CENTRAL NERVOUS SYTEM TUMORS(1)

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CNS TUMORS:

- may arise from the **cells of the coverings** (meningiomas), **the brain cells** (gliomas, neuronal tumors), or **other CNS cell populations** (primary CNS lymphoma, germ cell tumors), or they may originate elsewhere in the body (**metastases**).

- Can involve the **brain or spinal cord**

https://answers.childrenshospital.org/spinal-cord-injury/

EPIDEMIOLOGY:

- **INCIDENCE**:
  - The annual incidence of CNS tumors in the U.S →
    - 24 /100,000 for intracranial tumors , 1/3 malignant
    - 1-2/100,000 for intraspinal tumors

- **Metastases are more common than primary brain tumors.**

Characteristic features of CNS tumors:

- **No Premalignant stage: no** in situ lesions.

- **Metastasis is rare!**
  - Even the most highly malignant gliomas **rarely spread** outside of the CNS.
  - but the brain is **not comparably protected** against the spread of distant tumors.

Characteristic features of CNS tumors:

- **Growth pattern (infiltrative or not) and tumor location strongly influence the prognosis:**
  - Even low-grade lesions may infiltrate large regions of the brain, leading to serious clinical deficits, inability to be resected, and poor prognosis.
  - The anatomic site of the neoplasm can influence outcome independent of tumor type or grade due to local effects

LOCATION
LOCATION
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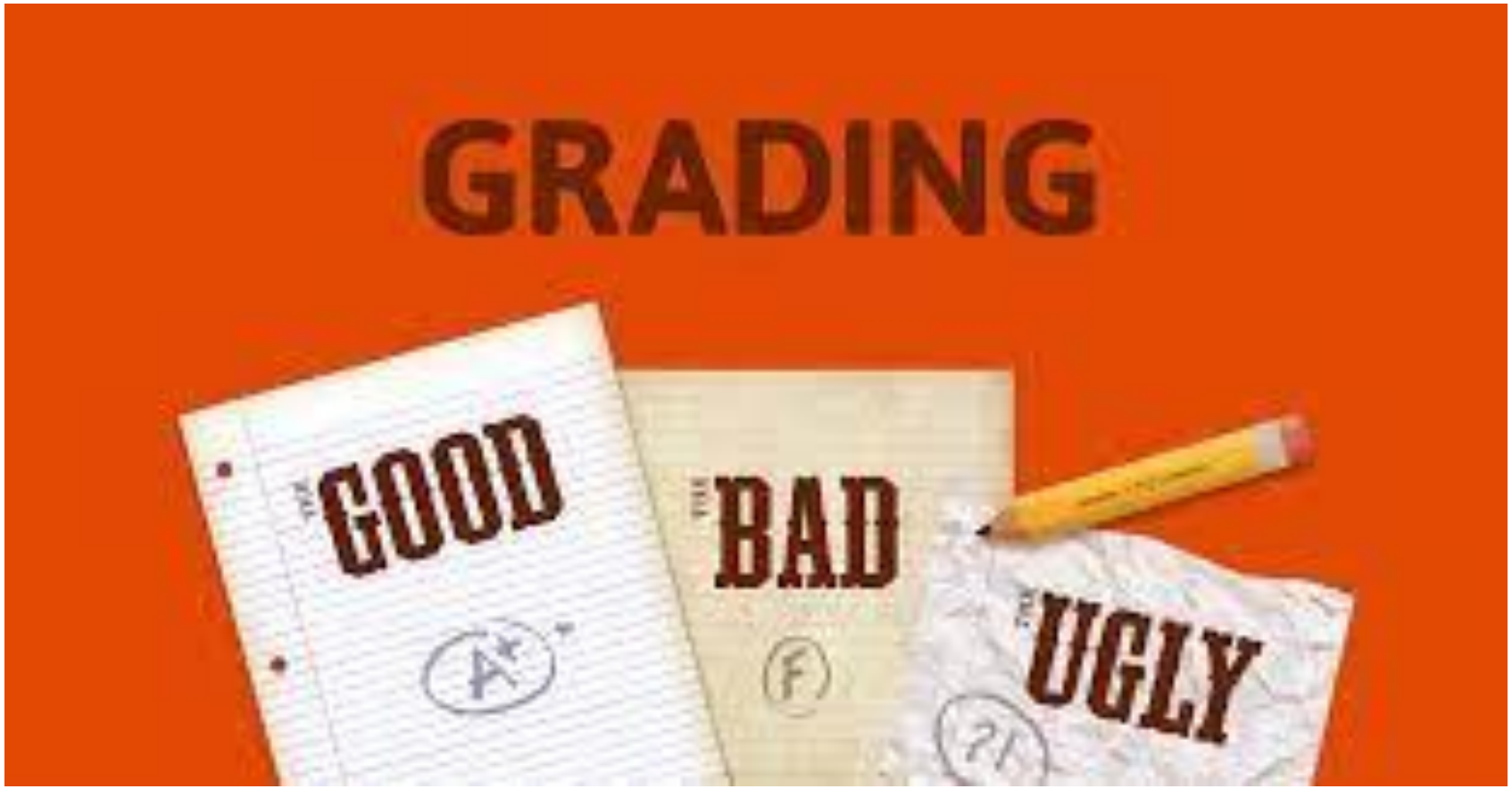
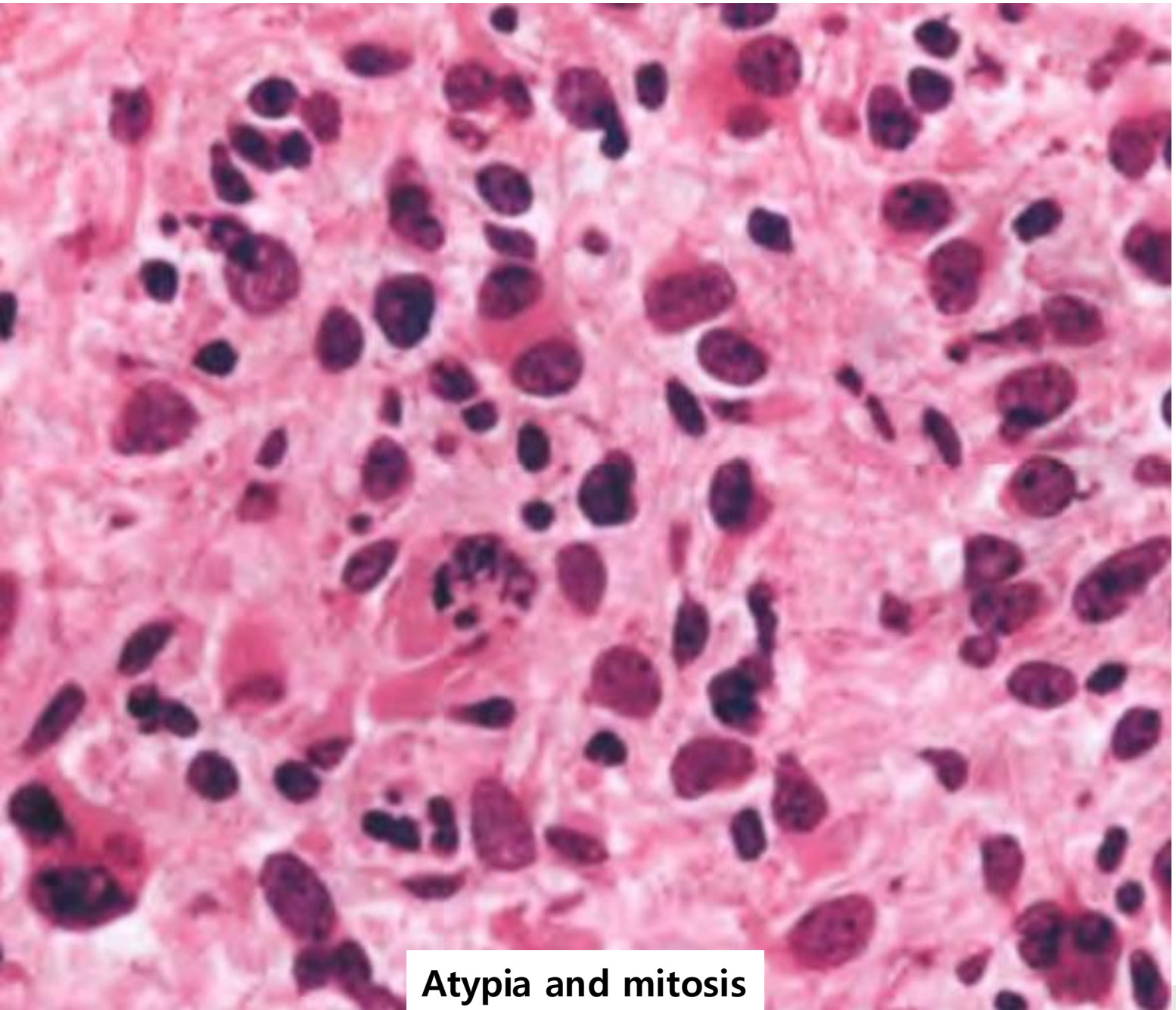
LOCATION

