group of malignant CNS neoplasms, primarily affecting young children and accounting for approximately 20% of childhood brain tumors.[57] These tumors have small, round, densely packed blue cells with scant cytoplasm and varying degrees of differentiation and were initially categorized as primitive neuroepithelial tumors (PNETs).[1,58] Those arising in the posterior fossa were called medulloblastomas, and those in the pineal region were called pineoblastomas — names still in common use despite the new classification — and those above the tentorium were called supratentorial PNETs.[58,59]

Molecular profiling has led to reclassification of these tumors on the basis of genetic drivers combined with histologic features.[29,60] The umbrella term "PNET" has been replaced by the term "CNS embryonal tumor," underscoring the molecular differentiation.[61] According to the WHO CNS5, the two types of embryonal tumors are medulloblastomas and other CNS embryonal tumors. The distinction is based on an inte-

Table 4. Medulloblastoma Molecularly Defined.*

Variable	WNT-Activated Medulloblastoma	SHH-Activated Medulloblastoma, *TP53* Wild Type or Mutation	Non-WNT, Non-SHH Medulloblastoma
Frequency (%)	10	30	60
Age group	Older children, adolescents	Infants, children, adults	Infants, children
Male:female ratio	1:1	1:1	2:1 or 3:1
Location	Midline, sometimes cerebellar peduncle, brain stem	Lateral cerebellum	Midline
Metastases at presentation (% of cases)	10	15–20	35–45
Histologic features	Classic, LCA rare	DNMB, MBEN, classic uncommon, LCA rare	Classic, LCA
Genomic mutations	*CTNNB1* (β-catenin), *DDX3X*, *SMARCA4*, *TP53*, *APC*†	*TP53*, *PTCH1*, *SUFU*, *TERT*‡	*KBTBD4*, *SMARCA4*
Genomic amplifications	—	*GLI1/2*, *MYCN*, *OTX2*	*MYC*, *MYCN*, *OTX2*, *CDK6*
Prognosis	Very good; 5-yr overall survival, 95%	*MYCN* amplification: poor *TP53* mutation: very poor *OTX2* amplification: intermediate	Infants: poor Metastatic disease: poor *MYC* amplification: poor Other histologic features: intermediate

* DNMB denotes desmoplastic nodular medulloblastoma, LCA large-cell anaplastic, and MBEN medulloblastoma with extensive nodularity. A comprehensive glossary is provided in section I of the Supplementary Appendix, available with the full text of this article at NEJM.org.
† *TP53* mutations in wingless/integrated (WNT)–activated medulloblastomas do not have prognostic significance.
‡ *TP53* mutations in sonic hedgehog (SHH)–activated medulloblastomas confer a significantly worse prognosis.

grated taxonomy with strong emphasis on molecular profiling.

MEDULLOBLASTOMAS

Although low-grade gliomas are the most common brain tumors of childhood, medulloblastomas are the most common malignant brain tumors of childhood.[62] They usually arise in the cerebellum, and patients present with signs of increased intracranial pressure or cerebellar dysfunction. Medulloblastomas account for more than 60% of childhood embryonal tumors, and 70% occur in children under the age of 10 years, affecting boys more than girls, though age and sex differences vary according to tumor subtype.[3,63,64] One third of cases arise in children under the age of 3 years.[65]

Factors associated with a poor outcome for children with medulloblastoma include large size, disseminated disease at presentation, young age (<3 years), and residual tumor of more than 1.5 cm^2 on postoperative imaging.[62] Previous morphologic classifications identified four subtypes: classic medulloblastoma, large-cell anaplastic medulloblastoma, desmoplastic–nodular medulloblastoma, and medulloblastoma with extensive nodularity.[61] The latter two histologic variants have a more favorable prognosis than the first two.[65]

The CNS5 system now recognizes two types of medulloblastoma: medulloblastoma molecularly defined and medulloblastoma histologically defined. The category medulloblastoma molecularly defined contains four subtypes, each with unique methylomic and transcriptomic profiles and distinctive clinical behavior (Table 4). Genetic analyses have identified subcategories of the subtypes and suggest new treatment strategies.[49] Subcategories of the subtypes of medulloblastoma are described in section IV of the Supplementary Appendix.

