Central Nervous System Tumor Classification

An Update on the Integration of Tumor Genetics

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KEYWORDS

• Brain tumor • Pathology • Molecular • Diagnosis • Classification • Grading

KEY POINTS

- Molecular markers have resulted in the clinical and pathologic refinement of diagnoses in central nervous system tumors.
- It is timely to update what we know regarding the incorporation of these markers in common central nervous system tumors.
- This review is based largely on the publications of the C-IMPACT group.

INTRODUCTION AND GENERAL PRINCIPLES

The Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy – Not Official WHO (C-IMPACT) group was established to outline principles for the tumor classification and grading of the central nervous system.[1] The group's primary focus was to incorporate accepted molecular findings into the World Health Organization (WHO) classification system. C-IMPACT has presented their recommendations in 7 peer-reviewed publications[2–8]; this article is based on those recommendations (in press). In addition to the classification recommendations, they have made several other general recommendations: "Entities" and "variants" are now referred to as "types" and "subtypes," respectively.

Type – "a neoplasm in which multiple parameters (eg, clinical, anatomic, histopathologic, and/or molecular) differ from other types."
Subtype – "a variant of type in which a single or couple of parameters suggest it differs from other subtypes."

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The WHO grades will use Arabic numerals.[7]

The WHO defines "not otherwise specified" as tumors for which the molecular status has not been fully assessed; the not otherwise specified designation indicates insufficient molecular information to assign a more precise diagnosis[2] that may arise because (1) necessary molecular testing cannot be performed, (2) testing failed, or (3) testing was not attempted. In contrast, "not elsewhere classified" reflects situations in which the necessary assays were performed, but do not allow for a specific WHO diagnosis.[2] Biomarker detection is method agnostic.

This article provides an overview of common central nervous system tumors encountered in the clinic that have been impacted by recent molecular findings that have resulted in a revision of our understanding of them.

DIFFUSE GLIOMAS

The WHO categories for the diffuse gliomas are summarized in **Table 1**.

Diffuse Astrocytomas

Arising anywhere along the neuraxis, infiltrative astrocytomas (IA) exhibit a diversity of histologic patterns. Graded 2 to 4, IA (see **Table 1**) exhibit infiltrative growth patterns and become progressively malignant. Histologic grading[9] is based on mitotic activity, vascular proliferation, and necrosis. Molecular typing of grades 2, 3, and 4 depends on mutated *isocitrate dehydrogenase 1* (*IDH1*) or *IDH2*.[9] The result of this heterozygotic mutation[10] is genome-wide methylation.

Diffuse Astrocytoma (DA-2) exhibits simplified fibrillary processes, nuclear pleomorphism and low proliferation activity (**Fig. 1**). DA-2 may progress to Anaplastic Astrocytoma (AA-3) as diagnosed by brisk mitotic activity (**Fig. 2**), or to astrocytoma, grade 4 (glioblastoma [GBM]), diagnosed by the addition of microvascular proliferation and/or necrosis[9] (**Fig. 3**A). Biomarkers found in IA grades 2 to 4, including epidermal growth factor receptor (EGFR) polysomy (see **Fig. 2**C), are summarized in **Table 2**. These markers can also be used to distinguish DA-2 from reactive gliosis.[11,12]

Although 5% of GBM exhibit evidence of progression from a prior DA-2 or AA-3, 95% seem to have arisen *de novo*. The distinction is made clinically or by the presence of IDH1/2$^{+/-}$ in progressive or secondary GBM (**Fig. 3**B). Homozygous loss of *CDKN2A/B* (loss of chromosome 9p21) is also found in secondary GBM-4.[13]

Alpha thalassemia/mental retardation syndrome X-linked (*ATRX*) mutations and *TP53* mutations are found in a majority of DA-2, AA-3, and secondary GBMs. *ATRX* WT, *TP53* mutations, and *TERT* promoter mutations are found in *de novo* adult GBMs.[14,15]

Table 1
WHO categories for diffuse gliomas

	Type	WHO Grade
Astrocytomas	Astrocytoma, IDH-mutant	2
	Astrocytoma, IDH-wt	
	Anaplastic astrocytoma, IDH-mutant	3
	Anaplastic astrocytoma, IDH-wt	
	Astrocytoma, IDH-WT with molecular features of grade 4 GBM, IDH-wt	4
Oligodendrogliomas	Oligodendroglioma, IDH-mutant, 1p19q-codeleted	2
	Anaplastic oligodendroglioma, IDH mutant, 1p19q-codeleted	3

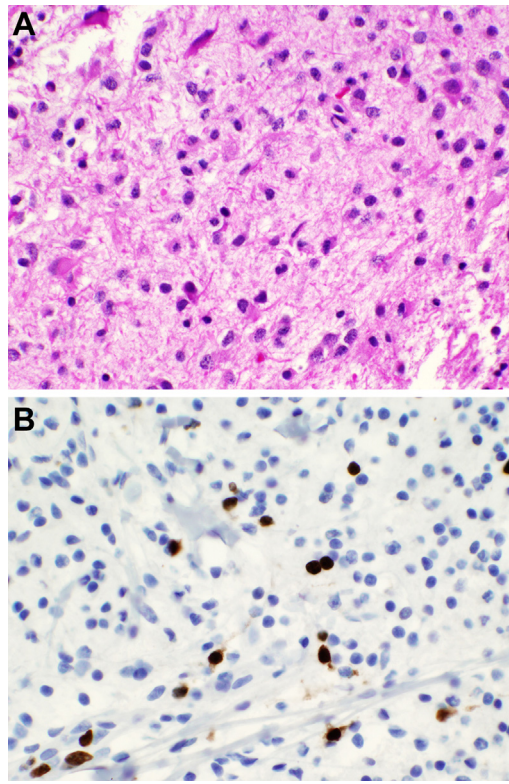

Fig. 1. DA-2 exhibits simplified fibrillary processes, nuclear pleomorphism and low proliferation activity (*A*, hematoxylin-eosin, original magnification ×40; *B*, Ki-67, original magnification ×40.)