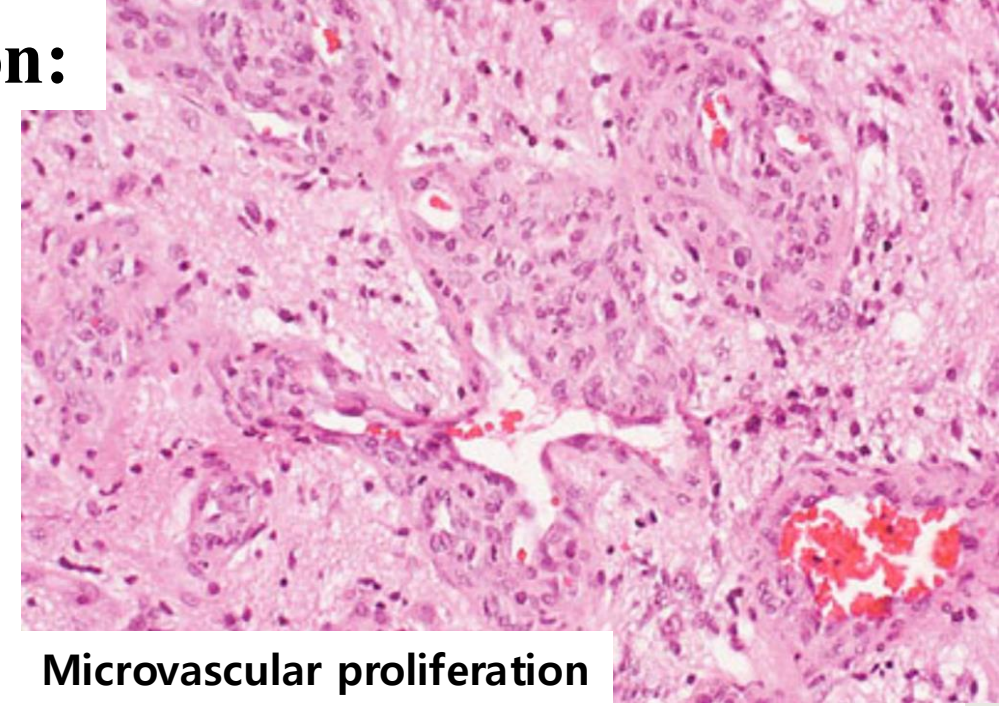
Histologic grading of CNS tumors



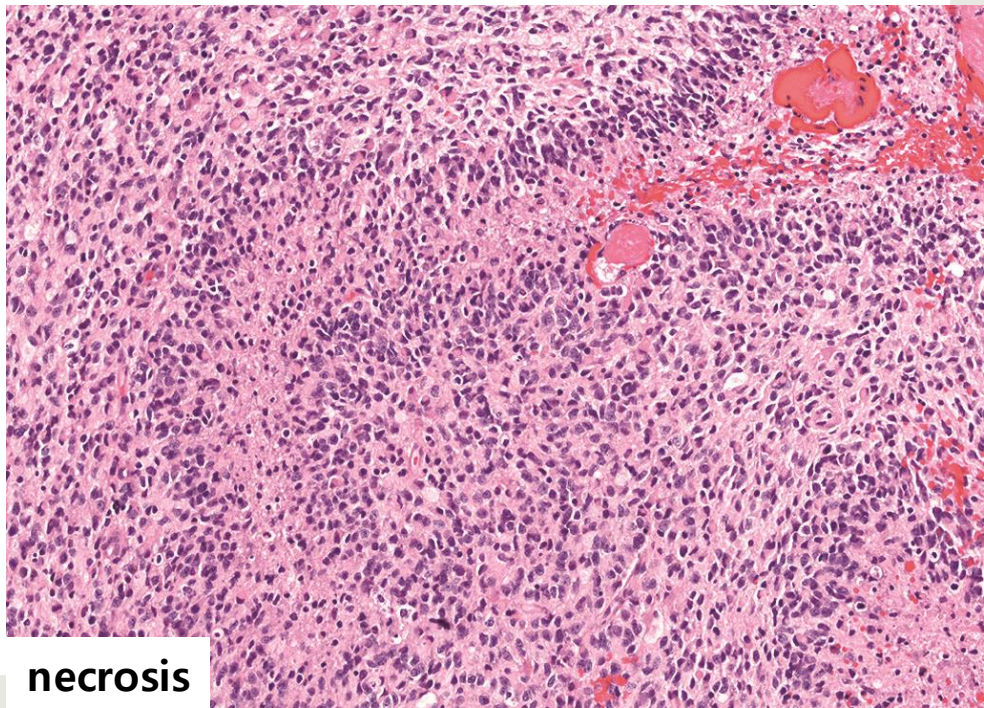
The histologic grading of CNS tumors depends on:



Atypia and mitosis



Microvascular proliferation



necrosis

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

Example: pilocytic astrocytoma (PA), subependymal giant cell astrocytoma (SEGA), choroid plexus papilloma, myxopapillary ependymoma

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

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

- **grade 3 lesions:**
  - clear histological evidence of malignancy(nuclear atypia and Higher proliferative activity (mitosis)).
  - In most settings, patients receive radiation and/or chemotherapy.

