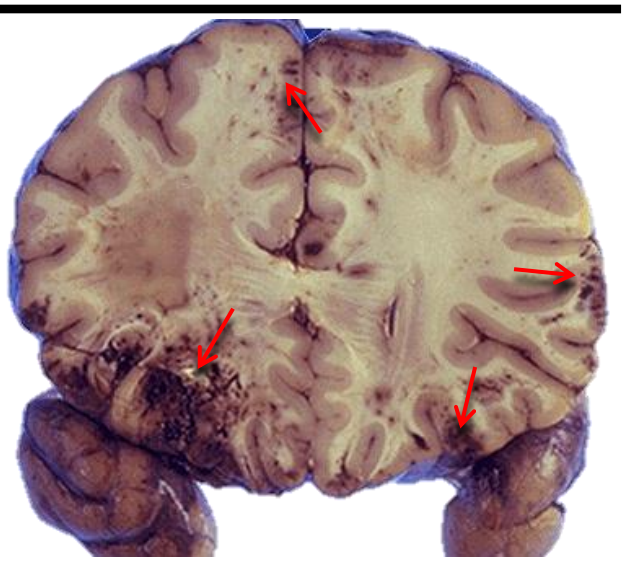
# Non-neoplastic CNS Lesions

## Trauma

Head trauma (including accidents, homicide, and suicide) is the leading cause of death in people under 45 years of age in developed countries.

### Cerebral contusions



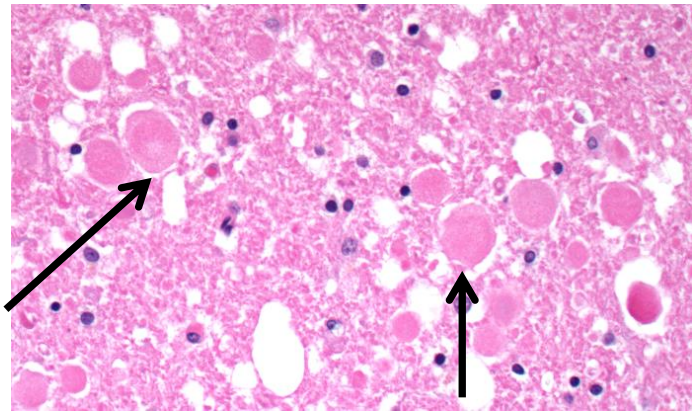
**Hemorrhage in the cortical ribbon due to vascular damage**.
Crests of gyri are most susceptible (→)
Can have subjacent intracerebral hemorrhage

With time → organizes into gliosis with hemosiderin

***Coup contusion***—at the site of impact (from moving skull hitting brain)

***Contrecoup contusion***—diametrically opposite site of impact (from brain hitting opposite side of skull). Happens when head is mobile in addition to coup contusion.

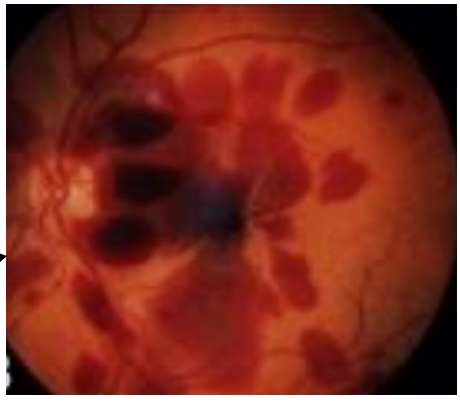
### Diffuse axonal injury



**Sudden acceleration**/deceleration motion → shear and **tear axons**.
See in **white matter** (paraventricular, corpus callosum, etc…)

Axonal swelling and hemorrhage.
Can see **axonal spheroids** (non-specific, but common)
Involved fiber tracts may degenerate.

### Childhood head trauma

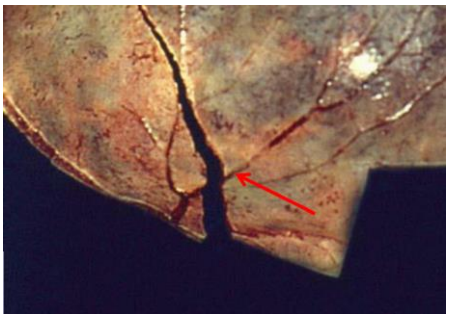


*"Shaken baby syndrome"*
Childhood "non-accidental trauma" can have minimal external signs of trauma with substantial internal injury.
Usually < 1 yr. Poverty is a significant risk factor.
Usually male perpetrators.
Frequent lifelong neurologic damage.

