DISEASES OF THE CENTRAL NERVOUS SYSTEM

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CNS Infections

- Portals of entry of infection into the CNS:
  - *Hematogenous spread*
    - the most common
  - *Direct implantation*
    - traumatic or in congenital CNS malformation
  - *Local extension*
    - occurs secondary to an established infection in a near by organ (air sinus, an infected tooth or middle ear)
  - Through the *peripheral nervous system into the CNS*
    - certain viruses, such as rabies and herpes zoster.

CNS Infections

Meningitis

An inflammatory process of the leptomeninges and CSF within the subarachnoid space.

CNS Infections

Pyogenic meningitis

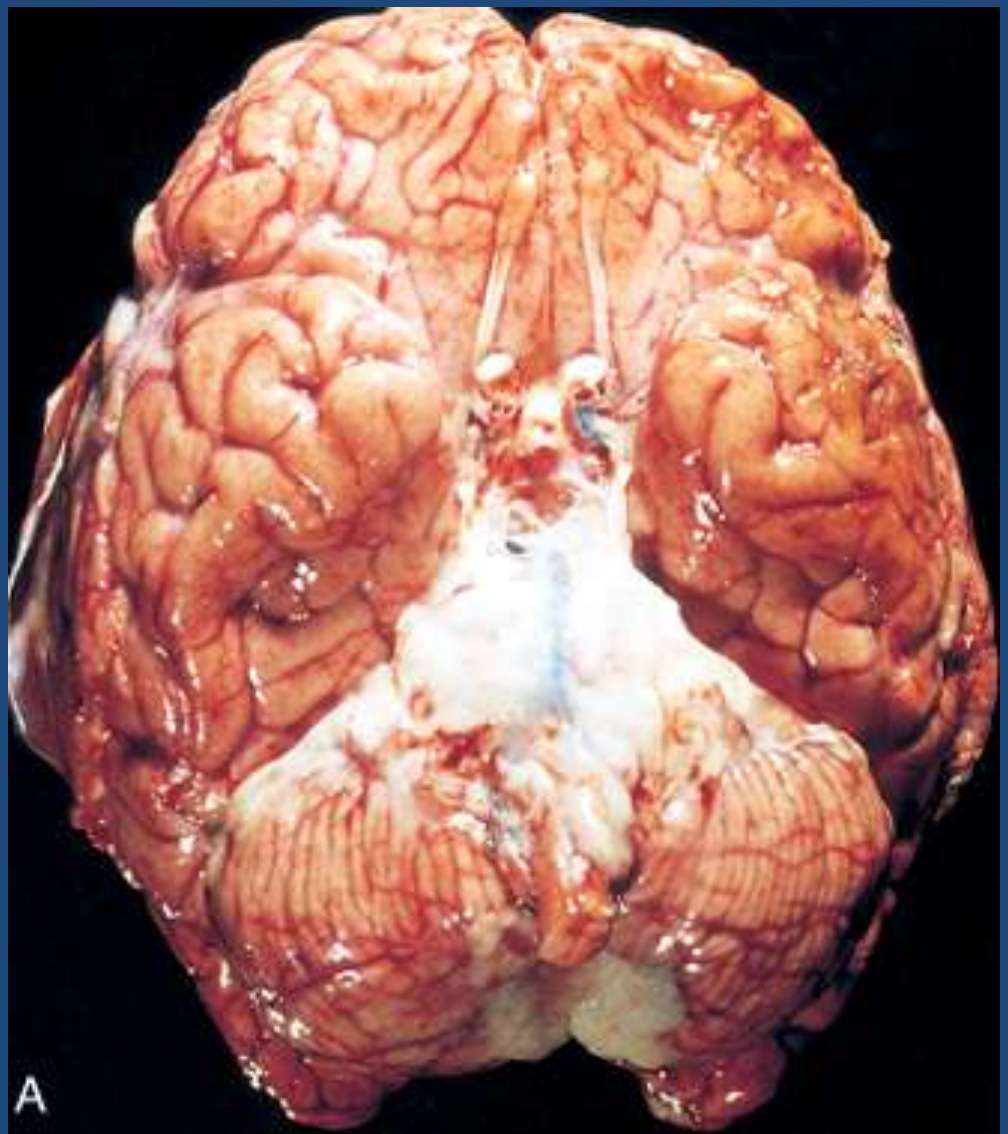
- Medical emergency
- The causative microorganisms:
  - **Neonates** : *Escherichia coli* and group B streptococci
  - Infants: *Streptococcus pneumoniae*
  - **Adolescents and young adults:** *,Neisseria meningitidis* (Meningococcal meningitis) and *Haemophilus influenzae (becoming less due to immunization)*
  - **Elderly:** listeria monocytogenes and *Streptococcus pneumoniae*

CNS Infections

Pyogenic meningitis

- **CSF Findings in spinal tap:**
  - cloudy or frankly purulent CSF
  - as many as 90,000 neutrophils /mm
  - raised protein level
  - markedly reduced glucose content
  - bacteria may be seen on a Gram stained smear or can be cultured, sometimes a few hours before the neutrophils appear

Acute meningitis



CNS Infections
Meningitis Clinical Features

- Systemic non-specific signs of infection
- Meningeal irritation signs and neurologic impairment:
  - Headache, photophobia, irritability, clouding of consciousness and neck stiffness
- Untreated, pyogenic meningitis can be fatal
- Effective antimicrobial agents markedly reduce mortality associated with meningitis

CNS Infections
Meningitis Complications

- Phlebitis may → venous occlusion → hemorrhagic infarction of the underlying brain
- Leptomeningeal fibrosis → hydrocephalus
- Septicemia → hemorrhagic infarction of the adrenal glands and cutaneous petechiae (known as Waterhouse-Friderichsen syndrome, particularly common with meningococcal and pneumococcal meningitis)
- Focal cerebritis & seizures
- Cerebral abscess
- Cognitive deficit
- Deafness

CNS Infections
Brain abscess

- Streptococci and staphylococci are the most common organisms identified in non-immunosuppressed populations
- Predisposing conditions:
  - Acute bacterial endocarditis (usually give multiple microabscesses)
  - Cyanotic congenital heart disease in which there is a right-to-left shunt
  - Loss of pulmonary filtration of organisms (e.g, bronchiectasis)
- Most common on cerebral hemispheres

CNS Infections
Brain abscess

- Morphologically,
  - Liquefactive necrosis
  - The surrounding brain is edematous , congested & contains reactive astrocytes & perivascular inflammatory cells
- Present clinically with progressive focal neurologic deficits in addition to the general signs of raised intracranial pressure
- The CSF
  - Contain only scanty cells
  - ↑ protein
  - Normal level of glucose
- Complications of Brain abscess:
  - Herniation
  - Rupture of abscess into subarachnoid space or ventricle