Among de novo GBM (IDH WT), tumors may exhibit gain of 7/loss of 10 (ie, *EGFR* amplification, PTEN monosomy) (**Fig. 4**), *TERT* promoter mutation, and/or expression of *EGFR* variant 3, *EGFRvIII*. The presence of any set of these markers can be used to render the diagnosis of diffuse astrocytic glioma, *IDH*-WT, with molecular features of GBM, WHO grade 4 in an undersampled biopsy.[4]

Patients with GBM, $IDH^{+/-}$, grade 4 have a better overall survival than GBM, IDH wildtype (WT). Similarly, patients with AA-3, $IDH^{+/-}$ have a better overall survival than those with AA-3 *IDH* WT.[16]

Because IA-2, IDH-WT frequently represent inadequately sampled GBM-4, the WHO no longer recognizes a diffuse astrocytoma, *IDH*-WT, grade 2; further investigation often demonstrates molecular findings of a GBM-4.[4]

Oligodendrogliomas, Isocitrate Dehydrogenase$^{+/-}$, and 1p19q Codeleted

Oligodendrogliomas (Oligo) (occurring as grades 2 or 3) are another type of infiltrating glioma (**Fig. 5**). Oligo grade 2 (WDO-2) is slow growing, although a few mitoses may be evident.[9] Anaplastic Oligo grade 3 exhibits necrosis and/or vascular proliferation. Oligo are defined by the presence of both *IDH1/2*$^{+/-}$ *and* monoallelic codeletion of chromosome arms 1p and 19q (1p,19q codel).[17] (see **Table 1**) In addition to *IDH1/2*$^{+/-}$, WDO-2 and anaplastic Oligo grade 3 typically also exhibit *TERT* promoter mutation,[14] but not *TP53* mutation. *TP53* mutations and 1p,19q codel are mutually exclusive.[13]

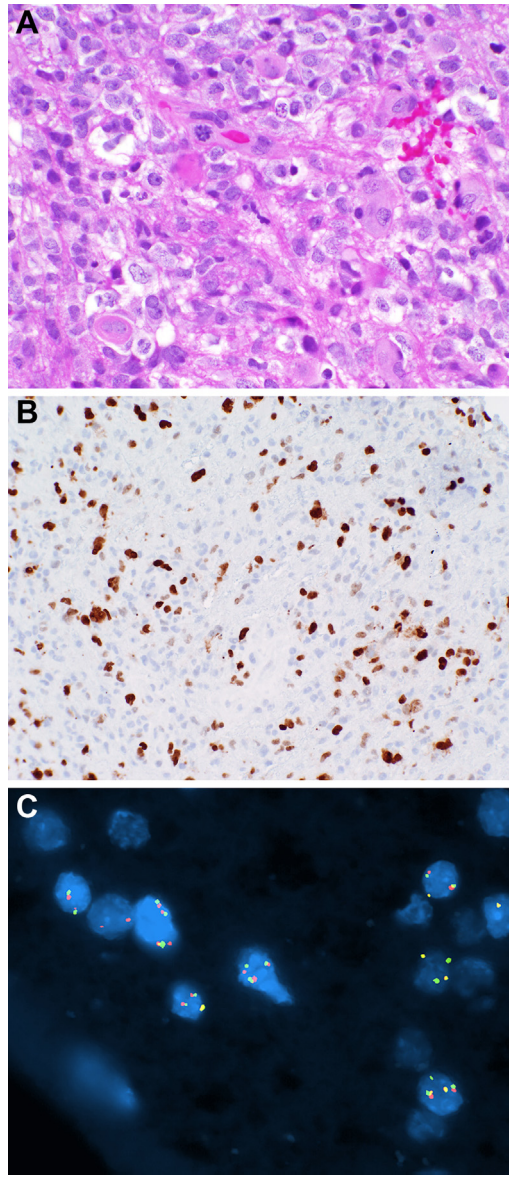

Fig. 2. (*A*) AA-3 with mitotic figure showing a (*B*) brisk Ki-67 proliferation index and (*C*) fluorescence in situ hybridization (FISH) demonstrating EGFR polysomy (*A*, hematoxylin-eosin, original magnification ×40; *B*, Ki-67 immunohistochemistry, original magnification ×20; *C*, FISH for EGFR [red] and 7 control [green], original magnification ×100.)

The issue of mixed oligo-astrocytomas also arises. Studies have found that most oligo-astrocytomas exhibit the genetic signatures of either Oligos or IA.[14]

Most Oligos (grades 2 and 3) and de novo GBM carry *TERT* promoter mutation. Oligos can be distinguished by the presence of *IDH1/2*$^{+/-}$ in contrast with de novo GBM (*IDH1/2* WT). An *IDH* WT infiltrative glioma bearing a *TERT* promoter mutation can be

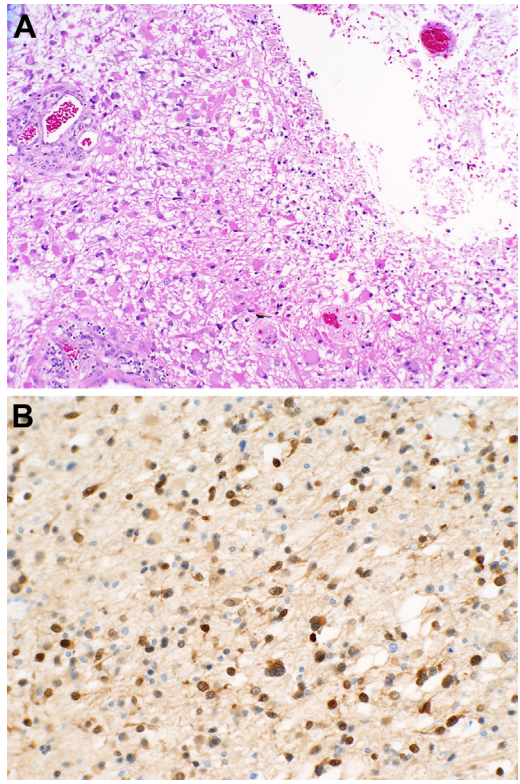

Fig. 3. (*A*) Secondary GBM showing focus of necrosis and (*B*) strong immunoreactivity for the R132H mutant protein (*A*, hematoxylin-eosin, original magnification ×20; *B*, immunohistochemistry for IDHR132H, original magnification ×20.)

considered a diffuse astrocytic glioma, *IDH*-WT, with molecular features of astrocytoma, WHO grade 4 (see **Table 1**). However, *TERT* promoter mutations are also found in pleomorphic xanthoastrocytoma (PXA) and ependymoma (EP).[18]

CIRCUMSCRIBED ASTROCYTOMAS

Circumscribed astrocytomas are summarized in **Table 3**.