Frequent additional findings:
**Retinal hemorrhages**
subdural and subarachnoid hemorrhage

In children dying of head injuries, the most common finding is a subdural hematoma with or without a skull fracture.

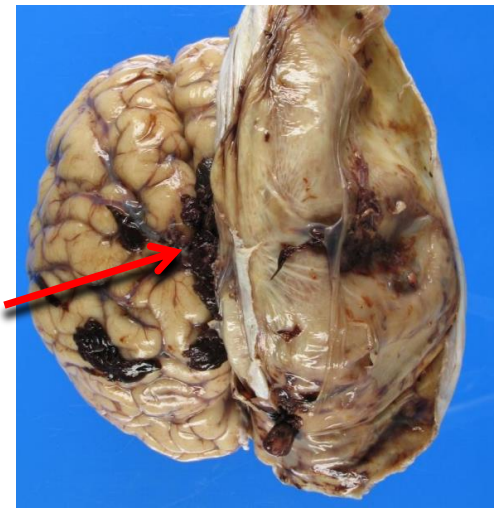
# Epidural Hematoma



Temporal bone fracture → Injury to middle meningeal artery
Slowly bleeds **arterial blood into epidural space** (peeling dura from skull).

Often, "lucent period" (minimal symptoms during slow bleed) → 4-8 hrs → herniate → death

# Subdural Hematoma

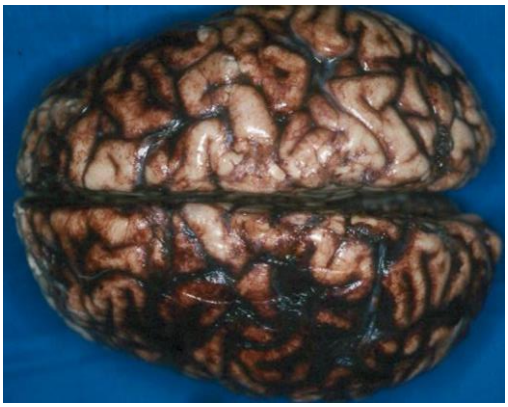


**Shearing of parasagittal bridging veins** during acceleration/deceleration injuries (brain moves relative to skull and venous sinuses, tearing veins)→ bleed beneath dura above arachnoid layer.

Most common in **elderly** and alcoholics (smaller, atrophied brains have more room to move in the skull).

Appears as freshly clotted blood on brain surface (without extension into sulci)

# Subarachnoid hemorrhage

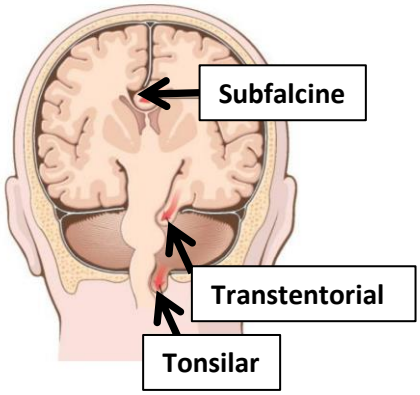


Bleeding between arachnoid membrane and pia surrounding brain.
Most common intracranial finding after blunt head trauma.
Non-traumatic causes: berry aneurysm and ruptured AVMs.

Extend down into sulci of brain.

Sudden, excruciating headache
*("The worst headache I've ever had.")*

# Herniation




The brain is confined by the skull the skull and two dural reflections. Any mass lesion or increase in volume → can cause herniation (displacement through a partition).

**Subfalcine herniation**: cerebral hemisphere displaces cingulate gyrus under the falx cerebri→ compresses anterior cerebral artery.

**Transtentorial (uncal) herniation**: temporal lobe is compressed by tentorium cerebelli→ compresses 3rd cranial nerve → pupillary dilation and impaired movement. Eventually can progress to hemorrhagic lesions in midbrain and pons.

