

Simplified Imaging Based Approach to Updated 2021 5th Edition WHO Classification of CNS Tumors of the Pediatric Age Group: What Neuroradiologists Must Know

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Background

- The 4th Edition of the 2016 WHO Central Nervous System (CNS) tumor classification marked a significant shift by beginning to incorporate molecular features into tumor assessment.
 - Introduced an integrated approach of layered tumor reports that combines both histological and molecular data for more precise diagnosis.
- Building on these advancements, the 5th Edition WHO CNS tumor update released in 2021 presents a more refined and sophisticated classification system.
 - Enables clinicians to group CNS tumors into more biologically and molecularly defined entities.
- This refined classification has important implications for clinical research, as it may impact subject enrollment, treatment assignment, and outcome stratification in clinical trials.
 - Neuroradiologists must familiarize themselves with the updated 2021 WHO Classification of CNS neoplasms, especially for the pediatric age group, to function appropriately as part of the multidisciplinary neuro-oncology clinical team.

Objectives

- We aim to emphasize the major changes of the 2021 WHO Classification of CNS Tumors that mainly affect the children and young adults age group.
- To present the clinical and molecular characteristics of these tumors.
- To demonstrate the neuroimaging features on multidisciplinary basic as well as advanced MRI modalities.

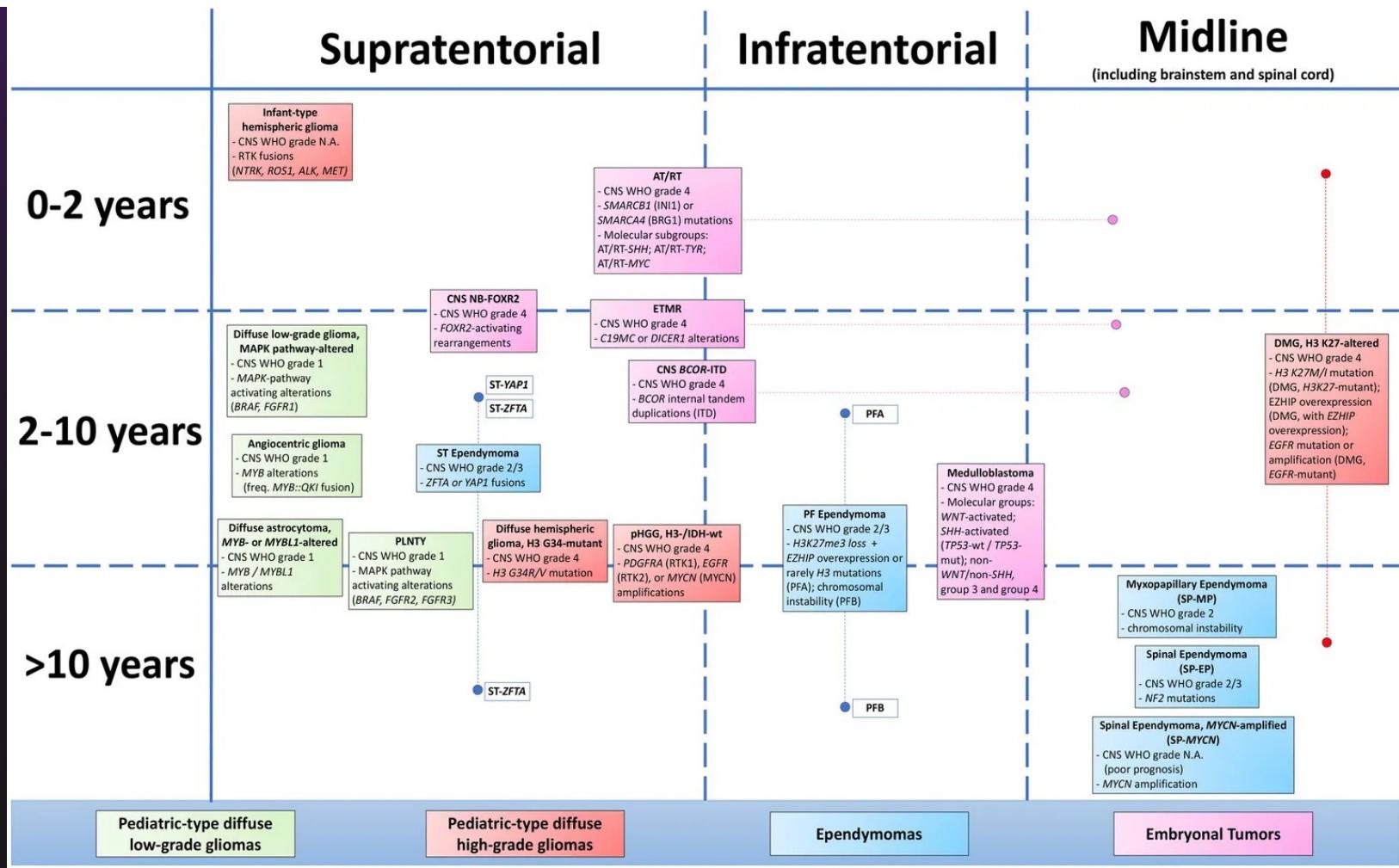
WHO CNS5: Integrated Molecular and Molecular Marker-based Diagnosis

- Further integration of histologic, immunophenotypic, and molecular genetic data (e.g. next-generation sequencing, DNA methylation profiling)
 - Notable advancements in the understanding of the distinct biology of pediatric brain tumors
- Some tumors consistently characterized by defining molecular features. For some, molecular parameters are not required but may support their classification. Others are rarely or never diagnosed using molecular approaches.
 - Resultant hybrid taxonomy with grouping by:
 - Genetic changes that enable a complete diagnosis (e.g. IDH and H3 status)
 - Looser oncogenic associations (e.g. MAPK pathway alterations)
 - Histological and histogenetic similarities even though molecular signatures vary
 - Using molecular features to define new types and subtypes (eg, medulloblastoma)
 - Division of diffuse gliomas into adult-type and pediatric-type.
- Newly recognized entities: out of 22 newly recognized tumor types, 15 are seen predominantly in children and adolescents
- Changes in nomenclature to some existing entities: diffuse midline glioma is now designated as “H3 K27-altered” rather than “H3 K27M-mutant” in order to recognize alternative mechanisms by which the pathogenic pathway can be altered in these tumors

Other General Changes in WHO 2021 CNS5

- “type” instead of “entity”, “subtype” instead of “variant”
- Arabic numerals instead of Roman numerals
- Neoplasms are graded within types (rather than across different tumor types); modifier terms like “anaplastic” are not routinely included
- Pathology report structure: Integrated Diagnosis and a Layered Report with histopathological classification, CNS WHO grade if indicated, and the relevant molecular information

	Tumor Type	Major molecular designations in WHO CNS5
Pediatric-type diffuse low-grade gliomas	Diffuse astrocytoma	<i>MYB</i> -altered; <i>MYBL1</i> -altered
	Diffuse LGG	MAPK pathway-altered
	Angiocentric glioma	<i>MYB</i> fusions (usually with QKI)
	Polymorphous low-grade neuroepithelial tumor of the young (PLNTY)	<i>BRAF</i> V600E, <i>FGFR2/3</i> , <i>NTRK</i>
Pediatric-type diffuse high-grade gliomas	Diffuse midline glioma	H3 K27-Altered
	Diffuse hemispheric glioma	H3 G34-mutant
	Diffuse pediatric-type HGG	H3 wildtype and IDH wildtype
	Infant-type hemispheric glioma	<i>NTRK</i> family, ROS, ALK, MET
Circumscribed astrocytic gliomas	Astroblastoma	<i>MN1</i> -altered
	High-grade Astrocytoma with	<i>cdkn2A/B</i> deletion, MAPK pathway alteration (affecting <i>NF1</i> , <i>BRAF</i> , and <i>FGFR1</i>), and <i>ATRX</i>
Ependymal tumors	Supratentorial ependymoma	<i>ZFTA</i> fusion+; <i>YAP1</i> fusion+
	Posterior Fossa ependymoma	group PFA; group PFB
	Spinal ependymoma	<i>MYCN</i> -amplified
Embryonal tumors	Medulloblastoma	WNT Activated; SHH activated and <i>TP53</i> -wildtype SHH-activated and <i>TP53</i> -mutant non-WNT/non-SHH
	Atypical teratoid/rhabdoid tumor (AT/RT)	ATRT-TYR; ATRT-SHH; ATRT-MYC
	Embryonal Tumor with Multilayered Rosettes (ETMR)	<i>C19MC</i> -altered; <i>DICER1</i> -mutant
	CNS Neuroblastoma	<i>FOXR2</i> -activated
Mesenchymal CNS tumors	CNS Tumor with <i>BCOR</i> Internal Tandem Duplication	<i>BCOR</i> internal tandem duplication
	Intracranial mesenchymal tumor	<i>FET-CREB</i> fusion+
	<i>CIC</i> -rearranged sarcoma	<i>CIC</i> -rearranged
	Primary Intracranial Sarcoma	<i>DICER1</i> -mutant



d'Amati et al., 2024

General Concepts: High vs Low Grade

- Most important/reliable differentiator: Low ADC (restricted diffusion)-higher grade (marker of cellularity)
 - Exception: diffuse midline glioma H3 K27-altered generally lack restricted diffusion (although higher-grade components may have lower ADC, and commonly enhance)
- Enhancement: variable-seen in low and high-grade
- Other generally high-grade features: infiltrative, poorly-defined margins, necrosis, hemorrhage, increased perfusion, again with exceptions/overlap-to be used in conjunction with ADC and other features
 - Example from one of the newly described entities:
 - High-grade astrocytoma with piloid features: non-diffusion restricting, non-necrotic, can have sharp/defined margins

Pediatric diffuse gliomas: two new families of tumor types

- Recognized as distinct from adult diffuse gliomas
 - Differences in genomic alterations, biological behavior, clinical course
- Pediatric-type diffuse low-grade gliomas: 4 entities
 - Require molecular differentiation from one another due to their similar, nonspecific, low-grade histologic characteristics.
 - Share in common MAPK-pathway signaling alterations
 - Diffuse astrocytoma, MYB- or MYBL1-altered
 - Angiocentric glioma
 - Polymorphous low-grade neuroepithelial tumor of the young (PLNTY)
 - Diffuse low-grade glioma, MAPK pathway-altered.
- Pediatric-type diffuse high-grade gliomas: 4 entities
 - Diffuse hemispheric glioma, H3 G34-mutant
 - Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
 - Infant-type hemispheric glioma.
 - Diffuse midline glioma, H3 K27-altered

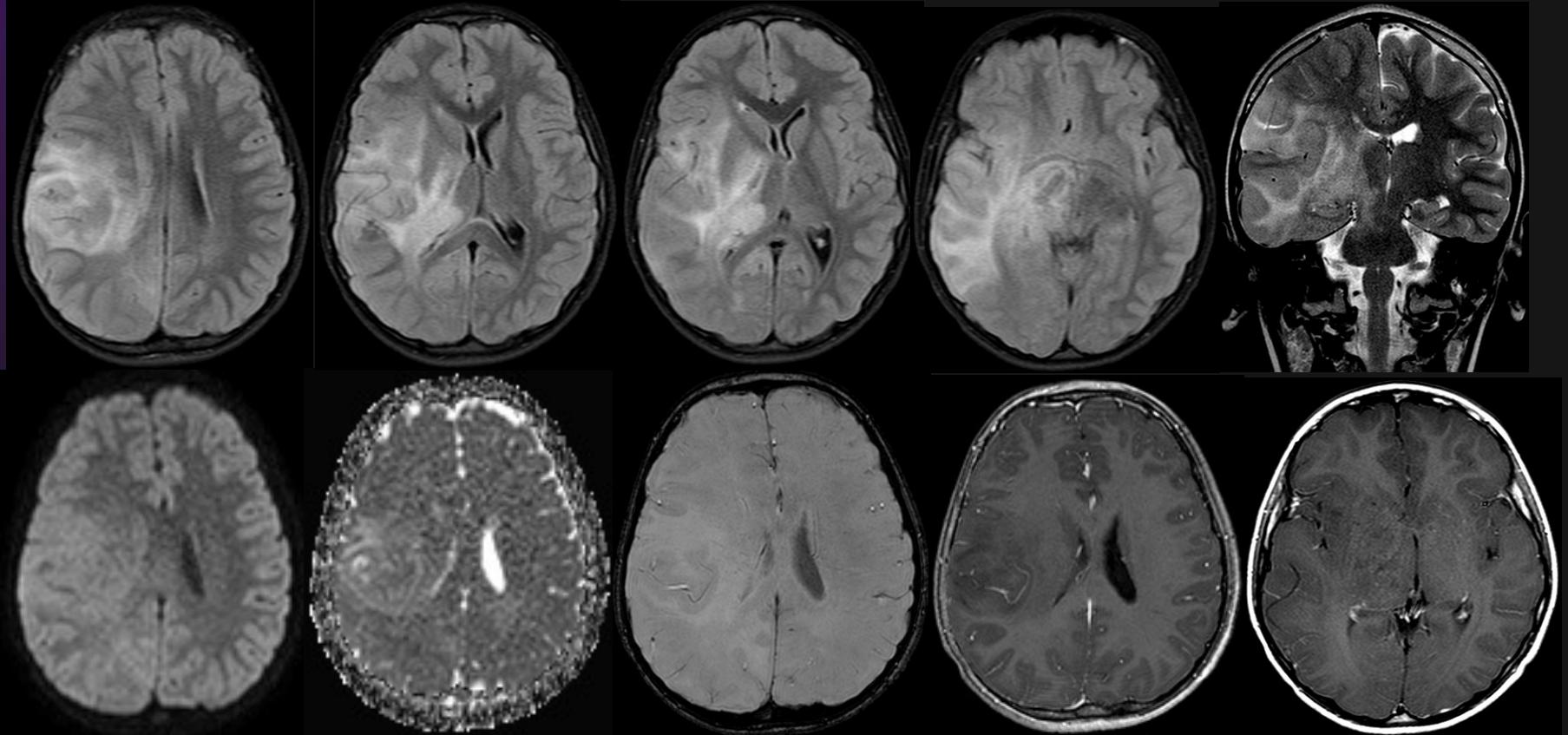
Pediatric-type diffuse low-grade gliomas

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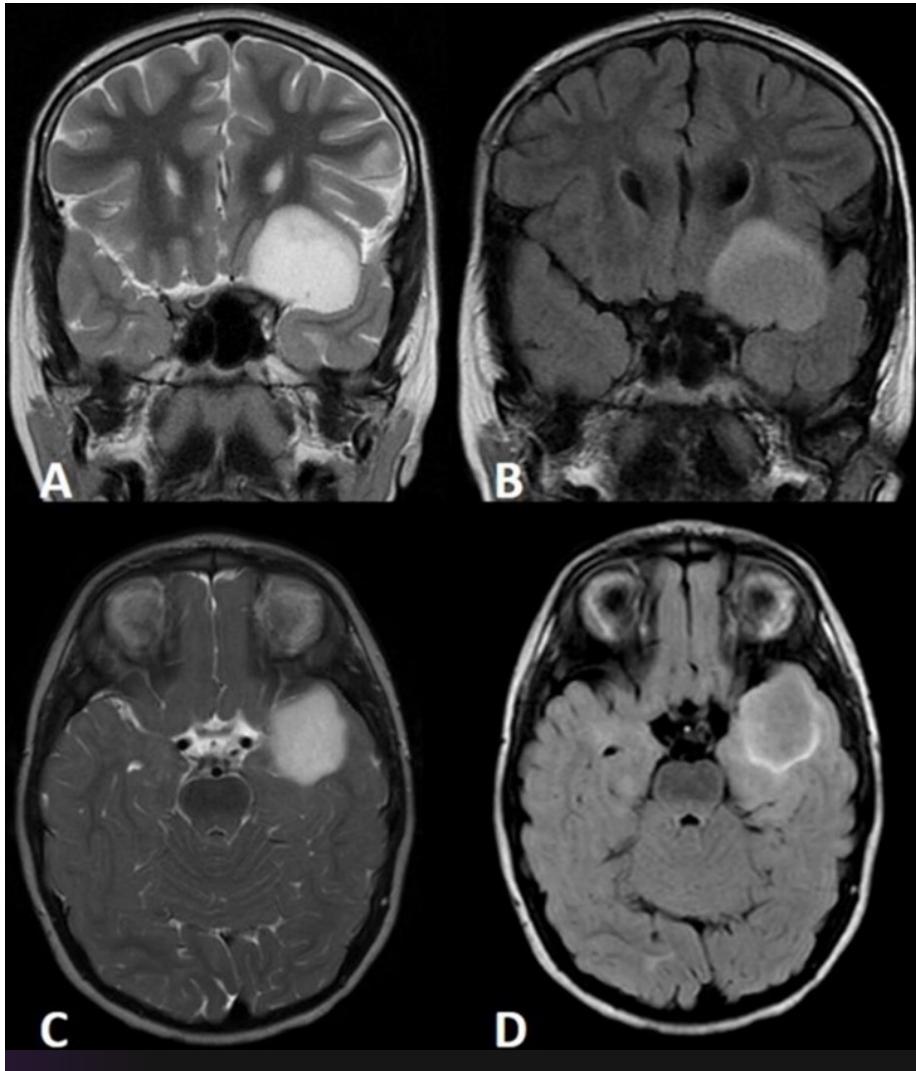
Diffuse Astrocytoma, MYB- or MYBL1-Altered

- Molecular: Defined by structural variation, such as fusion, rearrangements, or amplification, involving MYB or MYBL1, which are transcriptional regulators for cellular proliferation and differentiation.
- Clinical: median age at diagnosis 5-10 years, no sex predilection
 - Often diagnosed in the context of childhood drug-resistant epilepsy-included in the group of long-term epilepsy-associated tumors
- Location: Cerebral cortex, followed by supratentorial white matter/deep gray nuclei, then the brainstem
- Imaging: Infiltrative, heterogeneously T2-hyperintense, nonenhancing, non-diffusion-restricting mass.
 - T2-FLAIR mismatch (also common in angiocentric glioma and dysembryoplastic neuroepithelial tumors but rarely present in pilocytic astrocytomas or gangliogliomas)

