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ABSTRACT

SUMMARY: Cortically based brain tumors in children constitute a unique set of tumors with variably aggressive biologic behavior. Because radiologists play an integral role on the multidisciplinary medical team, a clinically useful and easy-to-follow flow chart 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 by using current molecular understanding.

ABBREVIATIONS: AB = astroblastoma; AG = angiocentric glioma; ATRT = atypical teratoid/rhabdoid tumor; BCOR-ITD = BCOR internal tandem duplication; DGONC = diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters; DHG = diffuse hemispheric glioma, *H3G34*-mutant; DIA = desmoplastic infantile astrocytoma; DIG = desmoplastic infantile glioma; DNET = dysembryoplastic neuroepithelial tumor; EP = ependymoma; ETMR = embryonal tumors with multilayered rosettes; FCD = focal cortical dysplasia; GG = ganglioglioma/gangliocytoma; ICP = intracranial pressure; IHG = infant-type hemispheric glioma; LEAT = long-term epilepsy-associated tumor; MVNT = multinodular and vacuolating neuronal tumor; NB-*FOXR2* = CNS neuroblastoma, *FOXR2*-activated; OS = overall survival; pHGG = pediatric diffuse high-grade gliomas; pLGG = pediatric diffuse low-grade gliomas; PLNTY = polymorphous low-grade neuroepithelial tumor of the young; PXA = pleomorphic xanthoastrocytoma; ST = supratentorial; WHO = World Health Organization

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 Substantial revisions of the World Health Organization (WHO) classification of tumors. This was reflected in the 2016 and 2021 editions of the 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 that 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. Because 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,

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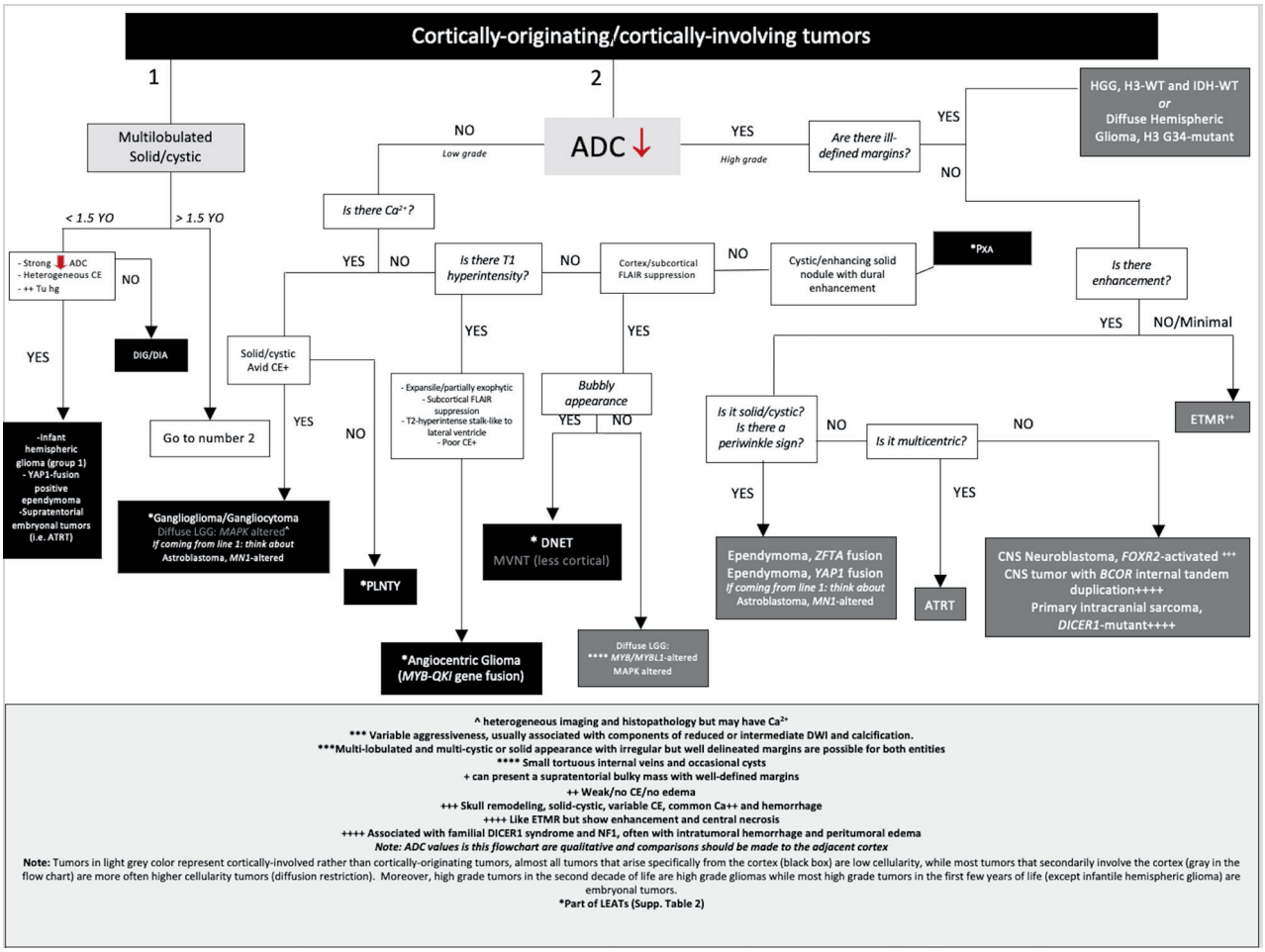