  Examples: astrocytoma, IDH- mutant, grade 3, oligodendroglioma, IDH-mutant and 1p/19q-codeleted, grade 3.

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

  examples: Glioblastoma, IDH-wildtype, medulloblastoma, pineoblastoma, and most embryonal neoplasms

WHO grades of select CNS tumours

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	II
Anaplastic astrocytoma, IDH-mutant	III
Glioblastoma, IDH-wildtype	IV
Glioblastoma, IDH-mutant	IV
Diffuse midline glioma, H3 K27M-mutant	IV
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III
Other astrocytic tumours	
Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III
Ependymal tumours	
Subependymoma	I
Myxopapillary ependymoma	I
Ependymoma	II
Ependymoma, *RELA* fusion-positive	II or III
Anaplastic ependymoma	III
Other gliomas	
Angiocentric glioma	I
Chordoid glioma of third ventricle	II
Choroid plexus tumours	
Choroid plexus papilloma	I
Atypical choroid plexus papilloma	II
Choroid plexus carcinoma	III
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	I
Gangliocytoma	I
Ganglioglioma	I
Anaplastic ganglioglioma	III
Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	I
Desmoplastic infantile astrocytoma and ganglioglioma	I
Papillary glioneuronal tumour	I
Rosette-forming glioneuronal tumour	I
Central neurocytoma	II
Extraventricular neurocytoma	II
Cerebellar liponeurocytoma	II
Tumours of the pineal region	I
Pineocytoma	II or III
Pineal parenchymal tumour of intermediate differentiation	
Pineoblastoma	IV
Papillary tumour of the pineal region	II or III
Embryonal tumours	
Medulloblastoma (all subtypes)	IV
Embryonal tumour with multilayered rosettes, C19MC-altered	IV
Medulloepithelioma	IV
CNS embryonal tumour, NOS	IV
Atypical teratoid/rhabdoid tumour	IV
CNS embryonal tumour with rhabdoid features	IV
Tumours of the cranial and paraspinal nerves	
Schwannoma	I
Neurofibroma	I
Perineurioma	I
Malignant peripheral nerve sheath tumour (MPNST) I	I, III or IV
Meningiomas	
Meningioma	I
Atypical meningioma	II
Anaplastic (malignant) meningioma	III
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour / haemangiopericytoma	I, II or III
Haemangioblastoma	I
Tumours of the sellar region	I
Craniopharyngioma	I
Granular cell tumour	I
Pituicytoma	I
Spindle cell oncocytoma	I

Pediatric CNS tumors:

- 20% of all pediatric tumors.
- Childhood CNS tumors differ from those in adults in:
  - **Location:**
    - 2/3 infratentorial in kids (posterior fossa)
    - 2/3 supratentorial in adults (cerebral hemispheres above tentorium)
  - **Mutation profile & histologic subtype:**
    - Kids: medulloblastoma, pilocytic astrocytoma, ependymoma
    - Adults: glioblastoma, metastases, meningiomas, diffuse gliomas constitute most gliomas in adults(including astrocytomas and oligodendrogliomas).

Classification of CNS tumors

- According to The 2016 WHO classification of brain tumors, the tumors are classified based on:

combined phenotype-genotype (integrated diagnoses):

1- phenotype: the histologic features and microscopic similarities with what's thought to be their cell of origin (based on the light microscopic appearance, the immunohistochemical expression of proteins, and the electron microscopic assessment of ultrastructural features).

2- genotype: tumor genetic profile and molecular studies

- The 2016 classification helped **improving treatment protocols and predicting prognosis.**

genetic alterations in gliomas:

1- **Mutations in isocitrate dehydrogenase (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

- ✓ Can be detected by immunohistochemical stains and molecular studies:
  - IDH1-R132H immune stain
  - IDH sequencing for IDH1 codon 132 and IDH2 codon 172

- ✓ Gain of function mutation→ lead to increased production of 2-hydroxyglutarate (oncometabolite)→interferes with the activity of several enzymes that regulate gene expression→ DNA hypermethylation & maintaining the cells in stem cell-like physiological states→ 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 →carry 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 → associated with genomic instability → induces P53 dependent cell death→ mutation in P53 helps these cells to survive.

Gliomas

WHO 2016

2.1: Diffuse astrocytic and oligodendroglial tumours

- 2.1.1: Introduction
- 2.1.2: Diffuse astrocytoma, IDH-mutant
  - 2.1.2.1: Gemistocytic astrocytoma, IDH-mutant
- 2.1.3: Diffuse astrocytoma, IDH-wildtype
- 2.1.4: Diffuse astrocytoma, NOS
- 2.1.5: Anaplastic astrocytoma, IDH-mutant
- 2.1.6: Anaplastic astrocytoma, IDH-wildtype
- 2.1.7: Anaplastic astrocytoma, NOS
- 2.1.8: Glioblastoma, IDH-wildtype
  - 2.1.8.1: Giant cell glioblastoma
  - 2.1.8.2: Gliosarcoma
  - 2.1.8.3: Epithelioid glioblastoma
- 2.1.9: Glioblastoma, IDH-mutant
- 2.1.10: Glioblastoma, NOS
- 2.1.11: Diffuse midline glioma, H3 K27M mutant
- 2.2.1: Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
- 2.2.2: Oligodendroglioma, NOS
- 2.2.3: Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codel
- 2.2.4: Anaplastic oligodendroglioma, NOS
- 2.2.5: Oligoastrocytoma, NOS
- 2.2.6: Anaplastic oligoastrocytoma, NOS

2.3: Other astrocytic tumours

- 2.3.1: Pilocytic astrocytoma
  - 2.3.1.1: Pilomyxoid astrocytoma
- 2.3.2: Subependymal giant cell astrocytoma
- 2.3.3: Pleomorphic xanthoastrocytoma

