REVIEW ARTICLE

Cortically-based Brain Tumors in Children: A Decision-tree Approach in the Radiology Reading Room.

Vanessa. Rameh, Ulrike. Löbel, Felice. D'Arco, Aashim. Bhatia, Kshitij. Mankad, Tina.Y. Poussaint, Cesar.A. Alves

ABSTRACT

Cortically-based brain tumors in children constitute a unique set of tumors with variably aggressive biological behavior. As radiologists play an integral role on the multidisciplinary medical team, a clinically useful and easy-to-follow flowchart for the differential diagnoses of these complex brain tumors is essential.

This proposed algorithm tree provides the latest insights into the typical imaging characteristics and epidemiologic data that differentiate the tumor entities, taking into perspective the 2021 World Health Organization's classification and highlighting classic as well as newly identified pathologic subtypes using current molecular understanding.

ABBREVIATIONS:

Astroblastoma=AB)

Angiocentric glioma (AG)

Atypical teratoid rhabdoid tumor (ATRT)

Central Nervous System tumor (CNS)

CNS neuroblastoma FOXR2-activated (NB-FOXR2)

Desmoplastic infantile glioma/astrocytoma (DIG/DIA)

Diffuse hemispheric glioma, H3 G34-mutant (DHG)

Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (DGONC)

Dysembryoplastic neuroepithelial tumor (DNET)

Embryonal Tumors with Multilayered Rosettes (ETMR)

Ependymoma (EP)

Focal cortical dysplasia (FCD)

Ganglioglioma/gangliocytoma (GG)

Infant-type hemispheric glioma (IHG)

Intracranial pressure (ICP)

Long-term epilepsy-associated tumors (LEATs)

Pediatric diffuse low-grade gliomas (pLGG)

MR spectroscopy (MRS)

Multinodular and vacuolating neuronal tumor (MVNT)

Overall survival (OS)

Pediatric diffuse high-grade gliomas (pHGG)

Received June 12, 2024; accepted after revision August 13, 2024.

From the Department of Radiology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA (VR. TYP. CA.V.), from the Department of Radiology, Great Ormond Street Hospital for Children, National Health Service Foundation Trust, London, UK (U.L. F.A. K.M), and from the Department of Radiology, Children's Hospital of Philadelphia, University of Pennsylvania, , Philadelphia, PA (A.B.)

The authors declare no conflicts of interest related to the content of this article.

Please address correspondence to Vanessa Rameh, MD, Department of Radiology, Harvard Medical School, 300 Longwood Avenue, Boston, MA, 02115, USA; vanessa.rameh@childrens.harvard.edu.

Brain tumors are the most common solid tumors in children, with gliomas representing approximately 45%. Pediatric brain tumors have an incidence of 1.1-1.78 per 100,000 children.[1]

Advances in the genomic and epigenomic landscape over the past decades have led to significant revisions of the World Health Organization (WHO) classification of tumors. This was reflected in the 2016 and 2021 editions of the Central Nervous System tumor (CNS) classifications with the inclusion of essential molecular signatures as part of the "integrated diagnoses".[2, 3] This resulted in new types and subtypes of tumors elucidating these signatures which have prognostic and therapeutic significance. Additionally, crucial changes have been made over the last years to emphasize the clear distinction between adult-type and pediatric-type tumors. This recognition stems from the understanding that pediatric tumors differ from their adult counterparts in terms of their developmental origin, genetics, and prognosis. Many of the new tumor types belong into the categories of pediatric-type low-grade and high-grade tumors and many are found in the supratentorial (ST) compartment of the brain[4].

Understanding genetic mutations in tumors is crucial for radiologists due to their significant implications in diagnosis, treatment planning, and prognosis. A comprehensive review of all the genetic alterations is outside the scope of this article. In Summary, molecular alterations such as MAPK dysregulation, MYCN amplification, MGMT methylation and TERT promotor gene alterations play important roles in tumoral cell growth and affect targeted therapies. For instance, MAPK dysregulation affects tumor progression and response to targeted therapies and the presence of MGMT methylation alters the sensitivity to alkylating agents.

This article narrows the scope of cortical brain tumors in children due to several considerations.
This category of tumors is complex and diverse, hence providing a concise summary is helpful for radiologists. As there is a gap in the current literature addressing these entities in Children, we aimed to summarize the existing knowledge and provide a helpful thought process for better understanding these tumors.

This review article proposes an easy-to-follow decision tree for the differential diagnosis of brain tumors in children, originating from and involving the cortex **(Fig. 1)**. It can be used to broadly classify a new brain tumor and may have impact in institutions with limited resources for molecular genetic analysis, therefore, bridging the gap between the current literature and clinical use.

Decision tree:

Our flow chart emphasizes the specific and typical imaging features of certain tumor types, it may not encompass the full imaging spectrum. Instead, its primary utility lies in the recognition of typical and characteristic imaging appearances of cortically-based tumors, as previously described and validated in the literature **(Fig.1)**.

The initial step in our proposed approach entails assessing whether the mass exhibits both solid and cystic characteristics, followed by considering the patient's age, which aids in distinguishing tumors more prevalent in the infantile age group.

For patients over one and a half years old, the next step is to evaluate the presence of decreased diffusivity within the cortical mass, comparing the ADC signal to the adjacent uninvolved cortex.

Subsequently, if the mass is in the low-grade category, noting "special" features is important for accurate diagnosis (e.g., presence of intrinsic T1 signal in angiocentric gliomas, coarse calcifications in cystic-solid enhancing mass in ganglioglioma/gangliocytoma) **(Supplementary table 1)**. If the tumor falls in the high-grade category, additional distinctive features such as the presence of edema, enhancement, and ill-defined borders help differentiate certain tumor types within this category. We will further elaborate how to differentiate these tumor types and subtypes, aligning with the recent WHO classification scheme.

1. Pediatric-type Diffuse High-Grade Gliomas (pHGG)

Pediatric diffuse high-grade gliomas (pHGG) are a heterogeneous but unique group of tumors with different clinical, genomic, and molecular characteristics compared to their adult counterparts.[5, 6]

This review will focus on three tumoral types within the pHGG family that commonly occur in the "peripheral" aspect of the brain including those involving the cortex.

a. Diffuse Hemispheric Glioma, *H3G34*-mutant (DHG)

Diffuse hemispheric glioma, *H3G34-mutant* (DHG) is a new addition to the 2021 WHO classification, designated as "CNS WHO grade 4".[2] This aggressive tumor is rare among all pediatric brain tumors, comprising less than 1% of all pediatric gliomas but approximately 15% of all pediatric high-grade pediatric tumors. This tumor typically affects teenagers and young adults with a median age of 17 years (14-23 years), demonstrates no significant sex predilection, and clinical presentation related to increased intracranial pressure (ICP).[7, 8]

DHG have a pathognomonic molecular signature characterized by a missense somatic recurring histone 3 mutation (*H3F3A*) at codon 34, where glycine is substituted with arginine or valine.[5, 6] Recent studies describe concomitant genetic alterations, commonly *TP53, ATRX, and PDGFRA* mutations, and the presence of *MGMT* promotor gene methylation amongst others.[5, 9] This tumor has a median overall survival (OS) of 1 year.[7, 10]

Histologically, there are high grade features within the tumoral cells that can be either astrocytic or embryonal tumor morphology.[11] The *H3G34R/V* genotype imparts a grade 4 even in the absence of high-grade features.[12]

As evident in their names, DHGs are typically hemispheric and affect cortex and white

matter of the frontal, parietal and temporal lobes.[13] Midline and deep gray matter extensions are described but only as extensions of non-midline locations.[10, 14]

Variable imaging features are described including well-defined margins, infiltrative gliomatosis-cerebri-like pattern or commonly a combination of both.[12, 15, 16] Well-defined masses are typically expansile and voluminous with variable T2 prolongation, and T1 shortening related to hemorrhage and calcifications. The infiltrative pattern presents as an expansile T2 prolongation with almost always associated with patches of decreased diffusivity and a mean ADC of 600-700 x 10^{-6} mm^2/s.[6, 7] The enhancement is variable ranging from none to minimal to intense. Some series describe increased cerebral perfusion and increased choline/N-acetylaspartate ratios on MR spectroscopy (MRS). Some series also suggest that the infiltrative pattern is seen in an older age group.[10] An example is shown in **Fig. 2**.

Differential diagnosis includes other HGGs or embryonal hemispheric tumors. Treatment strategy includes maximal safe surgical resection with radiation and temozolomide.

b. 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 introduced tumor type under the umbrella of pHGGs.[2] This rare, aggressive, and high-grade tumor (CNS WHO grade 4) lacks mutations in the IDH or H3 genes. Although there is limited epidemiologic data to date, this neoplasm appears to affect a wide age range of the pediatric population with a poor OS (median age of 22 months) according to a large pediatric series.[17, 18] As in most aggressive tumors, duration of symptoms is usually short, most often presenting with increased ICP.[19, 20]

Recently identified key oncogenic alterations have permitted its solid differentiation from its adult counterparts and have highlighted different molecular subgroups within this novel tumor entity. Hence, several molecularly and prognostically distinct subgroups are identified, including amplifications of the *MYCN, PDGFRA, and EGFR* genes, as well as mutations of the *TERT* promoter. Additionally, it is important to note that almost all secondary radiation-induced pHGG clusters harbor alteration of the *PDGFRA*.[21] Future studies are needed for further characterization of these subgroups as distinct entities.

Radiologically, diffuse pHGG, H3-wildtype and IDH-wildtype are similar to glioblastomas in adults.[18, 21, 22] Classically, these are large ST, “peripheral,” and highly cellular tumors with ill-defined margins. Commonly, hemorrhage and necrosis are present. Some studies suggest that their heterogeneous enhancement and minimal peritumoral infiltrative edema make them distinguishable from other high-grade ST tumors.[19, 20] An illustrative example is represented in **Fig. 3**.

Limited data revealed subtle radiological differences in the *MYCN*-amplified HGG subgroups, including their slight temporal lobe predilection, lack of calcification, homogeneous

enhancement, and well-circumscribed margins. However, validation of these observations is needed in large sample-size studies.[18]

Differential diagnostic considerations are the same as DHG.

In Summary, and following our proposed chart, DHG and diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype should be included in the differential of high-grade, cortically-involving tumors with ill-defined margins **(Fig.1)**. Additional helpful clues include the presence of leptomeningeal and/or ependymal contact, which were described in almost all cases on DHG. A prior history of radiation is helpful as a clue that the tumor in question is likely diffuse pHGG, H3-wildtype and IDH-wildtype. [7]

c. Infant-type hemispheric glioma (IHG)

Infant-type hemispheric glioma (IHG) is a subtype of glioma newly introduced in 2021 with no assigned grade yet.[2] IHG represents a distinct clinical and molecular entity usually present in the first year of life with a median age of 2.8 months and poor OS of 2 years.[23] They are hemispheric masses, mostly of high-grade histology and harboring receptor tyrosine kinase fusions, characteristically involving *NTRK1/2/3, ALK, ROS1, or MET* genes.[23-25]

From an imaging perspective, IHG should be high on the differential when encountered with a large cystic and solid masses with well-defined margins and lepto-/pachymeningeal contact in an infant **(Fig.1)**. Necrosis and hemorrhage are commonly present, as well as strongly decreased diffusivity of the solid portions.[15, 24] An illustrative example is represented in **Fig. 4**.

These may resemble the more commonly known desmoplastic infantile glioma/astrocytoma (DIG/DIA), sharing hemispheric location and age group; however, a few subtle differences should be taken into consideration. The presence of strongly decreased diffusivity and tumoral bleeding is seen in IHG as opposed to DIG/DIA, where most often there is absence or only moderately decreased diffusivity in the solid portions of these tumors **(Fig.1)**. Studies suggest that the presence of enhancement within the cyst walls, as well as bi-hemispheric involvement (crossing midline) are features of IHG. [24]

2. Pediatric-type Diffuse Low-Grade Gliomas (pLGG)

Distinct molecular alterations and histological features separate four entities under the pLGG umbrella. All of which are “peripheral”, hemispheric, and lack IDH and H3 mutations.

a. Angiocentric glioma (AG)

Angiocentric glioma (AG) is a rare epileptogenic pLGG, first recognized in the CNS 2007 edition.[2, 26] AGs occur in the first and second decades, commonly presenting as ST brain

lesions involving the cortex and subcortical white matter.[7] This explains their common clinical presentation (long history of intractable seizures). [27] Although commonly described in the ST brain with frontal and temporal lobes being more common, AG can be seen in other locations of the brain including the brainstem followed by the corpus callosum and basal ganglia.[7]

AGs are CNS WHO grade 1 tumors and the required criteria for the pathologic diagnosis include a diffuse glial architecture with an angiocentric pattern, the presence of monomorphic spindle cells, and a structure of astrocytic/ependymal differentiation. A desired criterion includes the MYB:QKI fusion, the most common pattern of MYB rearrangement.[15]

On imaging, superficial AGs are classically expansile and demonstrate a few characteristics features including variable components of high signal on the T1-weighted imaging and sometimes a "stalk-like" sign, which refer to the triangular shape of T2 prolongation with the apex extending from the tumor towards the ventricle. There is no to minimal enhancement and sometimes regional atrophy.[28-31] Some cases can present with the described T2-FLAIR mismatch, indicating incomplete attenuation of the hyperintense T2 signal within the tumor.[32]

Illustrative examples are represented in **Fig. 5**, emphasizing the importance of following our proposed flow-chart when encountered with a low-grade, cortically-based tumors with T1 hyperintense signal and no calcifications **(Fig.1)**.