Pilocytic astrocytomas (PAs) are grade 1 tumors that occur in children and young adults, commonly in the cerebellum (**Fig. 6**A). PXAs are grade 2 astrocytic gliomas with large, pleomorphic, and frequently multinucleated, xanthomatous (lipidized) cells, and a dense pericellular reticulin network. Both tumors exhibit eosinophilic granular bodies.[9] PXAs can be graded with tumors having 5 or more mitoses in 10 high-powered fields considered grade 3[9]; these tumors exhibit a tendency to persist, progress, and aggressively recur.

Biomarkers of Circumscribed Astrocytomas

BRAF abnormalities (KIAA/BRAF; and BRAFV600 E)

Seventy percent of all PAs exhibit the *KIAA1549/BRAF* duplication/translocation (**Fig. 6**B), particularly cerebellar PA,[19] however, *KIAA/BRAF* may also be found in D-Astros.[20] BRAFV600 E is found in PXAs, gangliogliomas, IAs, and extracerebellar PAs.[21] Pathways disrupted in these gliomas are shown in **Fig. 7**.

Table 2
Recurrent genomic abnormalities in glial/glioneuronal tumors

Tumor	Reported Mutations
Atypical teratoid/rhabdoid tumor	SMARCB1 mutation SMARCA4 mutation
Anaplastic astrocytoma with piloid features[57]	CDKN2A/B (chromosome 9p21 loss)
Diffuse astrocytoma	IDH1/2$^{+/-}$ TP53 mutation ATRX mutation EGFR polysomy
GBM (secondary)	IDH1/2$^{+/-}$ CDKN2A/B (chromosome 9p21) loss
GBM de novo	TERT mutation EGFR amp +7/-10 EGFRvIII
Cerebellar liponeurocytoma[58]	FABP4 hyperexpression
Cribriform neuroepithelial tumor	SMARCB1 mutations
Diffuse glioneuronal tumor with oligo-like features and nuclear clusters[59]	chromosome 14 monosomy
Diffuse leptomeningeal glioneuronal tumor (DLGNT)[60] DLGNT MC-1 DLGNT MC-2	Codeletion of 1p,19q KIAA1549:BRAF Chromosome 1q gain
Dysembryoplastic neuroepithelial tumor[61]	FGFR1 and BRAAFV600 E mutations
Dysplastic cerebellar gangliocytoma[9]	PTEN germline mutation
Embryonal tumor with multilayered rosettes	C19MC amplification
Extraventricular neurocytoma[62]	FGFR1/TACC-1 fusion
Ganglioglioma[21]	BRAFV600 E
Multinodular and vacuolating neuronal tumor	none identified
Myxoid glioneuronal tumor[63]	PDGFRA p.K385-mutant
Papillary glioneuronal tumor[64]	SKC44A1/PRKCA fusion
Pilocytic astrocytoma (cerebellar)	KIAA1549/BRAF fusion
Pilocytic astrocytoma (extracerebellar)	BRAFV600 E
Pleomorphic xanthoastrocytoma	BRAFV600 E
Polymorphous low-grade neuroepithelial tumor of young[61]	FGFR2/CTNNA3, BRAFv600 E
Rosette forming glioneuronal tumor[65]	PIK3CA & FGFR1 mutations

MALIGNANT GLIOMAS OF CHILDHOOD AND YOUNG ADULTS AND THEIR BIOMARKERS

An *H3 K27 M* mutation[9] is found in childhood high grade gliomas arising in the midline (eg, thalamus, brain stem, spinal cord) and is a major feature of diffuse, high-grade midline gliomas, grade IV. This mutation may also be found in EP, PA, nonmidline pediatric D-Astros, and gangliogliomas[3,4,22]

Alternatively, *H3 G34R* or *G34V* mutation also can be found in aggressive, nonmidline gliomas in children and young adults. An *H3 G34R/V* mutation found in a diffuse glioma of the lateral cerebral hemispheres, irrespective of histologic features[23] is considered by C-IMPACT as corresponding to WHO grade 4.[3]

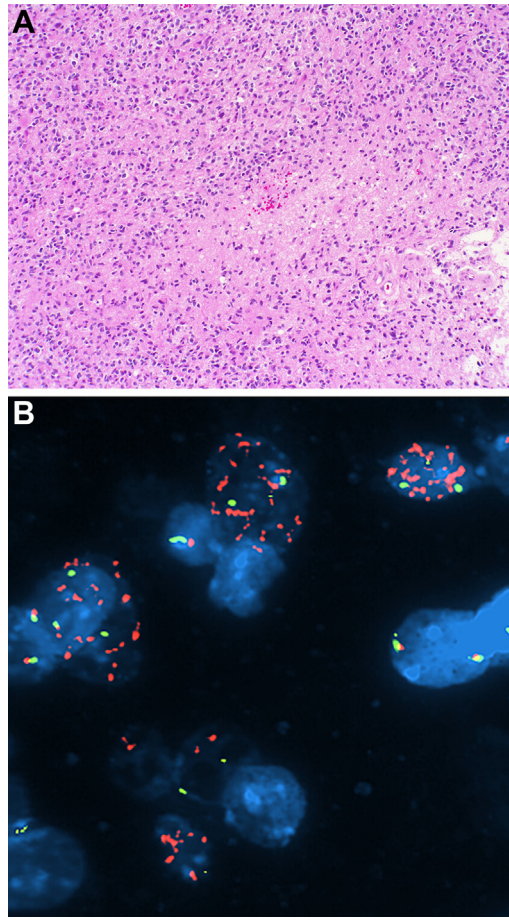

Fig. 4. (*A*) Primary (small cell) GBM with (*B*) fluorescence in situ hybridization (FISH) finding of EGFR (*red*) amplification (*A*, hematoxylin-eosin, original magnification ×10; *B*, FISH for EGFR [red] and CEP7 [green], original magnification ×100.)