FIG 1. Flow chart highlighting the important imaging features in the diagnosis of cortically based tumors in children.

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 older than 1.5 years, the next step is to evaluate the presence of decreased diffusivity within the cortical mass, comparing the ADC signal with the adjacent uninvolved cortex.

Subsequently, if the mass is in the low-grade category, noting "special" features is important for accurate diagnosis (eg, presence of intrinsic T1 signal in angiocentric gliomas [AGs], coarse calcifications in cystic-solid enhancing mass in ganglioglioma/gangliocytoma) (Online Supplemental Data). 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.

PEDIATRIC DIFFUSE HIGH-GRADE GLIOMAS

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

This review will focus on 3 tumoral types within the pHGG family that commonly occur in the "peripheral" aspect of the brain including those involving the cortex.

Diffuse Hemispheric Glioma, H3G34-Mutant

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]

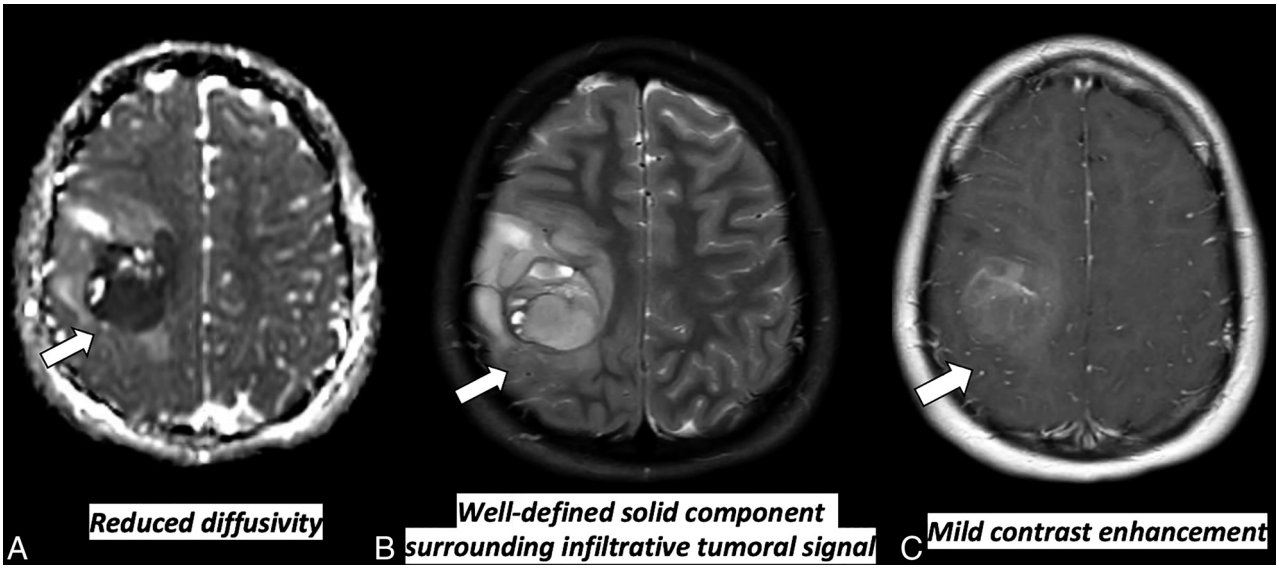

FIG 2. Seventeen-year-old with *H3 G34* mutant tumor. ADC map, T2-weighted, and T1-weighted postcontrast axial images of the brain show a well-defined solid, cortically involved tumor in the right parietal lobe (*white arrow*) with surrounding infiltrative tumoral signal involving the overlying cortex.

DHGs 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 among 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 nonmidline 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 almost always associated with patches of decreased diffusivity and a mean ADC of 600–700 $\times$ 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. 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.

Pediatric diffuse high-grade glioma, H3 Wild-Type, and IDH Wild-Type

pHGG, H3 wild-type, and IDH wild-type 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 are 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, pHGG, H3 wild-type, and IDH wild-type are similar to glioblastomas in adults.[18,21,22] Classically, these are large Supratentorial (ST) 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 radiologic 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 pHGG, H3 wild-type, and IDH wild-type should be included in the differential of high-grade, cortically-involving tumors with ill-defined margins (Fig 1). Additional helpful clues include the

