The 2021 WHO Classification for Gliomas and Implications on Imaging Diagnosis: Part 2—Summary of Imaging Findings on Pediatric-Type Diffuse High-Grade Gliomas, Pediatric-Type Diffuse Low-Grade Gliomas, and Circumscribed Astrocytic Gliomas

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The fifth edition of the World Health Organization (WHO) classification of central nervous system tumors published in 2021 advances the role of molecular diagnostics in the classification of gliomas by emphasizing integrated diagnoses based on histopathology and molecular information and grouping tumors based on genetic alterations. This Part 2 review focuses on the molecular diagnostics and imaging findings of pediatric-type diffuse high-grade gliomas, pediatric-type diffuse low-grade gliomas, and circumscribed astrocytic gliomas. Each tumor type in pediatric-type diffuse high-grade glioma mostly harbors a distinct molecular marker. On the other hand, in pediatric-type diffuse low-grade gliomas and circumscribed astrocytic gliomas, molecular diagnostics may be extremely complicated at a glance in the 2021 WHO classification. It is crucial for radiologists to understand the molecular diagnostics and imaging findings and leverage the knowledge in clinical practice.

Evidence Level: 3

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As stated in the Part 1 review, the 2021 World Health Organization (WHO) for the first time divides "adult-type" and "pediatric type" gliomas.[1] The need to do so has been considered for a long time due to the apparent clinical and biological differences, but the recent elucidation of different molecular landscape has now made this possible.[2] It is specifically hoped that this distinction will enable better care of children with brain tumors.

Pediatric diffuse high-grade gliomas and diffuse low-grade gliomas mostly occur in the pediatric population and there is lack of clear tumor border on histopathology. As their names suggest, pediatric diffuse high-grade gliomas show a relatively aggressive clinical behavior while diffuse low-grade gliomas show a relatively indolent clinical behavior. Gliomas with more well-defined borders that separate them from surrounding brain

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parenchyma, previously referred to as "other astrocytic tumors," are now categorized as circumscribed astrocytic gliomas. The term "circumscribed" refers to their more solid growth pattern, as opposed to the inherently "diffuse" tumors in adult-type diffuse gliomas, pediatric-type diffuse high-grade gliomas, and pediatric-type diffuse low-grade gliomas.

In the previous Part 1 review, major changes of the 2021 WHO classification on gliomas were summarized and imaging findings on adult-type diffuse gliomas were introduced. The Part 2 review will focus on the molecular diagnostics and imaging findings of pediatric-type diffuse high-grade gliomas, pediatric-type diffuse low-grade gliomas, and circumscribed astrocytic gliomas. We will also briefly discuss the treatment and prognosis of each tumor type in some tumors, because this information is less familiar to radiologists in practice compared to adult-type diffuse gliomas. The upcoming Part 3 review will introduce molecular diagnostics and imaging findings of glioneuronal and neuronal tumors.

Molecular Diagnostics

As stated in the Part 1 review, molecular biomarker testing is in continuum with adult-type diffuse gliomas. IDH1/2 mutation testing is mandatory on all diffuse gliomas at diagnosis.[3] Despite the focus on IDH mutation in adult gliomas, the pediatric diffuse gliomas very rarely have IDH mutation and it is not a major classifier in pediatric brain tumors. Predominantly majority of pediatric diffuse high-grade gliomas, pediatric diffuse low-grade gliomas, and circumscribed astrocytic gliomas are IDH-wildtype. The age and location along with histological findings for either low-grade or high-grade should be considered for the molecular testing for these tumors. For simplicity, the molecular diagnostics of pediatric diffuse high-grade gliomas will be discussed separately from pediatric diffuse low-grade gliomas and circumscribed astrocytic glioma.

Molecular Diagnostics of Pediatric-Type Diffuse High-Grade Gliomas

H3 K27M, EZHIP, and *EGFR* mutation testing should be performed in diffuse gliomas that involve the midline to diagnose diffuse midline glioma, H3 K27-altered. In older adults there is increasing evidence that the midline location of diffuse glioma is also tightly linked with H3 K27M mutation, warranting testing of all patients with midline gliomas

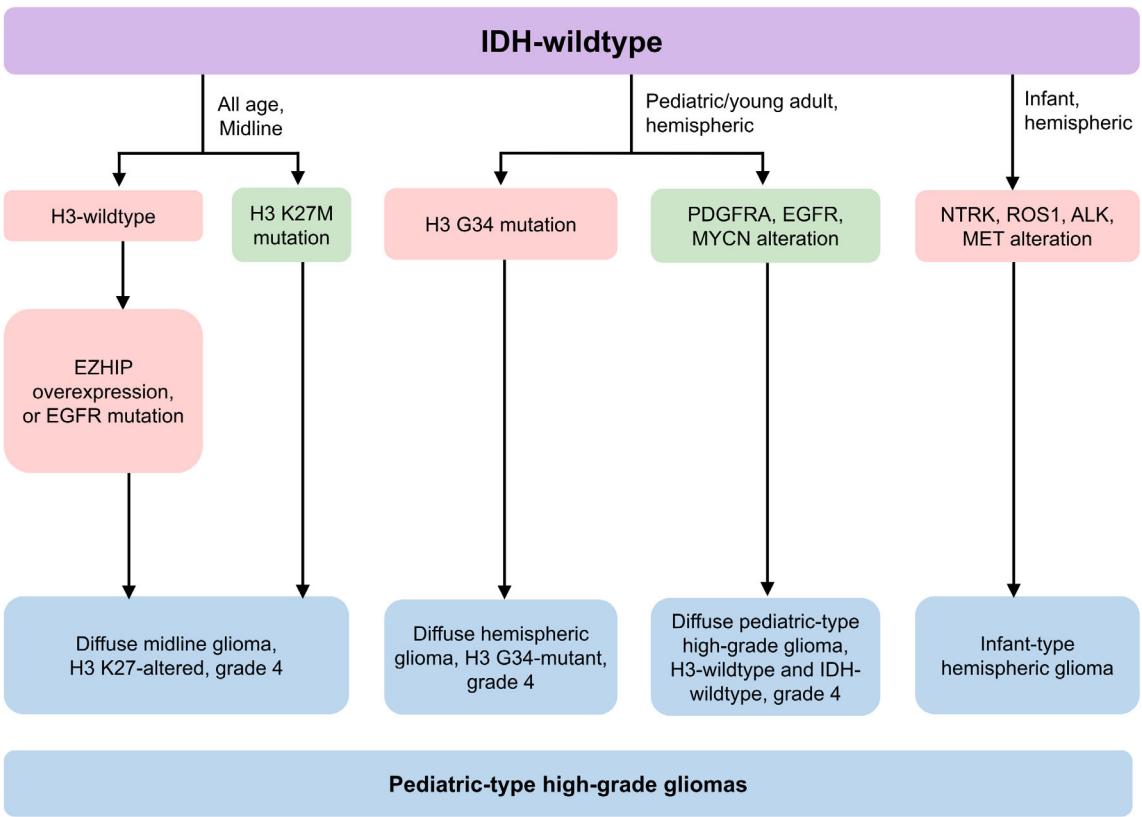

FIGURE 1: Molecular findings in the 2021 WHO classification that involve the classification of pediatric-type diffuse high-grade gliomas. As stated in the Part 1 review, molecular biomarker testing is in continuum with adult-type diffuse gliomas. Age and location should be considered in the testing algorithm. In midline located tumors, either H3 K27M mutation or EZHIP overexpression or *EGFR* mutation leads to diagnosis of diffuse midline glioma, H3 K27-altered. In children or young adults with hemispheric tumors, H3 G34 mutation is noted in diffuse hemispheric glioma, H3 G34-mutant, whereas *PDGFRA*, *EGFR*, or MYCN alterations are noted in diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype. In infants with hemispheric tumor, NTRK, *ROS1*, *ALK*, or *MET* alterations is seen in infant-type hemispheric glioma.

regardless of age.[3] H3 G34 testing may be performed in pediatric and young adults with IDH-wildtype diffuse gliomas. Testing for alterations in *ROS1*, *ALK*, *MET*, or MYCN may be performed in pediatric high-grade diffuse gliomas that are IDH-wildtype and histone H3 wildtype. A subset of molecular findings in the 2021 WHO classification that involve the classification of pediatric diffuse high-grade gliomas are summarized in Fig. 1.

Molecular Diagnostics of Pediatric Diffuse Low-Grade Gliomas and Circumscribed Astrocytic Gliomas

Although pediatric diffuse low-grade gliomas and circumscribed astrocytic gliomas belong to a different category in gliomas, they share many similar molecular alterations and thus will be discussed alongside. In many cases the different pathologic findings are readily distinguished, however cases of overlapping morphology are also documented.[2] In these overlapping and less specific histological features, molecular information helps to characterize and accurately classify the lesion. Compared to adult-type diffuse gliomas and pediatric-type diffuse high-grade gliomas, understanding the molecular diagnostics in these tumors may be challenging.