CNS Infections
Tuberculosis

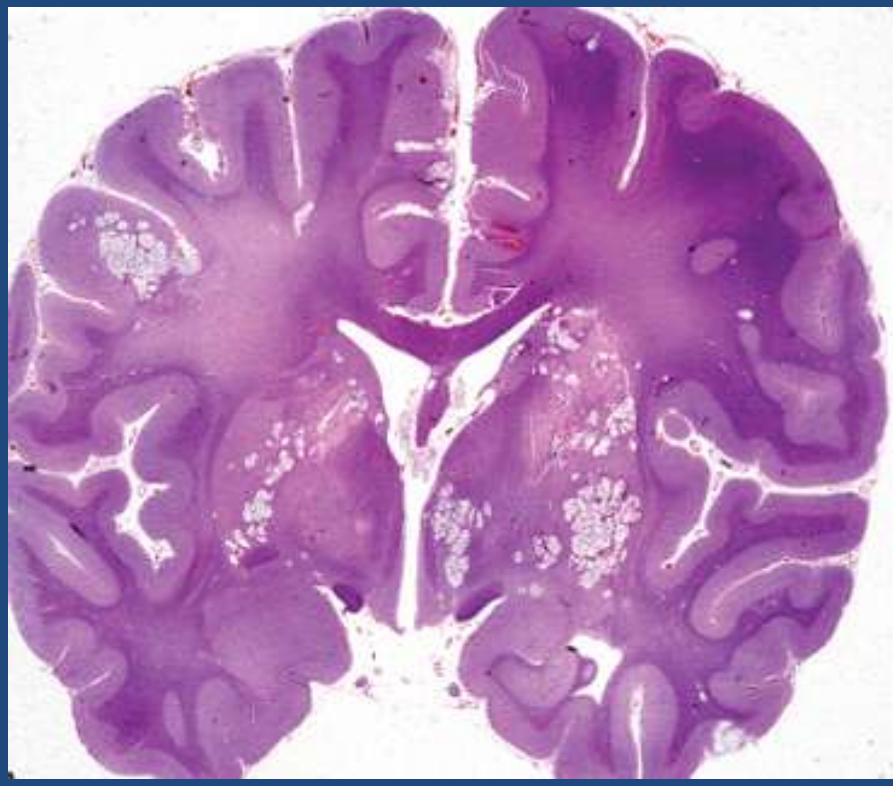
- The subarachnoid space contains a fibrinous exudate, most often at the base of the brain
- **Tuberculoma** is well-circumscribed intraparenchymal mass
  - Rupture of tuberculoma into subarachnoid space results in tuberculus meningitis
  - A tuberculoma may be up to several centimeters in diameter, causing significant mass effect
  - Always occurs after hematogenous dissemination of organism from primary pulmonary infection
- On microscopic examination, there is usually a central core of caseous necrosis surrounded by a typical tuberculous granulomatous reaction

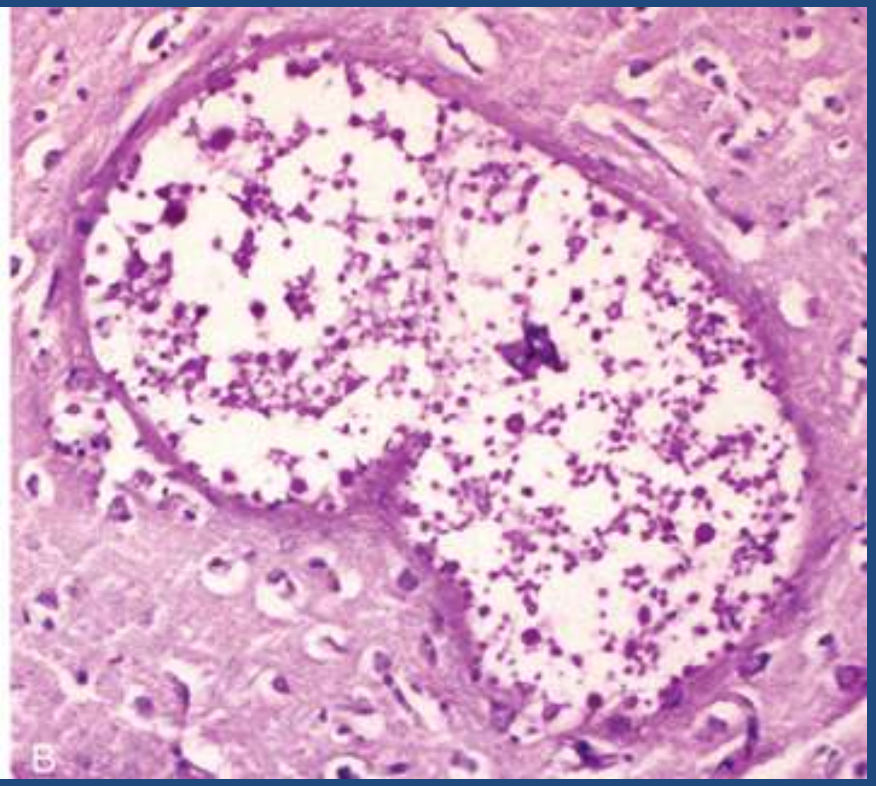
CNS Infections
CSF in TB

- There is only a moderate increase in cellularity of the CSF (pleiocytosis) made up of mononuclear cells, or a mixture of polymorphonuclear and mononuclear cells
- The protein level is elevated, often strikingly so
- The glucose content typically is moderately reduced or normal

CNS Infections
Fungal infection

- *Candida albicans, Mucor, Aspergillus fumigatus*, and ***Cryptococcus neoformans*** are the most common fungi that can cause encephalitis
- *Parenchymal invasion,* usually in the form of granulomas or abscesses, can occur with most of the fungi and often coexists with a meningitis





