CNS TUMOR MAP, 2020 REVISION WITH 2016 WHO DESIGNATIONS AND MOLECULAR INTEGRATION

LEGEND: E = EGBs; = Seizures; R = Rosenthals; = Enhancing; = Cyst+mural nodule; = Calcifications; b = BRAF alteration; i = IDH1/2 mutation; o = 1p/19q co-del; = Low grade; = Grade III; = Grade IV; = Ungraded

* Tumor summaries below may not necessarily state the formal WHO preferred terminology, in the name of brevity.

Not all CNS tumors are described here. Specifically, this chart will not address meningiomas, CNS lymphomas or mesenchymal tumors.

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Ref: WHO Tumors of the CNS (4th rev 2020)

SUPRATENTORIAL

INFANT HIGH-GRADE GLIOMA
MX: Usually embryonal "PNET-like" histology. Sometimes papillary, rosetted or spindled growth patterns. Occasionally lower-grade glial pattern.
IHC: POS (if mutated): ALK1, panNTRK, ROS1 NEG: retained INI1/BRG1
MOL: HGG pattern: ALK / ROS / NTRK / MET alterations LGG pattern: ALK alterations only
DDX: Usually don't have H3K27M or BRAF mutations

ANGIOCENTRIC GLIOMA
I
MX: Subtly infiltrative, spindle cell tumor with elongated cells radially arranged around vessels - akin to ependymomatous rosettes
IHC: POS: GFAP, **MYB**, EMA (dot-like) NEG:Ki67 (<5%), Synap, p53, IDH1
MOL: MYB (6q23) alterations or rearrangements
DDX: Ependymoma, pilomyxoid astrocytoma, astroblastoma

ASTROBLASTOMA
MX: Well defined tumor arranged in radial "rosettes" with broad bases. Prominent vascular hyalinization. Can have papillary like formation. Occasional necrosis.
IHC: POS: GFAP (var), S100, Ki67 (<20%), Ker (var) NEG: IDH1
MOL: aCGH: gains of 19 and 20q
DDX: Malignant var: anaplastic, >5 mites, palisading necr.

PLEOMORPHIC XANTHOASTROCYTOMA
II III
MX: Cellular tumor with epithelioid cells, sometimes lipidized with multinucleation & nuclear inclusions. Frequent perivascular lymphocytes and **reticulin**.
IHC: POS: GFAP, BRAF V600E, MAP2 (var), CD34 (var) NEG: **p16 null** (usually), IDH1
MOL: BRAF mut (80%), CDKN2A del (60%)
DDX: Grade 3 = >5 mitoses & necrosis | Epithelioid GBM

GLIOBLASTOMA, EPITHELIOID
MX: S100, GFAP (patchy), EMA/CK (focal), BRAF NEG: H3K27M, CK5/6, retained INI1/BRG1
IHC: IDH1 wildtype. BRAF V600E (50%) No H3K27M or SMARCB1/B4 mutations
MOL: Related to anaplastic PXA or may arise from Gr2PXA
DDX:

GLIOBLASTOMA (IDH MUT)
MX: Infiltrative glial tumor with: hypercellularity, mitoses, and vascular proliferation. **Less** pronounced **necrosis.** Often arising from lower grade glioma
IHC: POS: GFAP, IDH1 R132H, p53 NEG: H3K27M, ATRX, IDH1 (if alternative mutation)
MOL: IDH1 R132X mutated **or** IDH2 R172K mutated Additionally: TP53 mut, ATRX mut, MGMT hypermeth
DDX: IDH-wt GBM, IDH-mut anaplastic astro

GLIOBLASTOMA (IDH WT)
MX: Infiltrative glial tumor with: hypercellularity, mitoses, **pseudopalisading necrosis** and vascular proliferation. Small cell var = minimal atypia
IHC: POS: GFAP, IDH1 R132H, p53, S100, **focal** INI-1 loss NEG: H3K27M, CK5/6
MOL: IDH1 wildtype, TERT promoter mut., EGFR alterations (esp in small cell var.), TP53 mut
DDX: Epithelioid GBM, Oligodendroglioma (small cell var)

PEDIATRIC LOW-GRADE GLIOMA, ALK FUSION
MX: Glial or glio-neuronal tumor with moderate cellularity and mild atypia. High-grade versions also exist.
IHC: POS: GFAP, Alk, NEG: Ki67 (very low)
MOL: Alk-fusions: PPP1CB-Alk and rare other partners
DDX: PLNTY, Ganglioglioma