We suggest several simple rules to understand the molecular landscape of pediatric diffuse low-grade gliomas and circumscribed astrocytic gliomas. First, Ras-mitogen-activated protein kinase (MAPK) pathway alteration is the major genetic event driving the tumorigenesis in these tumors.[2,4] The upregulation of MAPK pathway alteration results in increased cell growth and differentiation.[5] Within MAPK pathway alteration, *BRAF* mutation (*BRAF p. V600E*, in which a valine is replaced with a glutamic acid at position 600), *BRAF* oncogenic fusion such as *KIAA1549::BRAF*, and FGFR alterations are most common pathway alterations in

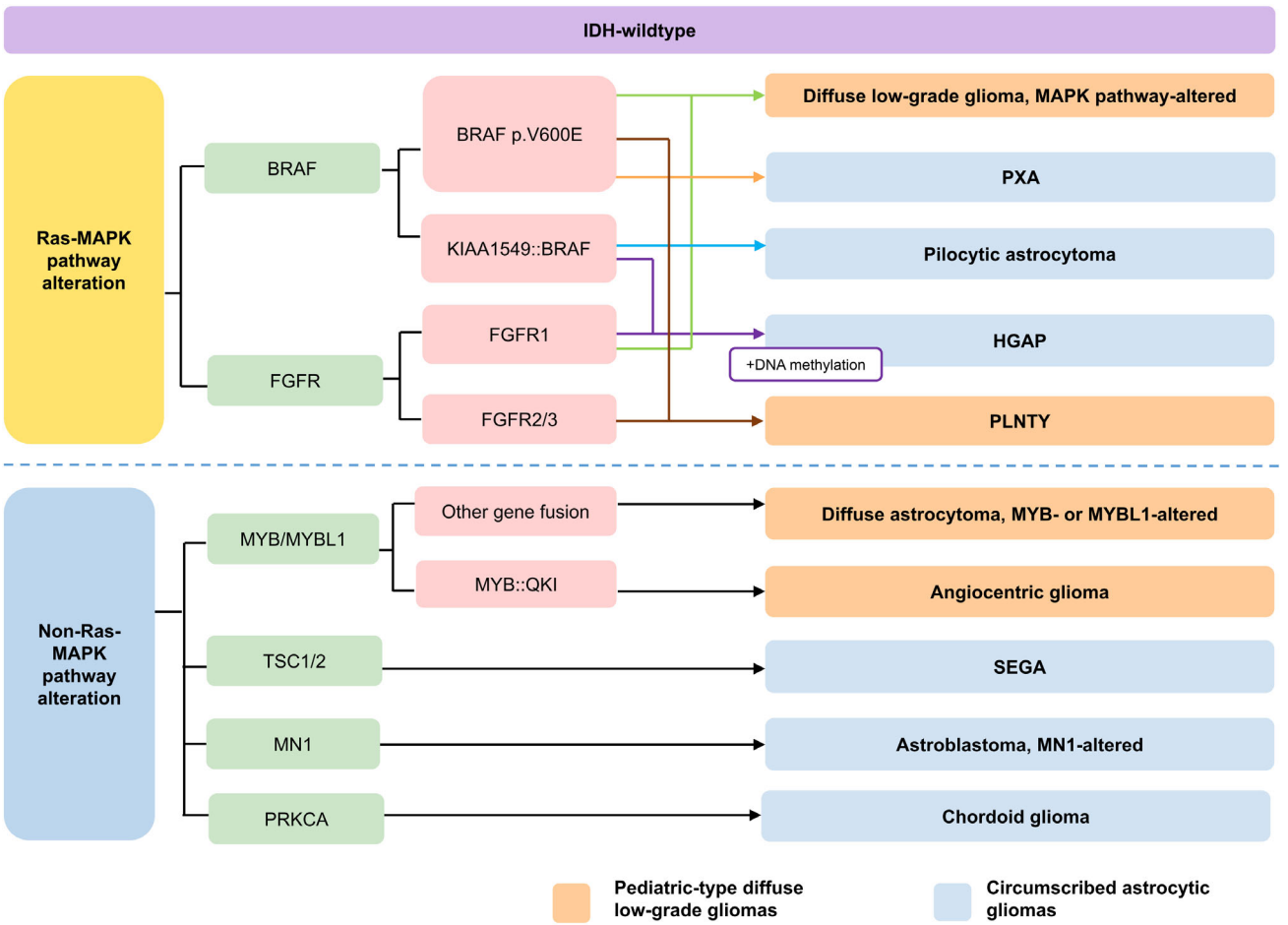

FIGURE 2: Molecular findings in the 2021 WHO classification that involve the classification of pediatric diffuse low-grade gliomas and circumscribed astrocytic gliomas. The most common genetic alterations are only shown in each type of tumor. Ras-mitogen-activated protein kinase (MAPK) pathway alteration is the major event driving the oncogenesis. Within MAPK pathway, *BRAF p.V600E* mutation and *FGFR1* alterations are commonly seen in diffuse low-grade glioma, MAPK pathway-altered. High-grade astrocytoma with piloid features (HGAP) is an astrocytoma that can only be definitely diagnosed with DNA methylation profile. *BRAF p.V600E* mutation and *FGFR2* or *FGFR3* alterations are seen in polymorphous low-grade neuroepithelial tumor of the young (PLNTY). Within non-MAPK pathway alterations, diffuse astrocytoma, *MYB*- or *MYBL1*-altered is characterized by genetic alterations in *MYB* or *MYBL1* other than *MYB::QKI* fusion. HGAP = high-grade astrocytoma with piloid features; PLNTY = polymorphous low-grade neuroepithelial tumor of the young; PXA = pleomorphic xanthoastrocytoma; SEGA = subependymal giant cell astrocytoma.

TABLE 1. Summary of key molecular alterations, WHO grade, age, location, and imaging features in each type of pediatric-type high-grade gliomas, pediatric-type diffuse low-grade gliomas, and circumscribed astrocytic gliomas

Tumor Type	Key Molecular Alteration	WHO Grade	Age	Location	Imaging Features
Pediatric-type diffuse high-grade gliomas					
Diffuse midline glioma, H3 K27-altered	H3 p.K28 (K27), *EGFR*, EZHIP	4	Children and adults	Midline	Heterogeneous imaging findings - Expansile or infiltrative mass with/without enhancement Frequent leptomeningeal metastases
Diffuse hemispheric glioma, H3 G34-mutant	H3 p.G35 (G34)	4	Children and young adults	Supratentorial, hemispheric	Heterogeneous imaging findings - Expansile or infiltrative mass with/without enhancement
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype	IDH-wildtype, H3-wildtype, methylome	4	Children and young adults	Supratentorial, hemispheric	Heterogeneous enhancement with mass effect *MYCN: well-defined, slight peritumoral edema, homogeneous enhancement
Infant-type hemispheric glioma	RTK genes	_*	Infants	Supratentorial, hemispheric	Large enhancing mass with mass effect Heterogeneous signal intensity with hemorrhage or necrosis
Pediatric-type diffuse low-grade gliomas					
Diffuse astrocytoma, MYB- or MYBL1-altered	*MYB*, *MYBL1*	1	Children and young adults	Supratentorial	Well-defined nonenhancing tumor
Angiocentric glioma	*MYB::QKI*	1	Children and young adults	Supratentorial	Well-defined nonenhancing tumor, some show cystic change, stalk-like extension to ventricle
PLNTY	*BRAF p.V600E, FGFR2/3*	1	Children and young adults	Supratentorial (esp. temporal)	Calcified, well-defined tumor, cystic and solid appearance, with or without enhancement
Diffuse low-grade glioma, MAPK pathway-altered	*BRAF p.V600E, FGFR1*	_*	Children and young adults	Supratentorial	Heterogeneous imaging findings (not established)
Circumscribed astrocytic gliomas					
PA	*KIAA1549::BRAF*	1	Children and young adults	Cerebellum	Cystic mass with enhancing mural nodule

TABLE 1. Continued

Tumor Type	Key Molecular Alteration	WHO Grade	Age	Location	Imaging Features
HGAP	DNA methylation	_*	Children and adults (not clear)	Cerebellum	Heterogeneous T2 signal with rim enhancement
PXA	*BRAF p.V600E*	2–3	Children and young adults	Supratentorial (esp. temporal)	Cystic mass with enhancing mural nodule located superficially with adjacent enhancing dural tail
SEGA	*TSC1, TSC2*	1	Children and young adults	Lateral ventricle adjacent to the foramen of Monro	Enhancing mass at typical location, Underlying findings of TS
Chordoid glioma	*PRKCA*	2	Adults (female predominance)	Third ventricle	Homogeneously enhancing mass at typical location
Astroblastoma, MN1-altered	*MN1*	_*	Children or young adults (marked female predominance)	Supratentorial	Solid or cystic masses ("bubbly" appearance) with heterogeneous/rim enhancement

HGAP = high-grade astrocytoma with piloid features; PA = pilocytic astrocytoma; PLNTY = polymorphous low-grade neuroepithelial tumor of the young; PXA = pleomorphic xanthoastrocytoma; SEGA = subependymal giant cell astrocytoma; TS = tuberous sclerosis.
*These types of tumors do not have an established CNS WHO grade yet.

these tumors. *BRAF* mutation is a gain-of-function mutation, while *BRAF* oncogenic fusion results in activation of its kinase domain, which eventually leads to tumorigenesis.[6] Second, outside of the canonical Ras-MAPK pathway, non-MAPK pathway alterations exist albeit the low event numbers. Among these alterations, *MYB* and *MYBL1* alterations are worth memorizing leading to a newly included tumor type named diffuse astrocytoma, *MYB*- or *MYBL1*-altered in the 2021 WHO classification. *MYB* and *MYBL1* alterations are gain-of-function mutations, which leads to overexpression of proto-oncogene MYB and consequently neoplastic cell proliferation.[7] Currently the efficacy of targeted therapy to inhibit *MYB* or its downstream genes is being investigated, and diffuse astrocytoma, *MYB*- or *MYBL1*-altered may benefit from potential therapeutic strategies.[8,9] Third, as mentioned earlier, many tumor types in pediatric diffuse low-grade gliomas and circumscribed astrocytic gliomas may have overlapping molecular information; for example, the differential diagnosis of low-grade glioma with a *BRAF p.V600E* mutation includes diffuse low-grade glioma, MAPK pathway-altered, pleomorphic xanthoastrocytoma, and pilocytic astrocytoma. An integrated diagnosis is made based on the histopathological and molecular information.

A subset of molecular findings in the 2021 WHO classification that involve the classification of pediatric-type diffuse low-grade gliomas and circumscribed astrocytic gliomas are summarized in Fig. 2.

Before Starting: Always Keep the "Big Picture" in Mind

As stated in the Part 1 review and emphasized again, we should refrain from being focused on a particular imaging finding to make a specific diagnosis. This is especially crucial in pediatric diffuse low-grade gliomas and circumscribed astrocytic gliomas. Apart from the relatively common tumor types such as diffuse midline glioma, H3 K27-altered or pilocytic astrocytoma, other types of tumors in these categories are rare and the prevalence is not clearly established yet. The age and location should be always considered when establishing an imaging diagnosis. Except for cases with typical imaging features and appropriate clinical settings (i.e. a child with a nonenhancing expansile pontine mass, suggesting high-probability of diffuse midline glioma, H3 K27-altered; a child with cystic mass with enhancing mural nodule in the cerebellum, suggesting high probability of pilocytic astrocytoma; or a continuously enlarging enhancing mass near the foramen Monro in a patient with tuberous sclerosis, suggesting subependymal giant cell tumor [SEGA], etc), most tumors in these categories should be included in the differential diagnosis on preoperative imaging, rather than giving just one definite imaging diagnosis.