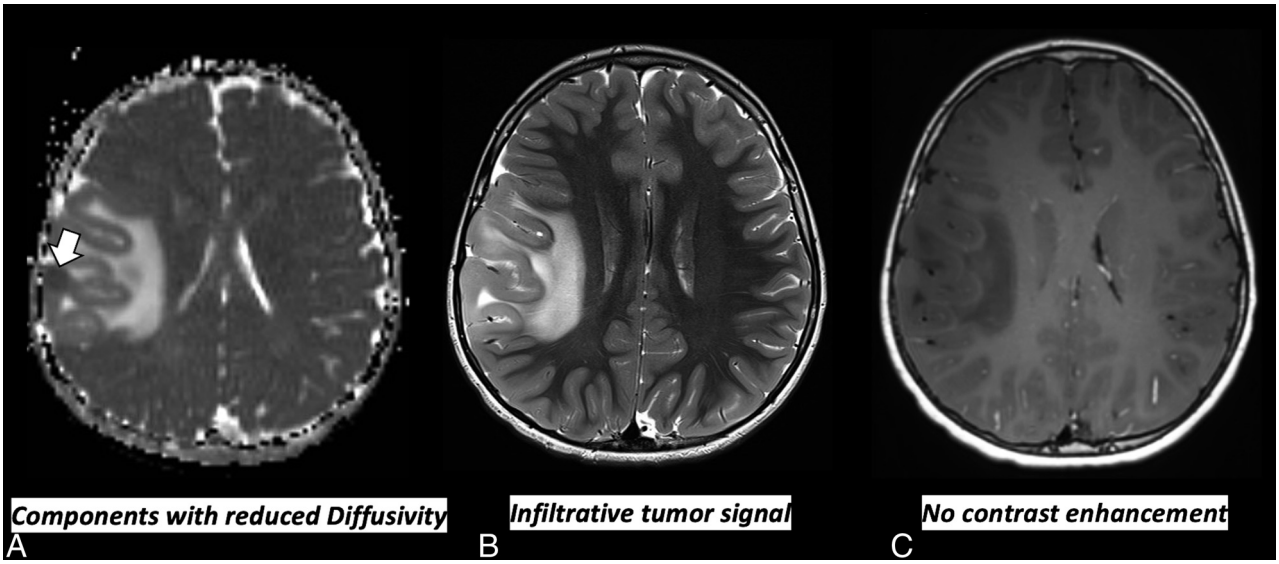

FIG 3. Eight-year-old with *EGFR* altered H3 wild-type and IDH wild-type. ADC map, T2-weighted, and T1-weighted postcontrast axial images of the brain show an infiltrative tumoral signal involving cortex and subcortical matter of the right parietal lobe. These images show a focus of decreased diffusivity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

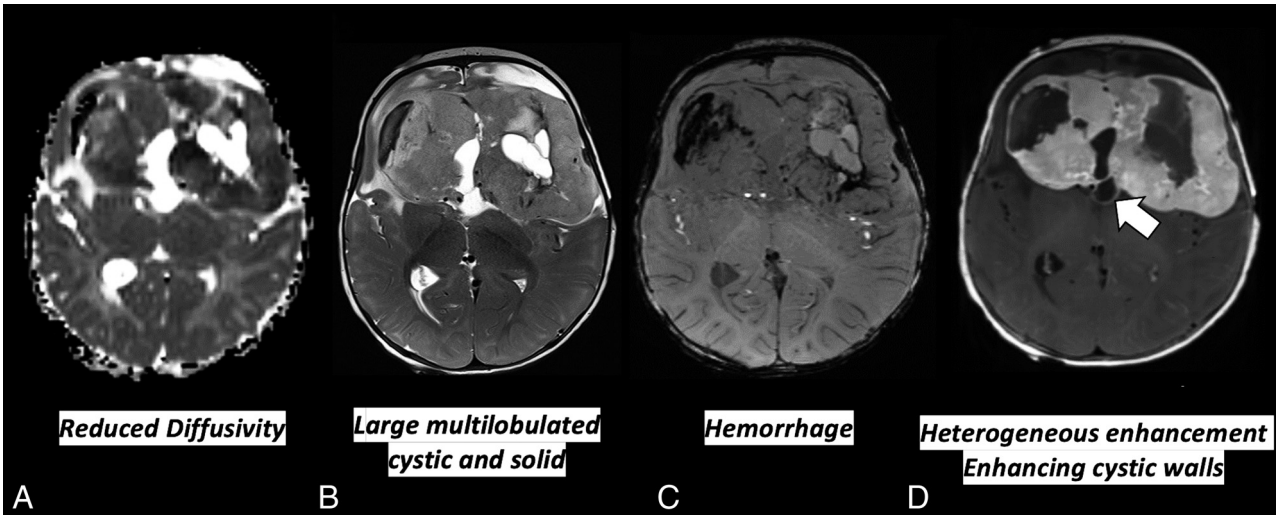

FIG 4. Nine-month-old with infantile hemispheric glioma, *RTK1* fusion positive. ADC map, T2-weighted, SWI, and T1-weighted postcontrast axial images of the brain show a large solid and cystic bifrontal mass with strong decreased diffusivity compared with adjacent cortex, hemorrhage, and enhancement. Note the enhancing cystic walls (*white arrow*).

presence of leptomeningeal and/or ependymal contact, which were described in almost all cases of DHG. A prior history of radiation is helpful as a clue that the tumor in question is likely pHGG, H3 wild-type, and IDH wild-type.[7]

Infant-Type Hemispheric Glioma

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 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 (DIG)/desmoplastic infantile astrocytoma (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