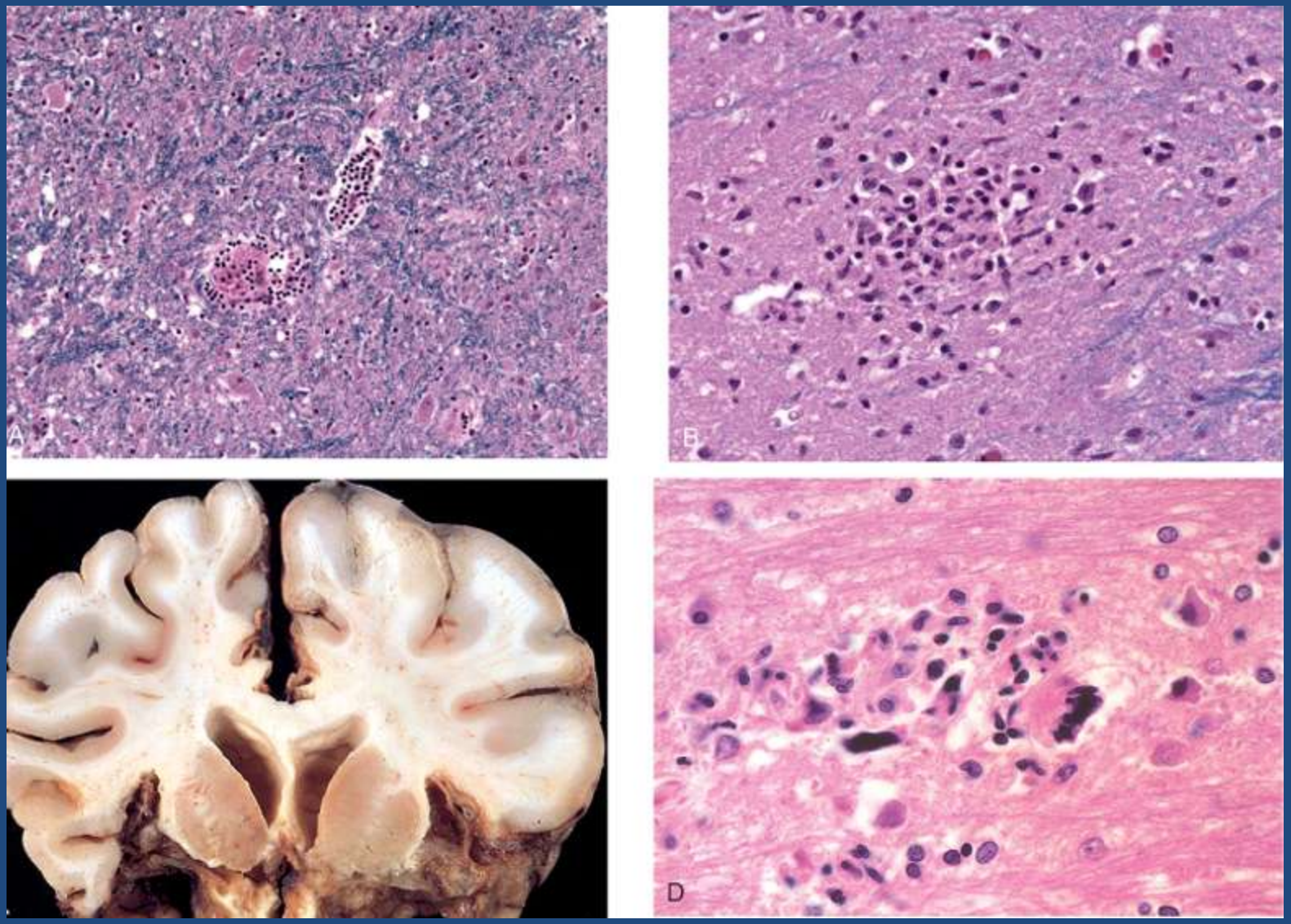
- *Cryptococcal meningitis and meningoencephalitis*
  - Observed often in association with AIDS. It can be fulminant and fatal in as little as 2 weeks, or indolent, or it can evolve over months or years

CNS Infections
Toxoplasmosis

- Causative organisms: Toxoplasma gondii
- The clinical symptoms are subacute, evolving during a 1- or 2-week period, and may be both focal and diffuse
- Ingestion of raw or partly cooked meat, especially pork, lamb, and Ingestion of contaminated cat faeces
- Transplacental transmission --> severe brain injury in neonate (Neonatal hydrocephalus, microcephaly, intracranial calcifications, chorioretinitis, blindness, epilepsy, mental retardation, Rare classic triad - Chorioretinitis, hydrocephalus, cerebral calcifications)
- Most common causes of neurologic symptoms and morbidity in patients with AIDS (40%) -Necrotizing encephalitis-and in immunocompromised Pt.
- Ocular toxoplasmosis (chorioretinitis)

CNS infections
Viral infections

- The most common cause of encephalitis
- Almost invariably associated with meningeal inflammation
- General features:
    - Perivascular inflammatory infiltrates (mononuclear cells)
    - Microglial nodules
    - Inclusion bodies


A
B
D

CNS Infections

Herpes simplex encephalitis

- HSV type 1 encephalitis causes hemorrhagic necrosis of temporal lobes & orbital frontal areas
- Most common in children and young adults
- Cowdry type A intranuclear viral inclusion bodies can be found in both neurons and glia

CNS Infections
HIV

- HIV patients are prone of multiple diseases that can affect the CNS, PNS and the skeletal muscle. Infection is just an example.

CNS Infections

HIV

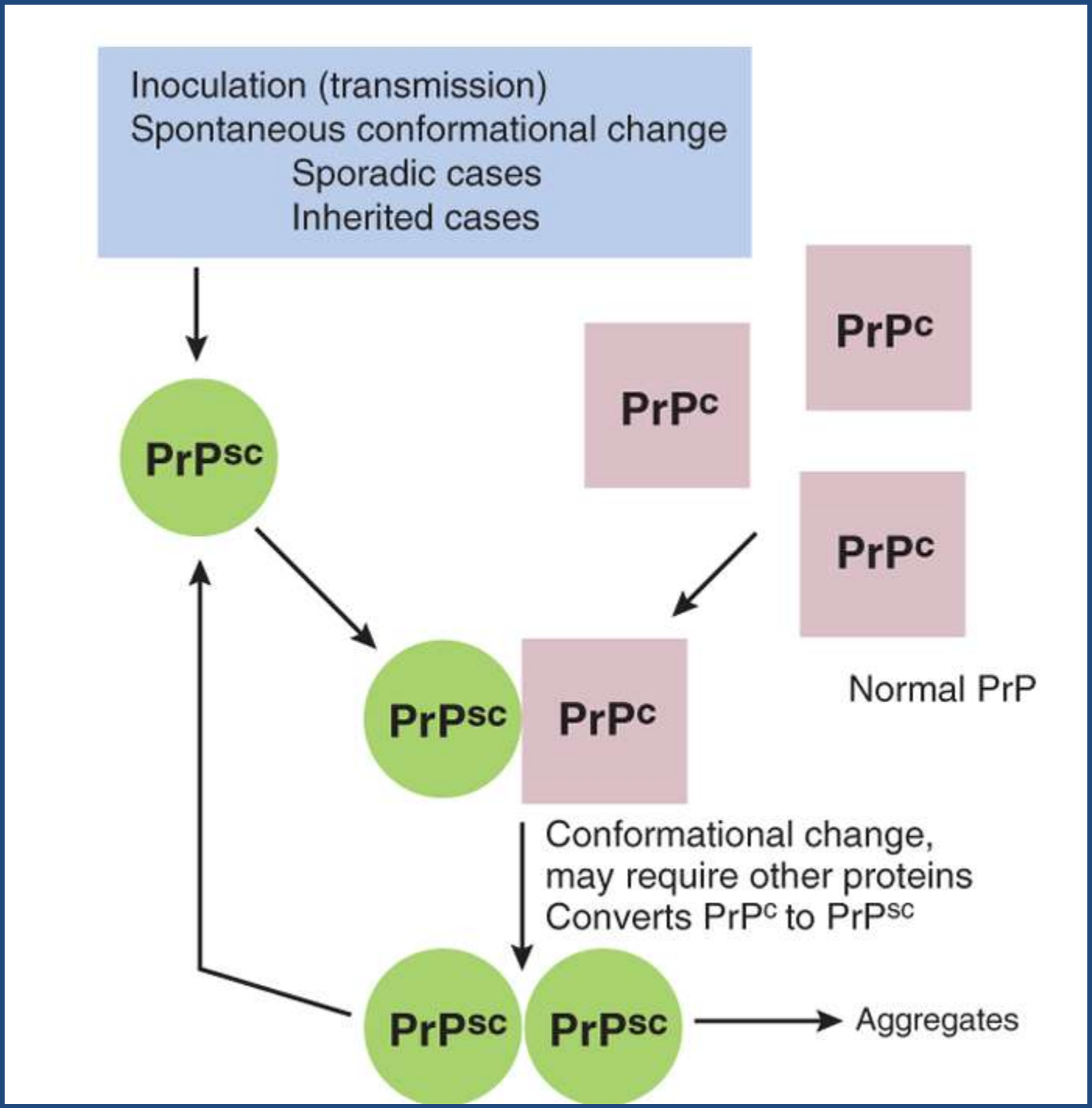
- Patients affected with **HIV encephalitis with dementia** referred to as AIDS-dementia complex
- The dementia begins insidiously, with mental slowing, memory loss, and mood disturbances, such as apathy and depression
- Motor abnormalities, ataxia, bladder and bowel incontinence and seizures can also be present