It is important to note however that these tumors demonstrate heterogeneous T1 signal and postcontrast enhancement, which present in up to 20-30% of cases.[7] Additionally, there is facilitated diffusivity as seen in pLGGs. Their CT attenuation is variable with no evidence of hemorrhage and calcifications occur very rarely but can be visualized. [33]

Intratumoral T1 signal, the presence of a stalk-sign, and regional atrophy are correlated with seizure length.[28] Theories explaining the "stalk-sign" includes the presence of focal cortical dysplasia (FCD), peritumoral gliosis, tumoral cell infiltration adjacent to vessels, and seizure-induced gliosis which explains the presence of regional atrophy.[7]

It is also worth mentioning that in our institutional experience, the internal and peripheral components of T1 hyperintensity of these tumors may often be neglected because the T1 shortening is overall similar to the adjacent normal appearance of white matter as opposed to the florid T1 shortening related to iron, manganese or calcium deposition for instance.

Differential diagnosis includes other cortical-based epileptogenic low-grade glial, neuronal, or neuroglial tumors including dysembryoplastic neuroepithelial tumor (DNET), ABs, and malformations of cortical development (such as FCD). Specific subtle differences of these entities are discussed throughout this paper.

b. Diffuse Astrocytoma, *MYB*- or *MYBL1*-altered

This is a rare entity newly recognized CNS WHO grade 1 tumors, most commonly involving young children with a median age of 5 years (range 0-26 years) and no sex predilection.[34]

As the name implies, structural alteration of *MYB* or *MYBL1* are necessary for the diagnosis in addition to a low-grade astrocytoma histology which lacks H3 and IDH mutations. Alternatively, the presence of a matching class of a whole genome methylation profile can suffice for the diagnosis.[34-36]

On imaging, this tumor is expansile, T2-hyperintense, and non-enhancing with no associated decreased diffusivity. The presence of accompanying subcortical cysts are all clues to the diagnosis and help differentiate it with other pLGG. Additionally, the established and specific T2-FLAIR mismatch sign identified in the adult neuroimaging literature, as a signature for Diffuse astrocytoma, IDH-mutant is found to occur in certain rare molecular subtypes of pLGGs, including but not limited to Diffuse astrocytoma, *MYB*-and *MYBL1*-altered, as well as DNET, and tumors with *FGFR1, FGFR1, FGFR4*.[32] An illustrative example is seen in **Fig.6**

c. Polymorphous low-grade neuroepithelial tumor of the young (PLNTY)

Polymorphous low-grade neuroepithelial tumor of the young (PLNTY) was first described in 2016 as part of the distinct group of entities that share clinical and molecular features with LEATs (.[3, 37] This unique group shares some genomic alterations (MAPK signaling pathway or mTOR alteration) and commonly has a CD34 marker protein expressed by immunohistochemistry.[38, 39] Clinically, this is an indolent WHO grade 1 tumor that occurs in adolescents with a median age at diagnosis of 18 years (range, 4-32 years) who present with long-standing seizures.[37, 39] Surgical resection is usually curative.

Histologically, PLNTYs exhibit a diffuse growth with pseudo-rosettes arranged in a nodular pattern consisting of distinct oligodendroglioma-like cellular components.[37, 39, 40] Classically, there is MAPK pathway dysregulation which is commonly found in other LEATs, giving us a clue about the common origin of these tumors.[41] Additionally, common genetic alterations include *BRAF-V600E* mutation and *FGFR2/3* rearrangement and a unique *FGFR2-CTNNA3* fusion.[33, 37, 41, 42]

This “superficial” lesion originates from the cortex layer and may involve the subcortical white matter of virtually all lobes but tend to occur more commonly in the right greater than left mesial temporal lobe. [37, 39]

PLNTYs are characterized by calcifications on CT, variable signal on T1WI and the characteristic “salt and pepper”/granulate appearance on T2WI. The latter is thought to be

related to the calcifications. There may be increased perfusion and minimal to no enhancement post contrast administration (**supplementary Fig.1**).[40]

As a non-aggressive entity, PLNTYs have no decreased diffusivity and they show only mass effect rather than disruption of adjacent white matter tracts on DTI.

Although DNETs and PLNTYs share some clinical and imaging features, there are few essential differences that are worth noting. First, DNETs are usually larger than PLNTYs (usually less than 3 cm).[43] Second, DNETs are solid-cystic, have clear demarcations and multinodular appearance resulting in their classic "soap-bubble" appearance compared to the "salt and pepper" appearance of PLNTYs. Moreover, one must also note that the common perivenular "linear" extension noted in DNETs is not an expected feature in PLNTYs and the calcifications are fine as opposed to the most characteristic coarse calcifications in PLNTYs (**supplementary Fig. 1).**[39, 41, 44]

Other differential diagnoses include gangliogliomа/gangliocytoma (GG) which tend to have a calcification morphology which sometimes can be large and irregular (rather than a "salt and pepper appearance), isointense to cortex on T1WI (rather than hypointense), cystic components, and enhancement.[45]

In Summary, PLNTY is high on the differential when encountered with a low-grade, solid, and cortically-based tumor with salt and pepper calcifications **(Fig.1)**.

d. Diffuse Low-Grade Glioma, *MAPK Pathway-altered*

The 2021 CNS WHO classification has recognized diffuse low-grade glioma, *MAPK pathway altered* as a new tumor type, however, no grade has been assigned yet[2]. Longstanding seizures is a common clinical presentation.

Clinical, morphological, and molecular data are still being defined and the prognosis is unclear as it depends on the type of genetic alteration.[15] Therefore, it is possible that this entity will be divided in the future given its vast heterogeneity.

Classically, there is a lack of IDH mutations, histone H3 mutations, and *CDKN2A* deletions. Common MAPK molecular alterations include *TKD* duplication, *FGFR1* mutation, *FGFR1* fusion, *BRAF V600E* mutation, BRAF fusion, or BRAF insertion mutation.[15, 46] On histology, there are infiltrative astrocytic and/or oligodendrocytic-like cells with calcifications, the latter is commonly seen with *FGFR1* mutations.[47]

This tumor can occur anywhere along the neuroaxis and its heterogeneity is reflected on imaging, as it depends on the histologic/molecular subtype. In the cerebrum, masses commonly involve the cortex, usually have low-grade features (T2 prolongation and low diffusivity) and commonly calcifications.[15, 46] Enhancement is usually strong, distinguishing it from PLNTYs.

Other differential diagnoses include DNETs and GGs.

Therefore, This tumor must be included in the diffenrential of a low-grade, cortically-involving, and solid neoplasm, that is primarily solid and enhancing with calcifications **(Fig.1)**.

Treatment is variable and can include surgical resection, *MEK* inhibitors and dabrafenib (if *BRAF V600E* mutant).[48, 49]

3. Circumscribed Astrocytic gliomas

The circumscribed astrocytic glioma family, for which the prototype is pilocytic astrocytoma, has expanded in the new WHO CNS 5.

a. Astroblastoma, *MN1-altered* (AB)

Astroblastoma (AB) is a rare neoplasm representing 0.45-2.8 % of all gliomas with a peak incidence in the second and third decades.[50, 51] Their biologic behavior can range from indolent (low-grade) to aggressive (high-grade) with no established WHO grade.

Previously, the existence of ABs has been debated as they often share some clinical, pathologic and radiologic criteria with ependymomas.[52] However, recently ABs have been defined as presenting with *MN1* alterations in the 2021 classification.[2, 53]

On histology, ABs most frequently exhibit perivascular pseudorosettes similar to ependymomas (ET) with vascular hyalinization and little fibrillary background. Higher grade tumor forms demonstrate rarely signet ring cells with necrosis, cellularity, and microvascular proliferation.[54]

As expected, studies show that the presence of anaplasia confers poor prognosis.[55]

Imaging usually shows a well-circumscribed solid and cystic mass with a “soap-bubble” appearance of the centrally located solid component. The solid component exhibits central calcifications on CT, isointensity to gray matter on T1WI and T2WI with heterogeneous contrast enhancement and intermediate diffusivity (ADC range, 1190 to 1250 x 10^{-6} mm^2/s).[50-55]

In our institutional experience, there is at least mild surrounding vasogenic edema present in most of the cases, in contrast to the studies in the literature where none/minimal edema is described. An illustrative example is represented in **supplementary figure 2**.

The main imaging differential is ST ependymomas, which should be suggested with confidence when the “periwinkle” sign is visualized, indicating the presence of large peripheral cystic components/central necrosis surrounded by calcifications and hemorrhage.

b. Pleomorphic xanthoastrocytoma (PXA)

Pleomorphic xanthoastrocytoma (PXA) is a rare glial tumor, thought to be originating from subpial astrocytes and consists of less than 1% of all astrocytic neoplasms. [56, 57]

While usually common in the second decade of life, they can occur in a wide range of ages including infancy till ninth decade.[57, 58] PXAs are cortically-based in 99% of cases with a presenting symptom of long-standing seizures. [57, 59] Generally, PXAs are indolent with an OS of 80% at 10-year .[58] PXAs are considered grade 2 or 3 neoplasms, which confer prognostic significance.[3, 15, 60]

This tumor exhibits alteration in the MAPK pathway and TERT promotor methylation.[15, 61] The latter designates a more aggressive phenotype and it will be interesting to study the presence of imaging clues suggesting this genotype.[62] Classic histology includes xanthomatous and multinucleated tumor cells as well as the presence of eosinophilic granular bodies in a reticulin matrix.

Classic imaging appearance is a cortically-based cystic lesion with an enhancing mural nodule in the temporal lobe. On CT, its appearance is variable, ranging from hypo to hyperdense with no calcifications or surrounding edema. There is often scalloping of the adjacent inner table of the skull. On MR, the cyst follows CSF signal on all sequences and the solid component exhibits T1 and T2 prolongation. Signal can be heterogeneous on the latter sequences and enhancement is always strong **(Supplementary Fig.3)**.[56, 57, 61, 63] Mean ADC values are $912 \pm 219 \times 10^{-6}$ $mm^{2/s}$ and do not correlate with tumor grade. However, ADC is useful to differentiate PXA from its two main differential diagnoses, PA and GG in which ADC values are usually higher.

In summary, PXAs must be high on the differential of a cortically-originating tumor with cystic and enhancing solid nodule with dural enhancement **(Fig.1)**.

4. Glioneuronal and neuronal tumors

This is a heterogeneous group encompassing neuroepithelial tumors with neuronal elements[2]. These tumors may share clinicopathologic, molecular, and prognostic features.

a. Multinodular and vacuolating neuronal tumor (MVNT)

Multinodular and vacuolating neuronal tumor (MVNT) is recognized as a low grade, distinct tumor type in the 2021 WHO classification. MVNTs most commonly occur in the fourth decade but there is a wide age range from 8 to 63 years. They require surveillance if asymptomatic/incidental and are surgically resected when symptomatic.[64, 65]

Alterations of the MAPK pathway including *BRAF* mutations and *FGFR2* fusions are frequently observed in MVNTs.[66, 67]

As MVNTs involve the deep cortex/subcortical white matter and spare the superficial cortical layer, their distinctive imaging appearance should be easily recognized by radiologists.
The hallmark radiologic appearance of this ST tumor is the subcortical clusters of T2 hyperintense nodules/bubbly appearing with no associated reduced diffusion, increased perfusion, calcification, edema, or contrast enhancement **(supplementary Fig.1).**[64, 68, 69]

The two main differential considerations are DNET and perivascular spaces. Rarely, MVNTs may also have a homogeneous T2/FLAIR hyperintense appearance that mimics any low grade infiltrative glioma.

b. Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (DGONC)

Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (DGONC) is an extremely rare tumor type that was provisionally added to the WHO 2021 with no established grade yet. [2, 70] DGONCs primarily affect the pediatric population, commonly in the first decade and they often demonstrate good prognosis following surgery. [70, 71]

These tumors have a signature DNA methylation profile in addition to moderate cellularity and mitotic index and monosomy of chromosome 14 is a frequently observed phenomenon.[70-72]

DGONCs tend to involve the cortex and subcortical white matter with a predilection to the frontal and temporal lobes.[70, 71] These tumors are sharply demarcated but can cross the midline. Moreover, these tumors are hyperintense relative to the cortex on T2 with various inhomogeneous diffusivity; they exhibit minimal enhancement, limited mass effect, and areas of cystic changes and calcifications. [70-72]

c. Gangliogliomа/gangliocytoma (GG)

This type of tumor was recognized in the first WHO classification due to its distinct histogenetic characteristics. GGs occur at any age, but tend to be more common in adolescent and young adults, and have a favorable prognosis after surgical resection.

GGs have characteristic MAPK pathway activation, notably *BRAF p.V600E* mutations and show low-grade features on histology.[73]

Imaging findings show a cortically-based, and expansile cystic-solid tumor. The solid component shows varying degree of enhancement and facilitated diffusivity. There are coarse calcifications and lack of peritumoral edema **(supplementary Fig.1).**[68] Studies have shown that ADC values tend to be lower in *BRAF p.V600E*-mutant GGs compared to the wild type GG, PAs, and oligodendroglioma.[74] Although, GGs are temporal lobe predominant lesions, they can also appear anywhere else in the neuraxis.