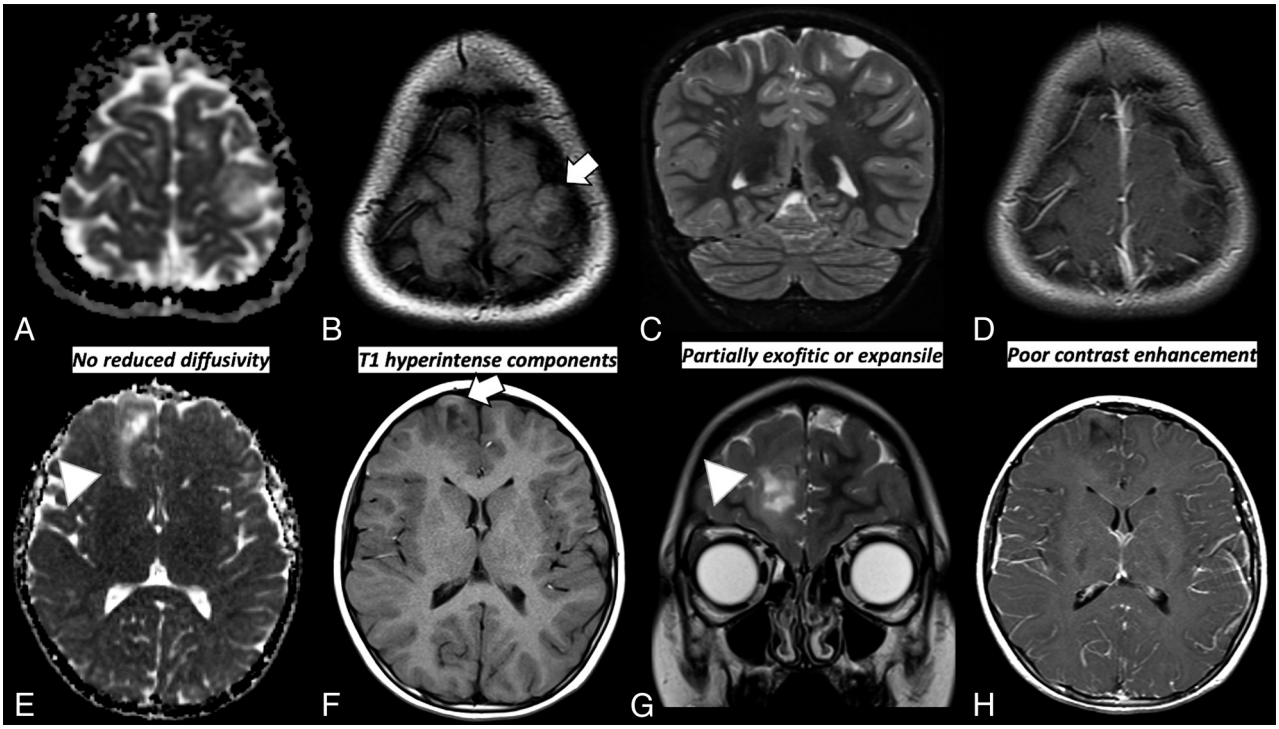

FIG 5. AG, *MYB-QKI* fusion positive in 2 different patients. Axial ADC map and T1-weighted as well as coronal T2-weighted, and axial T1-weighted postcontrast images of the brain in 2 different patients show a cortical-based lesion with internal T1-hyperintense components (similar to the adjacent white matter) (*white arrow*) and a stalklike sign (*arrowhead*).

portions of these tumors (Fig 1). Studies suggest that the presence of enhancement within the cyst walls, as well as bihemispheric involvement (crossing midline) are features of IHG.[24]

PEDIATRIC DIFFUSE LOW-GRADE GLIOMAS

Distinct molecular alterations and histologic features separate 4 entities under the pediatric diffuse low-grade gliomas (pLGG) umbrella, all of which are "peripheral," hemispheric, and lack IDH and H3 mutations.