CNS Infections
Morphology, HIV encephalitis

- On macroscopic examination:
  - Some ventricular dilation with sulcal widening but normal cortical thickness
- Microscopically:
  - a chronic inflammatory reaction with widely distributed infiltrates of **microglial nodules,** sometimes with associated foci of tissue necrosis and reactive gliosis.
  - **multinucleated giant cell the hallmark of HIV encephalitis**

CNS Infections
Prion diseases

- A group of **neurodegenerative** conditions characterized:
  - clinically by slowly progressive ataxia and dementia
  - pathologically by accumulations of fibrillar or insoluble prion proteins, degeneration of neurons, and vacuolization, termed **spongiform** degeneration
- Group of diseases includes in humans:
  - Creutzfeldt-Jakob disease (CJD),
  - Fatal familial insomnia
  - Bovine spongiform encephalopathy
- They are all associated with abnormal forms of a specific protein, termed **prion protein** (PrP)


Inoculation (transmission)
Spontaneous conformational change
Sporadic cases
Inherited cases
PrPsc
PrPc
PrPc
PrPc
PrPsc
PrPc
Normal PrP
Conformational change,
may require other proteins
Converts PrPc to PrPsc
PrPsc
PrPsc
Aggregates

CNS Infections
Prion diseases

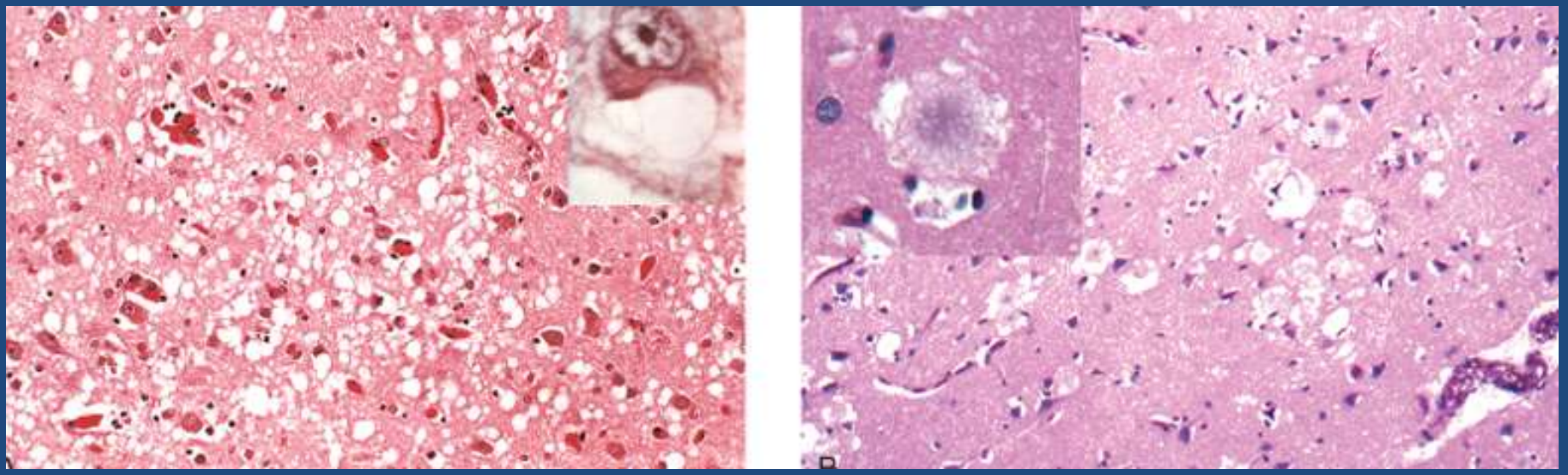
- **Pathogenesis**:

  Unique diseases can be genetic, sporadic or infectious

  – Misfolding or conformational change of the normal prion protein (PrP^{c}) converts it to an insoluble, protease resistant isoform PrP^{sc}·which precipitates as amyloid.(amyloid- rich deposited known as Kuru plaques)

  – Loss of function of (PrP^{c}) or toxicity of PrP^{sc}·cause neuronal degeneration and loss by unknown mechanism.