DIFFUSE LOW-GRADE GLIOMAS AND GLIONEURONAL TUMORS OF CHILDHOOD

In contrast, childhood D-Astros bearing mutations in *Fibroblast Growth Factor Receptor* (*FGFR1/2/3*), *MYB*, *MYBL*, or *BRAF* (*BRAFV600 E*)[5] are associated with prolonged survivals (see **Table 2**). A study of *IDH* WT/*H3* WT pediatric glioneuronal tumors found *BRAF* V600 E mutations, *FGFR* alterations, or rearrangement/fusions of *MYB* or *MYBL1* in 84% of patients. In a separate study of pediatric gliomas, pathogenic alterations in *FGFR1/2/3*, *BRAF*, or *MYB/MYBL1* occurred in 78% of patients (**Box 1**).[24,25]

Ependymal Tumors

This group includes classic EPs grades 2 and 3, subependymomas grade 1, and myxopapillary EPs grade 2. Recent molecular genetic analyses including DNA methylation profiling and genome-wide sequencing provide the basis for current classification that considers central nervous system location (supratentorial [ST], posterior fossa, spinal cord) and, for some tumors, defining mutations[26] of clinical significance.

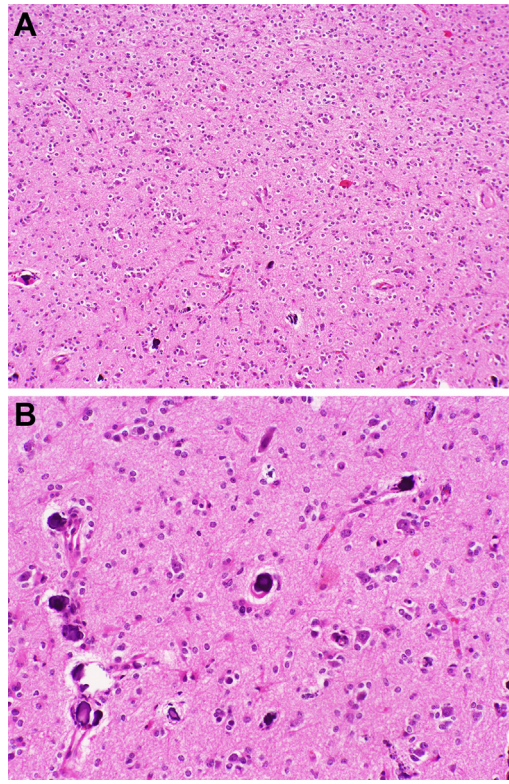

Fig. 5. Histologically, oligos exhibit round nuclei and clear cytoplasm with a tendency to satellite neurons and vessels. (*B*). Microcalcifications are common. (*A*, hematoxylin-eosin, original magnification ×10; *B*, stain: hematoxylin-eosin, original magnification ×20.)

Ependymoma

Ependymomas (EPs) are circumscribed gliomas having histologic uniformity, a fibrillary stroma, perivascular pseudorosettes (most cases), and even ependymal rosettes in some cases.[9] In addition to the classical type, 3 less common histologic patterns (papillary, clear cell, tanycytic) are also recognized. Both WHO grade 2 (EP-2) and grade 3 (EP-3) tumors are recognized. However, clinical outcome has not correlated well with histologic grading, instead extent of resection, which relates to central nervous system location, the use of adjuvant radiation therapy, and molecular grouping[27] are recommended to predict clinical outcome.

Table 3
World Health (WHO) Organization categories of circumscribed astrocytomas

	WHO 2016 Entity	WHO Grade
Circumscribed astrocytic tumors	Pilocytic astrocytoma	1
	Subependymal giant cell astrocytoma	1
	Pleomorphic xanthroastrocytoma	2
	Anaplastic pleomorphic xanthroastrocytoma	3

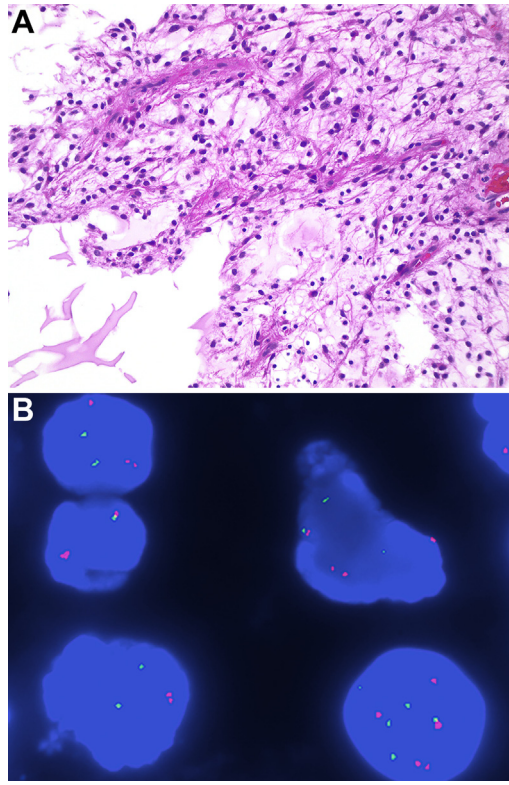

Fig. 6. PAs may have prominent bipolar processes with Rosenthal fibers. (*B*) Fluorescence in situ hybridization (FISH) for *KIAA*1549 (*red*) and *BRAF* (*green*) demonstrate the typical finding of fusion by the 2 adjacent *KIAA*1549 (*red*) and 1 *BRAF* (*green*) signal. (*A*, hematoxylin-eosin, original magnification ×20; *B*, FISH for KIAA [red] and BRAF [green], original magnification ×100).

Two major molecular groups have emerged within the ST compartment.[8] The more common group includes EP having a C11orf95-*RELA* fusion (**Fig. 8**). *RELA*-fusion ST-EP have a poor prognosis regardless of histologic grade. Another, less common group are ST-EP with the *YAP1–MAMLD1* fusion; patients with this fusion carry a better prognosis than the former group. Additional molecular subtypes of ST-EP[28] most likely exist. (C11orf95 is now shown to be ZFTA.)

