Genetic alterations in gliomas ~

1/ **Mutations in IDH**. -may occur in IDH1 or IDH2 genes. observed in: *astrocytomas* and *oligodendrogliomas*. -increased production of **2-hydroxyglutarate** > cells maintained in a stem cell-like state > self-renewal and tumorigenesis.	2/ **Co-deletion of 1p and 19q chromosomal segments**: present in *oligodendrogliomas*.
3/ **Mutations in the promoter for telomerase**: immortalization of tumor cells, eg. *glioblastomas*.	4/ **Other genetic alterations**: include mutations that lead to overexpression of the EGF receptor and other receptor tyrosine kinases or disable p53 or RB.

Astrocytoma ~

Classified into two major categories according to their **infiltrative potential**:

1- diffuse (infiltrating) astrocytoma.

Percentage	**80%** of adult gliomas.	Location	Cerebral hemisphere.	Outcome: • static or progressive • If the patient shows rapid clinical deterioration, it can be correlated with the appearance of higher-grade component and more rapid tumor growth.
Age at diagnosis	**40-60** years old.	Presentation:	seizures, headaches, and focal neurologic deficits related to the anatomic site of involvement.	

-On the basis of histologic features astrocytomas are stratified into three groups:

Grade	Mean survival	Notes
Grade 2 / diffuse astrocytoma	> 5 years.	• mild to moderate increase in the number of glial cells + fibrillary background made of fine astrocytic cell processes. • variable nuclear pleomorphism, however **not** prominent atypia • Mitotic activity is generally absent • NO necrosis • NO microvascular proliferation
Grade 3 / anaplastic astrocytoma	2-3 years	- more cellular - greater nuclear pleomorphism - mitotic figures are present - NO necrosis - NO microvascular proliferation
Grade 4 / Glioblastoma	15 months	Lesions can start as Glioblastoma from the beginning or progress from a previous grade 2 or 3 tumors to grade 4 • prognosis is very poor even with treatment (resection, radiotherapy, and chemotherapy).

- Microscopic Features ~

• cellular tumor with nuclear pleomorphism as in anaplastic astrocytoma with either

• Necrosis: irregular zones of necrosis surrounded by dense accumulations of tumor cells (palisading necrosis) or

• microvascular proliferation: the presence of abnormal vessels with walls composed 2 >= layers of vascular wall cells.

- Macroscopic Features ~

• variation in the gross appearance of the tumor from region to region is characteristic (was called glioblastoma multiforme).

• Some areas are firm and white[1], others are soft and yellow[2](due to tissue necrosis), others show regions of cystic degeneration[3]and hemorrhage[4].

2- circumscribed astrocytic gliomas.

Pilocytic Astrocytoma

Relatively benign, slow-growing, can be treated by resection.

Age at presentation	children and young adults.	Molecular profile: activating mutations or translocations involving the gene encoding the BRAF, which result in activation of the MAPK signaling pathway. • do not have mutations in IDH1 and IDH2, **supporting their distinction from the low-grade diffuse gliomas**.
Location	cerebellum > 3rd ventricle > optic pathways > spinal cord > cerebral hemispheres.	

- Microscopic Features ~

• bipolar cells with long, thin ***GFAP positive*** "hairlike" processes

• Rosenthal fibers

>are rounded or elongated, homogenous, and brightly eosinophilic structures within the astrocytic processes, made of clumped intermediate filament proteins, primarily glial fibrillar acidic protein(GFAP +VE) • Can be physiologic (gliosis) or pathologic (PA) and Alexander disease.

• **eosinophilic** granular bodies

rounded hyaline droplets in the cytoplasm of astrocytes seen in PA and ganglion-cell tumors.

• microcysts are often present

• necrosis and mitoses are rare.

END OF LECTURE 1

Oligodendroglioma ~

Prevalence	5-15% of gliomas.	Location	mostly in the cerebral hemispheres, mainly in the frontal or temporal lobes, white matter.	Treatment and prognosis: • The combination of surgery, chemotherapy, and radiotherapy yields an average survival of • **10-20** years for WHO grade 2. • **5-10** years for WHO grade 3.
Age at diagnosis	40-50.	Molecular profile	The presence of IDH mutation and 1p & 19q codeletion is diagnostic for oligodendroglioma.	

