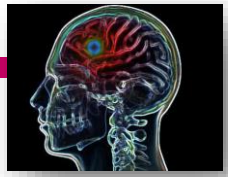


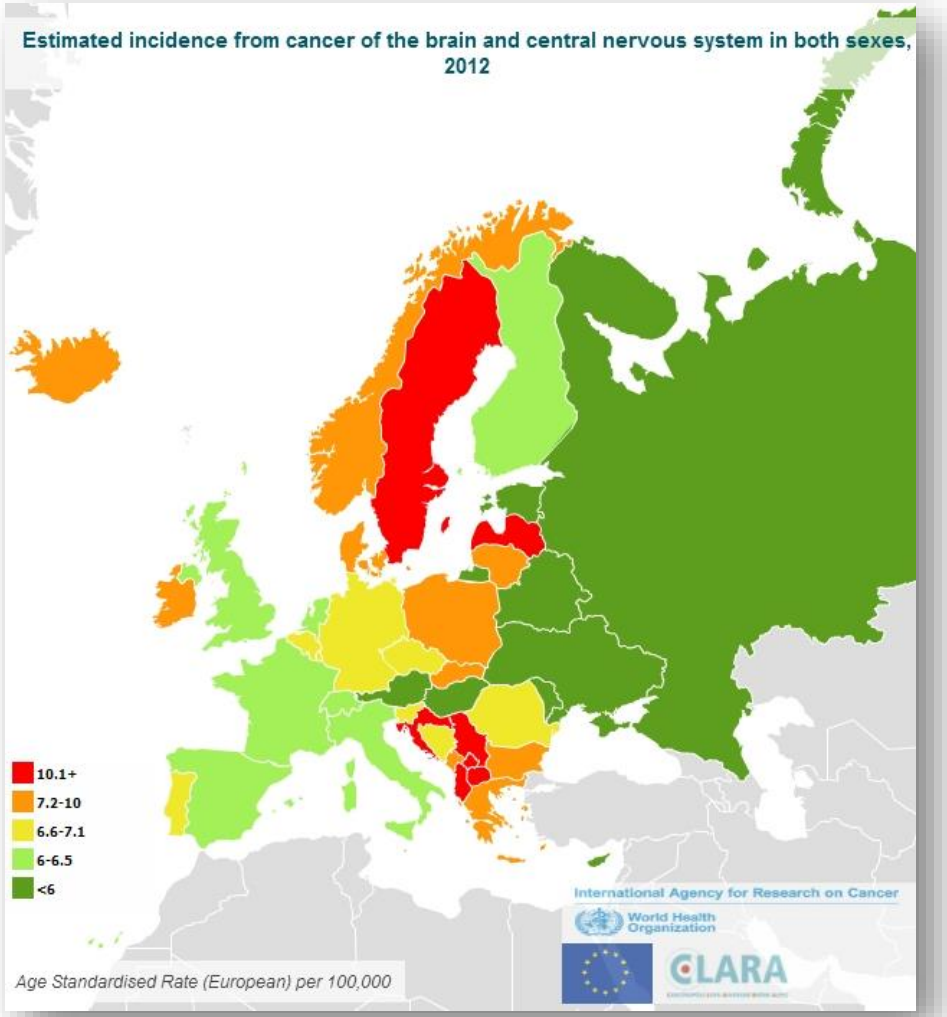
NEUROPATHOLOGY
NEOPLASIA

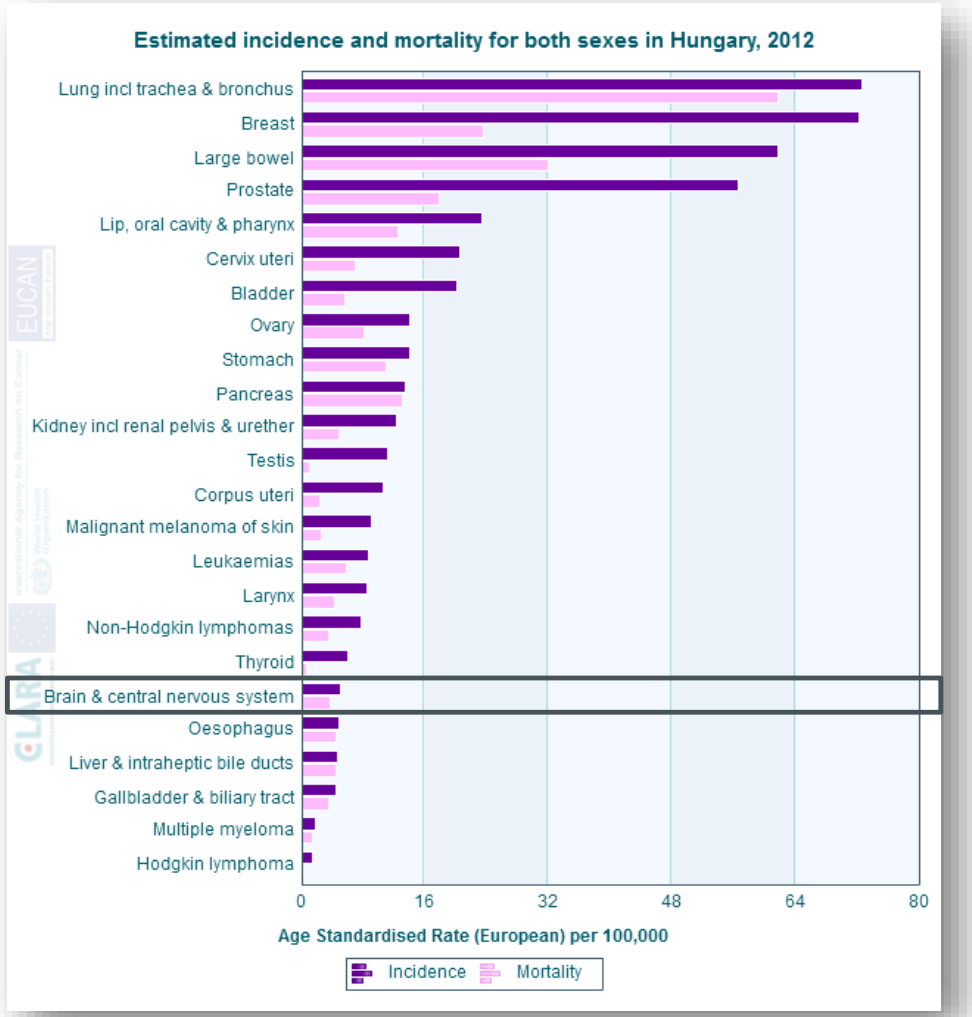
HAJNALKA RAJNAI

Semmelweis Egyetem – I. Patológiai és Kísérleti Rákkutató Intézet

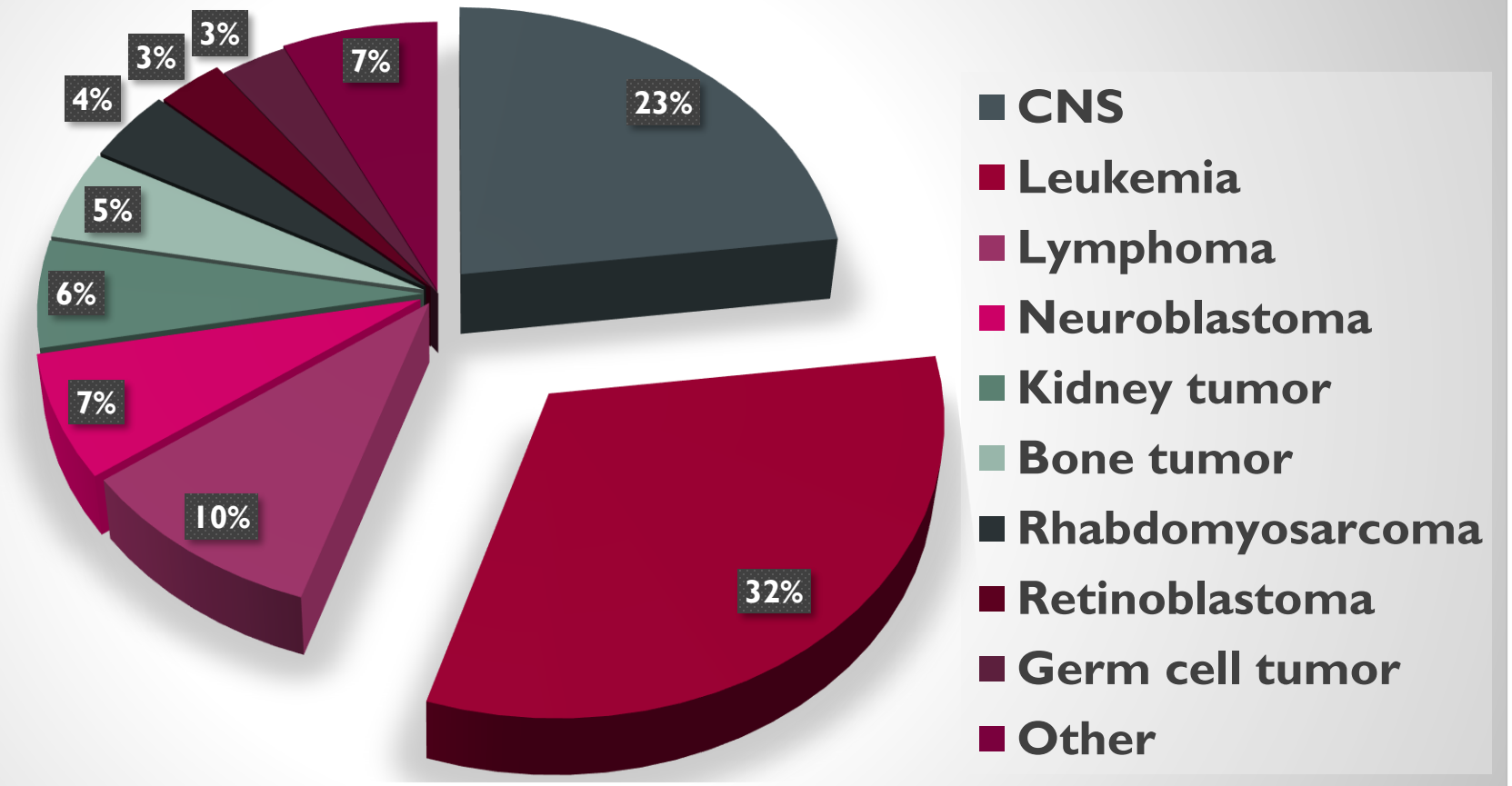
rajnai.hajnalka@med.semmelweis-univ.hu

PRIMARY CNS NEOPLASIAS

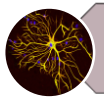




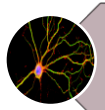
INCIDANCE OF CHILDHOOD NEOPLASMS



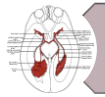
PRIMARY TUMORS OF THE CNS



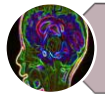
Gliomák



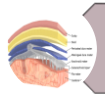
Neuronal or mixed glioneural tumors



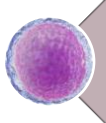
Choroid plexus neoplasms



Embryonal tumors

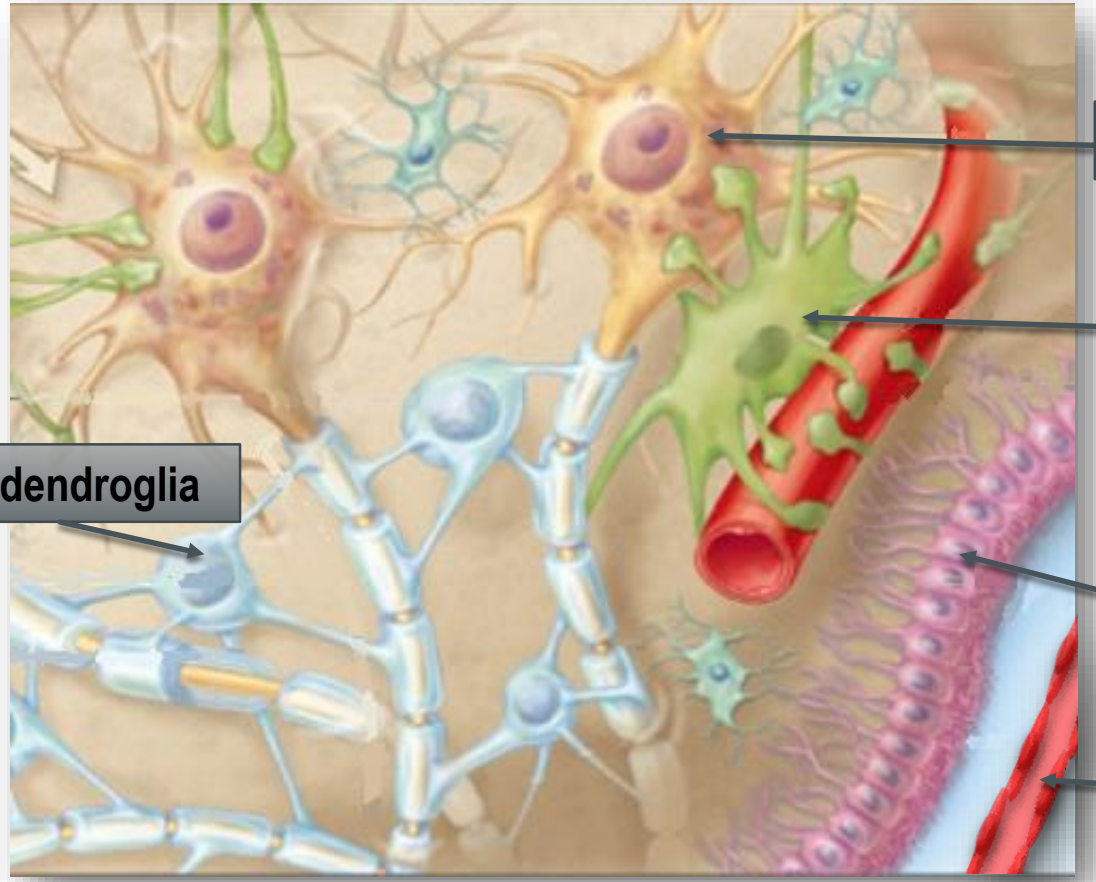


Meningial tumors



Other parenchymal tumors

- Haematologic malignancies
- Germ cell tumors



CHARACTERISTICS

- Diagnosis
  - Age
  - Sex
  - Site of neoplasm
  - Family history
- Do not have premalignant or in situ stages
- Rarely spread outside of the CNS

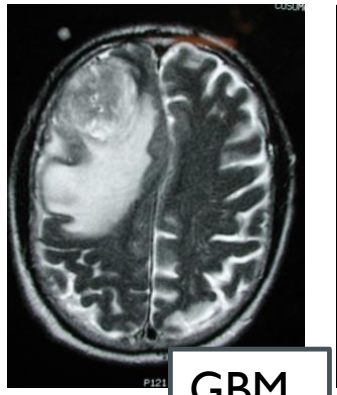
Grade

- Predicting the biological behaviour
- Grade I
  - Low proliferative potential
  - Possibility of curative resection
- Grade II
  - Infiltrative
  - Often recur
  - Progression
- Grade III
  - Histological evidence of malignancy
  - High mitotic activity, atypia
- Grade IV
  - Cytologically malignant
  - Rapid disease evolution

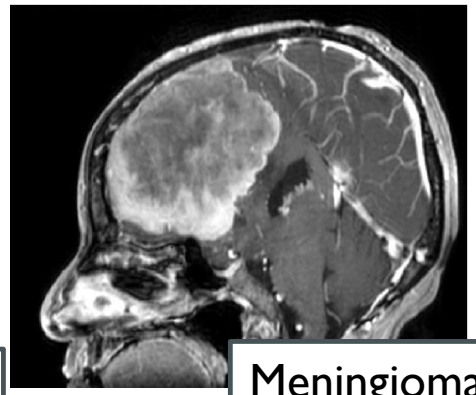
SYMPTOMS

Depends on site of tumor and growth speed

Symptoms of increased ICP

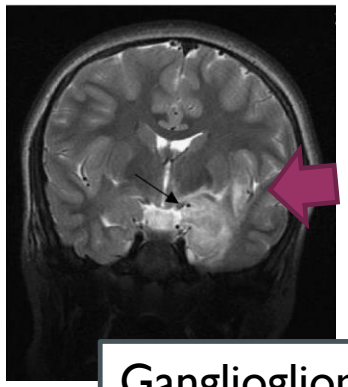


GBM



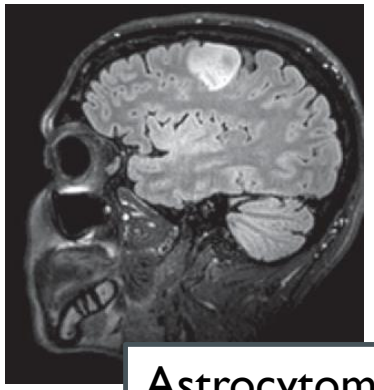
Meningioma

Epilepsy



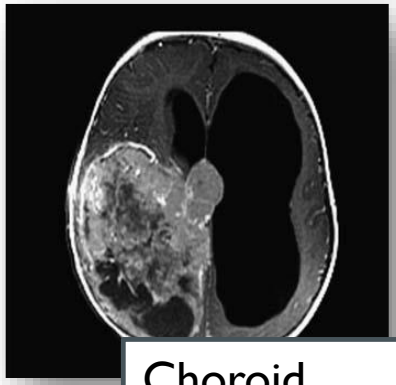
Ganglioglioma

Focal deficits



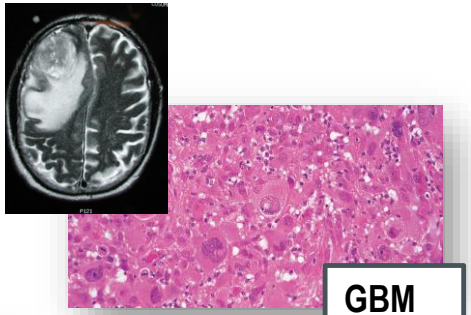
Astrocytoma

Hydrocephalus

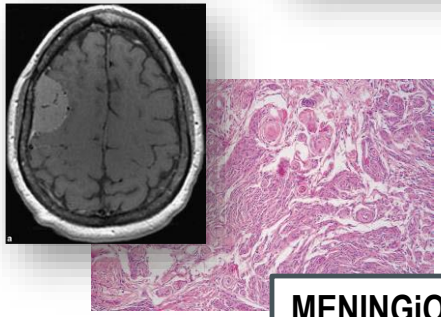


Choroid Plexus cc

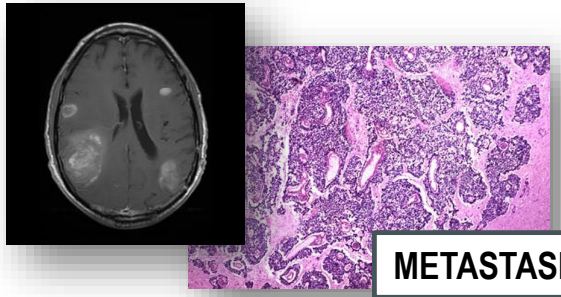
PRIMARY TUMORS OF THE CNS



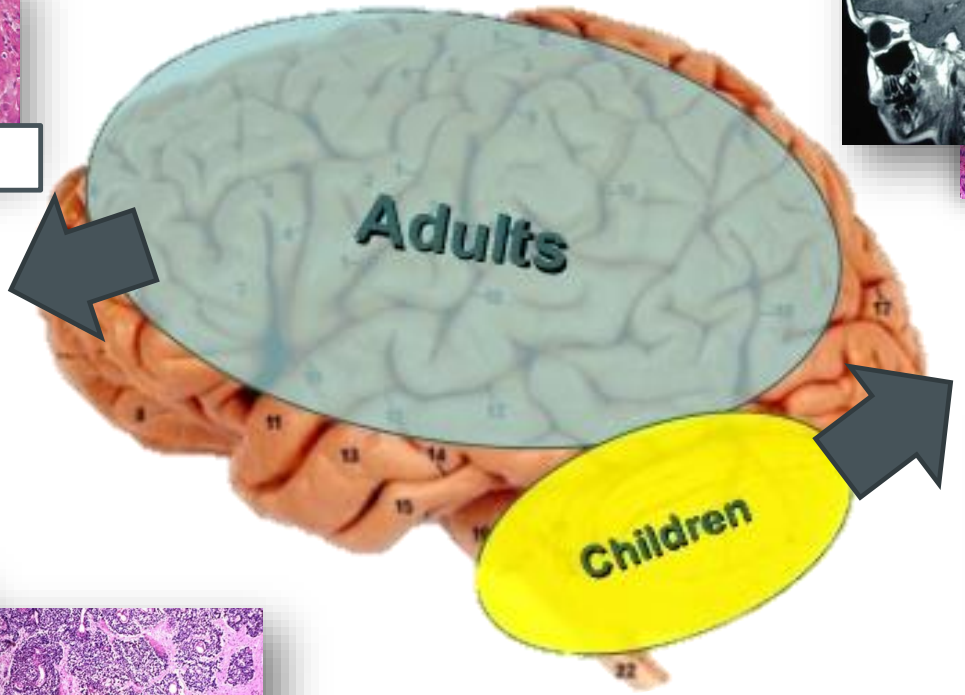
GBM

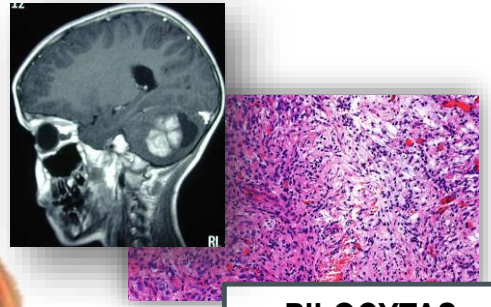


MENINGiOMA

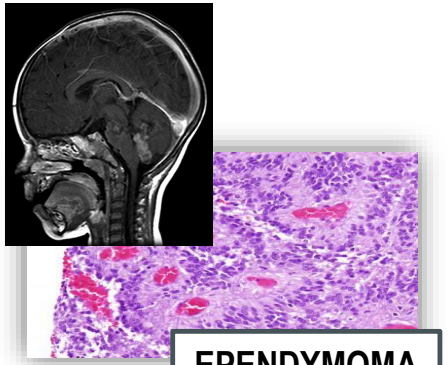


METASTASIS

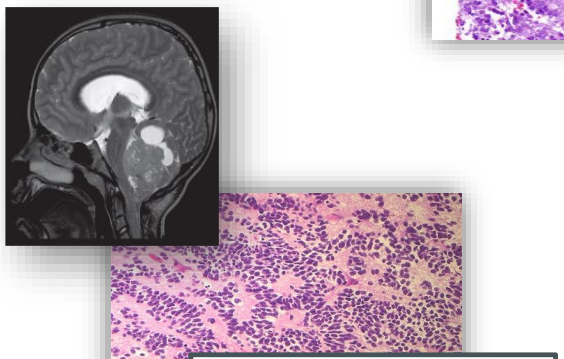




PILOCYTAS ASTROCYTOMA



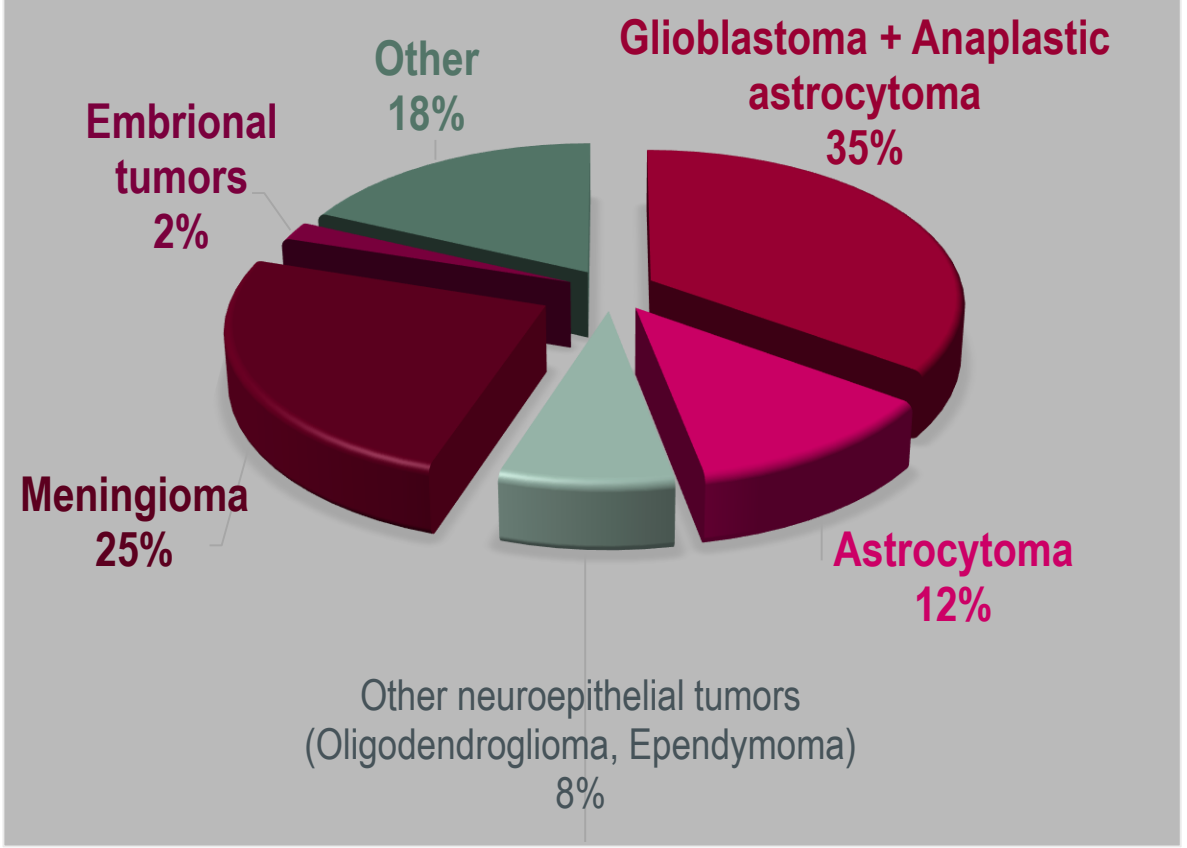
EPENDYMOMA



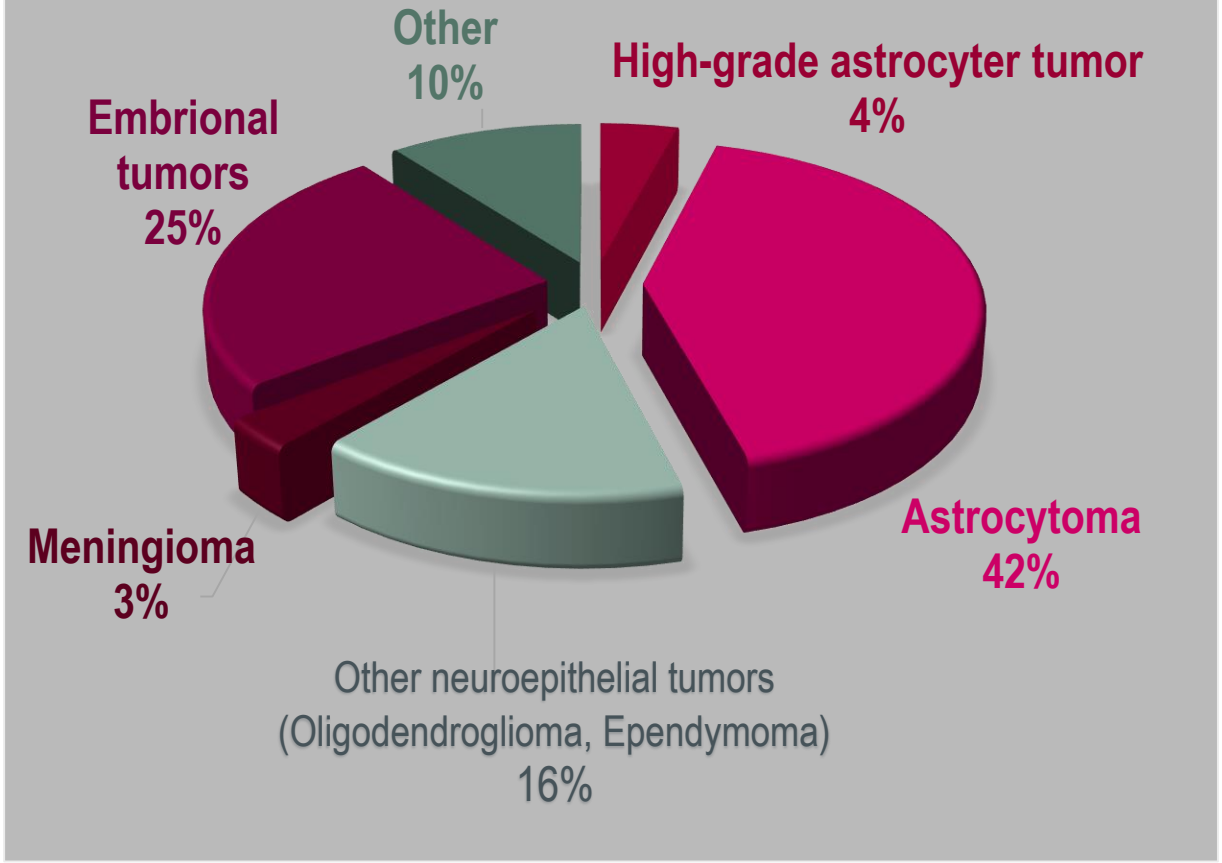
MEDULLOBLASTOMA

PRIMARY TUMORS OF THE CNS

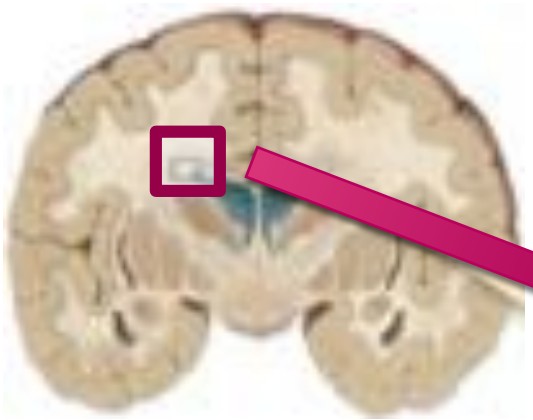
ADULT CNS TUMORS

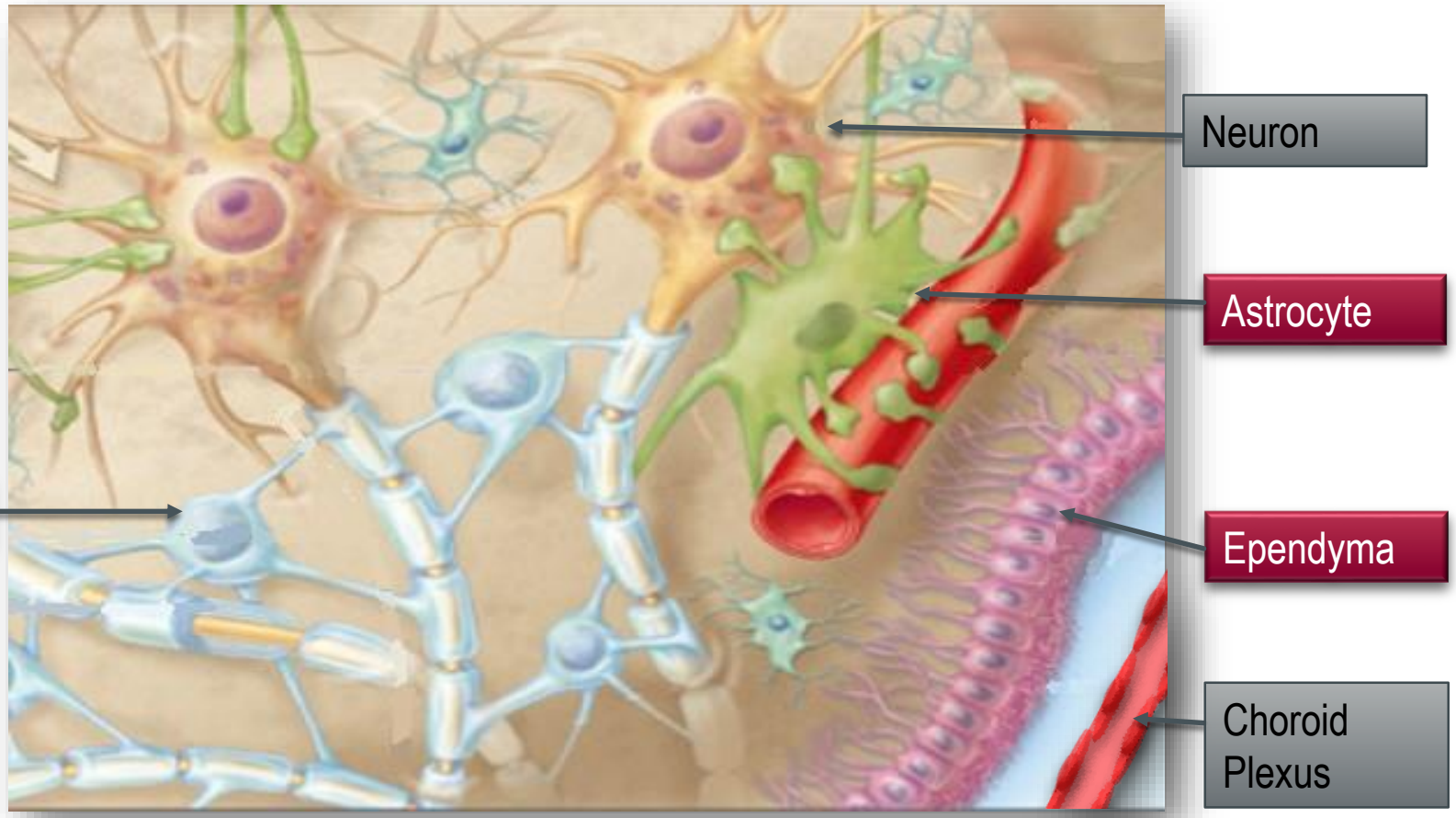


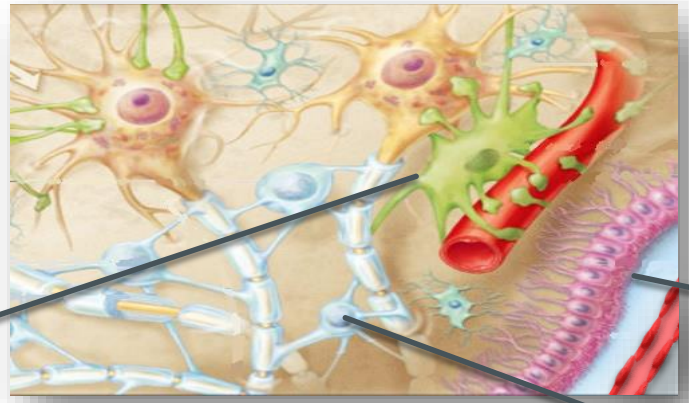
PEDIATRIC CNS TUMORS



I. GLIOMAS




Neuron
Astrocyte
Oligodendroglia
Ependyma
Choroid Plexus



Astrocytomas

Oligodendrogliomas

Ependymomas

GRADE I

Pilocytic astocytoma

GRADE II

Diffuse astocytoma

Oligodendroglioma

Ependymoma

GRADE III

Anaplastic astocytoma

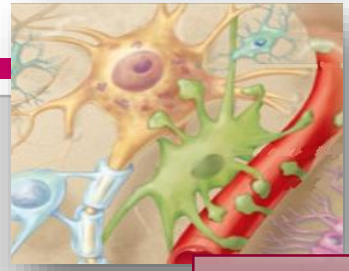
Anaplastic Oligodendroglioma

Anaplastic Ependymoma

GRADE IV

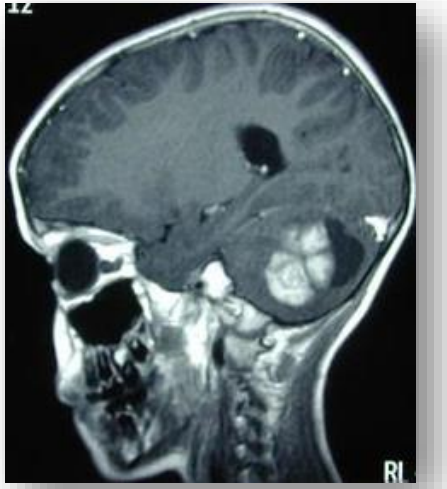
Glioblastoma

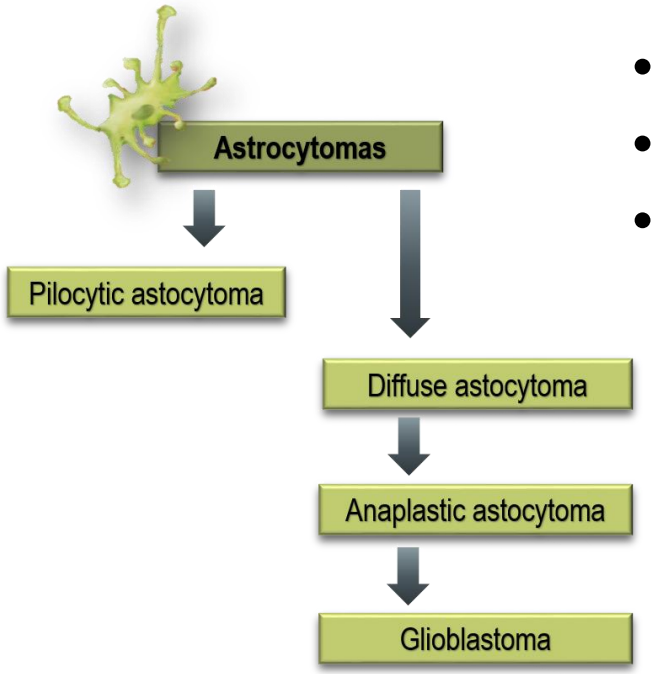
CNS Tumors with astrocytic differentiation



Pilocytic astrocytoma (Grade I)

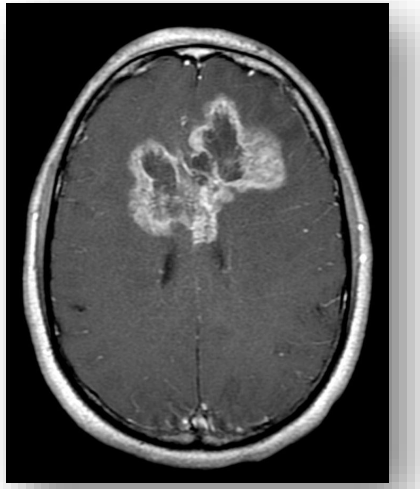
- Children, young adults
- Localised
- Posterior fossa





Diffuse astrocytomas (Grade II-IV)

- Middle aged, older patients
- Infiltrating
- Hemispherial



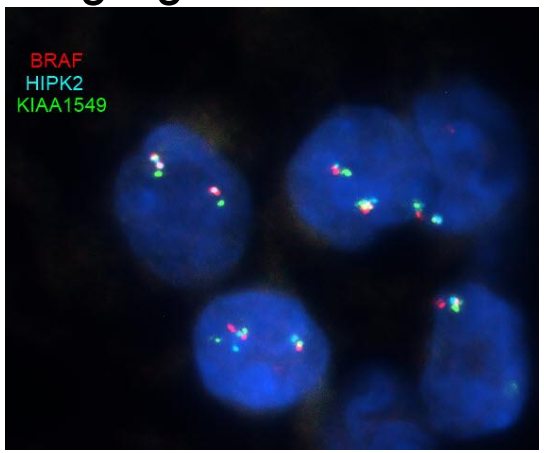
Pilocytic astrocytoma (Grade I)