Moreover, gangliocytomas are essentially indistinguishable from gangliogliomas on imaging.

In Summary, GGs must be high on the differential when encountered with a low-grade, cortically-originating, cystic and enhancing solid lesion with calcifications (Fig.1).

d. Desmoplastic infantile ganglioglioma and desmoplastic infantile astrocytoma (DIA/DIG)

This is a benign, low-grade tumor type that occurs in infants under 2 years-old and is composed of either glioneuronal (DIG) or glial (DIA) elements in a desmoplastic stroma [75]. The hallmark molecular alterations are those of the MAPK pathway and they exhibit a favorable prognosis. [76]

Radiologically, DIGs/DIAs present as cortically-based, large, and heterogeneous cystic-solid masses in the frontal or parietal lobes of an infant. There is usually a characteristic "dural-tail" of the solid portion which shows heterogeneous enhancement, calcifications, and a wide range of heterogeneous diffusivity.[76]

e. Dysembryoplastic Neuroepithelial tumors (DNET)

DNETs are CNS WHO grade 1, cortically-based tumors of neuroglial origin first described in 1988.[77, 78] DNETs present childhood and adolescence, usually with seizures.[43, 79] They are considered benign with a favorable outcome after total surgical resection.

Their signature molecular alteration is an *FGFR1* mutation and their histologic hallmark is the presence of glioneuronal elements.[43, 79]

DNETs are well-defined lesions classically found in the temporal lobe, exhibiting the characteristic "bubbly" or "soap and bubble" appearance, due to the presence of T2 hyperintense pseudocysts along with interspersed high T2/FLAIR signal, usually found in the subcortical white matter (Fig.1). They frequently exhibit a hyperintense rim on FLAIR and calcifications/hemorrhage are rare.[43] The latter is in a subcortical location if present **(Supplementary. Fig. 1)**. [80] Although enhancement (nodular or rim-like) can be seen in 30% of cases, DNETs classically exhibit minimal edema and no enhancement.[81] DNETs have lower ADC and rCBV values than normal brain parenchyma.[82]

The imaging differential diagnosis include MVNT, PLNTYs, AGs, and PXAs. Each one of them has a hallmark imaging feature described in this paper.

5. Embryonal tumors

Embryonal tumors of the CNS are highly malignant and aggressive tumors originating from undifferentiated or poorly differentiated neuroepithelial cells. Their classification has evolved over the years to reflect our understanding of their tumoral behavior.

a. CNS neuroblastoma, *FOXR2*-activated *(NB-FOXR2)*

Neuroblastomas have been included in the WHO classification for many decades. However, only in the last few years with advances in genetic analysis, a specific molecular profile has been identified. CNS neuroblastoma, *FOXR2*-activated (NB-*FOXR2*) is defined by alterations in *FOXR2*.[2, 83] This tumors exhibits foci of neuroblastic or neuronal differentiation, *FOXR2* activation, or a DNA-methylation profile that aligns with this diagnosis.[83]

NB-*FOXR2* is a CNS WHO grade 4 tumor, frequently noted in the first decade (mean age=5 years). Most common clinical symptoms include increased ICP and seizures.[84]

Most characteristic imaging features are large ST masses with a hyperdense attenuation of

the solid components and calcification along their inner rim on CT with thinning of the inner table of the skull have been reported. The tumor often shows minimal perilesional edema, heterogeneous enhancement of the solid component, and foci of increased susceptibility related to calcification and/or hemorrhage. Cystic and/or necrotic components are almost always present, and low mean ADC values are expected for all these tumors **(Supplementary Fig.4)**.

Metastases are uncommon at the initial presentation, although cases of leptomeningeal spread have been described and the prognosis, although representing an aggressive tumor, is relatively good (5-year OS of 85%) when adequate and early treatment is provided.[85]

b. CNS tumors with *BCOR* internal tandem duplication (CNS tumor *BCOR*-ITD)

CNS tumors with a *BCOR* internal tandem duplication (CNS tumor *BCOR*-ITD) are new, high-grade (CNS WHO grade 4) tumors that typically occur in early childhood at a median age at presentation of 3.5 years. These tumors are distinguished by a specific genetic alteration (a somatic ITD in exon 15 of *BCOR*) and typical histopathologic features including a mix of spindle and oval cells, along with cytologic and immunohistochemical signs of neuroepithelial differentiation. On the other hand, the typical embryonal morphology and clear neuronal differentiation is not present in these tumors.[83]

CNS tumors with *BCOR*-ITD are equally distributed among supra and infratentorial compartments.

From a neuroimaging perspective, these are typically large, "peripheral" lesions with reduced diffusivity, often involving the cortex and abutting the overlying dura without clear tumoral invasion (no thickening of the adjacent dura mater, or signs of leptomeningeal dissemination **(Supplementary Fig.5)**.[86] It is important to highlight, however, that although CSF dissemination is often absent at the initial presentation, CNS tumors with *BCOR*-ITD must be considered and treated as aggressive CNS lesions, necessitating close clinical and radiologic monitoring as they are often associated with early local recurrence, can relapse with leptomeningeal spread and poor OS.[86]

Additionally, there are variable degrees of signal heterogeneity and poor contrast enhancement with central areas of necrosis and blood products along with calcifications. Large central veins within the mass are also a common finding noted. Some reports also indicate a dissociation of tumor microvascular density and CBF values, most frequently exhibiting high microvascular density and low CBF values, a feature that has been described in other embryonal tumors and ETs.[87]

Differential diagnoses may include an embryonal tumor with multilayered rosettes (EMTR), which occurs in children of similar age and share some imaging features, such as lack of peripheral edema. However, these tumors differ from CNS tumors with *BCOR*-ITD as they do not frequently exhibit central areas of necrosis. Atypical teratoid/rhabdoid tumors (ATRT) often present mild to moderate edema, enhancement of solid tumor sections, and CNS dissemination at the time of diagnosis, providing useful clues for neuroimaging differentiation.

ST ependymomas have increased T2 hyperintensity than CNS tumors with *BCOR*-ITD, and

often present with avid heterogeneous enhancement along with intermediate decreased diffusivity. ST high-grade gliomas, another important differential with aggressive features, have more irregular and infiltrative margins, more peritumoral edema, and greater contrast uptake than CNS tumors with *BCOR*-ITD.

c. Embryonal Tumors with Multilayered Rosettes (ETMR)

ETMRs are aggressive tumors, CNS WHO grade 4, most often affecting children under the age of 3 years with a low 5-year survival rate.[88] ETMRs exhibit low intertumoral genetic heterogeneity and are characterized by an increased amplification of the *C19MC miRNA* cluster on chromosome 19q13.42, coupled with an expression of the RNA-binding protein, LIN28A[88] or *DICER1* mutation associated with germline alteration. Their histological signature consists of multilayered rosettes along with remnants of the undifferentiated neural tube, suggesting a prenatal oncogenic transformation leading to embryonal progenitor cells.

Unlike other embryonal tumors, ETMRs are more frequently seen in the supratentorial compartment, often involving the cortex and subcortical white matter. These tumors most often contain components of reduced diffusivity, a classic feature of embryonal tumors, and are usually isolated (non-multicentric) at presentation, although CSF dissemination is relatively common.

ETMRs are large with irregular but well-circumscribed margins and often exhibit none to mild enhancement. Peritumoral edema can be present, it tends to be disproportionately smaller than expected for the size of the tumor **(Supplementary Fig.6)**.[89]

Cystic components, hemorrhage, and microcalcifications are noted but not as frequently present as in other aggressive ST tumors such as EPs. Moreover, unlike ETMR, ST EPs especially those *ZFTA* fusion-positive, tend to present in older children.

d. Atypical teratoid rhabdoid tumor (ATRT)

ATRT is a rare, highly malignant embryonal tumor, predominantly affecting children under two years. Classified as grade 4 in the WHO classification, ATRT can present as a focal or multifocal tumor with evidence of leptomeningeal dissemination. This tumor is typically located in the posterior fossa, mostly the fourth ventricle, although it can occur anywhere in the CNS, including the optic nerves and intraspinal. An off-midline occurrence is not unusual, with predisposition sites including cerebellopontine angle cisterns, meninges, and cranial nerves. In this paper, we will briefly focus on the less common ST ATRT.

Prior research has linked tumor sites with a molecular profile of ATRT, where most pediatric ATRTs are classified into three molecular subgroups: ATRT–*MYC*, ATRT-*TYR*, and ATRT–*SHH*. Among these molecular profiles ATRT-*MYC* tumors have predominantly been described in the ST compartment in patients older than three years, while ATRT-*TYR* tumors are found in infratentorial locations in patients younger than one year, and ATRT-*SHH* tumors are found

in both supra- and infratentorial compartments, representing an intermediate subgroup with highly incidence around 2 years of age.[90]

It is worth mentioning that in adults, ATRTs are more frequently ST, mostly located in the suprasellar region.

As a rule, ST ATRTs tend to be larger compared to infratentorial tumors. Their neuroimaging characteristics include cystic components, higher evidence of thick and wavy enhancing of the wall surrounding the central cyst, and surrounding edema. These tumors also frequently show calcifications and heterogeneously low ADC values.[90]

In summary, the presence of a large tumor with eccentric cysts combined with other characteristic hallmarks (such as a very young age and the tendency to disseminate at diagnosis), represent clues to the diagnosis.[90]

6. Ependymal Tumors (EP)

EPs are primary tumors of the CNS that may occur at any site along the neuroaxis with variable degree of aggressiveness. These tumors are classified as Grade 2 or 3 depending on histopathological features. Microscopically, EPs are characterized by perivascular pseudorosettes, ependymal rosettes, glial fibrillary acidic protein reactivity, areas of fibrillary, and paranuclear dot as well as ring positivity for epithelial membrane antigen IHC stain.

The latest WHO CNS edition divides EPs into prognostically relevant groups based on a combination of molecular profile and anatomic location (ST, posterior fossa, and spinal compartments).[2] Within the focus on the ST compartment, EPs are divided into two large groups according to the presence of pathognomonic molecular fusions involving the *ZFTA* or the *YAP1* genes, noting that the *ZFTA* group represents a more prevalent entity in this group.[91]

a. *ZFTA* fusion-positive ependymomas

ST ET, *ZFTA* fusion-positive (initially classified as *RELA* fusion-positive) often occur in children with a median age of 7 year at the diagnosis, often presenting with signs of increased ICP.[2, 92] Survival analyses between *ZFTA* fusion-positive and other molecular subgroups conducted by Pajtler et al. showed a dismal outcome for the previously called *RELA* fusion subgroup, with a 10-year OS rates of 50% and a progression-free survival rates of 20%.[93]

Neuroimaging features include well-demarcated masses most often with reduced diffusivity located in the hemispheres with large peripheral cystic portion, central necrosis surrounded by calcifications and hemorrhage (periwinkle sign).[94] There is often a thick and heterogeneous solid enhancement after contrast administration. Peritumoral edema is often present and frequently abundant, which may serve as an important clue to the differential diagnosis **(supplementary Fig.7**).

b. *YAP1* fusion- positive ependymomas

YAP1 fusion-positive tumors are less common than *ZFTA* fusion-positive tumors and often present in the first year of life.[93] Despite the large size at presentation, these tumors are considered to have a better prognosis than the *ZFTA*-fusion subtype, with an OS of 10 years at rates ranging between 88% and 100%.

On imaging, these tumors are often presented as large masses with well-delineated contours as well as internal mixed solid and cystic components, where the solid components have intermediate to reduced diffusivity and often demonstrate similar T2 signal intensity to the cortex. Although potentially involving the cortex, *YAP1*-fused EPs may also be intraventricular and/or paraventricular with variable amount of surrounding edema[95, 96].

Conclusion

In Summary, this is a comprehensive review of "peripheral" ST tumors in children with a touch on relevant associated molecular alterations.
By following this decision-tree, radiologists should have the expertise of formulating appropriate neuroimaging rationales for the differential diagnoses of cortically-based tumors in the Pediatric population, including newly recognized entities.