**Better prognosis than astrocytoma of the same grade!

Grade 2 Oligodendroglioma	• infiltrative tumors • +/- cysts, focal hemorrhage, and calcification. • sheets of regular cells with spherical nuclei containing finely granular chromatin • The nuclei are surrounded by a clear halo of cytoplasm (fried-egg appearance). • delicate network of anastomosing capillaries "chickenwire" • **Calcification** in 90% of tumors. • Mitotic activity usually is low. • No spontaneous necrosis • No microvascular proliferation

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Ependymoma ~

**circumscribed glioma!

Location	**posterior fossa** (60%), supratentorial (30%), spinal (10%)	Age	• In the **first 2 decades of life**; near the 4th ventricle (post. Fossa) • In adults; the spinal cord and supratentorial ependymomas occur with almost equal frequency	• The clinical outcome for completely resected supratentorial and spinal ependymomas is **better** than for those in the posterior fossa.

Morphology ~

*Composed of uniform small cells with round to oval nuclei and **granular chromatin** in a **fibrillary matrix** and characterized by:

• Rosette formation:

Ependymal rosettes	diagnostic hallmark of ependymoma (25%) > not that common. - tumor cells arranged around a central canal or lumen that **resemble the embryologic ependymal canal**, with long, delicate processes extending into a lumen.
Perivascular pseudorosettes	**not specific** for ependymoma. - composed of tumor cells radially arranged around **vessels** with an intervening anucleated zone containing thin ependymal processes.

• Low cell density and a low mitotic count.
• Cilia and microvilli are seen on ultrastructural examination.

Anaplastic ependymomas ~ increased cell density, high mitotic rates, necrosis, microvascular proliferation, and less evident ependymal differentiation.

Neuronal tumors ~

• less frequent than gliomas
• composed of cells with neuronal characteristics and express neuronal markers, such as synaptophysin and neurofilaments.
• typically, lower-grade lesions BUT • often present with seizures.

Examples :]

Central neurocytoma	**WHO grade 2**	Affects young adults.	***low-grade*** neuronal tumor [not mixed] within and adjacent to the **lateral ventricle(s) and/or the third ventricle**.
Gangliogliomas	**WHO grade 1**	Affects children and young adults.	***Well-differentiated*** glioneuronal tumor. Composed of a mixture of neoplastic ganglion and glial cells, most commonly in the **temporal lobe**.
Dysembryoplastic neuroepithelial tumor (DNT)	**WHO grade 1**	Affects children and young adults.	***low-grade*** glioneuronal tumor affecting the **cerebral cortex**. Most commonly in the **superficial temporal lobe**.

Embryonal (Primitive) Neoplasms ~

• Primitive small round cell tumor of neuroectodermal origin resembling normal progenitor cells in the developing CNS.

Medulloblastoma [WHO grade 4]

Epidemiology	The **most** common CNS embryonal tumor. • 20% of pediatric brain tumors. -predominantly in children	Location	mainly in the **cerebellum**.	Outcome : -Grade 4 > all are highly malignant / prognosis for untreated patients is : dismal ***BUT*** > **radiosensitive**. With total excision, chemotherapy, and irradiation, the 5-year survival rate may be as high as 75%.

Morphology ~

• densely cellular, with sheets of anaplastic ("small blue") cells with little cytoplasm and hyperchromatic nuclei • mitoses are abundant.

Homer Wright Rosettes	• primitive tumor cells surrounding central neuropil (delicate pink material formed by neuronal processes). • Represents focal neuronal differentiation • seen also in **neuroblastomas** [NOT diagnostic!!]

Pathogenesis ~

•Medulloblastomas are classified according to **molecular characteristics** in addition to **histopathological** features.

•Clinical trials are ongoing that seek to tailor therapy targeted to molecular alterations, with the goal of avoiding radiation therapy when possible.

Oncogenic pathways in Medulloblastoma:

Wnt pathway activation	associated with gain of function mutations in the gene for **β-catenin**; have the most favorable prognosis of all of the genetic subtypes.
Hedgehog pathway activation	associated with 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**.
MYC overexpression	due to MYC amplification; these tumors have the poorest prognosis.