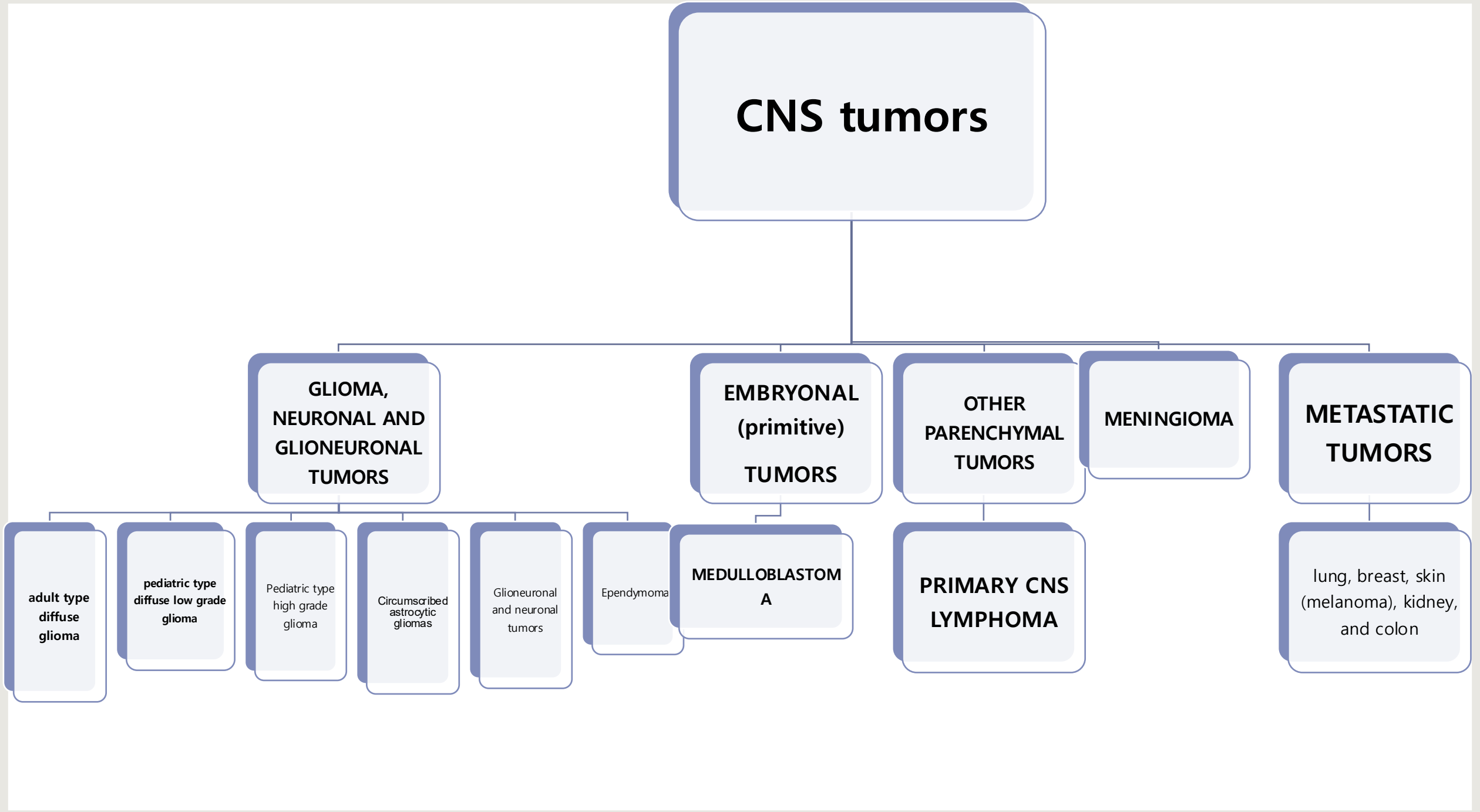
Gliomas, Glioneuronal and Neuronal Tumours