Diffuse Astrocytoma, MYB or MYBL1 altered

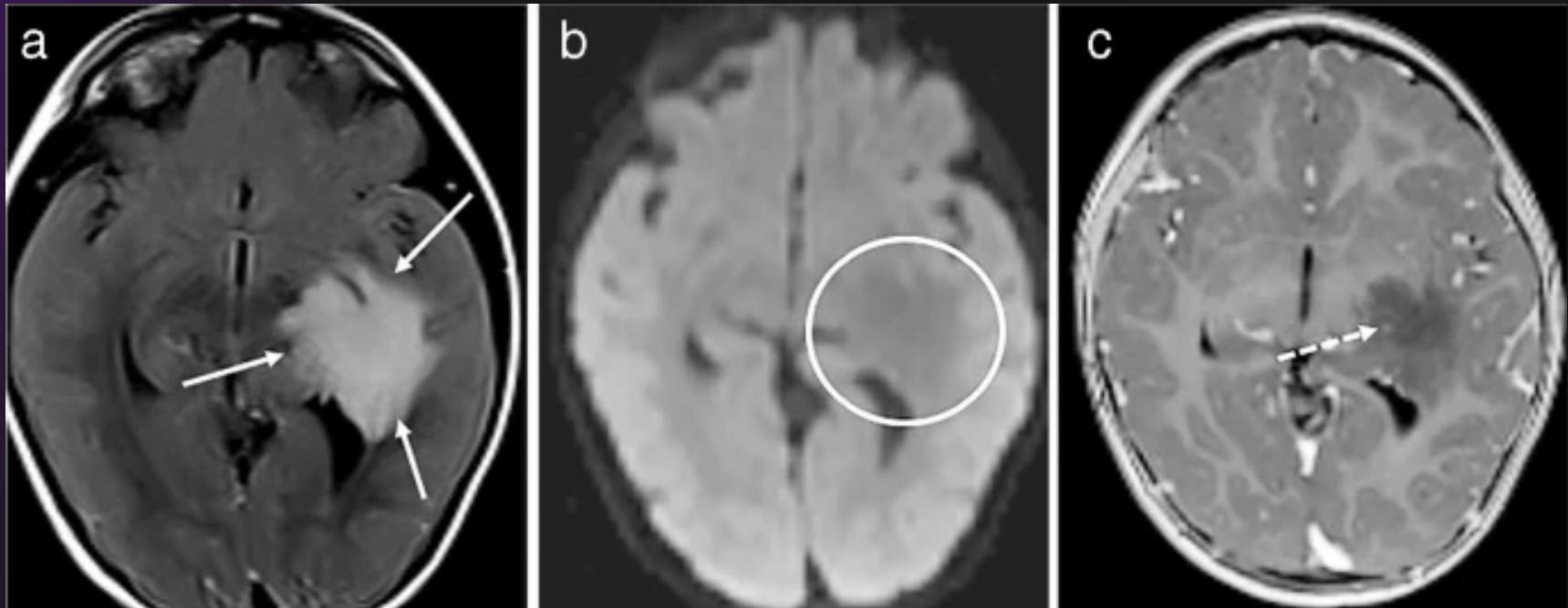


Infiltrative T2/FLAIR hyperintense mass without restricted diffusion, susceptibility, or enhancement involving the right opercular region, insula, thalamus and gangliocapsular region, and mesencephalic junction



Diffuse Astrocytoma, MYB- or MYBL1-Altered

- A 9-year-old boy with a left temporal tumor showing hyperintensity on T2WI (A) and a largely hypointense area on FLAIR within the tumor (B), characteristic of "T2/FLAIR mismatch".
- A 2-year-old girl with a left temporal tumor showing homogenous hyperintensity on T2WI (C) and a hyperintense rim on FLAIR (D).
- Coppola et al., 2025, American Journal of Neuroradiology June 2025, ajnr.A8894; DOI: <https://doi.org/10.3174/ajnr.A889>

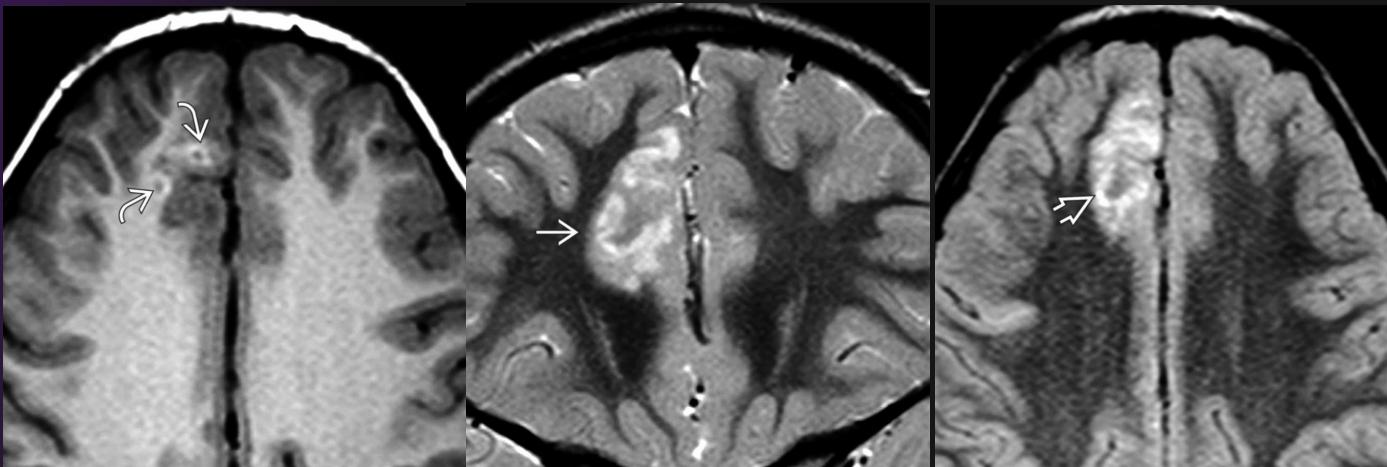


- Diffuse astrocytoma, MYB- or MYBL1-altered, in a 2-year-old girl.
- A) An axial fluid-attenuated inversion recovery (FLAIR) image shows an infiltrative left temporal hyperintense mass (arrows).
- B) An axial diffusion-weighted image does not show restricted diffusion (circle).
- C) An axial post-contrast T1-weighted image demonstrates a small, possible focus of enhancement (dashed arrow), but the mass is predominantly not enhancing
- Oztek, M.A., Noda, S.M., Romberg, E.K. et al. Changes to pediatric brain tumors in 2021 World Health Organization classification of tumors of the central nervous system. *Pediatr Radiol* 53, 523–543 (2023). <https://doi.org/10.1007/s00247-022-05546-w>

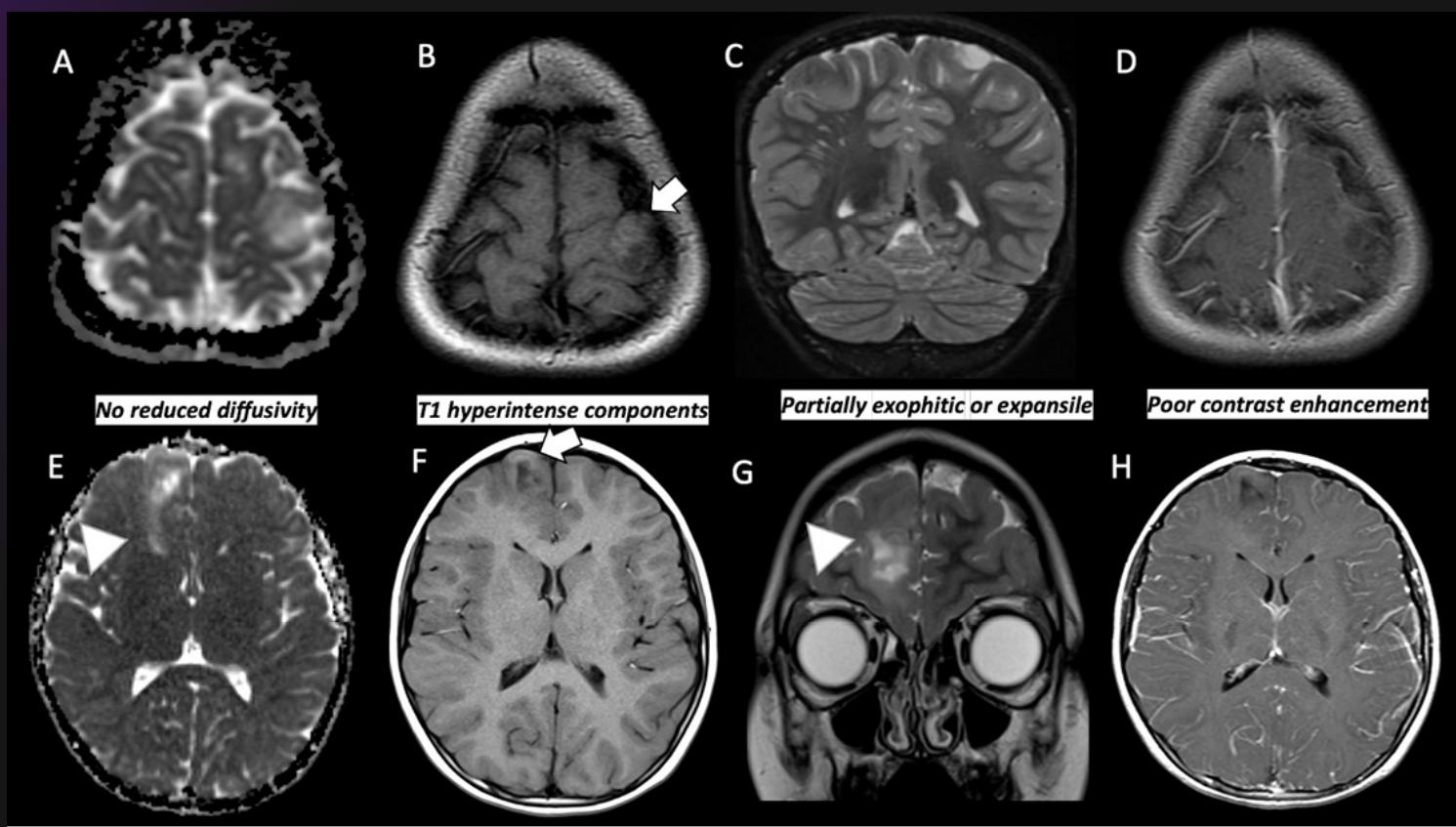
Angiocentric Glioma

- MYB::QKI fusion in > 85%
 - No *IDH1*, *IDH2*, *ATRX*, *TP53*, histone H3 mutations
- Clinical: Children, young adults (median: 13-15 years). Drug-resistant epilepsy
- Location: Cortex &/or subcortical white matter, frontal, temporal lobe
 - Brainstem lesions increasingly reported
- Imaging: Most commonly solid. Calcification may be present.
 - T1 hypo/iso/hyperintense (rim-like hyperintensity can be seen)
 - T2/FLAIR hyperintense (may have mismatch sign)
 - Stalk-like extension toward the ventricle
 - May have adjacent focal cortical dysplasia (type 3b)
 - No diffusion restriction
 - Usually no enhancement but variable

Angiocentric Glioma



- Images from STATdx: Axial T1 (left) in a 6-year-old child with refractory epilepsy shows an ill-defined cortical and subcortical mass. Note the hyperintense ring-like areas white findings sometimes seen in AG.
- Axial FLAIR MR in the same patient shows gyriform high signal intensity in the mass, which is ill-defined but does not demonstrate surrounding edema.
- Coronal T2 MR in the same patient shows high signal intensity of the cortical and subcortical right frontal lobe lesion.

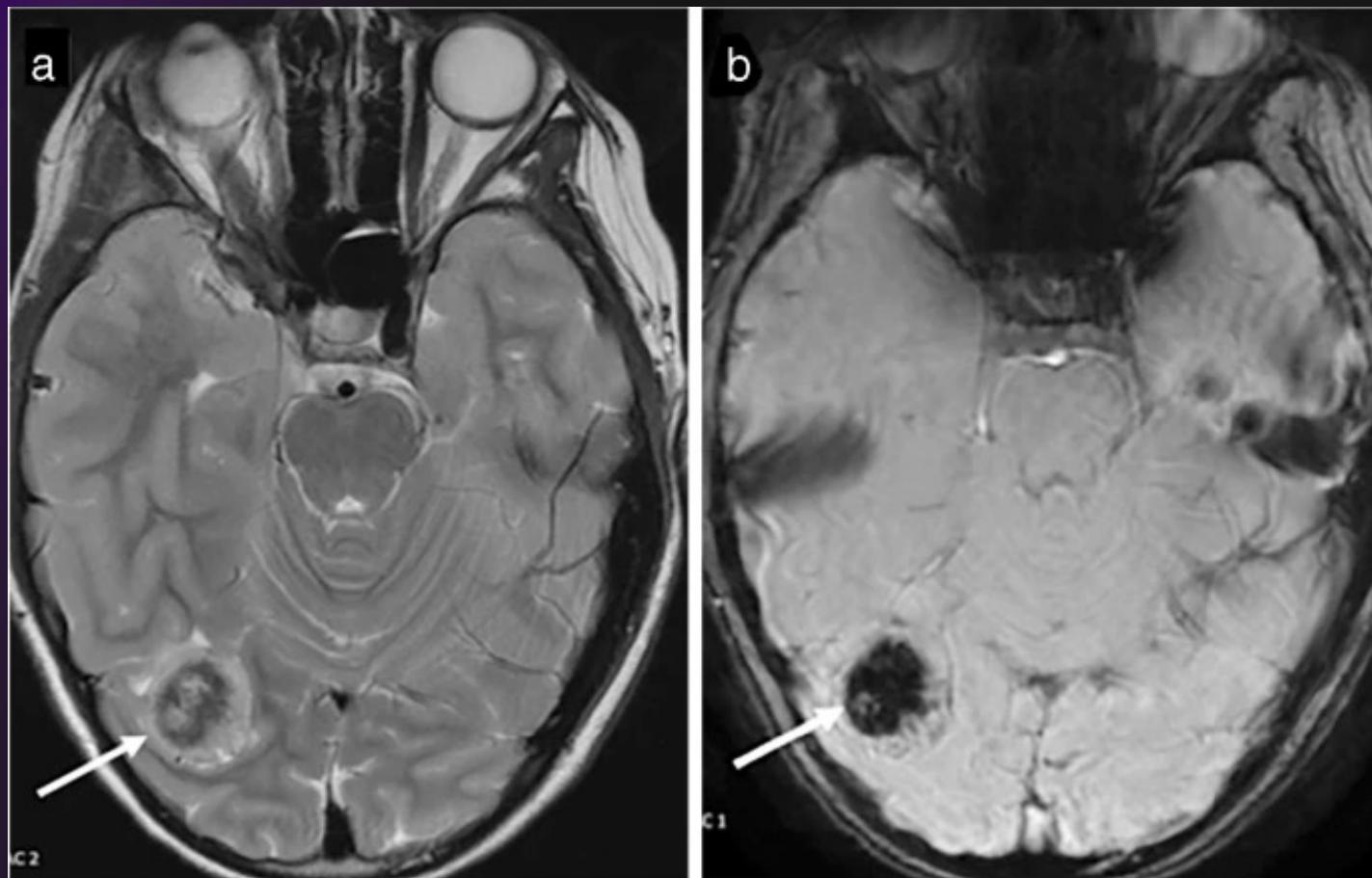


Angiocentric glioma, MYB-QKI fusion positive in two different patients. Axial ADC map and T1-weighted as well as coronal T2-weighted, and axial T1-weighted post contrast images of the brain in two different patients show a cortical based lesion with internal T1-hyperintense components (similar to the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

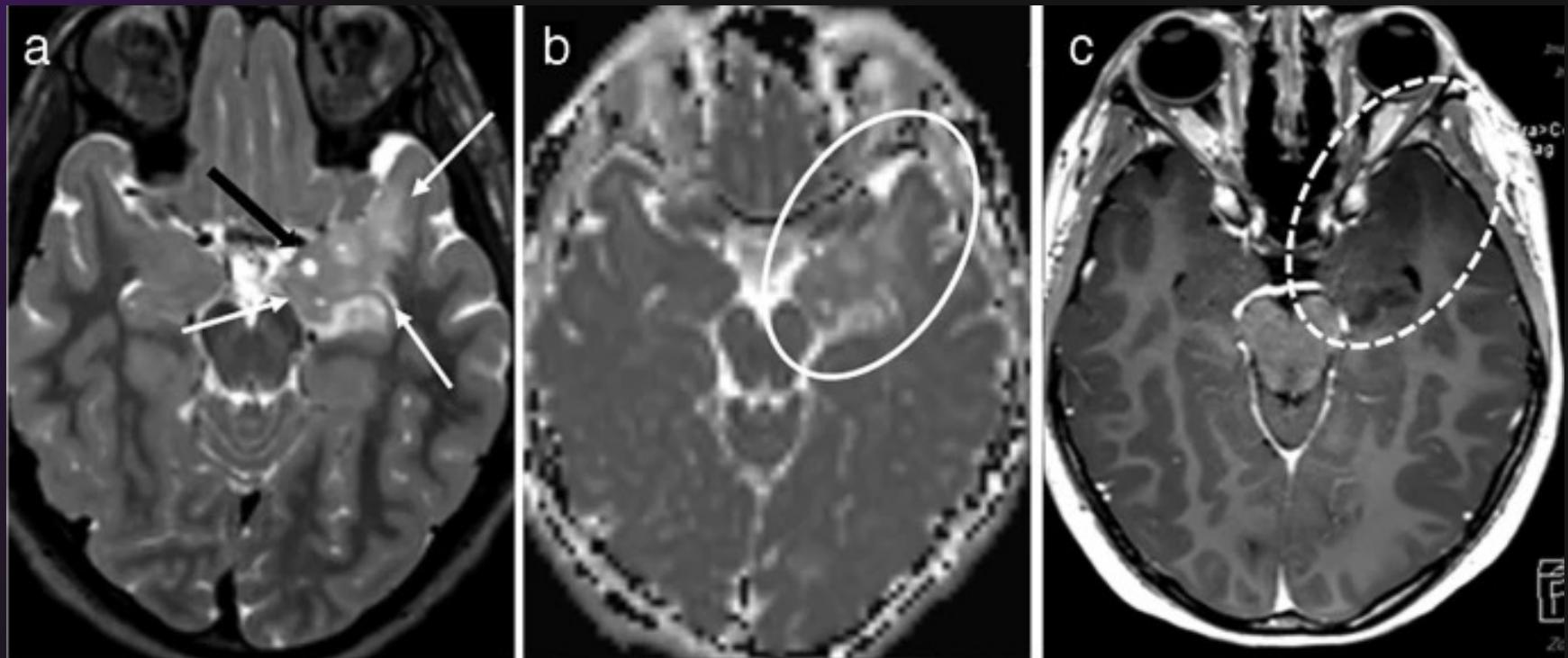
- Rameh et al., American Journal of Neuroradiology August 2024, ajnr.A8477; DOI: <https://doi.org/10.3174/ajnr.A8477>

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

- Molecular: BRAF mutations, specifically BRAF V600E, and fusions involving FGFR2 and FGFR3 are common.
- Clinical: refractory seizures in children and young adults. In the majority of cases, surgical excision improves seizures and recurrence is unlikely.
- Imaging: Calcifications are characteristically seen and tend to be central; the amount and pattern is unusual for other pediatric brain tumors and PLNTY should be strongly considered when present
- Cystic components in 40-89%, enhancement is present in up to one-third of cases, which can be irregular or nodular



- Polymorphous low-grade neuroepithelial tumor of the young (PLNTY) in a 12-year-old boy.
- A) An axial T2-weighted image demonstrates a right temporo-occipital mass with peripheral high and central low signal (arrow).
- B) An axial susceptibility-weighted image shows intense hypointensity in the central portion of the tumor (arrow), which corresponded to calcification on pathology