**Tonsillar herniation**: cerebellar tonsils displaced through foramen magnum→ brainstem compression → compromises respiratory center

# Developmental

*Occur during embryological development.*

## Neural Tube Defects

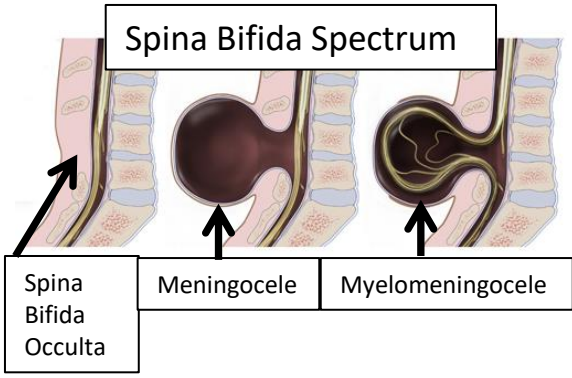
Most common CNS malformations.
**Failure of the neural tube to close in embryologic development** (or reopening after closure) → abnormalities of neural tissue, meninges, and/or overlying bone/soft tissue.
Associated with **folate deficiency** and genetic factors.
Increased maternal serum AFP in prenatal screening.

*From: Wikipedia*

**Anencephaly**: malformation of anterior end of the neural tube→ absence of brain and calvarium.

**Encephalocele**: diverticulum of malformed CNS tissue extending through a defect in the cranium. Usually in occipital region

**Spina bifida**: incomplete closing of the spine and the membranes around the spinal cord. Spectrum of disease.



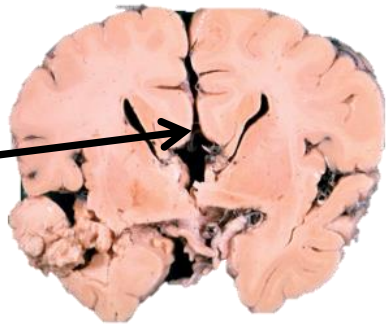

- **Spina bifida occulta**: vertebrae alone are not completely closed. Skin and meninges are intact, so defect is "hidden" (occult). Skin may have dimple or hair. Can be asymptomatic.
- **Meningocele**: Meninges extend through a defect in the vertebrae.
- **Myelomeningocele**: CNS tissue and meninges extend through a defect in the vertebral column. Most severe form.

## Forebrain Anomalies

**Microencephaly**: abnormally small brain volume. Seen in many settings including chromosomal anomalies, fetal alcohol syndrome, etc..

**Lissencephaly (agyria):** absence of brain gyri→ smooth surface. Various mutations can cause.

**Holoprosencephaly**: spectrum of malformations with incomplete separation of the cerebral hemispheres across the midline. Most severe form associated with midline facial defects and cyclopia.

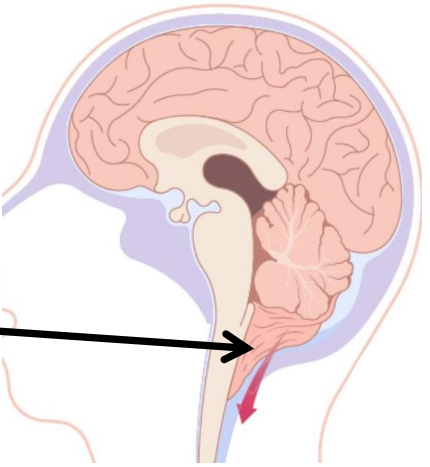


**Agenesis of the corpus callosum**: relatively common malformation. Can be normal or have cognitive impairment.

# Posterior Fossa Anomalies

**Dandy-Walker malformation**: enlarged posterior fossa with cerebellar vermis replaced by a midline ependymal cyst (expanded 4th ventricle)

**Arnold-Chiari Malformation** (Chiari type II malformation): small posterior fossa, misshapen cerebellum with downward extension of the vermis through the foramen magnum → hydrocephalus and lumbar myelomeningocele



# Hippocampal (mesial temporal) sclerosis

Associated with chronic epilepsy. Most common cause of temporal lobe epilepsy.
Severe segmental loss of neurons with accompanying gliosis in one or more regions of the hippocampus.

# Tuberous Sclerosis

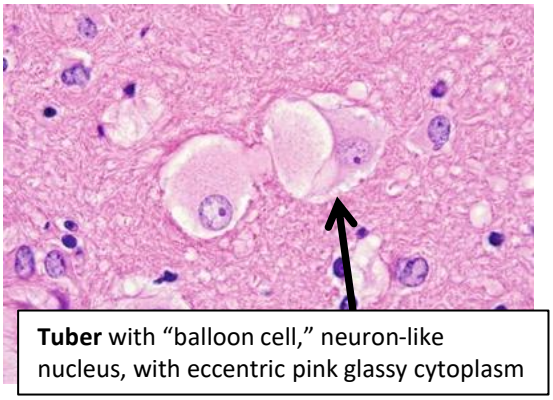
**Autosomal dominant** disorder of hamartomas and benign neoplasms. Many individuals are sporadic though.
Germline mutations in **TSC1 or TSC2**.
Most common hereditary tumor syndrome of CNS.
Highly penetrant with most individuals having CNS lesions.
Often have seizures (>80%) and mental retardation (~50%).