Posterior fossa EP are most common in children and tend to arise in the floor of the fourth ventricle, making gross total excision difficult. Posterior fossa EP are divided into PFA and PFB by DNA methylation profiling.[29] The PFA group occurs primarily in infants and young children and tends to have anaplastic features and a poor prognosis. A gain of chromosome 1q is observed in some PFA-EP and is associated with a poor prognosis.[30] Loss of nuclear expression of histone *H3K27* trimethylation (H3K27me3) is seen in PFA-EP, distinguishing this group from the *H3K27*me3 -expressing PFB group.[31] In contrast, PFB-EP (**Fig. 9**) are more common in adolescents and adults, exhibit widespread chromosomal rearrangements, and have a better prognosis.

Spinal cord EP (**Fig. 10**) arise in central regions of the cord and are the most common spinal tumor in adults. Although gross total resection often leads to good outcomes, MYCN amplification is associated with clinically aggressive features.[8,32]

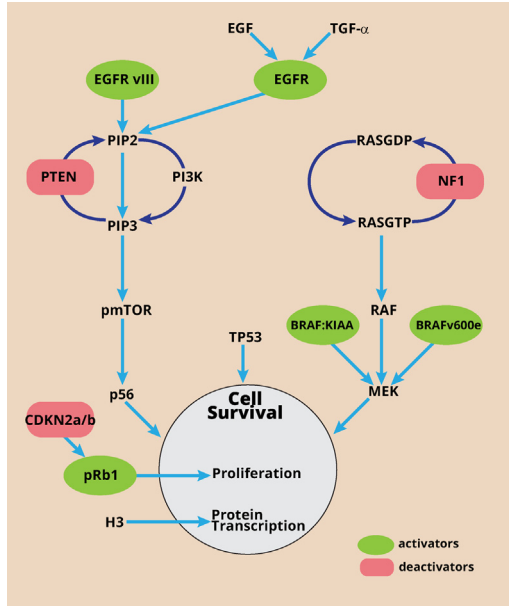

Fig. 7. Simplified scheme of growth pathways affected in glioma pathogenesis.

Subependymoma

Occurring mostly in adults, subependymomas present as nodular exophytic growths, that most often occur in the fourth ventricle or lateral ventricles (Fig. 11A, B). They may be encountered as incidental findings or produce symptoms by obstruction of cerebrospinal fluid flow. They feature a lobular growth pattern and clusters of small, bland-appearing tumor cell nuclei with adjacent areas of dense fibrillary stroma. Microscopic cysts may be seen, especially in ST examples. Subependymomas are WHO grade 1 and no clinically relevant molecular groups have been identified.[9]

Myxopapillary Ependymoma

Arising almost exclusively in the conus medullaris/filum terminale region, myxopapillary EPs (Fig. 12) often present clinically with adjacent nerve root compression. Gross

Box 1
Recurrent genomic abnormalities in diffuse low-grade gliomas of childhood

- Diffuse glioma, FGFR1 TKD-duplicated and diffuse glioma, FGFR1-mutant
  FGFR1 alterations in tumors exhibiting Oligodendrocyte-like cells
  82% of dysembryoplastic neuroepithelial tumors and
  40% of childhood oligodendrogliomas
- Diffuse glioma, MYB-altered and diffuse glioma, MYBL1-altered
  MYB-QKI fusions are present in 87% of angiocentric gliomas
  MYB fusion genes in 41% of diffuse astrocytomas
- Diffuse glioma, BRAF V600E-mutant
  BRAF V600 E mutations were in 35% of gangliogliomas and
  18% of diffuse astrocytomas[24]

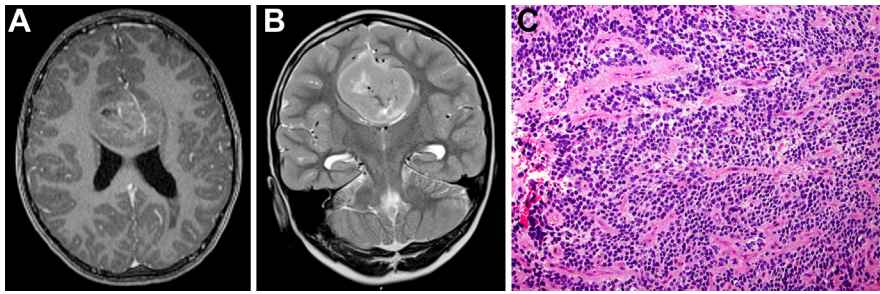

Fig. 8. EP, ZFTA fusion-positive. (*A*). T1-weighted, postcontrast MRI, and (*B*) T2-weighted MRI showing a midline ST neoplasm. (*C*) The tumor shows increased cellularity and focal perivascular pseudorosettes (*top left*). A *ZFTA* fusion was identified. (*A*, T1-weighted; post contrast MRI; *B*, T2-weighted MRI; *C*, hematoxylin-eosin, original magnification ×10.)

total excision often portends a good prognosis. However, occasional myxopapillary EPs attach to nerve roots or even disseminate along cerebrospinal fluid pathways. For this reason, a WHO grade 2 is suggested for this tumor type.[8] Clinically relevant molecular signatures have not yet been identified.

Medulloblastoma

Medulloblastoma (MB) is the second most common malignant brain tumor, comprising 20% of all primary intracranial tumors.[33] This tumor is associated with several inherited cancer syndromes,[34] including those involving germline mutations