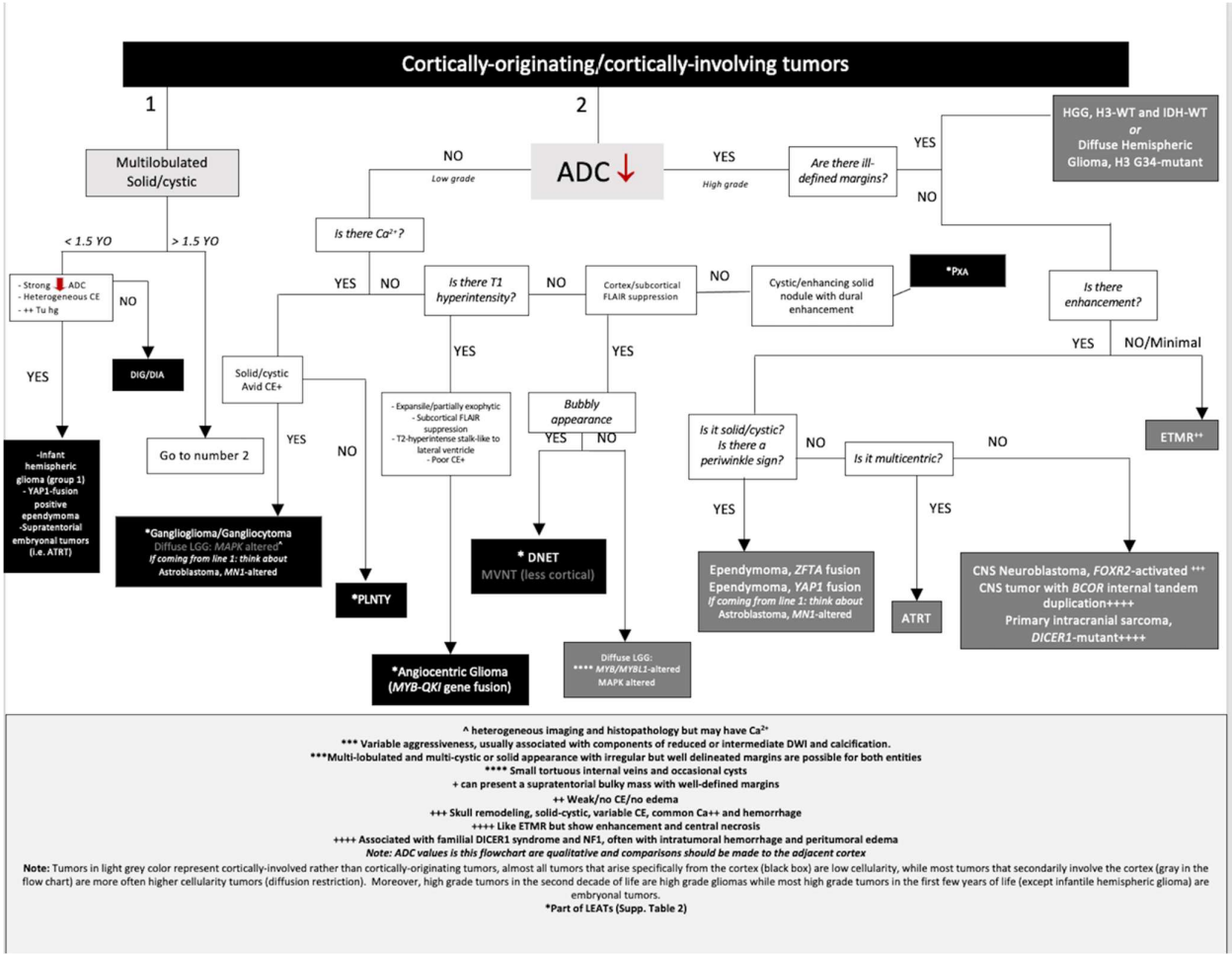


FIG 1. Flow chart highlighting the important imaging features in the diagnosis of cortically-based tumors in children.

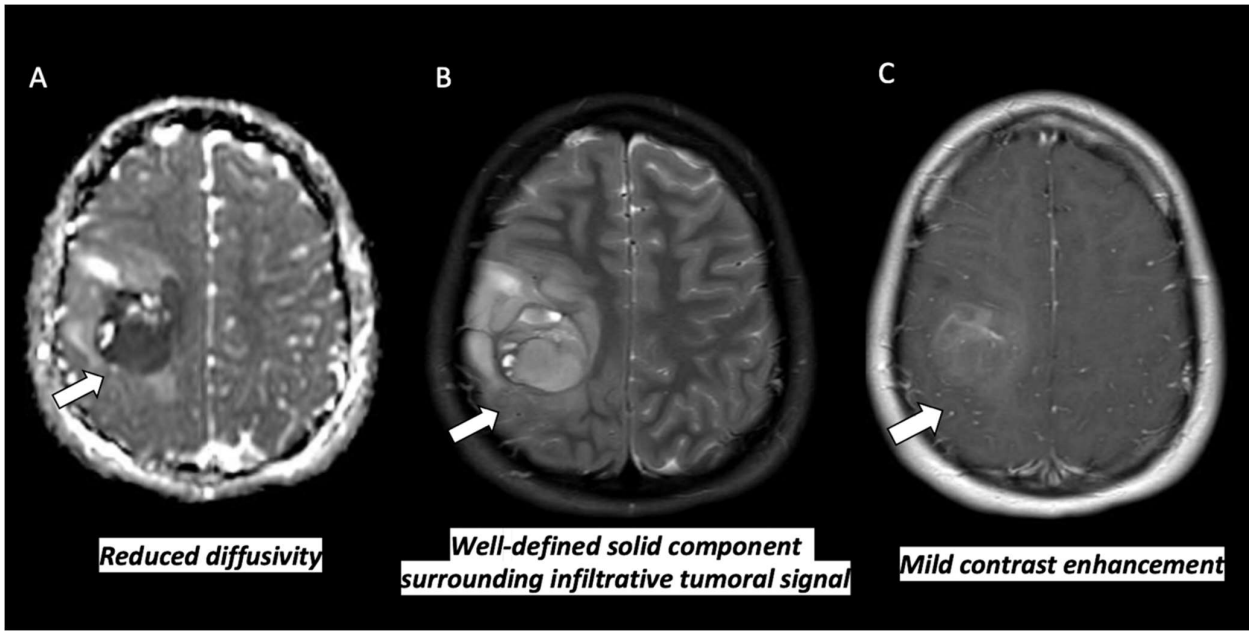


FIG 2. 17 years old with *H3 G34* mutant tumor. ADC map, T2-weighted, and T1-weighted post contrast axial images of the brain show a well-defined solid, cortically involved tumor in the right parietal lobe (white arrow) with surrounding infiltrative tumoral signal involving the overlying cortex.

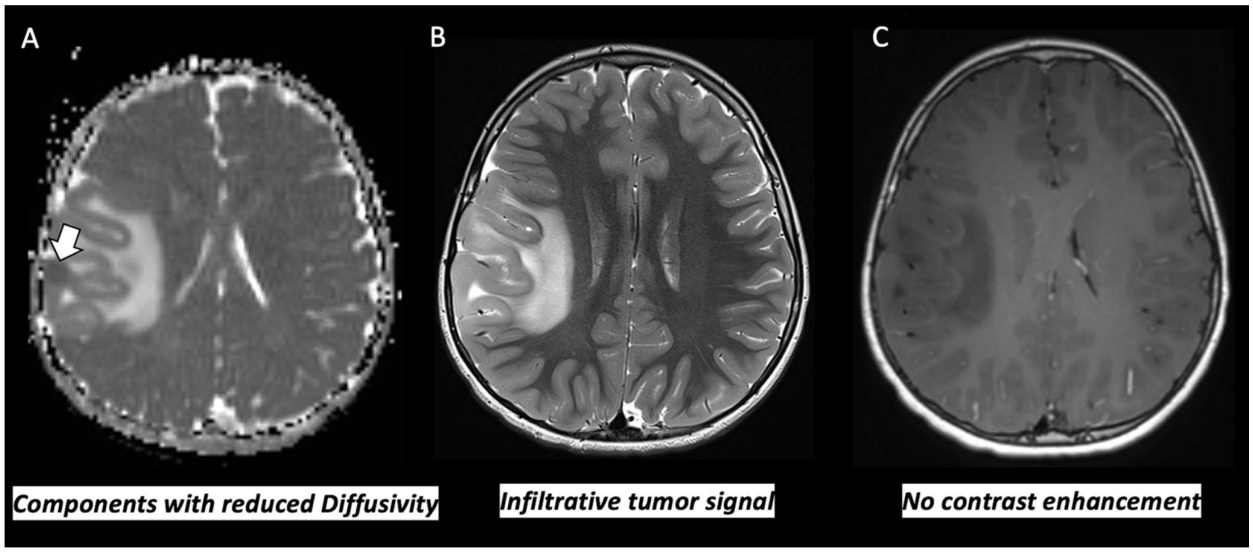


FIG 3. 8 years old with *EGFR* altered H3 WT and IDH WT. ADC map, T2-weighted, and T1-weighted post contrast axial images of the brain show an infiltrative tumoral signal involving cortex and subcortical matter of the right parietal lobe. These imaging show a focus of decreased diffusivity (white arrow).

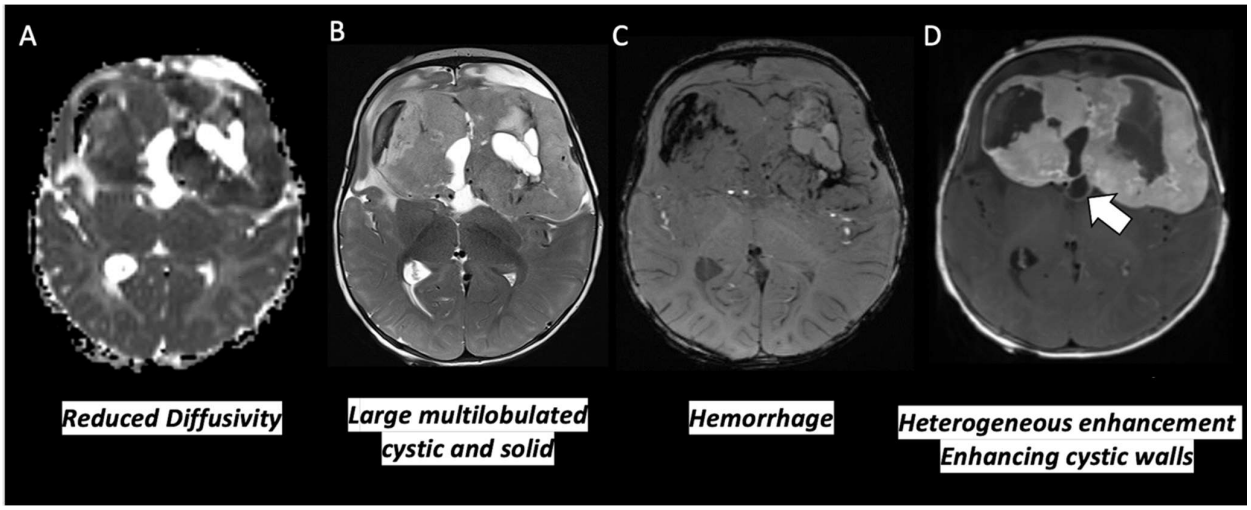


FIG 4. 9 months old with Infantile hemispheric glioma, *RTK1* fusion positive. ADC map, T2-weighted, SWI, and T1-weighted post contrast axial images of the brain show a large solid and cystic bi-frontal mass with strong decreased diffusivity compared to adjacent cortex, hemorrhage, and enhancement. Note the enhancing cystic walls (white arrow).

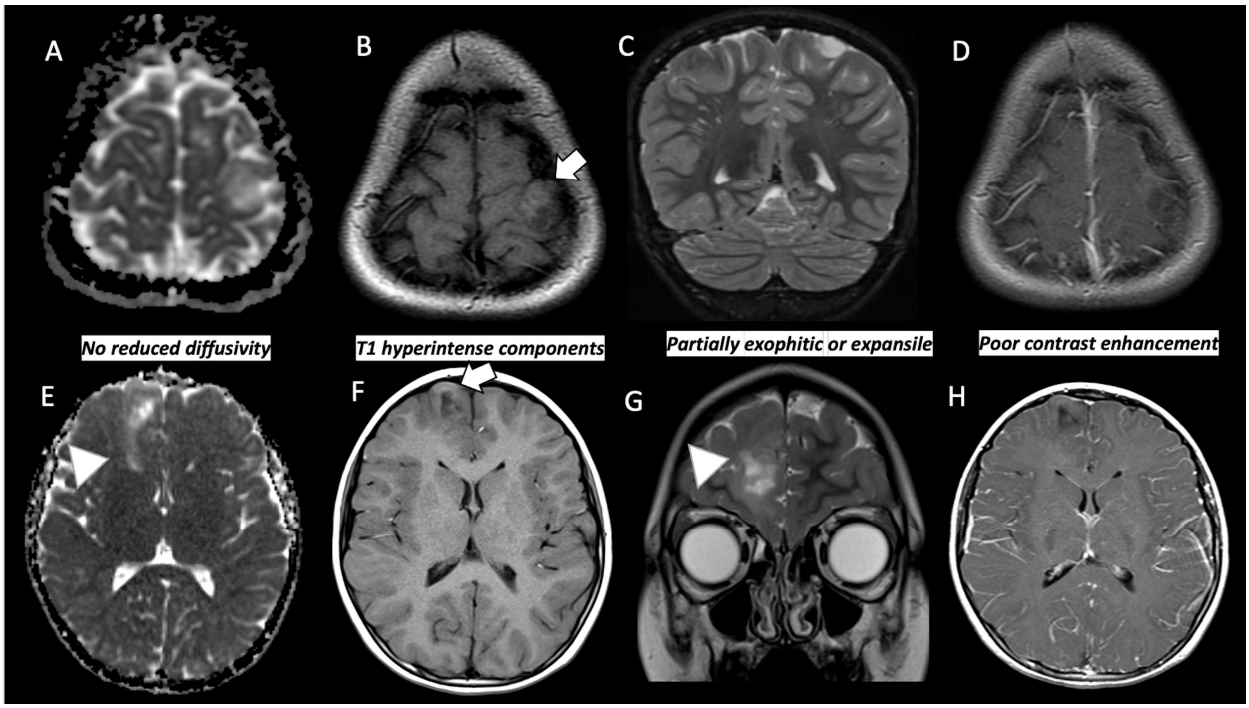


FIG 5. Angiocentric glioma, *MYB-QKI* fusion positive in two different patients. Axial ADC map and T1-weighted as well as coronal T2-weighted, and axial T1-weighted post contrast images of the brain in two different patients show a cortical based lesion with internal T1-hyperintense components (similar to the adjacent white matter) (white arrow) and a stalk-like sign (arrowhead).