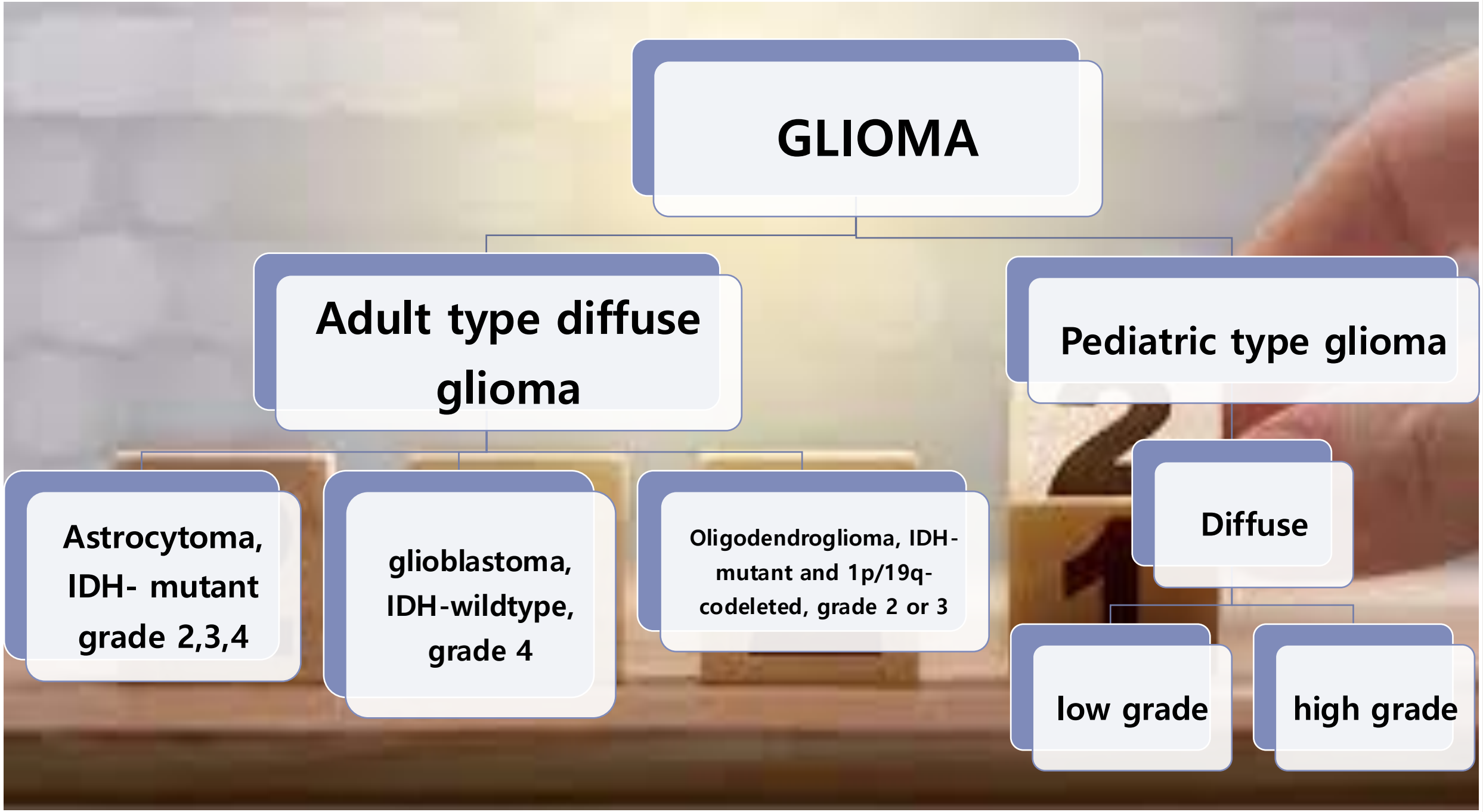
WHO 2021

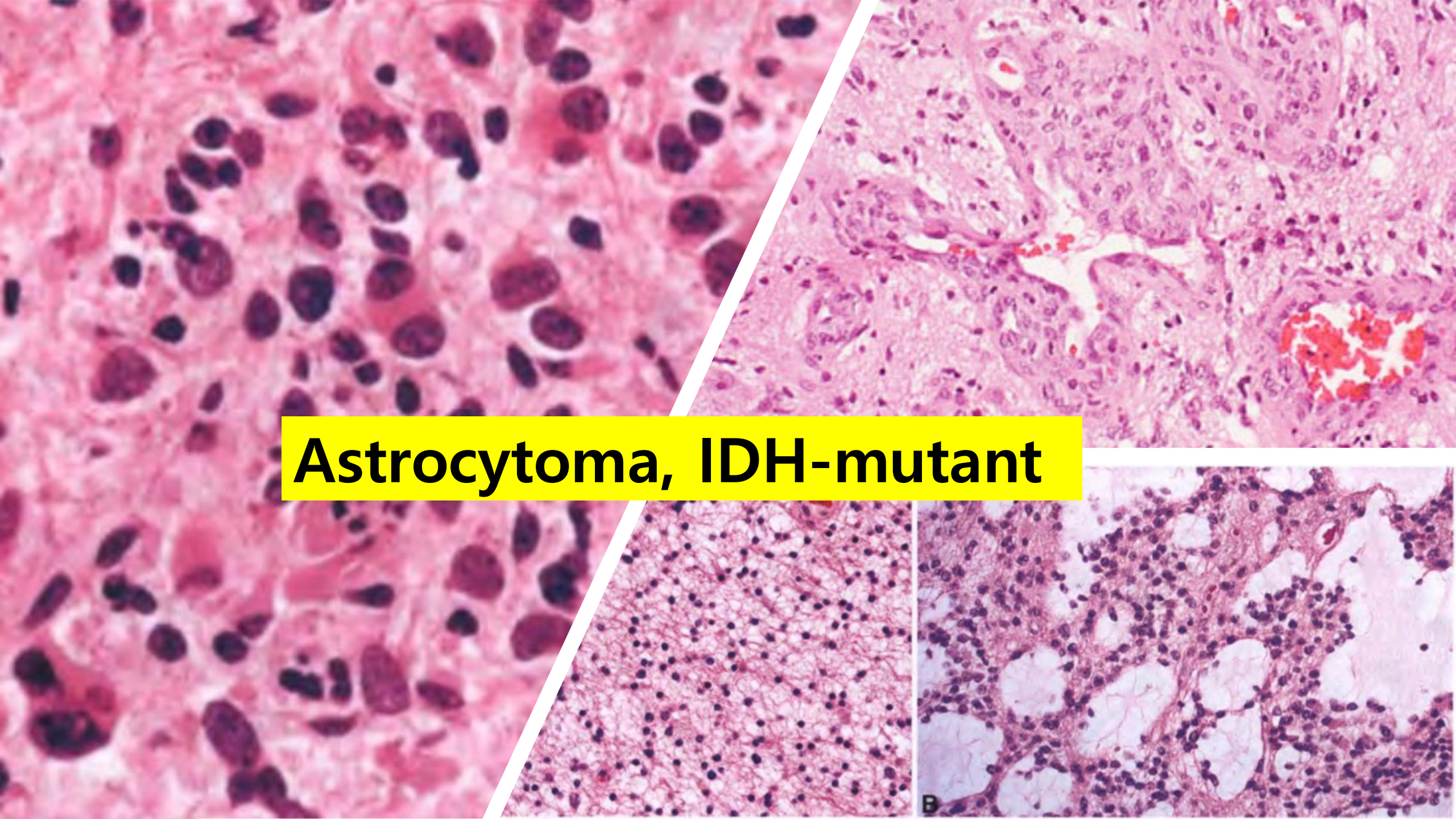
- 2.0.0.1: Introduction to gliomas, glioneuronal tumours, and neuronal tumours

2.1: Gliomas, Glioneuronal and Neuronal Tumours

- Adult-type diffuse gliomas
  - 2.1.1.1: Astrocytoma, IDH-mutant
  - 2.1.1.2: Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
  - 2.1.1.3: Glioblastoma, IDH-wildtype
- Paediatric-type diffuse low-grade gliomas
  - 2.1.4.1: Diffuse astrocytoma, MYB or MYBL1-altered
  - 2.1.4.2: Angiocentric glioma
  - 2.1.3.5: Polymorphous low-grade neuroepithelial tumour of the young
  - 2.1.5.1: Diffuse low-grade glioma, MAPK pathway-altered
- 2.1.2: Paediatric-type diffuse high grade gliomas
  - 2.1.2.1: Diffuse midline glioma, H3 K27-altered
  - 2.1.2.2: Diffuse hemispheric glioma, H3 G34-mutant
  - 2.1.2.3: Diffuse paediatric-type high grade glioma, H3 wildtype and IDH wild type
  - ~~2.1.2.4: Diffuse midline glioma, EGFR mutant (formerly Bithalamic glioma, EGFR mutant)~~
  - 2.1.2.4: Infant-type hemispheric glioma
- 2.1.3: Circumscribed astrocytic gliomas
  - 2.1.3.1: Pilocytic astrocytoma
  - 2.1.3.2: High-grade astrocytoma with piloid features
  - 2.1.3.3: Pleomorphic xanthoastrocytoma
  - 2.2.0.4: Subependymal giant cell astrocytoma
  - 2.2.0.1: Chordoid glioma
  - 2.2.0.2: Astroblastoma, MN1-altered
- 2.1.4: Glioneuronal and neuronal tumours
  - 2.1.3.7: Ganglioglioma
  - 2.1.3.9: Desmoplastic infantile ganglioglioma / Desmoplastic infantile astrocytoma
  - 2.1.3.10: Dysembryoplastic neuroepithelial tumour
  - 2.2.0.3: Diffuse glioneuronal tumour with oligodendroglioma-like features and nuclear clusters
  - 2.2.0.5: Papillary glioneuronal tumour


CNS tumors
GLIOMA, NEURONAL AND GLIONEURONAL TUMORS
EMBRYONAL (primitive) TUMORS
OTHER PARENCHYMAL TUMORS
MENINGIOMA
METASTATIC TUMORS
adult type diffuse glioma
pediatric type diffuse low grade glioma
Pediatric type high grade glioma
Circumscribed astrocytic gliomas
Glioneuronal and neuronal tumors
Ependymoma
MEDULLOBLASTOMA
PRIMARY CNS LYMPHOMA
lung, breast, skin (melanoma), kidney, and colon


GLIOMA
Adult type diffuse glioma
Pediatric type glioma
Astrocytoma, IDH- mutant grade 2,3,4
glioblastoma, IDH-wildtype, grade 4
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, grade 2 or 3
Diffuse
low grade
high grade


Astrocytoma, IDH-mutant
B

Definition:

Phenotype: It Is a diffusely infiltrating glioma

Genotype:

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

- **Age at diagnosis:** 40–60 year old.

- **Location:** cerebral hemispheres +/- cerebellum, brainstem, or spinal cord.

- **Presentation:**
  - seizures, headaches, and focal neurologic deficits related to the anatomic site of involvement.
  - Clinically: static for years or Progressive.

- **The prognosis gets poorer as the grade increases**

- **On the basis of histologic features astrocytomas, IDH- mutant are stratified into three groups:**
  - **astrocytomas, IDH- mutant,** grade 2, median survival is >10 years.
  - **astrocytomas, IDH- mutant** grade 3, median survival is 5-10 years
  - **astrocytomas, IDH- mutant** grade 4, median survival is 3 years.