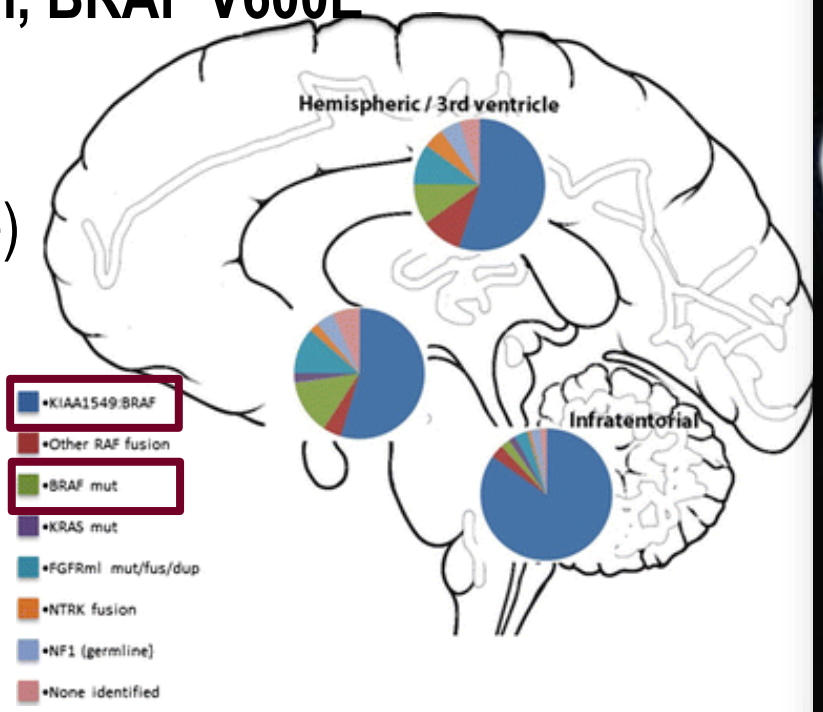

Astrocyta

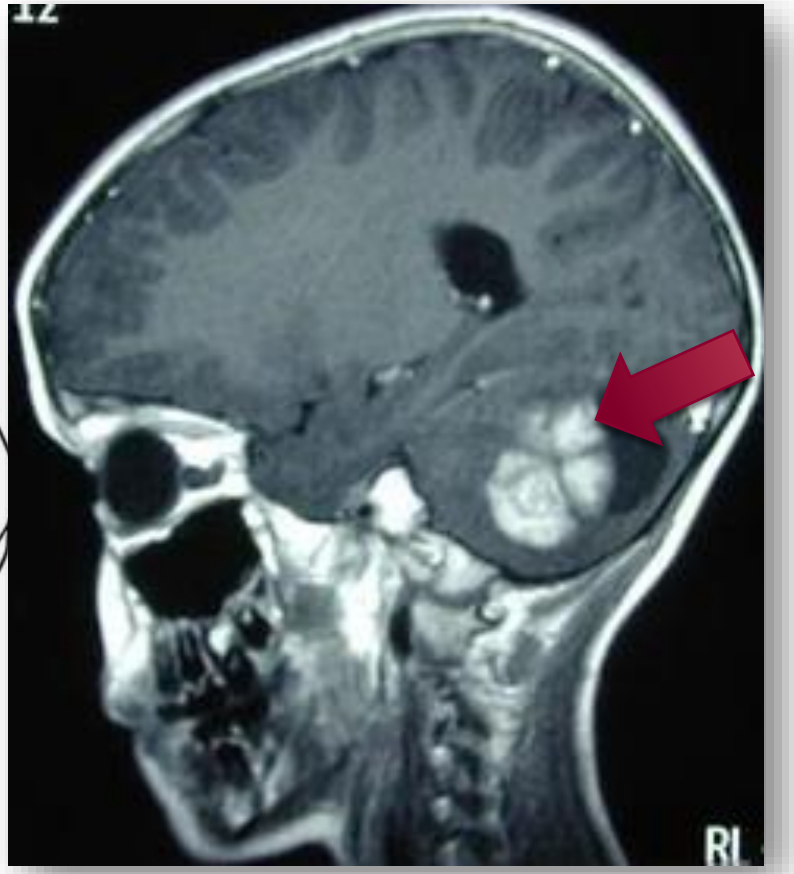
- Children and young adults
- Common(18%) benign CNS tumor in children
- Most commonly infratentorial – Cerebellum

- **BRAF/KIAA1549 translocation, BRAF V600E**
- MAPK pathway mutations

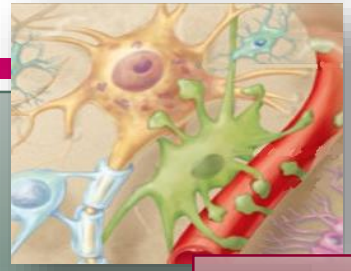
- High-grade transformation (rare)

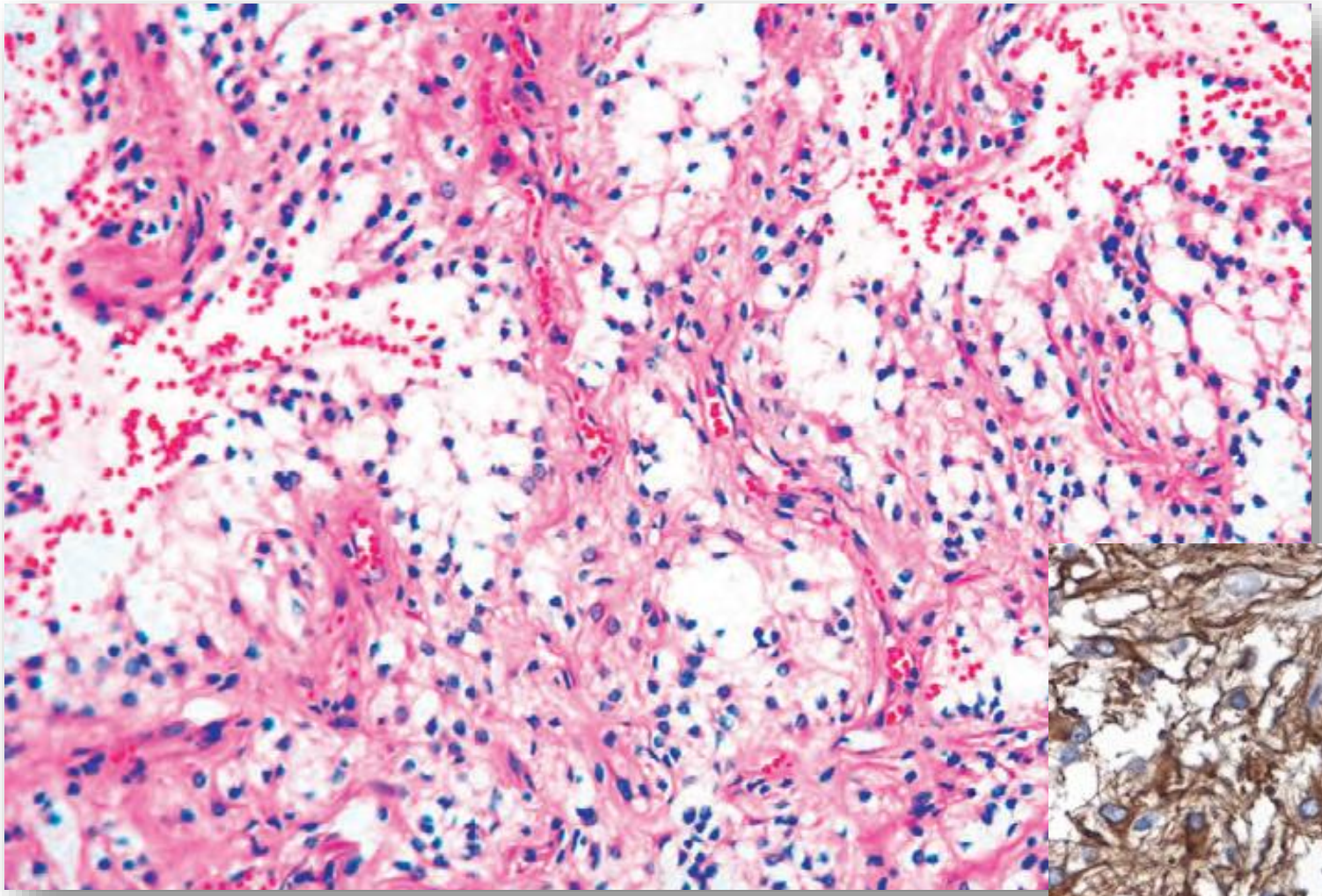




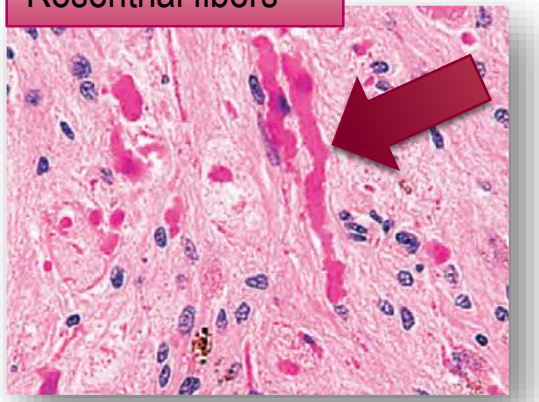


Pilocytic astrocytoma (Grade I)

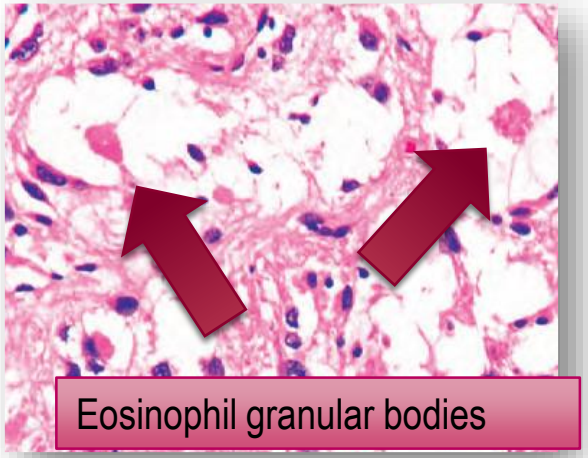

Astrocyte



Rosenthal fibers

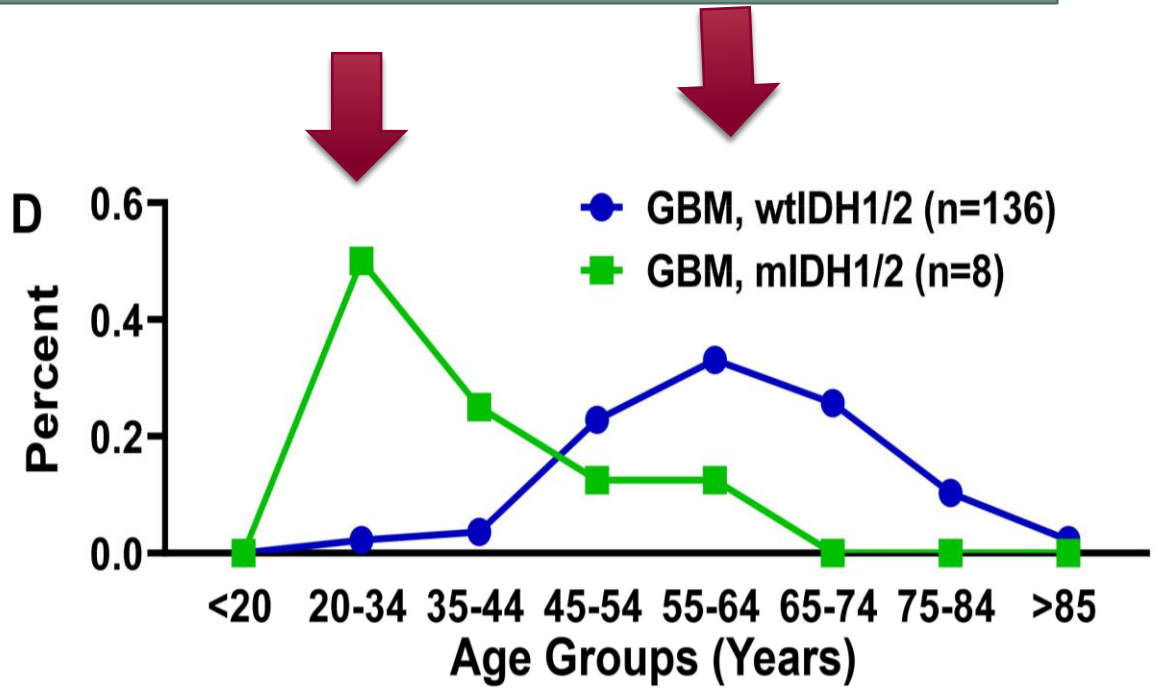


GFAP


Eosinophil granular bodies

Diffuse gliomas with astrocytic differentiation (Grade II-IV)

- Two age groups
  - 20-35 yeras
    - Grade II → Grade III → Grade IV
    - IDH gene mutation
  - >60 years
    - Grade IV
- Hemispherial – Focal neurological deficits



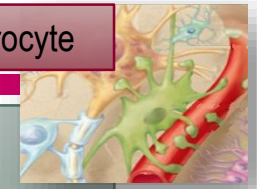
Well-differenciated diffuse astrocytoma Grade II

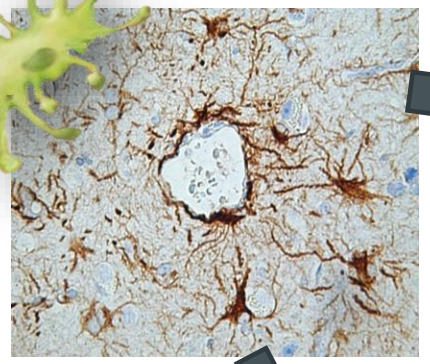
Anaplastic astrocytoma Grade III

Glioblastoma Grade IV

- Similar prognosis in both age groups
- Survival: 15-20 months

Diffuse gliomas with astrocytic differentiation (Grade II-IV)

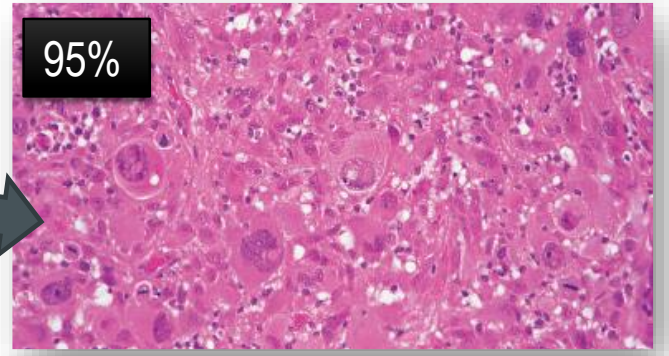




TERT mutation

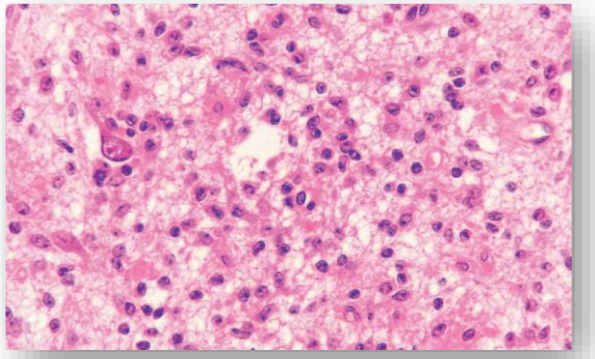
RTK/PI3K/AKT pathway

P53/pRB pathway



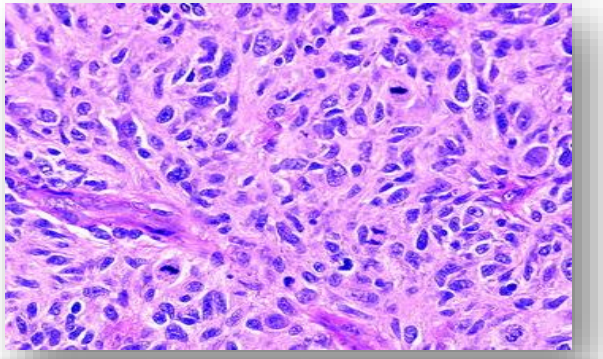
Primer Glioblastoma Gr. IV

IDH1/IDH2
P53/ATRX mut



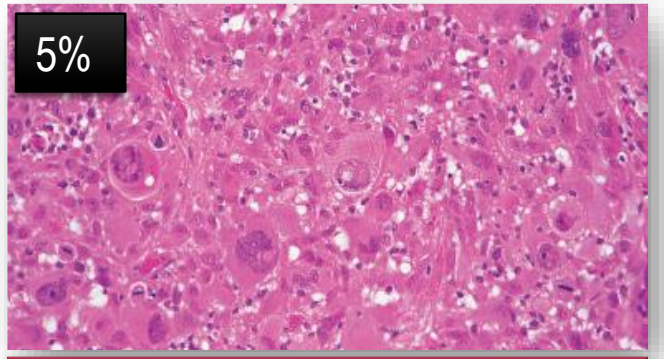
Astrocytoma Gr. II

MYC, CCND2



Anaplastic astrocytoma Gr. III

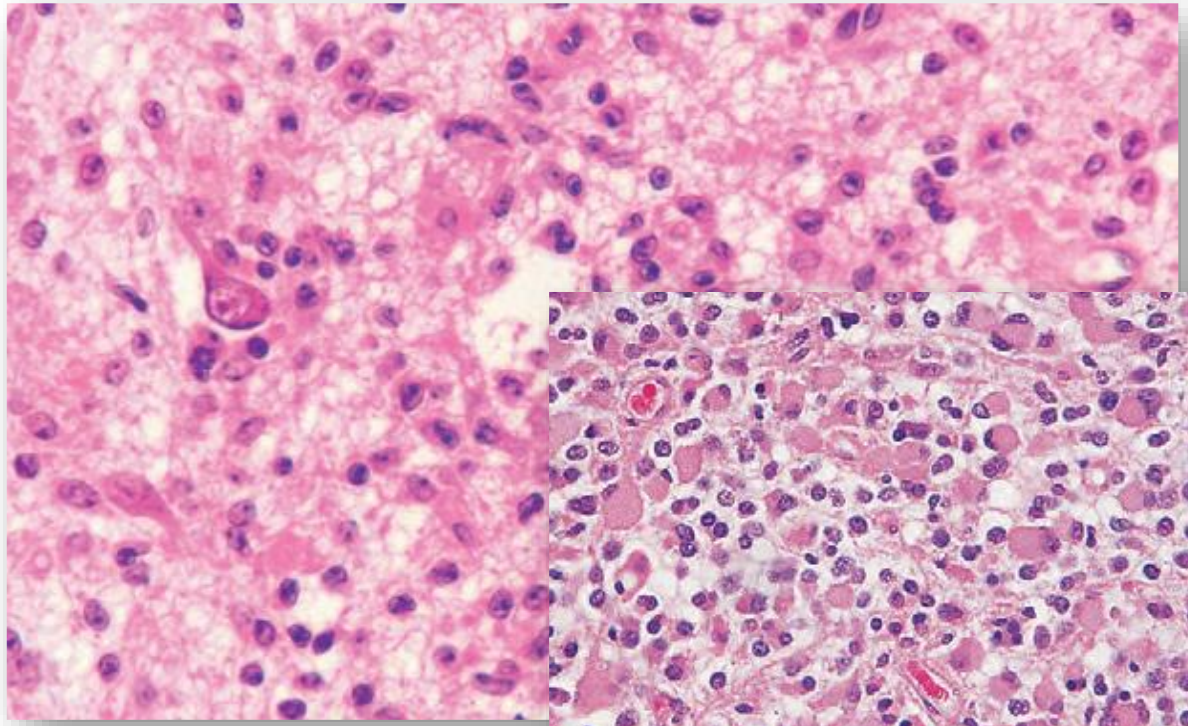
PIK3CA
MET

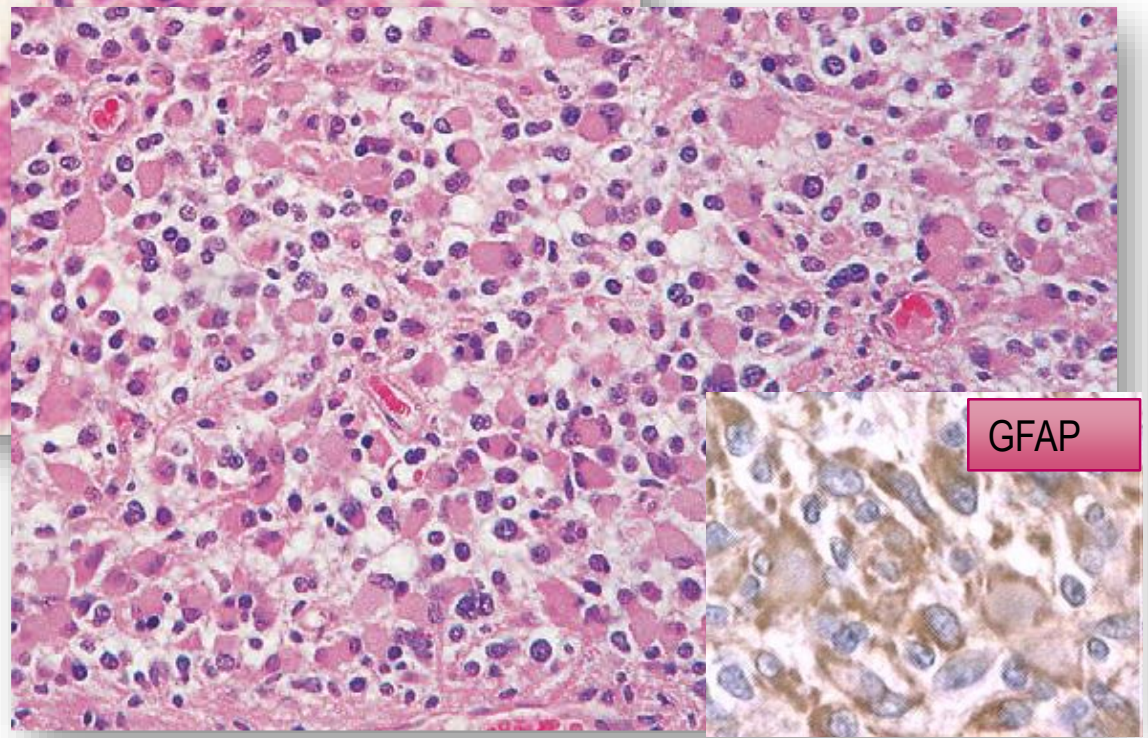


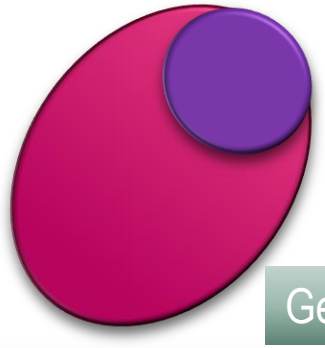
Secunder Glioblastoma Gr. IV

Diffuse astrocytoma Grade II

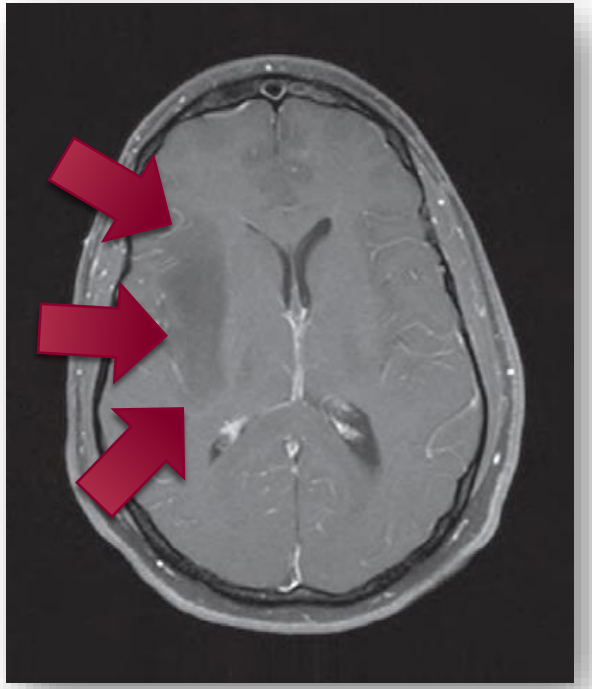
- Atypia+ High cellularity

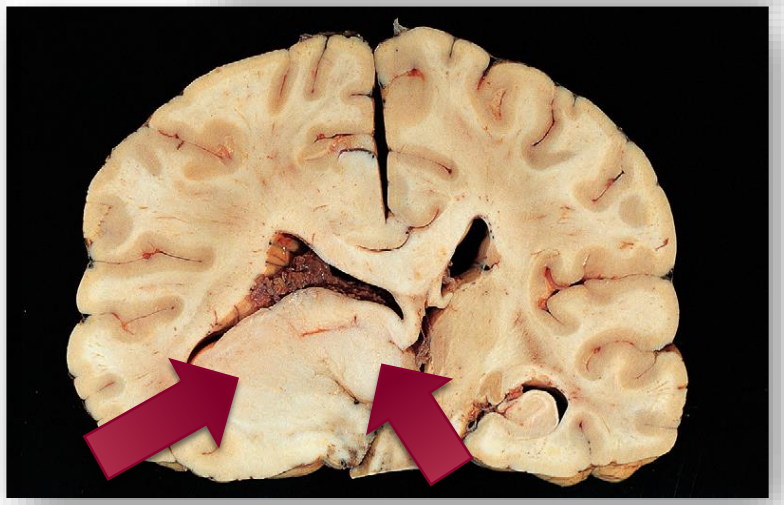






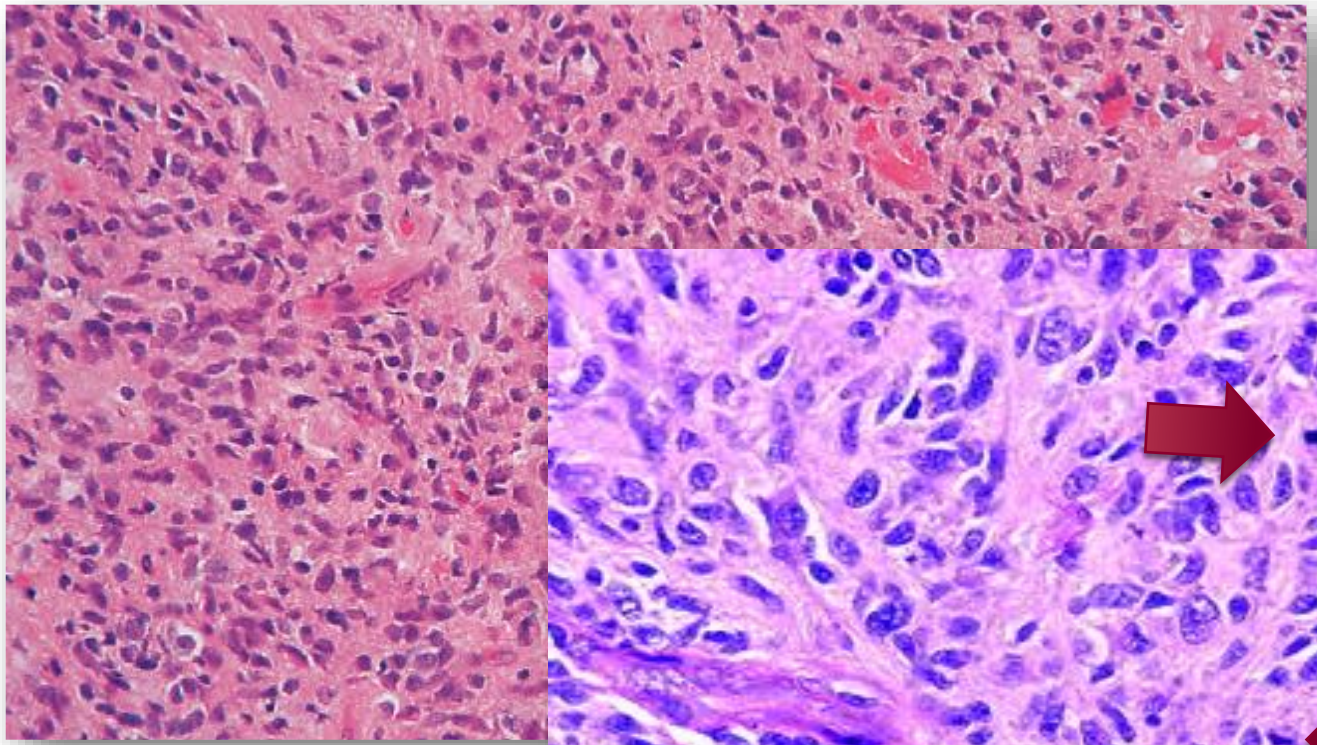
Gemistocyte

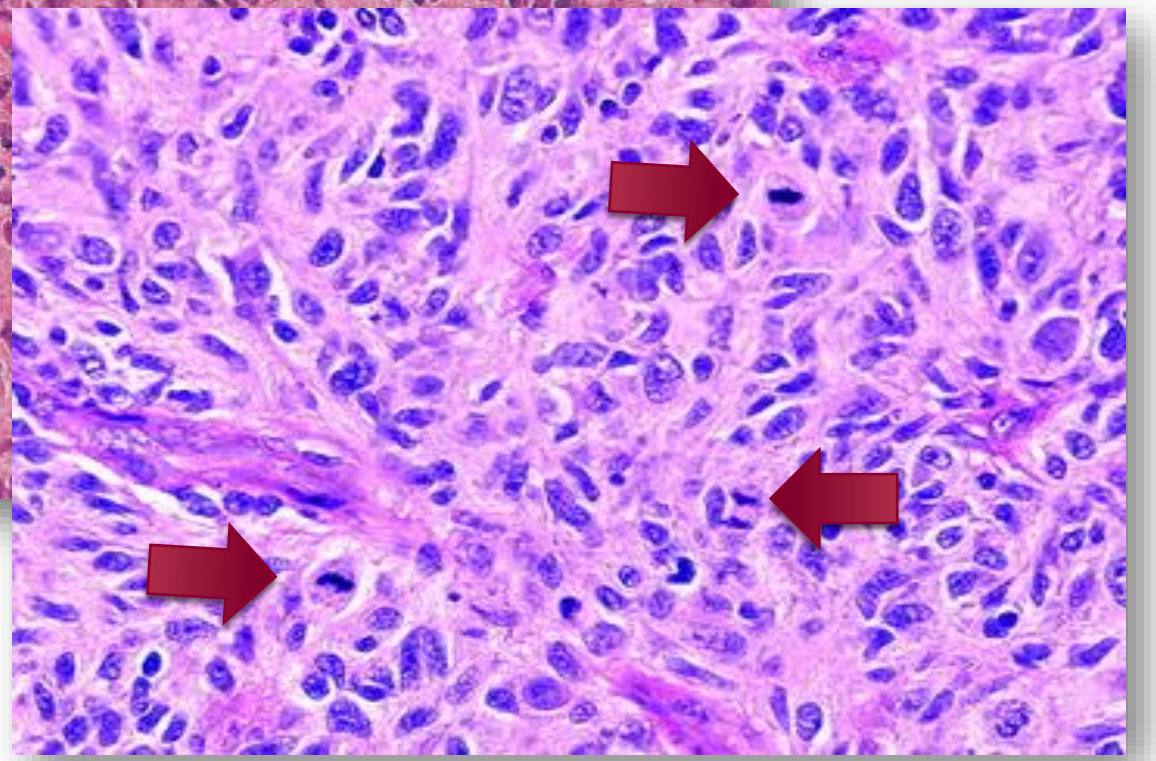


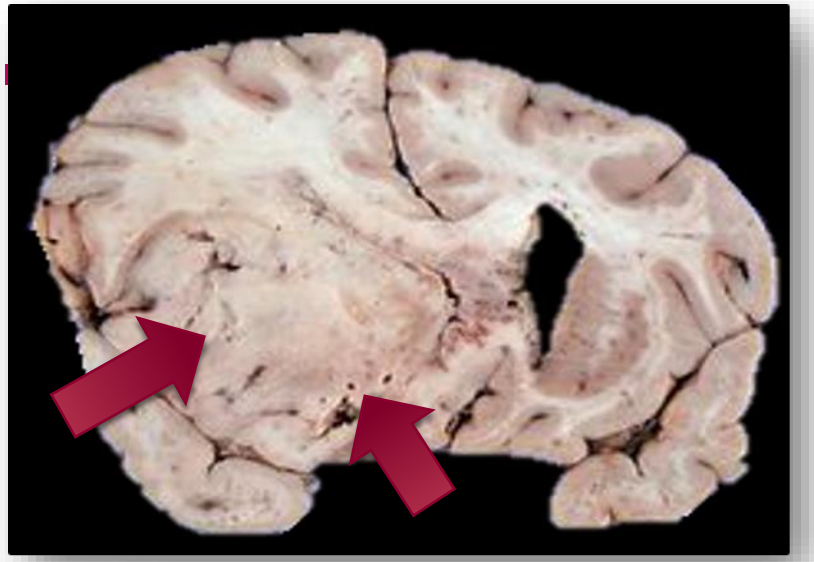


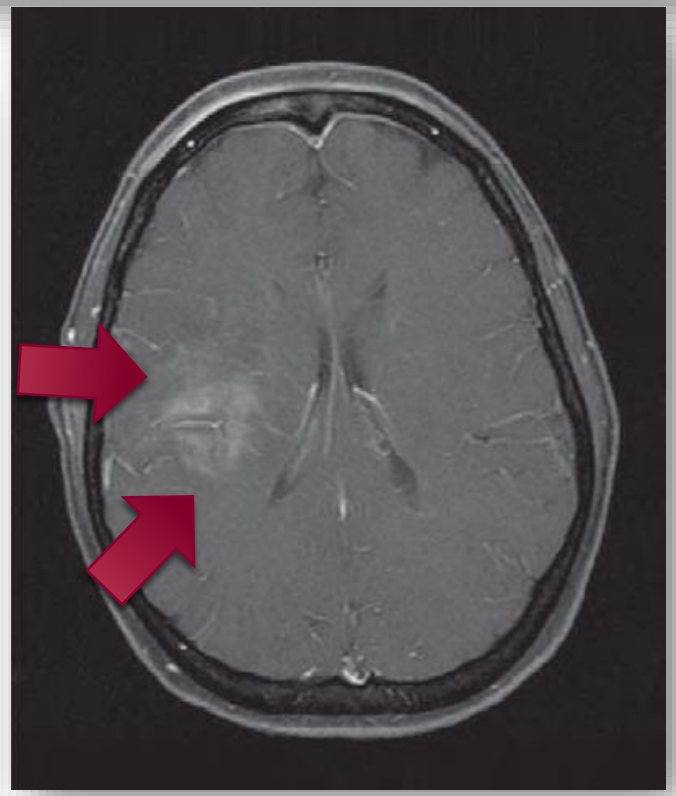
Anaplastic astrocytoma Grade III

- Atypia + High cellularity + High mitotic activity



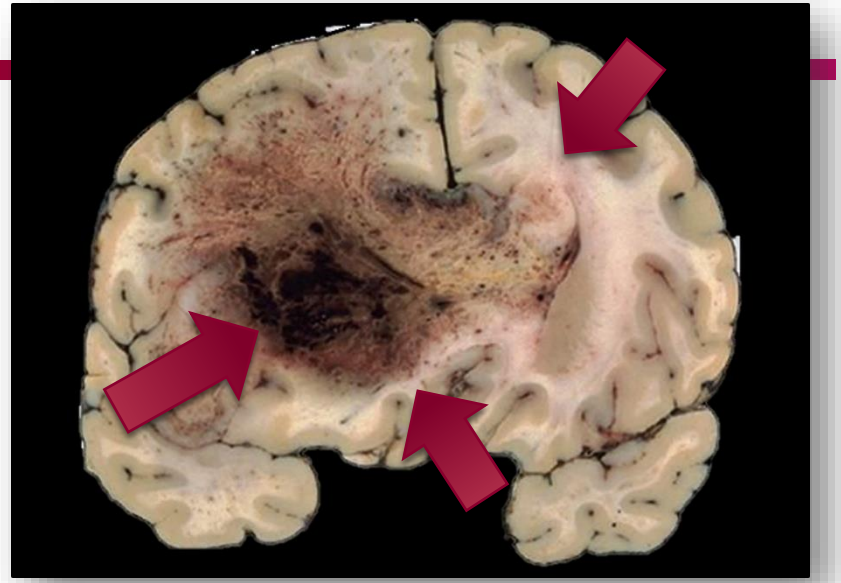


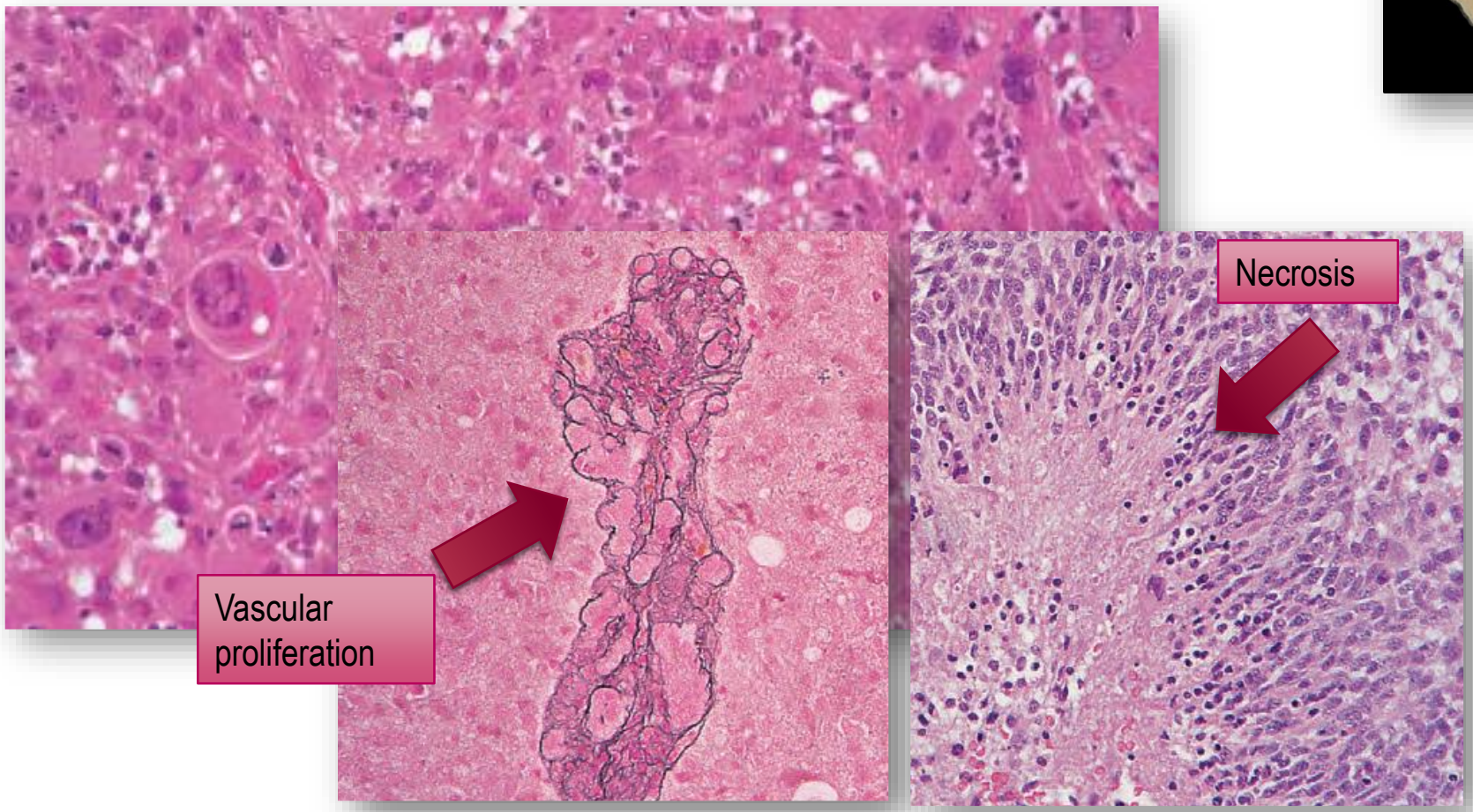


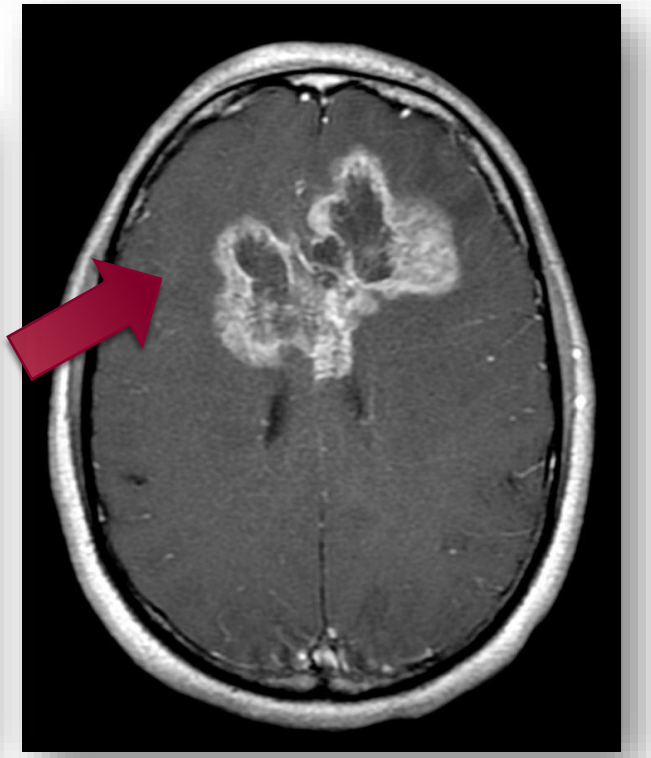


Glioblastoma Grade IV

- Atypia + High cellularity + High mitotic activity + Necrosis/Endothel proliferation