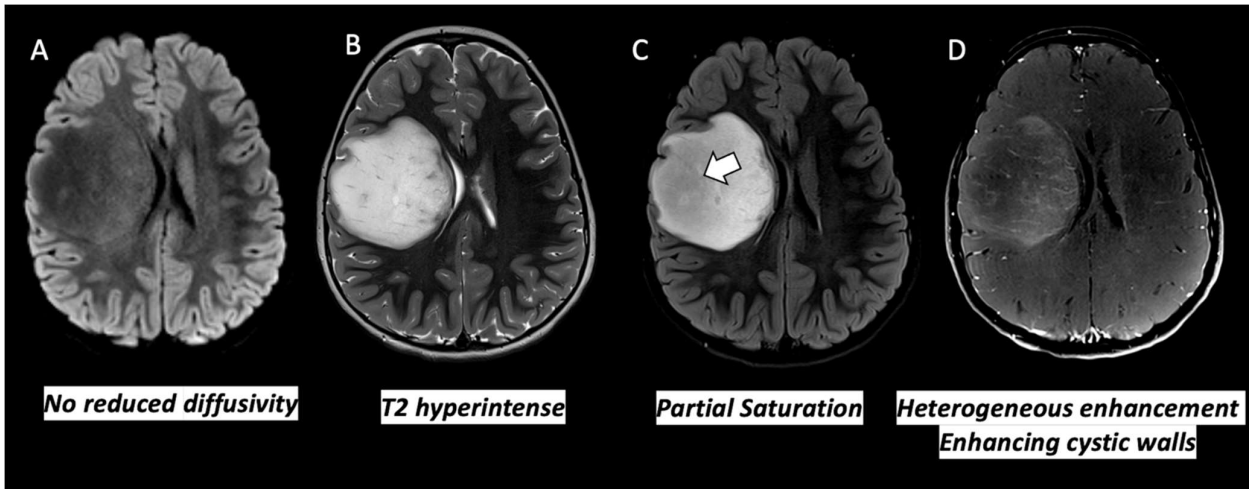


FIG 6. *MYB*-altered diffuse low grade astrocytoma. DWI, T2-weighted, FLAIR and T1-weighted post contrast axial images of the brain show a cortically involved lesion with no decreased diffusivity or calcifications, T2 hyperintensity, mild subcortical FLAIR suppression (T2-FLAIR mismatch) (white arrow), and poor enhancement.

REFERENCES

1. Ostrom QT, Price M, Neff C, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2016-2020. *Neuro Oncol* 2023;25:iv1-iv99
2. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol* 2021;23:1231-1251
3. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol* 2016;131:803-820
4. Jessa S, Blanchet-Cohen A, Krug B, et al. Stalled developmental programs at the root of pediatric brain tumors. *Nat Genet* 2019;51:1702-1713
5. Buccoliero AM, Giunti L, Moscardi S, et al. Pediatric High Grade Glioma Classification Criteria and Molecular Features of a Case Series. *Genes (Basel)* 2022;13
6. Kalelioglu T, Emerson D, Luk A, et al. Imaging features of diffuse hemispheric glioma, H3 G34-mutant: Report of 4 cases. *J Neuroradiol* 2023;50:309-314
7. Kurokawa R, Baba A, Emile P, et al. Neuroimaging features of angiocentric glioma: A case series and systematic review. *J Neuroimaging* 2022;32:389-399
8. Vuong HG, Le HT, Dunn IF. The prognostic significance of further genotyping H3G34 diffuse hemispheric gliomas. *Cancer* 2022;128:1907-1912
9. Onishi S, Amatya VJ, Karlowee V, et al. Radiological and Immunostaining Characteristics of H3.3 G34R-Mutant Glioma: A Report of 3 Cases and Review of the Literature. *Pediatr Neurosurg* 2020;55:319-325
10. Picart T, Barritault M, Poncet D, et al. Characteristics of diffuse hemispheric gliomas, H3 G34-mutant in adults. *Neurooncol Adv* 2021;3:vdab061
11. Korshunov A, Capper D, Reuss D, et al. Histologically distinct neuroepithelial tumors with histone 3 G34 mutation are molecularly similar and comprise a single nosologic entity. *Acta Neuropathol* 2016;131:137-146
12. Puntonet J, Dangouloff-Ros V, Saffroy R, et al. Historadiological correlations in high-grade glioma with the histone 3.3 G34R mutation. *J Neuroradiol* 2018;45:316-322
13. Wang L, Shao L, Li H, et al. Histone H3.3 G34-mutant Diffuse Gliomas in Adults. *Am J Surg Pathol* 2022;46:249-257

14. Lasocki A, Abdalla G, Chow G, et al. Imaging features associated with H3 K27-altered and H3 G34-mutant gliomas: a narrative systematic review. *Cancer Imaging* 2022;22:63
15. Johnson DR, Giannini C, Vaubel RA, et al. A Radiologist's Guide to the 2021 WHO Central Nervous System Tumor Classification: Part I-Key Concepts and the Spectrum of Diffuse Gliomas. *Radiology* 2022;304:494-508
16. Lavrador JP, Reisz Z, Sibtain N, et al. H3 G34-mutant high-grade gliomas: integrated clinical, imaging and pathological characterisation of a single-centre case series. *Acta Neurochir (Wien)* 2023;165:1615-1633
17. Nafe R, Porto L, Samp PF, et al. Adult-type and Pediatric-type Diffuse Gliomas : What the Neuroradiologist Should Know. *Clin Neuroradiol* 2023;33:611-624
18. Tauziède-Espariat A, Debily MA, Castel D, et al. The pediatric supratentorial MYCN-amplified high-grade gliomas methylation class presents the same radiological, histopathological and molecular features as their pontine counterparts. *Acta Neuropathol Commun* 2020;8:104
19. Gonçalves FG, Alves C, Vossough A. Updates in Pediatric Malignant Gliomas. *Top Magn Reson Imaging* 2020;29:83-94
20. Gonçalves FG, Viaene AN, Vossough A. Advanced Magnetic Resonance Imaging in Pediatric Glioblastomas. *Front Neurol* 2021;12:733323
21. DeSisto J, Lucas JT, Jr., Xu K, et al. Comprehensive molecular characterization of pediatric radiation-induced high-grade glioma. *Nat Commun* 2021;12:5531
22. Korshunov A, Schrimpf D, Ryzhova M, et al. H3-/IDH-wild type pediatric glioblastoma is comprised of molecularly and prognostically distinct subtypes with associated oncogenic drivers. *Acta Neuropathol* 2017;134:507-516
23. Guerreiro Stucklin AS, Ryall S, Fukuoka K, et al. Alterations in ALK/ROS1/NTRK/MET drive a group of infantile hemispheric gliomas. *Nat Commun* 2019;10:4343
24. Tauziède-Espariat A, Beccaria K, Dangouloff-Ros V, et al. A comprehensive analysis of infantile central nervous system tumors to improve distinctive criteria for infant-type hemispheric glioma versus desmoplastic infantile ganglioglioma/astrocytoma. *Brain Pathol* 2023;33:e13182
25. Olsen TK, Panagopoulos I, Meling TR, et al. Fusion genes with ALK as recurrent partner in ependymoma-like gliomas: a new brain tumor entity? *Neuro Oncol* 2015;17:1365-1373
26. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol* 2007;114:97-109
27. Ampie L, Choy W, DiDomenico JD, et al. Clinical attributes and surgical outcomes of angiocentric gliomas. *J Clin Neurosci* 2016;28:117-122
28. Amemiya S, Shibahara J, Aoki S, et al. Recently established entities of central nervous system tumors: review of radiological findings. *J Comput Assist Tomogr* 2008;32:279-285
29. Aguilar HN, Hung RW, Mehta V, et al. Imaging characteristics of an unusual, high-grade angiocentric glioma: a case report and review of the literature. *J Radiol Case Rep* 2012;6:1-10
30. Miyata H, Ryufuku M, Kubota Y, et al. Adult-onset angiocentric glioma of epithelioid cell-predominant type of the mesial temporal lobe suggestive of a rare but distinct clinicopathological subset within a spectrum of angiocentric cortical ependymal tumors. *Neuropathology* 2012;32:479-491
31. Ni HC, Chen SY, Chen L, et al. Angiocentric glioma: a report of nine new cases, including four with atypical histological features. *Neuropathol Appl Neurobiol* 2015;41:333-346
32. Wagner MW, Nobre L, Namdar K, et al. T2-FLAIR Mismatch Sign in Pediatric Low-Grade Glioma. *AJNR Am J Neuroradiol* 2023;44:841-845
33. Chen G, Wang L, Wu J, et al. Intractable epilepsy due to angiocentric glioma: A case report and minireview. *Exp Ther Med* 2014;7:61-65
34. Chiang J, Harreld JH, Tinkle CL, et al. A single-center study of the clinicopathologic correlates of gliomas with a MYB or MYBL1 alteration. *Acta Neuropathol* 2019;138:1091-1092

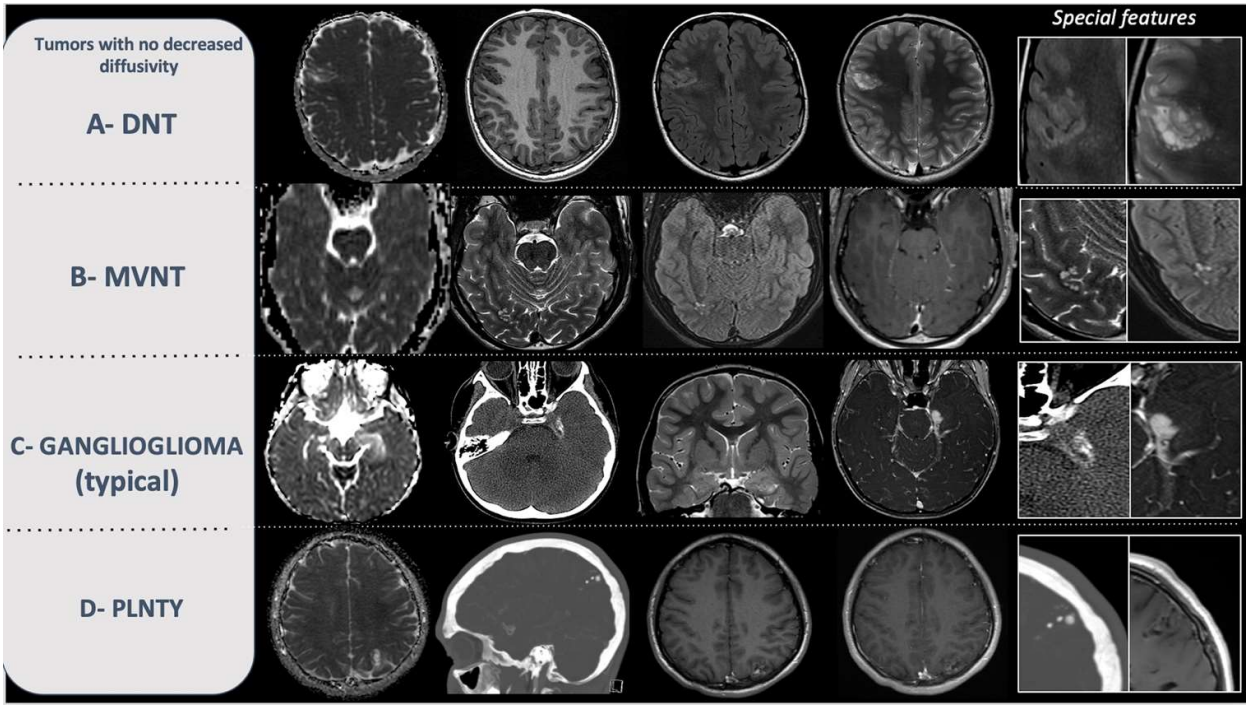
35. Wefers AK, Stichel D, Schrimpf D, et al. Isomorphic diffuse glioma is a morphologically and molecularly distinct tumour entity with recurrent gene fusions of MYBL1 or MYB and a benign disease course. *Acta Neuropathol* 2020;139:193-209
36. Purkait S, Mahajan S, Sharma MC, et al. Pediatric-type diffuse low grade gliomas: Histomolecular profile and practical approach to their integrated diagnosis according to the WHO CNS5 classification. *Indian J Pathol Microbiol* 2022;65:S42-s49
37. Huse JT, Snuderl M, Jones DT, et al. Polymorphous low-grade neuroepithelial tumor of the young (PLNTY): an epileptogenic neoplasm with oligodendroglioma-like components, aberrant CD34 expression, and genetic alterations involving the MAP kinase pathway. *Acta Neuropathol* 2017;133:417-429
38. AlRayahi J, Zapotocky M, Ramaswamy V, et al. Pediatric Brain Tumor Genetics: What Radiologists Need to Know. *Radiographics* 2018;38:2102-2122
39. Chen Y, Tian T, Guo X, et al. Polymorphous low-grade neuroepithelial tumor of the young: case report and review focus on the radiological features and genetic alterations. *BMC Neurol* 2020;20:123
40. Barretto BB, Mani J, Venkatraman S, et al. Polymorphous Low-Grade Neuroepithelial Tumor of the Young (PLNTY): A Newly Described Entity of Special Radiological Significance. *Indian J Radiol Imaging* 2023;33:567-570
41. Ida CM, Johnson DR, Nair AA, et al. Polymorphous Low-Grade Neuroepithelial Tumor of the Young (PLNTY): Molecular Profiling Confirms Frequent MAPK Pathway Activation. *J Neuropathol Exp Neurol* 2021;80:821-829
42. Bag AK, Chiang J, Patay Z. Radiohistogenomics of pediatric low-grade neuroepithelial tumors. *Neuroradiology* 2021;63:1185-1213
43. Isler C, Erturk Cetin O, Ugurlar D, et al. Dysembryoplastic neuroepithelial tumours: clinical, radiological, pathological features and outcome. *Br J Neurosurg* 2018;32:436-441
44. Mano Y, Kumabe T, Shibahara I, et al. Dynamic changes in magnetic resonance imaging appearance of dysembryoplastic neuroepithelial tumor with or without malignant transformation. *J Neurosurg Pediatr* 2013;11:518-525
45. Adachi Y, Yagishita A. Gangliogliomas: Characteristic imaging findings and role in the temporal lobe epilepsy. *Neuroradiology* 2008;50:829-834
46. Chen J, Qi X, Zhang M, et al. Review on neuroimaging in pediatric-type diffuse low-grade gliomas. *Front Pediatr* 2023;11:1149646
47. Qaddoumi I, Orisme W, Wen J, et al. Genetic alterations in uncommon low-grade neuroepithelial tumors: BRAF, FGFR1, and MYB mutations occur at high frequency and align with morphology. *Acta Neuropathol* 2016;131:833-845
48. Banerjee A, Jakacki RI, Onar-Thomas A, et al. A phase I trial of the MEK inhibitor selumetinib (AZD6244) in pediatric patients with recurrent or refractory low-grade glioma: a Pediatric Brain Tumor Consortium (PBTC) study. *Neuro Oncol* 2017;19:1135-1144
49. Perreault S, Larouche V, Tabori U, et al. A phase 2 study of trametinib for patients with pediatric glioma or plexiform neurofibroma with refractory tumor and activation of the MAPK/ERK pathway: TRAM-01. *BMC Cancer* 2019;19:1250
50. Hammas N, Senhaji N, Alaoui Lamrani MY, et al. Astroblastoma - a rare and challenging tumor: a case report and review of the literature. *J Med Case Rep* 2018;12:102
51. Sprenger F, da Silva EB, Jr., Cavalcanti MS, et al. Radiology-Pathology and Surgical Correlation in Astroblastoma. *AJNR Am J Neuroradiol* 2023;44:390-395
52. Port JD, Brat DJ, Burger PC, et al. Astroblastoma: radiologic-pathologic correlation and distinction from ependymoma. *AJNR Am J Neuroradiol* 2002;23:243-247
53. Lehman NL, Usubalieva A, Lin T, et al. Genomic analysis demonstrates that histologically-defined astroblastomas are molecularly heterogeneous and that tumors with MN1 rearrangement exhibit the most favorable prognosis. *Acta Neuropathol Commun* 2019;7:42