DESMOPLASTIC INFANTILE ASTRO/GANGLIO
I
MX: Triphasic tumor: glial cyst wall, desmoplastic embryonal mural nodule +/- ganglion cell component.
IHC: POS GFAP, reticulin fibres, Synap (neurons), desmin (rare)
MOL: Rare aneuploidy. Rare BRAF V600E mutations. No BRAF-fusions or TP53 mutations
DDX: Embryonal tumors, ganglioglioma, pilocytic astro

DNET
I
MX: Glioneuronal tumor with oligo-like cells in vertical rows, mucoid microcysts and "floating" neurons. Can have distinct glioma areas & separate FCD (IIIa)
IHC: **Oligo-like**: POS: S100, OLIG2, CD34 (focal) NEG: GFAP (in oligo-like), IDH1
MOL: BRAF mut (30%), Chr 5 and 7 gains (30%)
DDX: Pilocytic astro, oligodendroglioma, ganglioglioma

PLNTY
?I
MX: Glial tumor with piloid cells, set among prominent vasculature and heavy calcification
IHC: POS: Synap, CD34 (strong) NEG: Cga, IDH1, GFAP (mostly) , Ki67 usu low
MOL: FGFR2-CTNNA3 fusions
DDX: Pilocytic astrocytoma, DNET, ganglioglioma

PAPILLARY GLIONEURONAL TUMOR
I
MX: Low-grade biphasic glioneuronal tumor arranged in pseudopapillae surrounding **hyalinized vessels**. Intervening ganglionic cells with neuropil.
IHC: POS: GFAP and S100 (glial); OLIG2 (var), Synap NEG: CgA
MOL: SLC44A1-PRKCA fusion in most
DDX: Ependymoma, AVM

ASTROCYTOMA
II III
MX: Cellular astrocytic, fibrilar neoplasm with mild to moderate nuclear atypia, angulated nuclei + hyperchromasia. No necrosis allowed.
IHC: POS: GFAP, TP53, IDHR132H (80%) NEG: ATRX (loss)
MOL: (80%) IDH1/2 mut & TP53 mut + ATRX mut MGMT promoter methylation (50%)
DDX: Grade 3 = Hypercellular + increased mitoses

OLIGODENDROGLIOMA
II III
MX: Infiltrating gliomas with round, "fried-egg" cells in delicate chicken-wire vasculature background. **Grade 3** = Incr. mitoses + Microvasc prolif + necrosis
IHC: POS: IDHR132H (90%), ATRX (retained), S100, OLIG2 NEG: GFAP (mostly)
MOL: IDH1/2 mut + co-del 1p/19q | Often: CIC & TERT mut. NEG: mutations in ATRX or TP53
DDX: Neurocytoma, clear cell ependymoma, DNET, Pilocytic

EXTRAVENTRICULAR NEUROCYTOMA
II
MX: Round cell neurocytic tumor with prominent intralesional vessels and pseudorosettes. Oligo-like with occasional ganglod differentiation.
IHC: POS: Synap NEG: Cga, IDH1, GFAP (mostly) , Ki67 usu low
MOL: Rarely co-del 1p/19q. FGFR1-TACC1 fusions Never IDH1/2 mutation or BRAF V600E mutation
DDX: Oligodendroglioma, DNET, ganglioglioma, PGNT

CNS EMBRYONAL TUMORS, GENETICALLY DEFINED
MX: Many genetically defined embryonal tumors look similar to one another:
1. CNS NB-FOXR2: Resembles CNS neuroblastoma, ganglionic nodules
2. CNS HGNET-MN1: Solid + pseudopapillary tumor, resembles astroblastoma
3. CNS HGNET-EFT-CIC: Can resemble EWS
4. CNS HGNET-BCOR: Glial looking w/ rosettes or ependymoma-like
5. CNS HGG-ALK/ROS/NTRK

IHC: CNS NB-FOXR2: Olig2, Synaptophysin, GFAP
CNS HGNET-MN1: GFAP
CNS HGNET-EFT-CIC: NUT1
CNS HGNET-BCOR: GFAP, B-cat (nuc), BCOR
CNS HGG-ALK/ROS/NTRK: ALK1, ROS1, NTRK

MOL: CNS NB-FOXR2: Intrachromosomal rearrangement, FOXR2 upreg.
CNS HGNET-MN1: Various fusion partners
CNS HGNET-EFT-CIC: CIC-NUTM1 fusion
CNS HGNET-BCOR: BCOR ITD exon 15
CNS HGG-ALK/ROS/NTRK: Various fusion partners across all