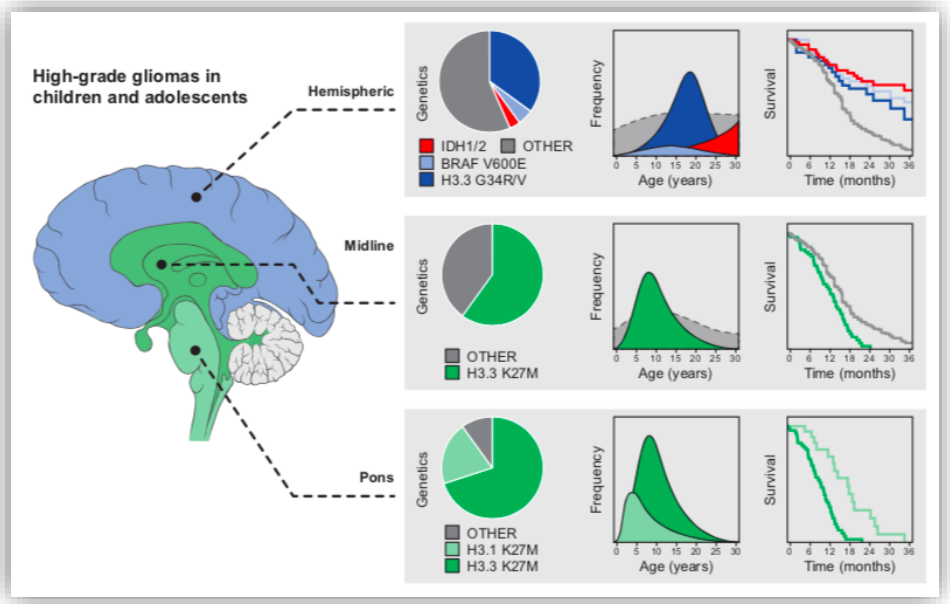


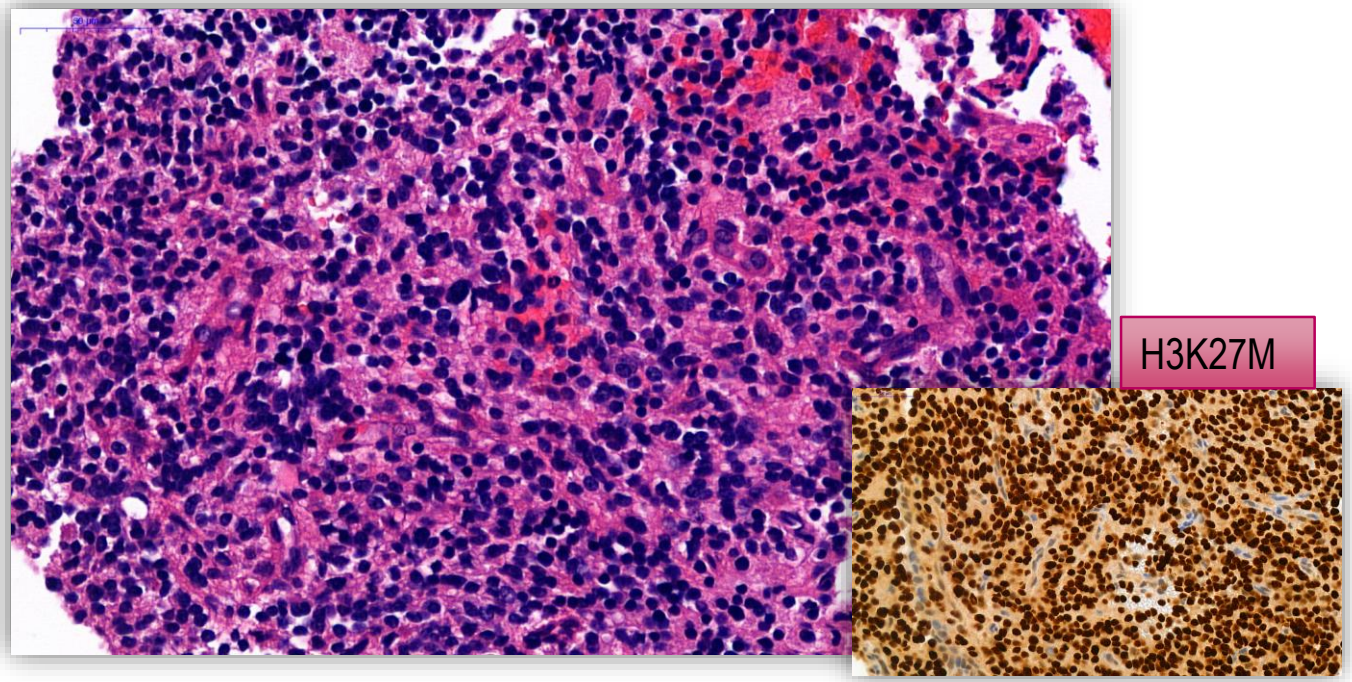


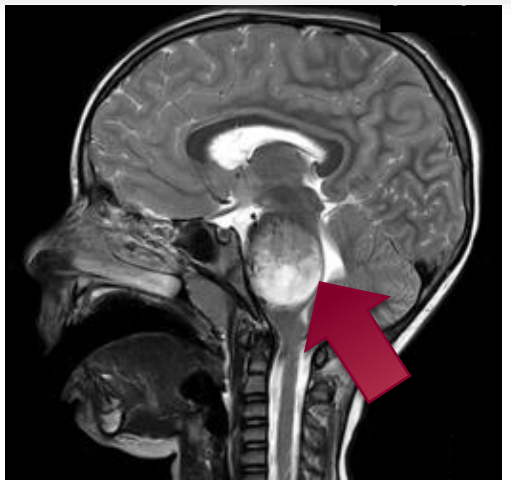


DIFFUSE MIDLINE GLIOMA, H3 K27M MUTANT (GRADE IV)

- 5 - 10 years of age, but older age groups
- 10% of all meligant pediatric CNS tumors
- Brainstem, thalamus and spinal cord
- High-grade even if low-grade morphology (~10%)

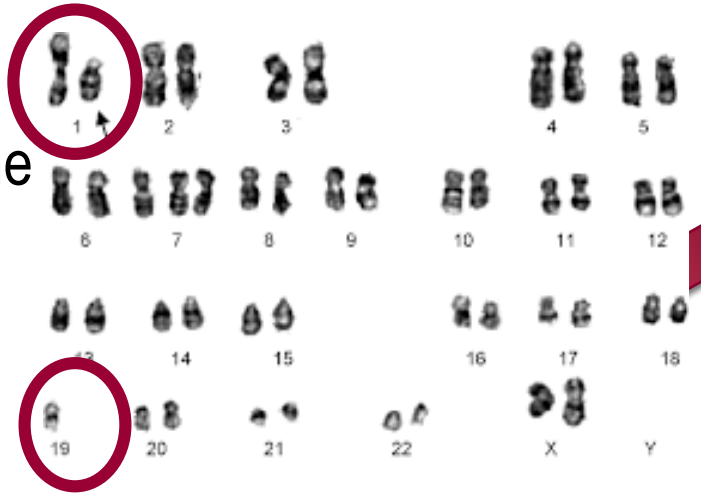


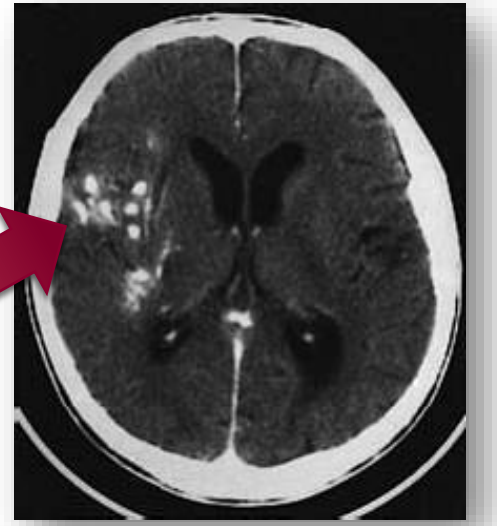


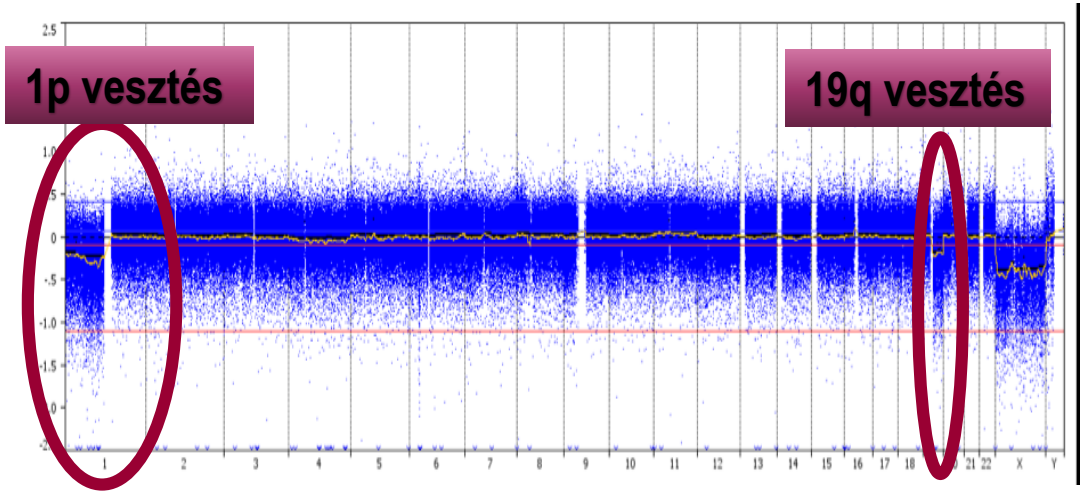


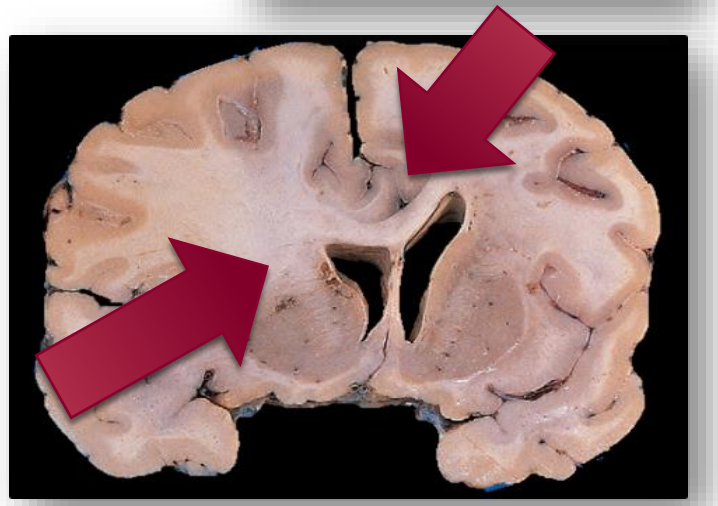
Oligodendroglial tumors(Grade II-III)

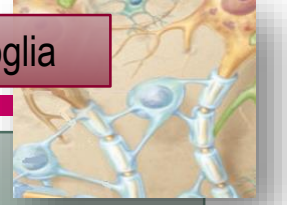
- Fourth and fifth decades of life
- Cerebral hemispheres – Seziure, headache
  - Frontal, temporal lobe
- 1p 19q codeletion



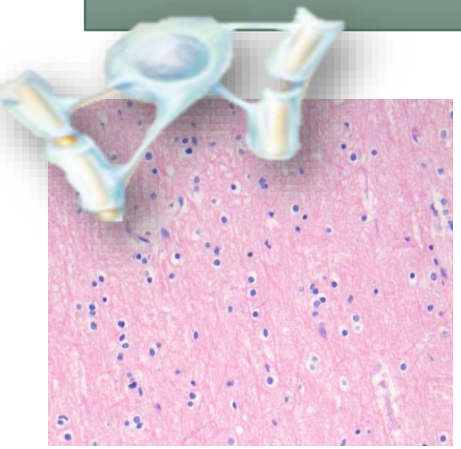




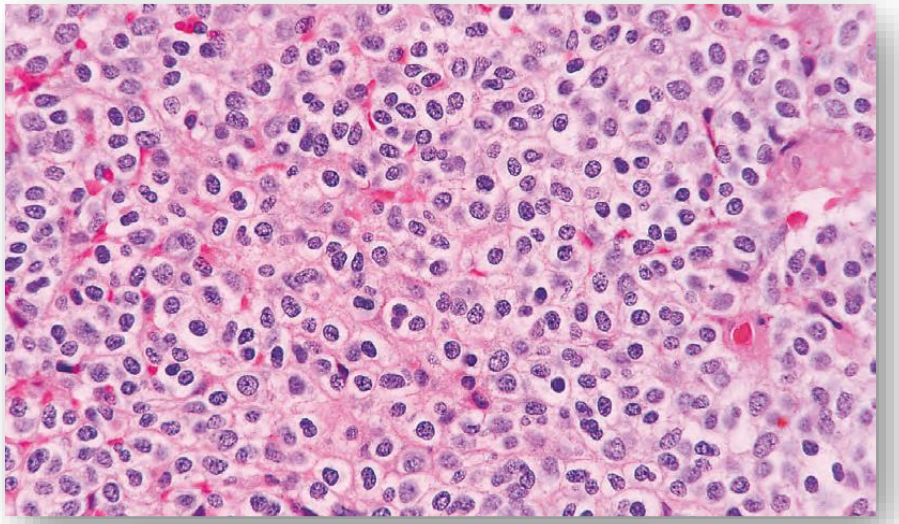




Oligodendroglial tumors(Grade II-III)

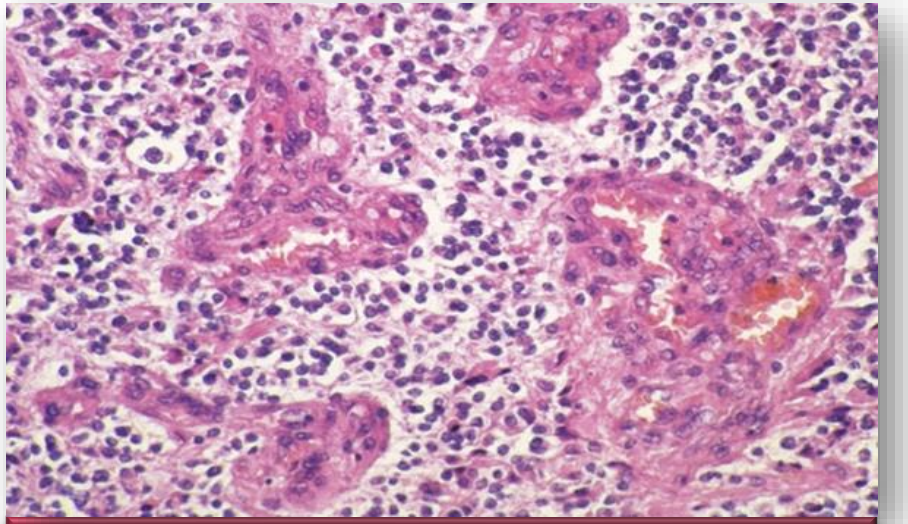


IDH1/IDH2
1p/19q codel, TERT,
CIC FUBP1



Oligodendroglioma Gr. II

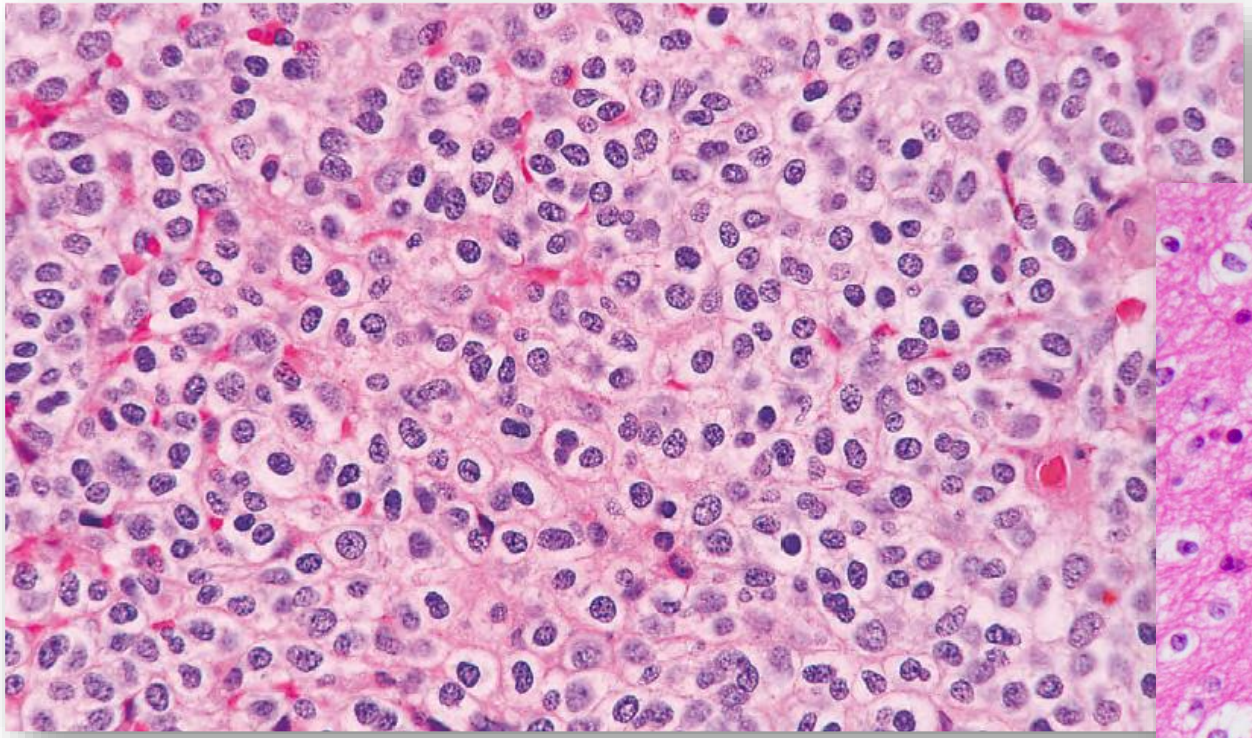
CDKN2A

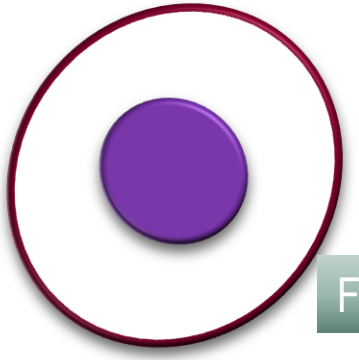


Anaplastic oligodendroglioma Gr. III

Oligodendroglioma Grade II

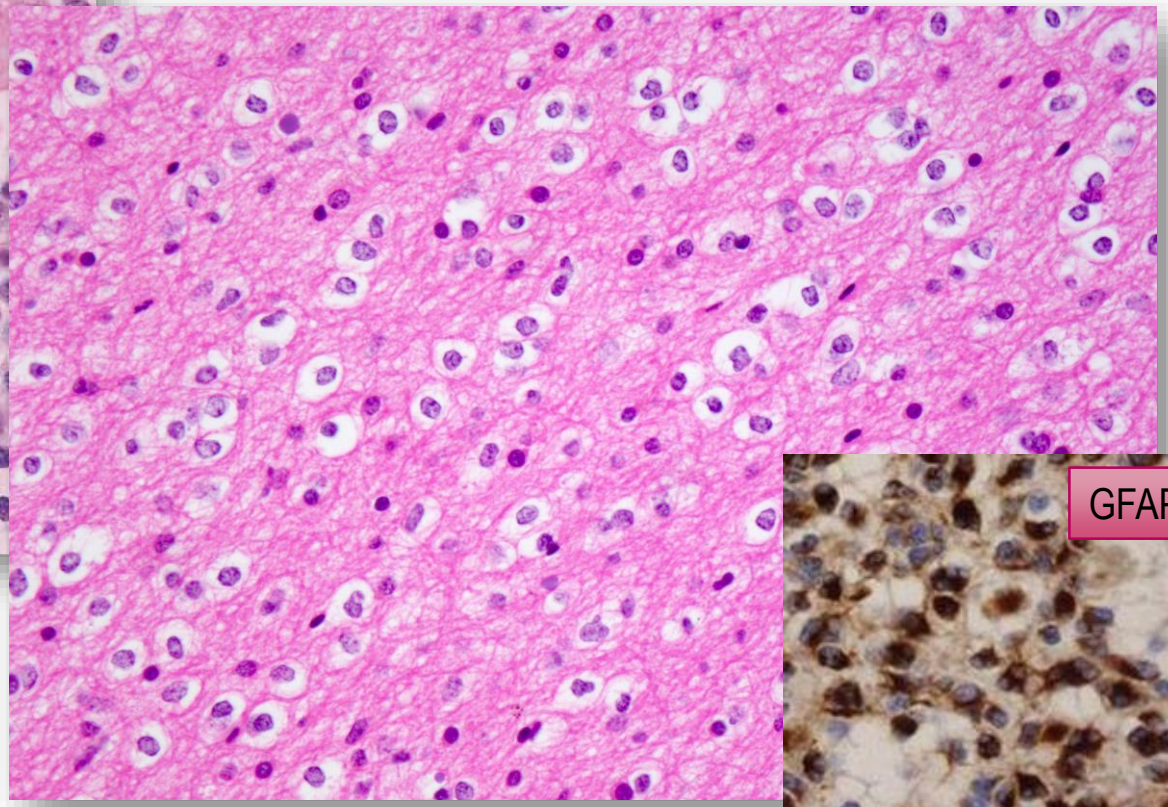
- Atypia+ High cellularity





Fried-egg cells

Oligodendroglia

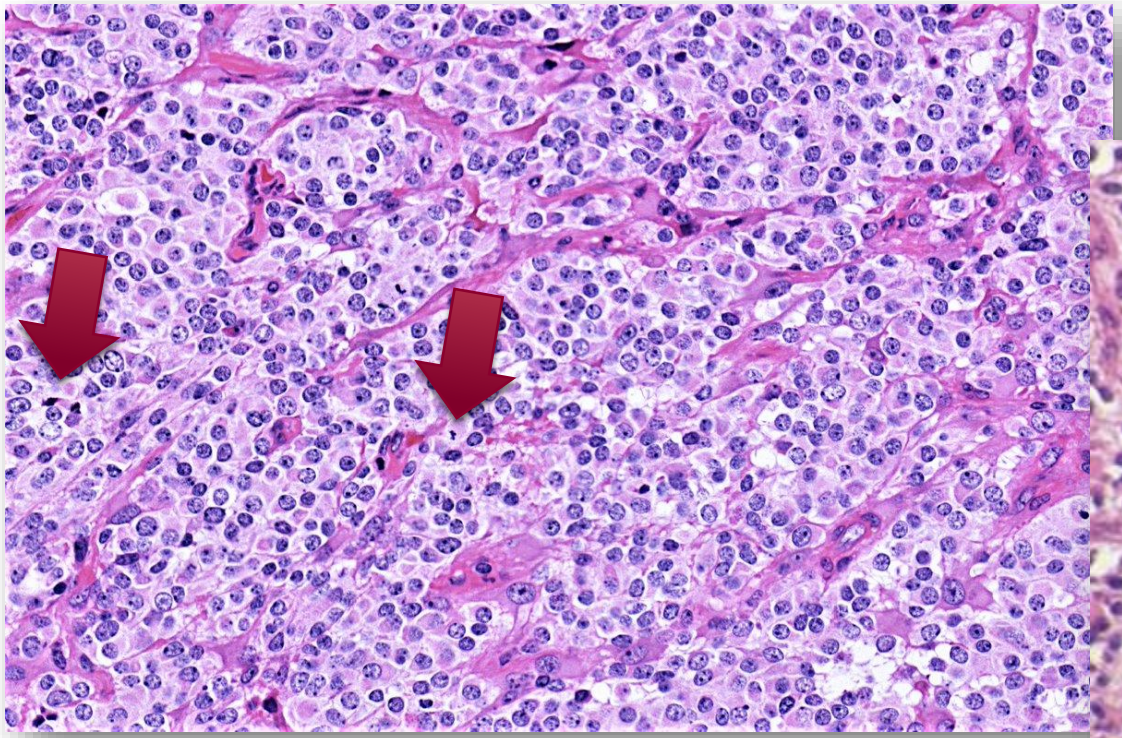


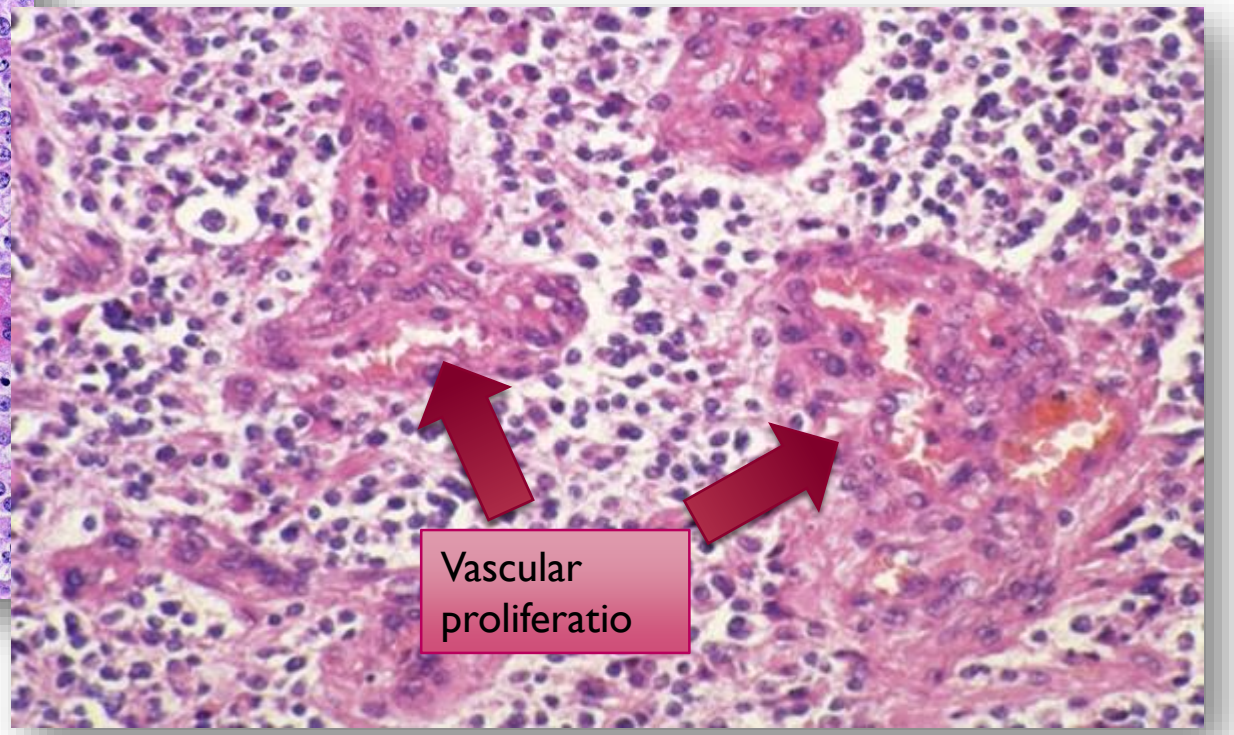
GFAP

Oligodendroglia

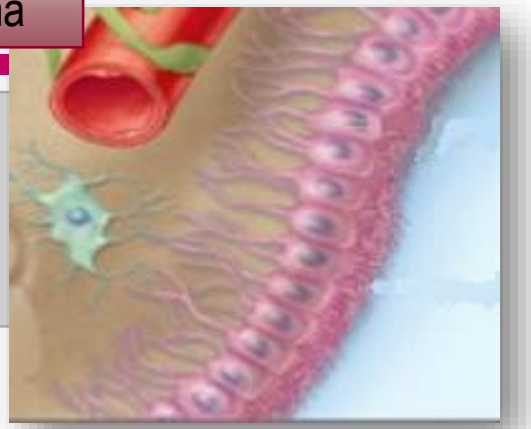
Anaplastic oligodendroglioma Grade III

- Atypia + High cellularity + High mitotic activity + Necrosis/Endothel proliferation

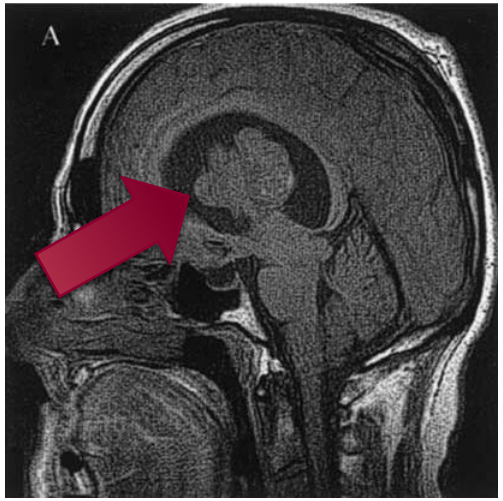


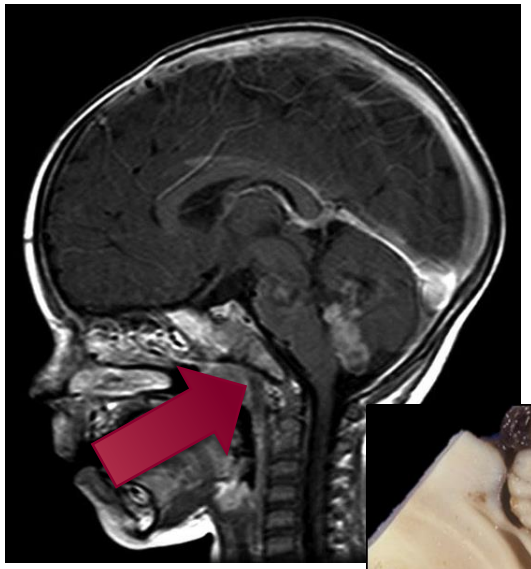


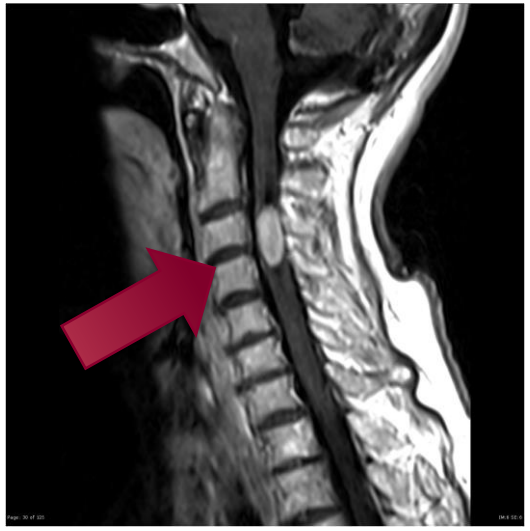
Ependymal tumors

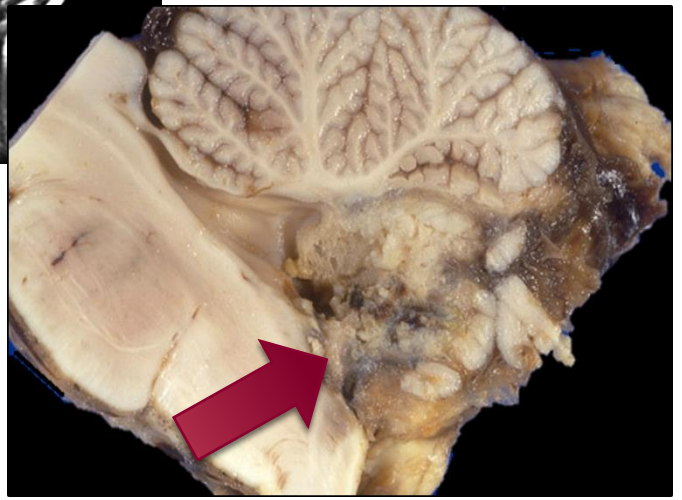


- Supratentorial
  - Lateral ventricles
  - Young adults
- Infratentorial
  - 4th ventricle
  - Childhood
- Spinal ependymoma
  - Canalis centralis
  - 20-40 years of age