Table 1 shows a summary of key molecular alterations, WHO grade, age, location, and imaging features in each type of tumor in pediatric diffuse high-grade gliomas, pediatric diffuse low-grade gliomas, and circumscribed astrocytic gliomas. The common locations of each type of tumors in pediatric diffuse low-grade gliomas and circumscribed gliomas are also shown in Fig. 3.

Recommended Imaging Protocol

Compared with the recommended imaging protocol of adult gliomas,[10] there are several differences in the recommended imaging protocol in pediatric diffuse high-grade and low-

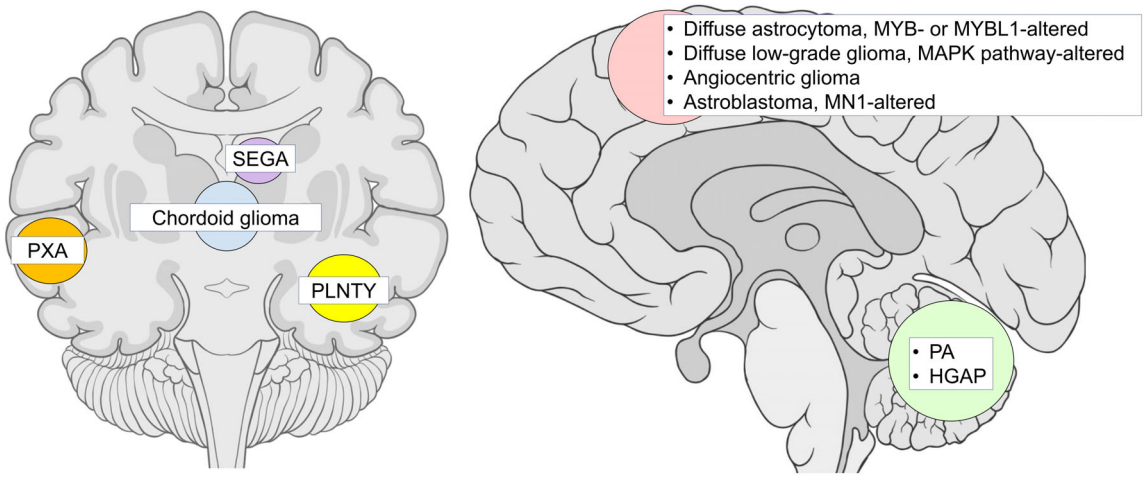

FIGURE 3: Common locations of pediatric diffuse low-grade gliomas and circumscribed astrocytic gliomas. Subependymal giant cell astrocytoma (SEGA) and chordoid glioma show characteristic locations of lateral ventricle near the foramen of Monro and third ventricle, respectively. PXA and PLNTY are shown commonly in the temporal lobe, while PXA shows a superficially located cortical mass. PA and HGAP show frequent cerebellar locations. The common locations of diffuse astrocytoma, *MYB*- or *MYBL1*-altered and diffuse low-grade glioma, MAPK pathway-altered are known to be cerebral hemispheres but further studies are required for precise localization. HGAP = high-grade astrocytoma with piloid features; PA = pilocytic astrocytoma; PLNTY = polymorphous low-grade neuroepithelial tumor of the young; PXA = pleomorphic xanthoastrocytoma; SEGA = subependymal giant cell astrocytoma.

grade gliomas from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group.[11,12] Compared to adult gliomas, a specific protocol on spinal MRI is recommended in pediatric diffuse high-grade and low-grade gliomas, and there is a higher reliance on FLAIR images as nonenhancing tumor growth is frequent. Orbital imaging with fat saturation is recommended in primary optic pathway or hypothalamic pediatric low-grade gliomas. In rare cases of completely nonenhancing pediatric low-grade gliomas, imaging without contrast can be considered in follow-up.[11]

Specific Molecular and Imaging Features

Pediatric-Type Diffuse High-Grade Gliomas

Pediatric diffuse high-grade gliomas are a newly added category in the 2021 WHO classification. All tumors within this category are WHO grade 4, except infant-type hemispheric glioma, in which a definite WHO grade has not been assigned yet. Except for diffuse midline glioma, H3 K27-altered with a revised nomenclature, all other tumors in this category are newly introduced in the new WHO classification.

DIFFUSE MIDLINE GLIOMA, H3 K27-ALTERED. The history of diffuse midline glioma, H3 K27-altered, should be briefly discussed to understand this revised nomenclature in the 2021 WHO classification. Previously referred as diffuse intrinsic pontine glioma (DIPG), it was acknowledged that DIPG was a childhood aggressive cancer that forms in the brainstem. Afterwards, studies showed that K27M-H3.3 mutation, which is seen in approximately 70%–80% of DIPG patients, defines clinically and biologically distinct subgroups in DIPG.[13,14] This K27M-H3.3 mutation was also noted in non-brainstem glioblastomas.[14,15] This led to the newly defined entity at the 2016 WHO classification termed "diffuse midline glioma, H3 K27M-mutant."[16] However, alterative mechanisms that alter the pathogenic pathway in diffuse midline glioma have been additionally reported since the 2016 WHO classification.[17–19] Thus, in the 2021 WHO classification, the nomenclature has been revised to "diffuse midline glioma, H3 K27-altered" because there are now four subtypes of DMGs that are defined by the driving oncohistone alteration: 1) H3.3 p.K28M (K27M)-mutant, 2) H3.1 or 3.2 p.K28M (K27M)-mutant, 3) H3-wildtype with EZHIP overexpression, and 4) *EGFR*-mutant. Diffuse midline gliomas are considered central nervous system (CNS) WHO grade 4, irrespective of the presence of necrosis or microvascular proliferation. Although diffuse midline glioma, H3 K27-altered, is a pediatric-type glioma, it is also frequently diagnosed in young adults and less frequently in older age.[20,21] Thus, a recent molecular diagnostic guideline suggests that H3 K27M alteration should be tested in diffuse gliomas that involve the midline, even in older adults.[3]

The location of diffuse midline glioma, H3 K27-altered may differ according to the age: pediatric population frequently show brainstem, pons, or bithalamic location, whereas adolescents and adult population show predominantly thalamus or spinal cord location.[20,22] Off-midline tumors are also rarely reported, despite the name indicating a midline location.[23,24] The imaging findings of diffuse midline glioma, H3 K27-altered is highly variable, ranging from expansile nonenhancing masses without necrosis or enhancing masses with or without large areas of surrounding infiltrative growth, which may reflect the histopathological heterogeneity.[24,25] A recent study from the international DIPG registry showed that the presence of ill-defined signal infiltrating pontine fibers is the only imaging feature associated with histone mutation in DIPG.[26] The rate of leptomeningeal metastases is high in diffuse midline glioma, H3 K27-altered; a large autopsy-based study described a rate of 40%,[27] and we recently reported that a similar detection rate of 39.8% can be achieved by routine imaging including postcontrast FLAIR imaging.[28] Figure 4 shows representative cases of typical imaging features of diffuse midline glioma, H3 K27-altered. Figure 5 shows a representative case with leptomeningeal metastases on follow-up imaging.

DIFFUSE HEMISPHERIC GLIOMA, H3 G34-MUTANT. Diffuse hemispheric glioma, H3 G34-mutant, is a newly included tumor type in the 2021 WHO classification. This tumor type is defined as an infiltrative hemispheric tumor with missense mutation of the H3-3A gene and predominantly found in adolescents and young adults.[29] Diffuse hemispheric glioma, H3 G34-mutant corresponds to CNS WHO grade 4, regardless of the presence or absence of necrosis or microvascular proliferation. The prognosis of diffuse hemispheric glioma, H3 G34-mutant is poor but shows a longer overall survival (median: 18.0 months) than diffuse midline glioma, H3 K27-altered.[30]

The typical MRI characteristics of H3 G34-mutant diffuse hemispheric glioma are similar to those of other high-grade non-midline gliomas. Tumors show hemispheric (supratentorial non-midline) location, with variable imaging findings ranging from expansile well-defined masses with regions of necrosis to infiltrative tumors with enhancement.[29–32] Necrosis, cystic changes, hemorrhage, and calcifications can be observed and the degree of enhancement is variable.[29] Figure 6 shows a representative case of H3 G34-mutant diffuse hemispheric glioma.