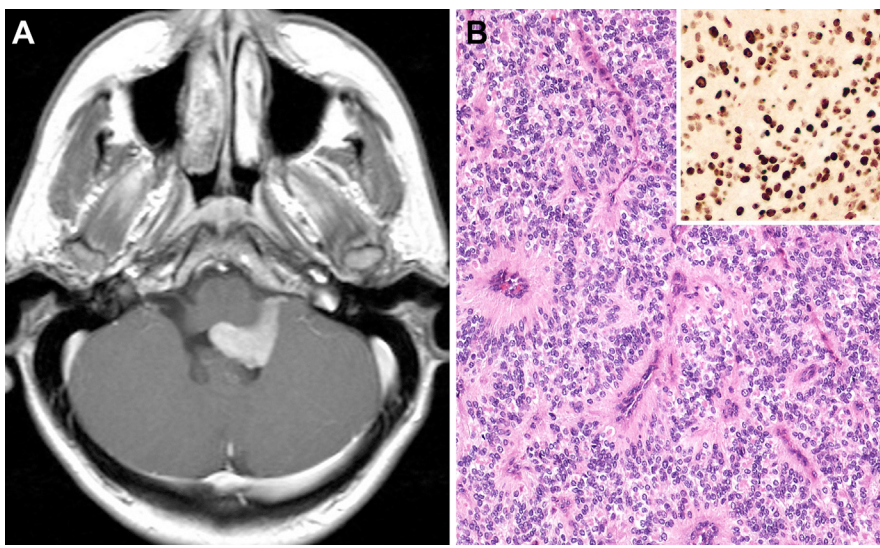

Fig. 9. EP, group posterior fossa-B. (*A*) T1-weighted, postcontrast MRI, showing a fourth ventricular EP expanding the left foramen of Luschka and extending focally into the subarachnoid space. (*B*) Classical histologic appearance with uniform cells and perivascular pseudorosettes (*left and bottom of image*). (*Inset*) Tumor cell nuclei showing strong reactivity for H3K27me3. (*A*, T2-weighted MRI; *B*, hematoxylin-eosin, original magnification ×10; *inset*, immunohistochemistry Ki-67, original magnification ×20.)

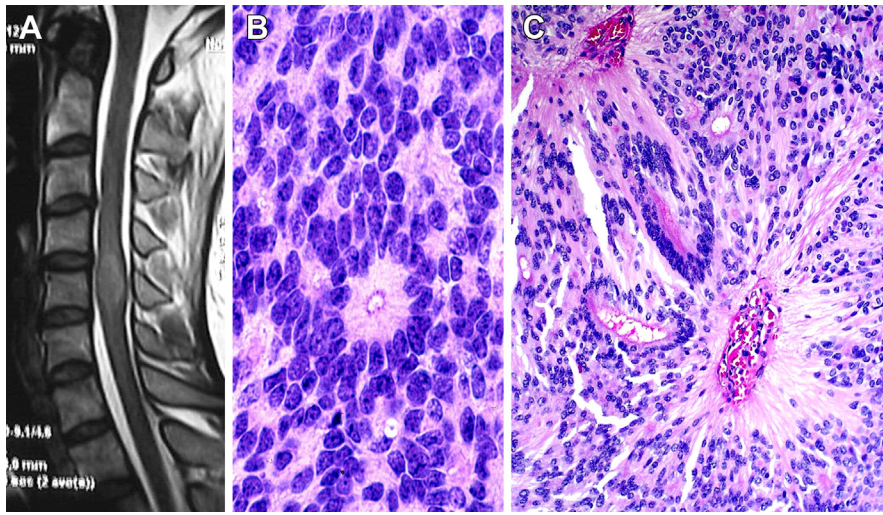

Fig. 10. Spinal cord EP. (*A*) T2-weighted MRI showing a neoplasm of the cervical spinal cord. (*B*) Ependymal rosettes may be seen in about 25% of cases. (*C*) Ependymal rosettes (*left of center and upper middle of image*) and perivascular pseudorosettes (*lower right and upper left of image*) are shown. (*A*, T2-weighted MRI; *B*, hematoxylin-eosin, original magnification ×40; *C*, hematoxylin-eosin, original magnification ×20.)

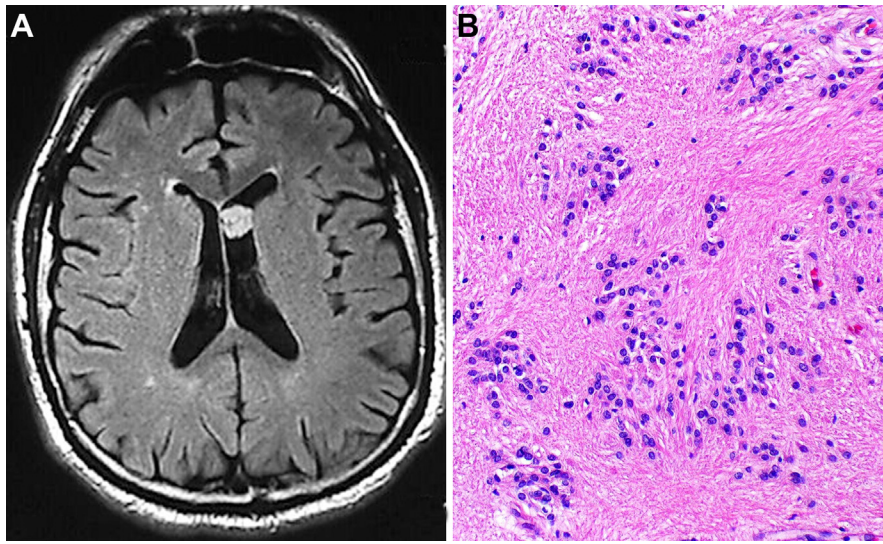

Fig. 11. Subependymoma. (*A*) Well-circumscribed lesion of rostral left lateral ventricle is shown. (*B*) Clusters of histologically bland tumor cell nuclei are located between fibrillary areas of stroma. (*A*, T2 fluid-attenuated inversion recovery MRI; *B*, hematoxylin-eosin, original magnification ×20.)

of *TP53*,[35] *SUFU* and *PTCH1*,[36] *APC*,[37] and *ELP1*.[38] The most common location is the vermis of the cerebellum; laterally located MB often belong to the Sonic Hedgehog (SHH)-activated group.[39] Wingless-activated (WNT) MBs are thought to derive from the dorsal brain stem and SHH-activated MB are thought to derive from cerebellar granule neuron precursors.[40] Typical features are small, poorly differentiated cells with high nuclear-to-cytoplasmic ratios and little cytoplasm, and frequent mitoses and apoptotic bodies. Nodule formation, ganglion cell, myogenic or melanotic differentiation may also be found.