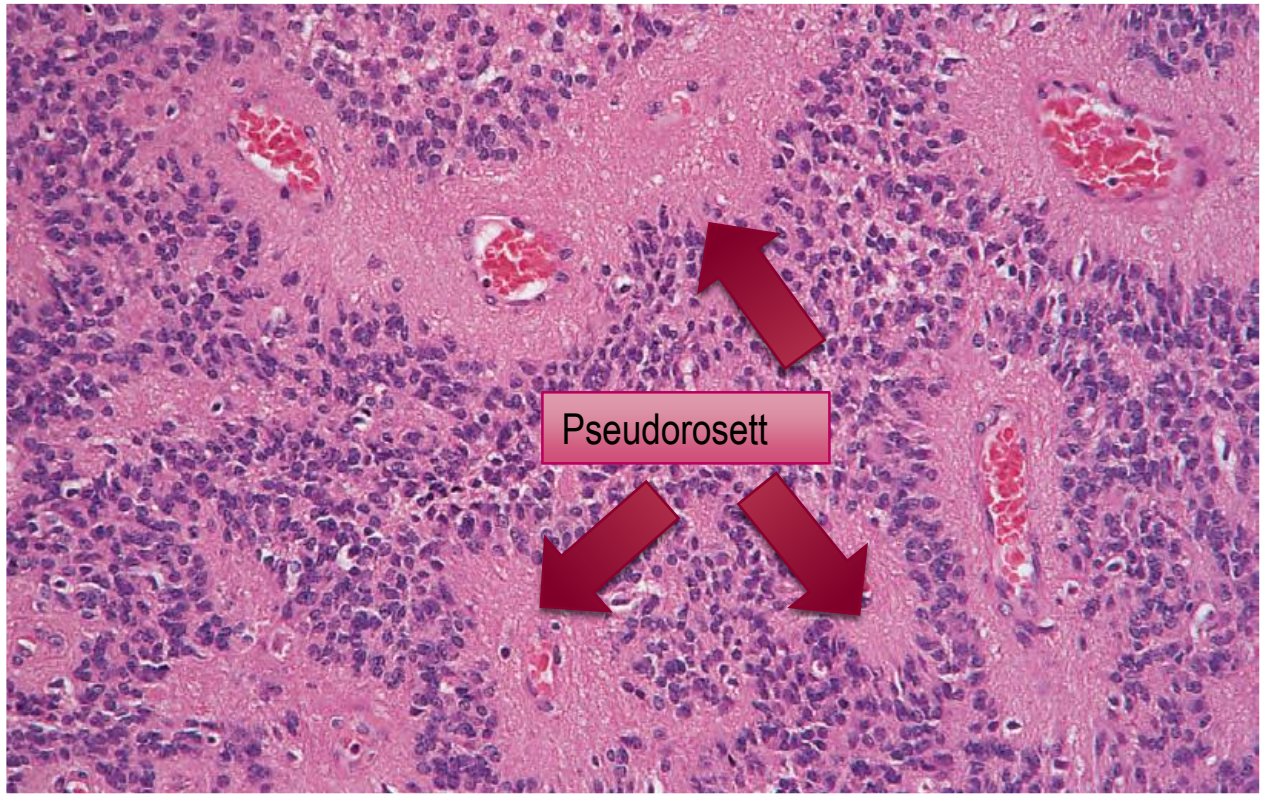




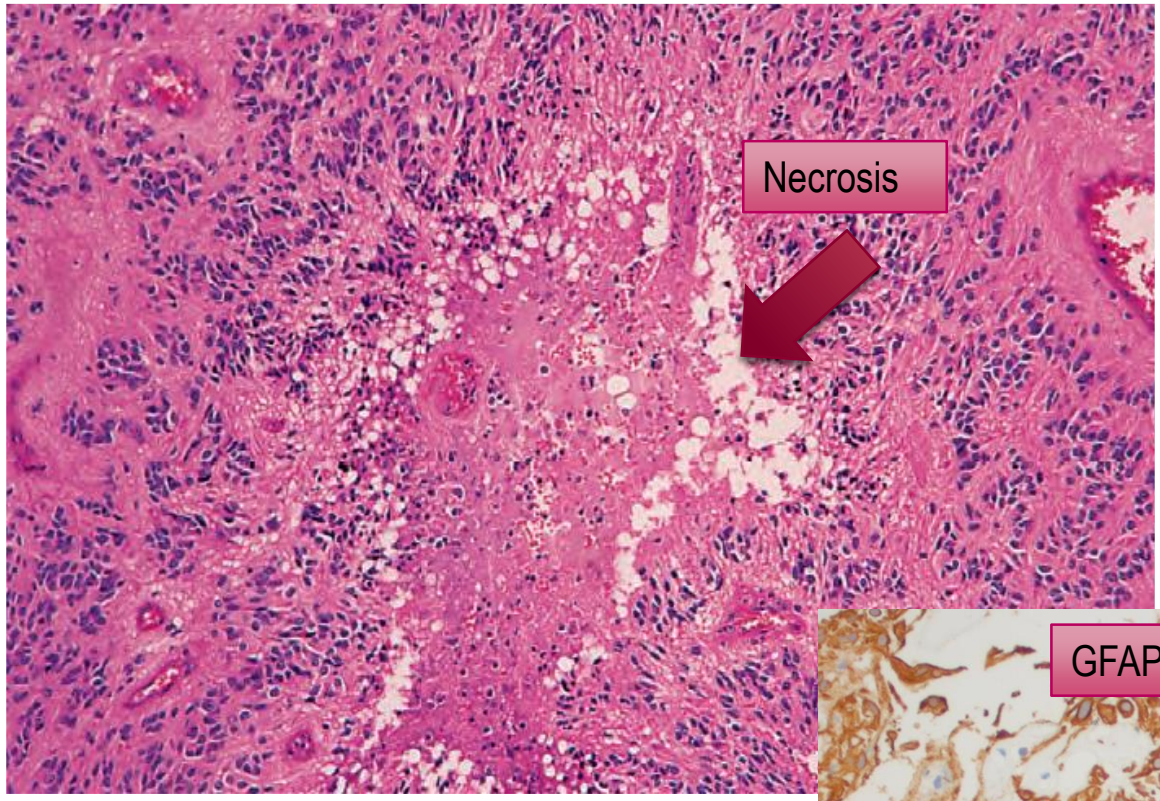


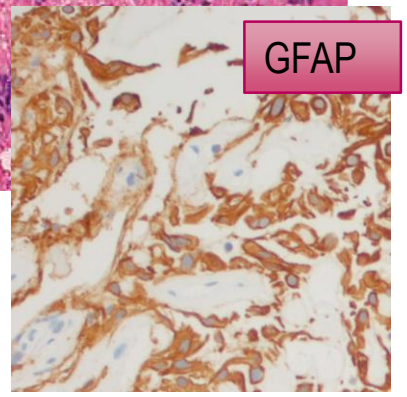


Ependymoma Grade II

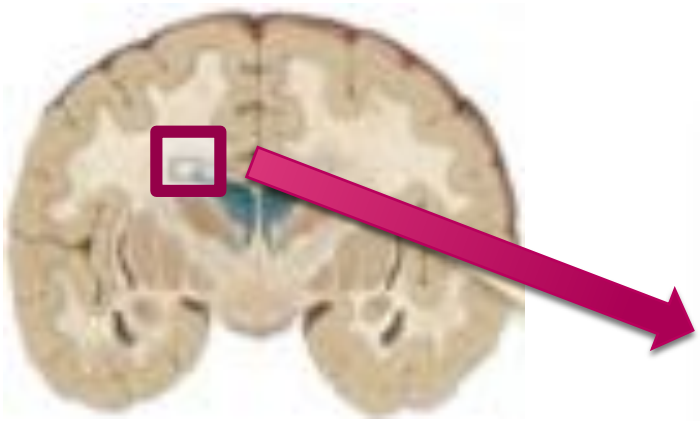


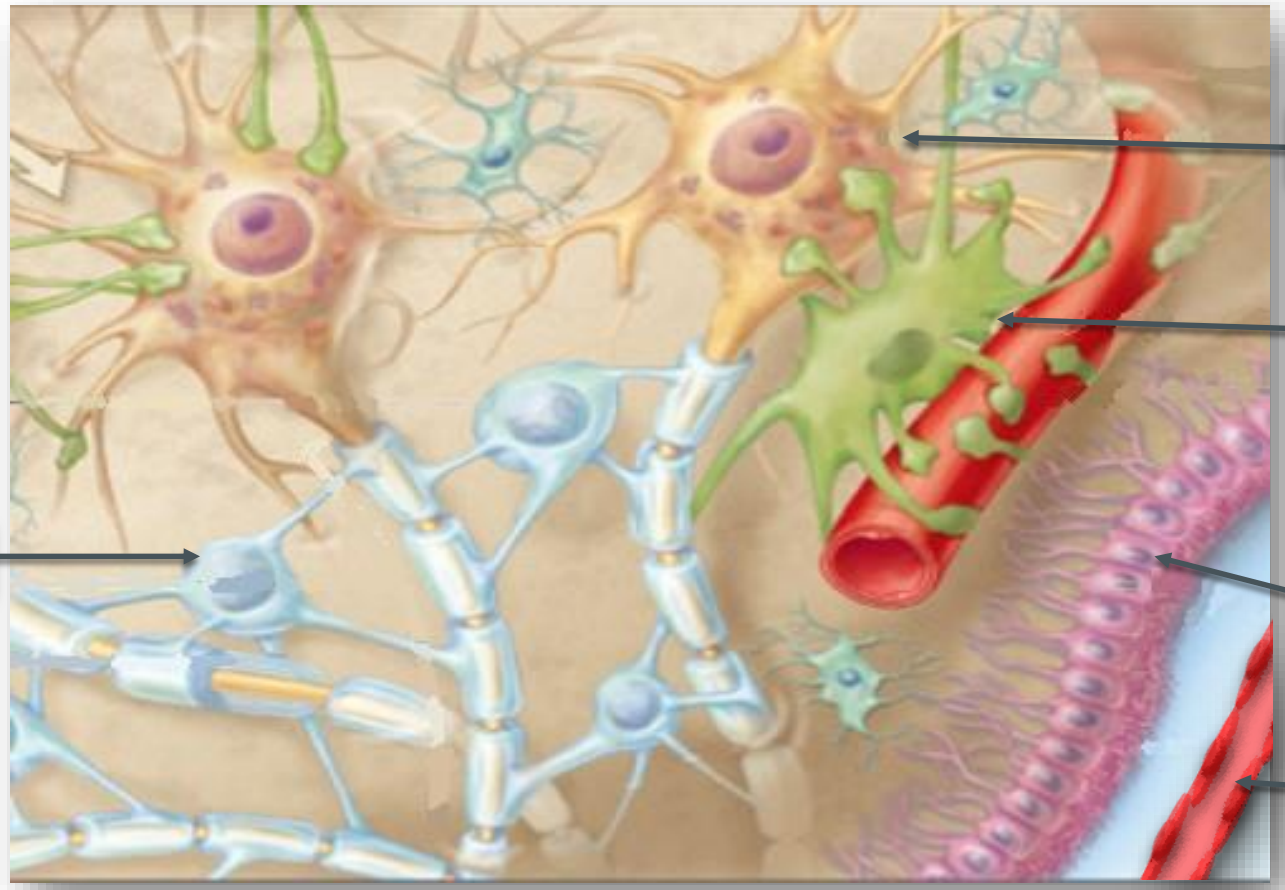
Anaplastic ependymoma Grade III





II. NEURONAL/GLIONEURONAL TUMORS

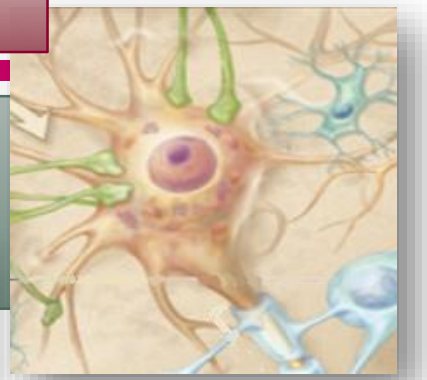


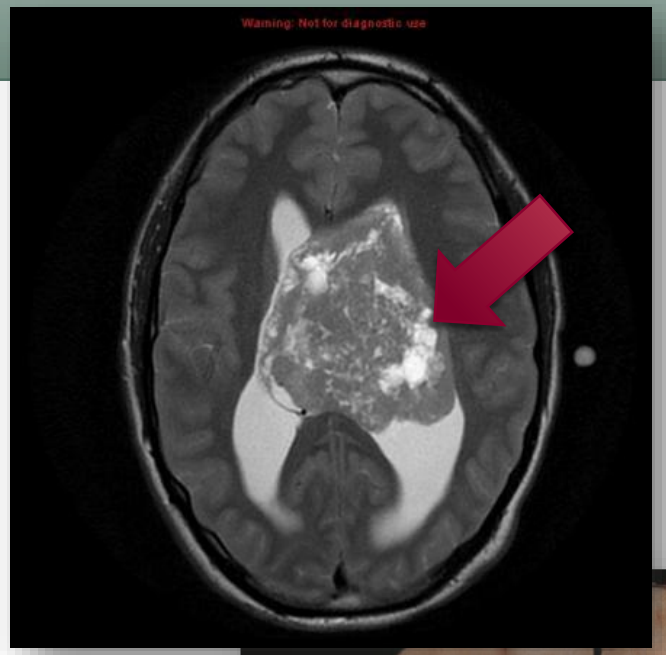


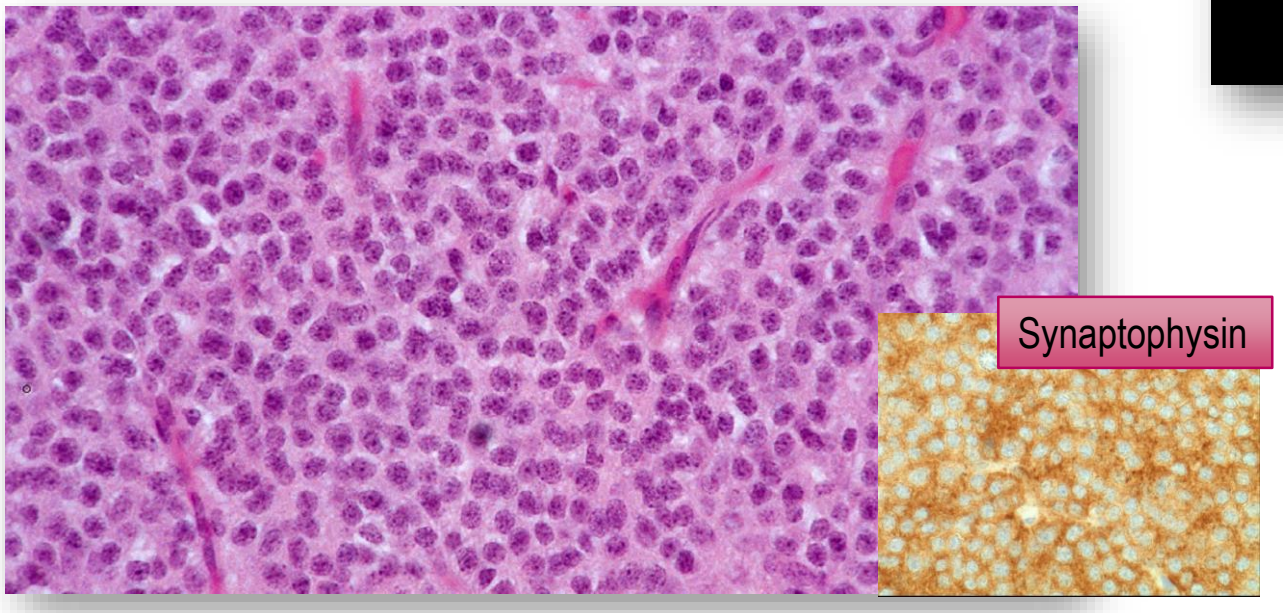
Central neurocytoma Grade II

- Young adults
- Rare tumor
- Location:
  - Lateral or 3rd vertricle
  - Septum pellucidum

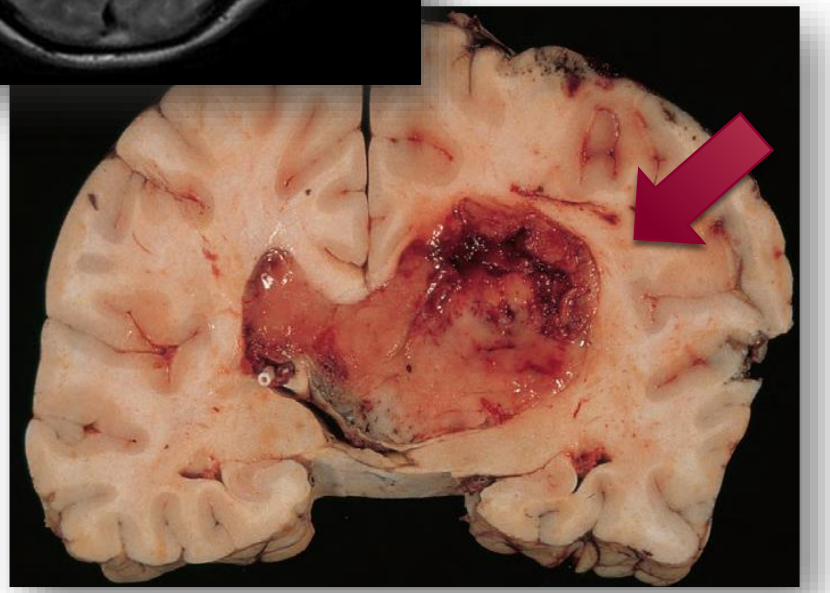
Neuron



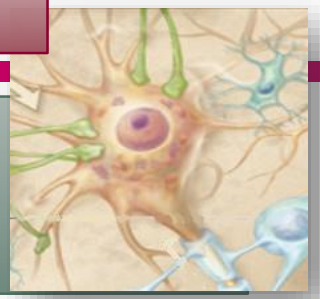




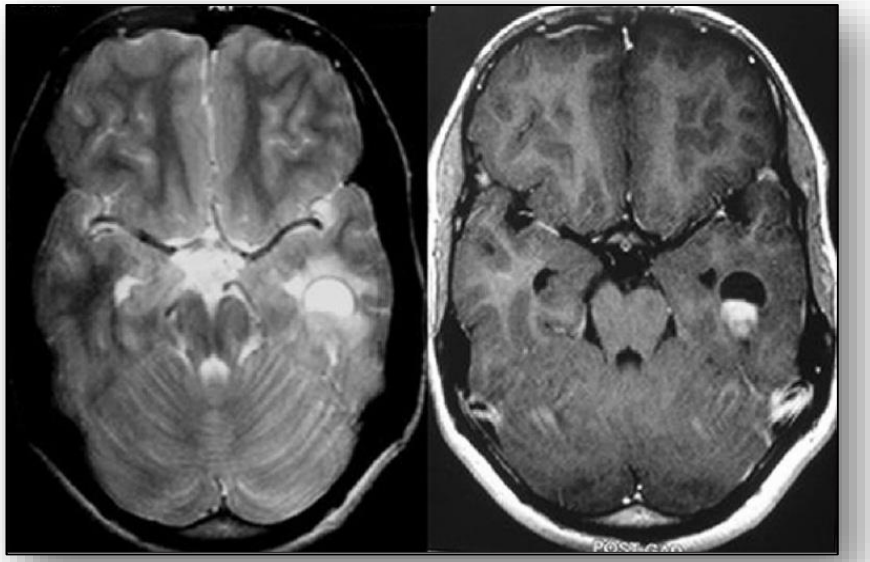
Synaptophysin

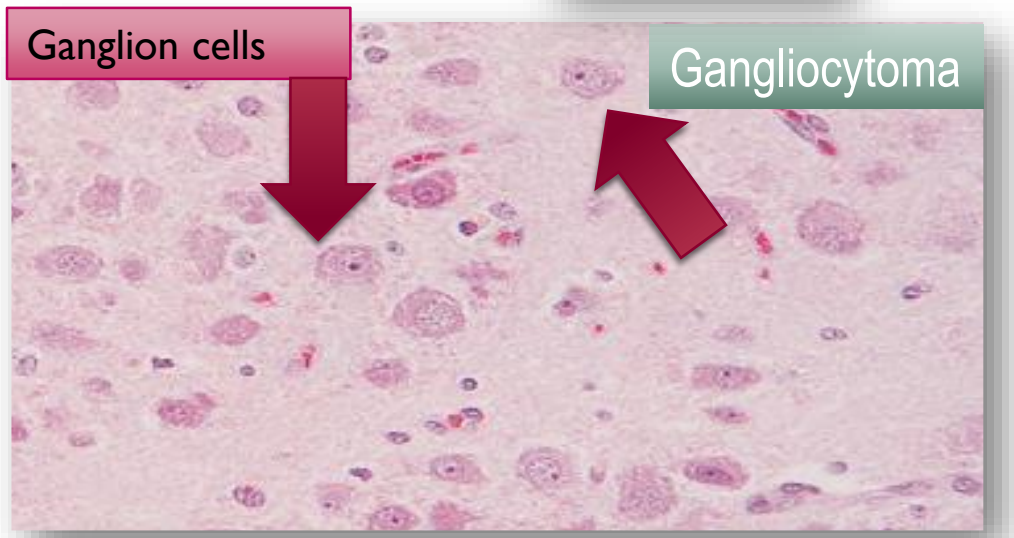


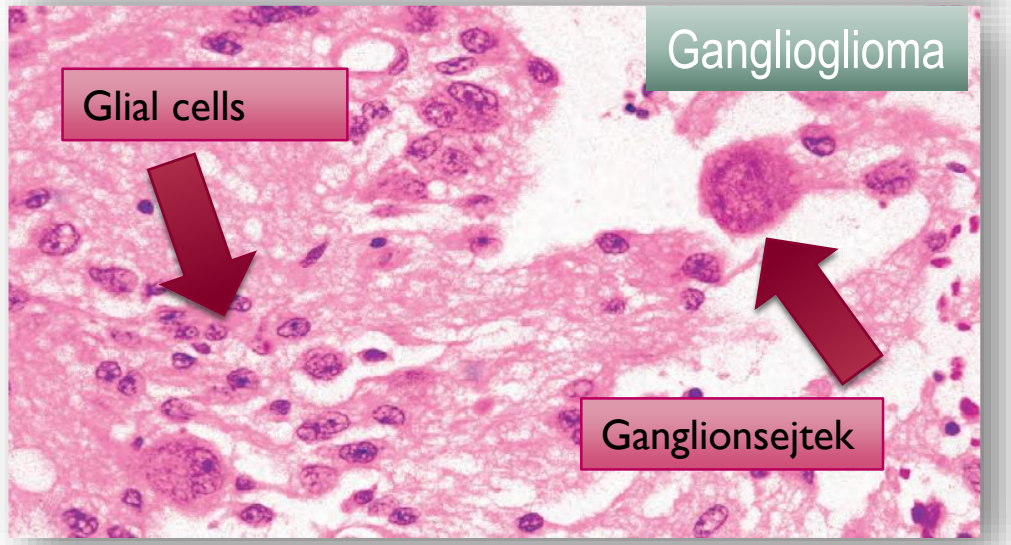
Gangliocytoma, ganglioglioma Grade I



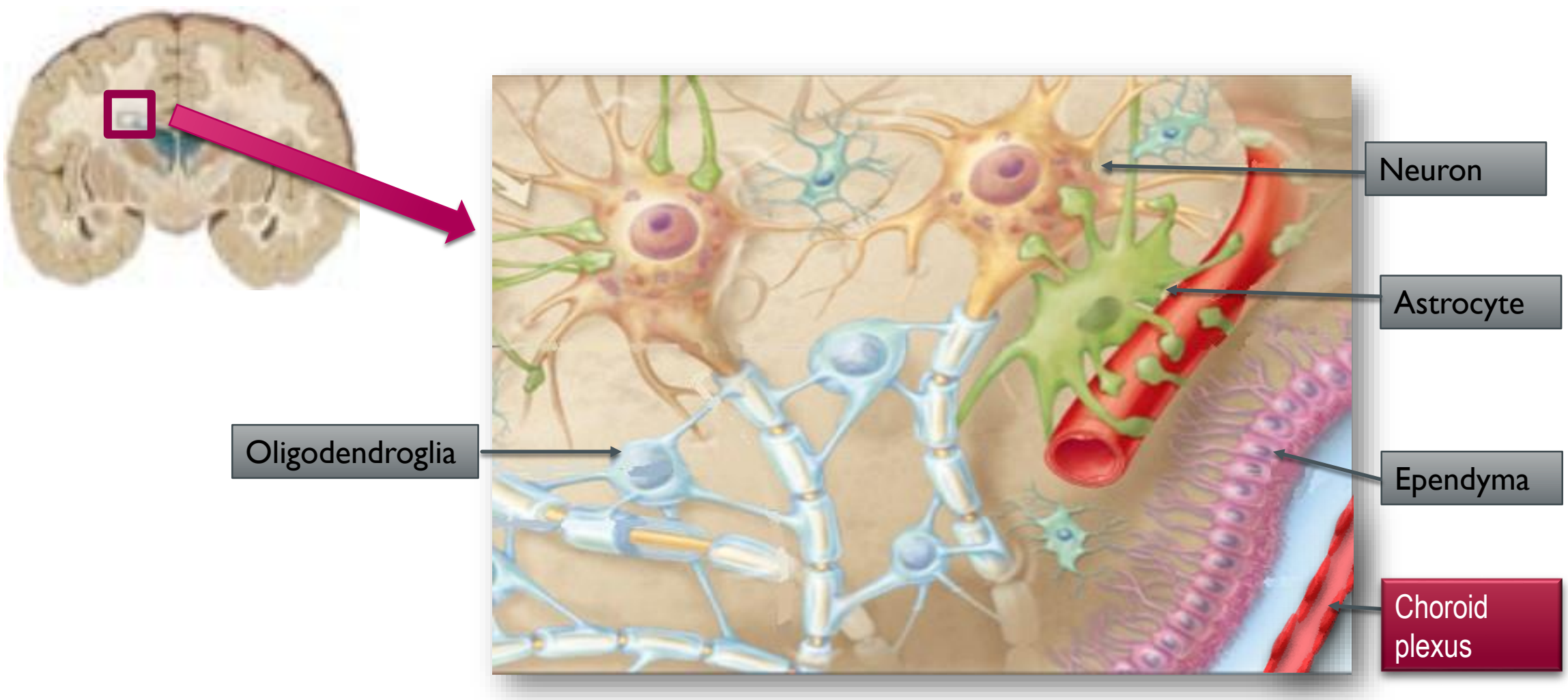
- Children, young adults
- Temporal lobe
  - Epilepsy
- **BRAF gene mutation (BRAF V600E v. BRAF/KIAA tr)**
- Mature appearing neurons ± Glial cells
- Glial compomonent – with time anaplastic







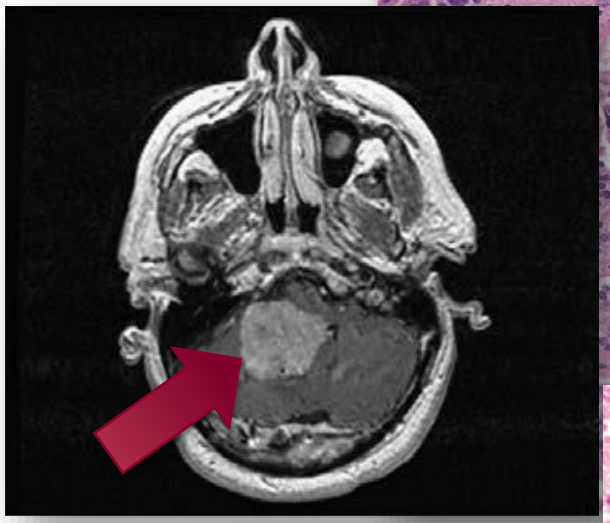
III. CHOROID PLEXUS NEOPLASMS

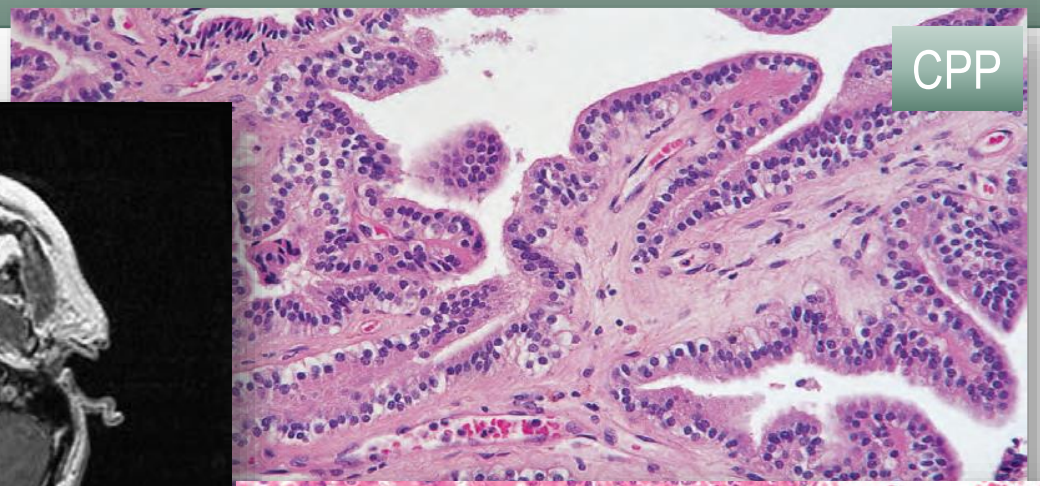


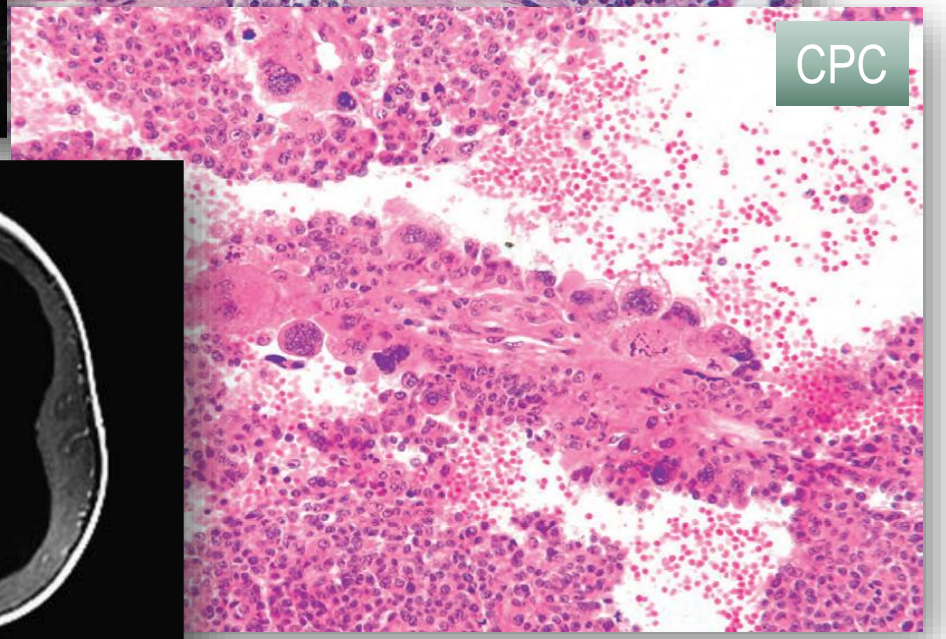
Choroid plexus papilloma/ Choroid plexus carcinoma

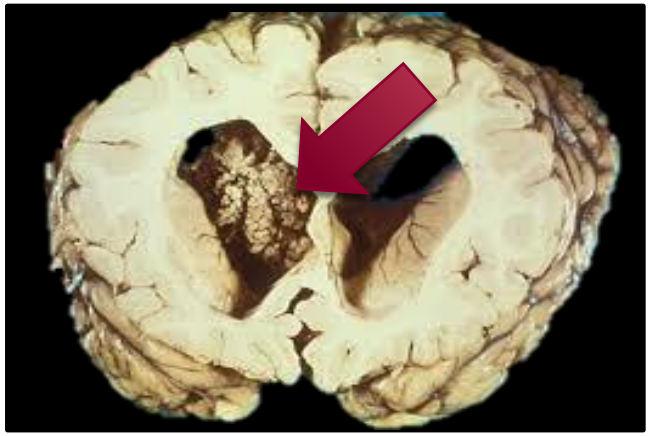
- Children
- Lateral or 4th ventricle

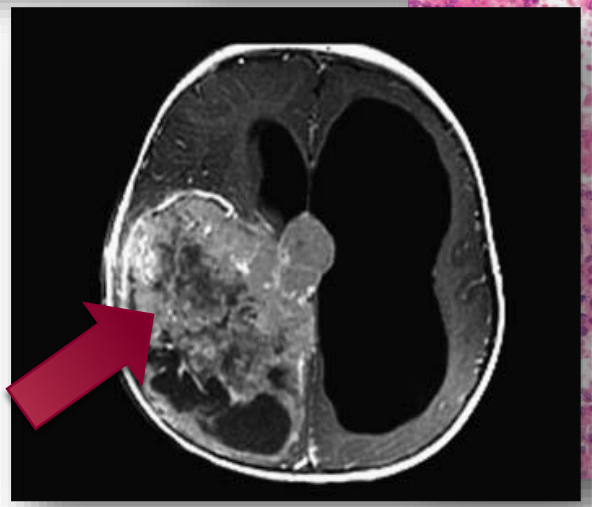
- Papilloma
  - More common
- Carcinoma
  - TP53 mutation
  - Poor prognosis

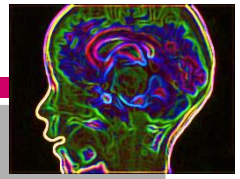






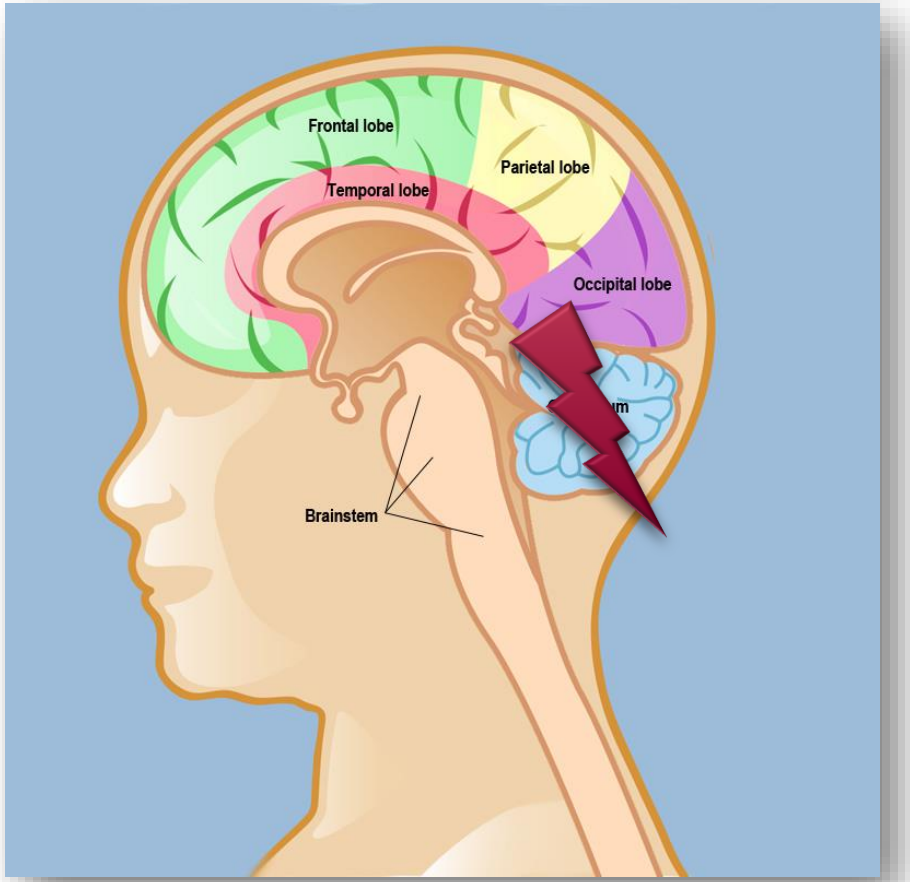




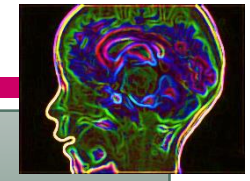


IV. EMBRIONAL NEUROEPITHELIAL TUMORS

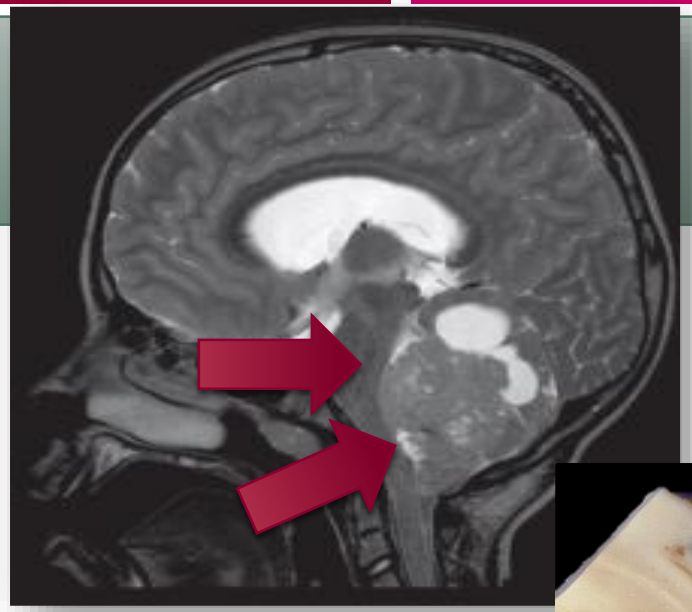
- Predominance in children
- Disseminate through CSF pathways
- Small undifferentiated cells
- High mitotic index, widespread apoptosis
- Potential for divergent neuroepithelial differentiation

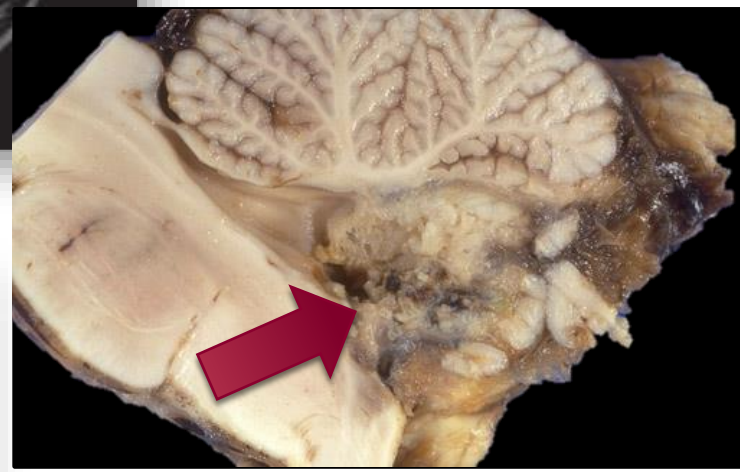


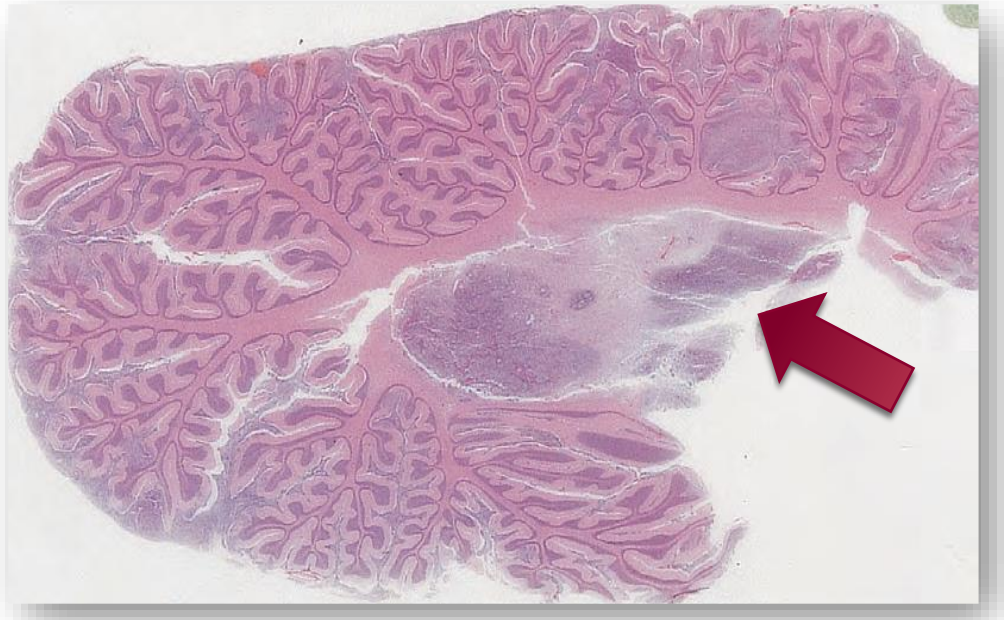
Medulloblastoma Grade IV



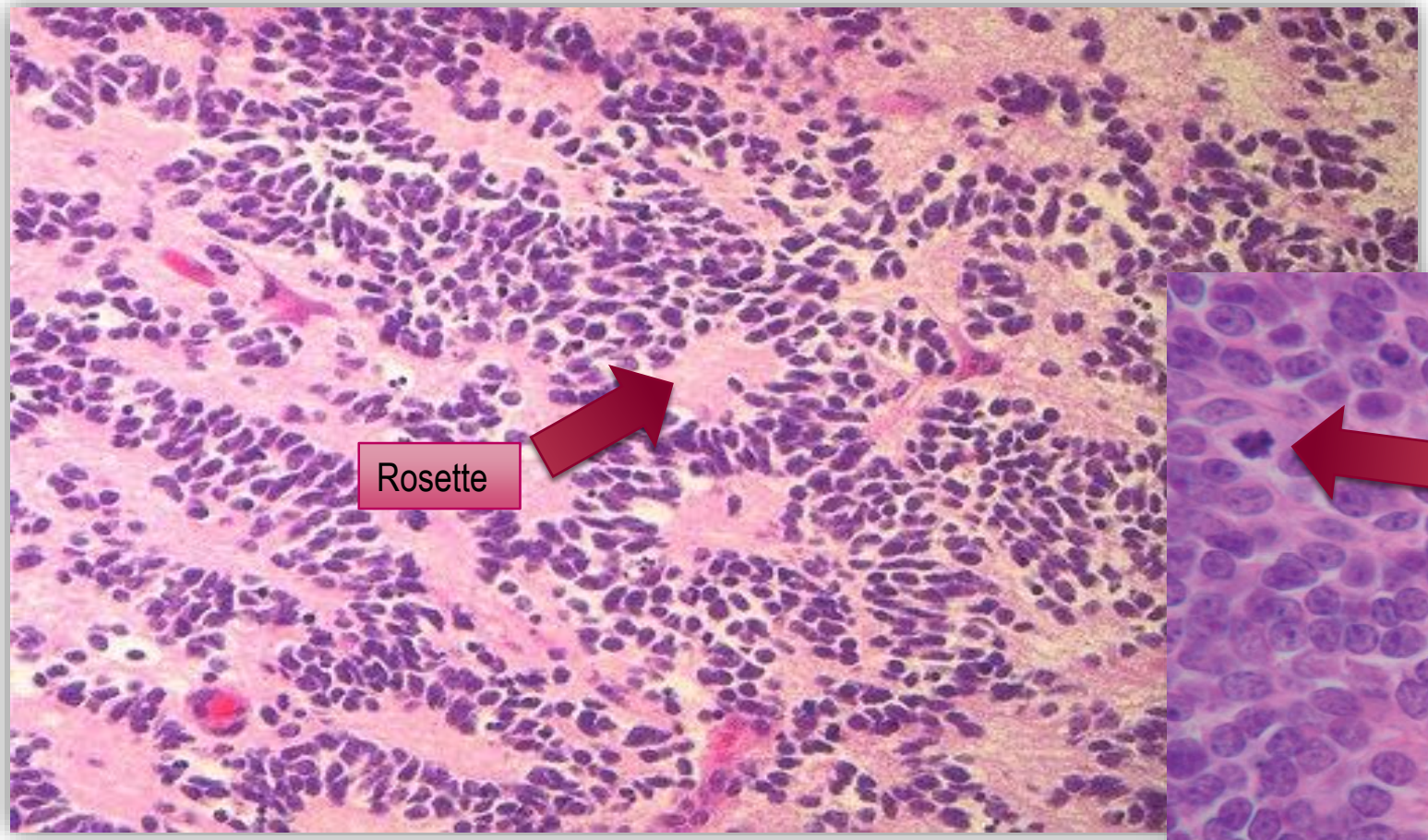
- 20% of pediatric brain tumor
- Infratentorial, 4th ventricle
- Four molecular subgroups :
  - WNT- activated (10%)
  - Sonic hedgehog (SHH)-activated (30%)
  - Group 3 (20%)
  - Group 4 (40%)