DIFFUSE PEDIATRIC-TYPE HIGH-GRADE GLIOMA, H3-WILDTYPE AND IDH-WILDTYPE. Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype, is a newly included tumor type in the 2021 WHO classification. A diffuse glioma with mitotic activity occurring in a child or young adult with absence of mutations in IDH1/2 or H3

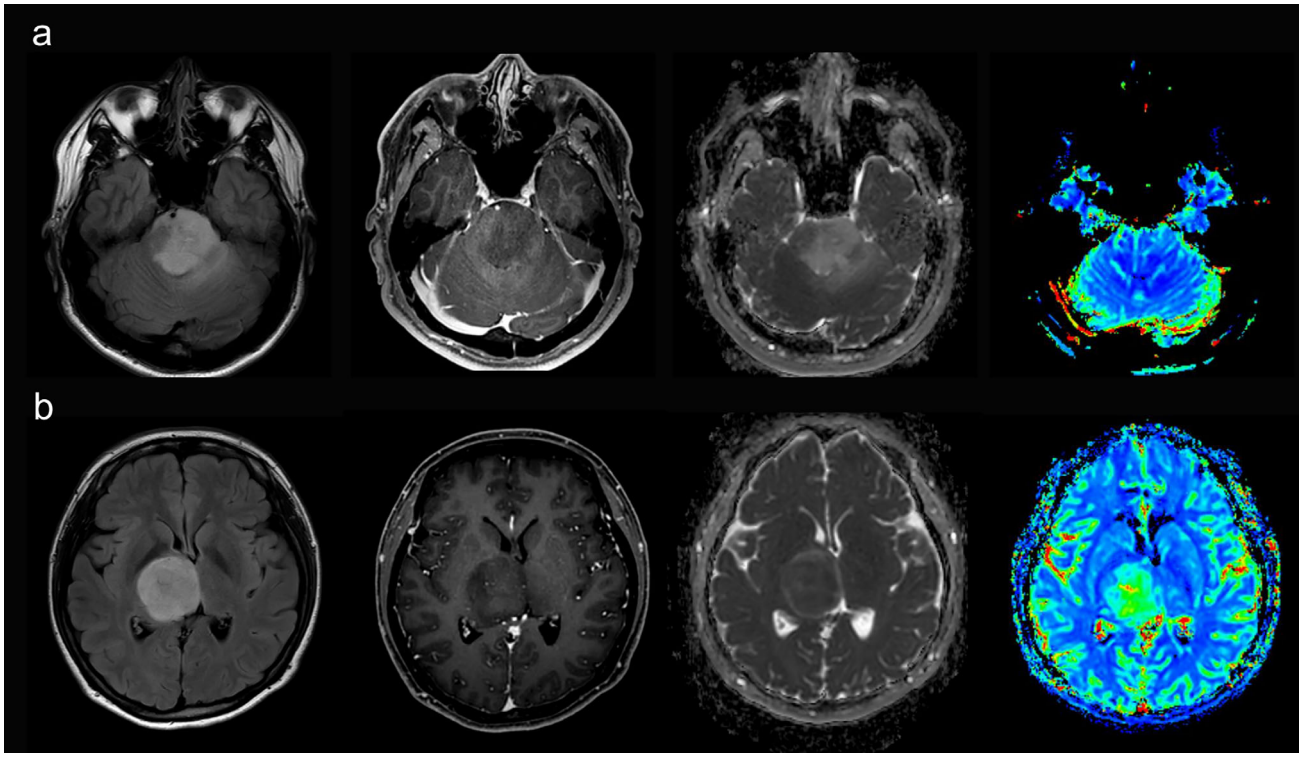

FIGURE 4: Images in two different patients with diffuse midline glioma, H3 K27-altered. (a) Images of a 28-year-old male show an ill-defined expansile nonenhancing mass at the pons. There is no cellularity increase or rCBV increase. (b) Images in a 30-year-old female show a well-defined expansile nonenhancing mass at the right thalamus. ADC map shows increased cellularity and CBV map shows increased rCBV.

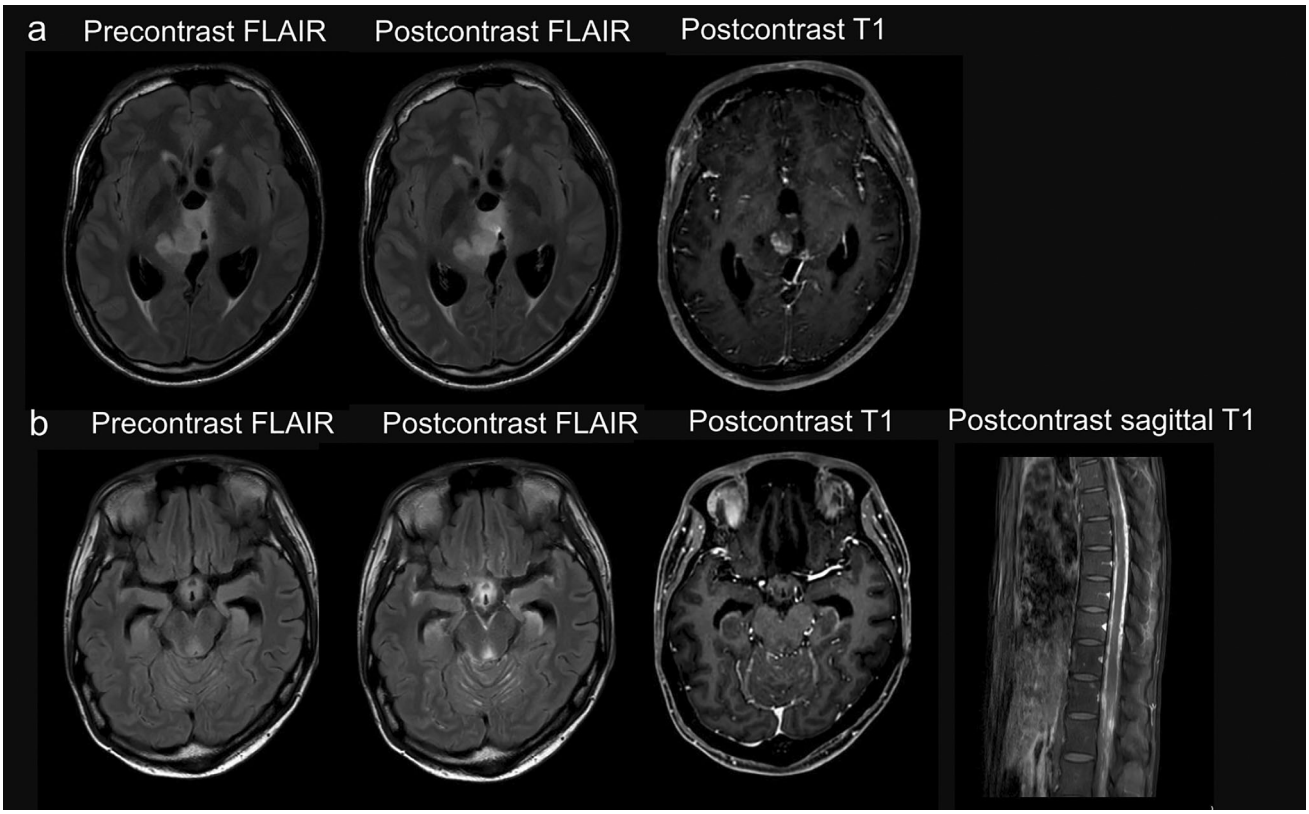

FIGURE 5: Preoperative and follow-up images in a 19-year-old male with diffuse midline glioma, H3 K27-altered. (a) On preoperative images, there is a T2 hyperintense mass with heterogeneously enhancing portion at the right thalamus without evidence of leptomeningeal metastases. (b) Follow-up imaging after 5 months shows diffuse leptomeningeal metastases, most well delineated in the postcontrast FLAIR images in the brain MRI. Whole spine MRI also shows diffuse leptomeningeal metastases along the entire spinal cord.

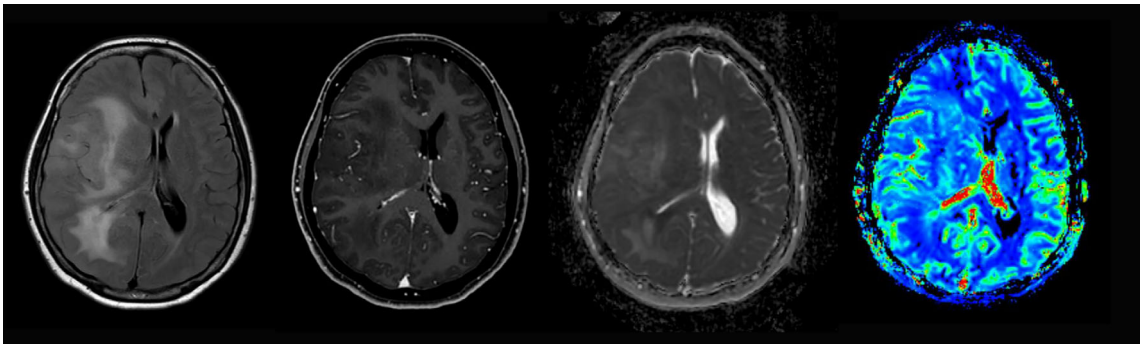

FIGURE 6: Images of a 54-year-old female with diffuse hemispheric glioma, H3 G34-mutant. Imaging shows a diffuse infiltrative nonenhancing tumor involving the right cerebral hemisphere. There is no cellularity increase on ADC map or rCBV increase on CBV map.

gene is essential for diagnosis. There are three subtypes, according to the type of molecular alterations; diffuse pediatric-type high-grade glioma receptor tyrosine kinase 2 (RTK2), diffuse pediatric-type high-grade glioma RTK1, and diffuse pediatric-type high-grade glioma MYCN.[33,34] Differently from what its name could erroneously suggest, the diagnosis of diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype is not a diagnosis of exclusion. Rather, based on the WHO definition, it is essential to demonstrate the alignment of the tumor DNA methylation profile with the RTK2, RTK1, or MYCN. Diffuse pediatric-type high-grade gliomas, H3-wildtype and IDH-wildtype, are aggressive tumors, and are considered as CNS WHO grade 4. Gliomas arising after therapeutic radiation, typically harbor molecular characteristics compatible with diffuse pediatric-type high-grade gliomas, H3-wildtype and IDH-wildtype.[35]

Majority of pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype occur in the supratentorium.[36] The imaging characteristics are similar to those of other high-grade gliomas. MRI typically reveals a heterogeneously enhancing tumor with mass effect. Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype, MYCN tumors may be better circumscribed, with only slight perilesional edema and homogeneous contrast enhancement.[33,34] Figure 7 shows a representative case in a patient with diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype.

INFANT-TYPE HEMISPHERIC GLIOMA. Infant-type hemispheric glioma is a hemispheric, high-grade cellular astrocytoma that arises in early childhood, mostly in the first year of life, typically with RTK fusions including those in the NTRK family or in *ROS1, ALK*, or *MET*. There are four subtypes: infant-type hemispheric glioma, NTRK-altered; infant-type hemispheric glioma, *ROS1*-altered; infant-type hemispheric glioma, *ALK*-altered; and infant-type hemispheric glioma, *MET*-altered.[37] A definite WHO grade has not been assigned.