*CNS lesions:*
**Cortical tubers**—in cortex, enlarged, dystrophic glioneuronal elements with associated astrocytosis and calcification.

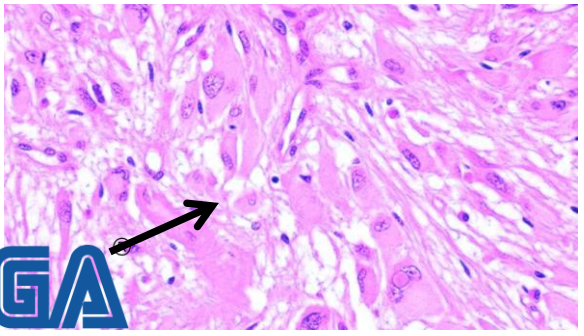
**Subependymal Giant Cell Astrocytoma** (SEGA) and **Subependymal nodules**—(indistinguishable) atypical enlarged, epithelioid to spindled glioneuronal cells forming sweeping fascicles. Well-demarcated.

**Radial glioneuronal heterotopias**

Systemic manifestations: Facial angiofibroma, Angiomyolipoma, Cardiac rhabdomyomas



**Tuber** with "balloon cell," neuron-like nucleus, with eccentric pink glassy cytoplasm



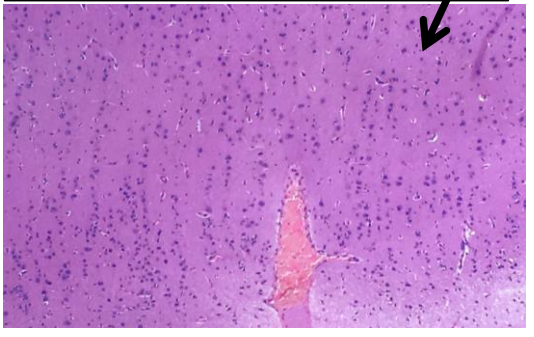

# Focal Cortical Dysplasia

**Diverse group** of disorders with abnormal cortex architecture due to **abnormal development** → **Epilepsy**.

***Spectrum*** of disease ranging from microscopic abnormalities (e.g., dystrophic neurons) to grossly abnormal (e.g., grey matter heterotopia in white matter)

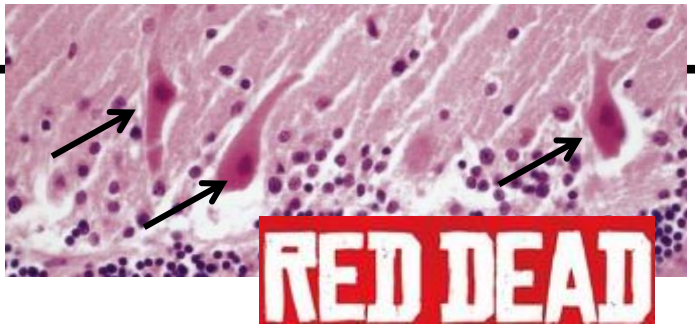
Has a very detailed classification system.

One example: Atypical linear arrangement of neurons in cortex ("*dyslamination*")