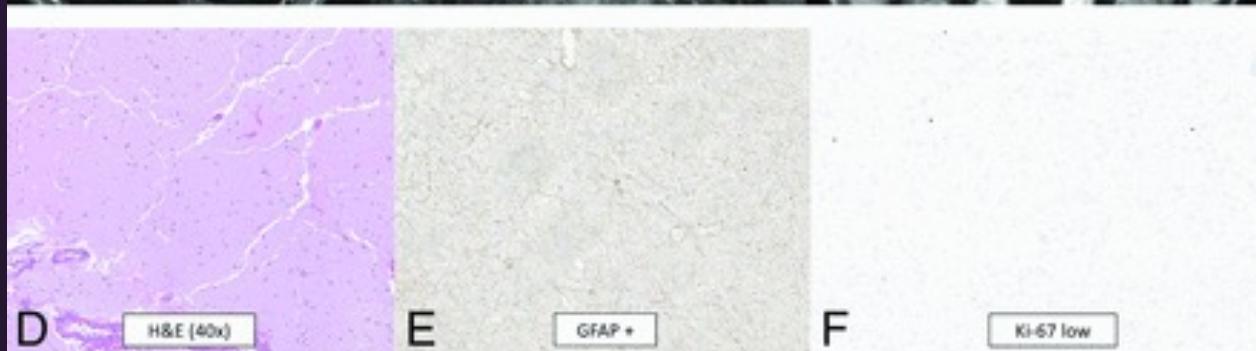
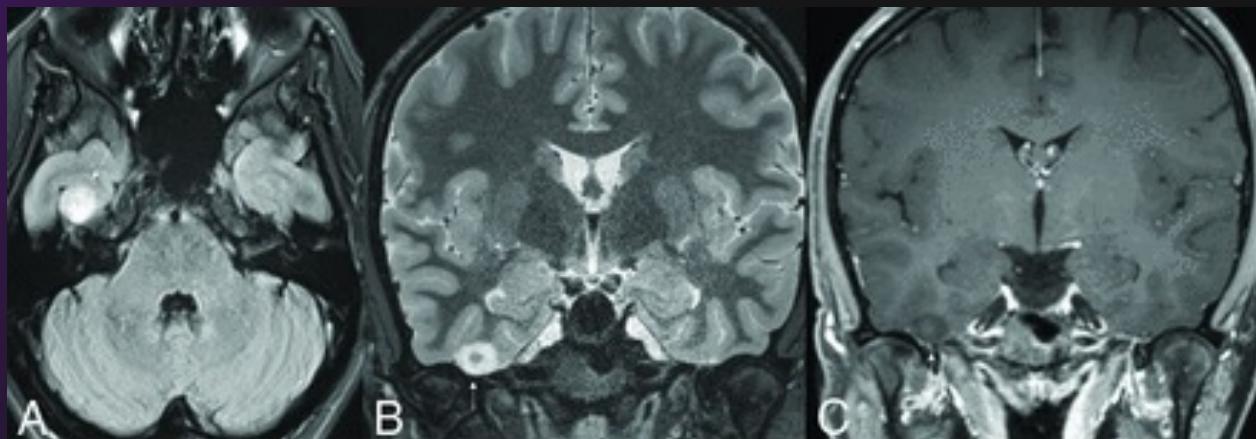


- Polymorphous low-grade neuroepithelial tumor of the young (PLNTY) in a 9-year-old girl.
- A) An axial T2-sampling perfection with application-optimized contrasts by using flip angle evolution (T2-SPACE) image demonstrates an ill-defined hyperintense lesion in the left temporal lobe (white arrows). Some cystic areas are noted (black arrow).
- B) There is no diffusion restriction on an axial apparent diffusion coefficient map (circle).
- C) An axial post-contrast T1-weighted image demonstrates no enhancement (dashed circle)

Diffuse Low-Grade Glioma, MAPK Pathway–Altered

- Histologically, behaves like a WHO grade 2 tumor with an oligodendroglial, astrocytic, or mixed pattern with infiltrative growth and typical low-grade cellular features.
- Molecular: may arise from numerous alterations which can activate the MAPK pathway
 - More common alterations involve FGFR1 and BRAF; less common alterations involve NTRK1/2/3, MET, FGFR2, and MAP2K1. IDH1/2 and H3F3s mutations and CDKN2A homozygous deletions must be absent.
- Clinical: commonly presents with epilepsy in the pediatric population and occasionally in adults
- Imaging: paucity of literature; presumed similar to other pediatric low-grade tumors: T2-FLAIR hyperintense, nonenhancing, non-diffusion restricting
- Tumors with FGFR1 mutations can demonstrate rapid progression in almost half of the cases, but death is relatively rare and usually occurs more than 10 years after diagnosis

Diffuse low-grade glioma, MAPK pathway-altered.



- A cortical T2-FLAIR (A) and T2-hyperintense mass (B) is noted within the right fusiform gyrus (arrows) with low T1 signal and no enhancement (C).
- A histologic section shows a diffusely infiltrating glioma of low cellularity with no mitotic activity, microvascular proliferation, or necrosis (D).
- Immunohistochemical staining is positive for GFAP (E) and shows a low Ki-67 proliferation index (F).
- Targeted next-generation sequencing identified a QKI-NTRK2 fusion, suggestive of MAPK pathway alteration.
- Rigsby et al., American Journal of Neuroradiology April 2023, 44 (4) 367-380; DOI: <https://doi.org/10.3174/ajnr.A7827>

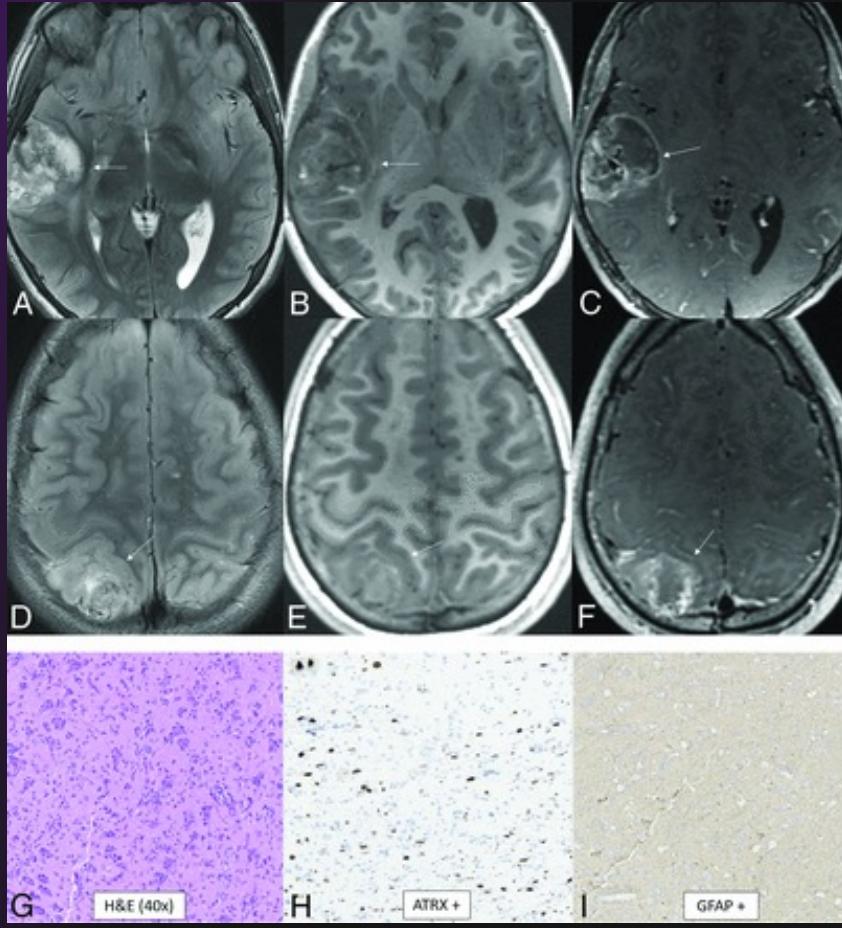
Pediatric-type diffuse high-grade gliomas

- Diffuse hemispheric glioma, H3 G34-mutant
- Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
- Infant-type hemispheric glioma.
- Diffuse midline glioma, H3 K27-altered

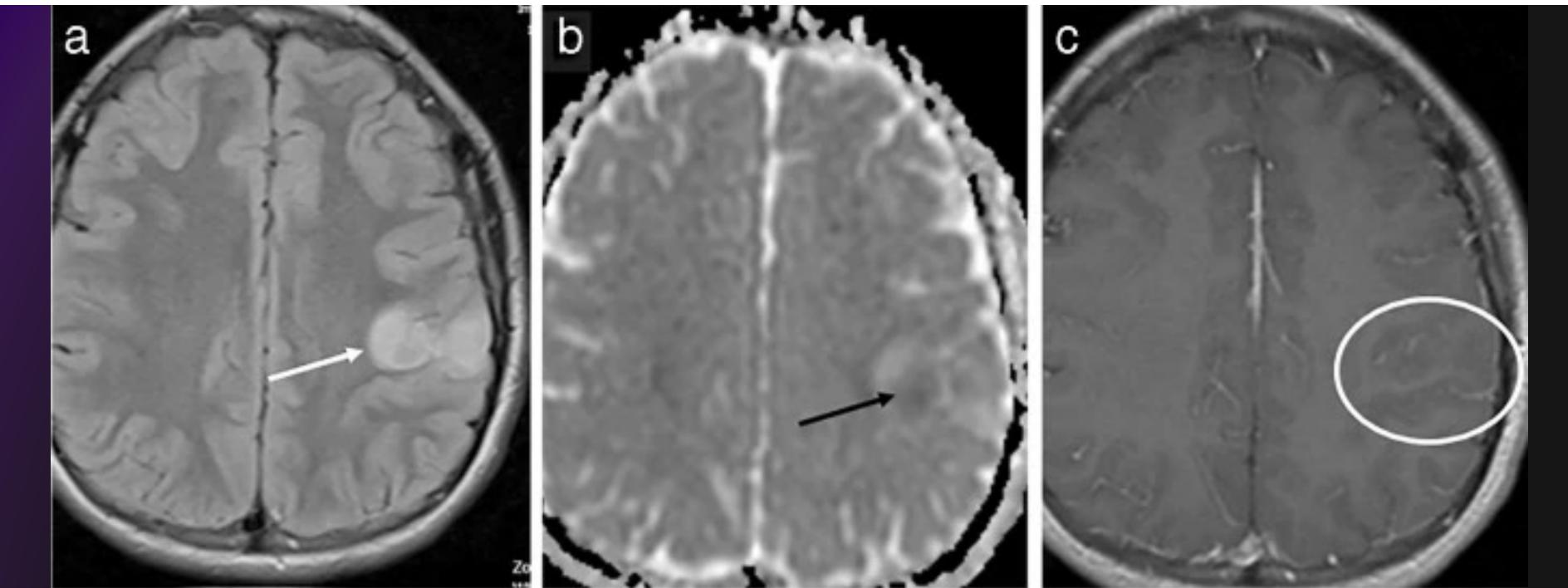
Diffuse Hemispheric Glioma, H3 G34-Mutant

- High-grade pediatric-type tumor, definitionally WHO grade 4, glioblastoma-type tumors
- Malignant, hypercellular gliomas with astrocytic differentiation, high mitotic rates, microvascular proliferation, and necrosis.
- Molecular: missense mutation of H3F3a, which codes for histone H3, causing arginine or less commonly valine to be substituted for the normal glycine 34
 - Strong association with ATRX and TP53 mutations.
 - PDGFRA amplification -glioblastoma morphology.
 - CCND2 amplification -primitive neuroectodermal tumor morphology.
- Demographics: median age at diagnosis is 15.8 years, slight male predominance
- Location: frontal and parietal lobes, frequent abutment of leptomeningeal or ependymal surfaces.
- Imaging: Margins may be sharp or ill-defined.
 - Most tumors are hyperdense, T1-hypointense, T2-hyperintense, enhancing, and diffusion-restricting.
 - Tumoral hemorrhage and necrosis can be seen and occasionally calcification
 - Despite the high-grade nature and otherwise relatively aggressive imaging features, these tumors generally do not exhibit peritumoral edema.
 - There have been cases without enhancement or necrosis [25]. Local recurrence and leptomeningeal dissemination are possible

Diffuse hemispheric glioma, H3 G34-mutant.



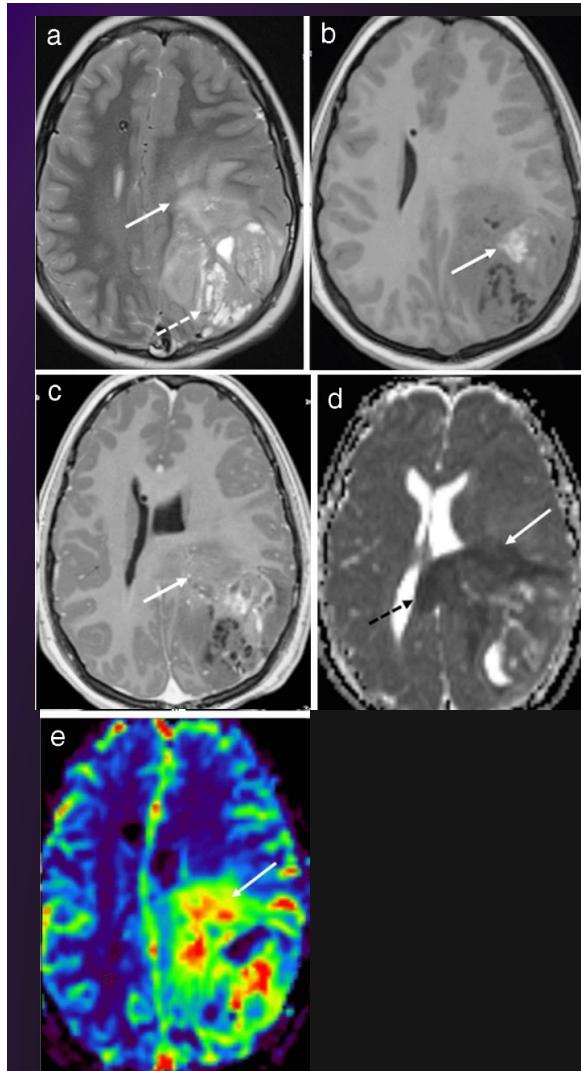
- Multifocal masses in the right temporal and parietal lobes.
- The temporal mass shows heterogeneously increased T2 signal (A), heterogeneously low T1 signal with a few foci of T1-hyperintense hemorrhage (B), and heterogeneous enhancement (C, arrows).
- The parietal mass shows similar signal characteristics with heterogeneous T2-FLAIR hyperintensity (D), T1-hypointensity (E), and enhancement (F, arrows).
- The histologic section reveals an infiltrating glioma with astrocytic morphology (G). Glioma cells are positive for ATRX (H) and GFAP (I) stains and negative for IDH1 R132H and OLIG2. There was a high Ki-67 proliferation index of up to approximately 20%. This immunophenotype suggested a mutation of H3 G34, warranting further genomic evaluation. Next-generation sequencing revealed a somatic mutation in H3-3A (also known as H3F3A). Currently, there are no clinically approved therapies specifically targeting H3-3A mutations.
- Rigsby et al., American Journal of Neuroradiology April 2023, 44 (4) 367-380; DOI: <https://doi.org/10.3174/ajnr.A7827>



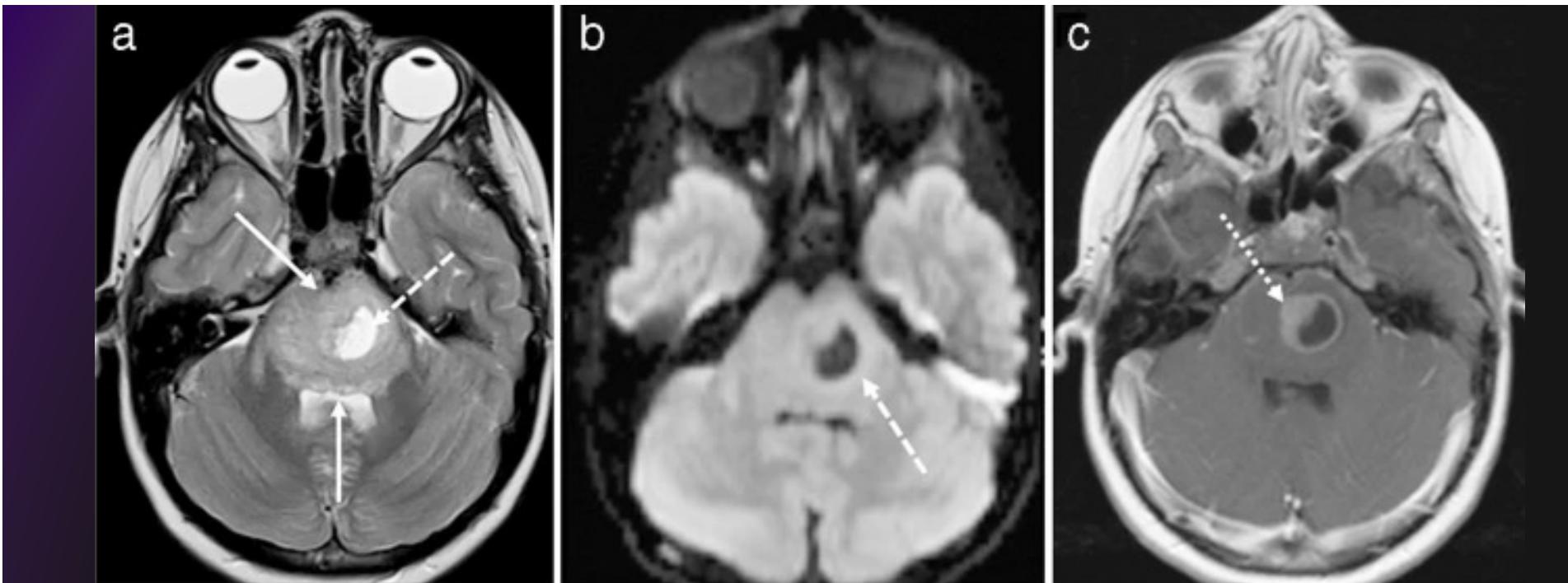
- Diffuse hemispheric glioma, H3 G34 mutant, in a 15-year-old boy.
- A) An axial fluid-attenuated inversion recovery (FLAIR) image demonstrates a hyperintense mass arising from the hemisphere (arrow).
- B) An axial apparent diffusion coefficient map shows a small area of restricted diffusion (arrow).
- C) An axial post-contrast T1-weighted image does not show appreciable enhancement (circle)
- Oztek, M.A., Noda, S.M., Romberg, E.K. et al. Changes to pediatric brain tumors in 2021 World Health Organization classification of tumors of the central nervous system. *Pediatr Radiol* 53, 523–543 (2023). <https://doi.org/10.1007/s00247-022-05546-w>

Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype

- No single defining molecular or genetic feature. Comprises the ~1/3-1/2 of pediatric-type diffuse high-grade gliomas that do not have H3 or IDH mutations.
- Three major molecular entities: MYCN-amplification (most common and aggressive), PDGFRA, and EGFR
- Median age at diagnosis: 8-11 years, no sex predilection, poor prognosis-median overall survival of 11.5–16.5 months and 3-year overall survival of 26%
- Location: usually supratentorial, with the posterior fossa approaching 20% of cases, depending on subtype.
- MYCN subtype: well-circumscribed mass with homogeneous enhancement, mild peritumoral edema, diffusion restriction and increased rCBV on perfusion imaging.
- Pontine lesions with MYCN alterations and no H3 mutations present similarly to the more common diffuse midline glioma, H3 K27-altered, but with a larger area of central necrosis, lower ADC and higher relative cerebral blood volume (rCBV) on arterial spin labelling (ASL) perfusion imaging
- Additional clues: leptomeningeal and/or ependymal contact, prior history of radiation



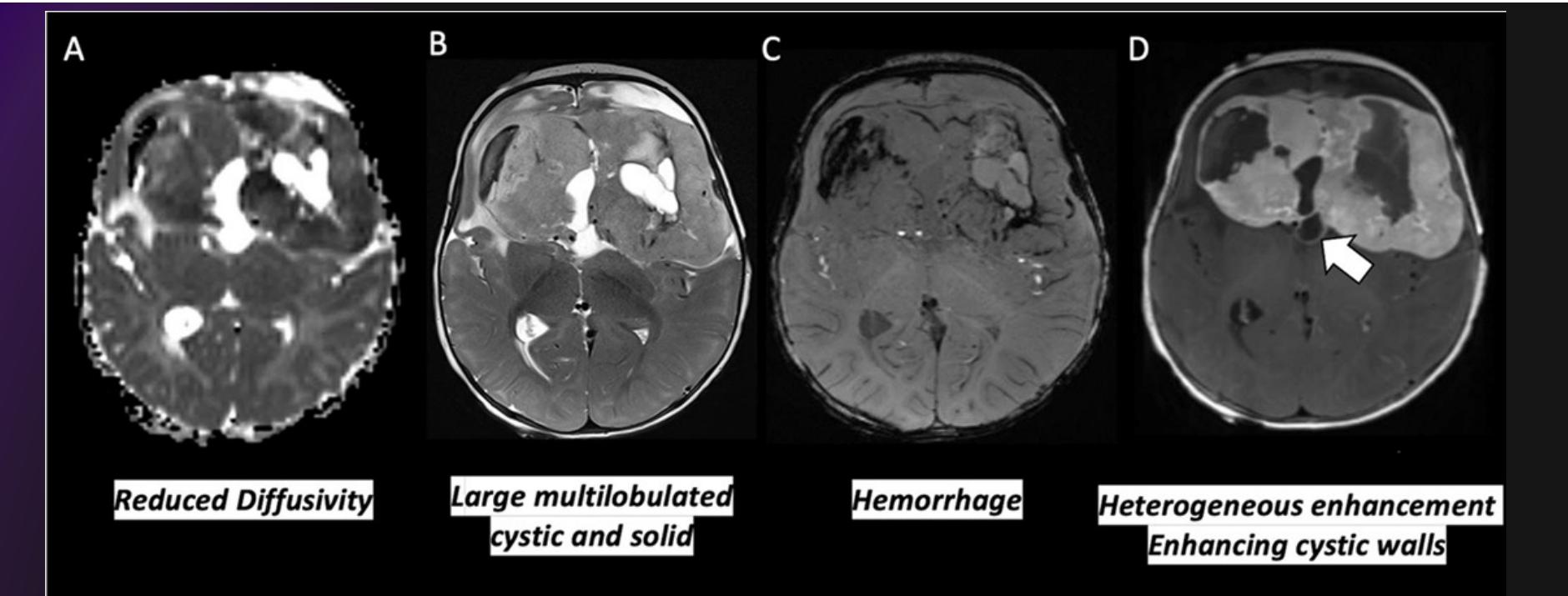
- Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype, in an 11-year-old girl.
- A) An axial T2-weighted image demonstrates a heterogeneous mass with cystic components laterally (dashed arrow) and a more infiltrative T2 hyperintense component extending anteromedially (solid arrow).
- B) An axial pre-contrast T1-weighted image demonstrates foci with intrinsic T1 hyperintensity (arrow).
- C) There is mild enhancement of the anteromedial infiltrative component (arrow) on an axial post-contrast T1-weighted image.
- D) On an apparent diffusion coefficient map, the enhancing portion also demonstrates restricted diffusion (white arrow). A component of the tumor crossing the midline is also noted (dashed black arrow).
- e) An axial dynamic susceptibility contrast perfusion image shows increased relative cerebral blood volume values of the solid portions, most conspicuous in the anteromedial portion (arrow), which also corresponds to the portion with restricted diffusion and mild enhancement



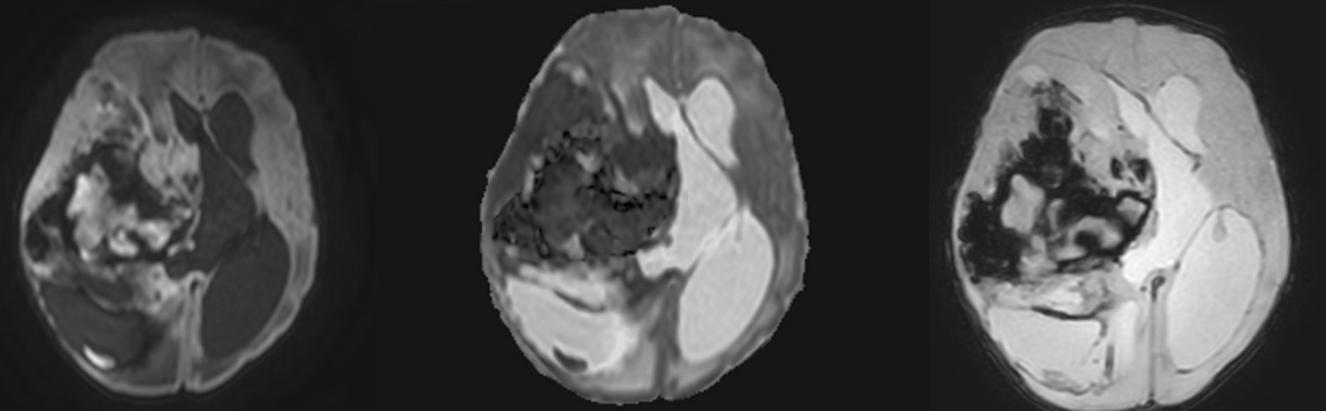
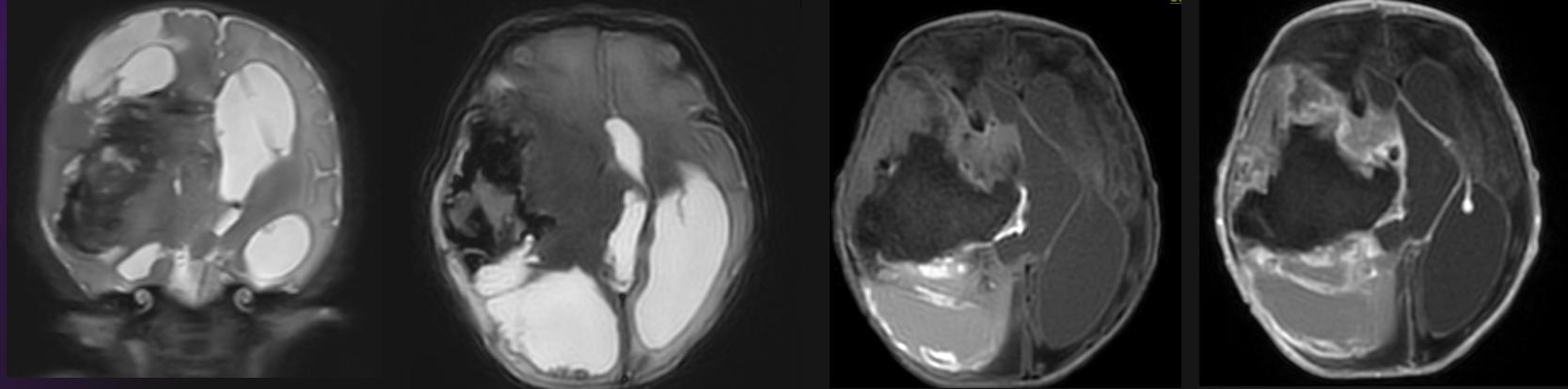
- Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype, MYCN amplified, in an 8-year-old girl.
- A) An axial T2-weighted image demonstrates a well-circumscribed, intermediate signal mass (solid arrows) with an area of central necrosis (dashed arrow).
- B) An axial diffusion-weighted image shows minimal diffusion restriction (dashed arrow) around the necrotic portion.
- C) On an axial post-contrast T1-weighted image, this portion also enhances (dotted arrow)

Infant-type hemispheric glioma (IHG)

- Receptor tyrosine kinase gene fusions of ALK, ROS1, NTRK1/2/3, or MET
- Relatively rare, occurring predominantly during the first year of life (median 2.8 months).
- Location: Almost always in the cerebral hemispheres.
- Prognosis is better than in other high-grade gliomas: depending on the specific underlying mutation, 5-year survival varies between 25% and 53.8%
- Imaging:
 - Large, heterogeneous supratentorial masses.
 - Diffusion restriction
 - Necrosis and intra-tumoral hemorrhage are frequent, and hemorrhage can cause presentation with acute changes in mental status.
 - There has been at least one case without enhancement.
 - Leptomeningeal spread can be seen during the course of disease
 - IHG vs DIG/DIA: IHG=more restricted diffusion hemorrhage, enhancement of cyst walls, bihemispheric involvement



- 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).



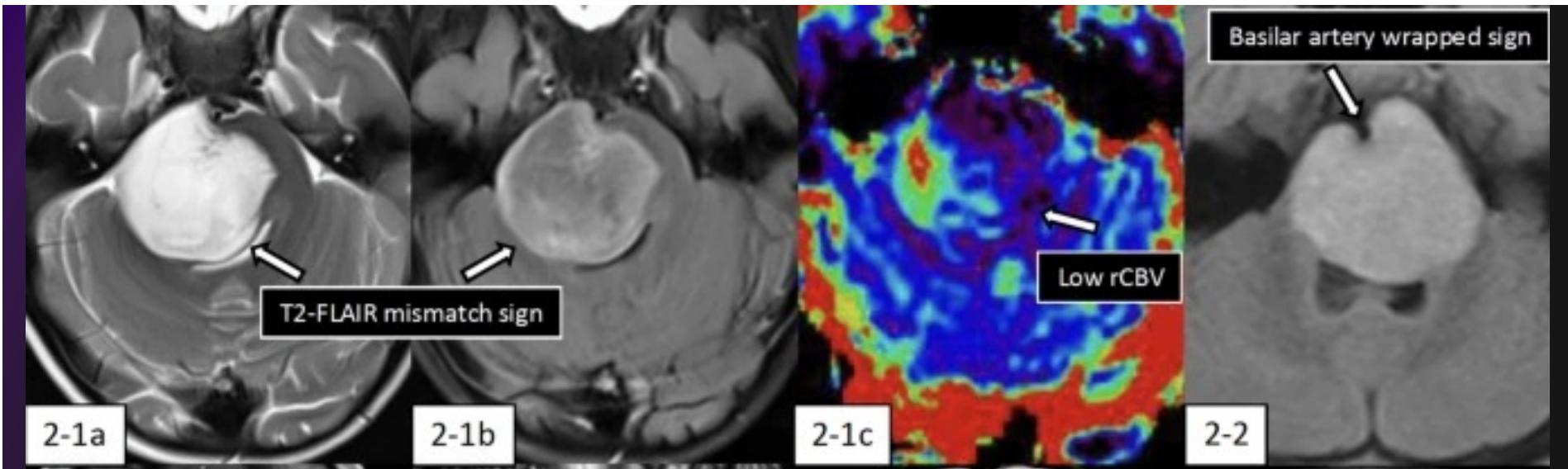
- (Left to right) Top Row: Coronal and Axial T2, T1 precontrast, T1 postcontrast. Bottom row: DWI, ADC, GRE
- Right hemisphere mass noted on 33-week ultrasound. MRI obtained shortly after birth demonstrate a large heterogeneous fronto-temporo-parietal mass with hemorrhagic, solid, and cystic/necrotic components, diffusion restriction. Areas of Intrinsic T1 hyperintensity from hemorrhage with areas of mild superimposed enhancement

Diffuse midline glioma, H3 K27-altered

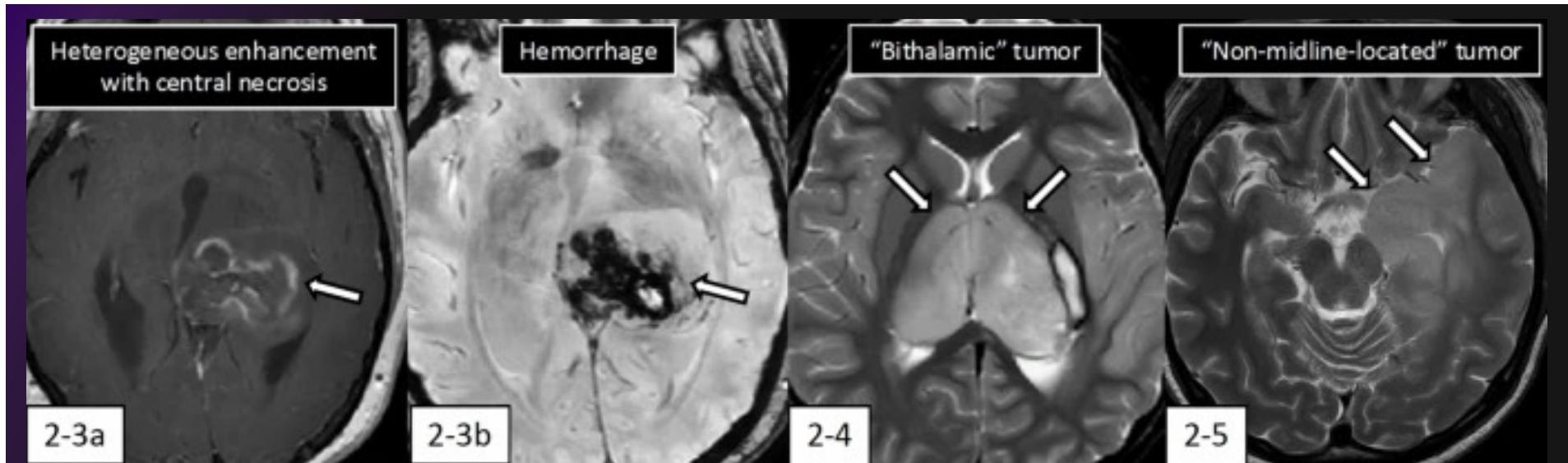
- Previously described in CNS4 as diffuse midline glioma, H3 K27-mutant.
 - Other changes now recognized in addition to H3 K27 mutations, such as EZHIP overexpression or EGFR mutation.
- Grade 4 regardless of histological features.
- Midline location is essential; the tumor typically involves the pons in children, although can involve any midline structure including thalamus or spinal cord.
- Imaging:
 - Expansile infiltrative tumor, classically centered in the pons with varying degrees of cranial or caudal extension. Growth into the prepontine cistern and engulfment of the basilar artery are common. Enhancement is absent or mild and heterogeneous
 - Generally lack restricted diffusion (although higher-grade components may have lower ADC, and commonly enhance).
 - Enhancement at baseline, increased enhancement over time and lower ADC are associated with shorter survival
 - Thalamic lesions are more likely than pontine lesions to demonstrate necrosis, moderate to marked contrast enhancement, and low ADC values. The formation of "bithalamic" lesions, involving both thalami, is occasionally observed and highly indicative of DMG-H3K27a



- Diffuse midline glioma, H3 K27-altered, in an 11-year-old boy. An axial T2-weighted image shows a solid, expansile mass (dashed arrows) encasing the basilar artery



- Diffuse midline glioma, H3 K27-altered.
- **2-1** (4 years old, girl): Pontine tumor mass shows “T2-fluid-attenuated inversion recovery (FLAIR) mismatch sign” (2-1a and 2-1b, arrows). The relative cerebral blood volume (rCBV) shows low values in most regions of the tumor (2-1c, arrow).
- **2-2** (6 years old, girl): FLAIR image shows “basilar artery wrapped sign (arrow).



- Diffuse midline glioma, H3 K27-altered.
- **2-3** (36 years old, woman): The left thalamic tumor mass shows heterogeneous enhancement with central necrosis on contrast-enhanced T1-weighted imaging (2-3a, arrow) with hemorrhage shown on susceptibility-weighted imaging (2-3b, arrow).
- **2-4** (11 years old, girl): The “bithalamic” tumor mass is observed on fat-suppressed T2-weighted imaging (arrows). This tumor harbored H3.1K27M-mutant and an EGFR A289V mutation with an allele fraction of 56%. **2-5** (25 years old, woman): “Non-midline-located” diffuse glioma with H3K27M-mutant. The tumor mass mainly involves the left temporal lobe (arrows)

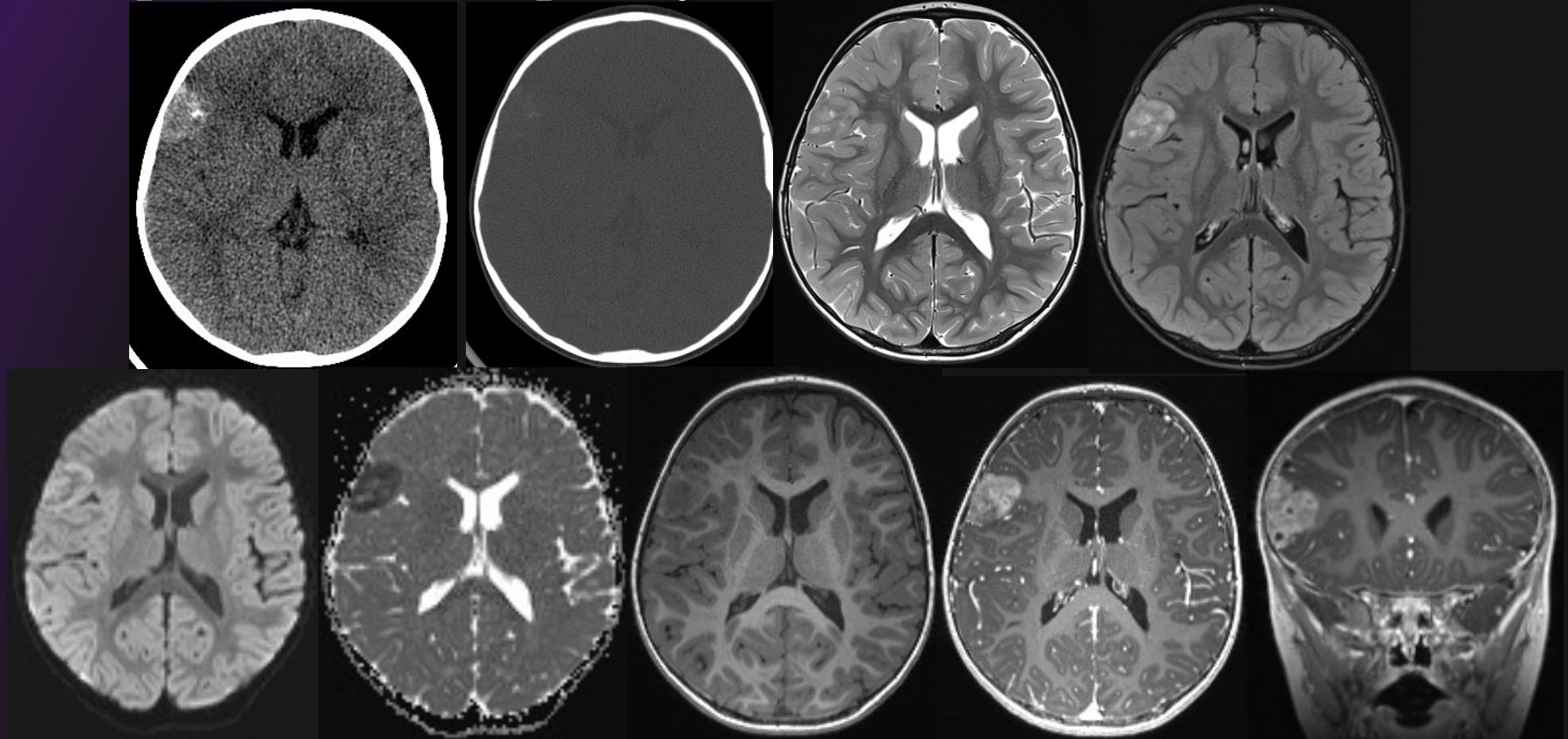
Ependymomas

- Now classified primarily on the basis of location, with subtypes based on molecular findings.
- Supratentorial:
 - ZFTA fusion-positive (ST-EPN-ZFTA)
 - YAP1 (ST-EPN-YAP1)
- Posterior fossa (PF)
 - PFA
 - PFB
- Spinal
 - MYCN
- Ependymomas typically demonstrate elevated myoinositol with some evidence of elevation of creatine, in addition to typical tumoral spectra of reduced N acetyl aspartate (NAA) and elevated choline