Infant-type hemispheric gliomas show supratentorial location, usually as large masses, with significant mass effect and heterogeneous signal intensity, with or without hemorrhage or necrosis, with varying degrees of enhancement.[37–40]

Pediatric-Type Diffuse Low-Grade Gliomas

Along with pediatric diffuse high-grade gliomas, pediatric diffuse low-grade gliomas are a newly added category in the 2021 WHO classification. Tumors within this category

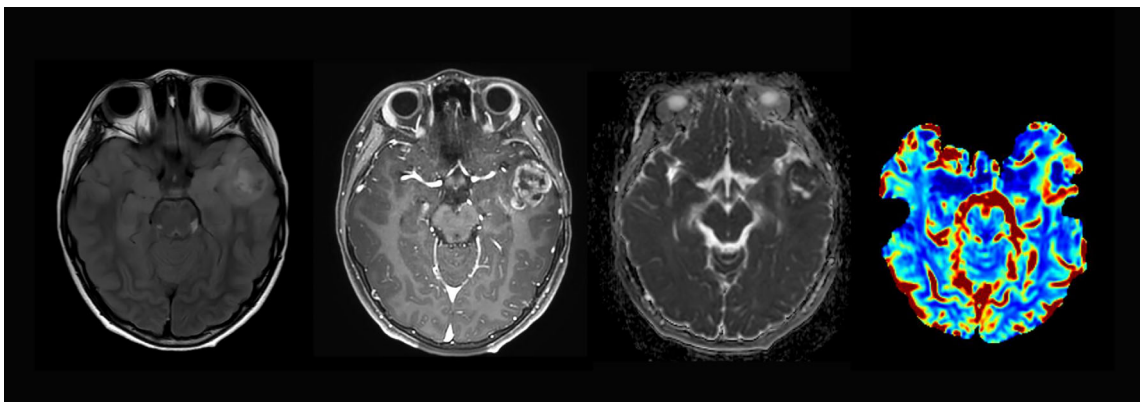

FIGURE 7: Images in an 8-year-old boy with diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype. Preoperative imaging shows a heterogeneously enhancing tumor with edema and mass effect. ADC map and CBV map show increased cellularity and increased rCBV at the enhancing portion.

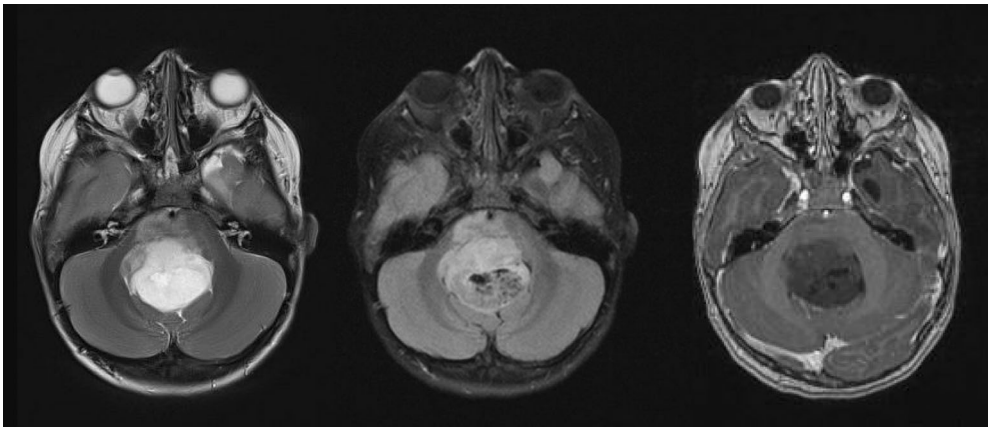

FIGURE 8: Images in a 6-year-old girl with diffuse astrocytoma, *MYB*-or *MYBL1*-altered. Imaging shows a large, predominantly solid, expansile,sp nonenhancing mass located in the fourth ventricle with involvement of the dorsal brainstem.

usually present with drug-resistant epilepsy, thus can be termed as long-term epilepsy-associated tumors (LEATs).[41] Surgical resection is usually curable in these tumors, and this benign clinical behavior leads to a grading of CNS WHO grade 1 in all of the tumors in this category except for diffuse low-grade glioma, MAPK pathway-altered, of which CNS WHO grade is yet to be assigned. Except for angiocentric glioma, all other tumors in this category are newly introduced in the new WHO classification.

DIFFUSE ASTROCYTOMA, MYB- OR MYBL1-ALTERED. Diffuse astrocytoma, *MYB*- or *MYBL1*-altered is characterized by genetic alterations in *MYB* or *MYBL1* other than *MYB::QKI* fusion. The most frequently reported partner genes that fusion with *MYB* or *MYBL1* are *PCDHGA1*, *MMP16*, and *MAML2*.[42,43] The *MYB::QKI* fusion is typically found in angiocentric glioma.[44] There are two subtypes, diffuse astrocytoma, *MYB*-altered, and diffuse astrocytoma, *MYBL*1-altered.

Diffuse astrocytoma, *MYB*- or *MYBL1*-altered belongs within the category of LEATs; patients typically present with drug-resistant epileptic seizures, mostly since childhood.[43] According to a previous study, about 90% of patients with epilepsy became seizure-free after resection.[43]

Diffuse astrocytoma, *MYB*- or *MYBL1*-altered most frequently occur in the supratentorial regions.[45] The imaging findings have been rarely reported. Reports show that diffuse astrocytoma, *MYB*- or *MYBL1*-altered is relatively well-defined nonenhancing tumor, with mixed or hyperintensity on T2-weighted image and does not show restricted diffusion.[42,46] A representative case is shown in Fig. 8.

ANGIOCENTRIC GLIOMA. Angiocentric glioma is a diffuse glioma composed mainly of thin, cytologically bland, bipolar cells aggregating mostly in perivascular spaces ("angiocentric" growth). This tumor was recognized as a distinct type of tumor since the 2007 WHO classification. A recent study showed that the *MYB::QKI* fusion is typically found in angiocentric glioma.[44]

Most cases occur in children and young adults, with a median age of 13 years (range: 2–79 years) at presentation.[47] This tumor also presents with a long history of intractable seizures, and is also within the category of LEATs. This tumor is usually cured by surgical resection alone.

Angiocentric gliomas most frequently occur in the supratentorial regions (86%), followed by the brainstem (14%).[48] On imaging, these tumors are often well-defined, nonenhancing, intratumoral T1 hyperintense, T2

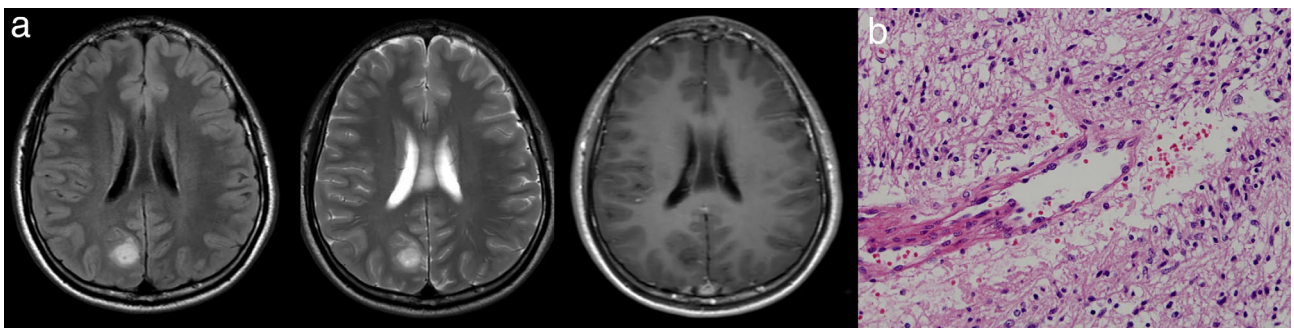

FIGURE 9: Images in a 16-year-old male with angiocentric glioma. (a) show a well-defined nonenhancing mass at the right occipital lobe cortex and subcortex. (b) On histopathology, bipolar spindle cells show a characteristic orientation around blood vessels ("angiocentric pattern").

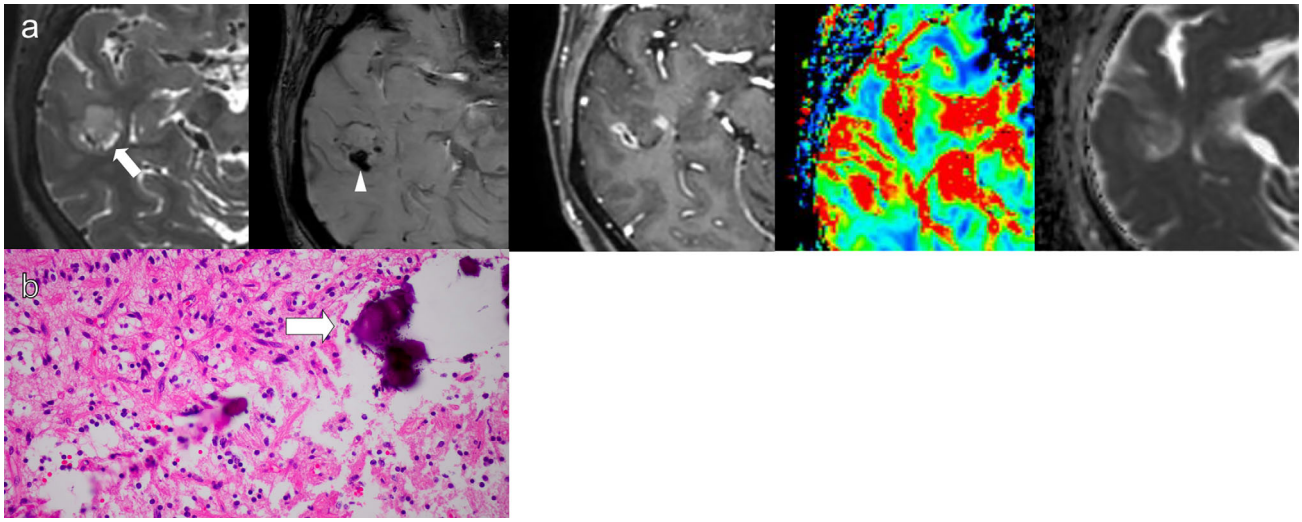

FIGURE 10: Images in a 64-year-old female with polymorphous low-grade neuroepithelial tumor of the young. This patient showed *FGFR3*::*TACC* fusion. (a) T2-weighted images show a well-defined T2 hyperintense mass with cystic components (arrow), while susceptibility-weighted images show a focal hypointense area corresponding to calcification (arrow). There is a small enhancing area in the mass. There is no cellularity increase on ADC map and increased rCBV on CBV map. (b) On histopathology, the tumor shows scattered calcifications (arrow).

hyperintense, and may sometimes show cystic change.[48,49] A stalk-like extension to the adjacent lateral ventricle and dystrophic calcification may also be noted in some cases.[48] A representative case is shown in Fig. 9.