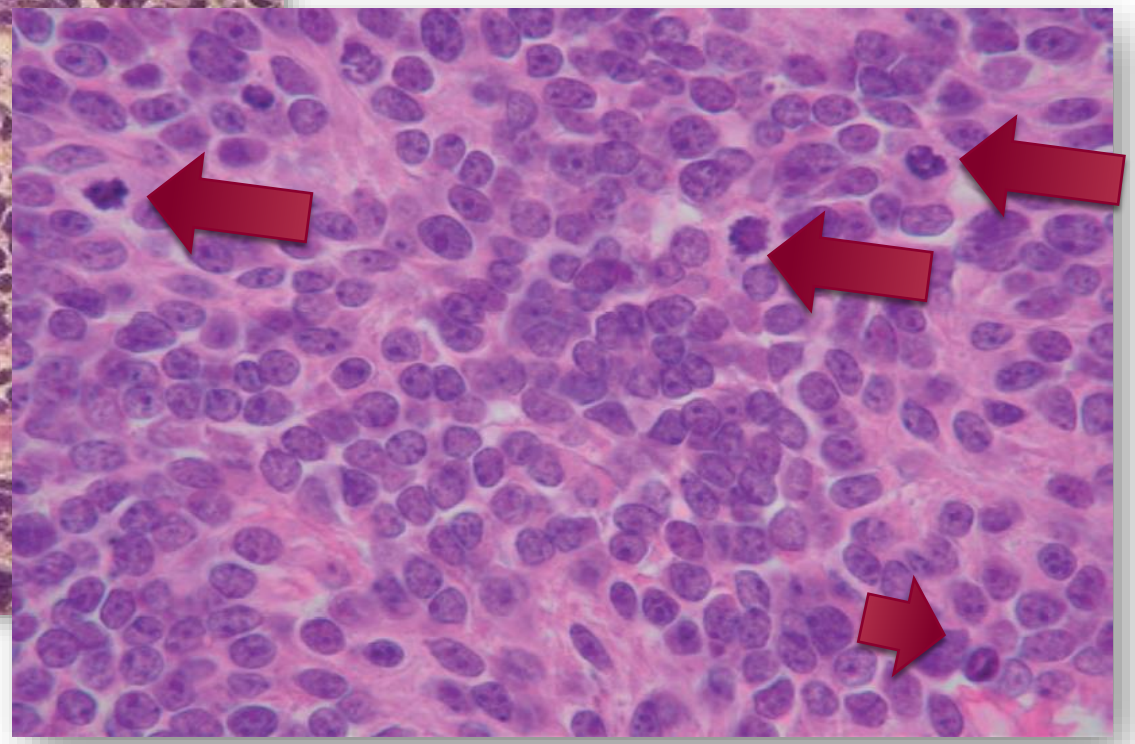






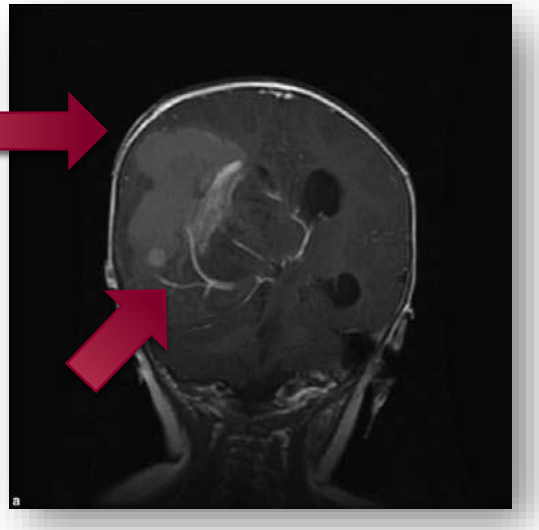
Medulloblastoma Grade IV

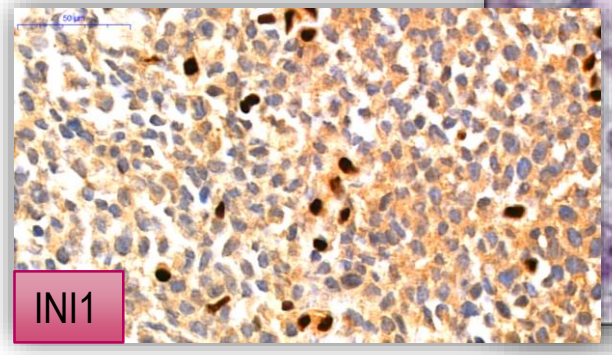


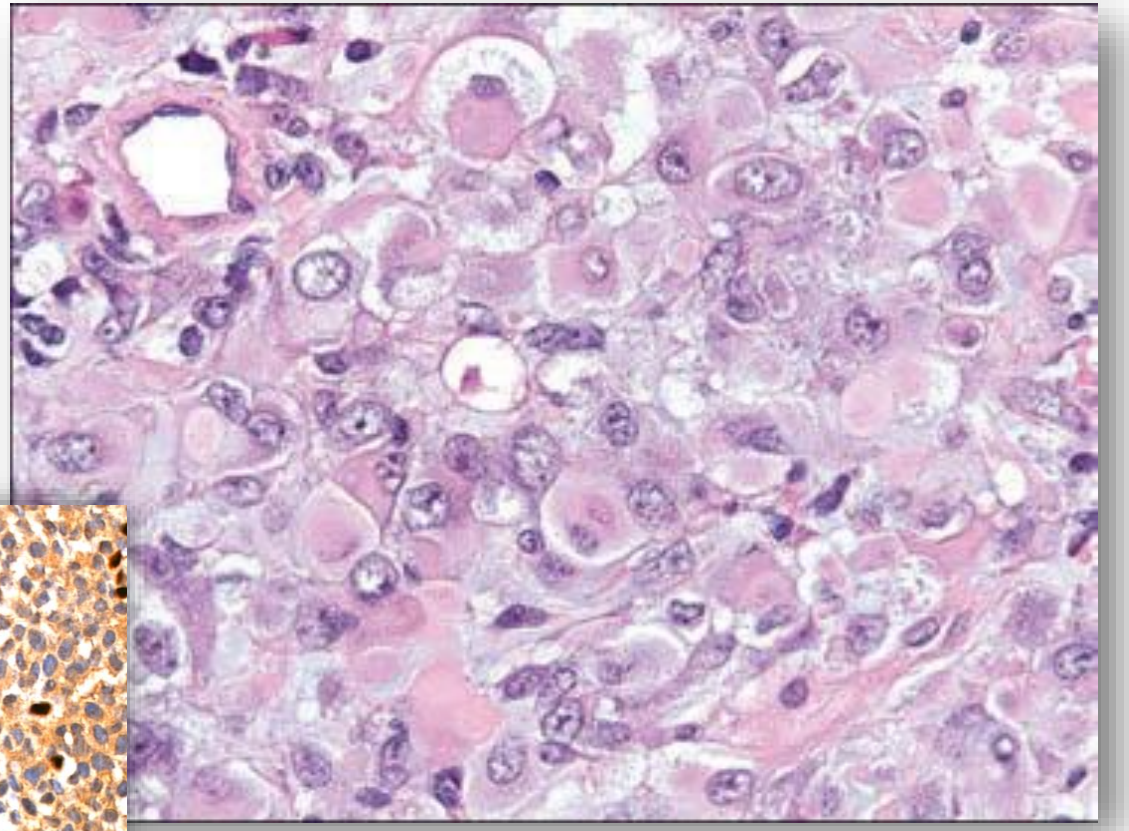


Atypical Teratoid Rhabdoid Tumor (AT/RT) Grade IV

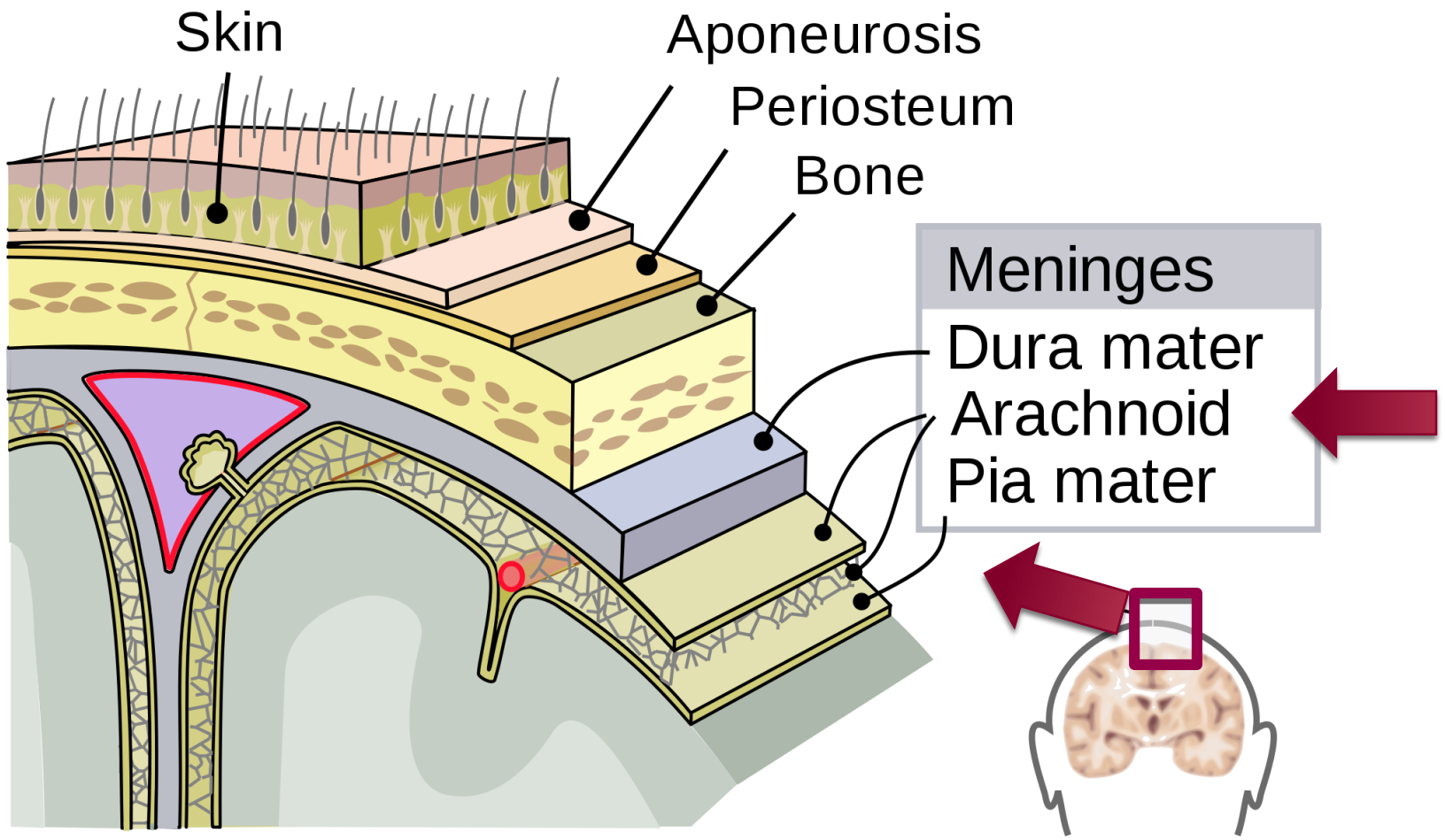
- Most commonly <5, years (most patients <1)
- Very poor prognosis
- 1% Childhood CNS tumors
- 10% Infant CNS tumors
- Supratentorial common, but anywhere
- INI1/SMARCB1 loss



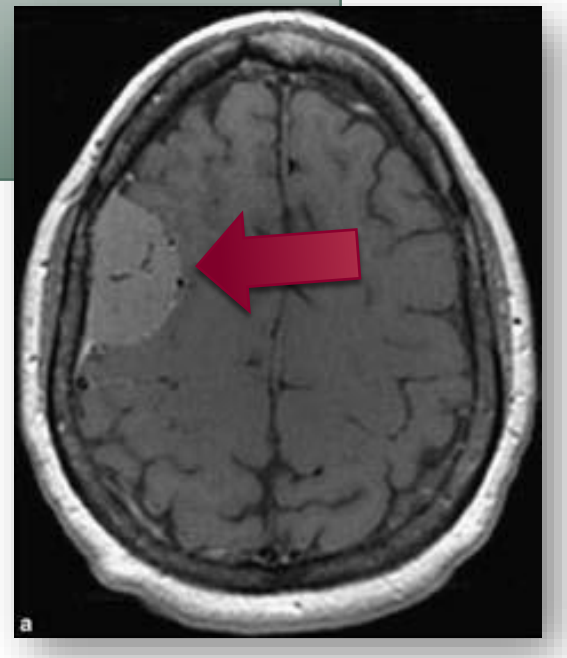




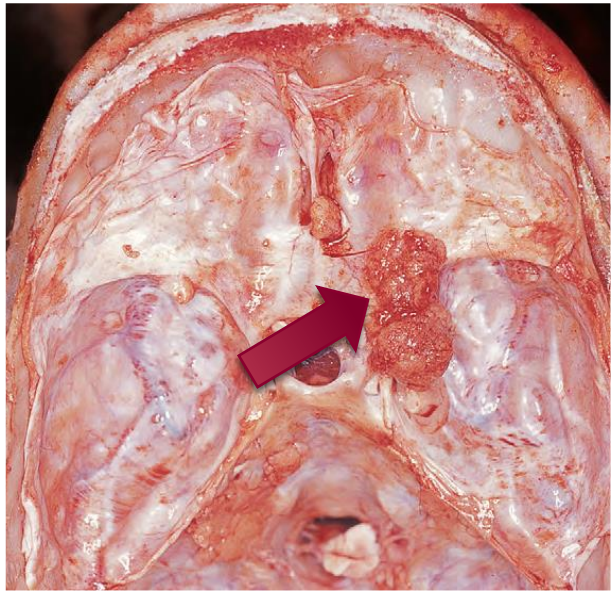
V. MENINGIOMAS

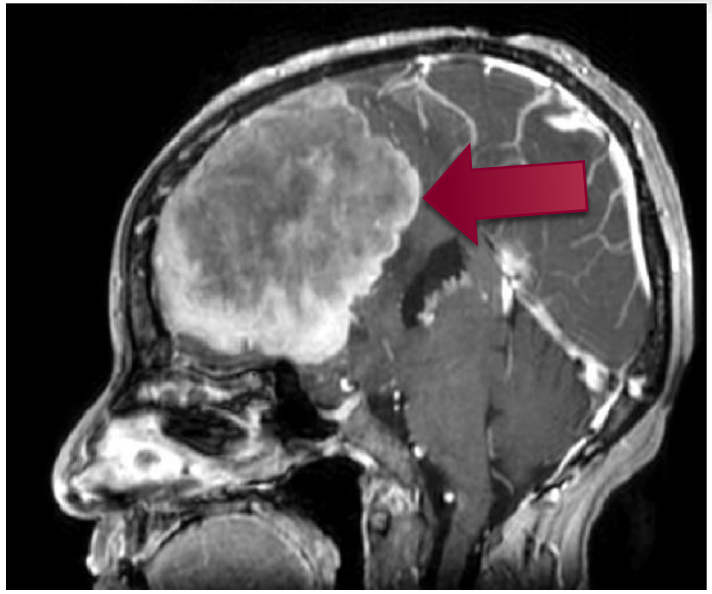


Meningeoma Grade I.

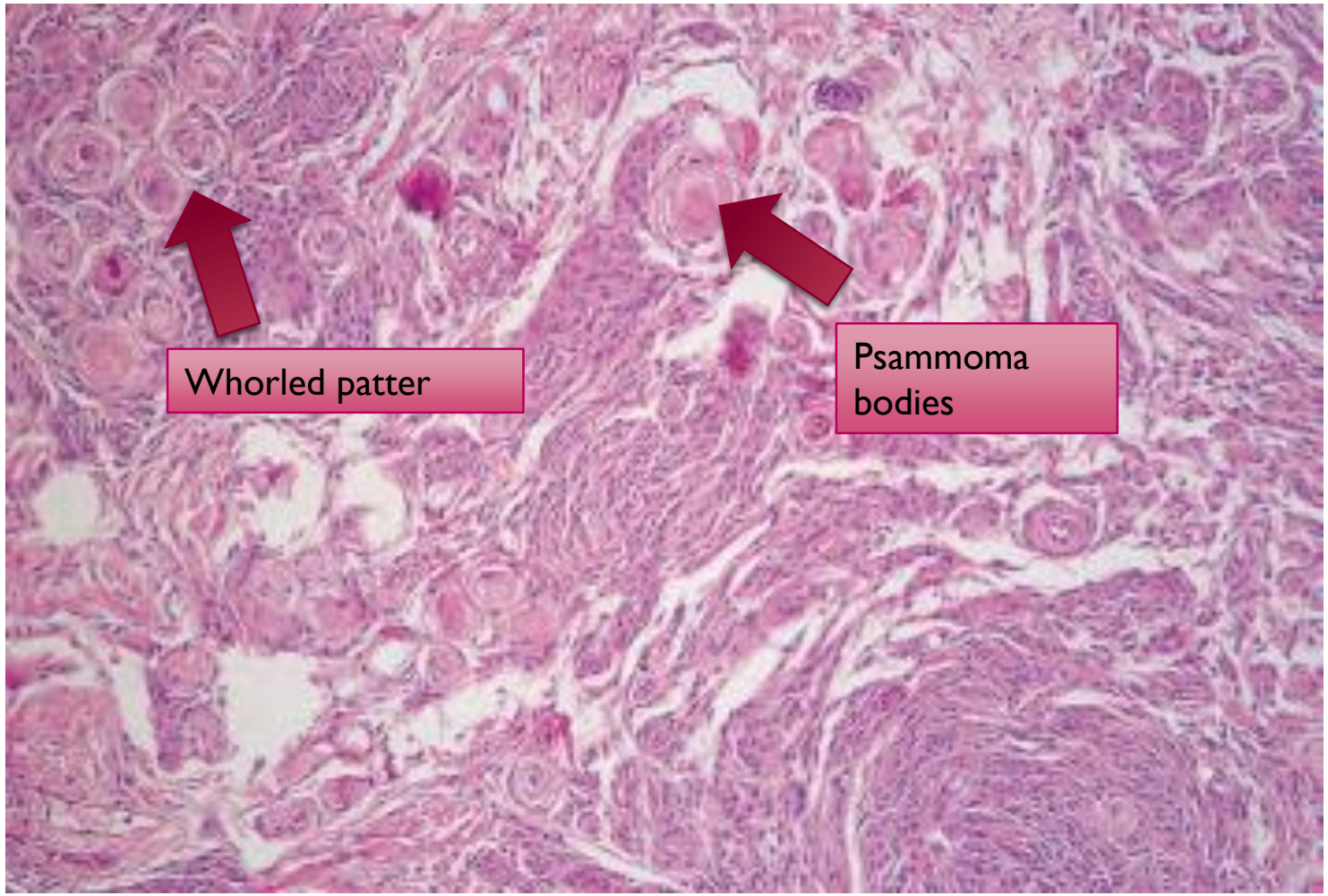


- Incidence increases with age
- Primary CNS tumors ~30% meningioma
- External surfaces or intraventricular (Rare)
- Focal neurological deficits
- Several histological variants





Meningeoma Grade I.



Several histological variants:

Meningothelial

Fibrosus

Transicional

Psammomatous

Angiomatous

Microcystic

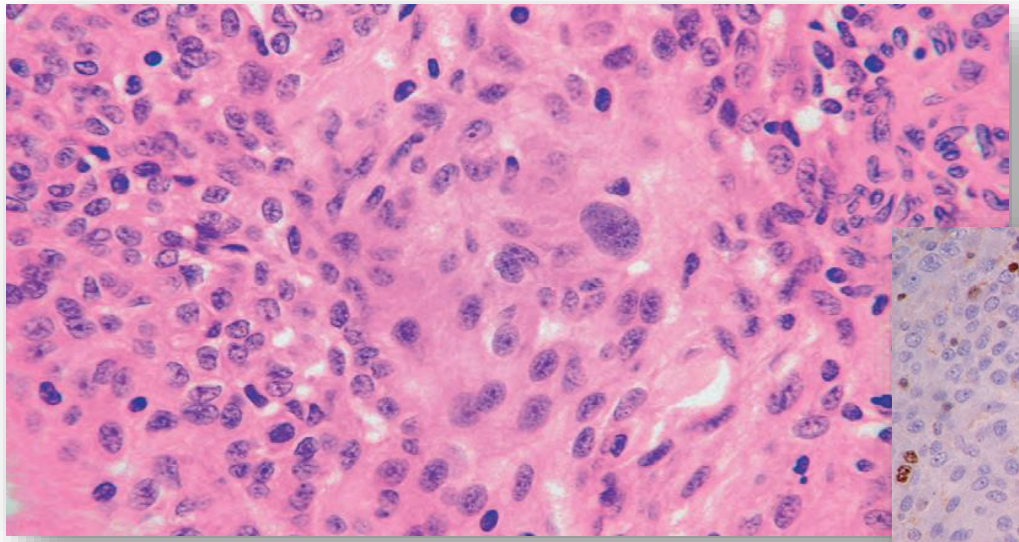
Secretory

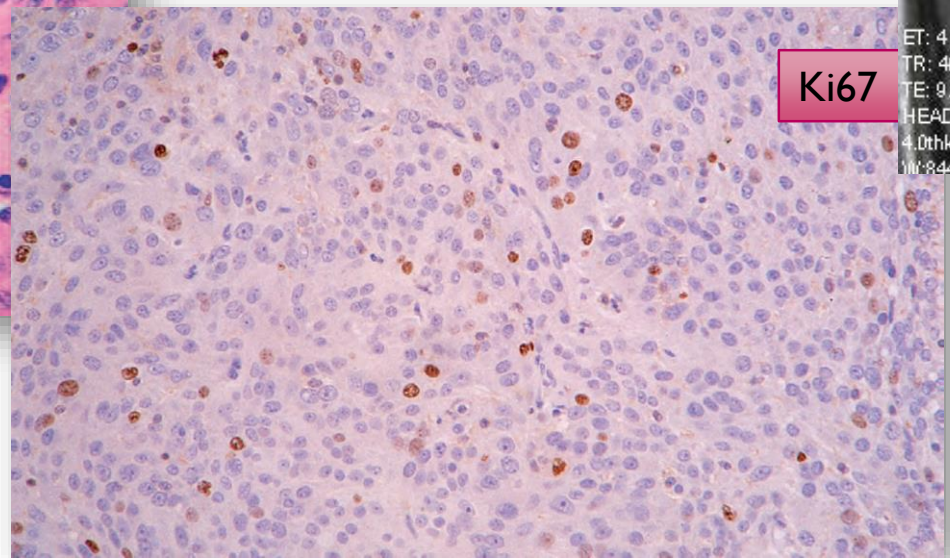
Lymphoplasmocyte rich

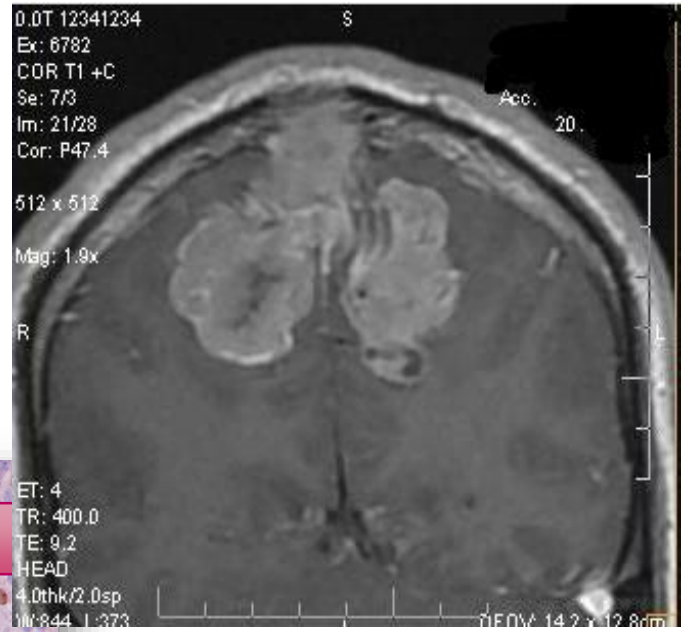
Metaplastic

ATYPICAL MENINGEOMA GRADE II.

- Grade II variants: Chordoid, clear cell, atypical
- Clear cell : Childhood lumbal tumor
- Brain invasion – Grade II

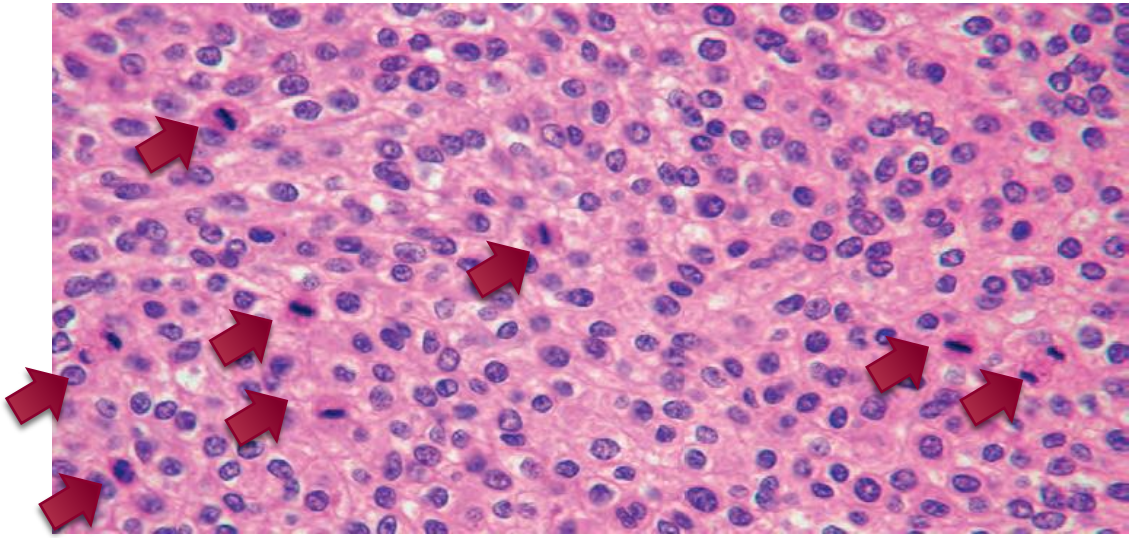


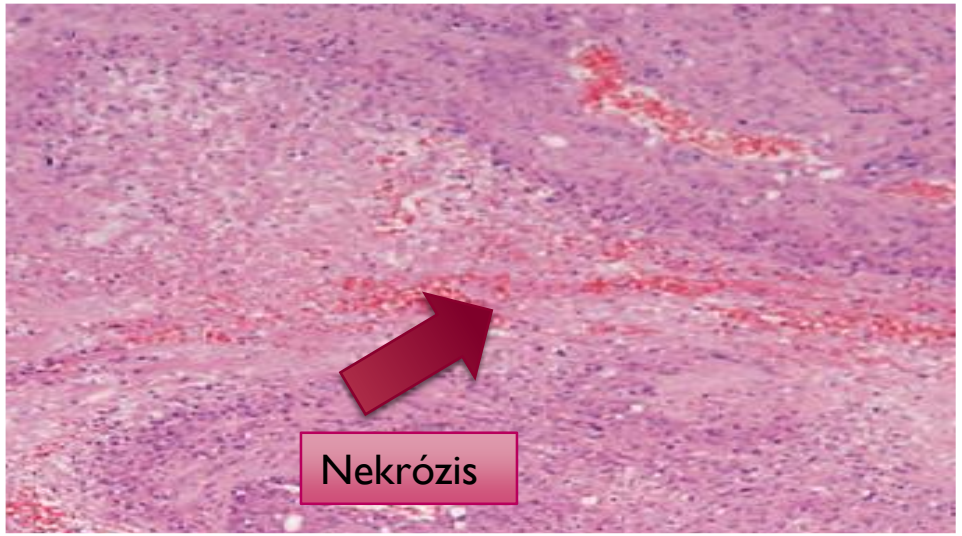




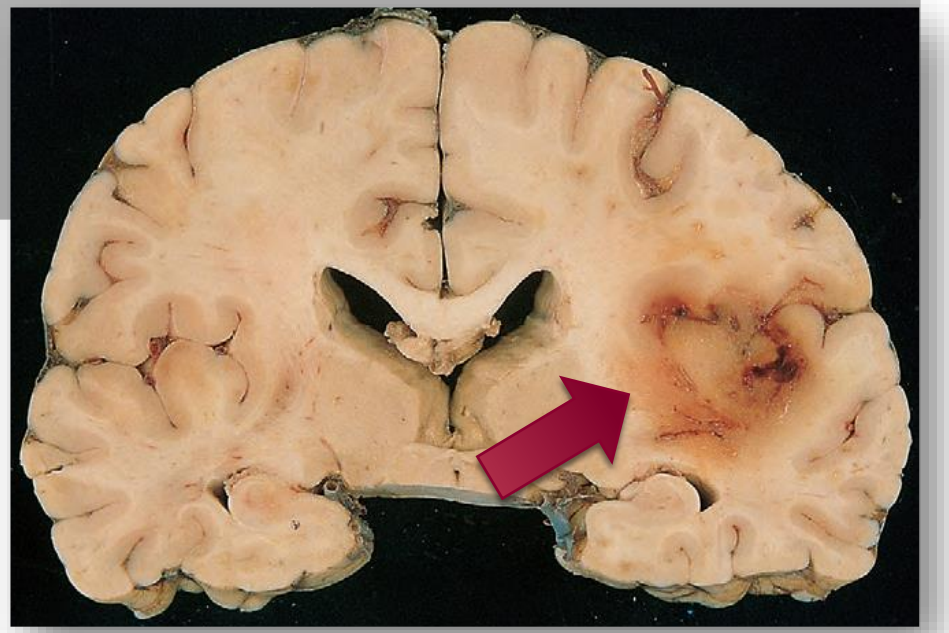
ANAPLASTIC MENINGEOMA GRADE III.

- Grade III variants: Papillary, rhabdoid, anaplastic
- Difficult differenntial diagnostics



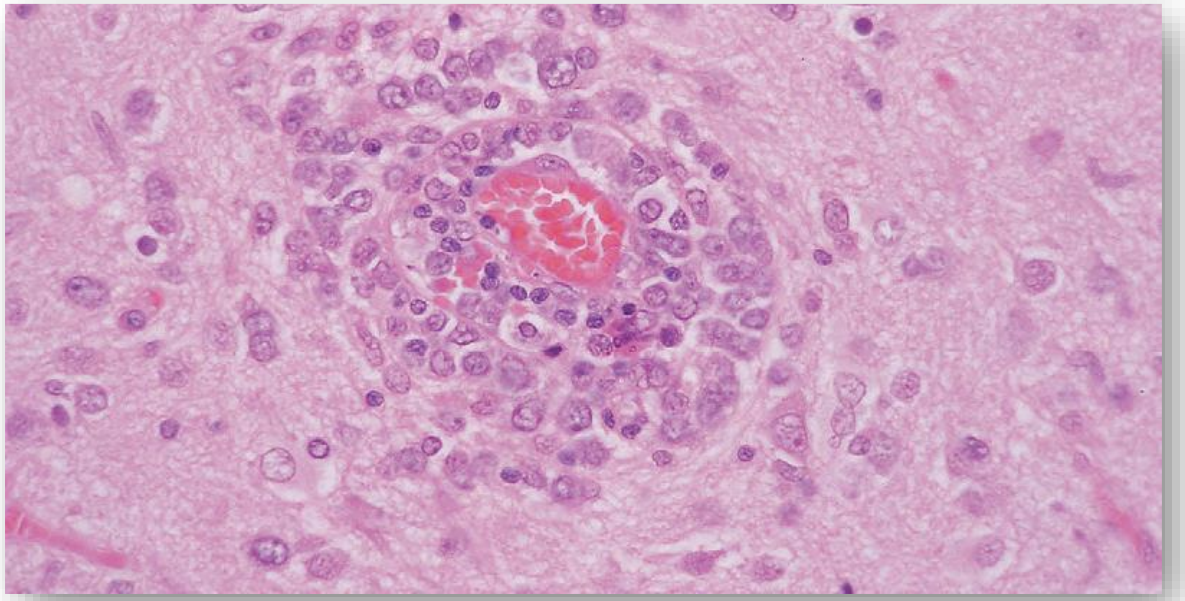


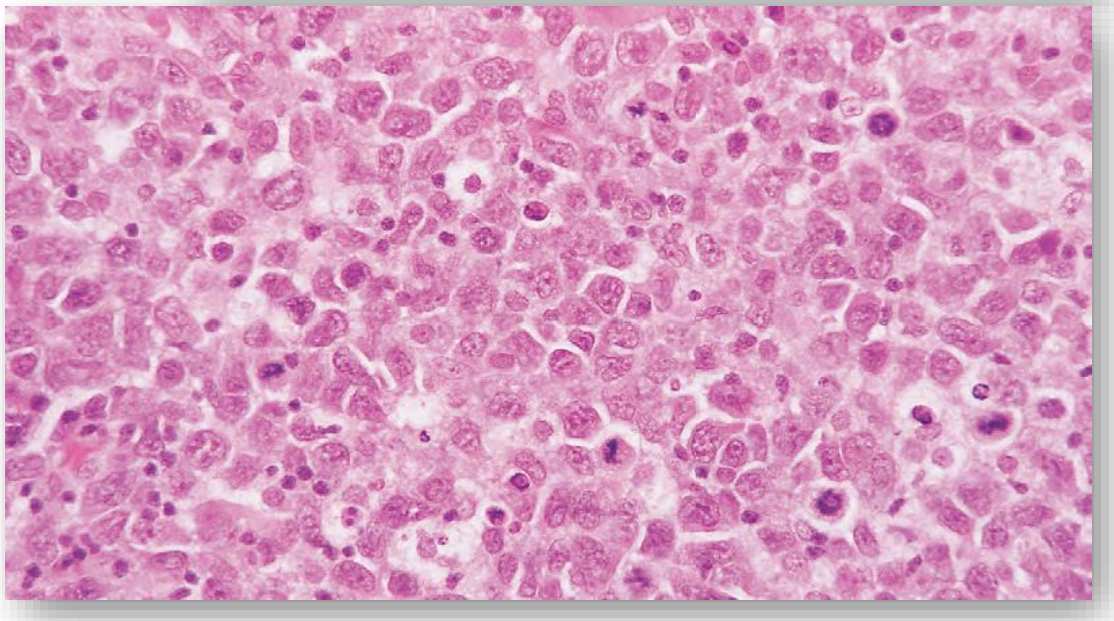
VI. PRIMARY CNS LYMPHOMA



- DLBCL type

- Immunosuppressed patients - EBV+
- But Not only!