WNT-Activated Medulloblastomas

The wingless/integrated (WNT)–activated subtype accounts for 10% of all medulloblastomas, affecting boys and girls equally and occurring in

older children or adolescents (Fig. 1G). The tumors are located in the cerebellar midline and sometimes involve the peduncles and brain stem. WNT medulloblastomas have classic histologic features and are frequently associated with accumulation of β-catenin, encoded by *CTNNB1*. Mutation of *CTNNB1* is present in 90% of cases and causes accumulation of nuclear β-catenin, which propels oncogenesis.[5,61,63,66,67]

These tumors have a very good prognosis, with the 10-year event-free survival rate exceeding 95%.[68] They have an aberrant fenestrated vasculature driven by excess levels of mutant β-catenin, which impairs the blood–brain barrier and may permit access for chemotherapy. This feature of WNT tumors may explain why some patients present with hemorrhage.[69,70] Because WNT tumors are associated with good survival, treatment strategies for the reduction of radiation therapy and chemotherapy are being investigated.[2,49,66,71]

SHH-Activated Medulloblastomas

Sonic hedgehog (SHH)–activated medulloblastomas account for 30% of medulloblastomas and have an equal sex distribution, affecting young children and young adults (Fig. 1H). They are usually located in the cerebellar hemispheres and are believed to arise from precursors in the external granule-cell layer of the cerebellum. In contrast to WNT medulloblastomas, SHH medulloblastomas have more biologically and clinically relevant heterogeneity. They commonly arise from germline or somatic alterations in the SHH–PTCH–SMO–GLI signaling pathway, including deletions or loss-of-function mutations in the tumor-suppressor gene *PTCH1* (43% of cases), activating mutations in the proto-oncogene *SMO* (9%), and amplifications in the oncogenes *GLI1* and *GLI2* (9%).[66,68,69]

SHH medulloblastomas have been stratified according to the presence or absence of the *TP53* tumor-suppressor gene. *TP53* mutations (occurring in 9% of cases) act as drivers of tumorigenesis and portend a poor prognosis, whereas *TP53* mutations in WNT tumors do not affect the outcome.[66,72] *TERT* promoter mutations, which affect structural maintenance of the telomere, occur in 40% of SHH medulloblastomas and are present in almost all cases in adults.[67] Molecular stratification of SHH medulloblastomas has led to clinical trials of targeted therapies. One example is the use of the new SMO inhibitors, vismodegib and sonidegib, for refractory or relapsed SHH medulloblastomas.[1,2,5,68,69,73]

Non-WNT, Non-SHH Medulloblastomas

In the current nomenclature, the non-WNT, non-SHH subtype includes group 3 and group 4 medulloblastomas. Unlike WNT and SHH medulloblastomas, these tumors affect boys more often than girls and are most likely to have metastasized at the time of presentation. They are located in the cerebellar midline and usually have classic or large-cell anaplastic histologic features.[5] Underlying driver mutations have not been identified (Fig. 1I).[63]

Group 3 tumors account for 25% of medulloblastomas, occur in infants and children, and have the poorest prognosis, with an overall survival rate of 50% at 5 years.[68] Cytogenetic abnormalities are common, including isochromosome (mirror image) 17q in almost half the cases.[1,66,67] For young children (<3 years old), new treatments have been administered after surgical resection, including high-dose chemotherapy with autologous stem-cell rescue and other risk-adaptive regimens to delay irradiation and avoid myeloablation.[5]

Group 4 tumors are the most common, accounting for 35% of all medulloblastomas.[2] They occur in older children and adolescents and have an intermediate prognosis, with a 5-year overall survival rate of 70%.[5] Genetic alterations include amplifications in the *MYCN* oncogene (in 6% of cases) and in *CDK6* (in 5 to 10% of cases).[1,24] Like group 3 medulloblastomas, these tumors have several chromosomal aberrations, with isochromosome 17q present in 80% of cases.[68] They have been divided into a high-risk group enriched for isochromosome 17q, with a 10-year overall survival rate of 36%, and a low-risk group with loss of chromosome 11 and *MYCN* amplification, with a 10-year overall survival rate of 72% — twice that of the high-risk group.[66,72] Medulloblastoma and hereditary brain tumor predisposition syndromes are discussed further in section V of the Supplementary Appendix.

Management of medulloblastomas consists of maximal safe resection followed by craniospinal irradiation and chemotherapy.[5] Current investigations are focused on de-escalation of treatment

for WNT medulloblastomas to reduce the toxic effects of craniospinal irradiation and chemotherapy, therapy that targets *SMO* and its downstream pathway for SHH medulloblastomas, and risk-adjusted treatments for the group 3 and 4 subtypes of non-WNT, non-SHH medulloblastomas.[5,66]

The rare but lethal atypical teratoid rhabdoid tumor is discussed in section VI of the Supplementary Appendix.

OTHER CNS EMBRYONAL TUMORS

The category of other CNS embryonal tumors is divided into subtypes. These include atypical teratoid-rhabdoid tumors; embryonal tumors with multilayered rosettes; CNS neuroblastomas, *FOXR2*–activated; and CNS tumors with *BCOR* internal tandem duplication.

SUMMARY

Genome sequencing and DNA methylome profiling have greatly altered the categorization of brain tumors in children. Although the prognosis for selected tumors has improved as a result of refinements in surgical and adjunctive treatment, molecular diagnostic insights have thus far provided only limited therapeutic advances. There is reason to hope, however, that targeted therapy will improve the outcome for intractable tumors and mitigate the adverse effects of treatment.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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