brain tumor → NO premalignant or in situ lesions.

The anatomic site of the neoplasm can influence outcome independent of tumor type or grade due to local effects → يعني حسب وين ممكن يصير السرطان هاد بيأثر على الأعراض الناتجة

Metastasis is rare → السرطان نادرًا ما ينتقل من الدماغ إلى أجزاء أخرى : لكن انتقال السرطان من أماكن أخرى

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histologic grading of CNS tumors →
- Atypia and mitosis
- necrosis
- Microvascular proliferation

Grade 1 lesions →
- low proliferative activity
- Can be cured after surgical resection alone.

→ astrocytoma, papilloma, ependymoma

Grade 2 lesions →
- low proliferative activity
- usually infiltrative and often recur
- Some grade II entities tend to progress to higher grades of malignancy.

→ astrocytoma, IDH-mutant, grade 2, oligodendroglioma, IDH-mutant and 1p/19q-codeleted, grade 2

grade 3 lesions → malignancy(nuclear atypia and Higher proliferative activity (mitosis)). → astrocytoma, IDH- mutant, grade 3, oligodendroglioma, IDHmutant and 1p/19q-codeleted, grade

grade 4 lesions: →
- cytologically malignant, mitotically active, rapid proliferation, necrosisprone neoplasms
- associated with rapid pre- and postoperative disease evolution and fatal outcome.
- Widespread infiltration of surrounding tissue and a risk of craniospinal dissemination.

→ Glioblastoma, IDH-wildtype, medulloblastoma, pineoblastoma, and most embryonal neoplasms

- Childhood CNS tumors differ from those in adults in:

ΦLocation:
Φ2/3 infratentorial in kids (posterior fossa)
Φ2/3 supratentorial in adults (cerebral hemispheres above tentorium)

Mutation profile & histologic subtype:
ΦKids: medulloblastoma, pilocytic astrocytoma, ependymoma
ΦAdults: glioblastoma, metastases, meningiomas, diffuse gliomas constitute most gliomas in adults(including astrocytomas and oligodendrogliomas).

For nearly a century, the classification of brain tumors has been done according to their microscopic similarities

2016 classification breaks with this nearly century-old tradition and incorporates well-established molecular parameters into the classification.

genetic alterations in gliomas:

1- Mutations in isocitrate dehydroaenase (IDH) genes:
- observed as an early event in gliomagenesis
- Seen in astrocytomas and oligodendrogliomas
- Gain of function Mutation affection IDH1 codon 132 or IDH2 codon 172.
- The most frequent is IDH1 R132H mutation (83-91%) of IDH mutant gliomas
- IDH2 mutation: R172K is the most frequent IDH2 mutation

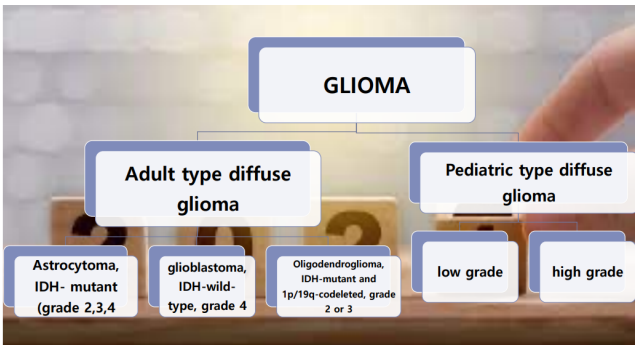
↓

- IDH1-R132H immune stain

IDH sequencing for IDH1 codon 132 and IDH2 codon 172

↓

Gain of function mutationà lead to increased production of 2-hydroxyglutarate (oncometabolite)àinterferes with the activity of several enzymes that regulate gene expressionà DNA hypermethylation & maintaining the cells in stem cell-like physiological statesà self- renewal and tumorigenesis




2- whole arm Co-deletion of 1p and 19q chromosomal segments:
- Diagnostic of oligodendrogliomas in the presence of IDH mutation.
- The vast majority of IDH mutant and 1p/19q co-deleted oligodendroglioma àcarry TERT promotor hotspot mutations
- TERT promotor hotspot mutations: telomerase stabilization, cellular immortalization and proliferation

3- ATRX and P53 loss of function mutation:
- Both occur in IDH mutant astrocytomas
- ATRX mutation induces abnormal telomeres maintenance mechanism known as "alternative lengthening of telomeres"
- ATRX mutation is Mutual exclusive with the activating promoter mutation of the TERT gene (1p/19q codeletion)
- P53 mutation: enable tumor cell survival
- ATRX à associated with genomic instability à induces P53 dependent cell deathà mutation in P53 helps these cells to survive.

diffusely infiltrating glioma

- IDH1 or less frequently IDH2 mutation.
- Inactivating mutation in TP53 and/or ATRX
- absence of 1p/19q codeletion

## Neuronal Tumors

- less frequent than gliomas

lower-grade lesions

seizures.

neuronal characteristics and express neuronal markers → synaptophysin, neurofilaments, and NeuN

synaptic vesicle protein p38

## Gangliogliomas

children and young adults → 20-50% have mutations in BRAF gene

neoplastic ganglion and glial cell

Slow growing tumor

temporal lobe

## Dysembryoplastic neuroepithelial tumor (DNT), WHO grade 1

- Rare
- children and young adults
- Slow growing tumor
- Present with seizure
- most commonly in the superficial temporal lobe.