Supratentorial Ependymomas

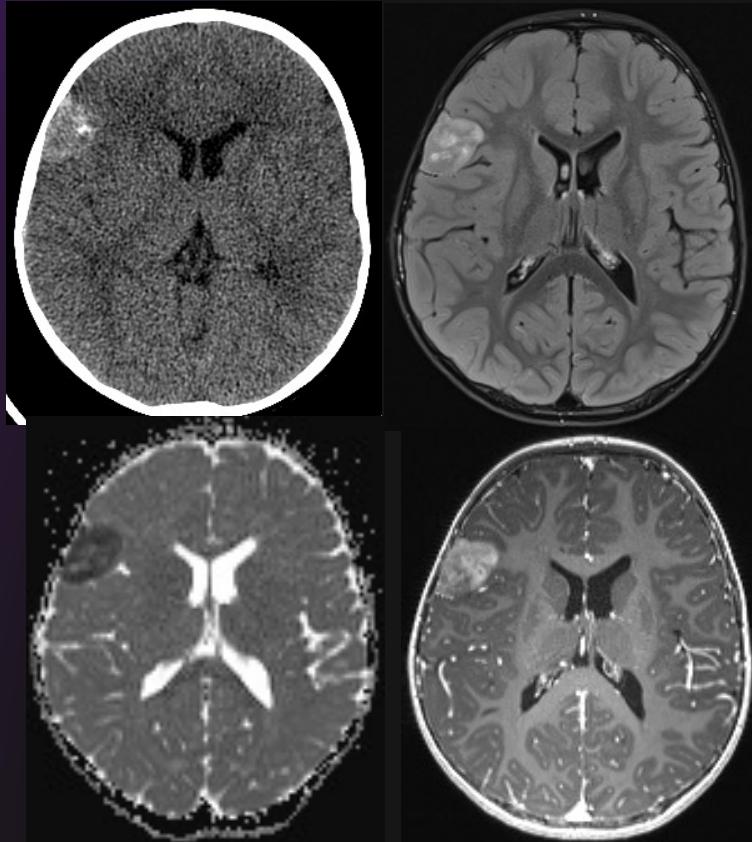
- ~30% of ependymomas, brain parenchyma>ventricular system, lobar/multilobar (frontal lobe most common)
- ZFTA fusion-positive (ST-EPN-ZFTA):
 - More common (~70% of ST-EPN)-median age 6.7-8 years.
 - Comprises higher risk patients (10-year survival rate of 50%)
 - 2 main imaging patterns:
 - More common-large, well-demarcated masses with large cystic portions and enhancement of solid component
 - The other pattern has prominent solid masses with no or small amounts of cystic contents, and demonstrates variable enhancement
 - Hemorrhage and calcifications also common, particularly centrally, with surrounding edema
 - Diffusion restriction: one case had an apparent diffusion coefficient (ADC) of $0.592 \times 10^{-3} \text{ mm}^2/\text{s}$
- YAP1 (ST-EPN-YAP1)
 - Rarer, median age 1.4 years
 - favorable prognosis (100% survival in some series)
 - Large at diagnosis, cystic and solid
 - Typically, heterogeneous enhancement of solid components is noted and hemorrhage can be present
 - The location tends to be intraventricular or paraventricular with variable peritumoral edema
 - “garlanded” appearance of peripherally enhancing, restricting components
- MR spectroscopy showing marked elevation of myoinositol may help to differentiate a supratentorial ependymoma from high grade glioma or ATRT (imaging DDx; also age to help differentiate from ATRT)

Supratentorial Ependymoma, ZFTA fusion-positive



Top Row: Axial CT (soft tissue and bone algorithm), T2 and FLAIR. Bottom Row: DWI, ADC, T1 pre, T1 C+ axial and coronal
Right inferior frontal gyrus mass, solid with foci of calcification and small cystic components, diffusion restriction and enhancement

Supratentorial Ependymoma, ZFTA fusion-positive



Site: Frontal lobe, right

Integrated diagnosis: Supratentorial ependymoma, ZFTA fusion-positive

Histopathological classification: Supratentorial ependymoma

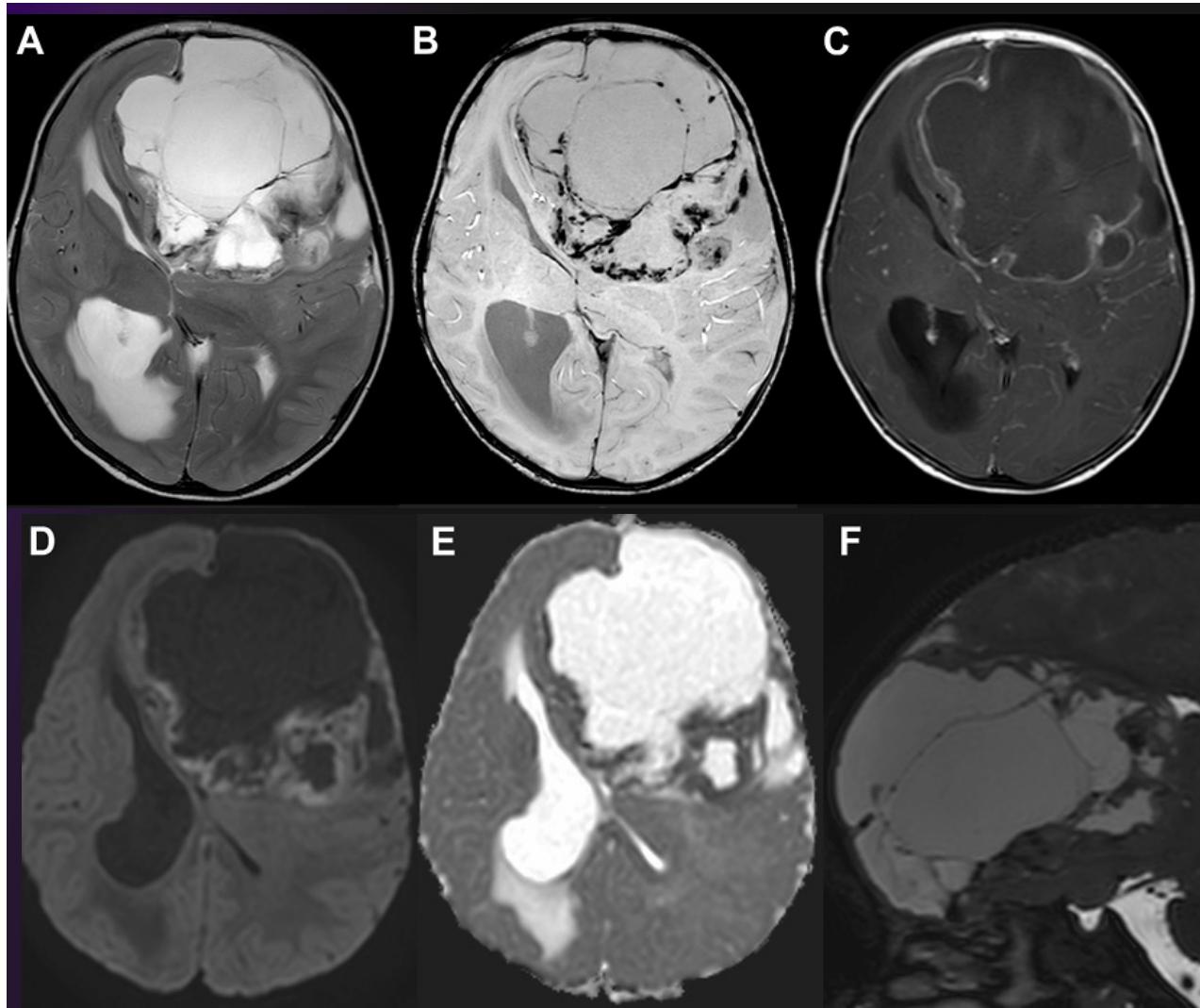
CNS WHO grade: 3

Molecular information: Present:

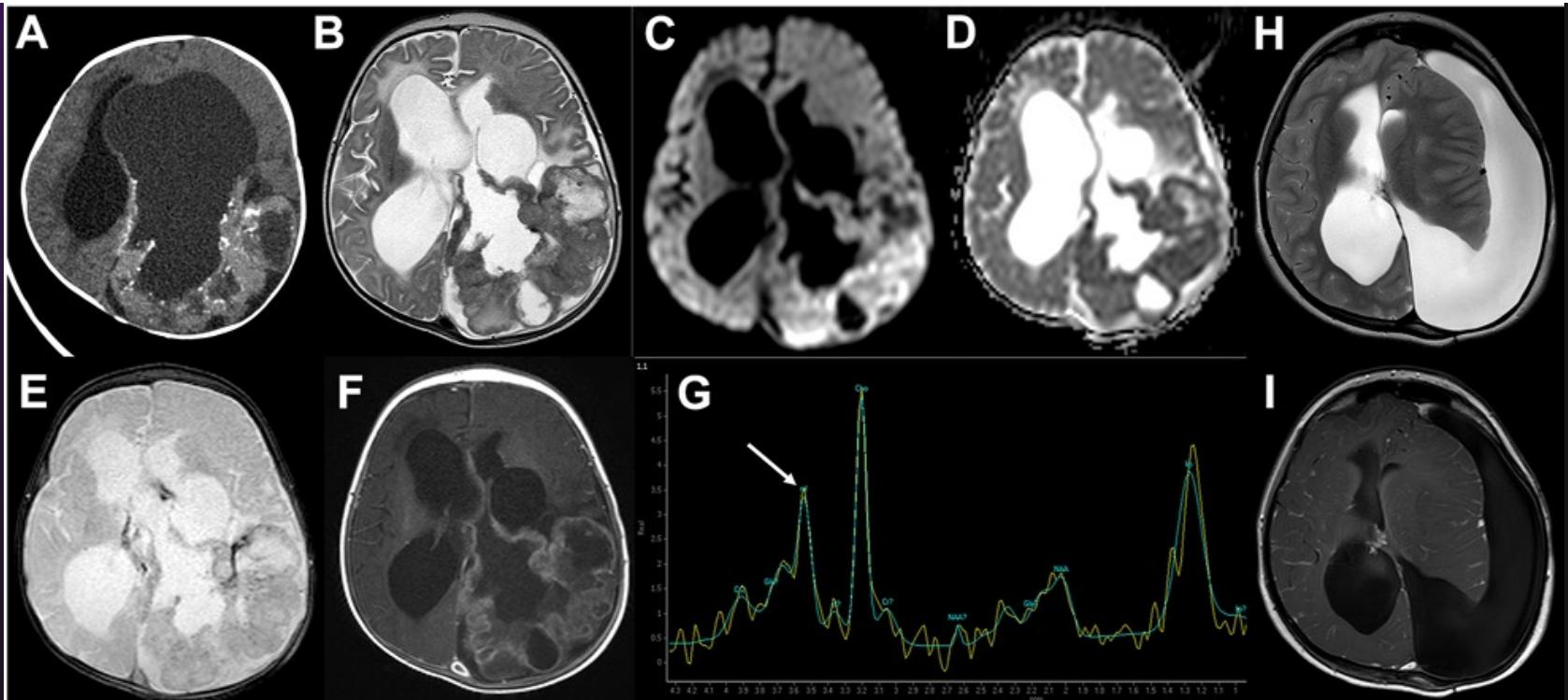
ZFTA (C11orf95)::RELA fusion (next-generation sequencing)
Chromothripsis on chromosome 11 (microarray)

Not present:

Copy number gain of chromosome 1q (microarray)



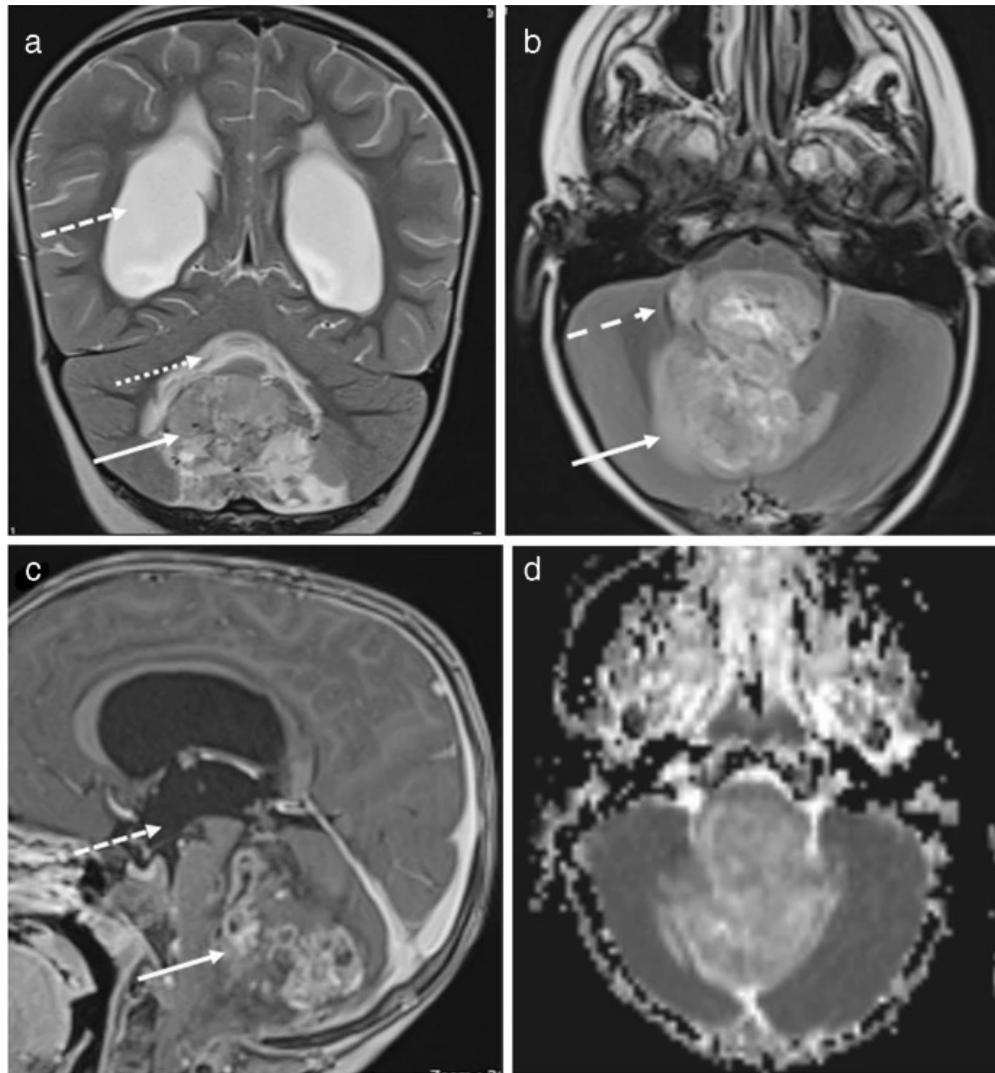
- Axial T2 (A), SWI (B), post-contrast T1 (C), DWI (D), ADC map (E), and sagittal CISS (F) of a ZFTA-fusion supratentorial ependymoma 14 month old girl presenting with developmental regression, right motor twitching and vomiting.
- The lesion is predominantly cystic, shows evidence of hemorrhage and diffusion-restriction of the solid component



- Axial CT (A), T2 (B), DWI (C), ADC (D), gradient echo (E), post-contrast T1 (F) and short TE MR spectroscopy (G) in a 3 month old female infant with rapid increase in head circumference showing a left parieto-occipital **YAP1-fusion** supratentorial ependymoma. There is multifocal calcification (A, E). The magnetic resonance spectroscopy (MRS) shows significant myoinositol elevation (arrow, G).
- Axial T2 (H) and post-contrast T1 (I) 14 years later showing post-treatment appearances in this long-term survivor. The peripherally enhancing, restricting material is said to have a “garlanded” appearance.