DICER1-ASSOCIATED CNS SARCOMA
MX: High-grade spindle cell neoplasm with PPB-like pattern, eosinophilic globules and ~ rhabdo cells.
IHC: POS: Desmin (focal), myogenin (focal) NEG: GFAP, Olig2, Synap, INI1 (retained)
MOL: Bi-allelic DICER1 mutations
DDX: Embryonal tumors, GBM, AT/RT

GANGLIOGLIOMA
I III
MX: Disorganized, variably cellular lesion with glial and neuronal component. Look for binucleated and dysplastic neurons. Perivascular **lymphocytes.**
IHC: POS (Neuron): MAP2, Synap, BRAF V600E, CD34 **Rarely: H3K27M** in non-infiltrative, temporal cases
MOL: BRAF V600E (~50%), BRAF fusions (rarely) **NO IDH1/2** mutations (excludes this diagnosis)
DDX: DNET, Oligodendroglioma, co-existing FCD (type IIIb)

ATYPICAL TERATOID/RHABDOID TUMOR
MX: Supratentorial > infratentorial & midline Polyphenotypic, hypercellular embryonal tumor with rhabdoid and ocasional anaplastic cells.
IHC: POS: INI1 or BRG1 (aberrant loss), GFAP (foca)
MOL: SMARCB1 > SMARCA4 alterations. Mut >> deletions 33% germline
DDX: All embryonal tumors in children

EMBRYONAL TUMOR WITH MULTILAYERED ROSETTES
MX: Cerebellar > Midline/Posterior fossa. Embryonal tumor with layered rosettes and islands of nucleus free neuropil
IHC: POS: LIN28 (strong & diffuse), Synap (neuropil) NEG: INI1 (retained), GFAP
MOL: C19MC-altered
DDX: Embryonal tumors, anaplastic ependymoma, CPC

EPENDYMOMA (SUPRATENTORIAL)
II III
MX: Can be papillary or clear cell morphology. Clear cell = arranged in cellular groups with perinuclear halos, focal perivascular rosettes.
IHC: POS: FOXJ1, GFAP, S100, EMA (dot-like) In SP-RELA: Cyclin-D1, L1CAM, **p16 null**
MOL: ST-EPN-RELA: C11orf95-RELA fusion, Chromothripsis ST-EPN-YAP1: YAP1 fusions
DDX: Oligodendroglioma, neurocytoma, hemangioblastoma

PAPILLARY TUMOR OF PINEAL REGION
? II ? III
MX: Biphasic solid and papillary tumor with ependymoma-like pattern, hyalinized vessels and occasional PAS+ cytoplasmic globules
IHC: POS: Keratins (AE1/3, CAM5/2, CK18), GFAP (var) NEG: NF, Synap (focal), CpA (focal)
MOL: aCGH: del 10, + 4. PTEN alteration occasional
DDX: Ependymoma, Germ cell tumor, Metastasis

PINEOCYTOMA
I
MX: Moderately cellular round cell tumor growing in sheets and multilayered (pinecytomatous) neuropil rosettes, set among rich vasculature.
IHC: POS: Synap, NF, MAP2 (var), CpA (var) NEG: GFAP, S100
MOL: No relevant diagnostic molecular genetic profile
DDX: PPTID, EV neurocytoma, Germinoma

PINEAL PARENCHYMAL TUMOR OF INTERMEDIATE DIFFERENTIATION
? II ? III
MX: Two patterns: Diffuse neurocytoma-like and lobulated/nested pattern w/ distinct vessels. More cellular and occasional dysplastic ganglioid cells.
IHC: POS: Synap, NF, CpA (var) NEG: GFAP, S100, NeuN
MOL: aCGH: gains of 4q, 12q and loss of 22
DDX: Pineoblastoma, Germinoma,

DIFFUSE MIDLINE HIGH-GRADE GLIOMA, H3K27M
More often H3G34R mut
MX: Infiltrative tumor involving midline nuclei or brainstem. Monomorphic tumor cells with variable morphology resembling pilocytic astro to GBM.
IHC: POS: GFAP (var), H3K27M, OLIG2, MAP2 NEG: retained INI1/BRG1, CGA, ATRX, OLIG2
MOL: H3K27M mutation (midline), H3G34R (hemispheric) TP53 (50%), PDGRFA amp.
DDX: Related to anaplastic PXA or may arise from Gr2PXA