54. Sugita Y, Terasaki M, Shigemori M, et al. Astroblastoma with unusual signet-ring-like cell components: a case report and literature review. *Neuropathology* 2002;22:200-205
55. Thiessen B, Finlay J, Kulkarni R, et al. Astroblastoma: does histology predict biologic behavior? *J Neurooncol* 1998;40:59-65
56. Detti B, Scoccianti S, Maragna V, et al. Pleomorphic Xanthoastrocytoma: a single institution retrospective analysis and a review of the literature. *Radiol Med* 2022;127:1134-1141
57. Moore W, Mathis D, Gargan L, et al. Pleomorphic xanthoastrocytoma of childhood: MR imaging and diffusion MR imaging features. *AJNR Am J Neuroradiol* 2014;35:2192-2196
58. Perkins SM, Mitra N, Fei W, et al. Patterns of care and outcomes of patients with pleomorphic xanthoastrocytoma: a SEER analysis. *J Neurooncol* 2012;110:99-104
59. Giannini C, Scheithauer BW, Burger PC, et al. Pleomorphic xanthoastrocytoma: what do we really know about it? *Cancer* 1999;85:2033-2045
60. Fukuoka K, Mamatjan Y, Tatevossian R, et al. Clinical impact of combined epigenetic and molecular analysis of pediatric low-grade gliomas. *Neuro Oncol* 2020;22:1474-1483
61. Phillips JJ, Gong H, Chen K, et al. The genetic landscape of anaplastic pleomorphic xanthoastrocytoma. *Brain Pathol* 2019;29:85-96
62. Ebrahimi A, Korshunov A, Reifenberger G, et al. Pleomorphic xanthoastrocytoma is a heterogeneous entity with pTERT mutations prognosticating shorter survival. *Acta Neuropathol Commun* 2022;10:5
63. Tekkök IH, Sav A. Anaplastic pleomorphic xanthoastrocytomas. Review of the literature with reference to malignancy potential. *Pediatr Neurosurg* 2004;40:171-181
64. Nunes RH, Hsu CC, da Rocha AJ, et al. Multinodular and Vacuolating Neuronal Tumor of the Cerebrum: A New "Leave Me Alone" Lesion with a Characteristic Imaging Pattern. *AJNR Am J Neuroradiol* 2017;38:1899-1904
65. Alsufayan R, Alcaide-Leon P, de Tilly LN, et al. Natural history of lesions with the MR imaging appearance of multinodular and vacuolating neuronal tumor. *Neuroradiology* 2017;59:873-883
66. Pekmezci M, Stevers M, Phillips JJ, et al. Multinodular and vacuolating neuronal tumor of the cerebrum is a clonal neoplasm defined by genetic alterations that activate the MAP kinase signaling pathway. *Acta Neuropathol* 2018;135:485-488
67. Choi E, Kim SI, Won JK, et al. Clinicopathological and molecular analysis of multinodular and vacuolating neuronal tumors of the cerebrum. *Hum Pathol* 2019;86:203-212
68. Park YW, Vollmuth P, Foltyn-Dumitru M, et al. The 2021 WHO Classification for Gliomas and Implications on Imaging Diagnosis: Part 3-Summary of Imaging Findings on Glioneuronal and Neuronal Tumors. *J Magn Reson Imaging* 2023;58:1680-1702
69. Lecler A, Chauvet D, Biassette HA, et al. Multiparametric Imaging Improves Confidence in the Diagnosis of Multinodular and Vacuolating Neuronal Tumor of the Cerebrum. *AJNR Am J Neuroradiol* 2018;39:E32-e33
70. Deng MY, Sill M, Sturm D, et al. Diffuse glioneuronal tumour with oligodendroglioma-like features and nuclear clusters (DGONC) - a molecularly defined glioneuronal CNS tumour class displaying recurrent monosomy 14. *Neuropathol Appl Neurobiol* 2020;46:422-430
71. Pickles JC, Mankad K, Aizpurua M, et al. A case series of Diffuse Glioneuronal Tumours with Oligodendroglioma-like features and Nuclear Clusters (DGONC). *Neuropathol Appl Neurobiol* 2021;47:464-467
72. Benesch M, Perwein T, Apfaltrer G, et al. MR Imaging and Clinical Characteristics of Diffuse Glioneuronal Tumor with Oligodendroglioma-like Features and Nuclear Clusters. *AJNR Am J Neuroradiol* 2022;43:1523-1529
73. Schindler G, Capper D, Meyer J, et al. Analysis of BRAF V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma. *Acta Neuropathol* 2011;121:397-405

74. Ramaglia A, Tortora D, Mankad K, et al. Role of diffusion weighted imaging for differentiating cerebral pilocytic astrocytoma and ganglioglioma BRAF V600E-mutant from wild type. *Neuroradiology* 2020;62:71-80
75. VandenBerg SR, May EE, Rubinstein LJ, et al. Desmoplastic supratentorial neuroepithelial tumors of infancy with divergent differentiation potential ("desmoplastic infantile gangliogliomas"). Report on 11 cases of a distinctive embryonal tumor with favorable prognosis. *J Neurosurg* 1987;66:58-71
76. Koelsche C, Sahm F, Paulus W, et al. BRAF V600E expression and distribution in desmoplastic infantile astrocytoma/ganglioglioma. *Neuropathol Appl Neurobiol* 2014;40:337-344
77. Daumas-Duport C, Varlet P, Bacha S, et al. Dysembryoplastic neuroepithelial tumors: nonspecific histological forms -- a study of 40 cases. *J Neurooncol* 1999;41:267-280
78. Daumas-Duport C. Dysembryoplastic neuroepithelial tumours. *Brain Pathol* 1993;3:283-295
79. Campos AR, Clusmann H, von Lehe M, et al. Simple and complex dysembryoplastic neuroepithelial tumors (DNT) variants: clinical profile, MRI, and histopathology. *Neuroradiology* 2009;51:433-443
80. Thom M, Gomez-Anson B, Revesz T, et al. Spontaneous intralesional haemorrhage in dysembryoplastic neuroepithelial tumours: a series of five cases. *J Neurol Neurosurg Psychiatry* 1999;67:97-101
81. Shin JH, Lee HK, Khang SK, et al. Neuronal tumors of the central nervous system: radiologic findings and pathologic correlation. *Radiographics* 2002;22:1177-1189
82. Bulakbasi N, Kocaoglu M, Sanal TH, et al. Dysembryoplastic neuroepithelial tumors: proton MR spectroscopy, diffusion and perfusion characteristics. *Neuroradiology* 2007;49:805-812
83. Sturm D, Orr BA, Toprak UH, et al. New Brain Tumor Entities Emerge from Molecular Classification of CNS-PNETs. *Cell* 2016;164:1060-1072
84. Shimazaki K, Kurokawa R, Franson A, et al. Neuroimaging features of FOXR2-activated CNS neuroblastoma: A case series and systematic review. *J Neuroimaging* 2023;33:359-367
85. Kalu IC, Kao CM, Fritz SA. Management and Prevention of Staphylococcus aureus Infections in Children. *Infect Dis Clin North Am* 2022;36:73-100
86. Wang R, Guan W, Qiao M, et al. CNS tumor with BCOR internal tandem duplication: Clinicopathologic, molecular characteristics and prognosis factors. *Pathol Res Pract* 2022;236:153995
87. Cardoen L, Tauziède-Espariat A, Dangouloff-Ros V, et al. Imaging Features with Histopathologic Correlation of CNS High-Grade Neuroepithelial Tumors with a BCOR Internal Tandem Duplication. *AJNR Am J Neuroradiol* 2022;43:151-156
88. Lambo S, von Hoff K, Korshunov A, et al. ETMR: a tumor entity in its infancy. *Acta Neuropathol* 2020;140:249-266
89. Meliti A, Gasim W, Al-Maghrabi H, et al. Embryonal tumor with multilayered rosettes; rare pediatric CNS tumor. A case report and review of literature. *Int J Pediatr Adolesc Med* 2022;9:174-178
90. Calandrelli R, Massimi L, Pilato F, et al. Atypical Teratoid Rhabdoid Tumor: Proposal of a Diagnostic Pathway Based on Clinical Features and Neuroimaging Findings. *Diagnostics (Basel)* 2023;13
91. Bethel JA, James KM, Tavakoli SG, et al. Supratentorial ependymoma, zinc finger translocation-associated fusion positive, with extensive synaptophysin immunoreactivity arising from malignant transformation of clear cell ependymoma: A case report. *Surg Neurol Int* 2022;13:168
92. Tauziède-Espariat A, Siegfried A, Nicaise Y, et al. Supratentorial non-RELA, ZFTA-fused ependymomas: a comprehensive phenotype genotype correlation highlighting the number of zinc fingers in ZFTA-NCOA1/2 fusions. *Acta Neuropathol Commun* 2021;9:135
93. Pajtler KW, Witt H, Sill M, et al. Molecular Classification of Ependymal Tumors across All CNS Compartments, Histopathological Grades, and Age Groups. *Cancer Cell* 2015;27:728-743

94. Mangalore S, Aryan S, Prasad C, et al. Imaging characteristics of supratentorial ependymomas: Study on a large single institutional cohort with histopathological correlation. *Asian J Neurosurg* 2015;10:276-281
95. Mu W, Dahmoush H. Classification and neuroimaging of ependymal tumors. *Front Pediatr* 2023;11:1181211
96. Andreiuolo F, Varlet P, Tauziède-Espariat A, et al. Childhood supratentorial ependymomas with YAP1-MAMLD1 fusion: an entity with characteristic clinical, radiological, cytogenetic and histopathological features. *Brain Pathol* 2019;29:205-216