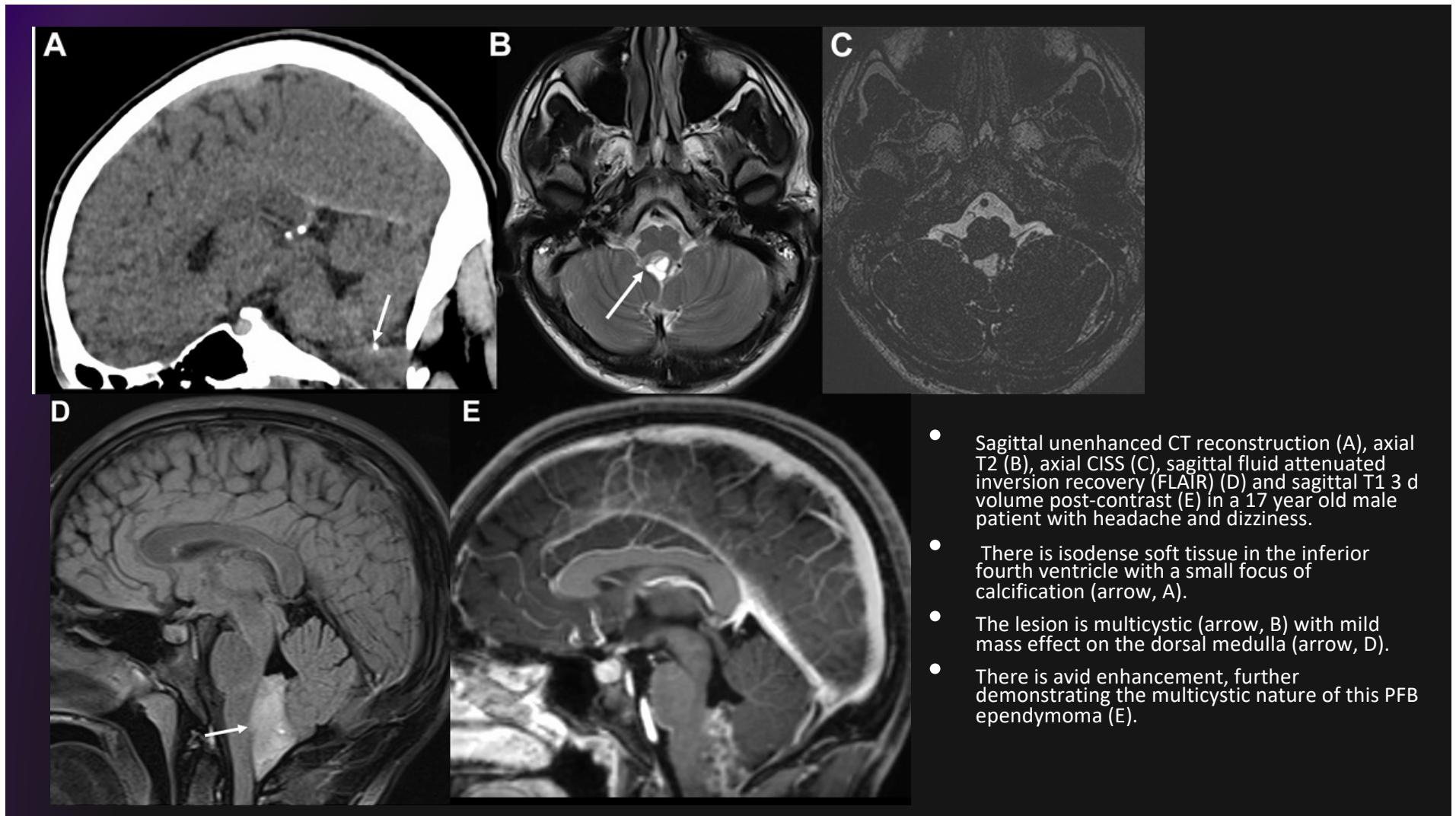
Posterior fossa ependymoma

- PFA: younger, median age at presentation of 2.4–4 years.
 - Children younger than 5 years of age almost exclusively have PFA.
 - However, almost half of teenagers with posterior fossa ependymoma will turn out to have PFB.
 - Worse prognosis: higher incidence of recurrence and mortality
 - Arise laterally, involving foramina of Luschka and Magendie to fill the cerebellomedullary cisterns and cisterna magna.
 - Heterogeneous enhancement, calcification.
 - Propensity of subarachnoid space extension and potential metastasis necessitates evaluation of the entire spinal and ventricular system both at diagnosis and follow-up.
- PFB: older children, adolescents, and adults and have a much better prognosis with much lower rates of metastasis and recurrence
 - Midline, smaller lesions, centered in the midline of the fourth ventricle, with a greater propensity for cyst formation and more extensive contrast enhancement
- ADC higher than medulloblastomas



Posterior fossa ependymoma, group A, in a 2-year-old girl.

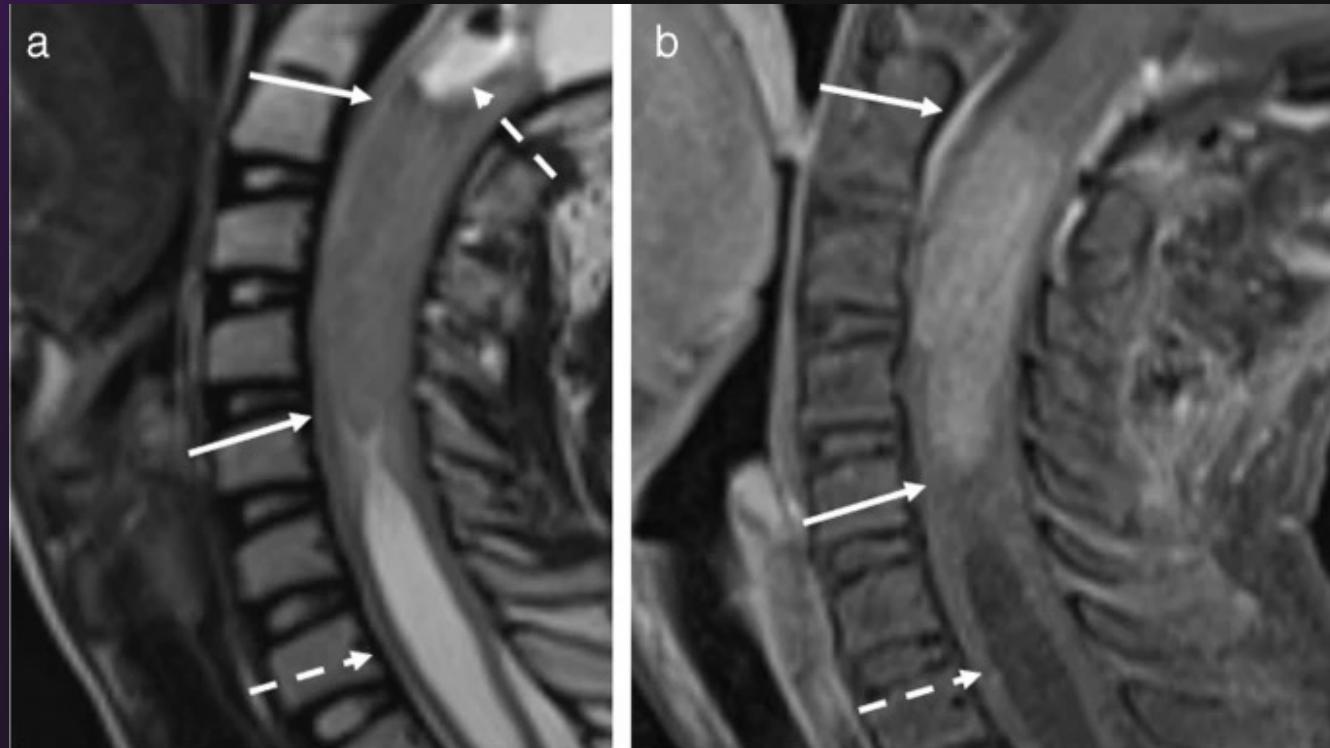
- A) A coronal T2-weighted image with an intermediate T2 signal mass in the fourth ventricle (solid arrow) with mild peritumoral edema (dotted arrow) and associated hydrocephalus (dashed line).
- B) An axial post-contrast fluid-attenuated inversion recovery (FLAIR) image shows the same mass (solid arrow). Note the lateral extension into the right foramen of Magendie (dashed arrow).
- C) A sagittal post-contrast T1-weighted image shows heterogeneous enhancement (solid arrow). Third ventriculomegaly is also noted (dashed arrow).
- D) On an axial apparent diffusion coefficient (ADC) map, the lesion does not demonstrate restricted diffusion, and the lowest ADC value measured in the tumor was approximately $1010 \times 10^{-6} \text{ mm}^2/\text{s}$ (not shown)



Spinal Ependymoma

- Two subtypes: ‘spinal ependymoma’, which lacks *MYCN* alterations and typically has *NF2* alterations, and ‘spinal ependymoma, *MYCN*-amplified’, which has *MYCN* amplification.
- “Spinal ependymoma”:
 - Represents 20.6% of pediatric primary spinal tumors and typically presents as an enhancing intramedullary mass
 - While prognosis is favorable with 90–100% survival in 5–10 years, late relapses are frequent
- Spinal ependymoma, *MYCN*-amplified:
 - Median age at diagnosis of 31 years; however, cases in children as young as 12 years old have been reported.
 - The outcome is worse than spinal ependymoma.
 - They can be intramedullary or extramedullary intradural, mostly in the cervical or thoracic cord.
 - Leptomeningeal dissemination is common, thus brain MRI should be acquired at diagnosis and follow-up

Spinal ependymoma in a 6-year-old boy

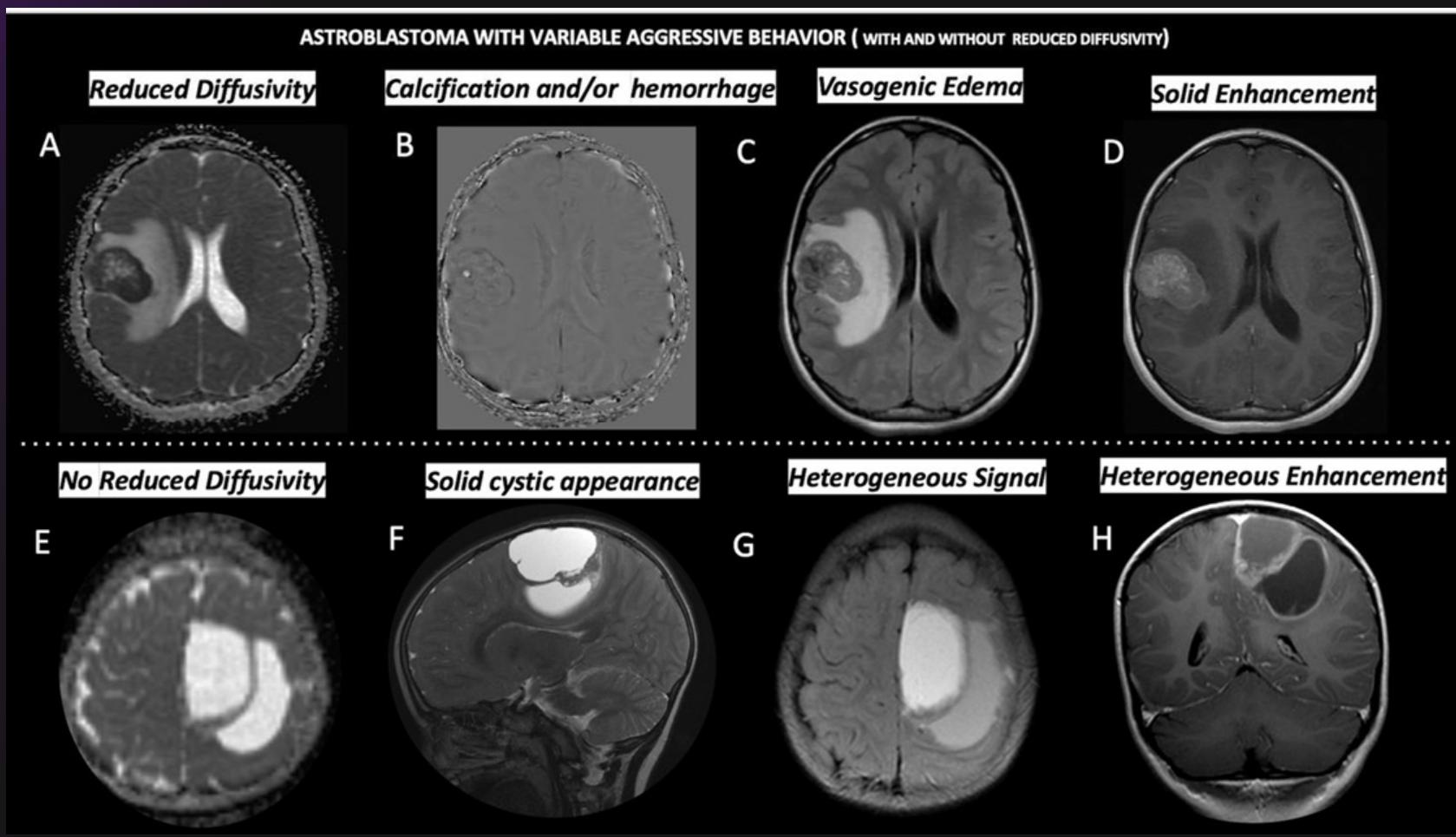


- **A)** A sagittal T2-weighted image demonstrates an expansile, intramedullary mass extending from C2 to C5 (*solid arrows*) with syrinx cranial and caudal to the mass (*dashed arrows*).
- **B)** A sagittal post-contrast T1-weighted image demonstrates enhancement of the entire mass (*solid arrows*). Note the syrinx caudal to the mass (*dashed arrow*), which is not specific to spinal ependymomas

Circumscribed astrocytic glioma: Astroblastoma, MN1-altered (AB)

- Rare, 0.45-2.8 % of all gliomas with a peak incidence in the second and third decades.
- Can range from indolent (low-grade) to aggressive (high-grade) with no established WHO grade.
- Imaging:
 - 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 $\times 10^{-6}$ mm²/s).
 - DDx is ST ependymomas

Astroblastoma, MN1-altered, in two different patients



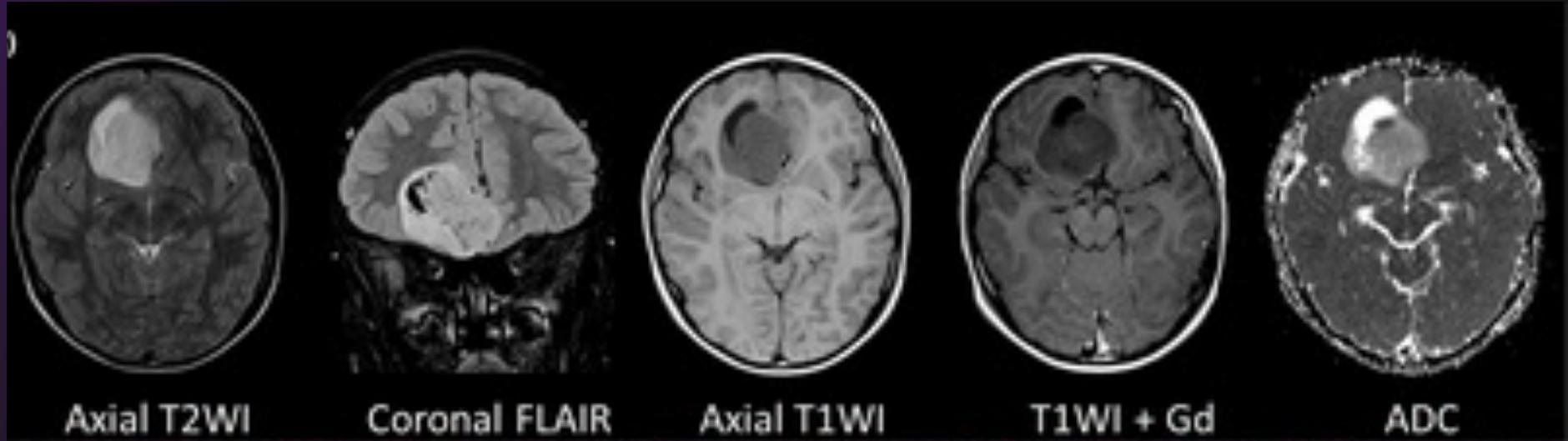
Glioneuronal and Neuronal Tumors

- **Diffuse glioneuronal tumor with oligodendrogloma-like features and nuclear clusters**
- **Myxoid glioneuronal tumor**
- **Multinodular and vacuolating neuronal tumor**

Diffuse glioneuronal tumor with oligodendrogloma-like features and nuclear clusters (Provisional Type)

- Extremely rare, predominantly occur in children with a median age of diagnosis at 9 years in the first report, although an additional series reported all 3 patients between 11 and 12 years old
- Tend to involve the cortex and subcortical white matter with a predilection to the frontal and temporal lobes.
- Sharply demarcated but can cross the midline.
- Hyperintense relative to the cortex on T2 with various inhomogeneous diffusivity
- Minimal enhancement, limited mass effect, and areas of cystic changes and calcifications.

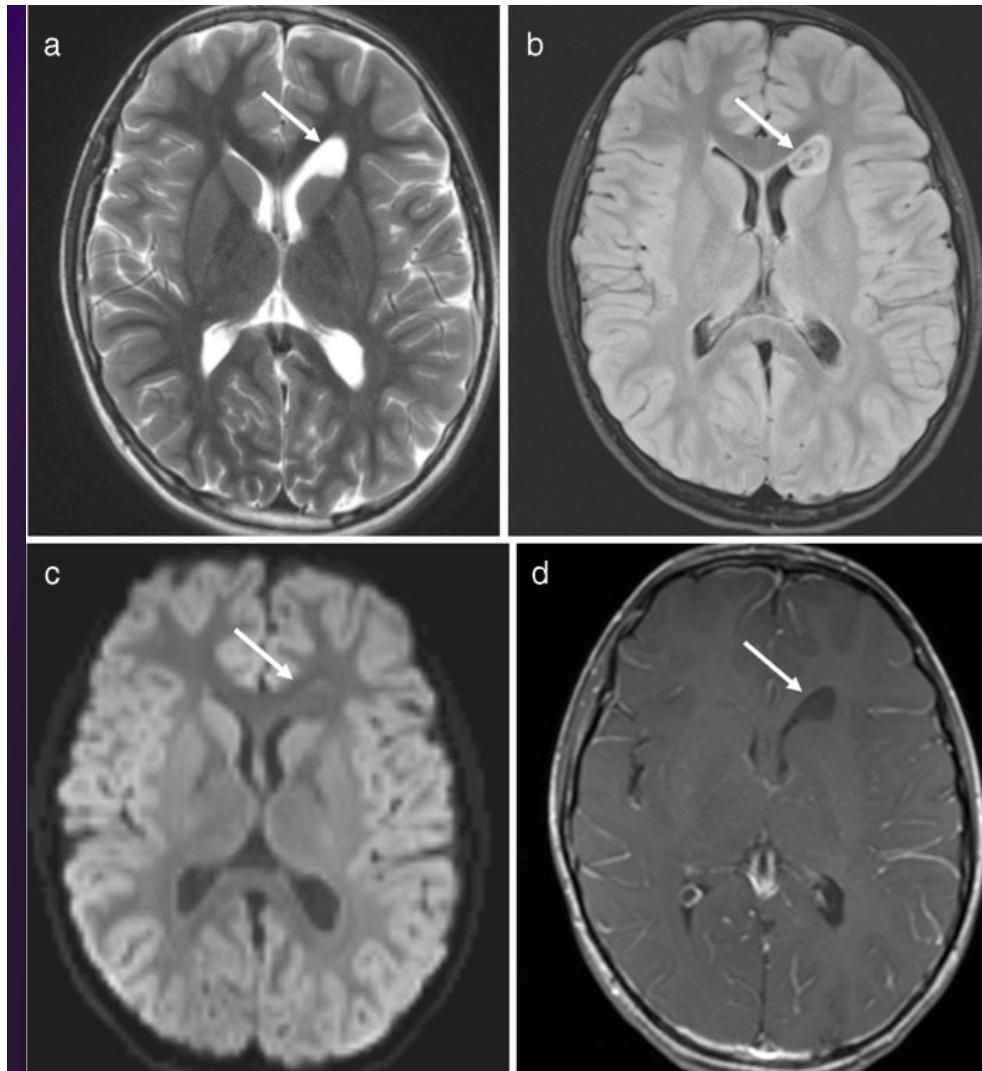
Diffuse glioneuronal tumor with oligodendrogloma-like features and nuclear clusters (Provisional Type)



- 11-year-old boy presenting with a mass in the right medial frontal lobe, heterogeneously hyperintense on T2- and FLAIR-weighted sequences with some internal cysts, poorly enhancing with contrast, and rather heterogeneous on diffusion, with a small focus of low ADC values. The CT scan (not shown) revealed calcification in the wall of the cystic area.