# Vascular/Ischemic

## Acute ischemic cell change



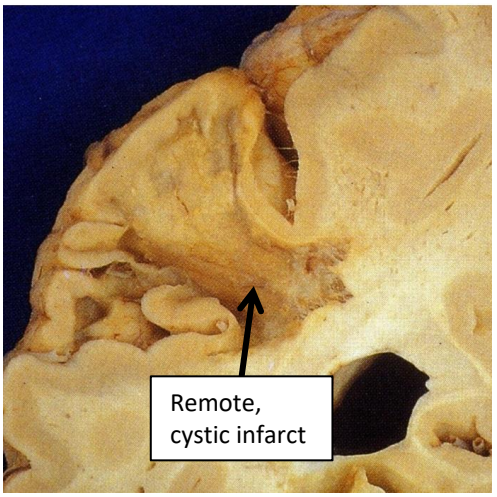

***"Red (dead) neurons"***

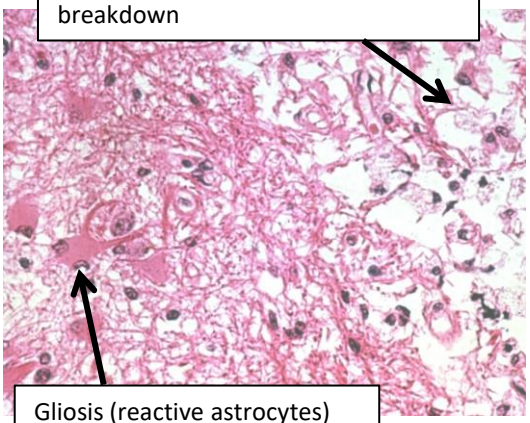
Seen after an **irreversible hypoxic/ischemic insult**.
Cell shrinkage, pyknosis, loss of nucleolus, intense eosinophilia.
Visible 12-24 hours after.

## Cerebrovascular Disease

Clinically called "**Stroke**."
Third leading cause of death in USA.
*Three major categories*:
**Thrombosis**—occlusion of a vessel, usually by atherosclerosis.
**Embolism**—occlusion of a vessel by an embolism (traveling blood clot, or other material).
*(both cause localized hypoxia, ischemia, and infarction from impaired blood flow and oxygenation)*
**Hemorrhage**—bleeding from ruptured vessels.

***Most common disease sequence***:
Atherosclerosis (with frequent preexisting hypertension and diabetes) → narrowing of vessel→ plaque rupture → thrombosis (± embolization of plaque).
Most common site: carotid bifurcation, origin of middle cerebral artery.



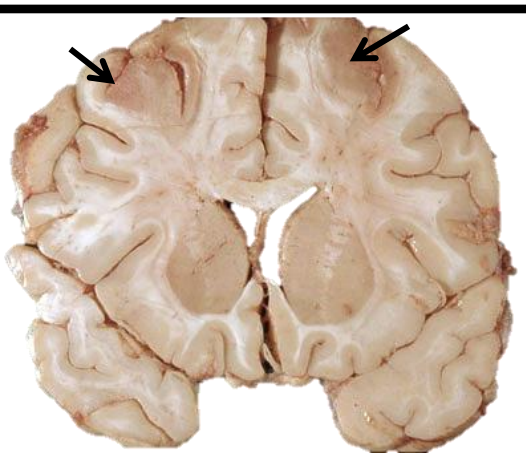




Infarcts are often classified as hemorrhagic vs non-hemorrhagic:
Hemorrhagic (red) infarction: hemorrhagic presumably because of reperfusion of damaged vessels. Usually embolic.

Non-hemorrhagic (pale, bland, anemic) infarction: associated with thrombus (without reperfusion). Stages of change: after 48 hrs pale, soft, swollen → after ~7 days gelatinous and friable → eventually fluid filled cavity.

## Global Cerebral Ischemia

**Severe hypotension** → *global* cerebral ischemia (diffuse hypoxic/ischemic encephalopathy)

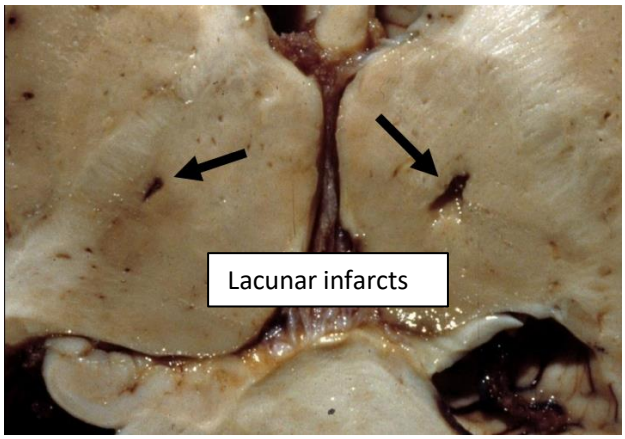


**Border zone ("watershed") infarcts** occur in the regions most distal to arterial supply.
In the cerebral hemispheres this is the area between the cerebral and middle cerebral arteries (→).