- **NO grade 1 astrocytoma, IDH- mutant, because by convention grade 1 implies benign behavior and all diffuse gliomas are considered malignant**

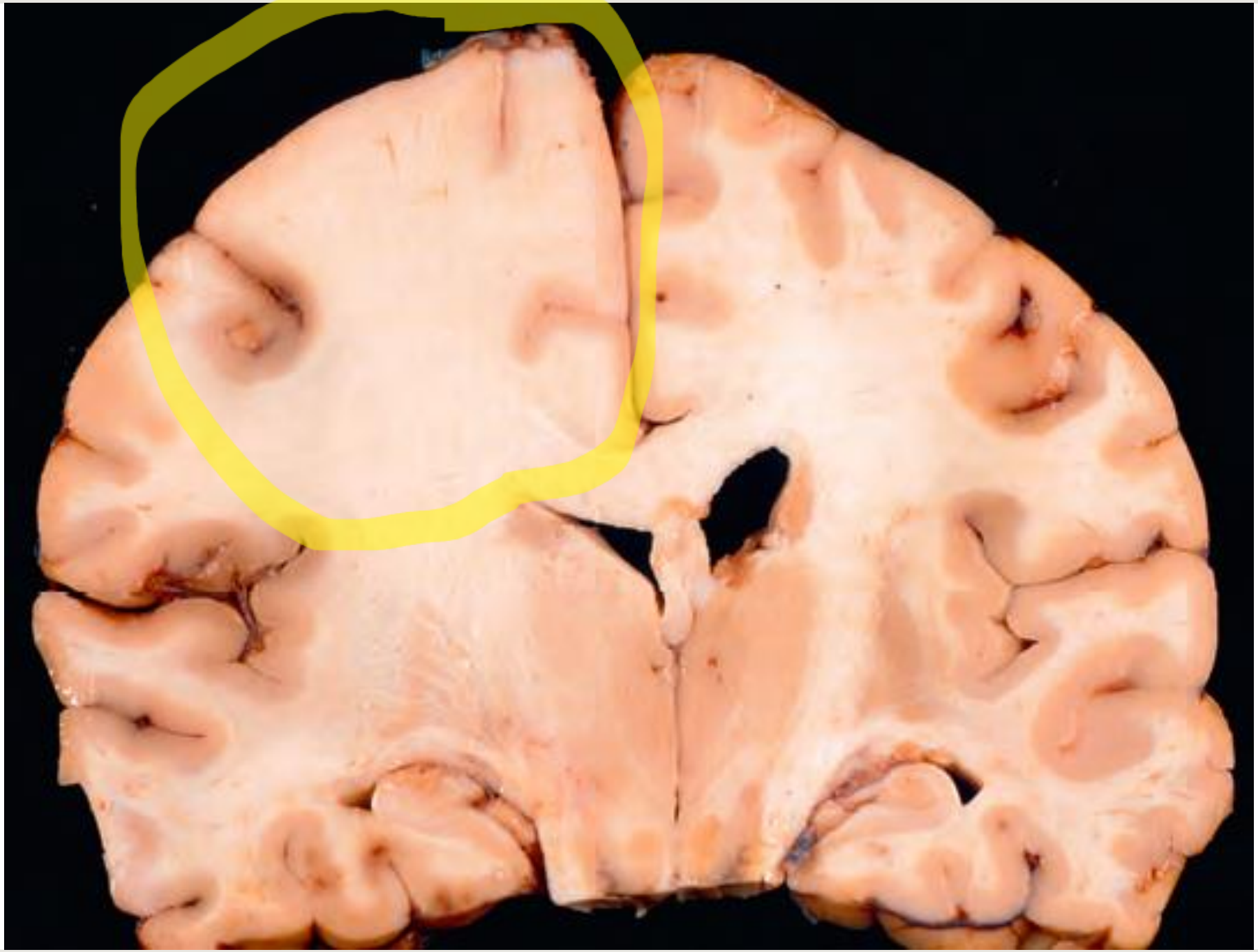
Morphology, macroscopic:

Grade 2 &3:

- poorly defined, infiltrative tumors
- expand and distort the invaded brain
- **NO** discrete mass, Infiltration beyond the grossly evident margins.

Grade 4:

- poorly defined, infiltrative tumors
- **lacks large** areas of central necrosis and hemorrhage seen in IDH-wild-type GBM



Diffuse astrocytoma, IDH- mutant, WHO grade 2, Microscopic:

- The transition between neoplastic and normal tissue is **indistinct**
- tumor cells infiltrate normal tissue many centimeters from the main lesion.

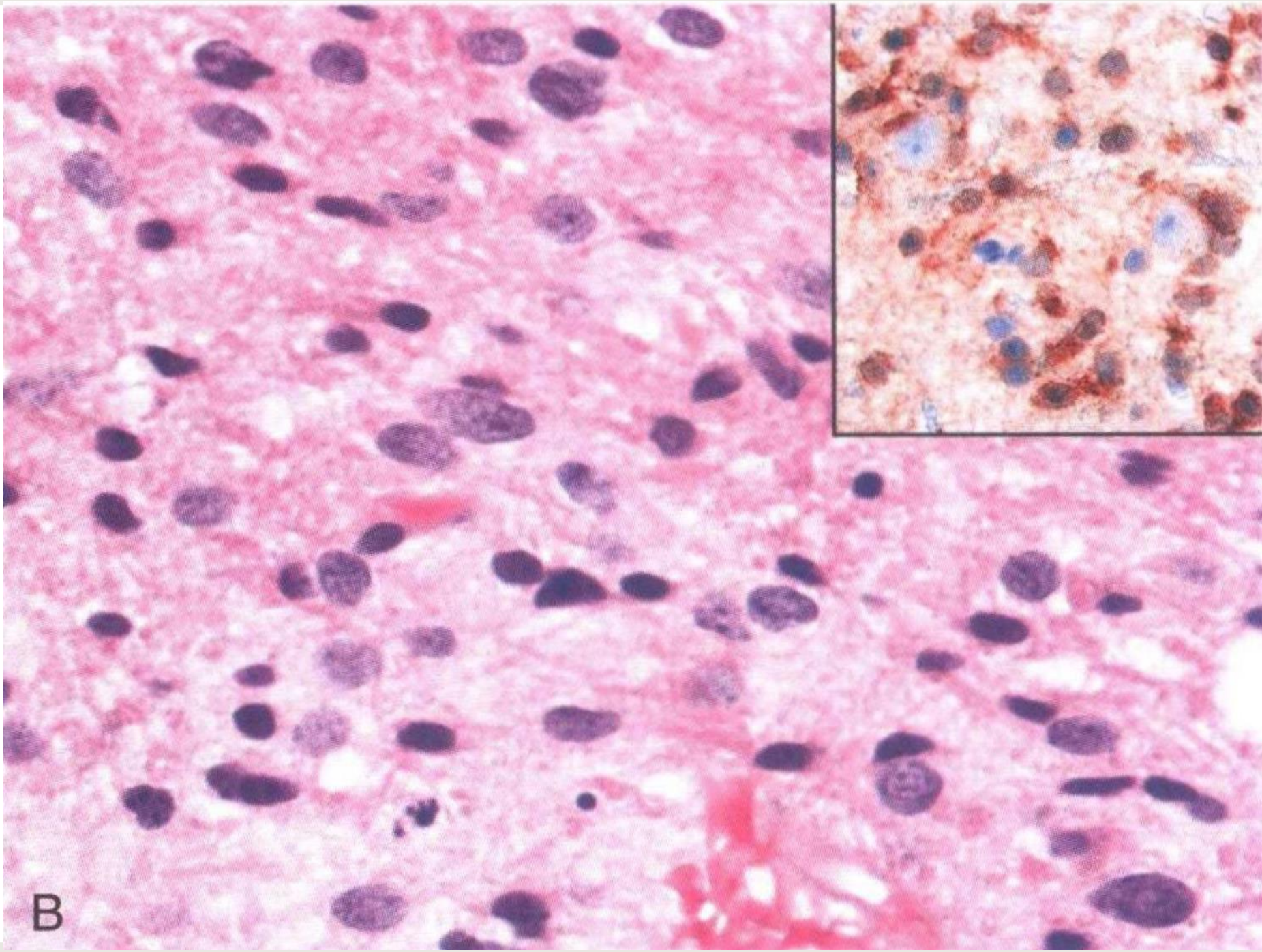
- **Hypercellular** (compared to normal white matter): **mild to moderate** increase in the number of glial cell nuclei.
- **Cytologic atypia**:
  - mild
  - enlarged, elongated or irregular hyperchromatic nuclei
  - No prominent atypia