Myxoid glioneuronal tumor

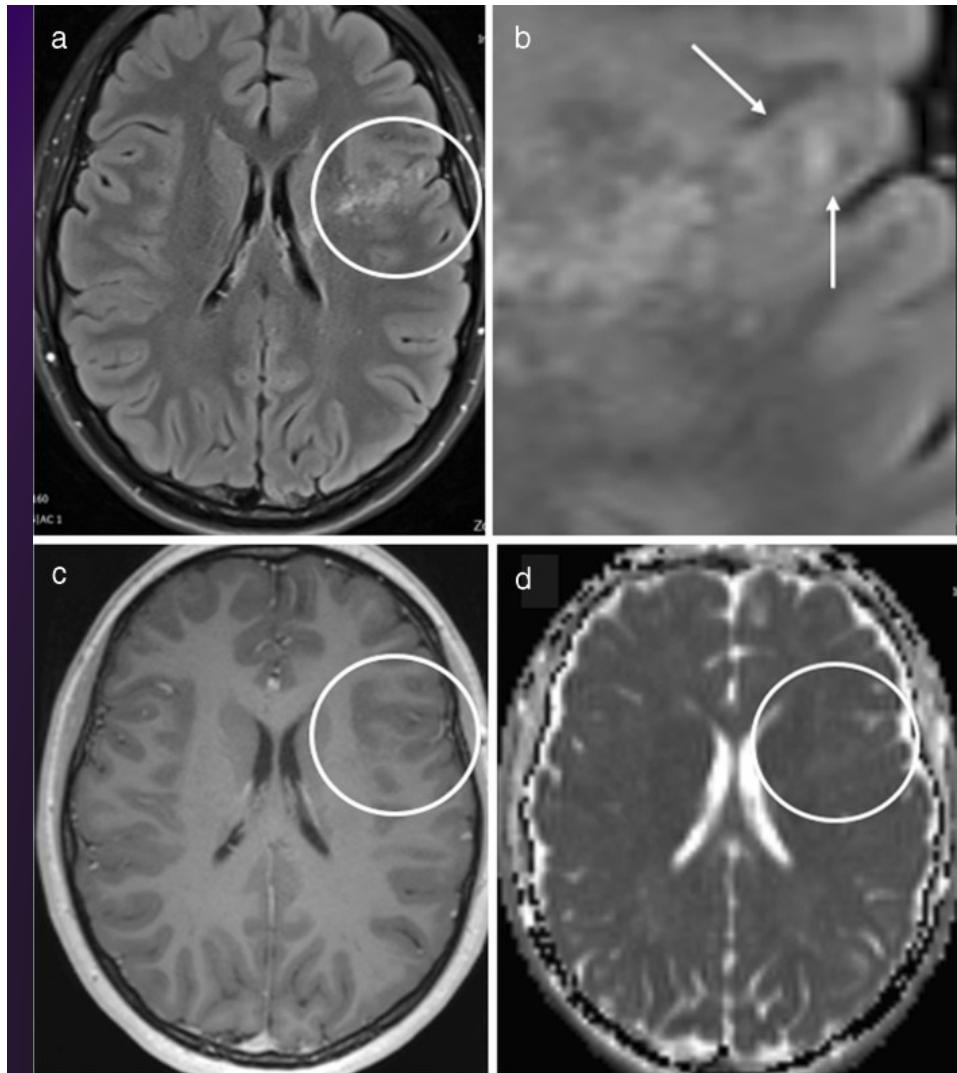
- Benign WHO grade 1
- The defining feature is a *PDGFRA* p.K385 mutation. Abnormalities in *FGFR1*, *IDH1/2*, *BRAF*, *MYB*, and *MYBL1* are absent.
- Median patient age was 23.6 years (range, 6–65 years) with no sex predilection.
- Propensity for the septum pellucidum.
- A typical mass is well-defined, lobulated, T1-hypointense, T2-hyperintense, nonenhancing, non-diffusion-restricting, and without surrounding edema.
- T2-FLAIR shows relative hypointensity centrally and hyperintensity peripherally (mismatch).
- No elevated CBF.
- Larger lesions can appear L-shaped and have mass effect
- Previously called dysembryoplastic neuroepithelial tumor-like neoplasm of the septum pellucidum and intraventricular dysembryoplastic neuroepithelial tumor (DNET)



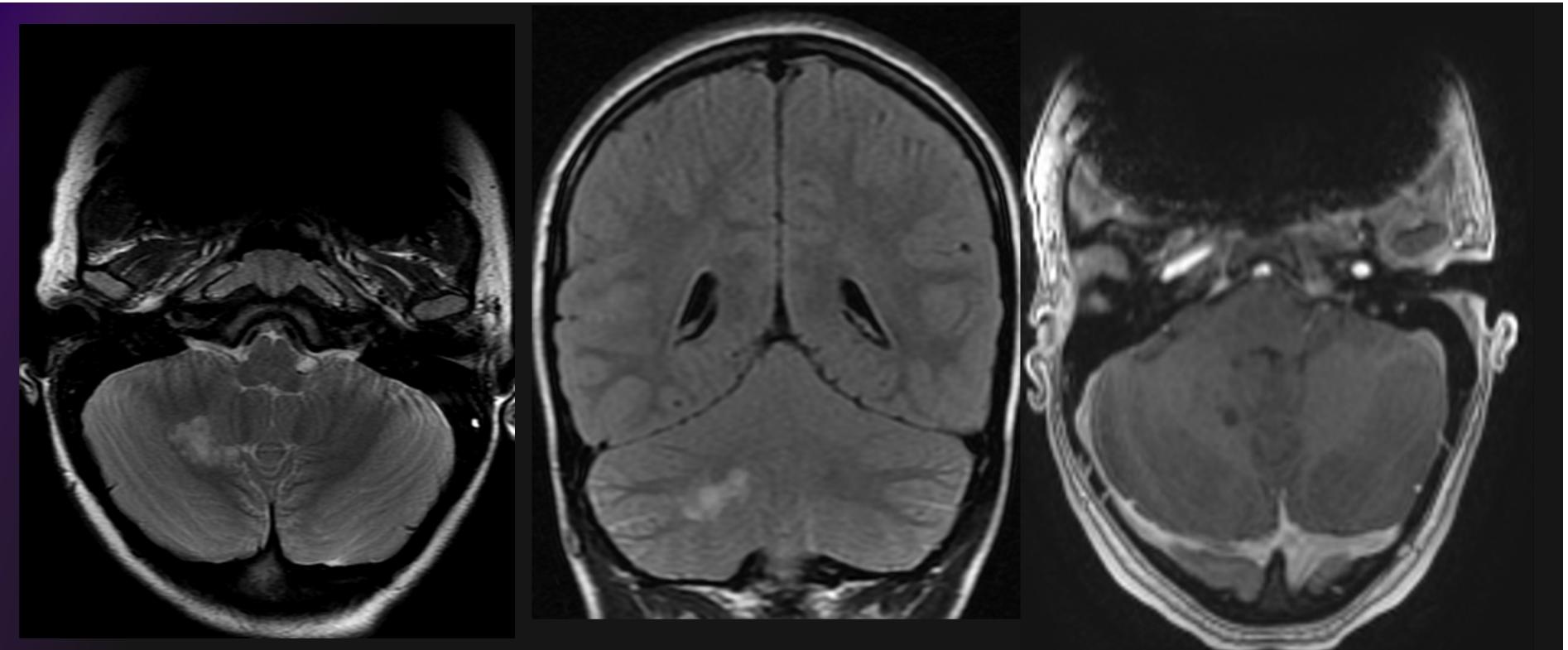
- Myxoid glioneuronal tumor in a 22-year-old woman.
- **A)** An axial T2-weighted image demonstrates a hyperintense lesion in the left frontal horn (*arrow*), which cannot be well differentiated from adjacent cerebrospinal fluid.
- **B)** An axial fluid-attenuated inversion recovery (FLAIR) image clearly demonstrates the mass (*arrow*), which has high FLAIR signal and a heterogeneous appearance.
- **C)** The lesion (*arrow*) does not have restricted diffusion on an axial diffusion-weighted image.
- **D)** No enhancement is noted in the lesion (*arrow*) on an axial post-contrast T1-weighted image

Multinodular and vacuolating neuronal tumor

- May be incidental or present with seizures (inherent selection bias), reported between 6 to 67 years of age.
- Characteristic appearance as a cluster of variably sized T2/FLAIR hyperintense nodules located in the subcortical ribbon (no cortical involvement, differentiating from DNET or cortical dysplasia)
- Follows the gyral contour without significant mass effect and no enhancement
- Indolent course. It is suggested these lesions, when exhibiting typical imaging characteristics, can be followed without biopsy



- Presumed multinodular and vacuolating neuronal tumor in a 14-year-old girl presenting with worsening headaches.
- **A)** An axial fluid-attenuated inversion recovery (FLAIR) image demonstrates a cluster of small, FLAIR high signal nodules in the subcortical and deep white matter (*circle*).
- **B)** On the zoomed axial FLAIR image, note the overlying cortex (*arrows*) is not involved.
- **C)** There is no contrast enhancement on an axial post-contrast T1-weighted image (*circle*).
- **D)** No diffusion restriction is seen on an axial apparent diffusion coefficient map (*circle*).
- This lesion was not biopsied given the imaging findings and absence of symptoms (the patient's headaches were presumed unrelated to this incidental finding)



Right cerebellar presumed MVNT

Embryonal tumors

- **Cribriform neuroepithelial tumor (CRINET), Provisional Type**
- **CNS Neuroblastoma, FOXR2-Activated**
- **CNS Tumor with *BCOR* Internal Tandem Duplication**

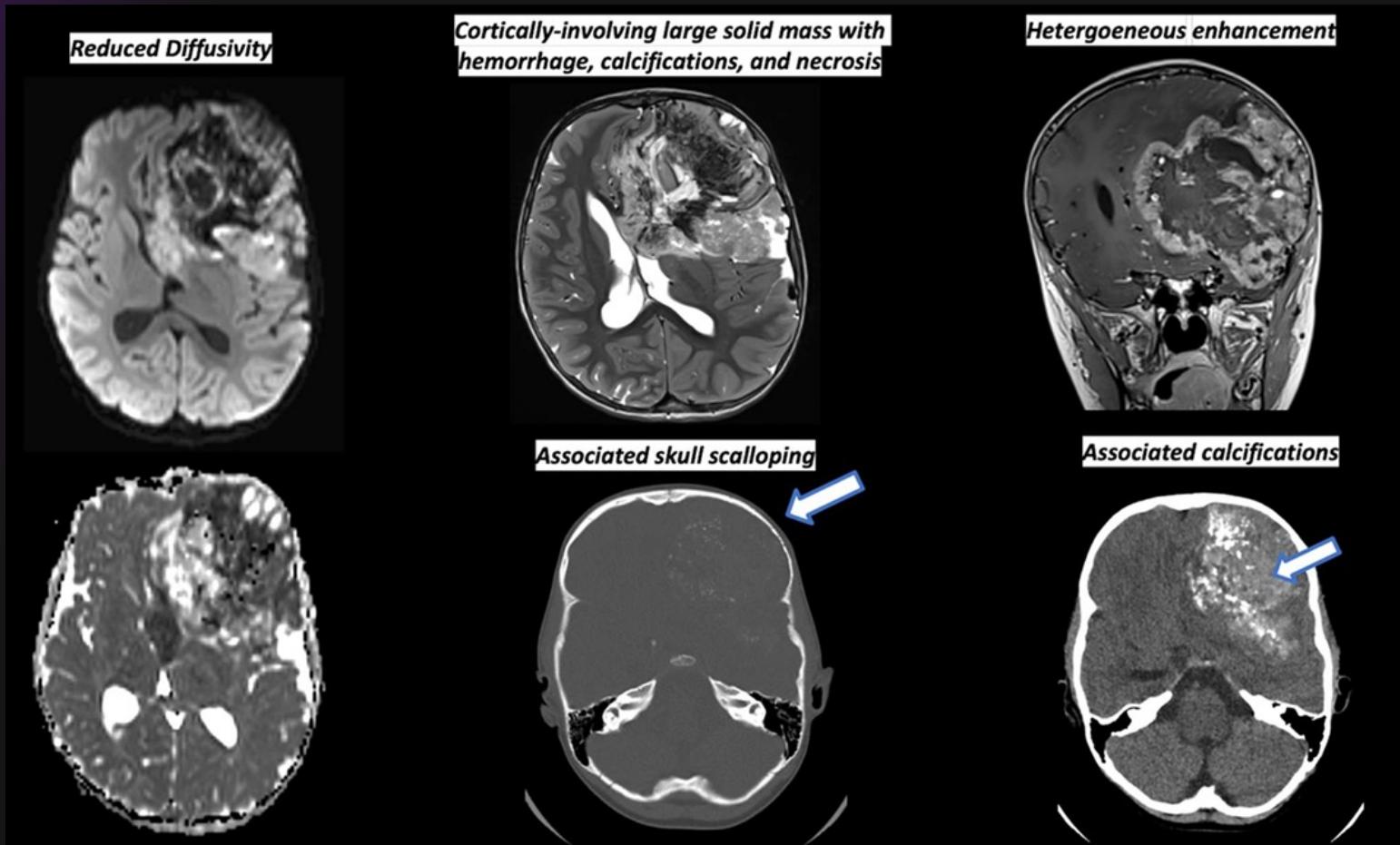
Cribriform neuroepithelial tumor (CRINET), Provisional Type

- Benign tumor that has not yet been assigned a WHO grade. It is defined by a large, heterozygous deletion in *SMARCB1*, which is also seen in atypical teratoid/rhabdoid tumor (AT/RT).
- Essentially all reported cases are in young patients, ranging from 7 months to 11 years of age with a median age at diagnosis of 20 months.
- Relatively good response to treatment
 - Among reported cases, a considerable number have survived beyond 5 years, with a mean overall survival of 125 months-has been suggested that patients diagnosed with AT/RT in the past but had an uncharacteristically long survival could have actually had CRINET
- Intraventricular, mostly third and fourth ventricles, lesser extent near the lateral ventricles
- Aggressive appearance on MRI, with heterogeneous enhancement and complex solid-cystic structure
- One case that was retrospectively re-diagnosed CRINET was partially calcified on imaging
- DDx on imaging includes choroid plexus neoplasms, germ cell tumors and AT/RT

CNS Neuroblastoma, *FOXR2*-Activated

- Rare, highly malignant embryonal tumor, CNS WHO grade 4.
- *FOXR2* overexpression-promotes MYC-related transcriptional activities
- First decade (mean age=5 years).
- Large ST masses with hyperdense solid components and calcification along their inner rim on CT, with thinning of the inner table of the skull have been reported.
- 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
- Low mean ADC values are expected for all these tumors.
- 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.

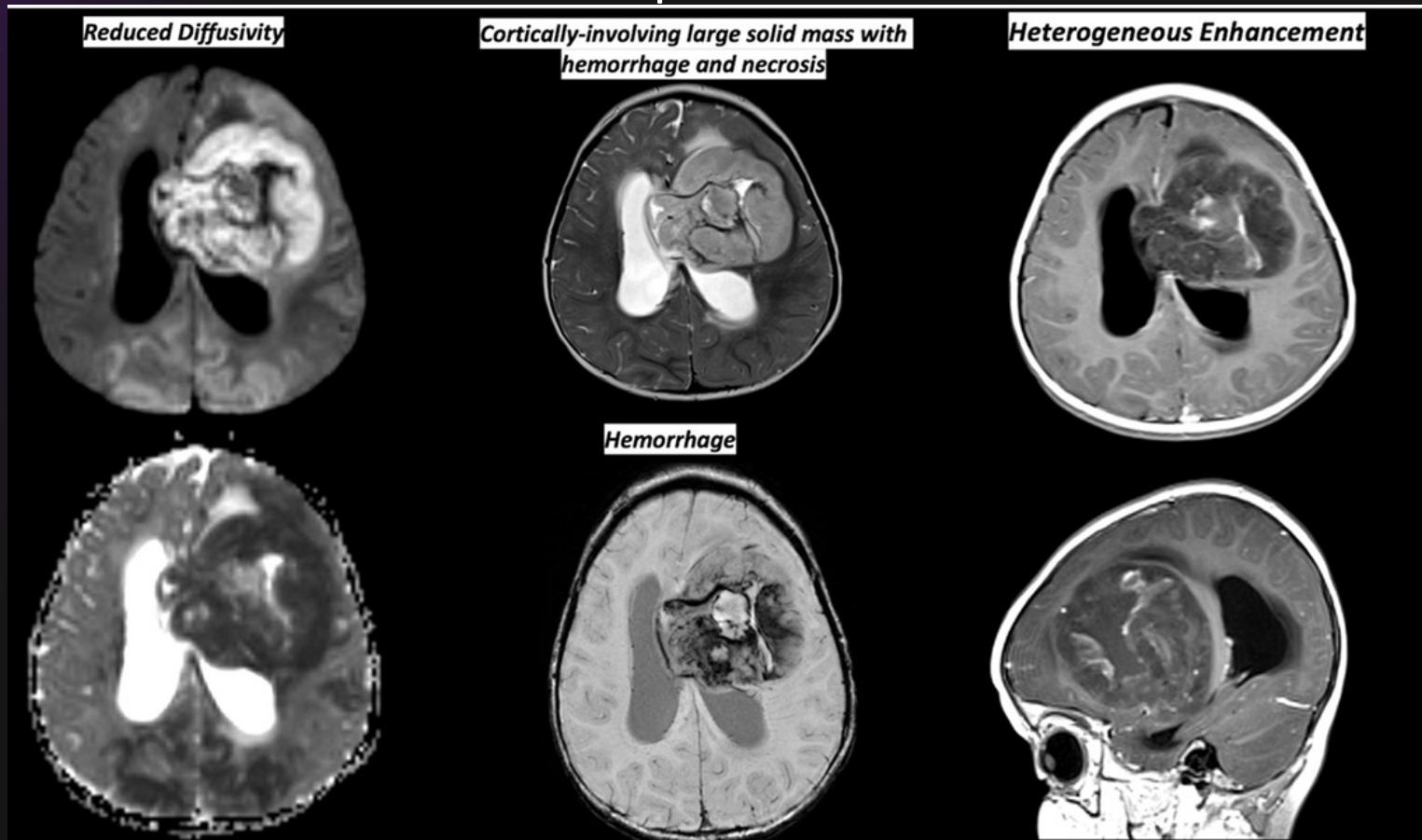
5-year-old Male with FOXR2-activated neuroblastoma.



CNS tumor with BCOR internal tandem duplication.