POLYMORPHOUS LOW-GRADE NEUROEPITHELIAL TUMOR OF THE YOUNG. Polymorphous low-grade neuroepithelial tumor of the young (PLNTY) is an indolent cerebral tumor characterized by diffuse growth patterns. Pediatric tumors displaying oligodendroglial morphology do not usually harbor the IDH1/2 mutations and 1p/19q codeletion as seen in adult oligodendrogliomas,[50] and thus a new tumor type was specifically assigned in the 2021 WHO classification. On histopathology, oligodendroglioma-like components are present, and calcification is commonly seen. PLNTYs are consistently associated with MAPK pathway-activating abnormalities, such as *BRAF p.V600E* mutations, as well as fusions involving *FGFR2* or *FGFR3*.[50,51]

PLNTY also shows a strong association with seizures in young individuals, controlled by surgical resection.

PLNTY typically represents a calcified, well-defined mass in the supratentorial cortical or subcortical regions, most common in temporal lobe.[52] Cystic and solid appearance is common, with T2 hyperintensity, either with or without enhancement, and without diffusion restriction.[52] A representative case is shown in Fig. 10.

DIFFUSE LOW-GRADE GLIOMA, MAPK PATHWAY-ALTERED. Diffuse low-grade glioma, MAPK pathway-altered, is a low-grade glioma with diffuse astrocytic, oligodendroglial, or mixed morphology that is characterized by a pathogenic alteration in a gene that codes for a MAPK pathway protein. These are *FGFR1* and *BRAF v.600E* genes, leading to three subtypes: diffuse low-grade glioma, *FGFR1* tyrosine kinase domain-duplicated; diffuse low-grade glioma, *FGFR1*-mutant; and diffuse low-grade glioma, *BRAF p.V600E*-mutant. Due to the heterogeneity in the morphologic and molecular features, it is currently uncertain to what extent MAPK-altered diffuse low-grade gliomas, as a group, will resolve into distinct tumor types. Also, the WHO grade of this tumor is not established yet.

Long standing epilepsy is also common in diffuse low-grade glioma, MAPK pathway-altered. The prognosis in this tumor type requires further data accumulation.

Diffuse low-grade gliomas, MAPK pathway-altered are described throughout the neuroaxis, and most commonly in the cerebral hemispheres. On imaging, diffuse low-grade gliomas, MAPK pathway-altered, may have a more diffuse pattern than pilocytic astrocytomas, but there are heterogeneous imaging findings reported given the broad spectrum of histological features.[53,54] Representative cases from two different patients are shown in Fig. 11.

Circumscribed Astrocytic Gliomas

High-grade astrocytoma with piloid features (HGAP) is the only newly introduced type of tumor in the 2021 WHO classification in this tumor category. Tumors in this category mostly range from WHO grade 2 to 3, except for pilocytic astrocytoma and subependymal giant cell astrocytoma being WHO grade 1. The WHO grades in HGAP and astroblastoma, *MN1*-altered is not established yet. Pilocytic astrocytoma and pleomorphic astrocytoma can be included in the category of LEATs.[41]

PILOCYTIC ASTROCYTOMA. Pilocytic astrocytoma is an astrocytic neoplasm with variable proportions of bipolar hair-

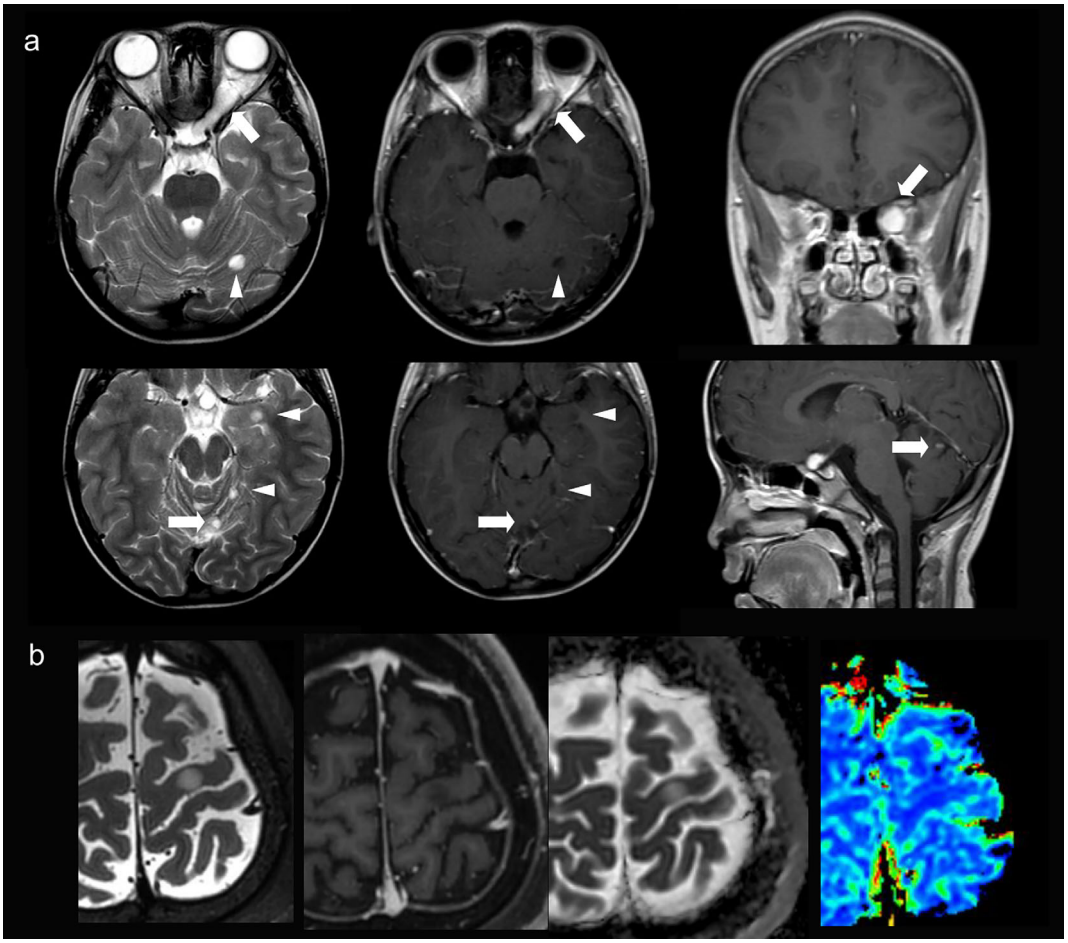

FIGURE 11: Images in two different patients diffuse low-grade glioma, MAPK pathway-altered. (a) An 8-year-old girl with a homogeneously enhancing optic glioma is noted (arrow), while there are multiple well-defined nonenhancing cystic lesions at the left temporal lobe and left superior cerebellum (arrowheads). Note that one cystic lesion at the left superior cerebellum shows focal enhancement (arrow). (b) A 31-year-old male with a well-defined nonenhancing mass at the left precentral gyrus. There is no cellularity increase on ADC map or rCBV increase on CBV map.

like ("pilocytic") cells, Rosenthal fibers, myxoid regions, and eosinophilic granular bodies. Pilocytic astrocytoma is associated with MAPK pathway gene alterations, most often *KIAA1549::BRAF* gene fusions. *BRAF* mutations such as *p. V600E* occur in less than 10% of patients.[55] There are two subtypes apart from the classic pilocytic astrocytoma, which are pilomyxoid astrocytoma and pilocytic astrocytoma with histological features of anaplasia. Pilomyxoid astrocytoma is defined as a tumor with monomorphic piloid cytology, a diffusely myxoid background, and increased cellularity compared with that of classic pilocytic astrocytoma. Although the 2007 WHO classification assigned pilomyxoid astrocytoma as grade II, a specific WHO grade has not been provided in the following 2016 and 2021 WHO classifications. Apart from the fact that pilomyxoid astrocytomas have a poor prognosis than pilocytic astrocytomas, the similarity in genetic alterations as well as the better prognosis in pilomyxoid astrocytomas compared to other diffuse gliomas in the same age group has left this issue on grading debatable.[56] Pilocytic astrocytoma with histological features of anaplasia has been proposed for tumors with morphological features of pilocytic astrocytoma but showing brisk mitotic activity with or without necrosis.