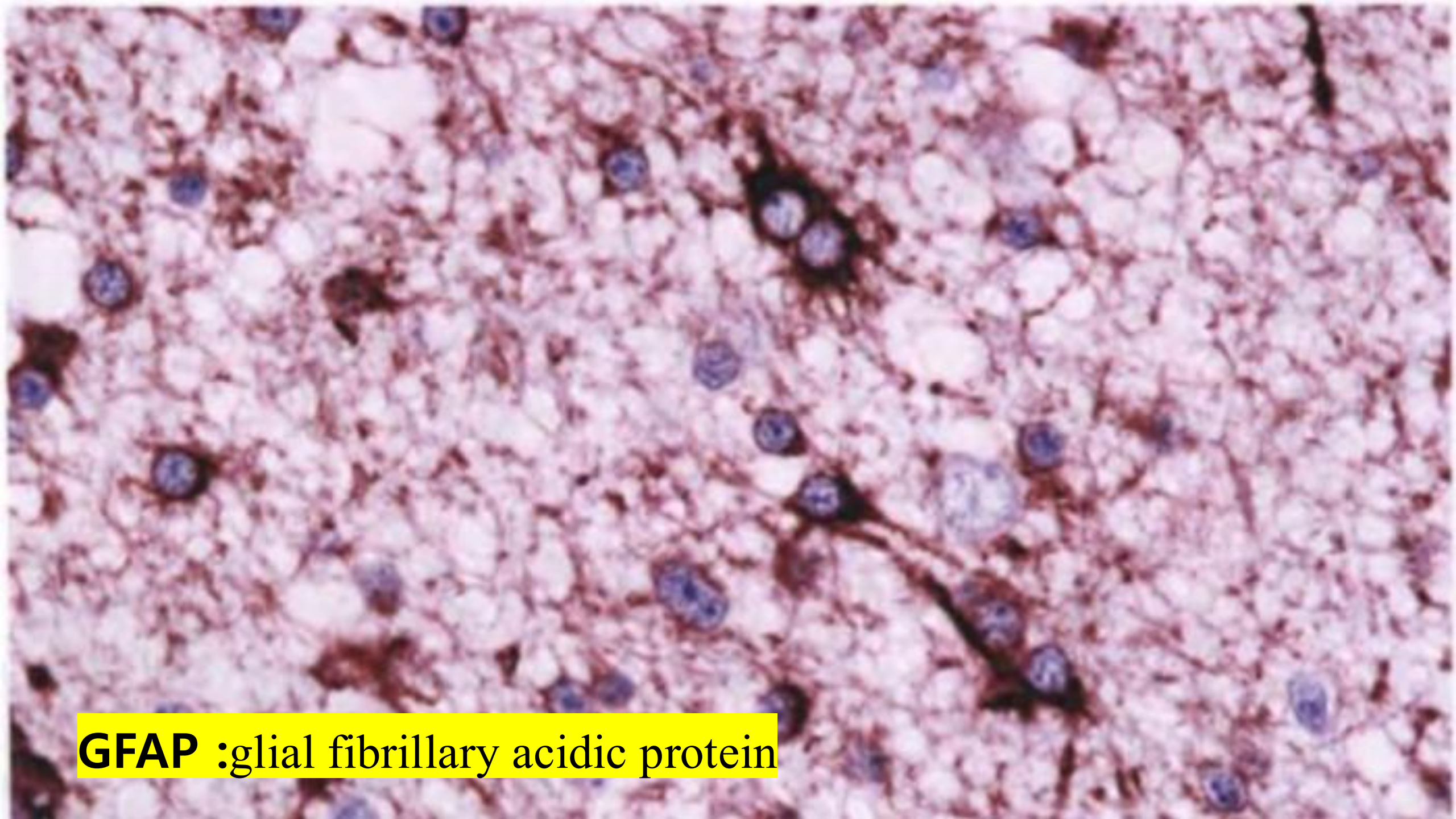
+ **fibrillary background** made of a network of fine astrocytic cell processes

- **NO or rare** Mitotic activity
- **NO** necrosis
- **NO** microvascular proliferation