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 characteristic features including variable components of high signal on the T1-weighted imaging and sometimes a "stalklike" sign, which refers to the triangular shape of T2 prolongation with the apex extending from the tumor toward 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 tumor 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" include 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

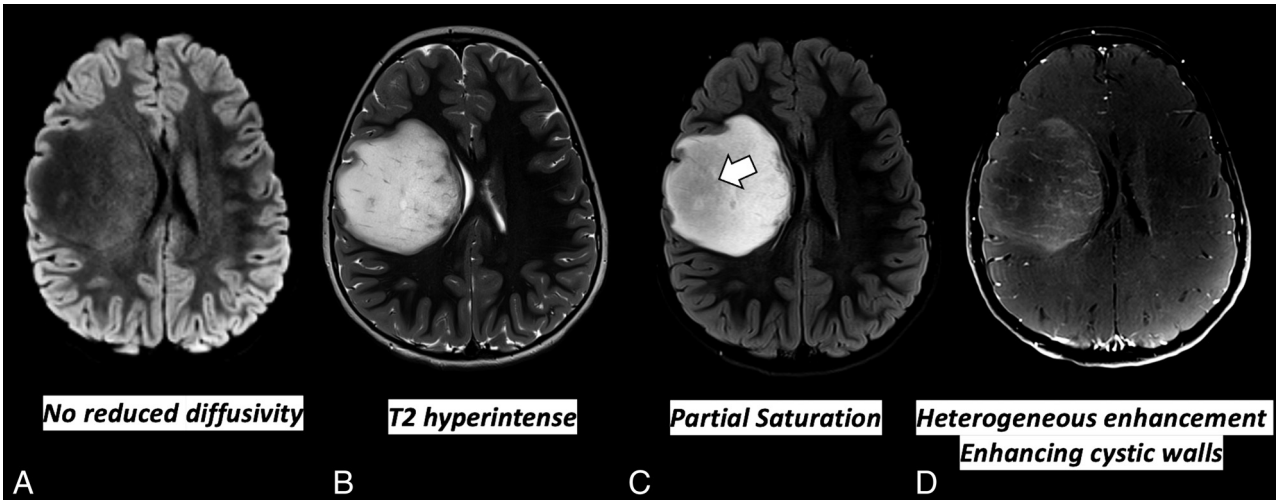

FIG 6. *MYB*-altered diffuse low-grade astrocytoma. DWI, T2-weighted, FLAIR, and T1-weighted postcontrast axial images of the brain show a cortically involved lesion with no decreased diffusivity or calcifications, T2 hyperintensity, mild subcortical FLAIR suppression (T2-FLAIR mismatch) (*white arrow*),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

dysembryoplastic neuroepithelial tumor (DNET), astroblastomas (ABs), and malformations of cortical development (such as FCD). Specific subtle differences of these entities are discussed throughout this paper.

Diffuse Astrocytoma, MYB- or MYBL1-Altered

This is a rare entity, a newly recognized CNS WHO grade 1 tumor, 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 that 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 nonenhancing 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*, and *FGFR4*.[32] An illustrative example is seen in Fig 6.

Polymorphous Low-Grade Neuroepithelial Tumor of the Young

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 long-term epilepsy-associated tumors (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 pseudorosettes arranged in a nodular pattern consisting of distinct oligodendroglioma-like cellular components.[37,39,40] Classically, there is MAPK pathway dysregulation that 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 tends 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 (Online Supplemental Data).[40]

As a nonaggressive 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 with 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 possibly fine as opposed to the most characteristic coarse calcifications in PLNTYs (Online Supplemental Data).[39,41,44]

Other differential diagnoses include ganglioglioma/gangliocytoma (GG) that tend to have a calcification morphology that 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).

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] Long-standing seizures are a common clinical presentation.

Clinical, morphologic, 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 differential of a low-grade, cortically involving, and solid neoplasm, which 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]

CIRCUMSCRIBED ASTROCYTIC GLIOMAS

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

Astroblastoma MN1-Altered

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] The 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 because they often share some clinical, pathologic, and radiologic criteria with ependymomas (EPs).[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 pseudo-rosettes similar to EP 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, 1190–1250 $\times$ 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 the Online Supplemental Data.