Embryonal (Primitive) Neoplasm → undifferentiated small round cell tumor of neuroectodermal origin resembling normal progenitor cells in the developing CNS.

Medulloblastoma → accounting for 20% of pediatric brain tumors

embryonal tumor

- predominantly in children
- mainly in cerebellum
- All are highly malignant, WHO grade 4
- radiosensitive.
- the prognosis for untreated patients is dismal → كئيب
- 5-year survival rate may be as high as 75% with total excision, chemotherapy, and irradiatio

Medulloblastomas have tendency to spread to the subarachnoid space

- Very Cellular

In children (midline) while in adults (lateral)

well circumscribed (often)

may extend to the cerebellar surface and involve the Leptomeninges

Oncogenic pathways in Medulloblastoma

Wnt pathway activation → β-catenin; have the most favorable prognosis of all the genetic subtypes

MYC overexpression: → MYC amplification; these tumors have the poorest prognosis

Hedgehog pathway activation(gain of function) → loss of function mutations in PTCH1 (a negative regulator of the Hedgehog); these tumors have an intermediate prognosis, but the concomitant presence of P53 mutation confers a very poor prognosis.

## Glioblastomas

→ The most common malignant glioma (50% of all primary malignant brain tumors in adults)

→ Always grade 4

→ (butterfly glioma)

microvascular proliferation

- Some areas are firm and white, others are soft and yellow (due to tissue necrosis), others show regions of cystic degeneration and hemorrhage.

Prominent nuclear atypia, Brisk mitotic activity and Necrosis: irregular zones of necrosis surrounded by dense accumulations of tumor cells (palisading necrosis

The presence of any of the following Molecular features (even in the absence of necrosis or microvascular proliferation) lead to the designation of glioblastoma, IDH wildtype, grade 4:
- TERT promotor mutation
- EGFR gene amplification
- +7/-10 chromosome copy number change

## oligodendroglioma

→ with IDH1 or IDH2 mutation and codeletion of chromosomal arms 1p and 19q.

→ Grade 3 is more aggressive than grade 2 oligodendroglioma

→ Have best prognosis among diffuse glial tumors

NO grade 1 OR 4 oligodendroglioma

- Mitotic activity usually is absent or low (Ki67<5%)
- No spontaneous necrosis
- No microvascular proliferation

Microscopic:
- sheets of regular uniform cells resembling oligodendrocytes
- spherical nuclei containing finely granular chromatin (salt and pepper)
- The nuclei are surrounded by a clear halo of cytoplasm à fried-egg appearance

oligodendroglioma , IDH- mutant, & 1p/19q- codeleted WHO grade 3: → pathological microvascular proliferation and/or brisk mitotic activity with or without necrosis).

## Circumscribed astrocytic gliomas

→ Pilocytic Astrocytoma, WHO grade 1

→ Relatively benign tumor

- well circumscribed (discrete) Cystic tumor +/- calcification

- activating mutations or translocations involving the gene encoding the BRAFà resulting in activation of the MAPK signaling pathway.
- do not have mutations in IDH1 and IDH2, supporting their distinction from the adult type low-grade diffuse gliomas.

Treatment: Well circumscribed tumor curable with complete resection

Macroscopic:
- bipolar cells with long, thin GFAP positive "hairlike" processes
- Rosenthal fibers
- eosinophilic granular bodies
- microcysts are often present
- necrosis and mitoses are rare

# Ependymoma

- posterior fossa: near the 4th ventricle, accounting for 5-10% of tumors in the first two decades of life
- supratentorial
- Spinal: the most common location in adults and in patients with NF2

In adults the spinal cord and supratentorial ependymomas occur with
almost equal frequency

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Ependymoma, WHO grade 2, microscopic:

- uniform small cells with round to oval nuclei and granular chromatin in a fibrillary background
- low cellularity
- low mitotic count
- No necrosis or MVP
- Cilia and microvilli are seen on ultrastructural examination.

- Tumor cells may form glandlike structures (rosettes) à Rosette formation:
- Ependymal rosettes: diagnostic hallmark of ependymoma (25%)
- perivascular pseudorosettes: not specific for ependymoma (seen in glioblastoma and medulloblastoma)

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Ependymal rosettes:
- tumor cells arranged around central canal or lumen

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Perivascular pseudorosettes:
- tumor cells radially arranged around vessels.

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- ependymomas, WHO grade 3:
- Show less evident ependymal differentiation.
- brisk mitotic rates, and microvascular proliferation carry more prognostic impact
than necrosis and atypi

Done By Layan Daoud