The original consensus statement proposed 4 molecular tumor groups: WNT-activated, SHH-activated, group 3, and group 4[41,42] (**Table 4**). Patients and their tumors exhibited different molecular pathogeneses, clinical features, and survival risks by group. Patients with WNT-activated MB had the best 5-year survival of more than 90%, whereas patients in group 3 had the worst 5-year survival of only 50% (**Fig. 13**). Patients whose SHH activated tumors had *TP53* mutation had poorer outcomes than those with *TP53* WT tumors.[43] SHH-activated MB is the most common molecular group, but uncommonly occurs in adult patient tumors.[42,44]

Group 3 and group 4 tumors are now grouped together in the new WHO 2021 Classification[45] into a single non-WNT/non-SHH group because the molecular features of the 2 subgroups overlap.[43,46] Recent studies have revealed potentially 4 SHH subgroups and 8 non-WNT/non-SHH subgroups[43,47] (see **Table 4**).

Although molecular profiling is clinically more important, a classification based on histology still exists and includes: classic, desmoplastic/nodular, large cell/anaplastic, and MB with extensive nodularity.[45] The WHO now collects these histologic groups under a single section (MB), histologically defined. Some molecular correlations exist: all truly desmoplastic/nodular and MB with extensive nodularity MBs belong to the SHH group[48]; the bulk of pediatric WNT tumors have classic morphology, and most large cell/anaplastic tumors belong either to the SHH-3 subgroup or to the non-WNT/non-SHH group 3/4 subgroup 2[49] (see **Table 4**).

Atypical Teratoid or Rhabdoid Tumor

A tumor that may be confused with MB is atypical teratoid/rhabdoid tumor (AT/RT). AT/RT is a highly malignant tumor consisting of poorly differentiated cells and a

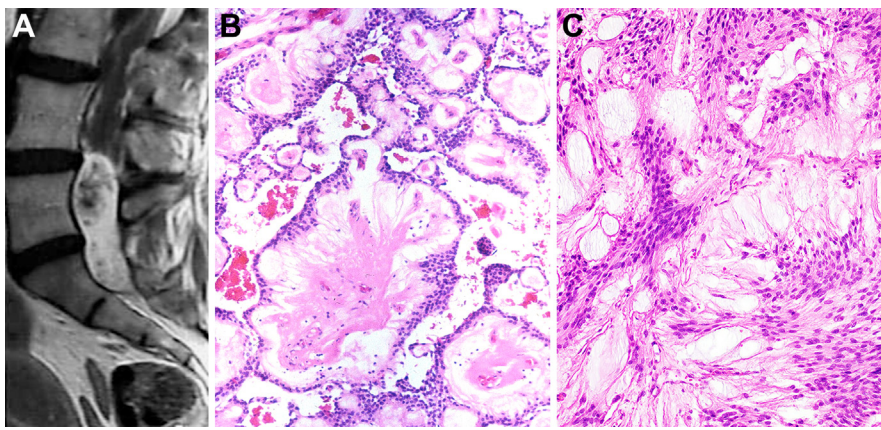

Fig. 12. Myxopapillary EP. (*A*) MRI showing well-delineated filum terminale mass. (*B*) Papillary structures may be seen focally. (*C*) A more myxoid area with spindled tumor cells is shown. (*A*, T1-weighted, postcontrast MRI; *B*, hematoxylin-eosin, original magnification ×20; *C*, hematoxylin-eosin, original magnification ×20.)

Table 4
Molecular groups of medulloblastoma

	WNT-Activated	SHH-Activated *TP53*-Wild type	SHH-Activated *TP53*-Mutant	Non-WNT/non-SHH Group 3	Non-WNT/non-SHH Group 4
Common age group	Children	Infants/adults	Children	Infants/children	All age groups
Main histology	Classic	Nodular/desmoplastic	Anaplastic	Anaplastic/classic	Classic
Frequent diagnostic genetic alterations (not exhaustive) when not using transcription[a] or methylation profiling[b]	Monosomy 6 *CTNNB1*, *DDX3X* mutation	*PTCH1* deletion 9q loss *PTCH1*, *SUFU*, *SMO*, *DDX3X*, *KMT2D*, *ELP1*	17p loss *MYCN* amplification *GLI2* amplification *TP53*, *DDX3X*, TERT mutation	*MYC*, *MYCN* amplification Iso17q *SMARCA4*, *KBTBD4*, *KMT2D* mutation	*MYCN*, *OTX2* amplification Iso17q *KDM6A*, *KMT2C*, *KMT2D*, *KBTBD4* mutation
Frequency	10%	20%	10%	25%	35%

[a] The most commonly used method for transcription profiling is by nanostring technology.[66]
[b] The most widely used platform for methylation profiling is the Illumina Human Infinium Bead Array (450K or 850K) and uploading the file onto the DKFZ website (https://www.molecularneuropathology.org/mnp/).
Data from Refs.[41,49,67]

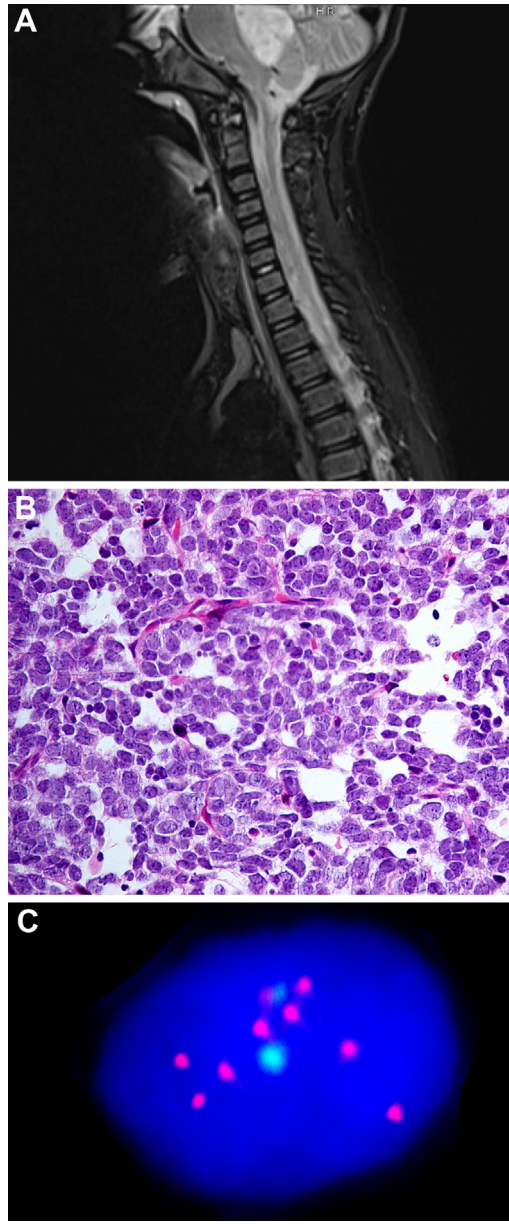

Fig. 13. (*A*) Group 3, anaplastic/large cell MB. A 5-year-old boy has a cerebellar tumor with a drop metastasis to spinal cord. (*B*) Histology shows an anaplastic MB. (*C*) Fluorescence in situ hybridization shows amplification of MYC (*pink signals*). (*A*, T1-weighted, postcontrast MRI; *B*, hematoxylin-eosin, original magnification ×40; *C*, fluorescence in situ hybridization for MYC [*pink*] and control [*aqua*], original magnification ×100).