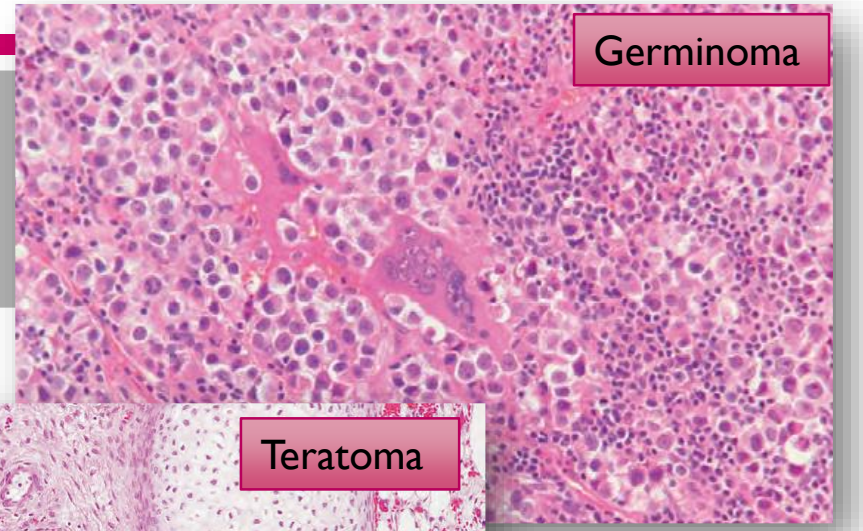


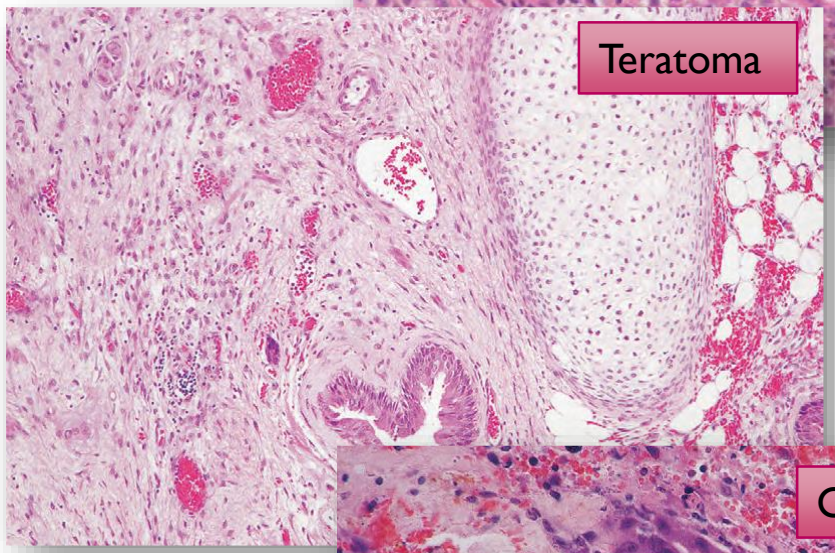
VII. CNS GERM CELL TUMORS

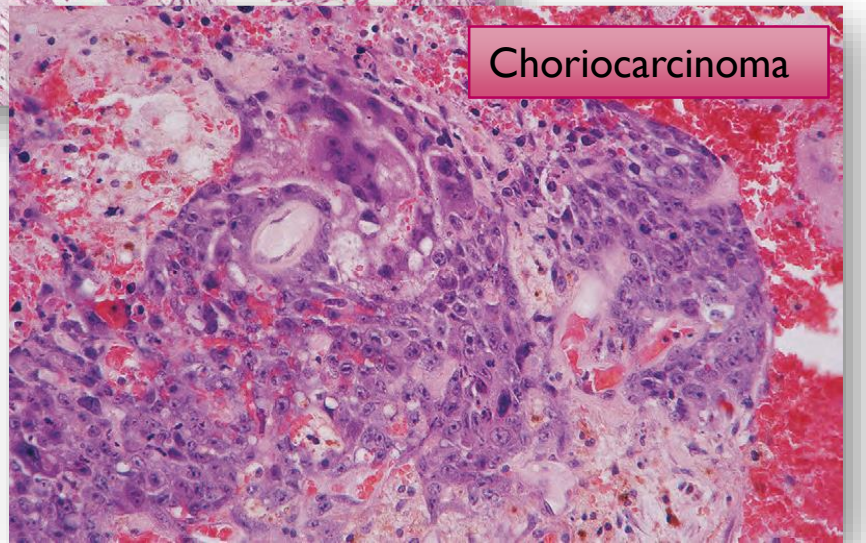
- Germinoma - 50%
- Teratoma - 20%
  - Mature teratoma
  - Immature teratoma
  - Teratoma with malignant transformation
- Yolk sac tumor
- Embryonal carcinoma
- Choriocarcinoma

} 5%

- Mixed tumor - 25%

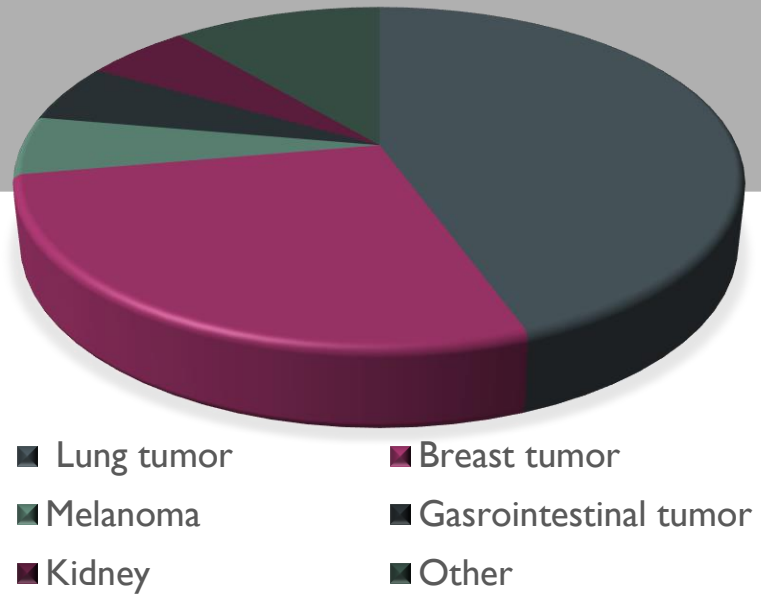


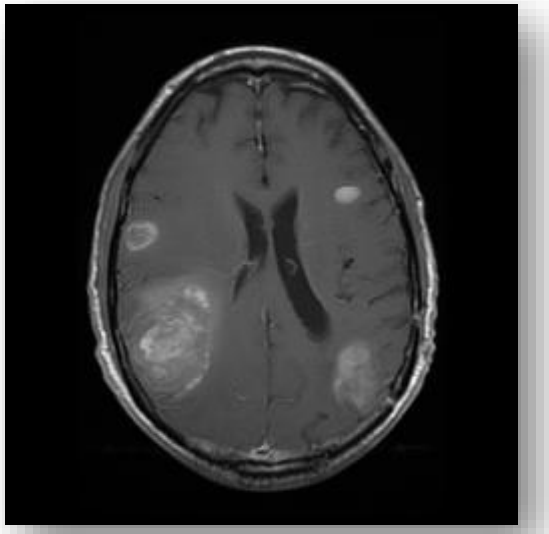


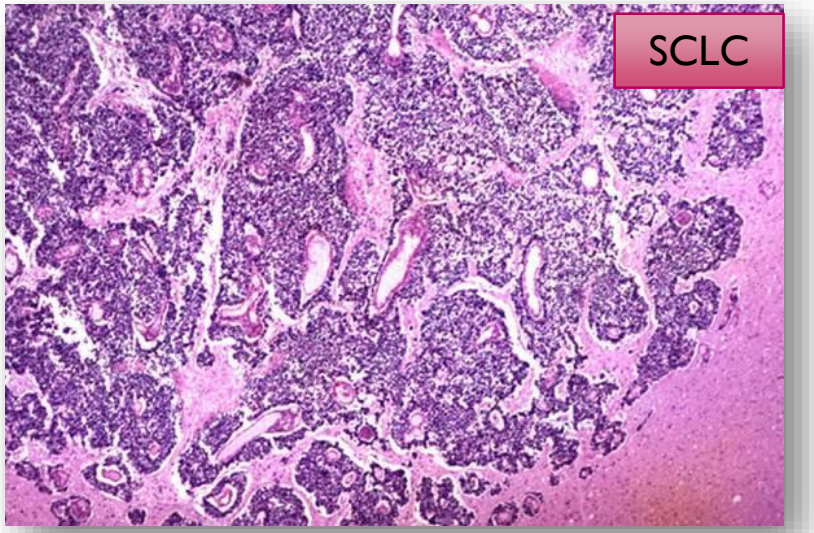


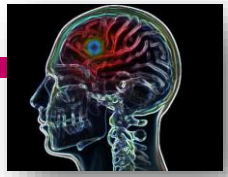
VIII. METASTATIC TUMORS

- 25-50% of all CNS tumors
- Gray-white junction
- Sharply demarcated masses
- Perifocal edema









NEUROPATHOLOGY
INFECTIONS

HAJNALKA RAJNAI

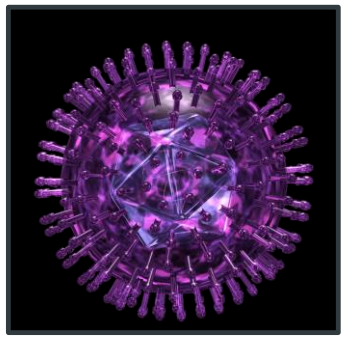
Semmelweis Egyetem – I. Patológiai és Kísérleti Rákkutató Intézet

rajnai.hajnalka@med.semmelweis-univ.hu

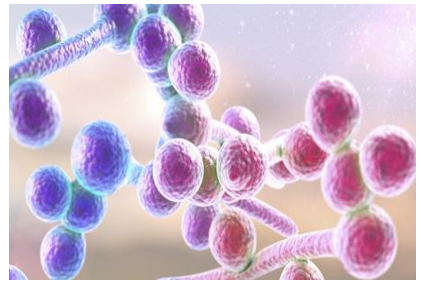
INFECTIOUS AGENTS

1. Baterial infection
   - Bakterial meningitis
   - Brain abcessus
   - Tuberculosis
   - Neurosyphilis

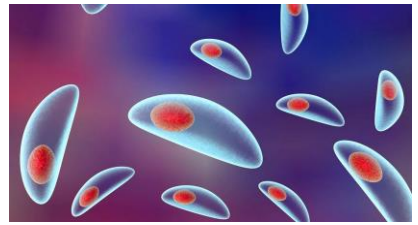
2. Viral infection
   - Viral meningitis
   - Herpesvirus
   - Cytomegalovirus
   - Poliovirus
   - Rabies
   - HIV
   - Progressive multifocal leukoencephalopathy



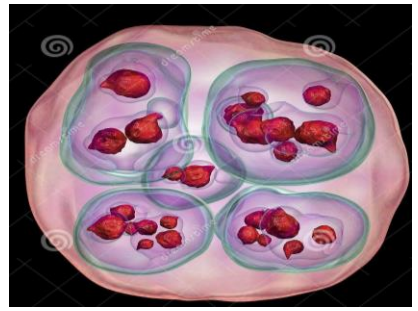
3. Fungal infection
   - Candida
   - Mucormycosis
   - Aspergillus
   - Cryptococcus



4. Protozoal infection
   - Toxoplasma



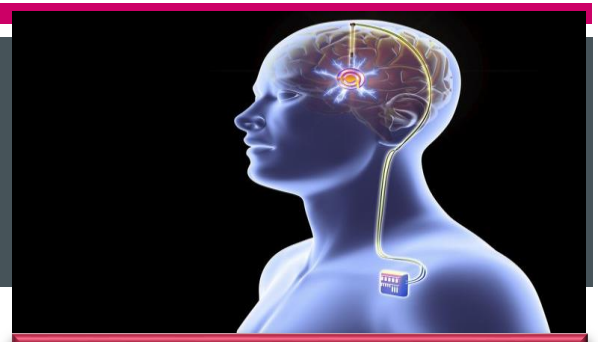
5. Parazite infection
   - Cystercosis
   - Echinococcus



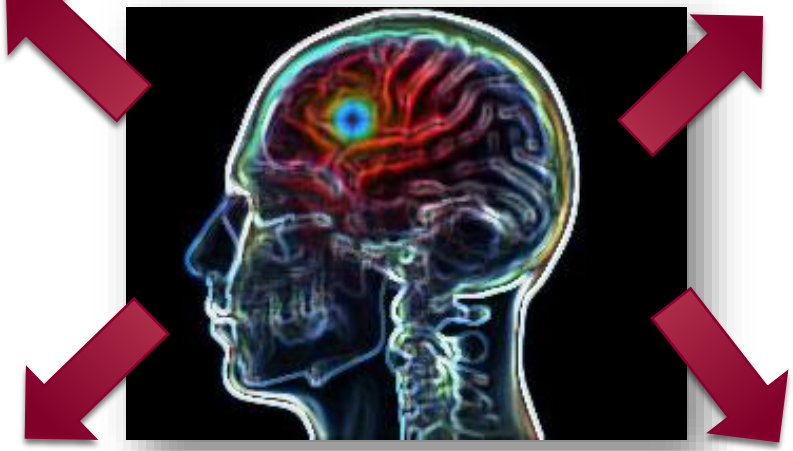
SPREAD

1. Hematogenous spread
2. Direct implantation
   - Trauma, Iatrogenic (Epilepsy, surgery)
3. Local extension
   - Sinuses, Otitis media, Congenitalis malformatio
4. Retrograde, peripheral nerves

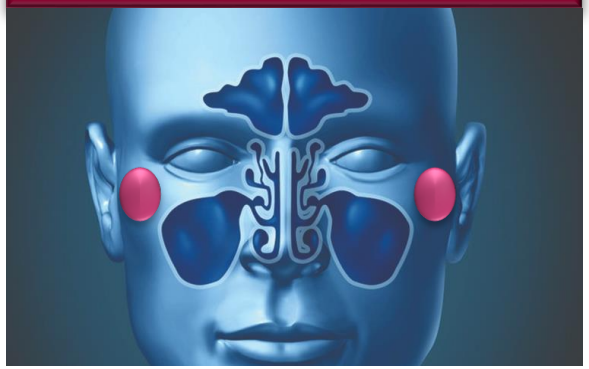
Hematogenous spread



Direct implantation



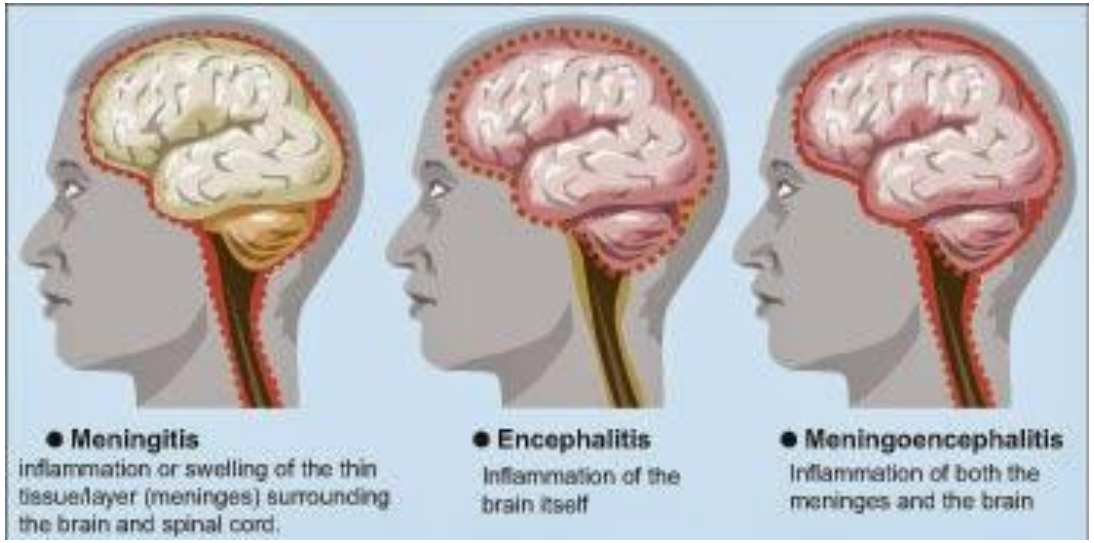
Local extension



Peripheral nerves

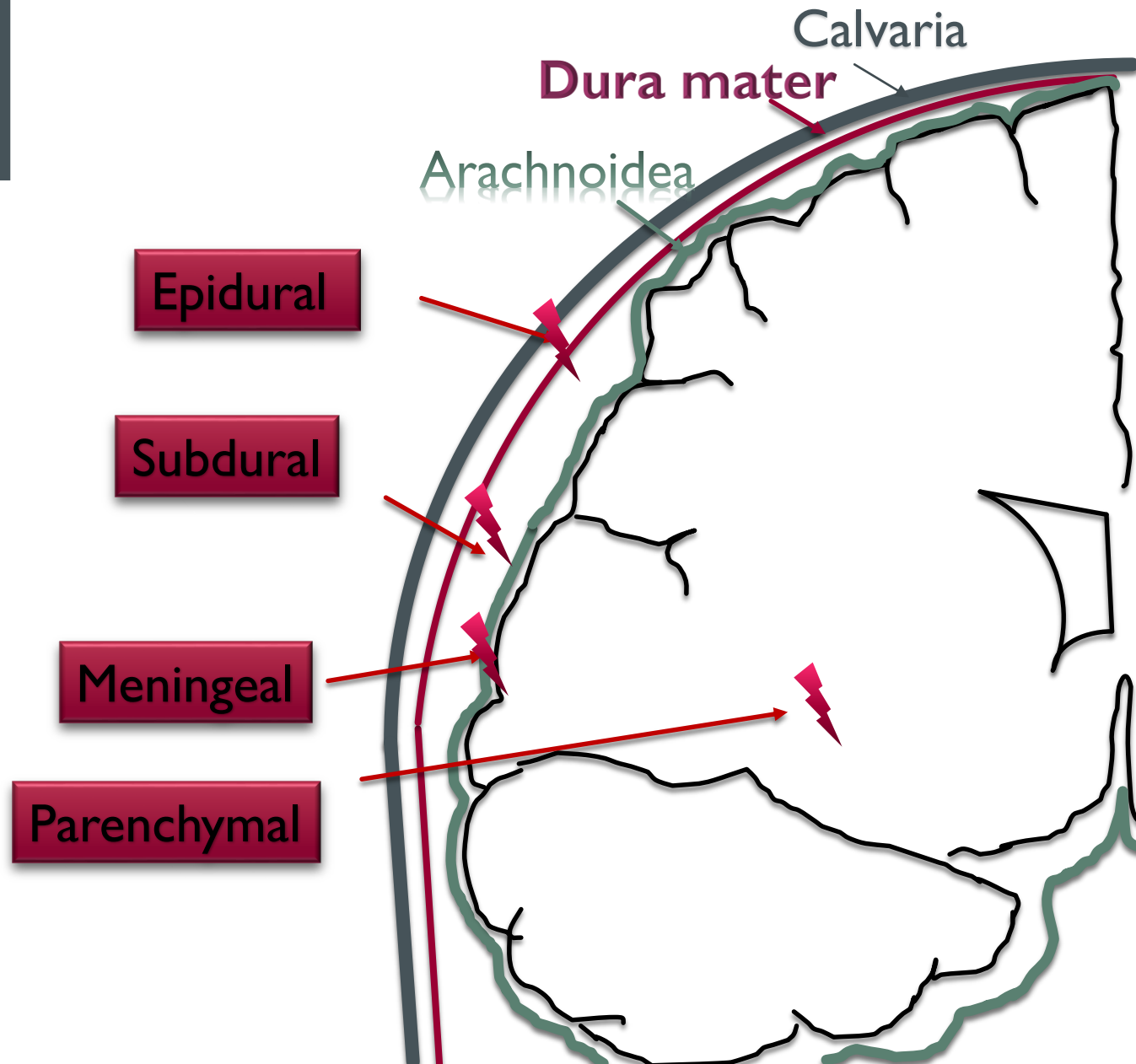
LOCATION

1. **Parenchyma:** encephalitis , myelitis, encephalomyelitis.
2. **Meninges:** meningitis, pachymeningitis.
3. **Parenchyma and Meninges:** meningoencephalitis.



LOCATION

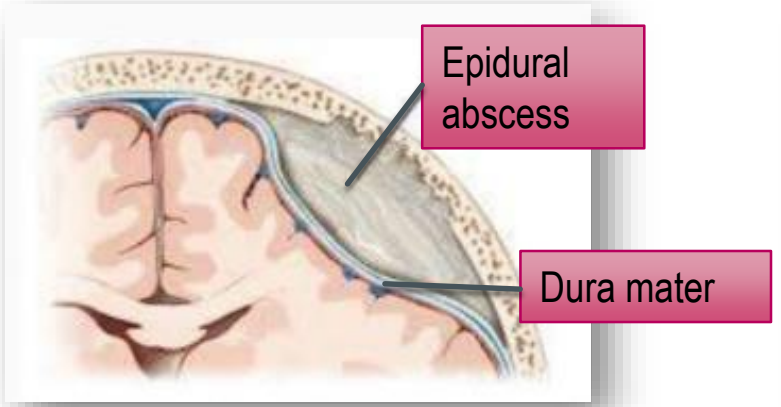
1. **Epidural infection**
2. **Subdural infection**
3. **Meningeal infection – meningitis**
4. **Parenchymal infections – Encephalitis**

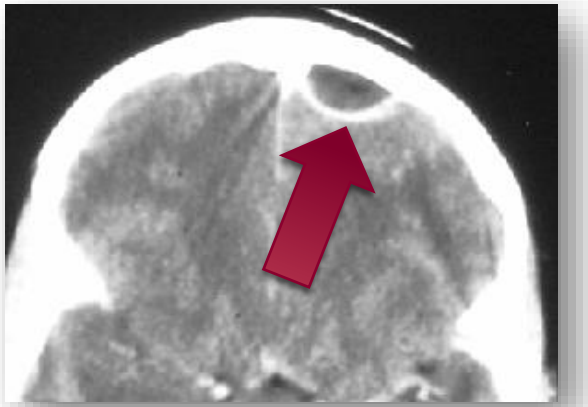


EPIDURAL AND SUBDURAL INFECTIONS

Epidural abscess

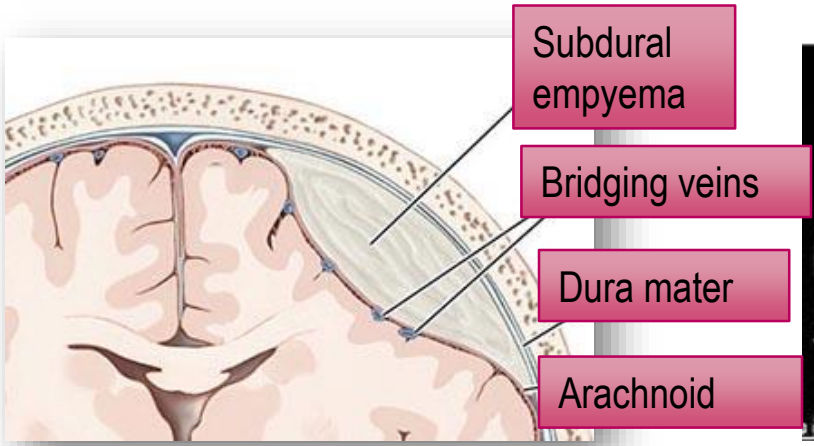
- Local spread – sinuitis, osteomyelitis
- Bacterial, fungal
- Spinal - spinal cord compression

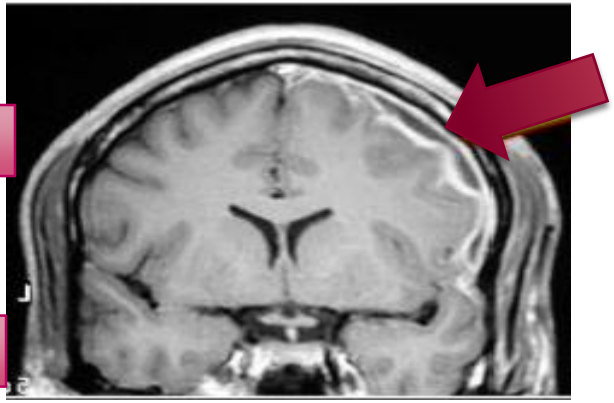




Subdural empyema

- Local spread – sinus, otitis
- Arachnoid, subarachnoid space is unaffected
- Thrombophlebitis in the bridging veins

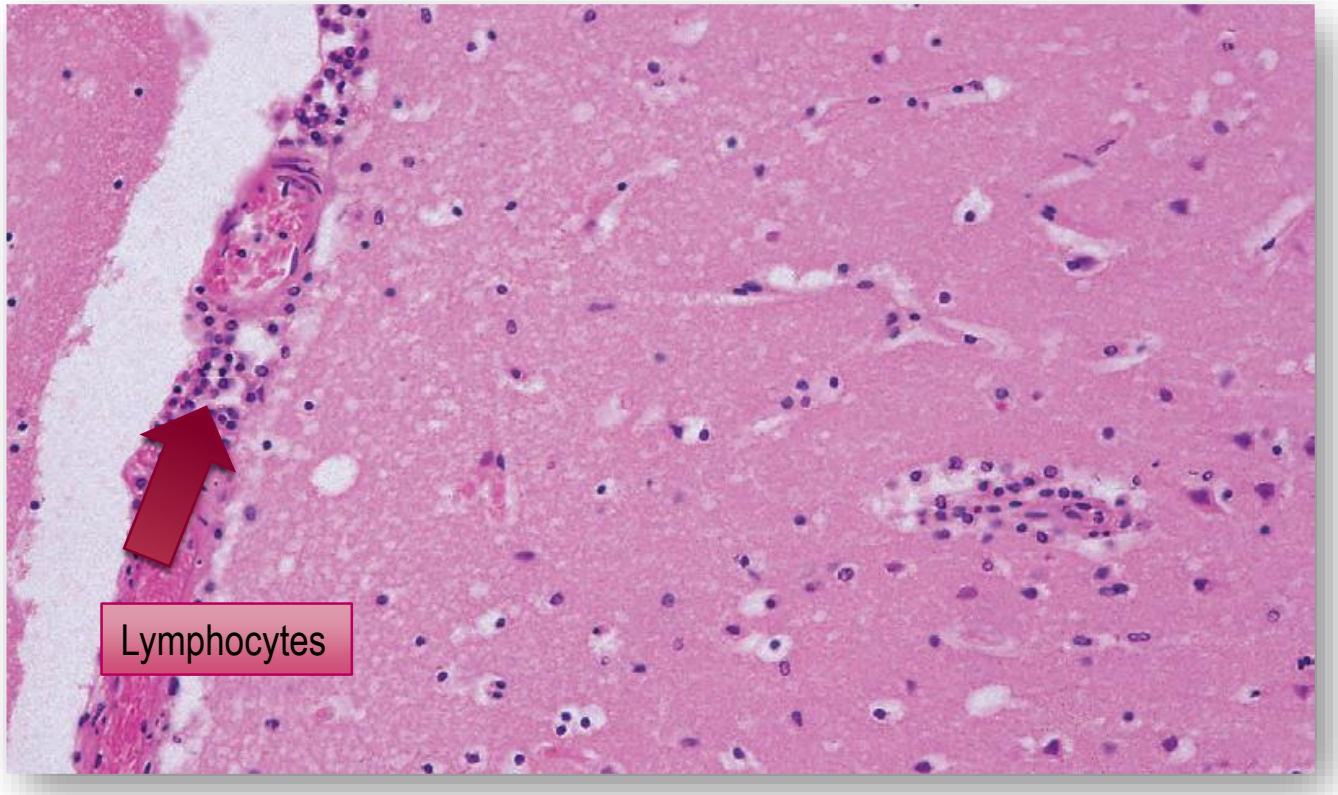




MENINGITIS

Aseptic/Viral meningitis

- Mostly associated with encephalitis
- Mild meningial symptoms
- Viral agents: Echovirus
  Coxsackie B
  Coxsackie A
  Herpes simplex virus (HSV)-2
  Mumps
  Human immunodeficiency virus (HIV)
  Lymphochoriomeningitis virus
  Arbovirus
  Rubeola
  Parainfluenza virus
  Adenovirus

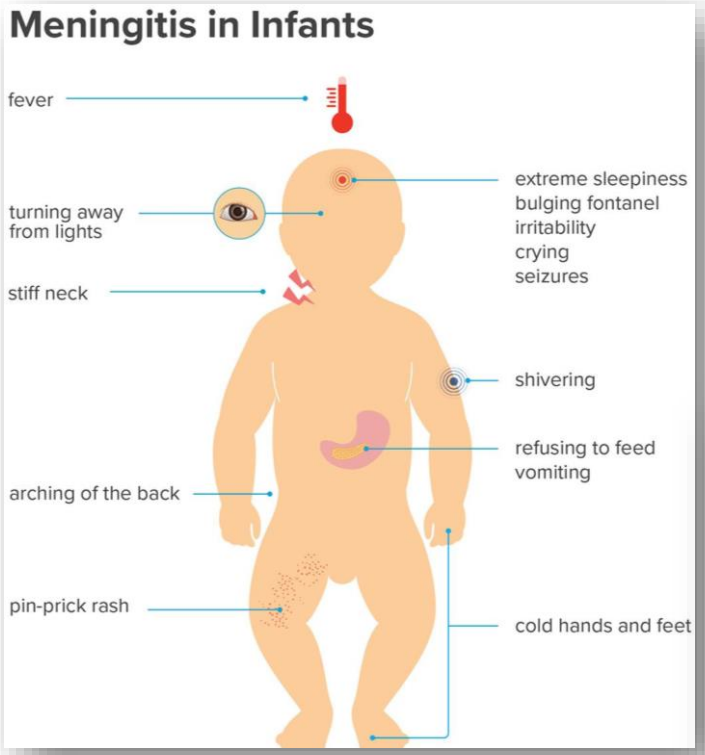


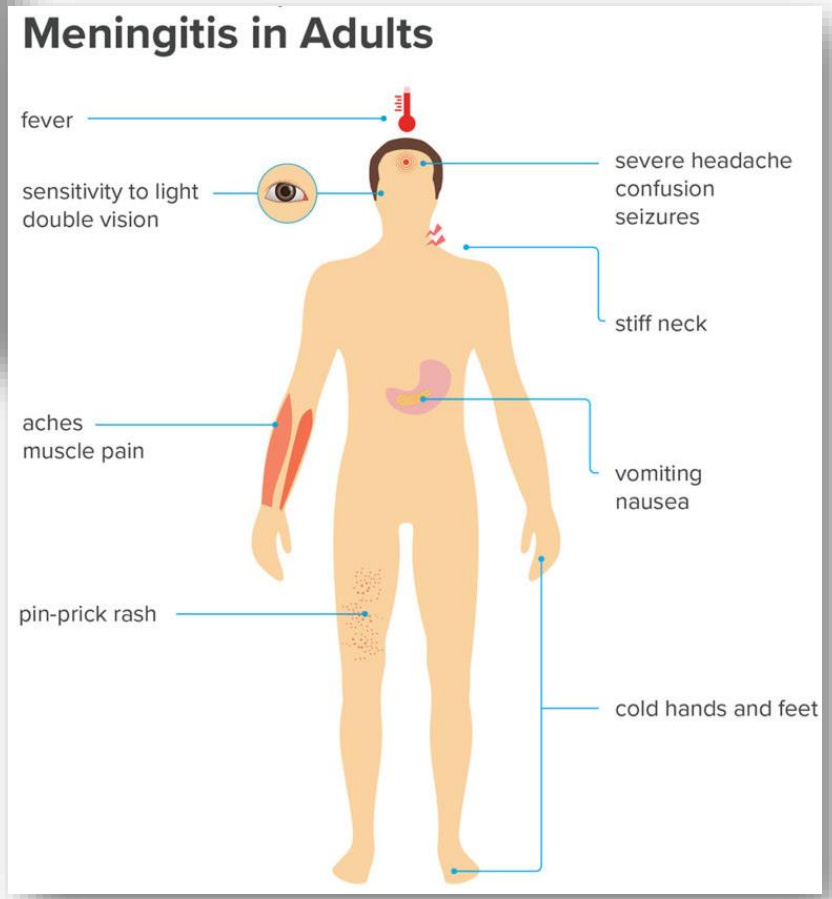
Bacterial meningitis

1. Neonates
   - Escherichia coli
   - B Streptococcus

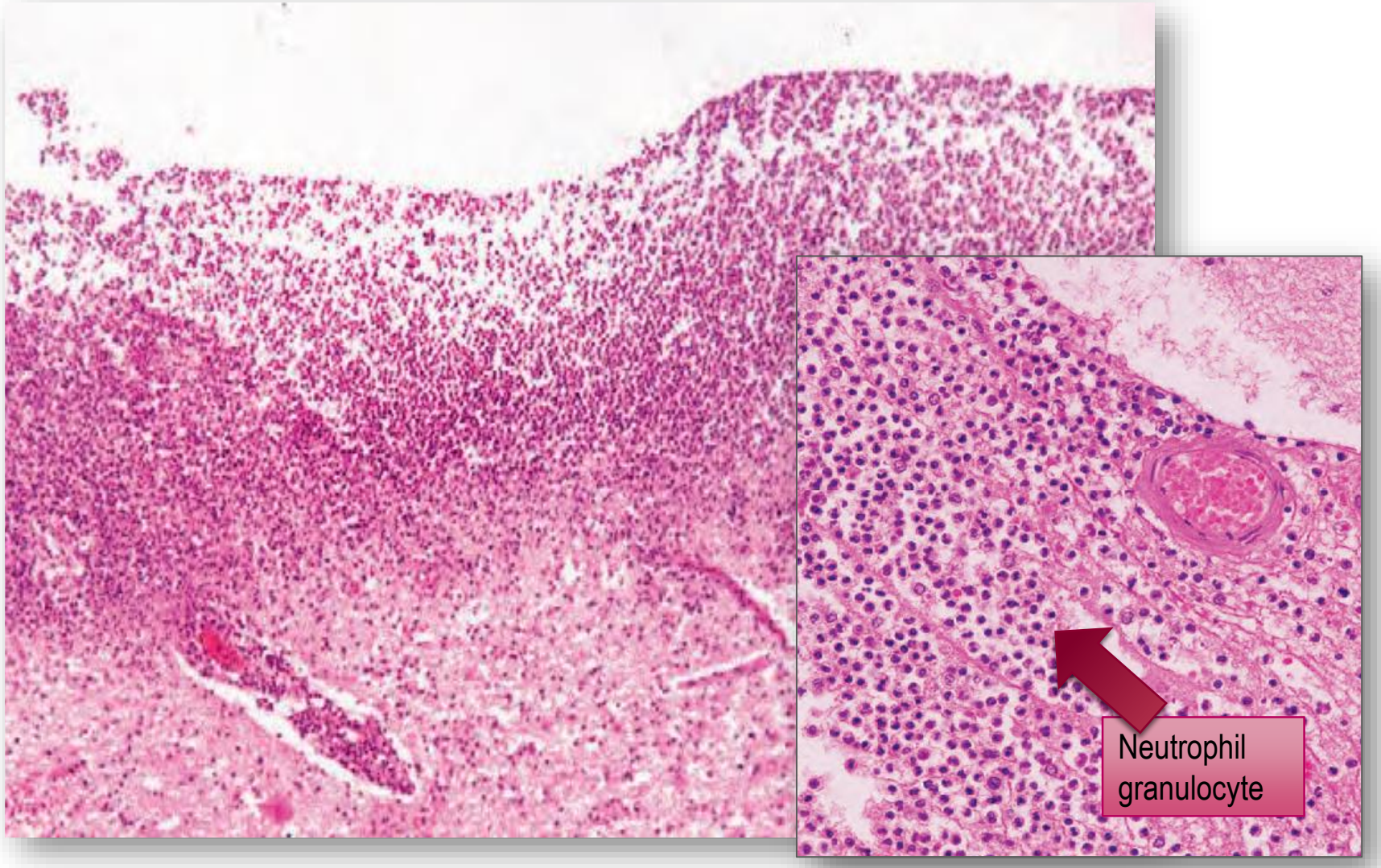
2. Children young, adults
   - Neisseria meningitidis
   - Streptococcus pneumoniae

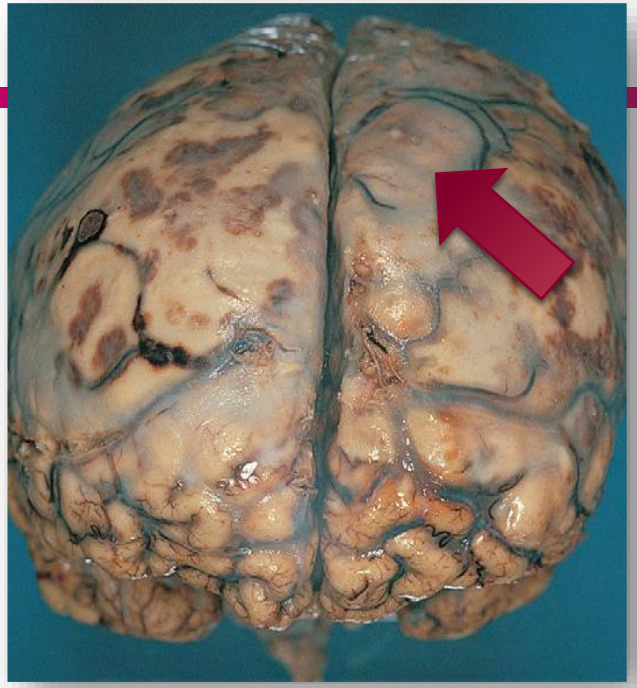
3. Older individuals
   - Streptococcus pneumoniae
   - Listeria monocytogenes

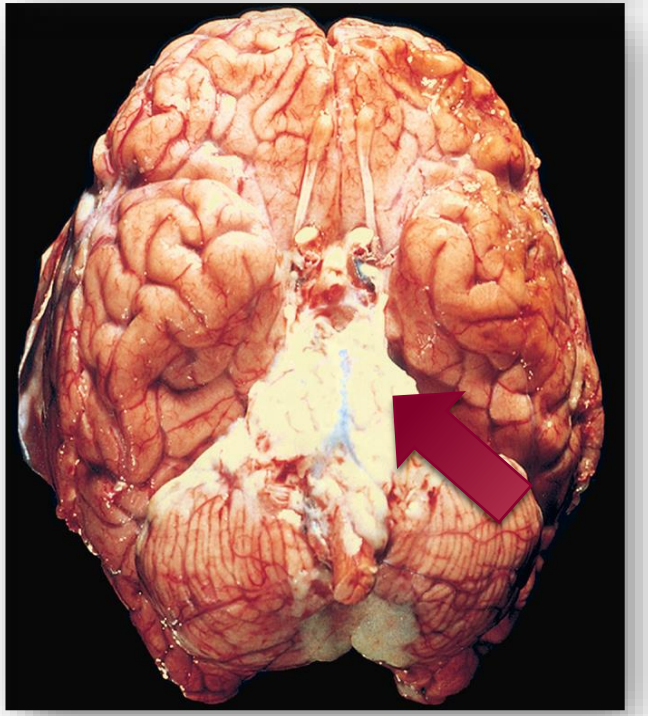




Bacterial meningitis



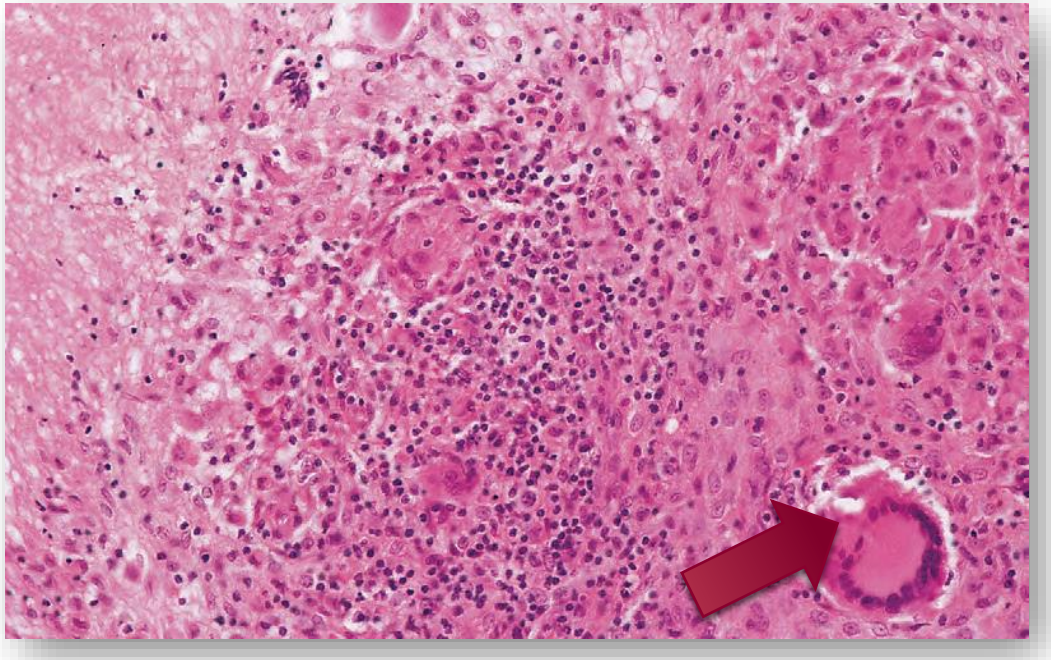


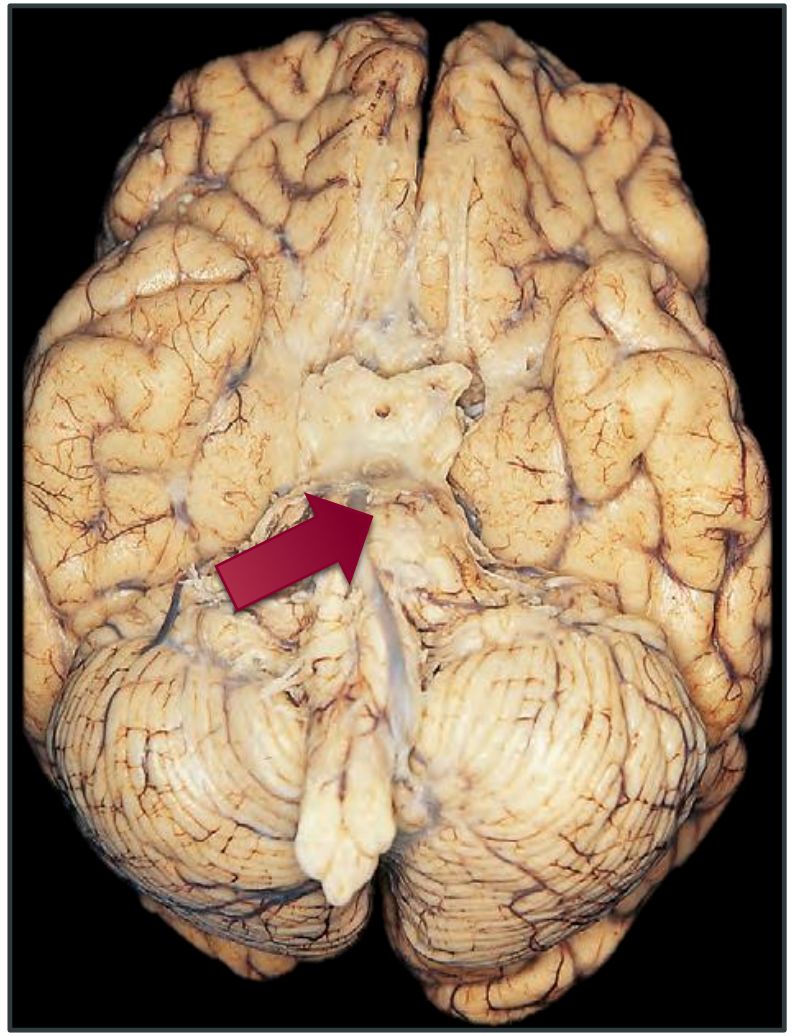


Chronic meningitis

Mycobacterium tuberculosis

- Meningitis – Fibrinuos exudate
- Intraparenchymal mass (tuberculoma)
- Chronic tuberculotic infection - arachnoideal fibrosis - hydrocephalus