  – Transmitted via ingestion of infected foodstuffs and via iatrogenic means (e.g. blood transfusion, Instrument)



CNS Infections
Prion diseases

- **Creutzfeldt-Jakob Disease/Sub acute Spongiform Encephalopathies:** (the most common human form)
  - A rare but well-characterized disease
  - Long incubation period
  - Manifests clinically as a rapidly progressive dementia and diffuse atrophy of the brain
  - Primarily sporadic (about 85% of cases) but familial forms also exist (15% of cases are autosomal dominant)

CNS Infections
Prion diseases

- The disease has a peak incidence in the seventh decade.
- There are well-established cases of iatrogenic transmission, notably by corneal transplantation, deep implantation of neural electrodes, and contaminated preparations of human growth hormone
- Inflammatory infiltrates are usually absent
- The disease is uniformly fatal, with an average duration of only 7 months

CNS Tumors

- General concepts:
  - The anatomic site of the neoplasm can have lethal consequences irrespective of histological classification (i.e. benign tumors can be fatal in certain locations)
  - The pattern of spread of primary CNS neoplasms differs from that of other tumors:
    - rarely metastasize outside the CNS
    - the subarachnoid space does provide a pathway for spread

CNS Tumors
General manifestations

- Seizures, headaches, vague symptoms
- Focal neurologic deficits related to the anatomic site of involvement
- Rate of growth may correlate with history

CNS tumors

- May arise from:
  - cells of the coverings (meningiomas)
  - cells intrinsic to the brain (gliomas, neuronal tumors, choroid plexus tumors)
  - other cell populations within the skull (primary CNS lymphoma, germ-cell tumors)
  - they may spread from elsewhere in the body (metastases)

Tumours of the CNS
Gliomas

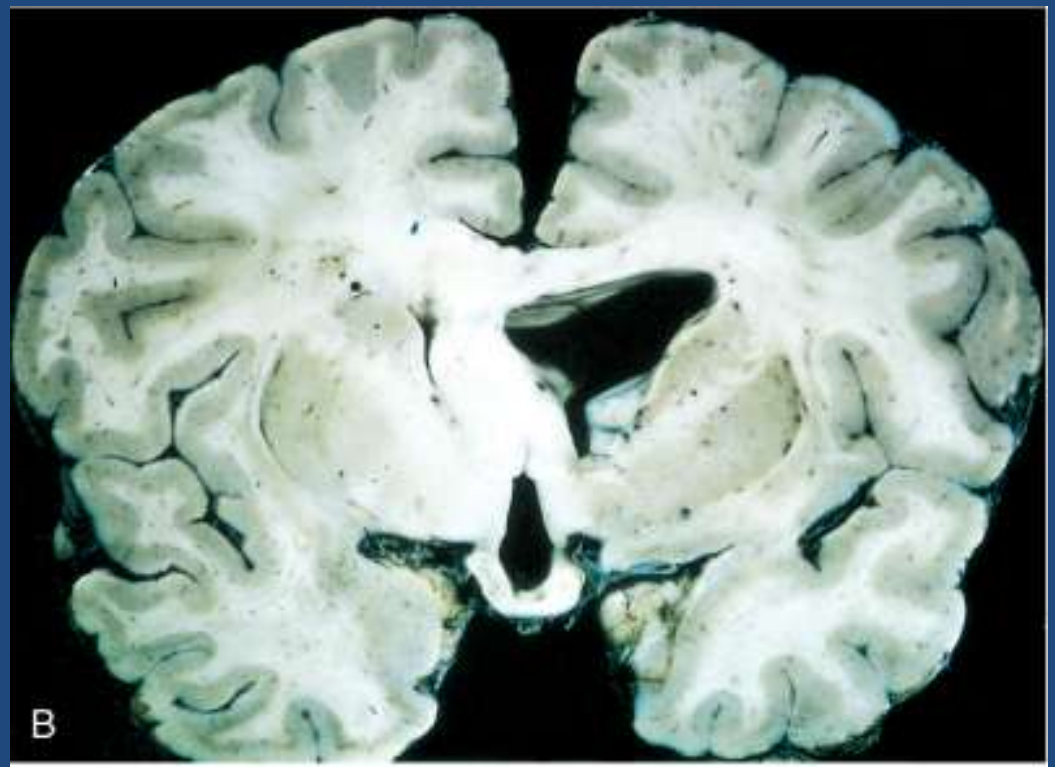
- *Astrocytomas*
- *Oligodendrogliomas*
- *Ependymomas*

CNS Tumors
Astrocytomas

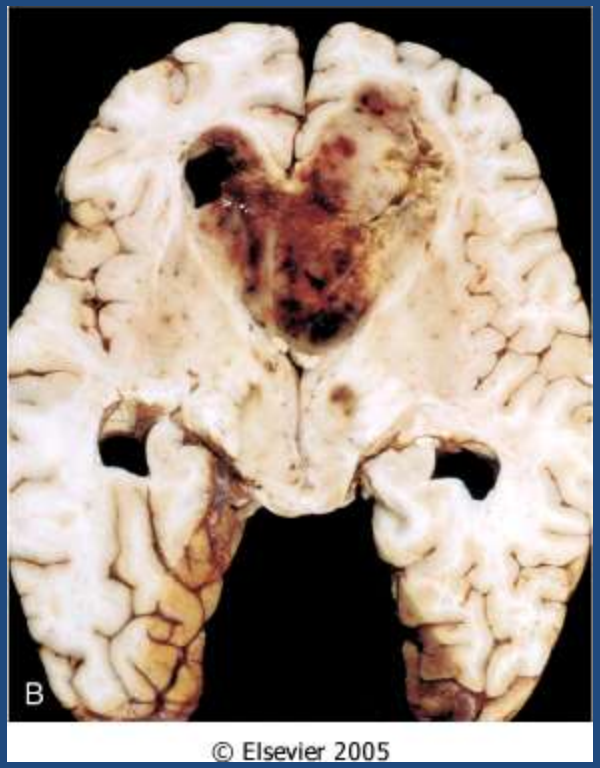
- Fibrillary:
  - 4th to 6th decade
  - Commonly cerebral hemisphere
  - Variable grades:
    - Diffuse astrocytoma
    - Anaplstic astrocytoma
    - Glioblastoma
- Pilocytic
  - Children and young adults
  - Commonly cerebellum
  - Relatively benign