- Rare, CNS WHO grade 4, aggressive
- Specific genetic alteration (a somatic ITD in exon 15 of BCOR)
- Early childhood (median 3.5 years).
- Equally distributed among supra and infratentorial compartments.
- 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)
- Variable heterogeneity and poor contrast enhancement with central areas of necrosis and blood products along with calcifications, large intratumoral central veins

1-year-old Female with CNS tumor with BCOR internal tandem duplication.

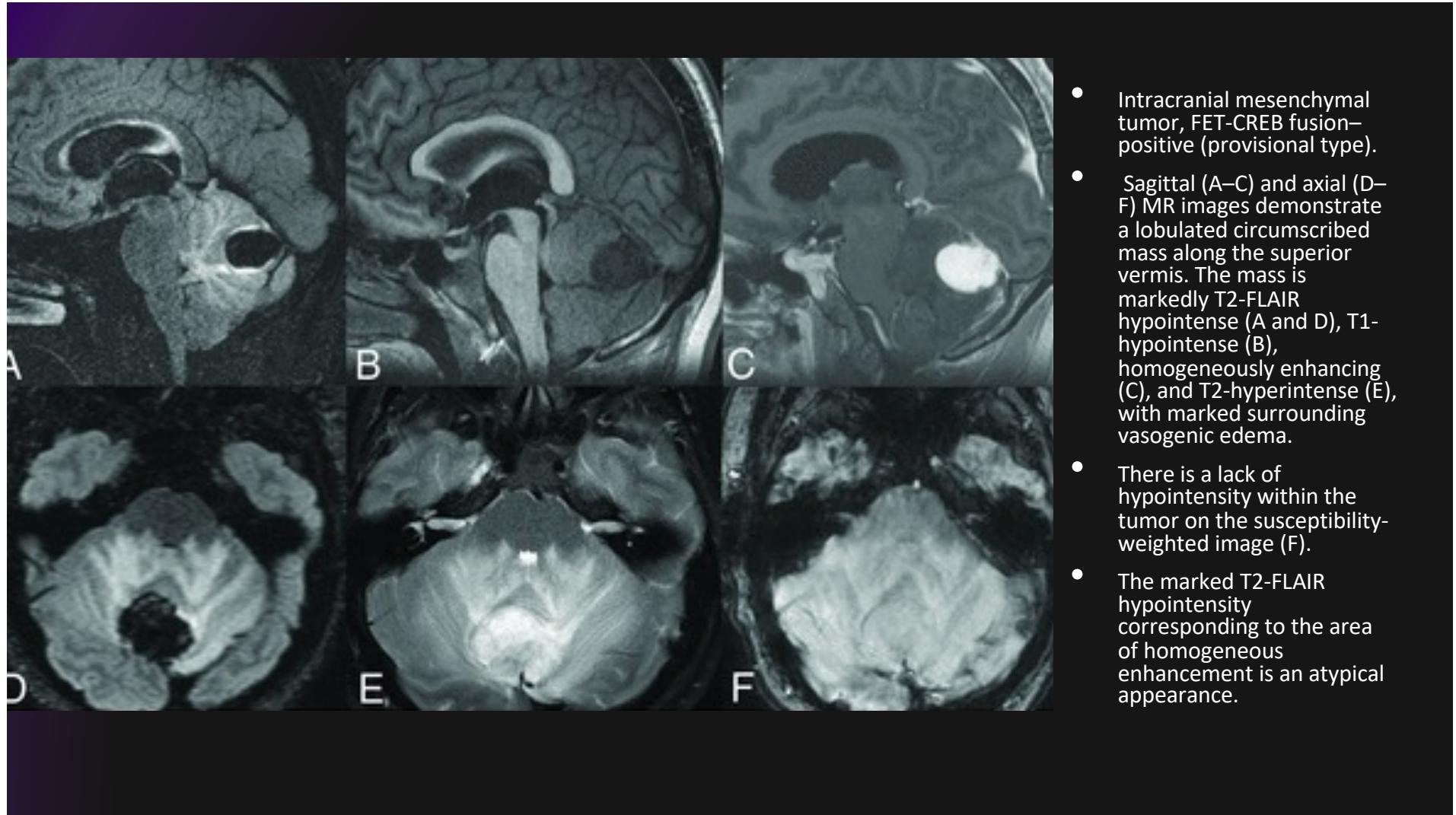


Mesenchymal Tumors

- **Intracranial Mesenchymal Tumor, FET-CREB Fusion-Positive (Provisional Type)**
- **Primary Intracranial Sarcoma, *DICER1*-Mutant**
- ***CIC*-Rearranged Sarcoma**

Intracranial Mesenchymal Tumor, FET-CREB Fusion-Positive (Provisional Type)

- Group of rare mesenchymal CNS tumors without an assigned WHO grade
- In-frame genetic fusion of a FET RNA-binding protein (EWSR1 or FUS) to a CREB transcription factor (ATF1, CREB1, or CREM).
- Median age is 17 years (range, 4–70 years) with a female predominance (male/female ratio, 1:2.2).
- Location: typically extra-axial, most commonly along the cerebral convexities but can be intraventricular or infratentorial. A dural tail and calvarial involvement may be present.
- Well-circumscribed, lobulated, and cystic and solid with T2 and T2-FLAIR hyperintensity and enhancement.
- Internal blood products may be present. Extensive adjacent vasogenic edema is common



- Intracranial mesenchymal tumor, FET-CREB fusion-positive (provisional type).
- Sagittal (A–C) and axial (D–F) MR images demonstrate a lobulated circumscribed mass along the superior vermis. The mass is markedly T2-FLAIR hypointense (A and D), T1-hypointense (B), homogeneously enhancing (C), and T2-hyperintense (E), with marked surrounding vasogenic edema.
- There is a lack of hypointensity within the tumor on the susceptibility-weighted image (F).
- The marked T2-FLAIR hypointensity corresponding to the area of homogeneous enhancement is an atypical appearance.

CIC-Rearranged Sarcoma

- Highly aggressive WHO grade 4 round cell mesenchymal neoplasm that is one of the most common and best characterized subgroups of “Ewing-like sarcomas” and is predominantly extraskeletal
- *CIC* rearrangements with multiple fusion partners identified (*DUX4*, *FOXO4*, *LEUTX*, *NUTM1*, *NUTM2A*). *CIC-NUTM1* fusion pair-greater predilection for the CNS.
- Data are limited for *CIC*-rearranged sarcoma of the CNS, but cases have been reported in both pediatric and adult patients.
- Location is anywhere along the neuroaxis.
- A typical tumor is extra-axial, solid, variably lobulated; T2 iso- to hyperintense; and homogeneously or heterogeneously enhancing Peritumoral edema can be present

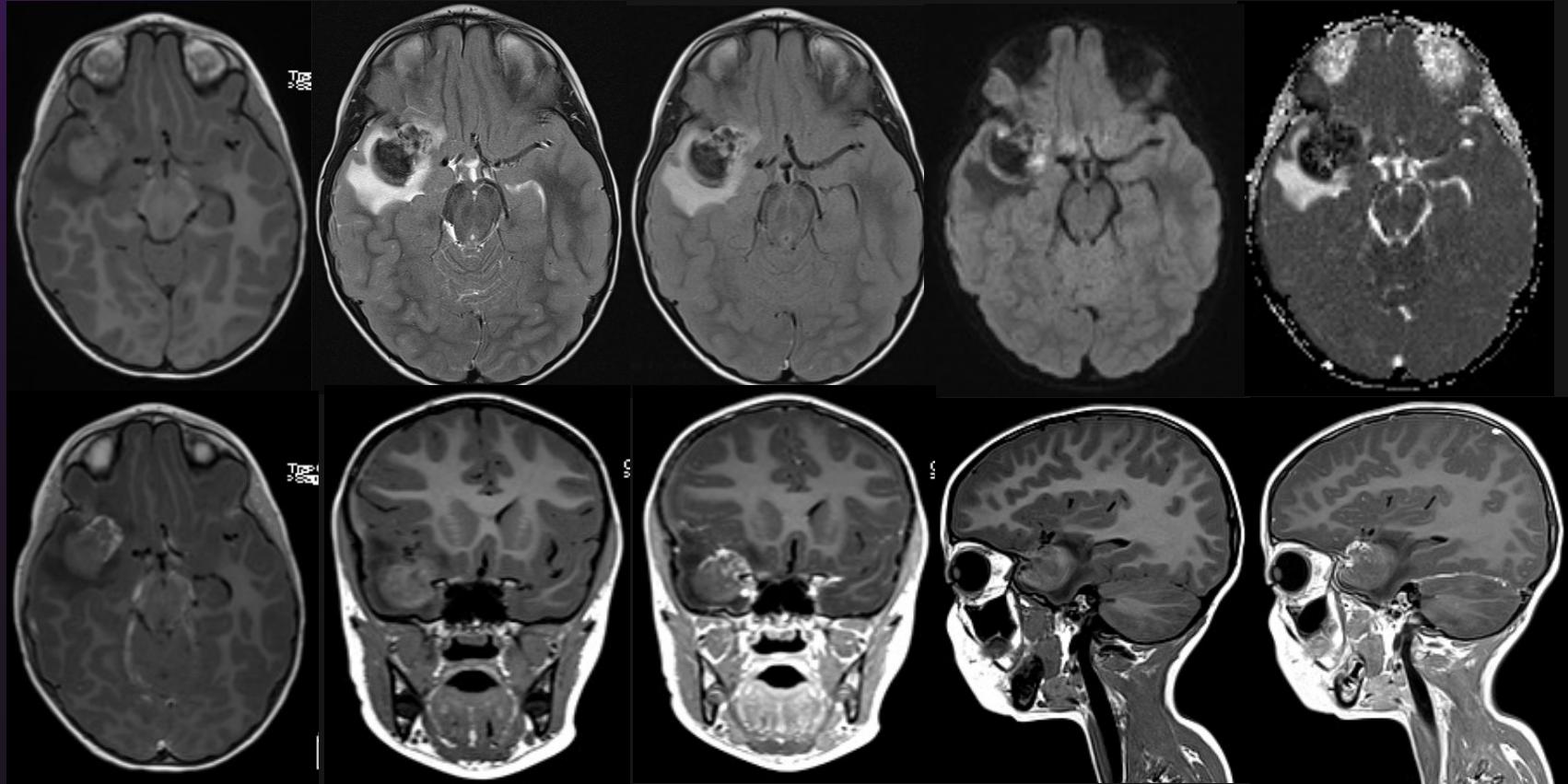


- *CIC*-rearranged sarcoma. MR images reveal a small well-circumscribed peridural mass in the midthoracic region (*arrows*).
- The mass is T2-hyperintense (A), T1-isointense (B), and avidly enhances (C–E).
- The tumor extends through the left neural foramen into the paraspinal space and also exerts moderate mass effect on the cord, displacing it to the right (D and E).

Primary Intracranial Sarcoma, *DICER1*-Mutant

- Highly malignant tumor, associated with familial DICER1 syndrome and occasionally neurofibromatosis type. A specific WHO grade has not yet been assigned.
- Median age is 6.0 years (range, 2.0–17.5 years) without a sex predilection.
- Presumed to arise from mesenchymal progenitor cells located within the meninges or perivascular spaces and thus can present as intra-axial or extra-axial masses.
- Intra-axial masses tend to be peripheral and within the cerebral hemispheres.
- The typical appearance is hyperdense, T2 iso- to hypointense, diffusion-restricting, and enhancing, with intratumoral hemorrhage and peritumoral edema

Primary Intracranial Sarcoma, DICER1 mutation



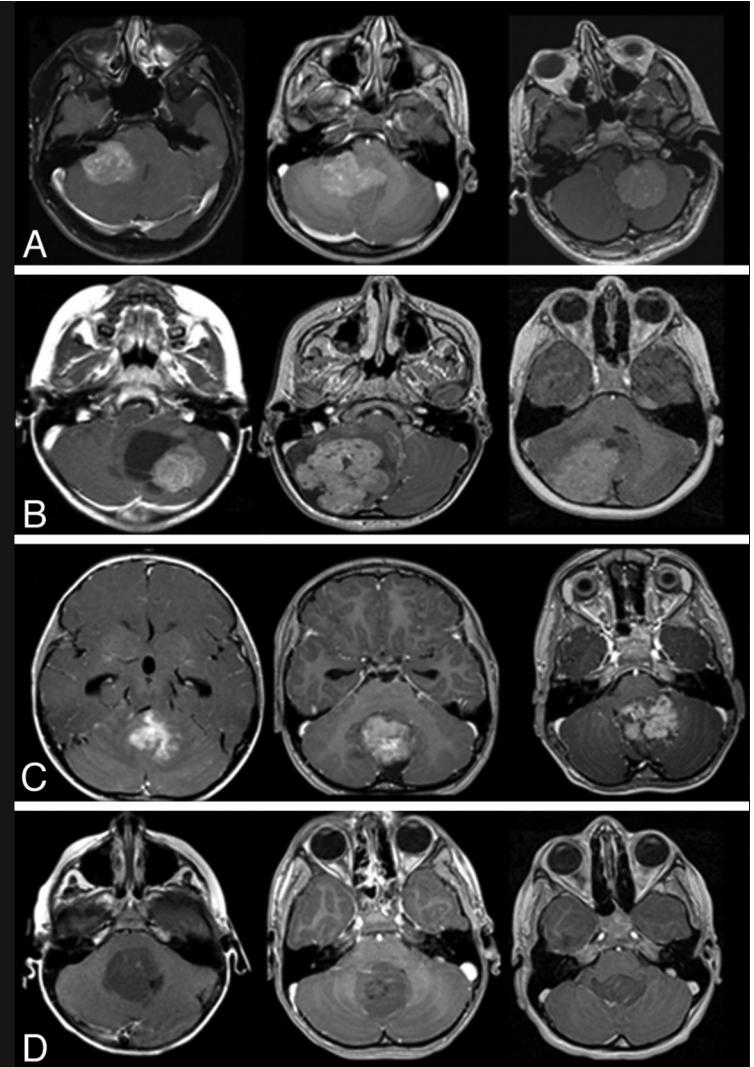
Top Row: Axial T1 pre, T2, FLAIR, DWI, ADC. Bottom: Axial T1 C+, Coronal T1 pre, Coronal T1 C+, Sag T1 pre, Sag T1 C+
Right anterior temporal lobe heterogeneous T1 hyperintense, T2 hypointense with regions of restricted diffusion, peripheral enhancement, surrounding edema

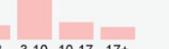
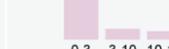
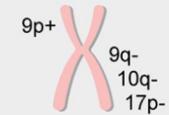
Medulloblastomas

- 4 principal subgroups were initially established: WNT-activated, sonic hedgehog (SHH)-activated, group 3, and group 4.
- New subgroups have emerged at a more granular level below the 4 principal molecular groups: 4 subgroups of SHH and 8 subgroups of non-WNT/non-SHH medulloblastomas
- Delineation of 2 (out of 4) SHH subgroups, SHH-1 and SHH-2, both dominated by medulloblastomas from young children.
 - Significantly different outcomes, and recent clinical trial data suggest that specific chemotherapeutic regimens can help those patients with tumors in the poor prognosis subgroup
- Morphologic types (classic, desmoplastic/nodular, medulloblastoma with extensive nodularity (MBEN), and large cell/anaplastic) combined into 1 section as morphologic patterns of an inclusive tumor type *Medulloblastoma, histologically defined*.
- All true desmoplastic/nodular medulloblastomas and MBENs align with the SHH molecular group, and most are in the SHH-1 and SHH-2 subgroups. Nearly all WNT tumors have classic morphology, and most large cell/anaplastic tumors belong either to the SHH-3 subgroup or to the Grp3/4 subgroup 2.

4 major subgroups

- All: Restricted diffusion-hypercellularity
- WNT (~10%): Lateral location (foramen of Luschka, cerebellopontine angle [CPA]) children and adults (not seen in infancy)
 - Prognosis: 5-year survival 95% (best prognosis)
 - M:F 1:2
 - More predisposition to frank intratumoral hemorrhage
- SHH-activated (30%): cerebellar hemisphere
 - Prognosis: 5-year survival 75% (intermediate prognosis)
 - TP53-wildtype (~20%)
 - infants and adults (rare in children)
 - M:F 1:1
 - TP53-mutant (~10%)
 - children
 - M:F 3:1
- Group 3 (~25%): midline/4th ventricle
 - Prognosis: 5-year survival 50% (poor prognosis)
 - infants and children (rare in adults)
 - M:F 2:1
 - Enhancement in majority
- Group 4 (~35%):L midline/4th ventricle
 - Prognosis: 5-year survival 75% (intermediate prognosis)
 - typically children but encountered in all age groups
 - M:F 3:1
 - Less enhancement



Subgroup		WNT	SHH			
Subtype			α	β	γ	δ
Demographics	Frequency	100%	29%	16%	34%	21%
	Age					
	Gender	45 ♂ 55 ♀	63 ♂ 37 ♀	47 ♂ 53 ♀	55 ♂ 45 ♀	69 ♂ 31 ♀
Clinical features	Histology	Classic	Classic > Desmoplastic > LCA	Desmoplastic > Classic	Desmoplastic > MBEN Classic	Classic > Desmoplastic
	Metastasis	12%	20%	33%	9%	9%
	5-year OS	98%	70%	67%	88%	89%
Molecular features	Cytogenetics					
	Driver events	CTNNB1, DDX3X, SMARC4 mutation	MYCN, GLI2 amplification TP53 mutation PTCH1 mutation (less)	PTCH1, KMT2D mutation SUFU mutation/deletion PTEN deletion	PTCH1, SMO, BCOR mutation PTEN deletion	PTCH1 mutation TERT promoter mutation

SHH-Alpha: TP53 mutation, worse prognosis

Subgroup		Group 3/4							
Subtype		I	II	III	IV	V	VI	VII	VIII
Demographics	Frequency	4%	13%	9%	10%	8%	9%	22%	25%
	Age	0-3 3-10 10-17 17+	0-3 3-10 10-17 17+	0-3 3-10 10-17 17+	0-3 3-10 10-17 17+	0-3 3-10 10-17 17+	0-3 3-10 10-17 17+	0-3 3-10 10-17 17+	0-3 3-10 10-17 17+
	Gender	60 40	77 23	78 22	68 32	71 29	67 33	66 34	75 25
Clinical features	Histology	Classic > Desmoplastic	LCA, Classic	Classic > LCA	Classic	Classic	Classic	Classic	Classic
	Metastasis	35%	57%	56%	58%	62%	45%	45%	50%
	5-year OS	77%	50%	43%	80%	59%	81%	85%	81%
Molecular features	Cytogenetics	 balanced	 8+ 1q+	 7+ i17q 10q-	 14+ 7+ no i17q 8-10-11-16-	 7+ i17q 16q-	 7+ i17q 8-11-	 7+ i17q (less) 8-	 i17q
	Driver events	GFI1/GFI1B activation OTX2 amplification	MYC amplification GFI1/GFI1B activation KBTBD4, SMARCA4, CTDNEP1, KMT2D mutation	MYC amplification (less)	no common driver events	MYC, MYCN amplification	PRDM6 activation MYCN ampl. (less)	KBTBD4 mutation	PRDM6 activation KDM6A, ZMYM3, KMT2C mutation

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