Spirochaetal infections

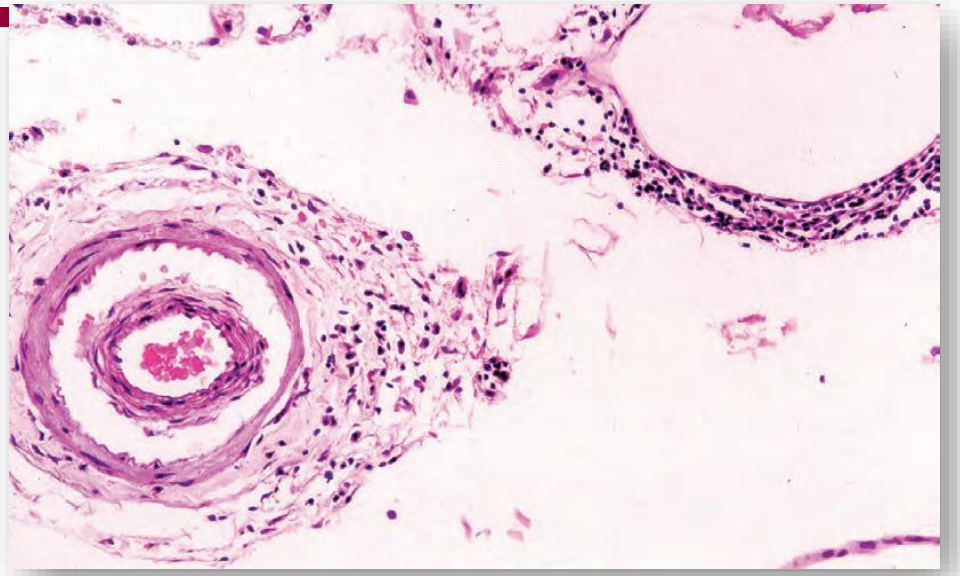
A. Neurosyphilis (3rd stage) – Treponema pallidum

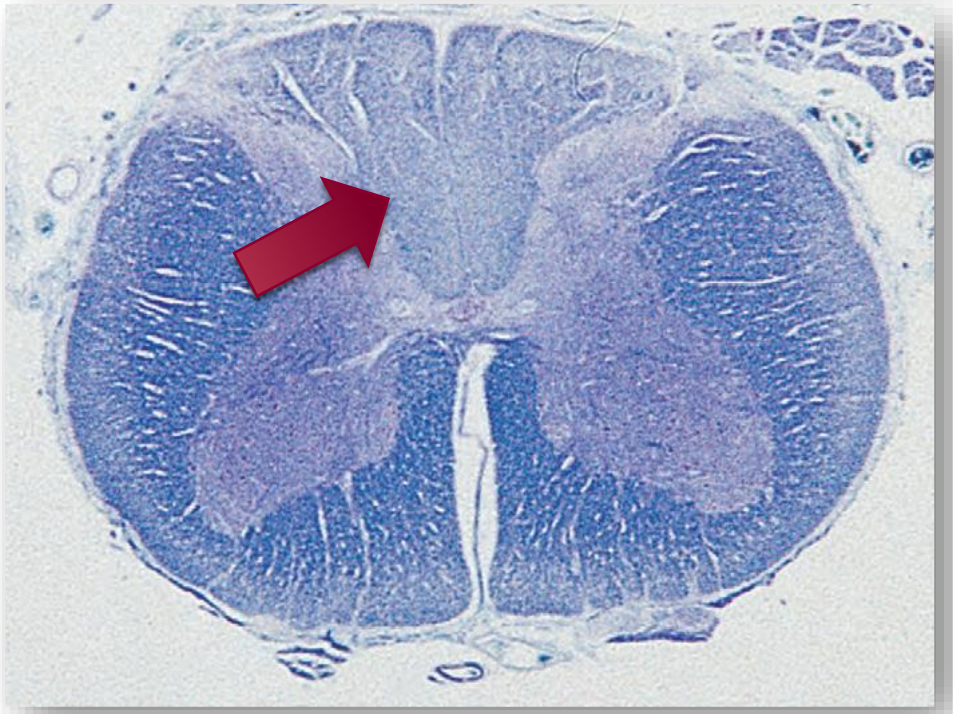
- 10% of persons with untreated infection

1. Chronic meningitis/meningovascular neurosyphilis
   - Involves the base of the brain
2. Paretic neurosyphilis
   - Neuron loss – loss of mental, physical functions
3. Tabes dorsalis
   - Sensory nerves in the dorsal roots
   - Sensory ataxia

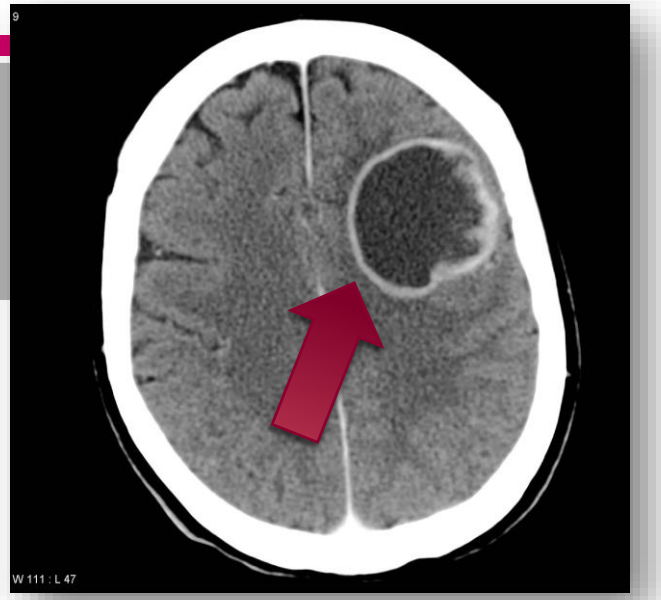
B. Neuroborreliosis – Borrelia burgdorferi

- Aseptic meningitis
- Facial nerve palsies
- Mild encephalopathy
- Polyneuropathies



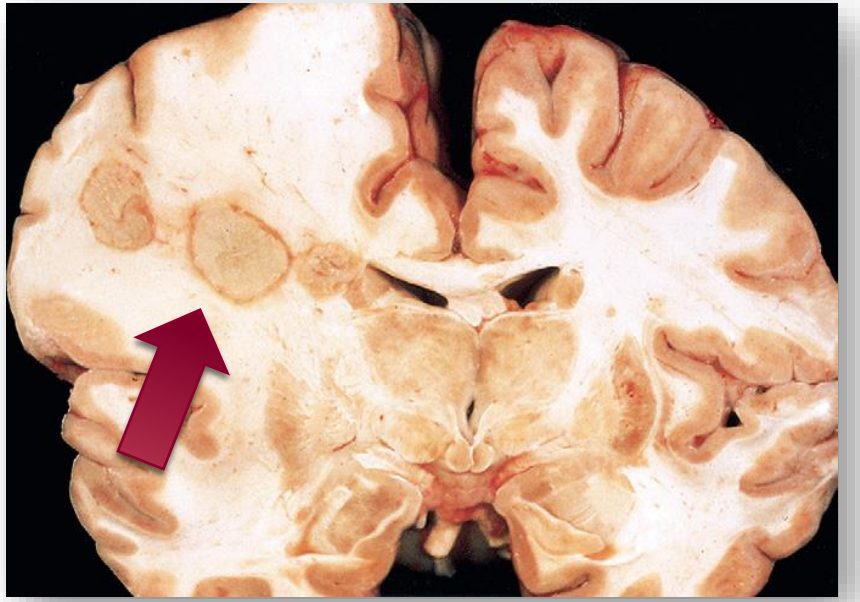


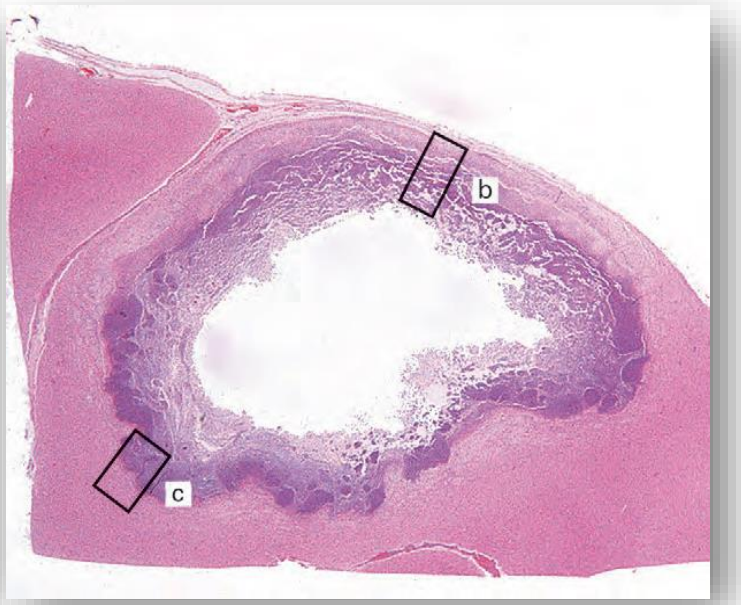
PARENCHYMAL INFECTIONS



Brain abscesses

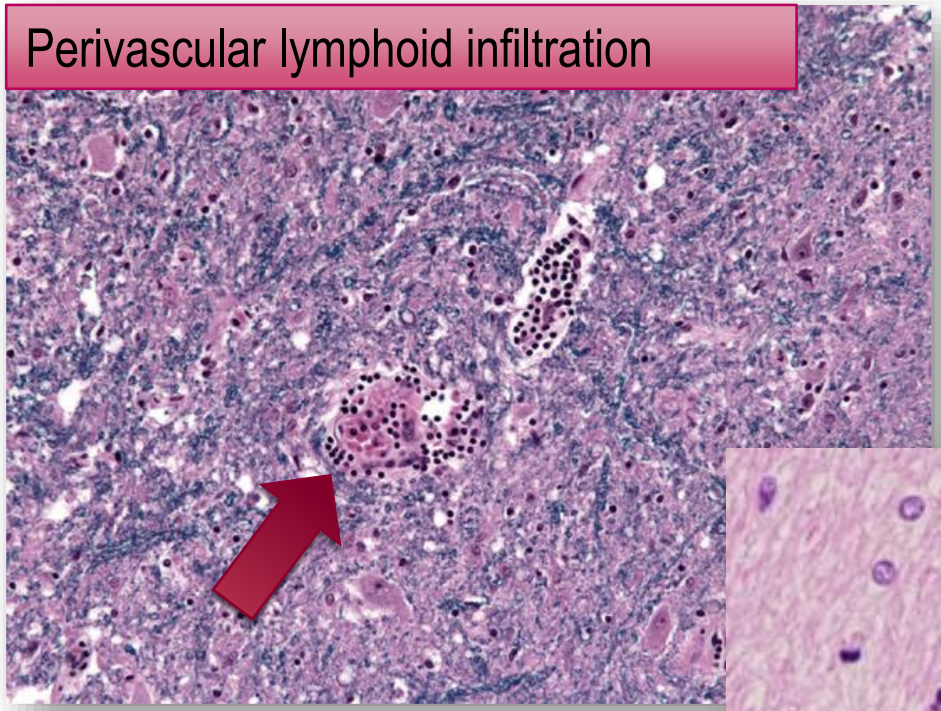
- Bacterial infections
- Spread:
  - Direct implantation
  - Local extension
  - Hematogenous spread
- Symptoms - Focal



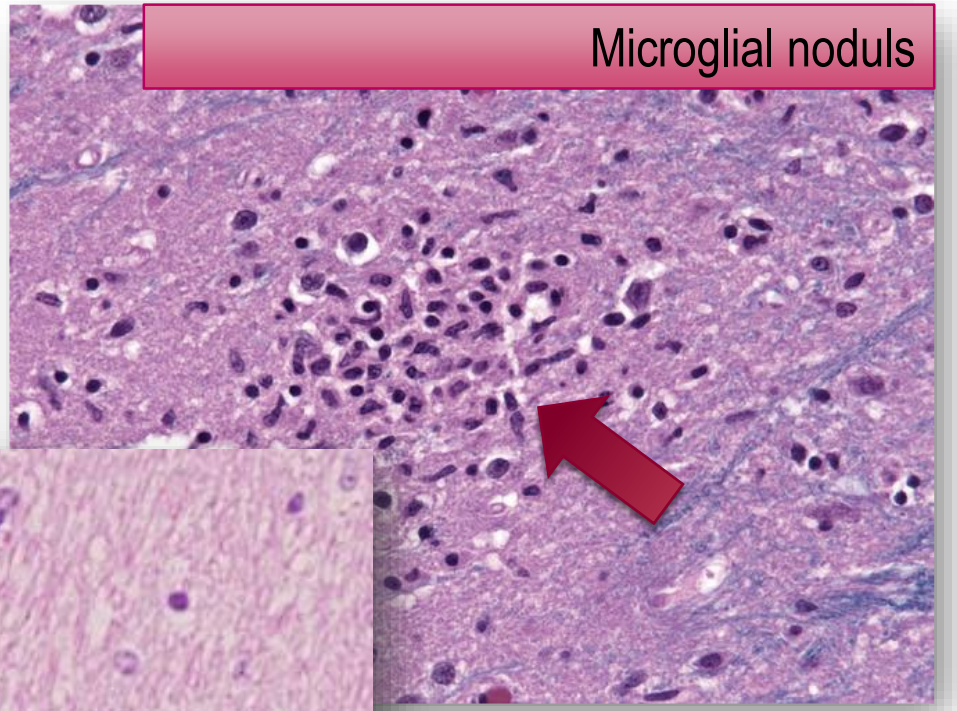


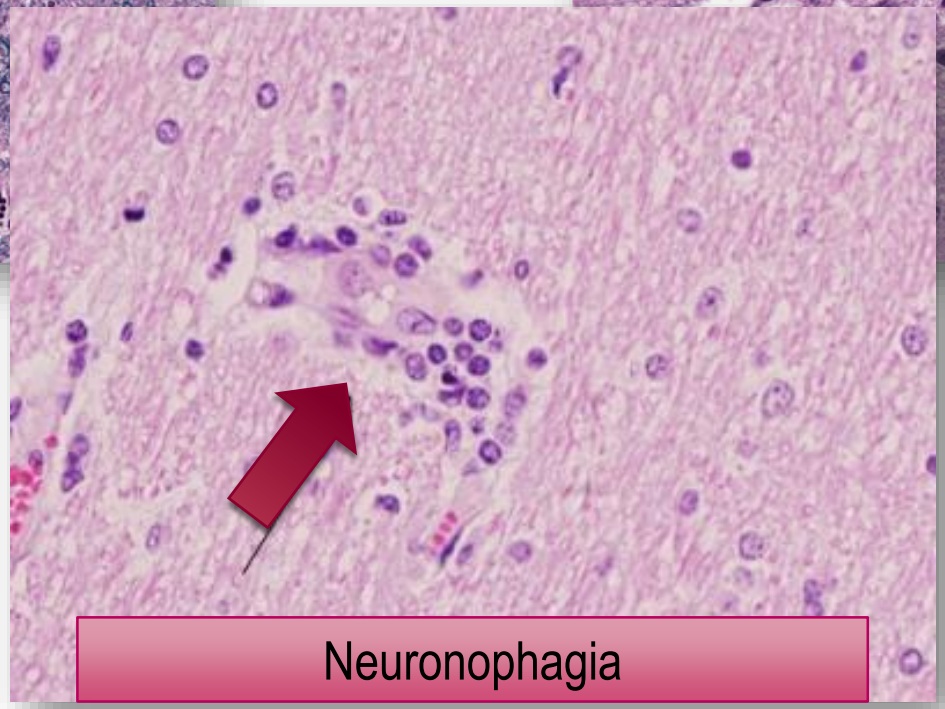
Viral encephalitis

Perivascular lymphoid infiltration



Microglial noduls





Neuronophagia

Herpes virus

A. Herpes simplex-1

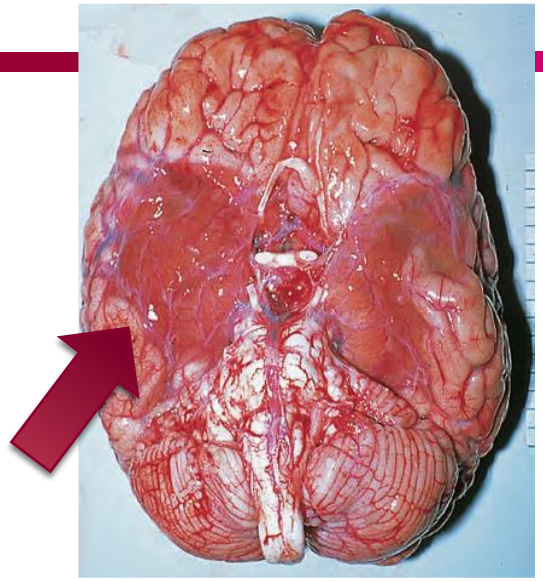
- Children and young adults
- Frontal, temporal lobe involvement
- Necrotizing encephalitis

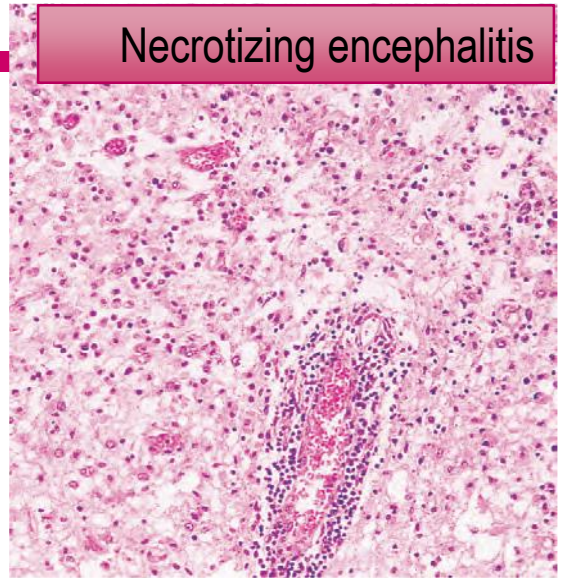
B. Herpes simplex-2

- Adults
- Viral meningitis
- Primary HSV genital inf - neonates

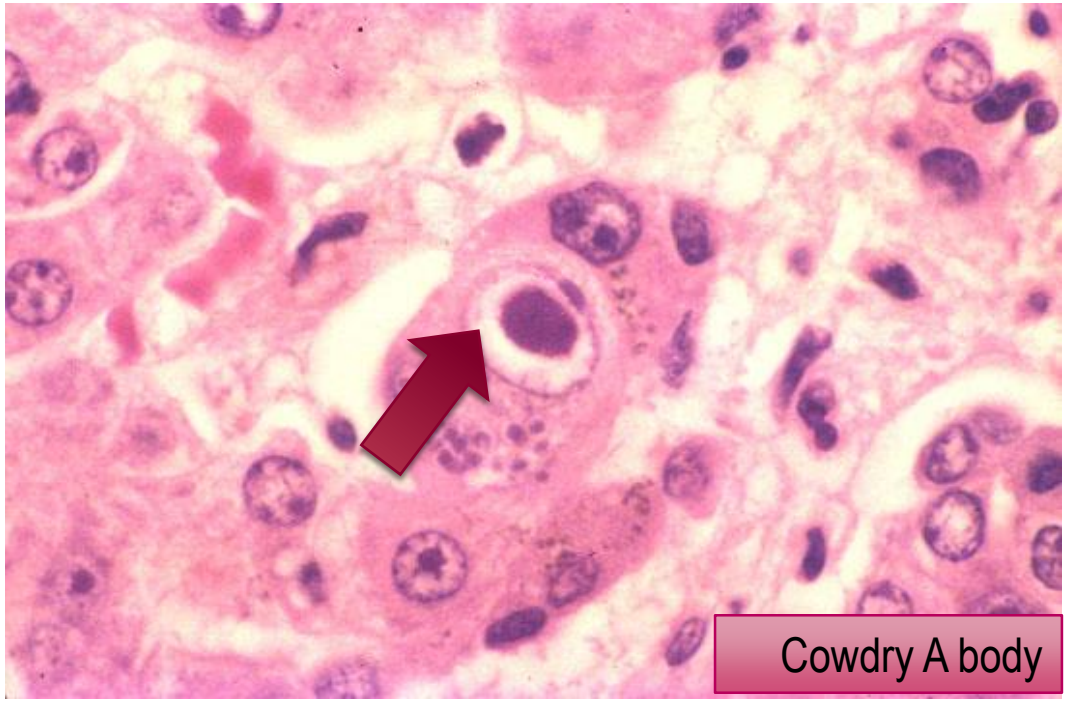
C. Varicella zoster

- Immunosuppressed patients
- HZV encephalitis





Necrotizing encephalitis

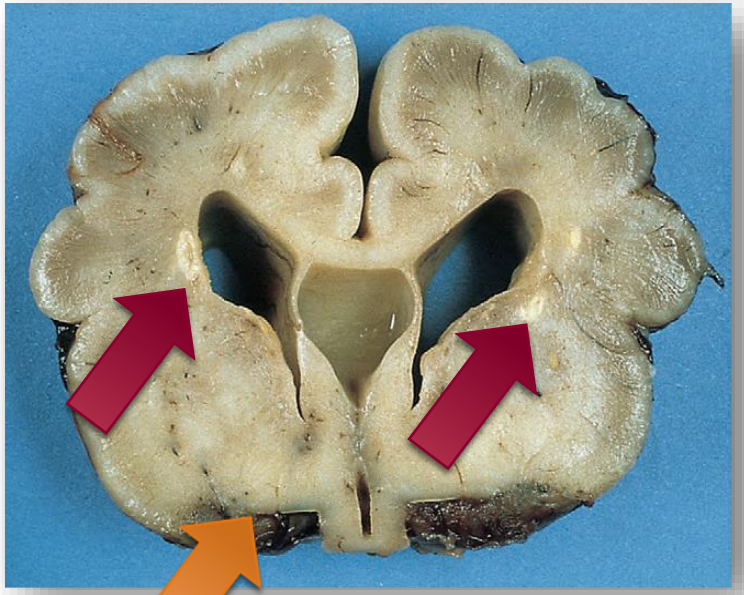


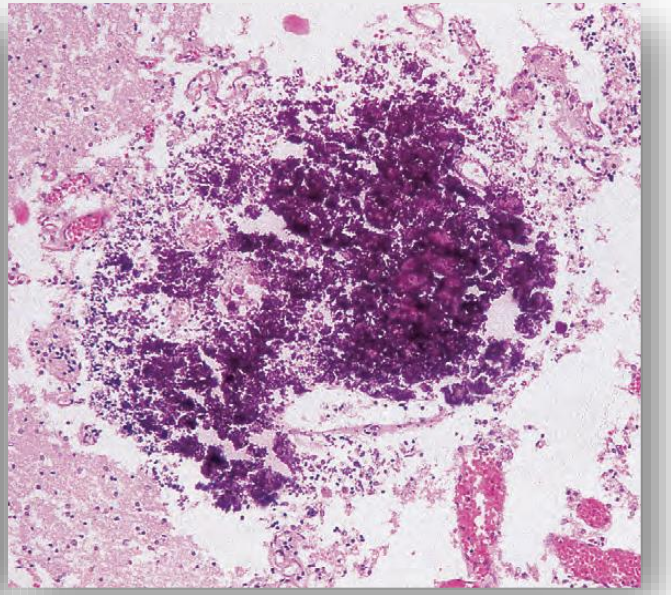
Cowdry A body

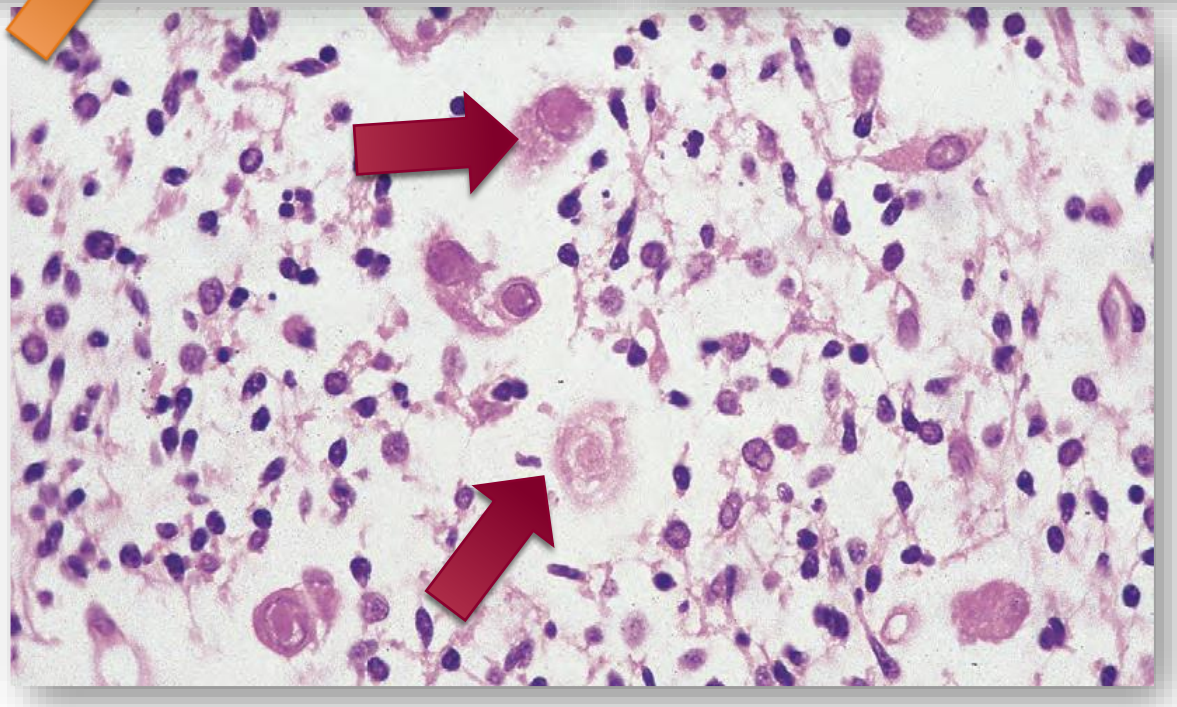
Cytomegalovirus

A. Fetal infection

- **TORCH**
- Periventricular necrosis
- Microcephalia
- Periventricular calcification



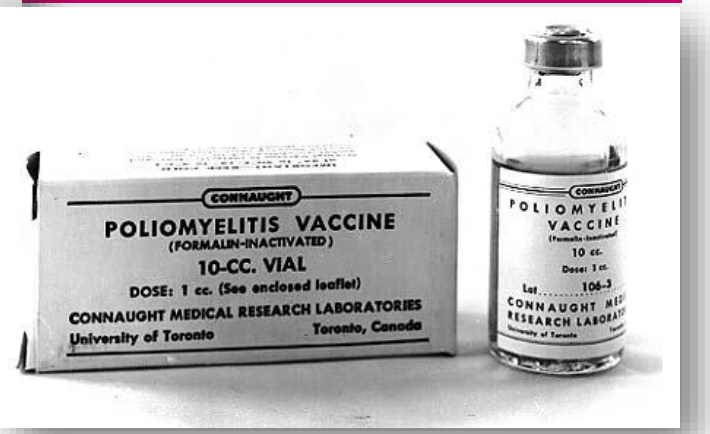




B. Adult infection

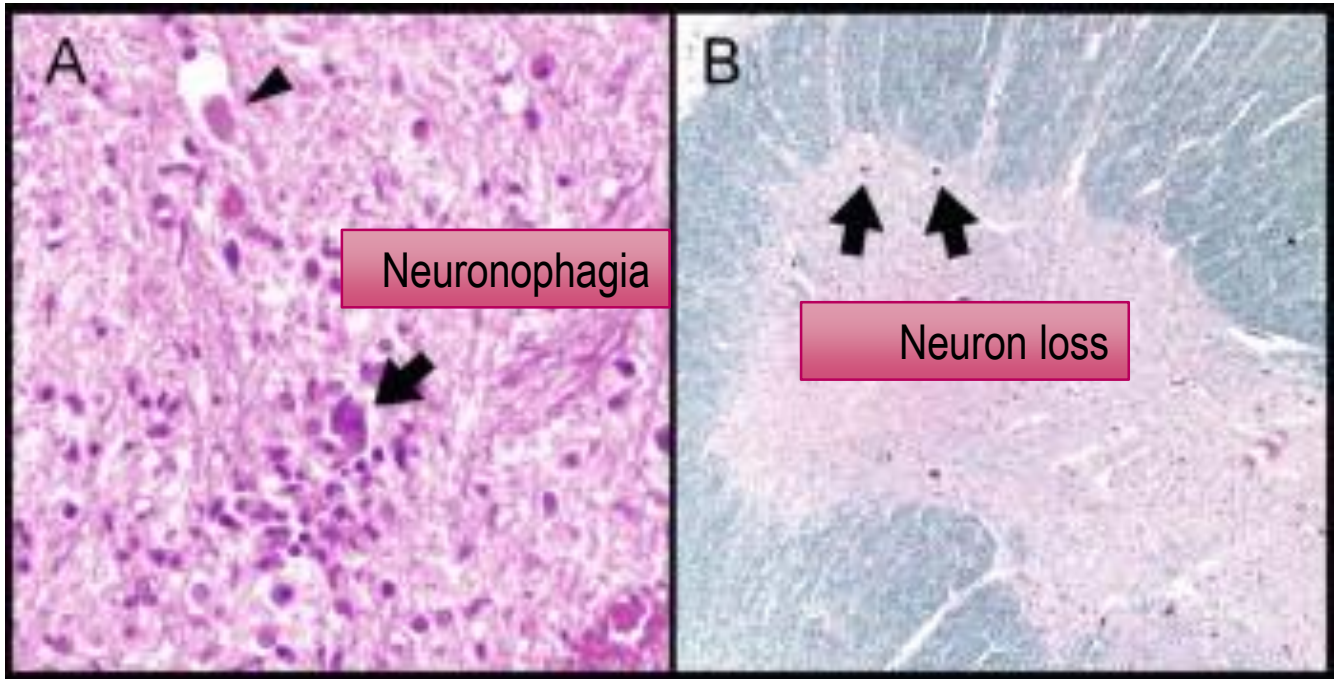
- Immunosuppressed patients
- Periventricular
- Subacut encephalitis

Poliovirus



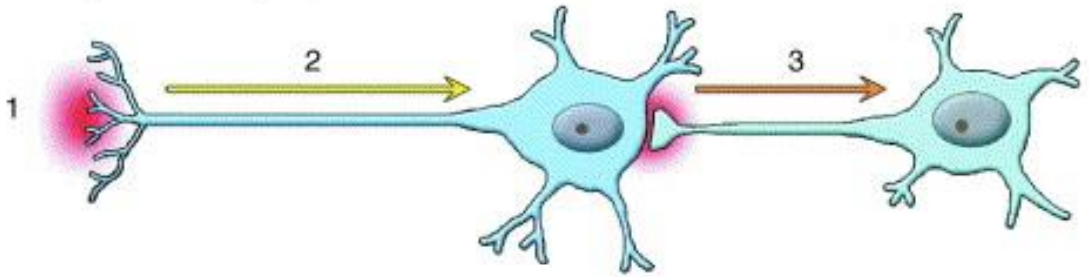
- Gastroenteritis – Secunder CNS spread
  - **Poliomyelitis anterior acuta /Paralytic poliomyelitis**
  - Damages motor neurons in the spinal cord and brain stem
  - Flaccid paralysis with muscle wasting and hyporeflexia

- 25 to 35 years – **Postpolio syndrome**
  - Progressive weakness, pain



Rabies Virus

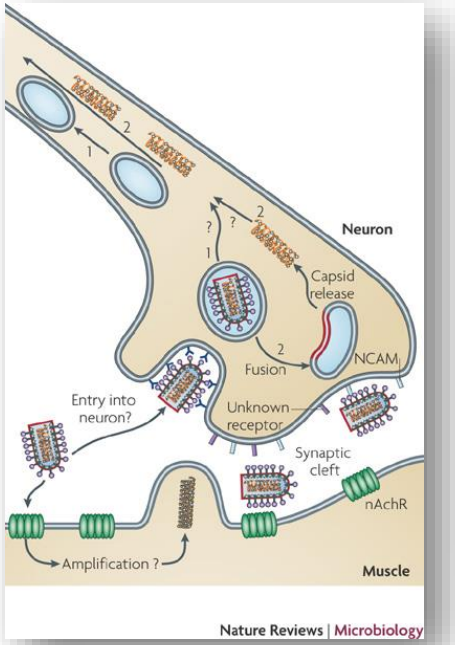
Retrograde trans-synaptic spread

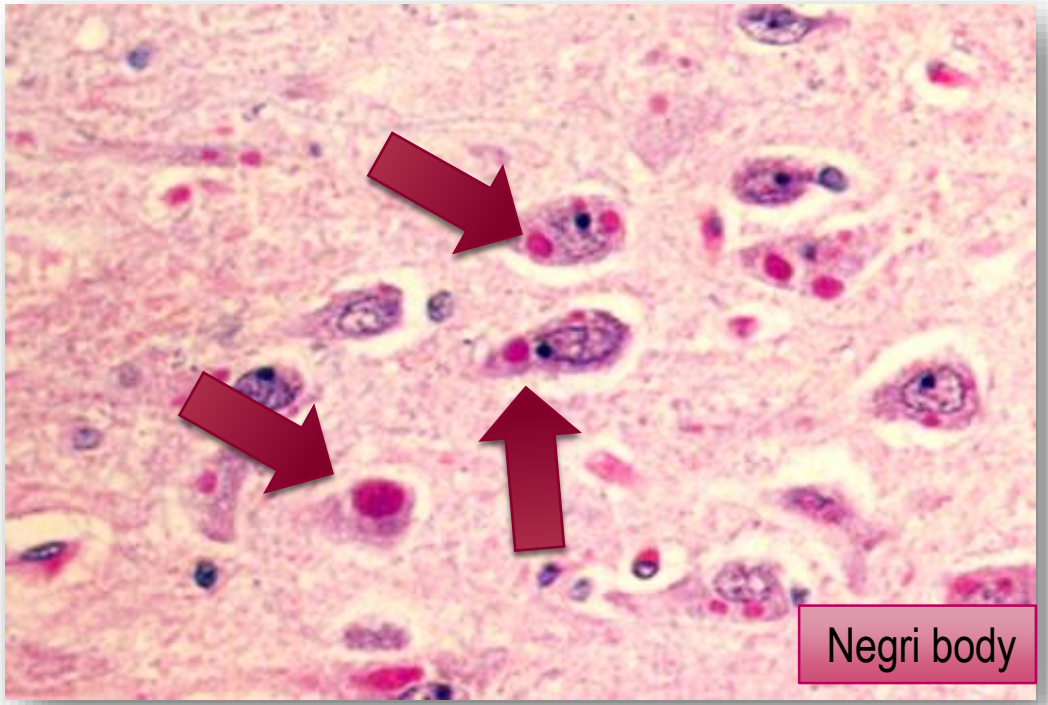


Rabies

- Rabid animals, usually by a bite
- Ascending along the peripheral nerves
  - The incubation period depends on the distance between the wound and the brain

- Symptoms:
  - Non specific
  - Signs of CNS excitability
    - Pain, hydrophobia
    - Mania-coma





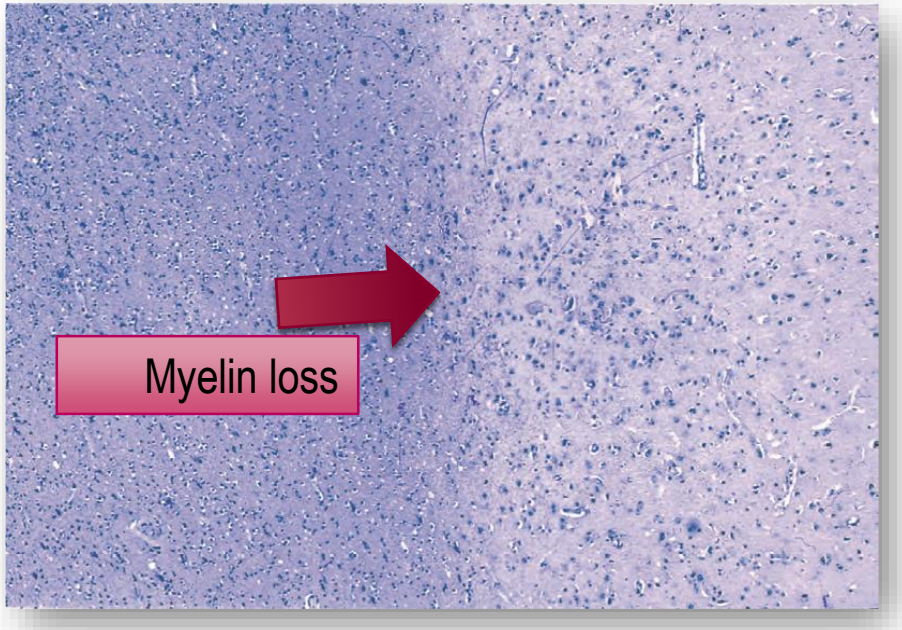
Human Immundeficiency virus

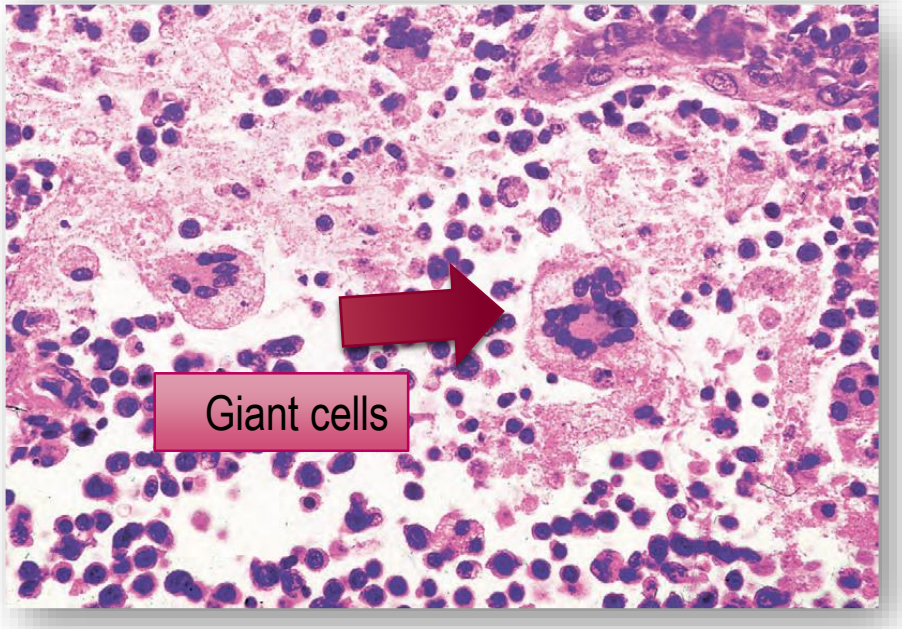
A. Asepticus meningitis
- Within 1 to 2 weeks in about 10% of patients