SUPPLEMENTAL FILES



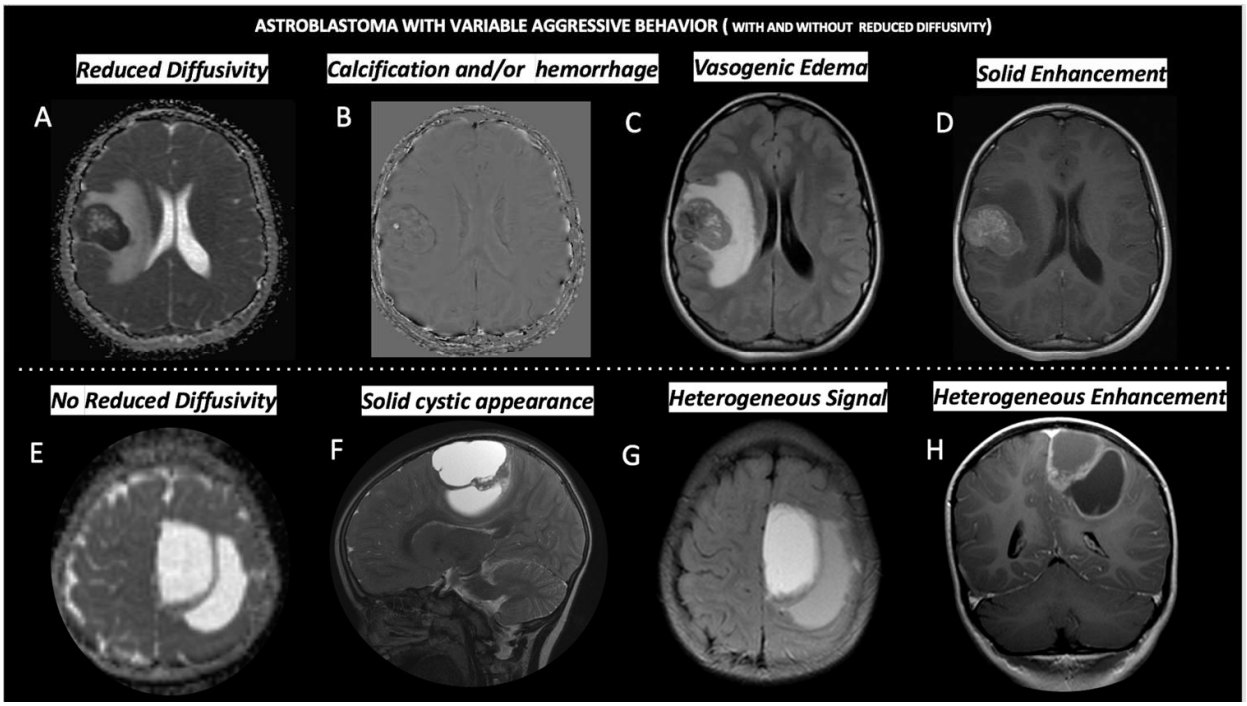
Supp.FIG 1. Special MRI features of some of the cortical/juxtacortical low grade diffuse glial and glioneuronal tumors

A- DNT: ADC map, T2-weighted, FLAIR, and T2-weighted axial images of the brain show a cortically based lesion demonstrating a soap-bubble appearance with no decreased diffusivity or calcifications, T2 hyperintensity and mild internal FLAIR suppression (T2-FLAIR mismatch).

B- MVNT: ADC map, T2-weighted, FLAIR, and T1-weighted axial images of the brain show a juxta-cortical lesion demonstrating a clusters of cysts that do not suppress on the FLAIR. No associated enhancement, edema, and mass effect.

C- Ganglioglioma: axial ADC map, axial CT, coronal T2-weighted, and axial T1-weighted images of the brain show a calcified, cortically based, and enhancing cystic-solid lesion.

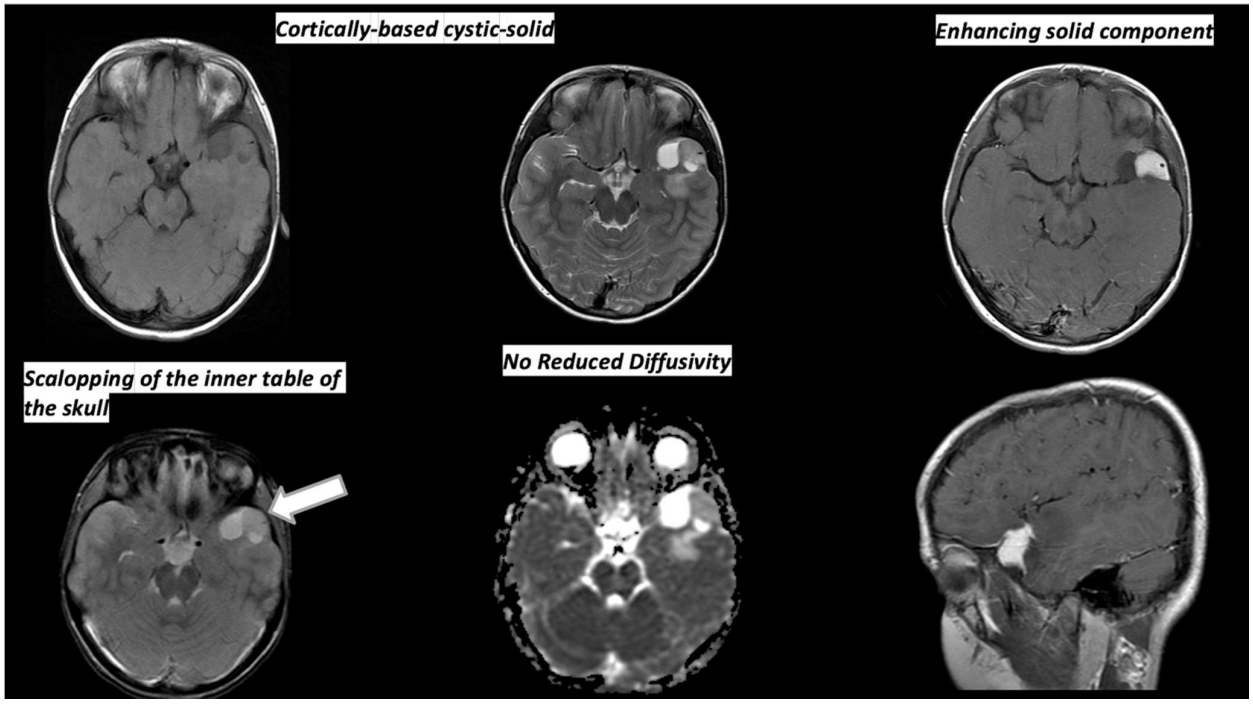
D- PLNTY: axial ADC map, coronal CT, axial T1-weighted pre and post contrast images of the brain show cortically based, primarily solid lesion that shows salt-and-pepper calcifications and no enhancement.



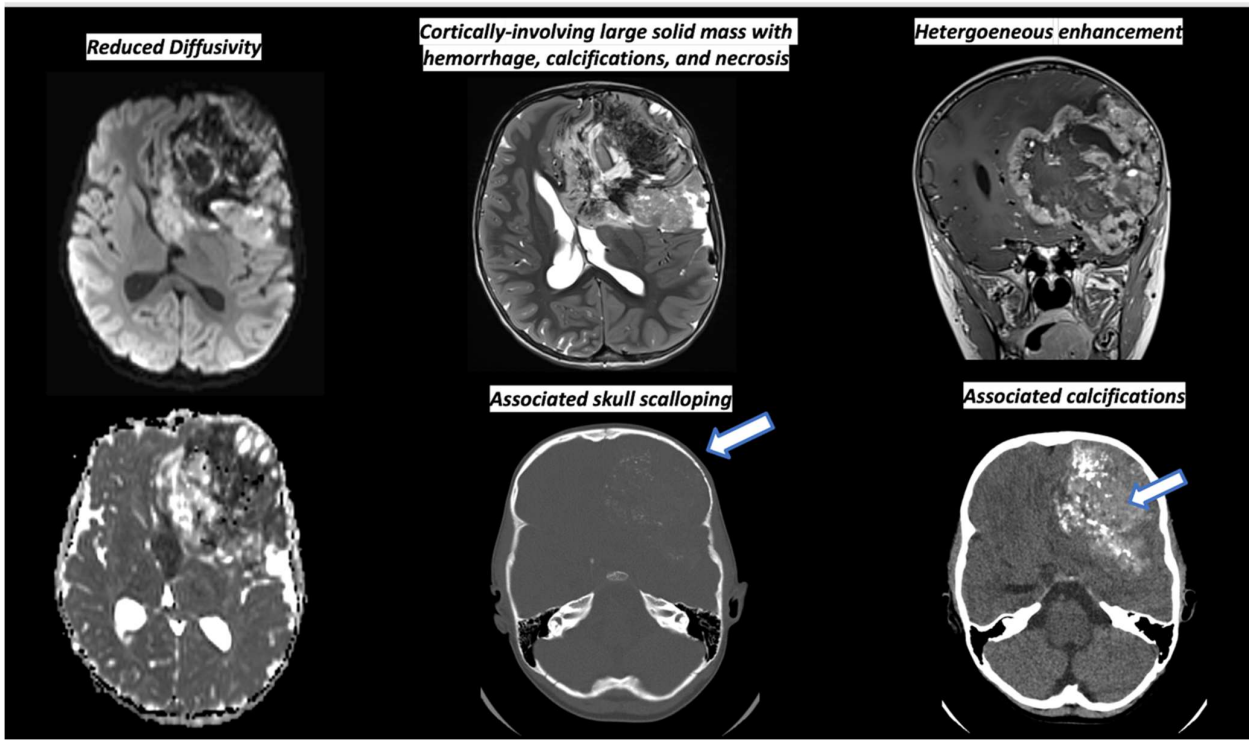
Supp.FIG 2. Astroblastoma, *MN1*-altered, in two different patients

ADC map, susceptibility Phase, FLAIR, and T1-weighted post contrast axial images of the brain show a solid-predominant and cortically-based mass with decreased diffusivity, calcifications and blood products (white arrow), predominant T2 hypointensity, surrounding edema and enhancement.

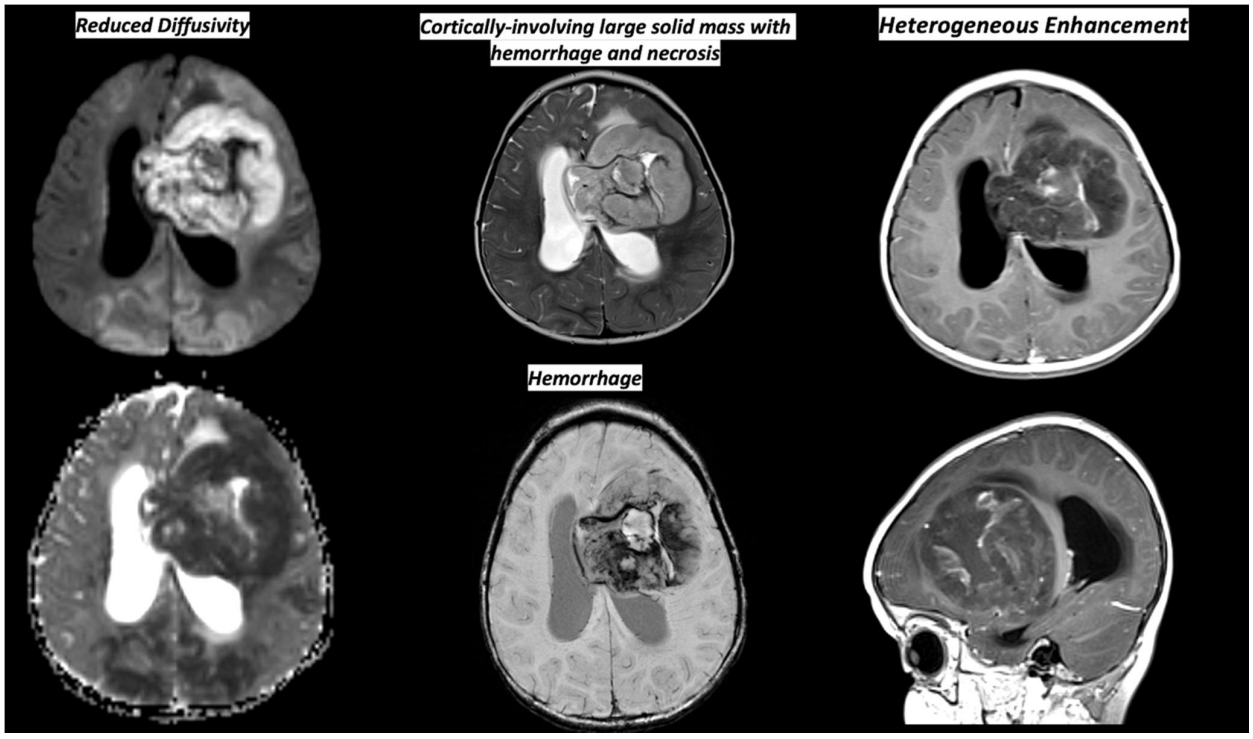
ADC map, susceptibility Phase, FLAIR, and T1-weighted post contrast axial images of the brain show a cystic-predominant and cortically-based mass with no decreased diffusivity, surrounding edema or calcifications, heterogeneous T2 signal, and enhancement.