Pilocytic astrocytoma is most common during the first two decades of life and accounts for 17.6% of all childhood primary brain tumors. However, it also accounts for up to 1.5% of adult brain tumors.[57] Pilocytic astrocytomas show a favorable prognosis even after multiple progressions.[58,59] On the other hand, pilomyxoid astrocytoma and pilocytic astrocytoma with histological anaplasia have a less favorable prognosis.[60,61] Pilomyxoid astrocytomas usually occur during infancy and has a higher rate of recurrence as well as propensity for leptomeningeal metastases.[62,63]

Pilocytic astrocytoma usually arises from the cerebellum, but it can also occur in the supratentorial compartment including the optic nerve and chiasm, hypothalamus, cerebral hemispheres, or ventricles.[57] Supratentorial location is more common in adults, up to 47.8% in a recent meta-analysis.[64] The most characteristic imaging finding is the "cystic mass with enhancing mural nodule" appearance in the cerebellum, seen in approximately two thirds of pilocytic astrocytomas.[65]

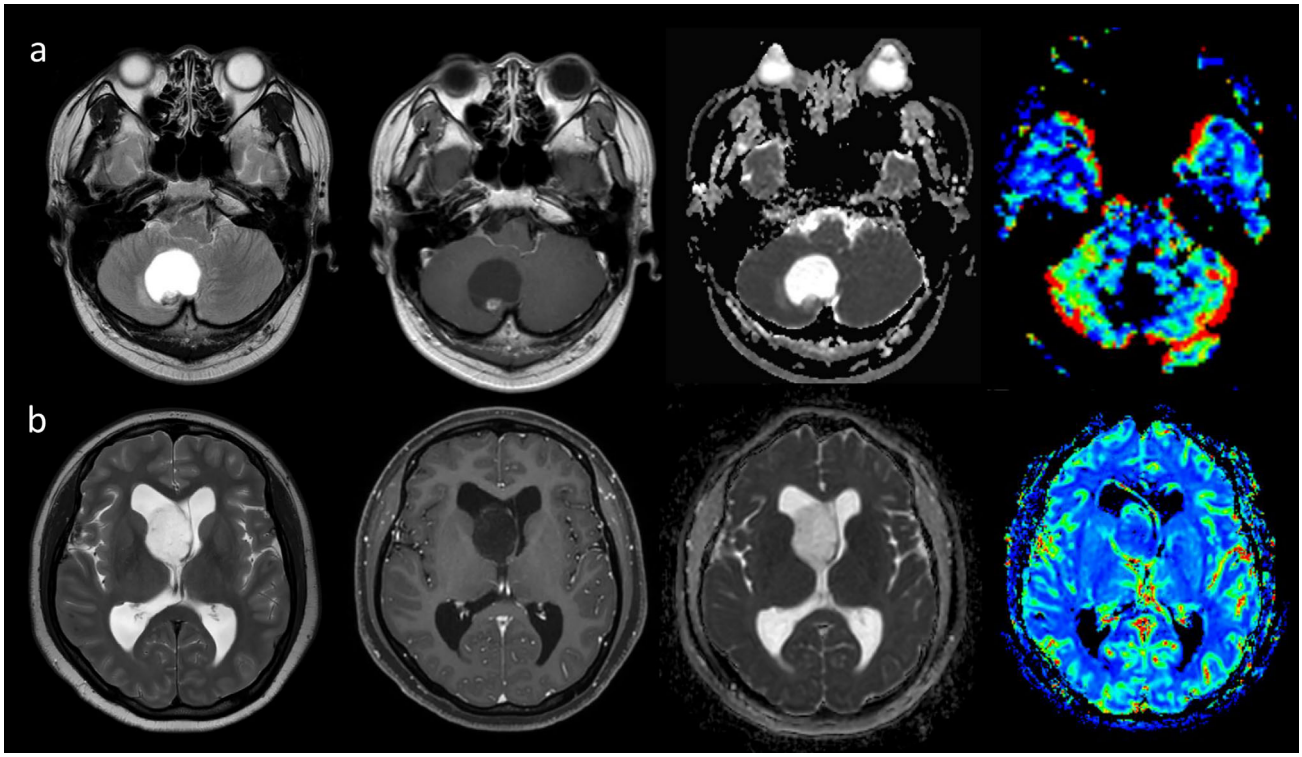

FIGURE 12: Images in two different patients with pilocytic astrocytoma. (a) A 26-year-old male shows a typical "cystic mass with mural nodule appearance" at the right cerebellar hemisphere. There is no cellularity increase or rCBV increase on ADC map and CBV map, respectively. (b) A 42-year-old male without a typical imaging appearance of pilocytic astrocytoma shows a poorly enhancing mass with T2 hyperintensity at the right lateral ventricle. There is no cellularity increase on ADC map and focal mildly increased rCBV on CBV map.

Pilocytic astrocytomas around the optic nerve and hypothalamus tend to be solid and infiltrating. The characteristic "cystic mass with enhancing mural nodule" appearance is less common in adult pilocytic astrocytoma with an incidence of 32.3% according to our recent research.[66] It may also manifest as a heterogeneously enhancing mass mimicking high-grade tumors.[67,68] Calcification may be present. On apparent diffusion coefficient (ADC) map, pilocytic astrocytoma shows a high ADC value suggestive of low cellularity.[69] Perfusion imaging may sometimes show relatively high relative cerebral blood volume (rCBV), thus mimicking high-grade tumors.[69] Pilomyxoid astrocytoma arises at the hypothalamic/chiasmatic region,[70] with less frequent cystic component, more frequent hemorrhage, and homogeneous enhancement.[63,65] Representative cases from two different patients with pilocytic astrocytoma are shown in Fig. 12.

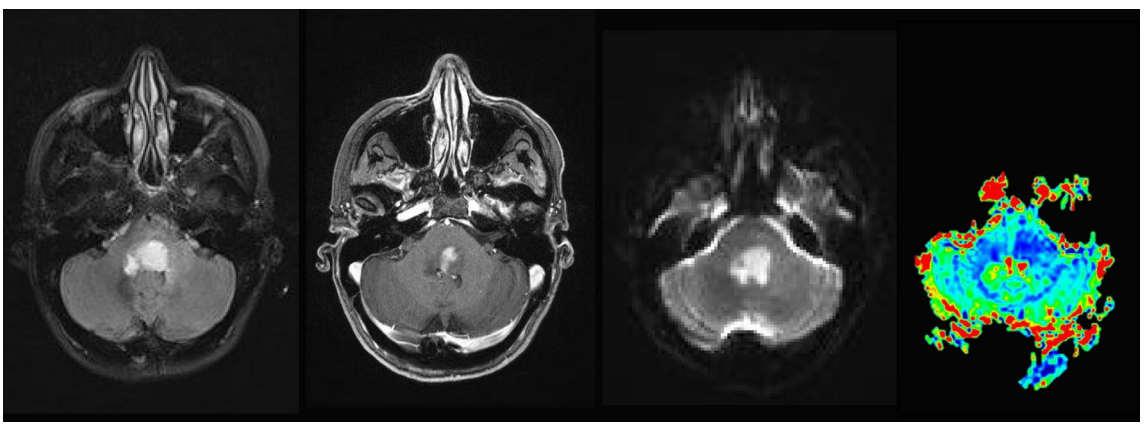

FIGURE 13: Images in a 44-year-old female with high-grade astrocytoma with piloid features. On imaging, a T2 hyperintense and inhomogeneous enhancing mass in the dorsal pons with extension to the left superior cerebellar peduncle and medulla oblongata is seen. There is no diffusion restriction on ADC. Focal rCBV elevation is seen at the tumor at the dorsal pons bordering the fourth ventricle.

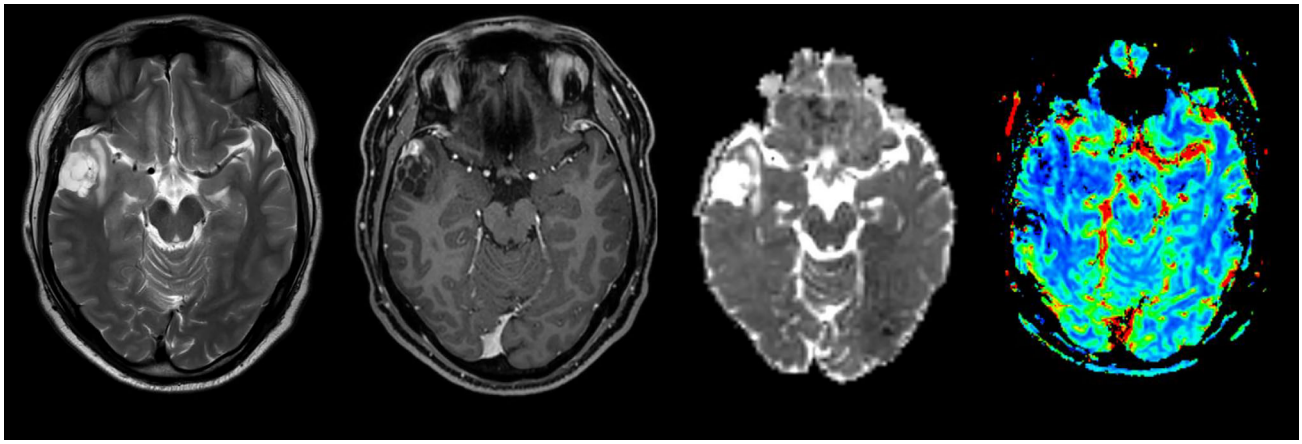

FIGURE 14: Images in a 33-year-old male with pleomorphic xanthoastrocytoma. Imaging shows a superficially located well-defined tumor at the right temporal lobe with a multiloculated cystic mass and mural nodule appearance. The lesion shows strong heterogeneous enhancement. There is no increased cellularity on ADC map and CBV map shows no increase of rCBV.

HIGH-GRADE ASTROCYTOMA WITH PILOID FEATURES. HGAP is defined as an astrocytoma showing a distinct DNA methylation profile, often with high-grade piloid and/or glioblastoma-like histological features. This tumor type can be diagnosed only with DNA methylation testing, which is not reimbursed in some countries and may pose a diagnostic problem. Alterations of MAPK pathway genes are often combined with homozygous deletion involving the *CDKN2A* and/or *CDKN2B* locus, and/or *ATRX* mutation or loss of nuclear ATRX expression. A wide range of gliomas represent relevant differential diagnoses, including glioblastoma, IDH-wildtype, pleomorphic xanthoastrocytoma, and pilocytic astrocytoma. The WHO grade is not established yet.

The incidence of HGAP is not clearly revealed, and the median age of HGAP is reported to be 40 years. A single institutional study of 83 HGAP patients showed 5-year overall survival rate of approximately 50%.[71]

The most frequent location of HGAP is posterior fossa (74%).[71] The imaging findings are rarely described, and in a recent case series of six patients, heterogeneous T2 signal intensity with rim enhancement was noted.[72] The tumors are either well-defined or infiltrative.[72] A representative case is shown in Fig. 13.

PLEOMORPHIC XANTHOASTROCYTOMA. Pleomorphic xanthoastrocytoma is an astrocytoma with large pleomorphic (frequently multinucleated) cells, spindle cells, and xanthomatous cells. *BRAF p.V600E* mutation and homozygous *CDKN2A* and/or *CDKN2B* deletion is common.[73] This tumor is graded as CNS WHO grade 2 or 3 according to the mitotic rate. The terminology anaplastic pleomorphic xanthoastrocytoma is no longer recommended for CNS WHO grade 3.