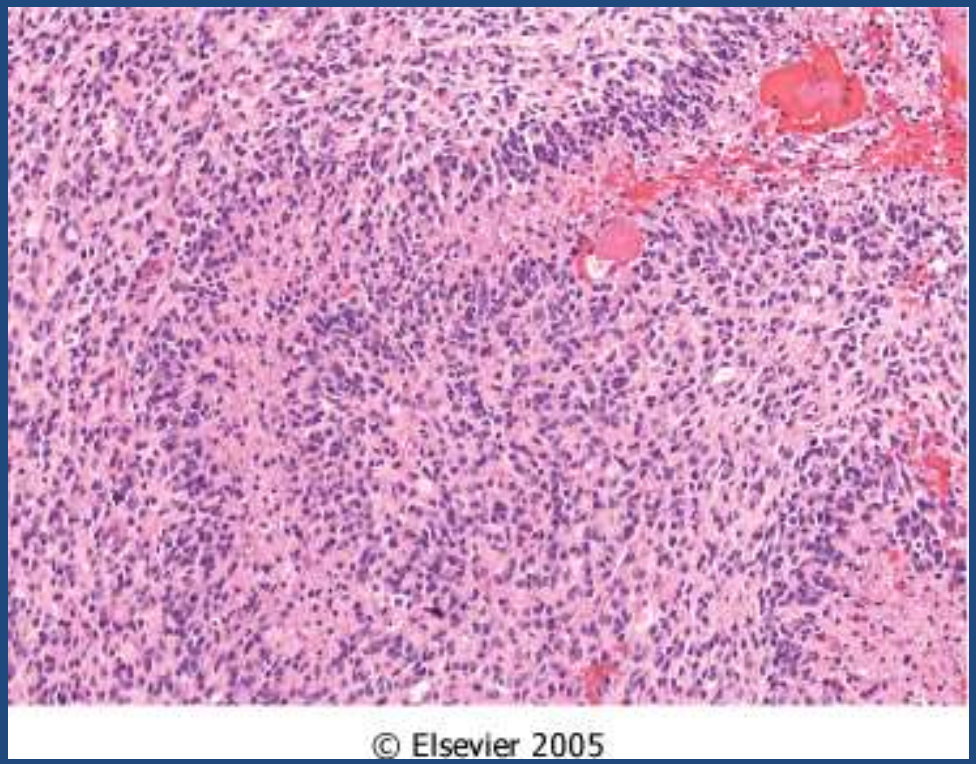
CNS Tumors
Fibrillary Astrocytoma

- Well differentiated “diffuse astrocytoma” (WHO grade II) :
  - Static or progress slowly (mean survival of more than 5 years)
  - Moderate cellularity
  - Variable nuclear pleomorphism
- Less differentiated (higher-grade) :
  - Anaplstiac astrocytoma (WHO grade III)
    - More cellular
    - Greater nuclear pelomrophism
    - Mitosis
  - Glioblastoma (WHO grade IV)
    - With treatment, mean survival of 8-10 months
    - ***Necrosis* and/or *vascular or endothelial cell proliferation***



- Note that diffuse astrocytoma are poorly demarcated





- GBM
  - **Pseudopalisading necrosis <u>AND/OR</u>**
  - **Vascular proliferation**

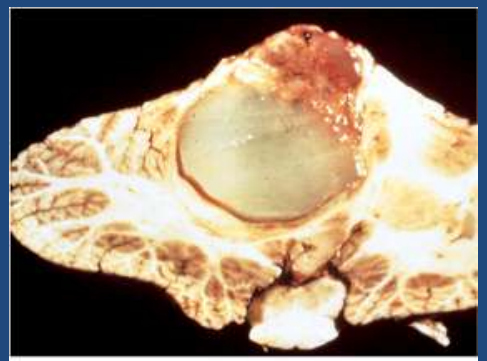
CNS Tumors
Glioblastoma

It became clear that **secondary** glioblastomas shared ***p53*** mutations that characterized low-grade gliomas

- While **primary** glioblastomas were characterized by amplification of the epidermal growth factor receptor **(*EGFR*)** gene

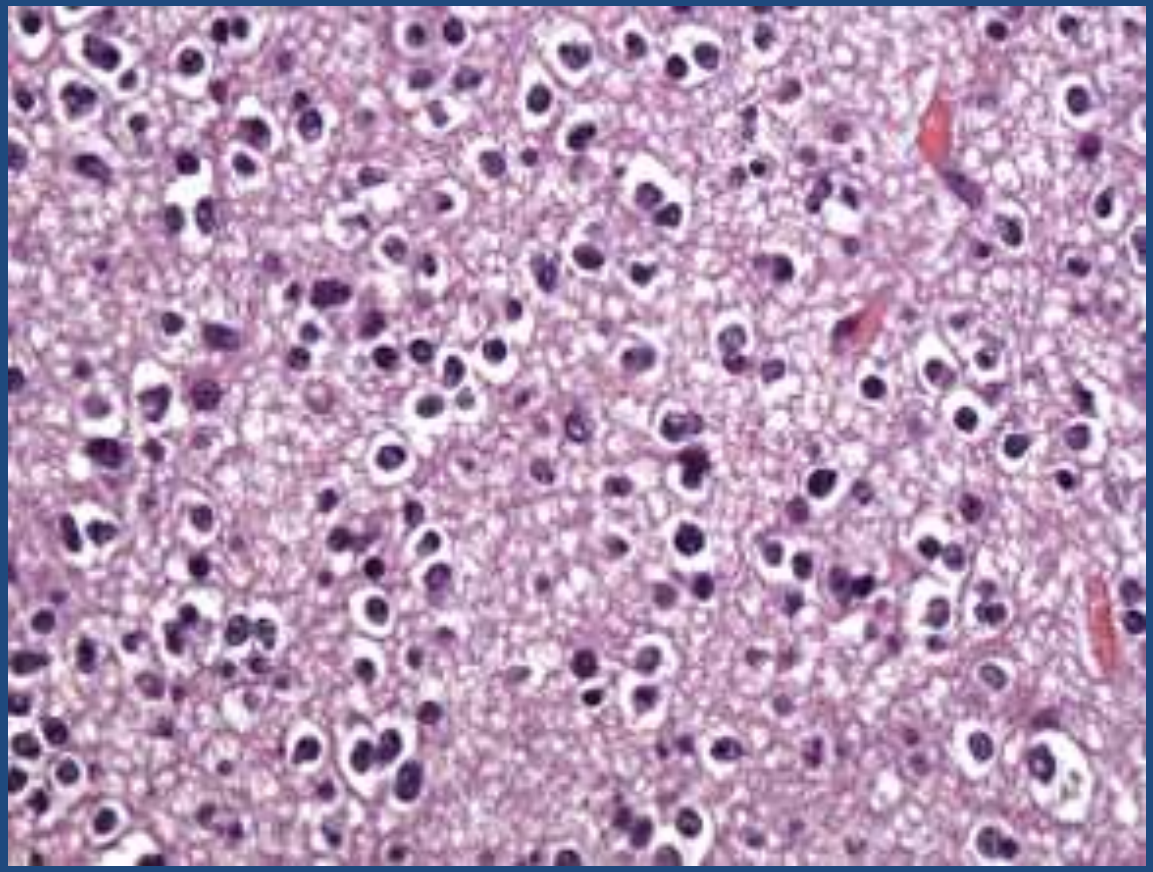
CNS Tumors
Pilocytic Astrocytoma

- Often cystic, with a mural nodule
- Well circumscribed
- "hairlike“=pilocytic processes that are GFAP positive
- Rosenthal fibers & hyaline granular bodies are often present
- Necrosis and mitoses are typically absent



Oligodendroglioma

- The most common genetic findings are loss of heterozygosity for **chromosomes 1p and 19q**
- Fourth and fifth decades
- Cerebral hemispheres, with a predilection for white matter
- Better prognosis than do patients with astrocytomas (5 to 10 years with Rx)
- Anaplastic form do worse