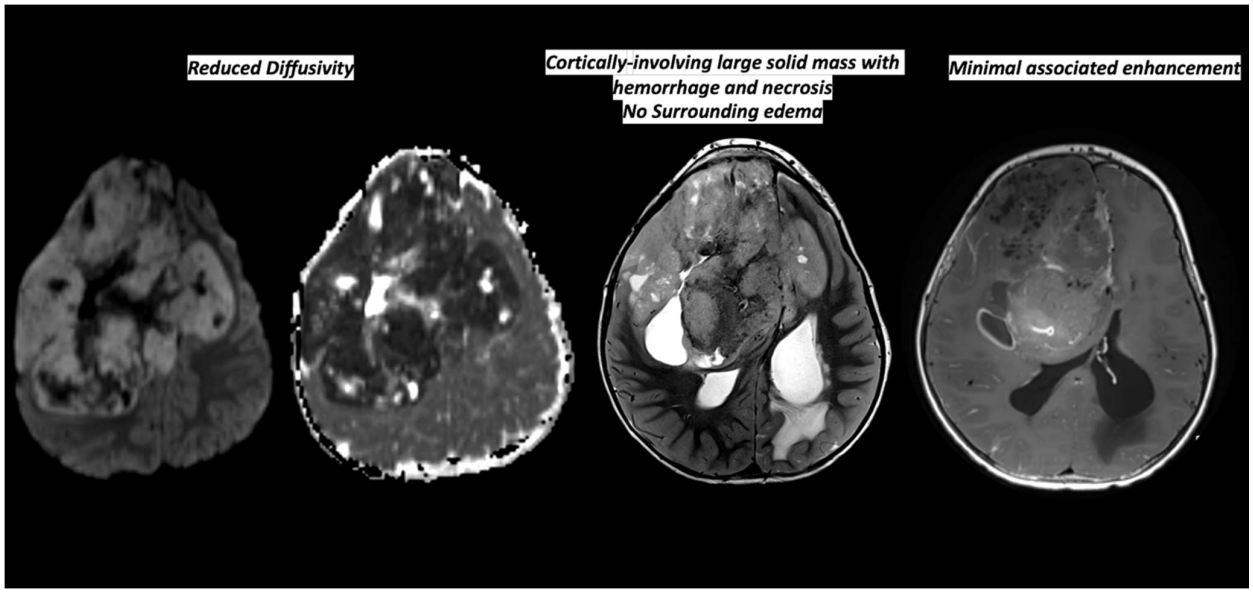
Supp.FIG 3. 8-year-old Female with pleomorphic xanthoastrocytoma, WHO Grade 2



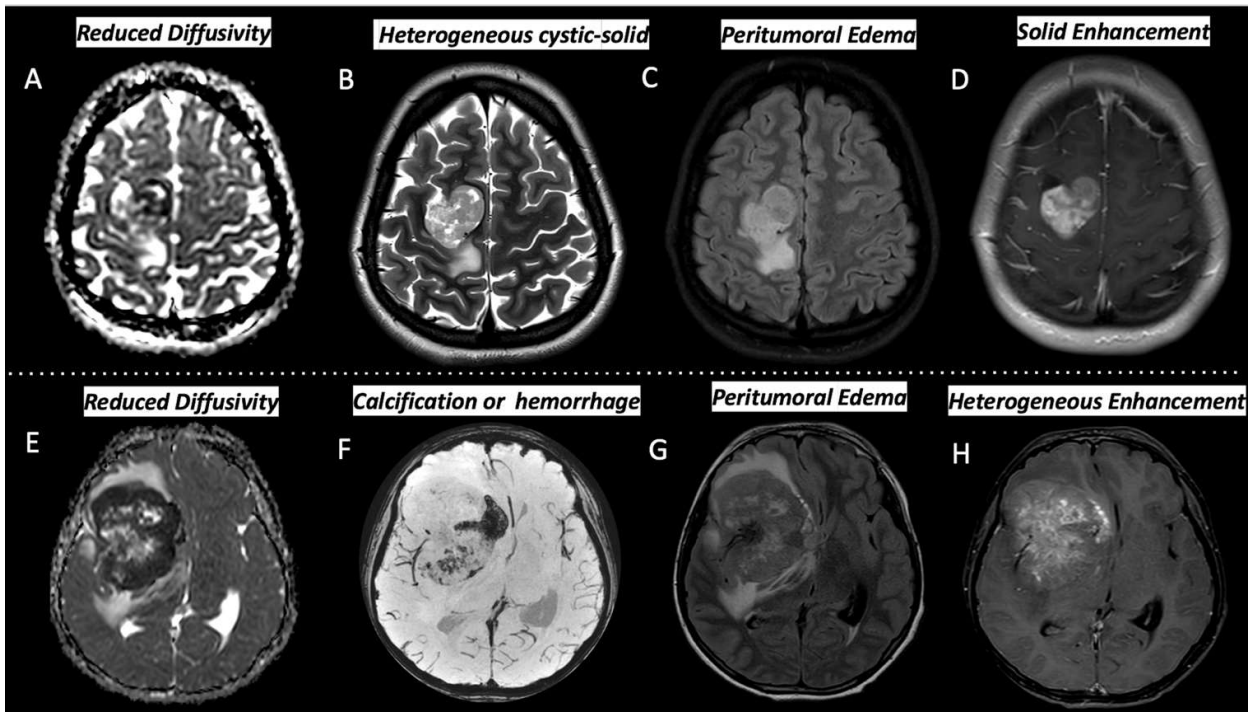
Supp.FIG 4. 5-year-old Male with *FOXR2*-activated neuroblastoma.



Supp.FIG 5. 1-year-old Female with CNS tumor with *BCOR* internal tandem duplication.



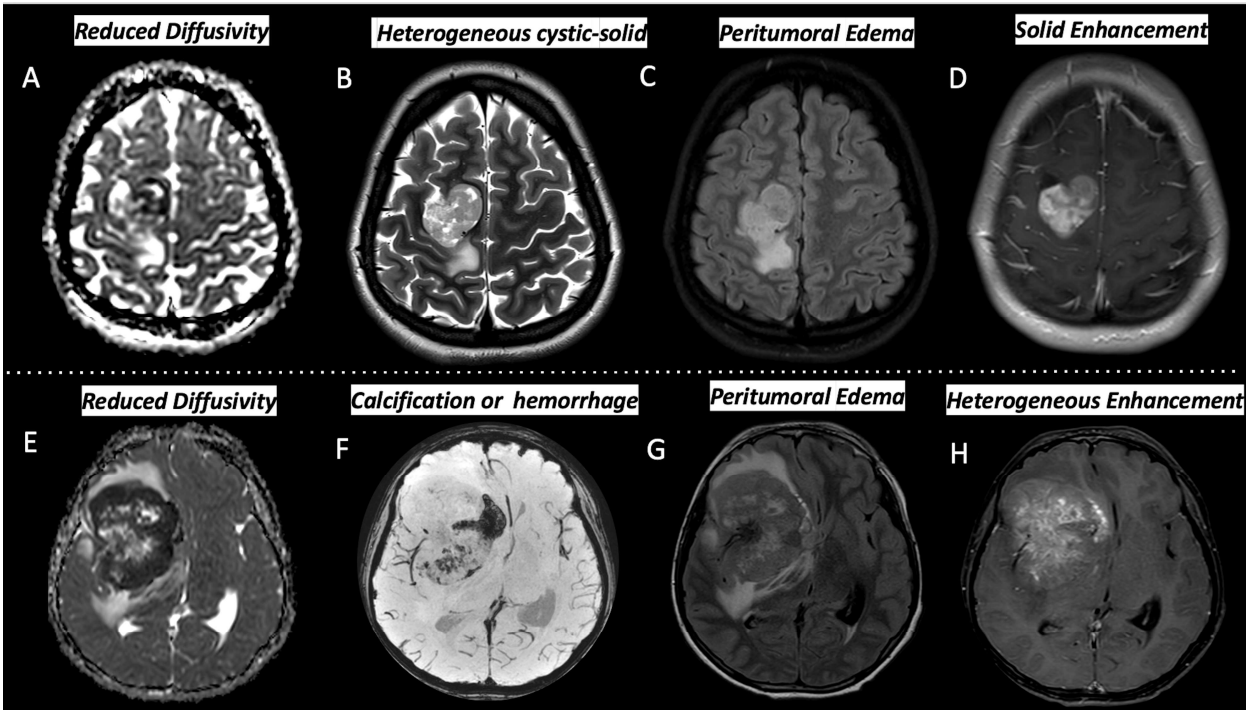
Supp.FIG 6. 4-year-old with ETMR.



Supp.FIG 6. ST, *ZFTA*-fused Ependymoma in two different patients

ADC map, T2-weighted, FLAIR, and T1-weighted post contrast axial images of the first patient brain show a right frontal lobe solid/cystic predominant and cortically-involved mass in the right frontal demonstrate with decreased diffusivity, predominant T2 hypointensity, surrounding edema, and enhancement.

ADC map, SWI, FLAIR and, T1-weighted post contrast axial images of the brain in a second patient show a solid-predominant and cortically-involved mass in the right parietal lobe with decreased diffusivity, calcifications and blood products, predominant T2 hypointensity, surrounding edema, and enhancement.



Supp.FIG 7. ST, *ZFTA*-fused Ependymoma in two different patients

ADC map, T2-weighted, FLAIR, and T1-weighted post contrast axial images of the first patient brain show a right frontal lobe solid/cystic predominant and cortically-involved mass in the right frontal demonstrate with decreased diffusivity, predominant T2 hypointensity, surrounding edema, and enhancement.

ADC map, SWI, FLAIR and, T1-weighted post contrast axial images of the brain in a second patient show a solid-predominant and cortically-involved mass in the right parietal lobe with decreased diffusivity, calcifications and blood products, predominant T2 hypointensity, surrounding edema, and enhancement.

Angiocentric glioma	• Expansile/partially exophytic • Hyperintense signal on T1WI (slightly higher than adjacent white matter) • Subcortical FLAIR suppression • T2-hyperintense stalk-like to lateral ventricle • Poor contrast enhancement
Diffuse Astrocytoma, *MYB*- or *MYBL1*-altered	• T2-FLAIR mismatch • Peritumoral cysts
Polymorphous low-grade neuroepithelial tumor of the Young	• "Salt and pepper"/granulate appearance on T2WI. • Presence of calcifications • Poor contrast enhancement
Astroblastoma, *MN1-altered*	• Solid and cystic mass with a "soap-bubble" appearance of the centrally located solid component • Peritumoral edema, calcifications, and hemorrhage, variably present
Pleomorphic Xanthoastrocytoma	• Cystic and nodular enhancing solid lesion with dural enhancement
Multinodular and vacuolating neuronal tumor	• Cluster of non-enhancing micronodules in the cortical-subcortical junction
Ganglioglioma/Gangliocytoma	• A Cortical/subcortical cyst with a contrast-enhancing nodule • Frequently located in the temporal lobe • Calcifications (1/3 of the cases)
Dysembryoplastic Neuroepithelial tumors	• Cortical-based multiloculated non-enhancing cysts • Poor contrast enhancement • No calcifications

***ZFTA* fusion-positive ependymomas**	• Periwinkle sign: large peripheral cystic portion, central necrosis surrounded by calcifications and hemorrhage

Supplemental Table 1: Table outlining relevant "special" imaging features in cortical brain tumors.

LONG-TERM EPILEPSY-ASSOCIATED TUMORS
GANGLIOGLIOMA/GANGLIOCYTOMA
PLEOMORPHIC XANTHOASTROCYTOMA
DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMOR
MULTINODULAR AND VACUOLATING NEURONAL TUMOR
ANGIOCENTRIC GLIOMA

Supplemental Table 2: Table outlining long-term epilepsy-associated tumors.

Cortical Tumors	Incidence (common, uncommon, rare)	Median Age at presentation
Diffuse Hemispheric Glioma, *H3G34*-mutant	Uncommon	17 years
Diffuse Pediatric-type High-Grade Glioma, H3-wildtype and IDH-wildtype	Uncommon	22 months
Infant-type hemispheric glioma	Rare	2.8 months
Angiocentric glioma	Rare	
Diffuse Astrocytoma, *MYB*- or *MYBL1*-altered	Rare	5 years
Polymorphous low-grade neuroepithelial tumor of the young	Uncommon	18 years
Diffuse Low-Grade Glioma, *MAPK Pathway-altered*	Rare	Variable
Astroblastoma, *MN1-altered*	Rare	14 years
Pleomorphic xanthoastrocytoma	Uncommon	20 years

Multinodular and vacuolating neuronal tumor	Uncommon	Variable
Ganglioglioma/gangliocytoma	Common	8-26 years
Desmoplastic infantile ganglioglioma and desmoplastic infantile astrocytoma	Uncommon	6 months
Dysembryoplastic Neuroepithelial tumors	Common	9 years
CNS neuroblastoma, *FOXR2*-activated	Rare	
CNS tumors with *BCOR* internal tandem duplicatio	Rare	3.5 years
Embryonal Tumors with Multilayered Rosettes	Rare	4 years
***ZFTA* fusion-positive ependymomas**	Common	7 years
***YAP1* fusion- positive ependymomas**	Uncommon	1.4 years

Supplemental Table 3: Table outlining the incidence and typical median age at presentation of cortical brain tumors.