PINEOBLASTOMA
MX: Embryonal, hypercellular tumor of pineal region with focal rosette formation. Often invasive and disseminated.
IHC: POS: Synap (var), NF (focal), CpA (focal) NEG: INI1 & BRG1 (retained)
MOL: RB1 deletion, DICER1 mutation
DDX: All embryonal tumors of childhood, AT/RT

PILOMYXOID ASTROCYTOMA
MX: Piloid astrocytic tumor with subtle angiocentric growth, myxoid background & microcysts. Variable mitotic activity. +/- Pilocytic-like areas
IHC: POS: GFAP, S100, -CD34, Ki67 (up to 20% labeling) NEG: BRAF V600E, H3K27M
MOL: Rarely can have BRAF rearrangement
DDX: Pilocytic astrocytoma, Angiocentric glioma

PILOCYTIC ASTROCYTOMA
MX: Astrocytic tumor with elongated processes, biphasic density, microcysts and occasional multinucleation. Low mitoses. +/- Vasc prolif, Leptomening. spread
IHC: POS: GFAP, -OLIG2, BRAF (hemispheric) NEG: p53, IDH1/2
MOL: Posterior fossa: KIAA1549-BRAF fusion Cortex/Midline: BRAF mut, FGFR1 (5%), NTRK (~5%)
DDX: Pilomyxoid (no EGBs/ Rs), Oligodendo., DNET

MEDULLOBLASTOMA
MX: Embryonal tumor with variable nodules of neuronal differentiation. Cerebellum and 4th ventricle
IHC: POS: Synap, MAP2, p53, B-Cat (WNT),, GAB1 (SHH) NEG: GFAP, INI1 (retained)
MOL: 4 molecular groups: WNT - Older children, some adults. SHH - Often hemispheric & Desmoplastic/EN. TP53 mut confers worse prognosis G3/4 - Infants/children. Large/anaplasia & MYC amp

EPENDYMOMA (PF)
II III
MX: Monomorphic glioma arranged in rosettes with perivascular anuclear zones. Can have dense cellularity, focal necrosis and hemorrhage
IHC: POS: FOXJ1, GFAP, S100, EMA (dot-like) ***H3K27me3:*** Lost in EPN-A, Retained in EPN-B
MOL: PF-EPN-A: Few copy # changes, CpG-me + PF-EPN-B:Chromosomal instability, Cpg-me -
DDX: Choroid plexus tumor, Medulloblastoma, Metastasis

MYXOPAPILLARY EPENDYMOMA
?II
MX: Typically found in distal spinal cord. Radially arranged tumor cells in papillary / balloon arrangement around myxoid substance.
IHC: POS: GFAP, S100, CD99, Ker AE1/3 NEG: CK5/6, CK7, CK20, EMA, Ki67 (<1%)
MOL: Whole chromosome aneuploidy **MYCN amplification** (more aggressive variant)
DDX: Metastatic papillary tumors (adult), Chordoma

EPENDYMOMA (SPINAL CORD)
II III
MX: Often Tanycytic morphology: Monomorphic glioma in spinal cord growing as spindle cell fascicles with elongated nuclei. Rosettes typically subtle.
IHC: POS: FOXJ1, GFAP, S100, EMA (dot-like) NEG:
MOL: Frequent NF2 mutations, del Chr 22
DDX: Pilocytic astrocytoma, Schwannoma, Met.

DYSPLASTIC CEREBELLAR GANGLIOCYTOMA
?I
MX: Expansion of molecular and internal granule layers with variably sized ganglionic cells that preserves overall architecture.
IHC: POS: Syna NEG: PTEN (loss in adult cases)
MOL: Adult: PTEN mutations (Cowden syndrome) Children: no PTEN mutations
DDX: Ganglioglioma, Glioneuronal tumors

ANAPLASTIC ASTROCYTOMA WITH PILOID FEATURES
MX: Cellular, moderately pleomorphic infiltrative tumor with pilocytic morphology, vascular proliferation and focal areas of necrosis.
IHC: POS: GFAP NEG: ATRX (loss), IDH1, H3K27M
MOL: Defined by methylation studies. Characteristic: NF1/BRAF alterations + del ATRX + del CDKN2A
DDX: Pilocytic astrocytoma, IDH-wt GBM

CEREBELLAR LIPONEUROCYTOMA
II
MX: Cerebellar version of neurocytoma with prominent neoplastic adipocyte-like component.
IHC: POS: Synap, NeuN, MAP2, GFAP (focal) NEG: Ki67 (usu <10%)
MOL: TP53 mutation (20%), No BRAF or IDH mutations
DDX: Astrocytomas, lipid-rich SFT?