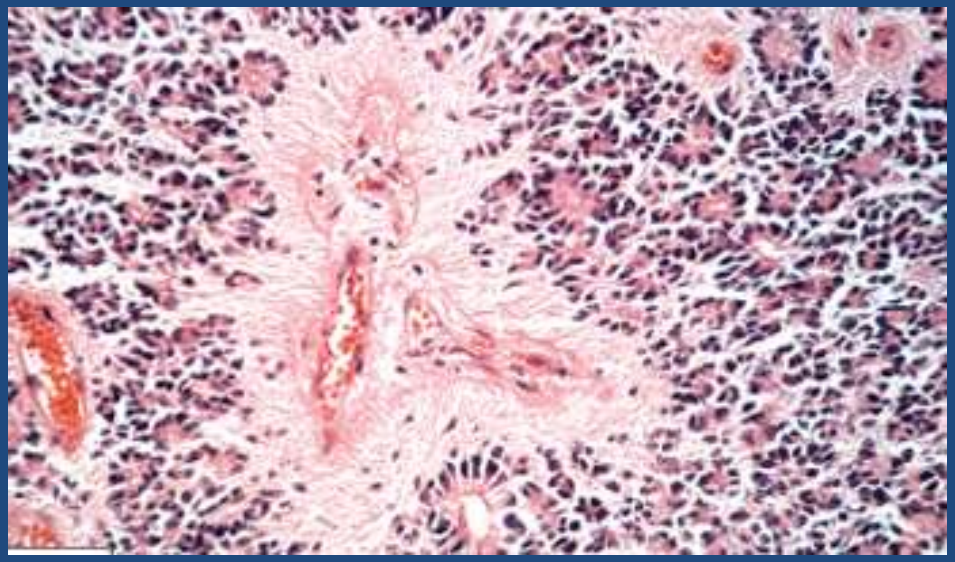


- In oligodendroglioma tumor cells have round nuclei, often with a cytoplasmic halo
- Blood vessels in the background are thin and can form an interlacing pattern

CNS Tumors
Ependymoma

- Most often arise next to the ependyma-lined ventricular system, including the central canal of the spinal cord
- The first two decades of life, they typically occur near the fourth ventricle
- In adults, the spinal cord is their most common location

CNS Tumors
Ependymoma

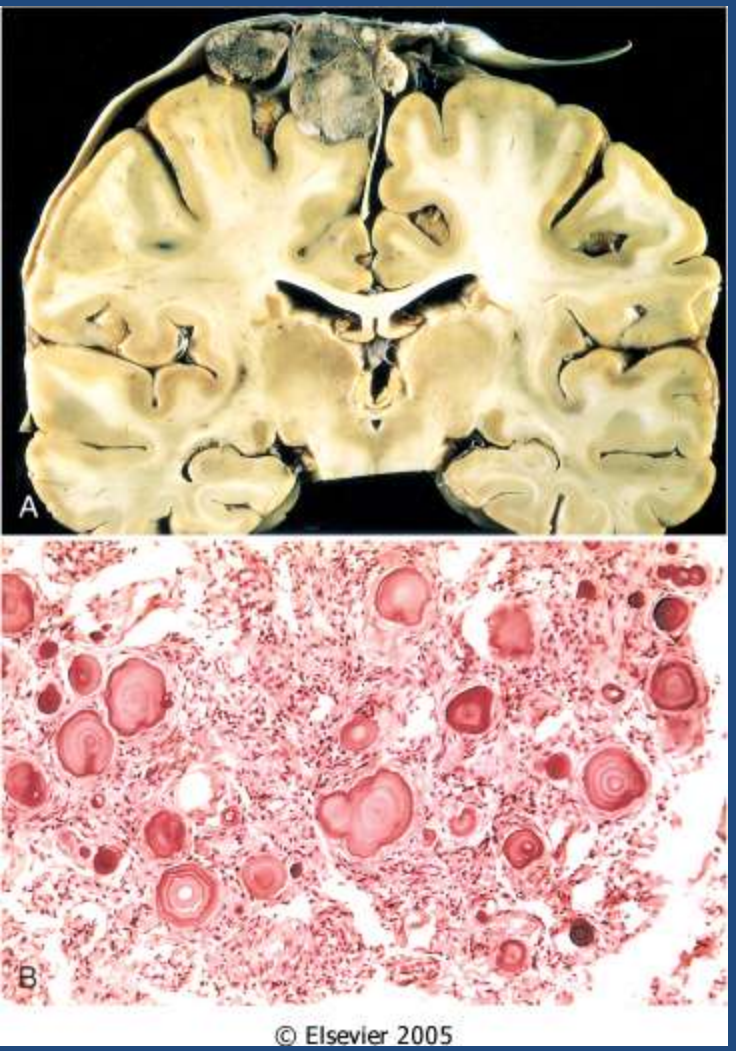


- Tumor cells may form round or elongated structures (**rosettes,** canals)
- **perivascular pseudo-rosettes**
- Anaplastic ependymomas show increased cell density, high mitotic rates, necrosis and less evident ependymal differentiation

CNS Tumors
Meningioma

- Predominantly benign tumors of adults
- Origin: meningothelial cell of the arachnoid

CNS Tumors
Meningioma



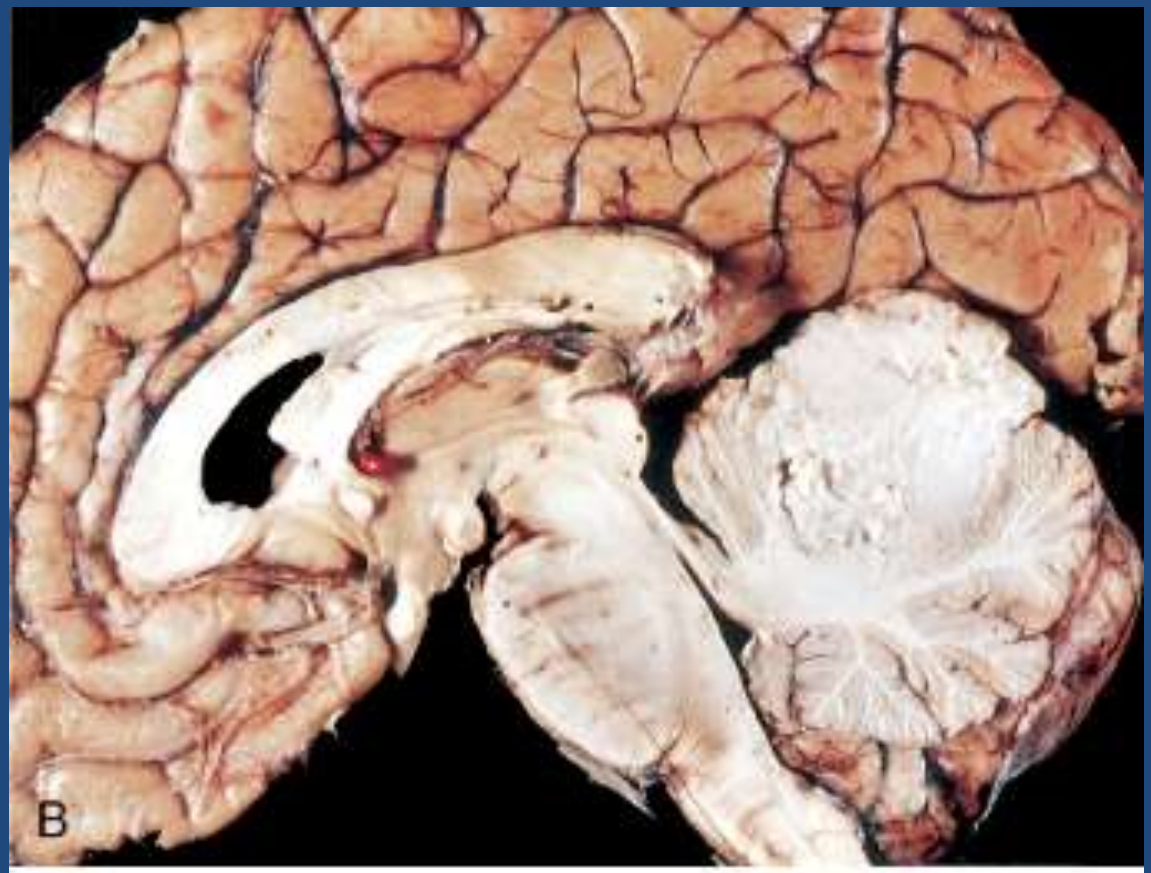
- Well demarcated
- Attached to the dura with compression of underlying brain
- **Whorled** pattern of cell growth and **psammoma** bodies