The main imaging differential is ST EPs, 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.

Pleomorphic Xanthoastrocytoma

Pleomorphic xanthoastrocytoma (PXA) is a rare glial tumor, thought to originate from subpial astrocytes and consisting 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 until the 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 years.[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 hyperattenuated 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 (Online Supplemental Data).[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 2 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).

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.

Multinodular and Vacuolating Neuronal Tumor

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]

Because 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 (Online Supplemental Data).[64,68,69]

The 2 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.

Diffuse Glioneuronal Tumor with Oligodendroglioma-like Features and Nuclear Clusters

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 Classification 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]

Ganglioglioma/Gangliocytoma

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 (Online Supplemental Data).[68] Studies have shown that ADC values tend to be lower in *BRAF p.V600E*-mutant GGs compared with 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).

Desmoplastic Infantile Glioma and Desmoplastic Infantile Astrocytoma

This is a benign, low-grade tumor type that occurs in infants younger than 2 years 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 that shows heterogeneous enhancement, calcifications, and a wide range of heterogeneous diffusivity.[76]

Desmoplastic Neuroepithelial Tumor

DNETs are CNS WHO grade 1, cortically based tumors of neuroglial origin first described in 1988.[77,78] DNETs present in 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 (Online Supplemental Data).[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 relative CBV values than normal brain parenchyma.[82]

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

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.

CNS Neuroblastoma, FOXR2-Activated

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] These tumors exhibit 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 hyperattenuation of the solid components and calcification along their inner rim on CT with thinning of the inner table of the skull having 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 (Online Supplemental Data).

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]

CNS Tumors with BCOR Internal Tandem Duplication

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 internal tandem duplication 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) (Online Supplemental Data).[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 have 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 attenuation and CBF values, most frequently exhibiting high microvascular attenuation and low CBF values, a feature that has been described in other embryonal tumors and EPs.[87]

Differential diagnoses may include an embryonal tumor with multilayered rosettes (ETMR), which occurs in children of similar age and shares some imaging features, such as lack of peripheral edema. However, these tumors differ from CNS tumors with *BCOR*-ITD because they do not frequently exhibit central areas of necrosis. Atypical teratoid/rhabdoid tumors (ATRTs) 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 EPs have increased T2 hyperintensity compared with 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.

Embryonal Tumors with Multilayered Rosettes

ETMRs are aggressive tumors, CNS WHO grade 4, most often affecting children younger than 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 histologic 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 ST 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 (nonmulticentric) 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, and it tends to be disproportionately smaller than expected for the size of the tumor (Online Supplemental Data).[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.

Atypical Teratoid/Rhabdoid Tumors

ATRT is a rare, highly malignant embryonal tumor, predominantly affecting children younger than 2 years of age. 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 spine. 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, in which most pediatric ATRTs are classified into 3 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 3 years, while ATRT-*TYR* tumors are found in infratentorial locations in patients younger than 1 year, and ATRT-*SHH* tumors are found in both supra- and infratentorial compartments, representing an intermediate subgroup with high 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 with infratentorial tumors. Their neuroimaging characteristics include cystic components, higher evidence of thick and wavy enhancement 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]

EPENDYMAL TUMORS

Ependymal tumors 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 histopathologic features. Microscopically, EPs are characterized by perivascular pseudo-rosettes, ependymal rosettes, glial fibrillary acidic protein reactivity, and paranuclear dot as well as ring positivity for epithelial membrane antigen immunohistochemistry 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 2 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]

ZFTA Fusion-Positive EPs

ST EP, *ZFTA* fusion-positive (initially classified as *RELA* fusion-positive) often occur in children with a median age of 7 years 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[93] 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%.

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 (Online Supplemental Data).

YAP1 Fusion-Positive EPs

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]

CONCLUSIONS

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.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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