MIDLINE

INFRATENTORIAL

BRAIN STEM & CORD

VENTRICLES

CHOROID PLEXUS CARCINOMA
MX: Malignant intraventricular tumor w/ sheet-like growth, focal papillary formation, necrosis and brain invasion. Usu freq. Mitoses.
IHC: POS: CK7, p53 (50%) NEG: S100, TTR, EMA, INI1 (Retained)
MOL: Germline TP53 mut (40%)
DDX: Anaplastic ependymoma, Embryonal tumors

CHOROID PLEXUS TUMOR
I II
MX: Papillary tumor with delicate fronds with crowded cuboidal cells. **Atypical** = >2/10 mits + incr. cellularity, pleomorph., solid growth and/or necrosis.
IHC: POS: CK7, TTR, S100 (var) NEG: CK20, EMA (weak)
MOL: aCGH: hyperdiploidy. MGMT promoter methylation
DDX: CP carcinoma, Endolymphatic sac tumor, Metastasis

SUBEPENDYMAL GIANT CELL TUMOR
I
MX: Circumscribed glio-neuronal tumor with large gemistocytic or ganglion-type cells. Mitoses, tumor lymphocytes and hyalinized vessels present.
IHC: POS: GFAP, S100, Synap (var), NeuN (var) NEG: CD34
MOL: TSC1 and TSC2 mutations common 60% sporadic, 40% TS syndromic
DDX: Ganglioglioma, PXA (if not obviously near ventricle)

MYXOID GLIONEURONAL TUMOR
MX: DNET-like tumor arising in septum pellucidum > lateral ventricles. Myxoid stroma, microcysts and rosette-formations.
IHC: POS: OLIG2, MAP2, S100, GFAP (focal) NEG: CD34, NeuN, IDH1
MOL: Defined by PDGFRA K385I/L mutation

DIFFUSE LEPTOMENINGEAL TUMOR
MX: Oligodendroglial-like tumor with predominant leptomeningeal growth pattern and lesser ganglion cell / neuropil component
IHC: POS: OLIG2, MAP2, S100, GFAP (focally) NEG: EMA, NeuN, IDH1
MOL: KIAA-BRAF fusion (75%), del 1p (50%), rare 1p/19q del. No BRAF V600E or IDH1/2.
DDX: Oligodendroglioma, Pilocytic astro, PXA

ROSETTE FORMING GLIONEURONAL TUMOR
I
MX: Biphasic solid-cystic, tumor: neurocytic rosettes and piloid astrocytic components. Neurocytic rosettes surround neuropil core.
IHC: POS: Neurocytic = Synap, MAP2; Glial = GFAP NEG: BRAF V600E, IDH1/2
MOL: FGFR1 mut, PIK3CA mut in some No BRAF alterations or IDH1/2 mutations
DDX: Pilocytic astro, neurocytoma, Oligodendroglioma

CENTRAL NEUROCYTOMA
II
MX: Intraventricular round cell neurocytic tumor with prominent intralesional vessels and pseudorosettes. Anaplastic cytology = "atypical central neurocytoma".
IHC: POS: Synap, NeuN, MAP2 NEG: Cga, GFAP, Ki67 usu <2%. If >2% = "atypical"
MOL: aCGH: copy # alterations, MYCN amplification
DDX: Ependymoma, Pineocytoma

SUBEPENDYMOMA
I
MX: Ventricular tumor. Clusters of small nuclei arranged in fibrilar matrix with occasional microcysts. Rarely forming rosettes.
IHC: POS: GFAP NEG: EMA, Ki67 (<1%)
MOL: Not really relevant
DDX: Ependymoma variants

CHORDOID GLIOMA OF 3RD VENTRICLE
II
MX: Solid neoplasm w/ cords and nests of epithelioid tumor cells. Lymphoplasmacytic infiltrates present. Mucinous stroma common. Rarely fibrotic.
IHC: POS: GFAP, TTF-1, CD34, Ker (var), S100 (var) NEG: P53 (weak), Synapto, IDH1
MOL: aCGH: 11q13 and 9p21 losses. No TP53 mutations
DDX: Metastasis, Chordoma.

0 - 24 months | 2- 20 years | 20-50 years | > 50 years