variable number of rhabdoid cells (Fig. 14A, B). AT/RT is a ST tumor in the very young; most patients are aged less than 2 years and one-third are aged less than 12 months.[50] Familial cases arise in the setting of rhabdoid tumor predisposition syndromes.[51] AT/

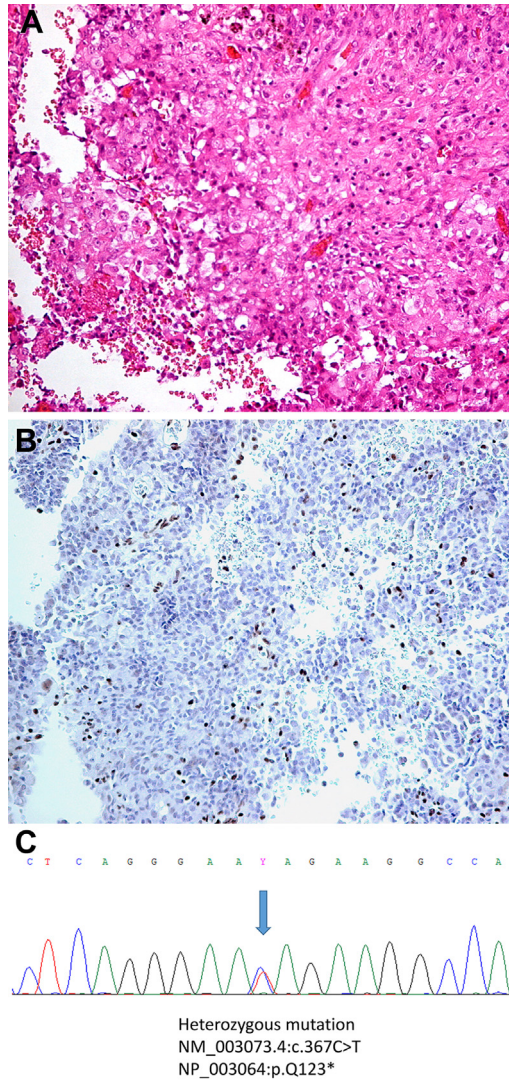

Fig. 14. (*A*) Atypical teratoid rhabdoid tumor. A 6-month-old boy with a cerebellar tumor. This area represents the area of the tumor with rhabdoid cells. (*B*) INI1-immunohistochemistry is negative for tumor cells. (*C*) Germline mutation of SMARCB1 exon 4. (*A*, hematoxylin-eosin, original magnification ×20; *B*, immunohistochemistry for INI-1, original magnification ×20; *C*, DNA sequence.)

RT shows biallelic inactivation of the *SMARCB1* (*hSNF5/INI1/BAP47*) gene or rarely the *SMARCA4* (*BRG1*) gene.[52,53] Loss of nuclear SMARCB1 (INI1) is a highly sensitive diagnostic marker[54]; however, the cribriform neuroepithelial tumor may also exhibit this finding.[55] Germline molecular analysis is recommended (**Fig. 14**C) for these patients. Three distinct molecular AT/RT subtypes are now identified.[56]

Other Central Nervous System Embryonal Tumors

Although beyond the scope of the present article, a number of glial, glioneuronal and primitive embryonal tumors are also listed in **Table 1** along with characteristic biomarkers.

CLINICS CARE POINTS

- Typing IA grade 2 to 4 using *IDH1* and *IDH2* is clinically important.
- DA "*IDH* WT" grade 2 is rarely low grade and needs further investigation.
- Oligodendrogliomas are defined by the presence of both *IDH1/2* mutation and monoallelic 1p and 19q codeletion.
- Oligoastrocytoma can usually be typed by *IDH* and 1p,19q codeletion status.
- De novo GBM and oligodendrogliomas both carry *TERT* promoter mutation.
- An IA *IDH*-WT with *TERT* promoter mutation is a molecular GBM, grade 4.
- Cerebellar PA often carry the *KIAA1549/BRAF* duplication/translocation.
- PXAs, gangliogliomas, diffuse malignant astrocytomas, and extracerebellar PA may exhibit *BRAFV600 E.*
- Not all D-Astros of childhood inexorably progress to higher grade tumors, particularly those bearing mutations affecting *FGFR1/2/3*, *MYB*, *MYBL*, or *BRAFV600 E.*
- Not all *H3K27 M* mutant gliomas qualify for diffuse, high grade midline glioma, grade 4.
- The detection of an *H3G34 R/V* mutation in a diffuse glioma of the lateral cerebral hemispheres, irrespective of histologic grade, indicates high grade.
- EPs are classified by 3 locations, 3 histologies, and at least 4 molecular groups.
- ST-EP subtypes include *ZFTA* fusion (poor prognosis) and *YAP1-MAMLD1* fusion (better prognosis) groups.
- PFA EPs occur in infants and children and have a poor prognosis, whereas the PFB group arises in adolescents and adults with a good prognosis.
- Spinal cord EP tend to have a good prognosis except those having MYCN-amplification (poor prognosis).
- Clinically useful molecular signatures are not yet available for subependymomoas and myxopapillary EPs.
- The most common location of MB is the vermis of the cerebellum.
- MBs can be divided into at least 4 molecular groups and 4 histology groups.
- Loss of SMARCB1 (INI1) protein expression in the tumor nuclei is a highly sensitive, but not specific, diagnostic marker for atypical teratoid/rhabdoid tumors.

DISCLOSURE

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