Pleomorphic xanthoastrocytoma typically develops in children and young adults. It frequently recurs after resection and is associated with decreased survival compared with other CNS WHO grade 1 or grade 2 gliomas.

Pleomorphic xanthoastrocytoma typically manifests as a supratentorial cortical mass with adjacent enhancing dural tail, most commonly at the temporal lobe. "Cystic mass with enhancing mural nodule" is a characteristic imaging finding, followed by a predominantly solid mass with cystic changes.[74] The overlying skull may be remodeled and calcifications are

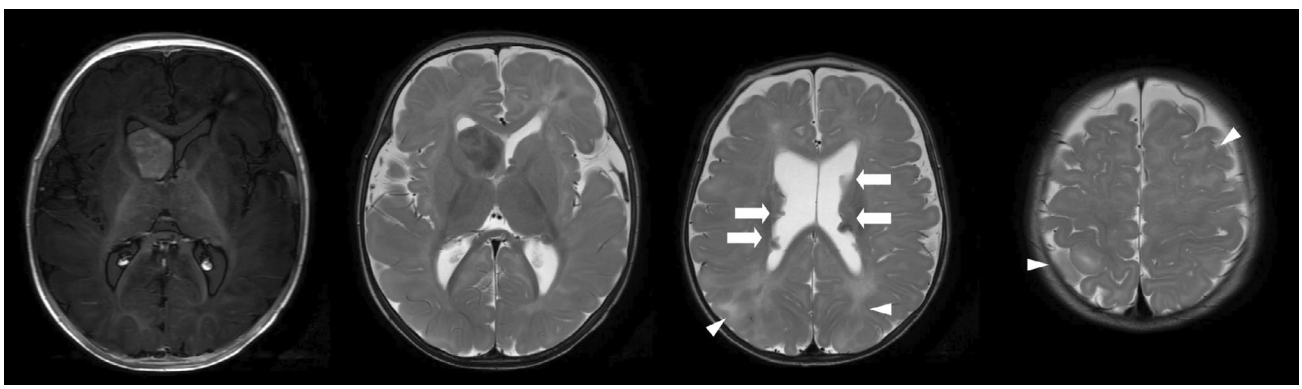

FIGURE 15: Images in a 6-month-old with subependymal giant cell astrocytoma and underlying tuberous sclerosis. There is an enhancing solid mass at the right lateral ventricle, near the foramen of Monro. Multiple subependymal nodules (arrows) and cortical/subcortical tubers (arrowheads) are also seen. This patient was confirmed as tuberous sclerosis with *TSC2* gene mutation.

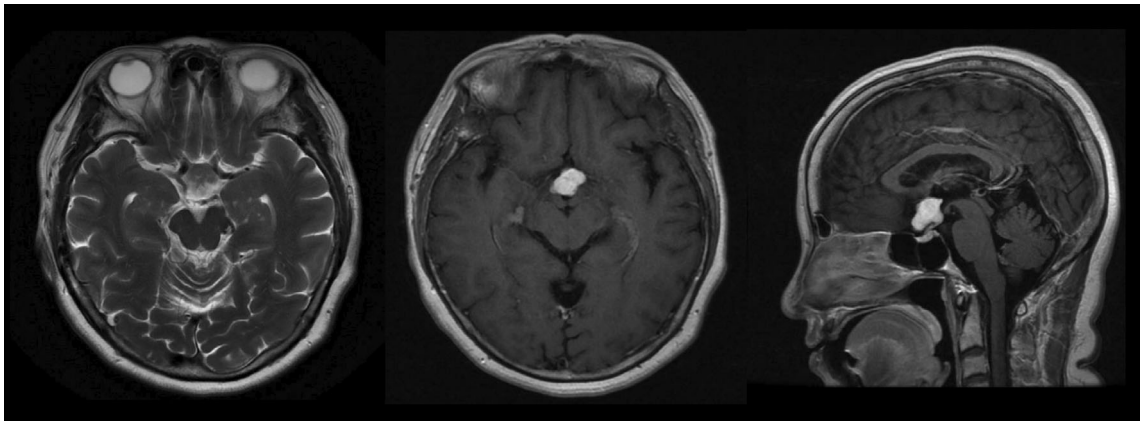

FIGURE 16: Images of a 60-year-old female with chordoid glioma. A well-defined mass at the anterior wall of the third ventricle shows marked homogeneous enhancement.

common on CT. Relatively lower ADC values are not uncommon.[75] A representative case is shown in Fig. 14.

SUBEPENDYMAL GIANT CELL ASTROCYTOMA. Subependymal giant cell astrocytoma (SEGA) is a periventricular tumor composed partly of large ganglion-like astrocytes. SEGAs have a strong association with tuberous sclerosis and typically show evidence of biallelic inactivation of *TSC1* or *TSC2*.

SEGA shows a favorable prognosis when gross total resection is achieved. Inhibition of mTOR with everolimus has been reported to result in reduction of tumor volume.[76]

SEGAs typically arise from the subependymal tissue of the lateral ventricles adjacent to the foramen of Monro. A slowly enlarging enhancing mass near the foramen of Monro in a patient with other imaging findings of tuberous sclerosis (cortical/subcortical tubers and subependymal nodules) supports the diagnosis.[77] SEGA shows heterogeneous enhancement and partial calcification or cyst formation may be common.[78] It may be indistinguishable from a subependymal nodule when it is small, therefore, serial imaging follow-up should be performed. A representative case is shown in Fig. 15.

CHORDOID GLIOMA. Chordoid glioma is a well-circumscribed glial neoplasm that originates from the ependymal cells of lamina terminalis (anterior wall of the third ventricle).[79] It is histologically characterized by GFAP-expressing epithelioid cells and exhibits a recurrent p.D463H missense mutation in the *PRKCA* gene. The location has been removed from the tumor nomenclature in the 2021 WHO classification for simplification, thus the terminology "chordoid glioma of the third ventricle" is no longer recommended. Chordoid glioma is WHO grade 2.

Chordoid glioma is usually diagnosed in adults (median age of 45 years) with a female predominance.[80] The treatment is based on maximal tumor resection.

Chordoid gliomas have a typical location in the anterior portion of the third ventricle, with larger tumors filling the middle and posterior aspects. A well-defined homogeneously enhancing third ventricular mass that is clearly separated from the pituitary gland and stalk may be suggestive of chordoid glioma, although the differential diagnosis of intraventricular meningioma or papillary craniopharyngioma should be considered.[81] A representative case is shown in Fig. 16.

ASTROBLASTOMA, MN1-ALTERED. Astroblastoma, *MN1*-altered, is a circumscribed glial neoplasm with *MN1*

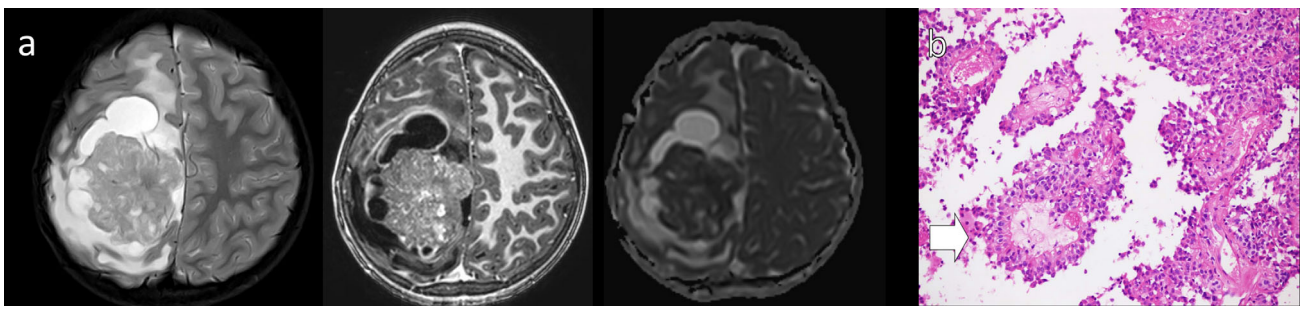

FIGURE 17: Images in a 7-year-old girl with astroblastoma, *MN1*-altered. *MN1* rearrangement was confirmed in fluorescent in situ hybridization (FISH). (a) Imaging shows a superficially located well-defined tumor with a cystic and solid "bubbly" appearance. The lesion shows heterogeneous enhancement with marked high cellularity on ADC map. (b) On histopathology, astroblastic pseudorosettes (arrow) and a perivascular structuring of neoplastic cells are noted.

alteration. In the 2021 WHO classification, astroblastoma has been specified as "astroblastoma, MN1-altered" to provide a more diagnostic focus for this entity. The WHO grade is not established yet.

Astroblastoma, *MN1*-altered, is diagnosed in child or young adults (median age: 15 years), with a remarkable female predominance, and with an odds of female 9.4 times than that of male gender.[82] Apart from surgical resection, no additional prognostic factors have been identified.[83]

Astroblastoma, *MN1*-altered, occurs predominantly in the cerebral hemispheres, most often in the frontal and parietal lobes, On MRI, *MN1*-altered astroblastomas are well-demarcated, solid or cystic masses ("bubbly" appearance) that are T1 isointense or hypointense and T2 hyperintense, with heterogeneous enhancement or rim enhancement and perilesional edema.[84,85] Calcification and hemorrhage are common. The lesion shows diffusion restriction.[85] A representative case is shown in Fig. 17.

Conclusion

The key points in 2021 WHO classification and imaging features of pediatric-type diffuse high-grade gliomas, pediatric-type diffuse low-grade gliomas and circumscribed astrocytic gliomas were reviewed and summarized in a radiologist's viewpoint. Most tumors in these categories show low incidence, and there are newly included tumor types in the pediatric-type diffuse high- and low-grade gliomas. Thus the current state of knowledge reflected in this review may not be complete and the integrative diagnosis based on molecular features will continue to evolve as the knowledge expands. Nonetheless, full acknowledgement of the current context of classification will improve the quality of radiologists for daily interpretation and communication with clinicians. We hope this review series serves as a motivation to fully elucidate the glioma classification system.

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