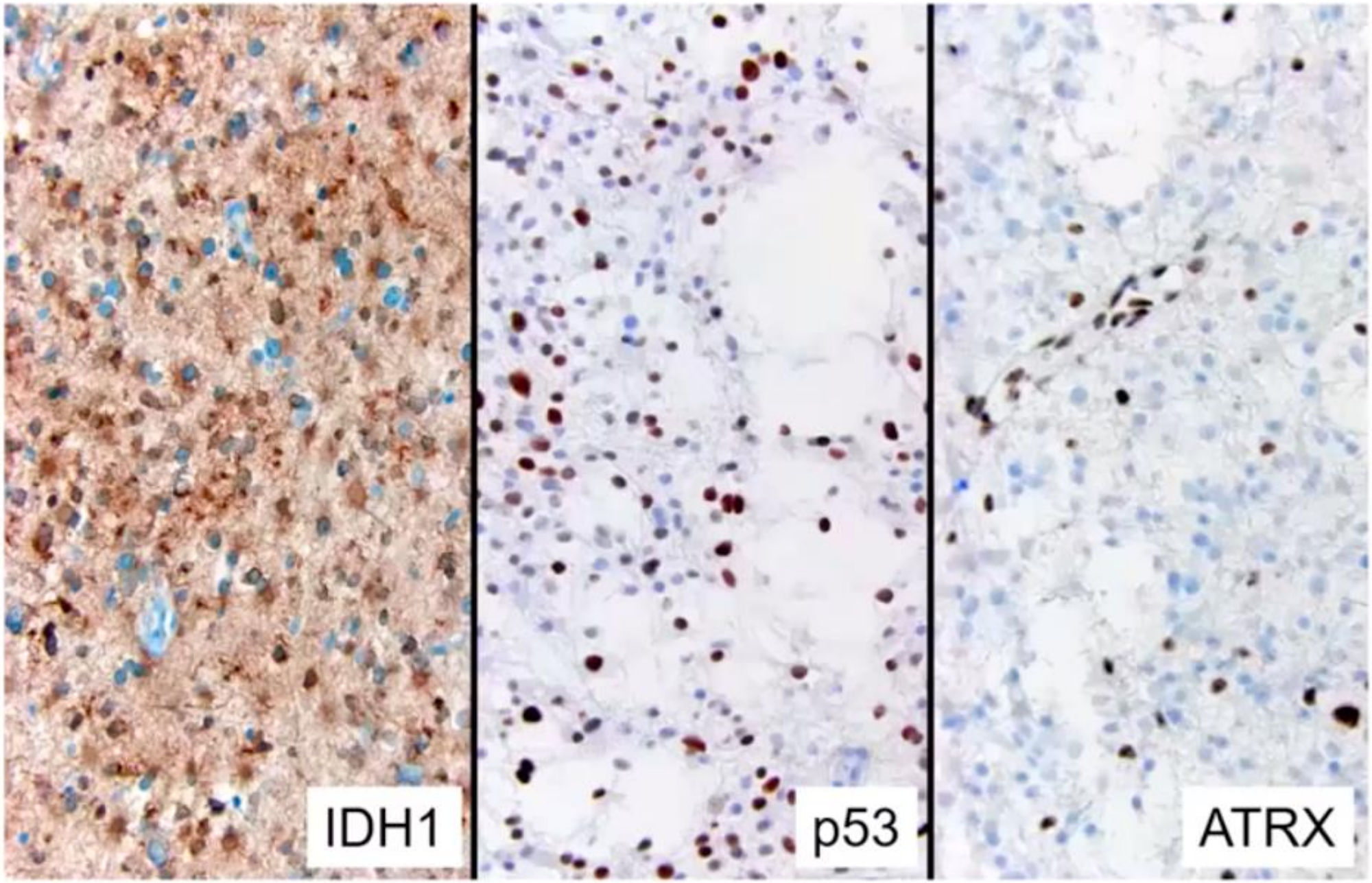
Enlarged irregular nuclei embedded within fbrillar matrix of the brain

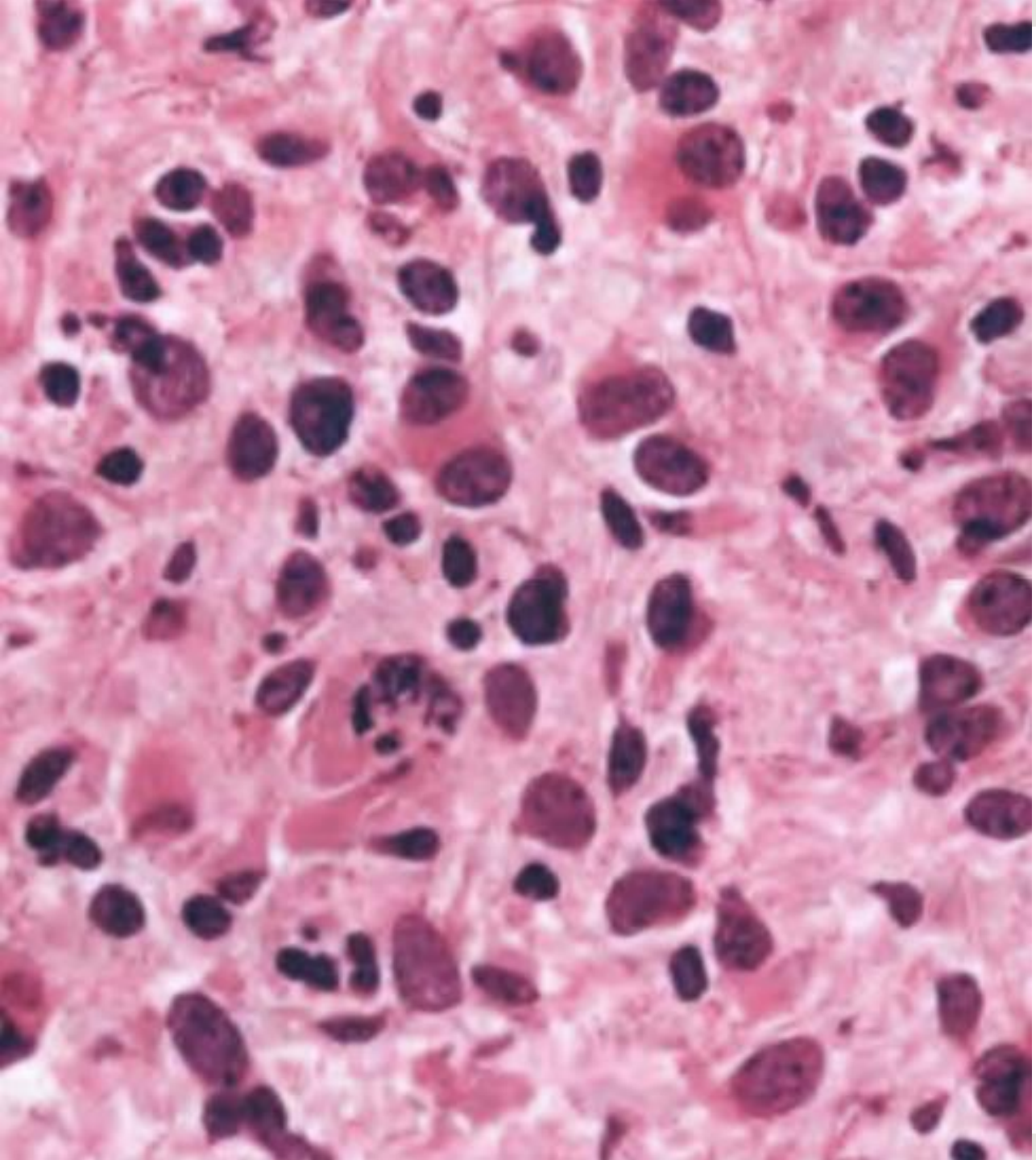
Inset: IDH1 immune stain is positive in tumor cells




GFAP :glial fibrillary acidic protein

Astrocytoma, IDH-mutant, CNS WHO grades 2-4





Astrocytoma, IDH-mutant, grade 3:

- More densely cellular
- More nuclear pleomorphism
- mitotic figures are **present**
- **NO** necrosis
- **NO** microvascular proliferation

Astrocytoma, IDH-mutant, grade 4:

- Same as grade 3 with Microvascular proliferation and/or necrosis

- The presence of homozygous deletion of CDKN2A &/or CDKN2B → **astrocytomas, IDH- mutant, grade 4 (EVEN IF THE HISTOLOGY SUGGESTS A LOWER GRADE).**


thank you