CNS Tumors
Meningioma

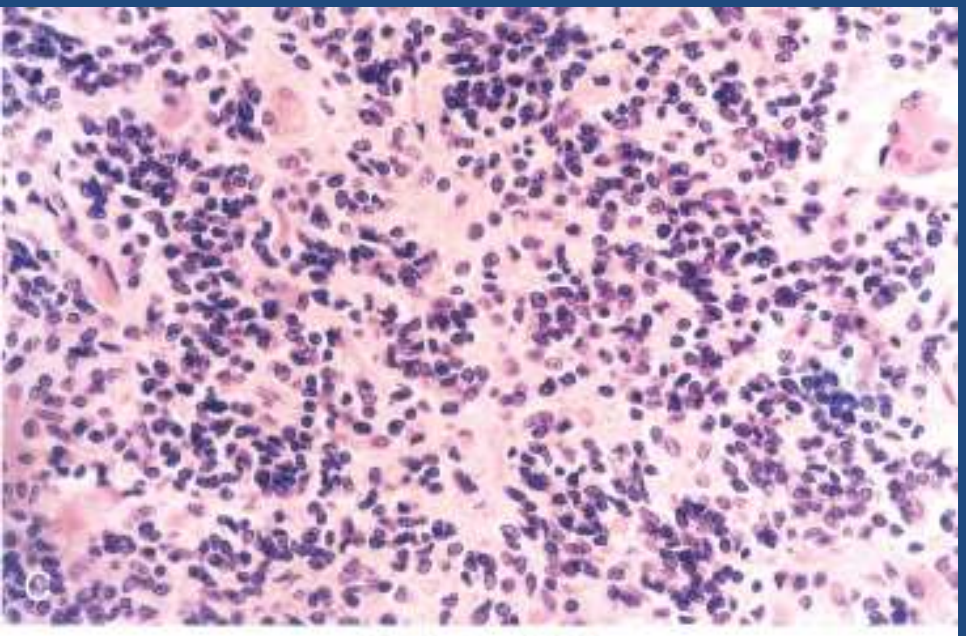
- Main subtypes:
  - Syncytial
  - Fibroblastic
  - Transitional
- Also note:
  - Atypical meningiomas
  - Anaplastic (malignant) meningiomas

CNS Tumors
Medulloblastoma

- Children and exclusively in the cerebellum
- Neuronal and glial markers may be expressed, but the tumor is often largely undifferentiated
- The tumor is highly malignant, and the prognosis for untreated patients is dismal; however, it is exquisitely radiosensitive
- With total excision and radiation, the 5-year survival rate may be as high as 75%



CNS Tumors
Medulloblastoma



extremely cellular, with sheets of anaplastic ("small blue") cells

small, with little cytoplasm and hyperchromatic nuclei; mitoses are abundant.

CNS Tumors
Haemangioblastoma

- Commonly cerebellar tumor
- Can occur in association with *Von Hippel-Lindau Disease (cyst in pancreas, liver & kideny and renal cell carcinoma)*
- Highly vascular neoplasm that occurs as a mural nodule associated with a large fluid-filled cyst
- Intervening stromal cells of uncertain histogenesis characterized by vacuolations

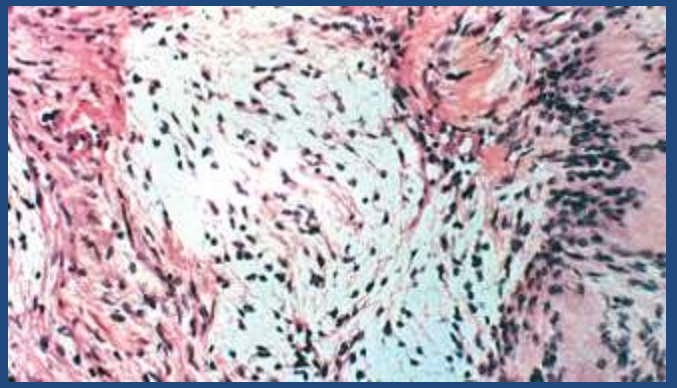
Nervous system Tumors
Schwannoma

- They are often encountered within the cranial vault, in the cerebellopontine angle, where they are attached to the vestibular branch of the eighth nerve (tinnitus and hearing loss)

Nervous system Tumors
Schwannoma

- Sporadic schwannomas are associated with mutations in the *NF2* gene
- Bilateral acoustic schwannoma is associated with NF2
- Attached to the nerve but can be separated from it

Nervous system Tumors
Schwannoma



- Cellular Antoni A pattern and less cellular Antoni B
- nuclear-free zones of processes that lie between the regions of nuclear palisading are termed Verocay bodies

Nervous system Tumors
Neurofibroma

- Examples: (*cutaneous neurofibroma*) or in peripheral nerve (*solitary neurofibroma*)
- These arise sporadically or in association with type 1 neurofibromatosis, rarely malignant
- *plexiform neurofibroma,* mostly arising in individuals with NF1, potential malignancy
- Neurofibromas cannot be separated from nerve trunk (in comparison to shcwannoma)

Nervous system Tumors
Metastatic tumours

- About half to three-quarters of brain tumors are primary tumors, and the rest are metastatic
- Lung, breast, skin (melanoma), kidney, and gastrointestinal tract are the commonest