B. HIV Encephalitis (HIVE)
- Perivascular lymphoid infiltration
- Myelin loss in the hemispheres (Leukoencephalopathia)
- Microglial noduls
- Giant cells

C. Opportunistic infections
- Toxoplasma
- Cryptococcal
- Progressive multifocal leukoencephalopathy (PML)
- Cytomegalovirus (CMV)

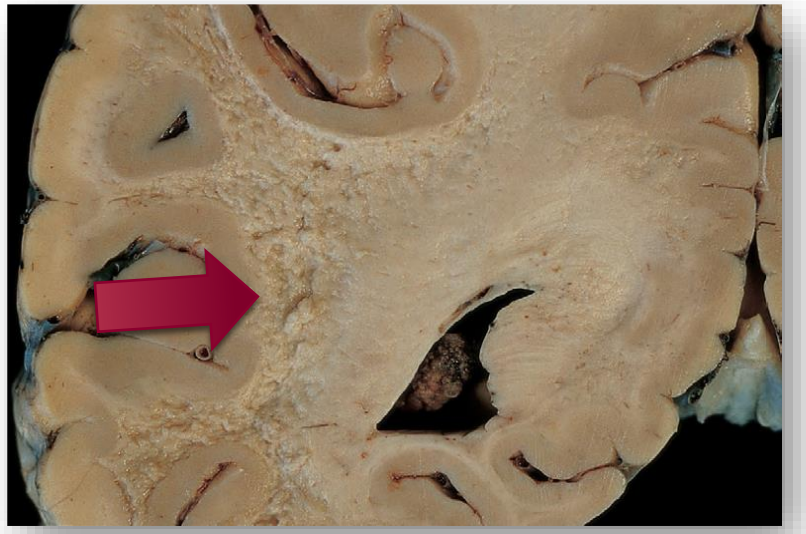
D. Primary CNS lymphoma
- EBV +

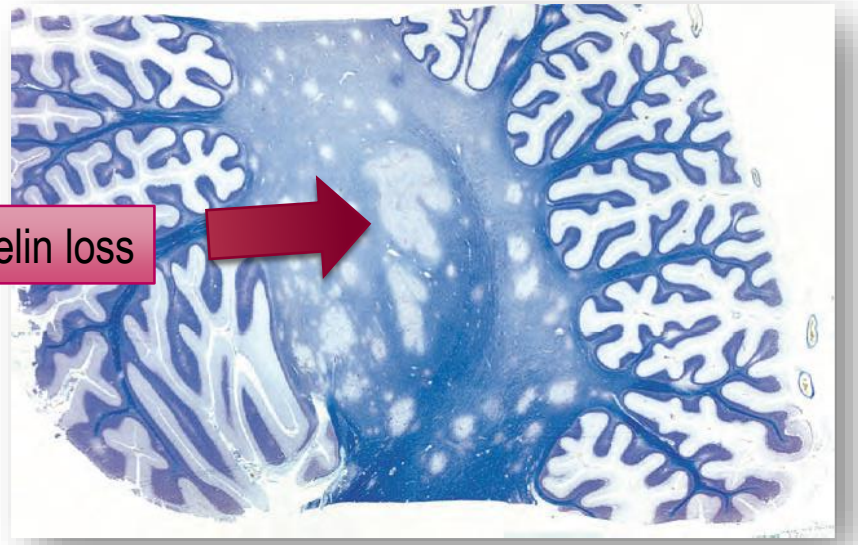


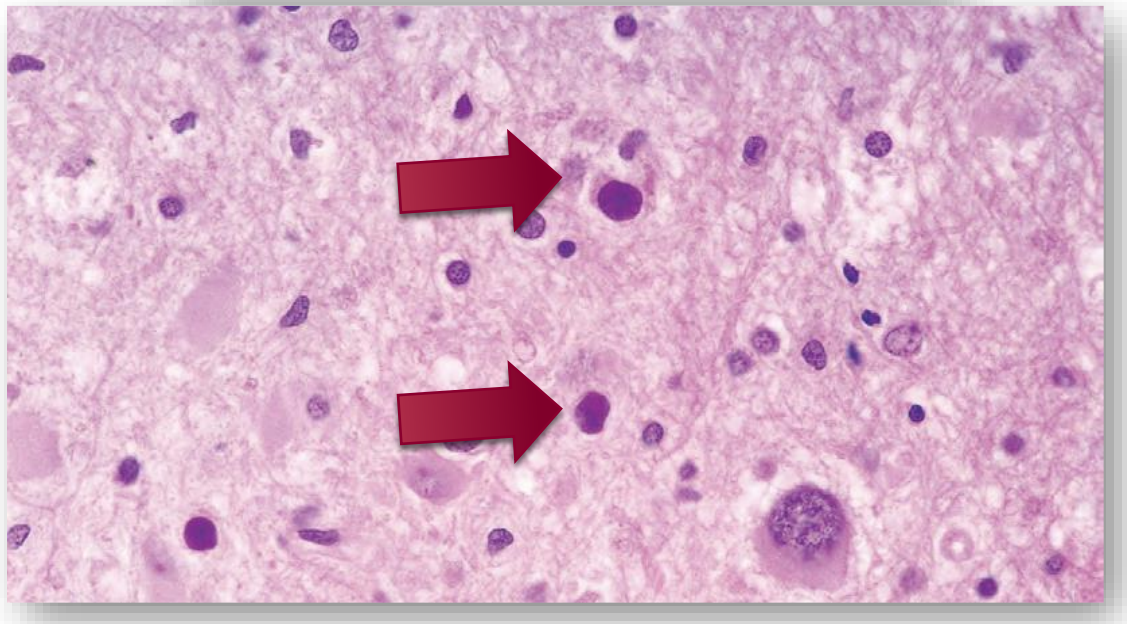


JC virus / Progressive multifocal leukoencephalopathy (PML)

- Polyoma virus
- Infects oligodendroglial cells
  - Demyelinisation
  - White matter – Hemispheres, Cerebellum
- Progressive neurologic symptoms







Fungal infections

A. Candida Albicans

- Multiplex microabscesses

B. Mucormycosis

- Nasal cavity, sinus infection
- Direct extension, Vascular invasion

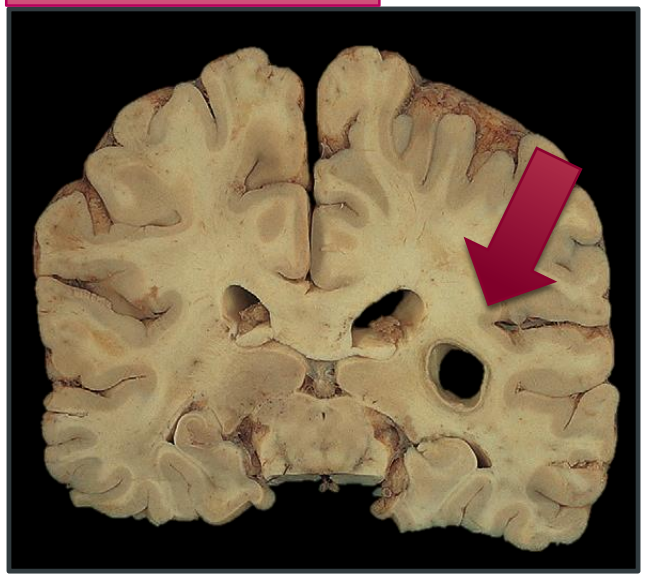
C. Aspergillus fumigatus

- Hemorrhagic infarctions
- Vascular invasion

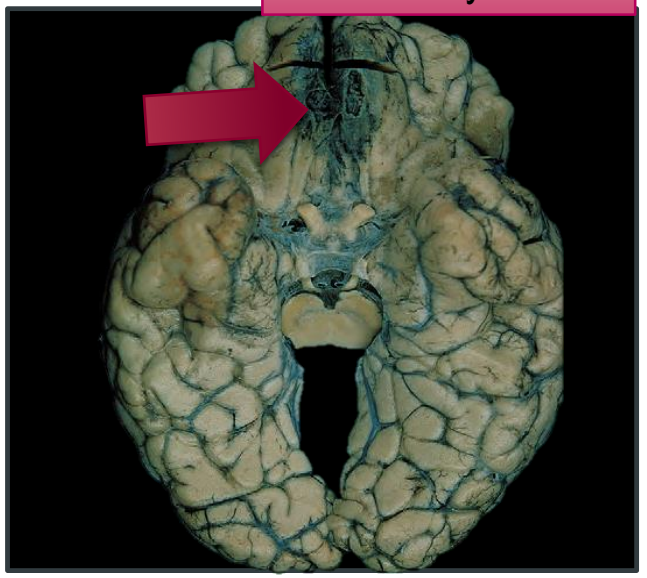
D. Cryptococcus neoformans

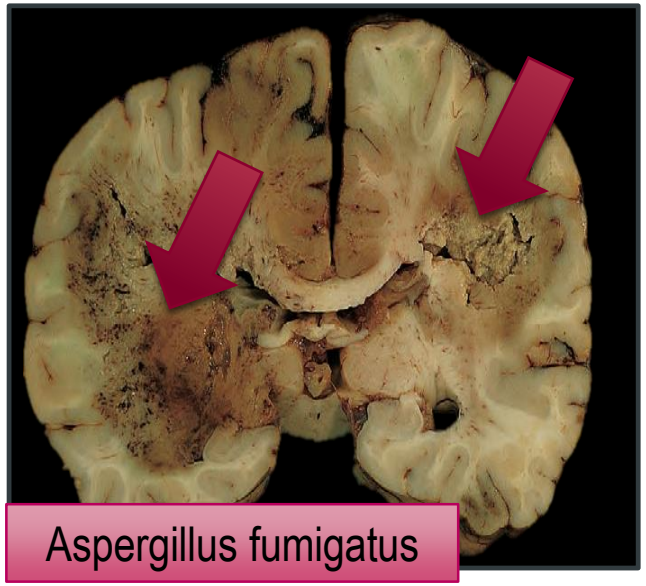
- Meningitis, Meningoencephalitis
- Fulminant

Candida albicans

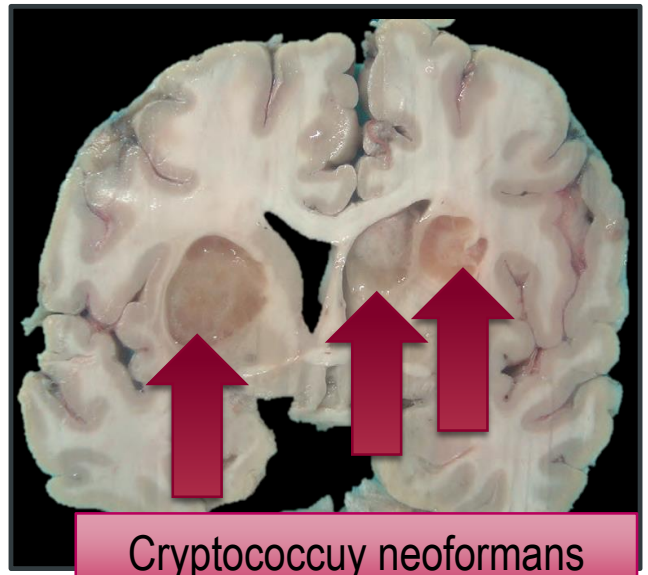


Mucormycosis

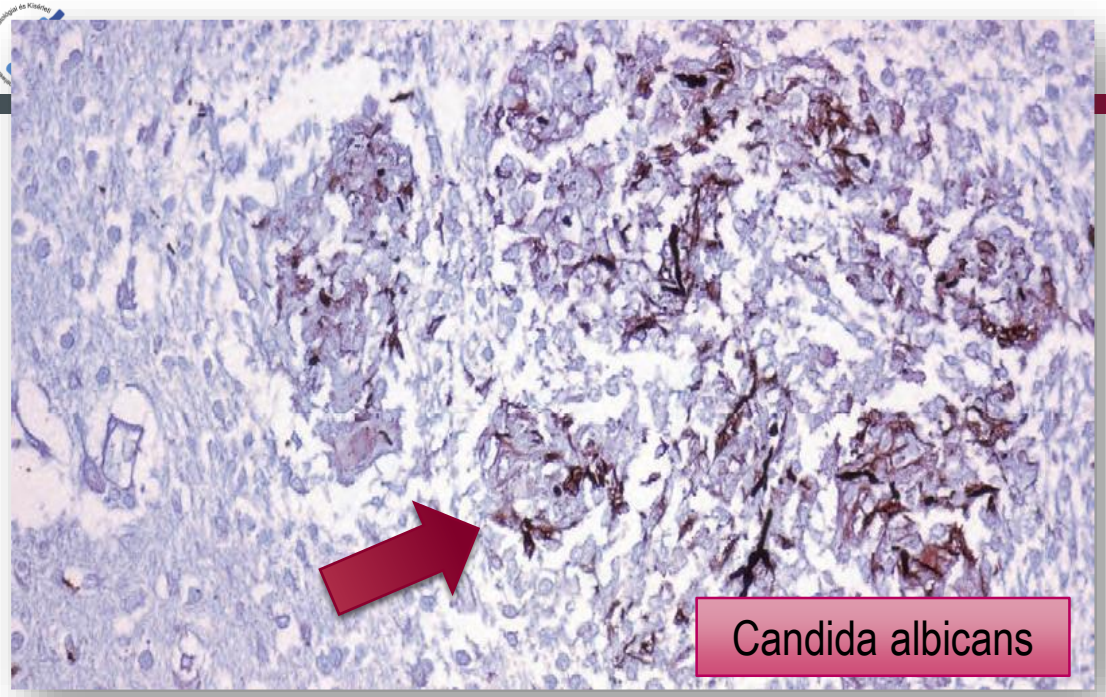


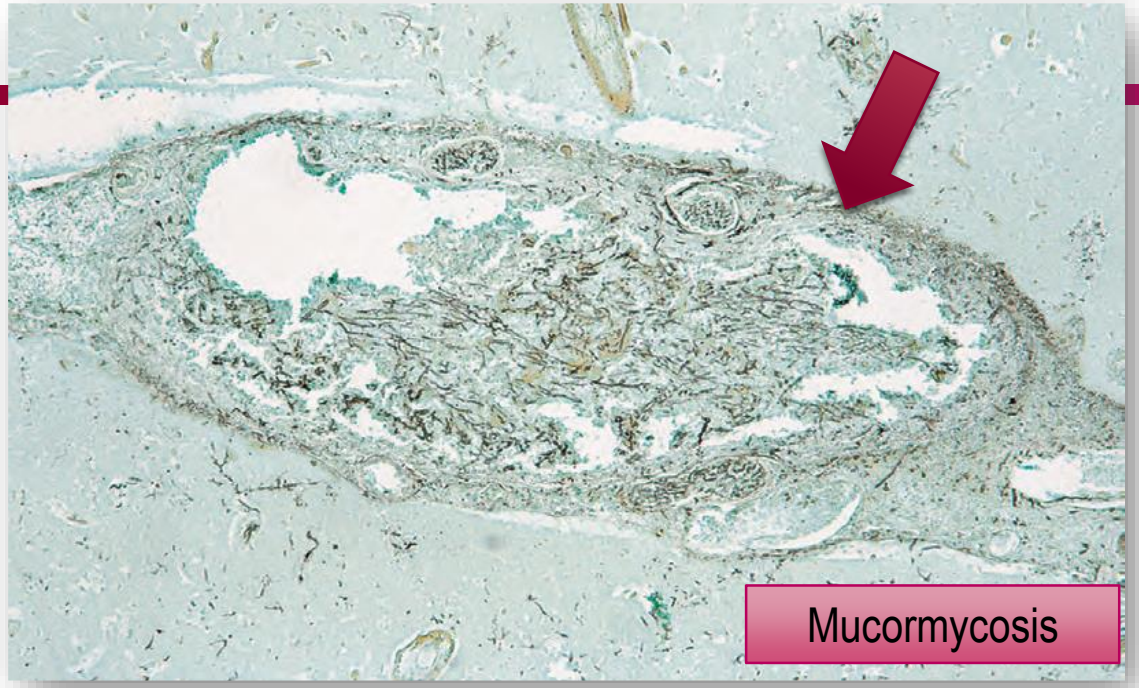


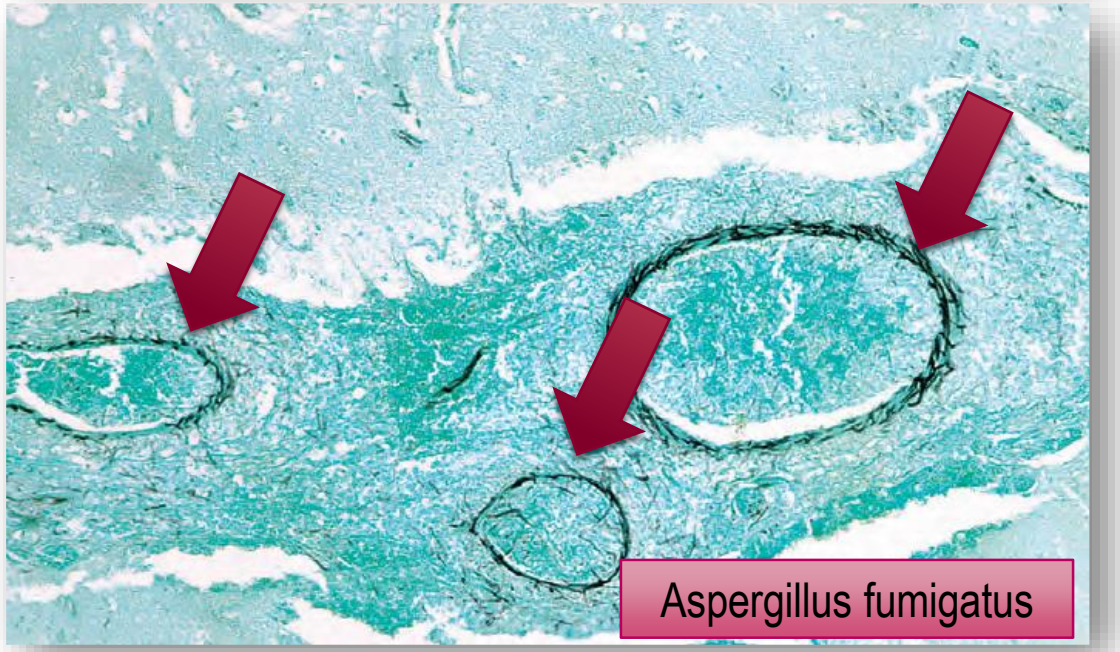
Aspergillus fumigatus

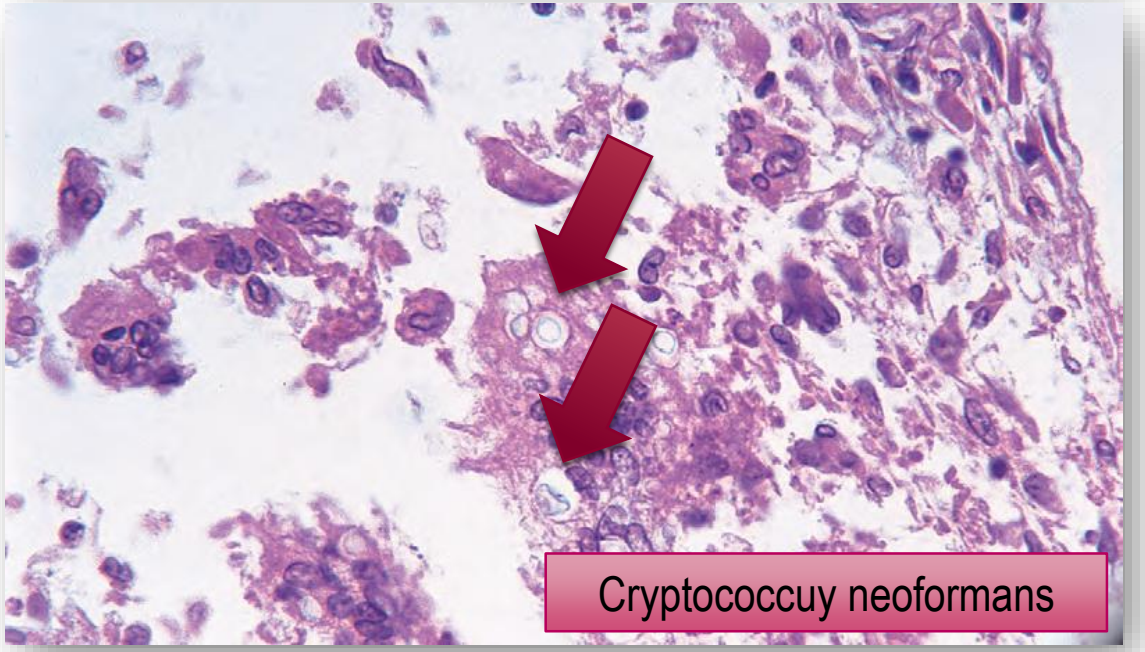


Cryptococcuy neoformans


Candida albicans


Mucormycosis


Aspergillus fumigatus


Cryptococcuy neoformans

Protozoal infections - Toxoplasmosis

Toxoplasma gondii

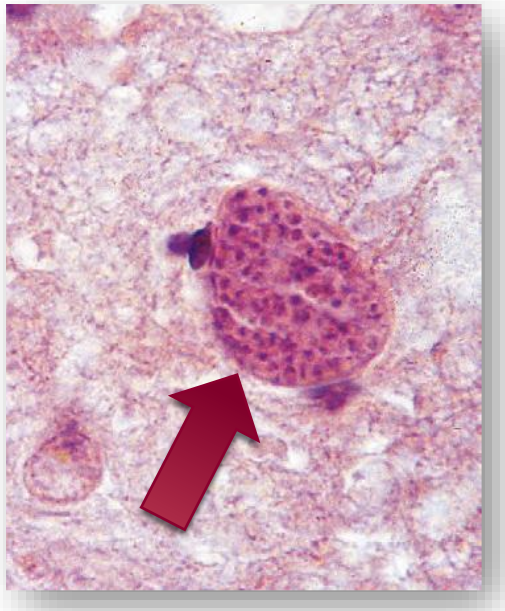
- Humans intermedier hosts
- Definitive host - Cat

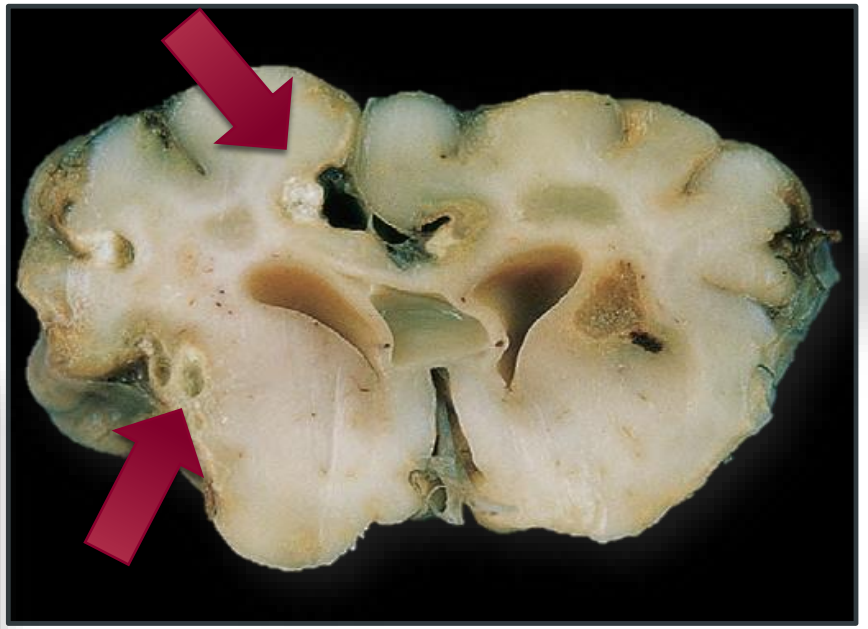
A. Fetal infection

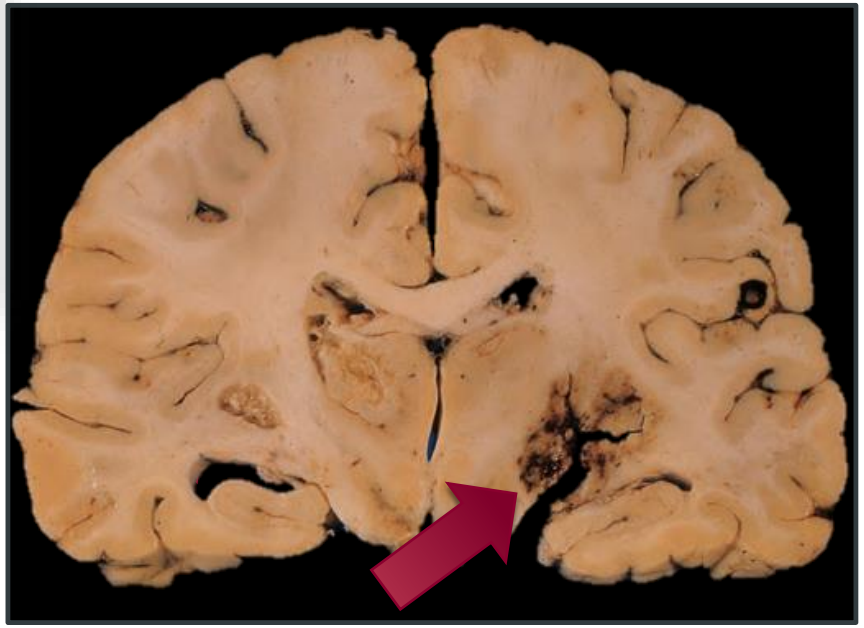
- **TORCH**
- Chorioretinitis
- Hyprocephalus
- Intracranial calcificatio

B. Adult infection

- Immunosuppressed adults
- Subacut symptoms
- Evolving in 1 or 2 week period
- Focal-diffuse

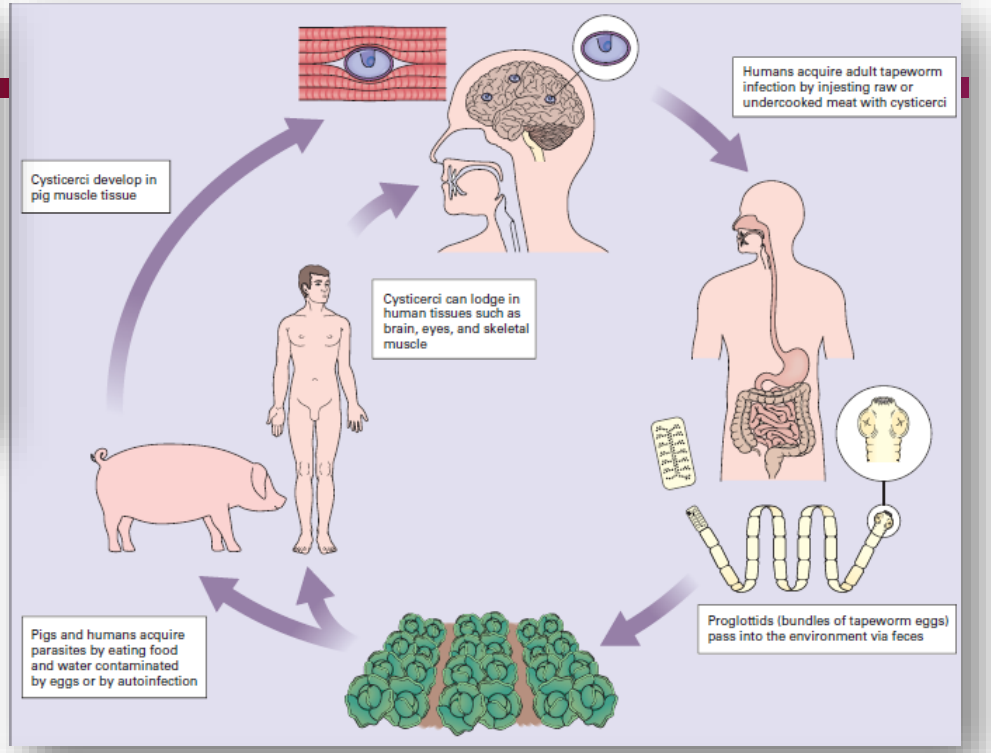






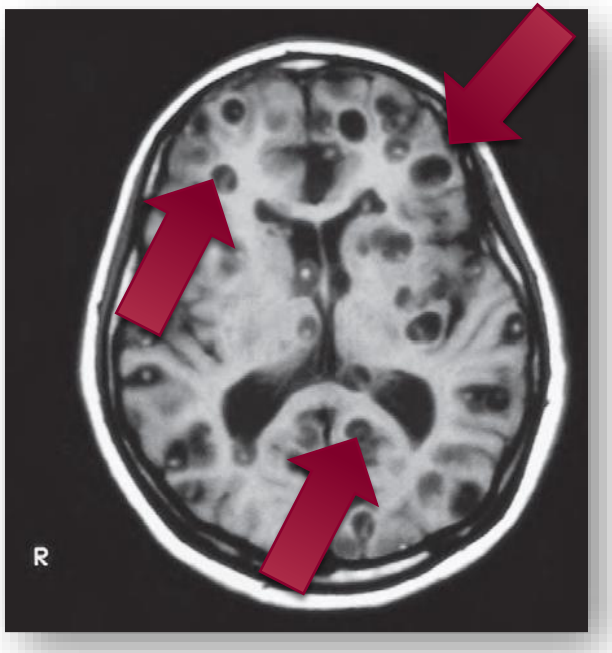
Parasitic Infections

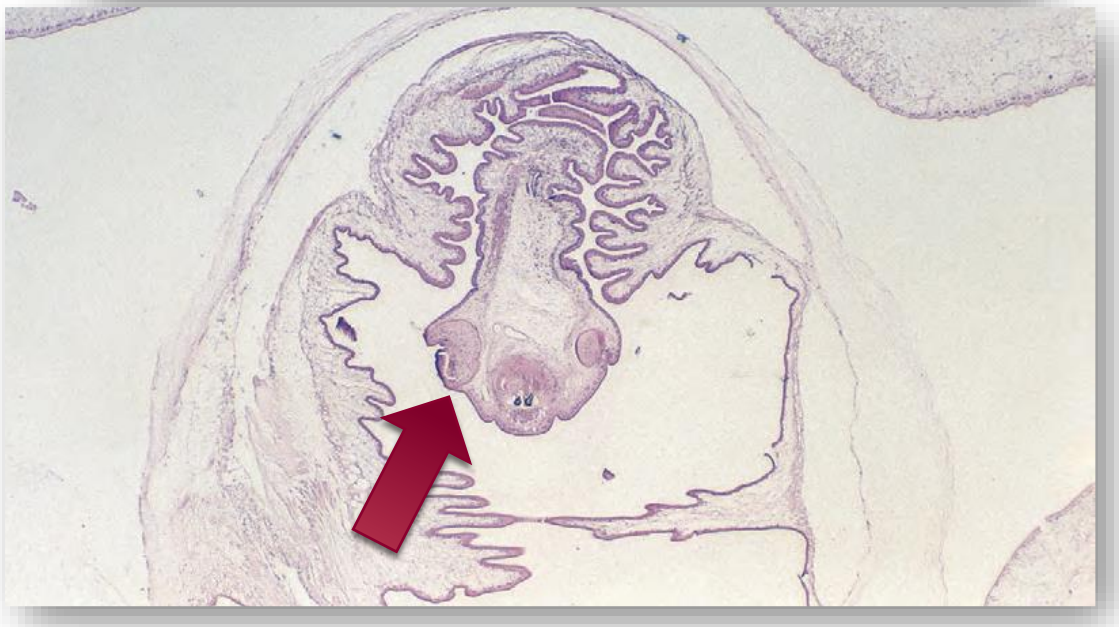
Tenia solium - Cysticercosis



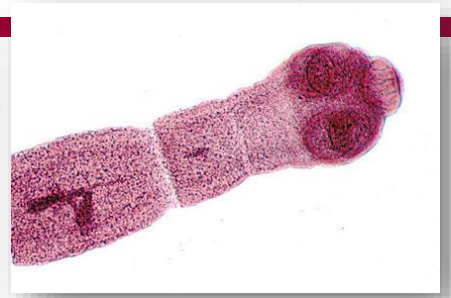
- End-stage infection
  - Larval organisms leave the lumen of the gastrointestinal tract
  - Encyst – Brain – subarachnoid space

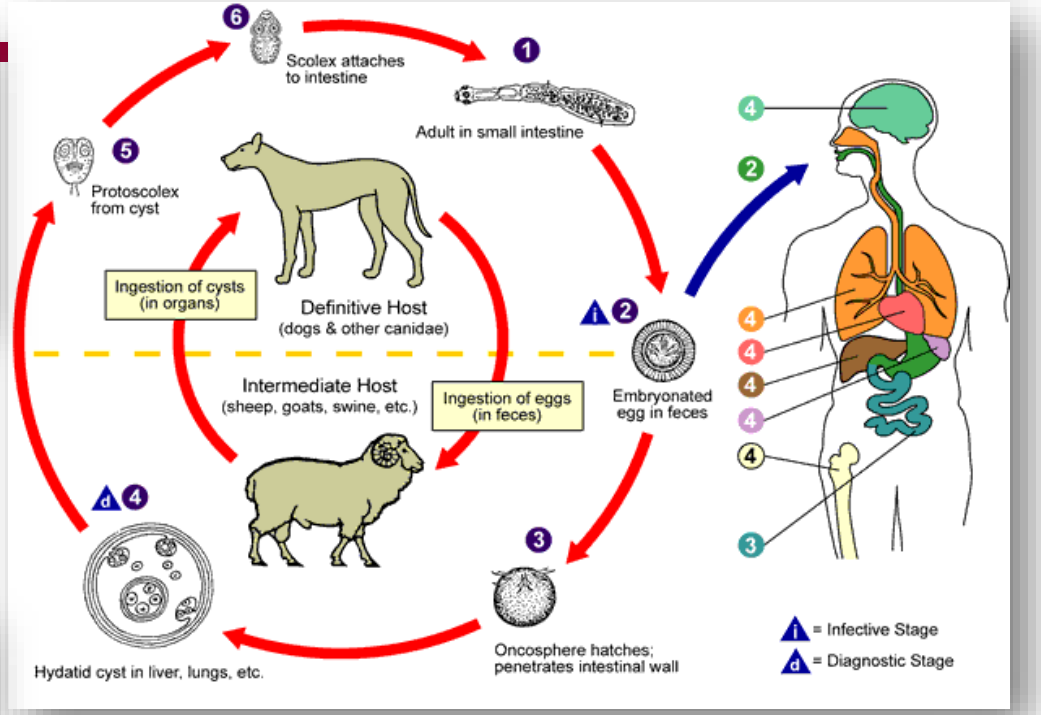
- Symptoms
  - Focal symptoms
  - Epilepsy



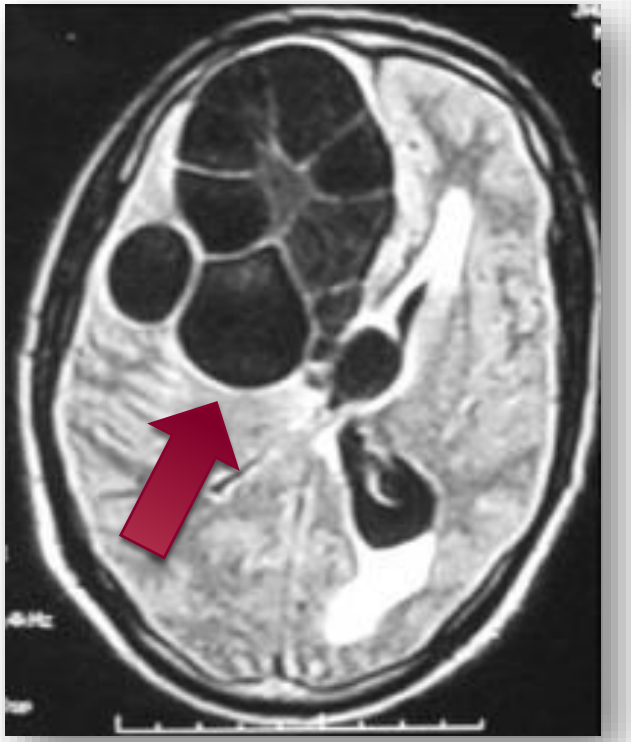


Echinococcus /Hydatidosis/

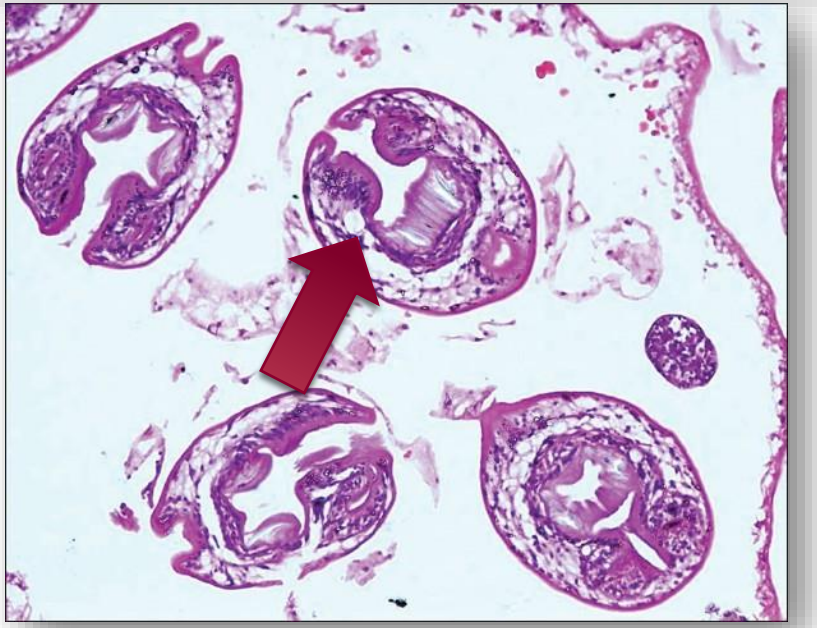




- Childhood
- Contact with dogs
  - Encysts – Usually liver, lung rarely brain



- Symptoms
  - Focal signs
  - Epilepsy



- Robbins Basic Pathology, 10th Edition
- Neuropathology: A Reference Text of CNS Pathology, 3rd Edition