# Hypertensive changes

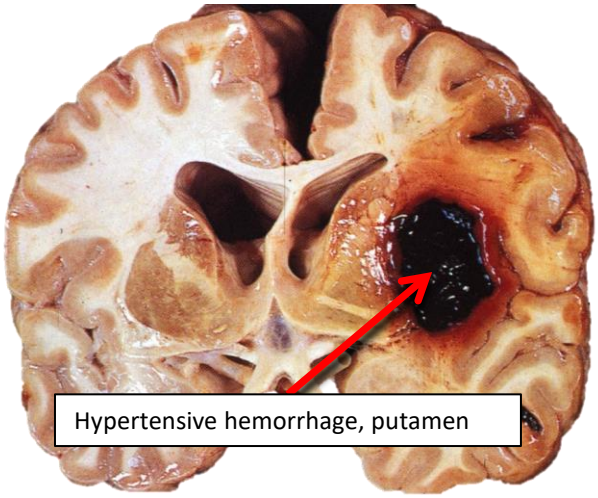
Hypertension damages blood vessels and can lead to a variety of lesions:

**Lacunar infarcts**
HTN causes arteriolar sclerosis of the deep penetrating arterioles of the basal ganglia, hemispheric white matter and brainstem→ eventual occlusion → small cavitary infarcts (called lacunae)




**Slit hemorrhages**
HTN can also cause rupture of small penetrating vessels. In time, these can resorb leaving behind a slit-like cavity (slit hemorrhage)

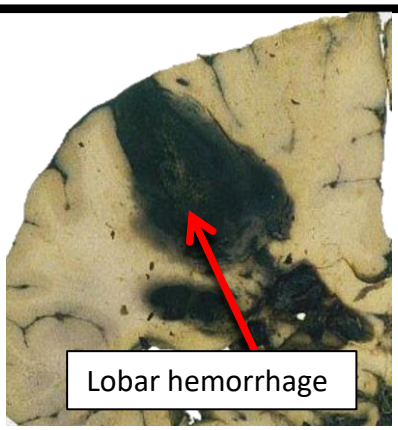
**Intracerebral (intraparenchymal) hemorrhage**
Rupture of small intraparenchymal vessels.
Usually, site of weakening by HTN via atherosclerosis, arteriolosclerosis, or necrosis→ causes aneurysms, including Charcot-Bouchard microaneurysms (other causes are cerebral amyloid angiopathy, malformations, etc..) → Rupture causing hemorrhage.
Most common in putamen.

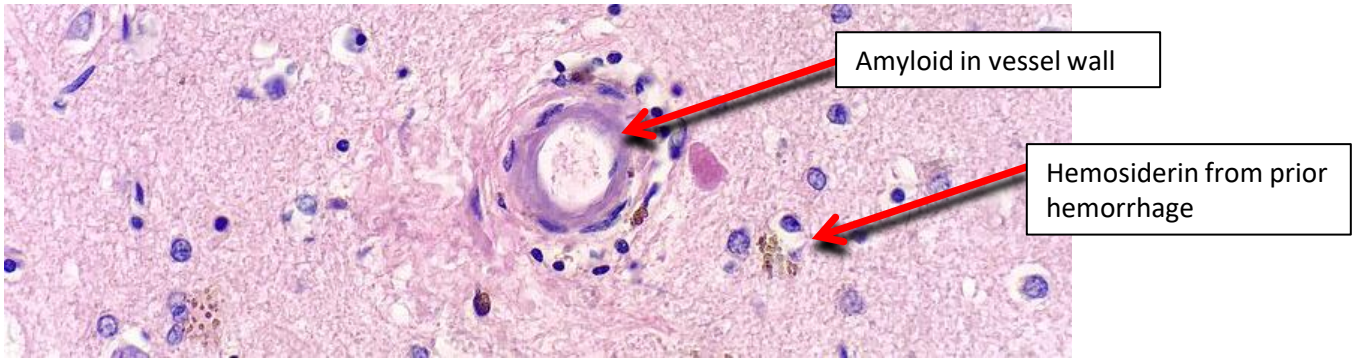



# Cerebral amyloid angiopathy

Amyloidogenic peptides, nearly always the same ones found in Alzheimer disease ($A\beta_{40}$), deposit in the walls of small and medium-sized cortical and meningeal vessels (restricted to brain) → weakens vessel wall → rupture & hemorrhage.

Can see dense deposits microscopically with open “rigid” vessels.

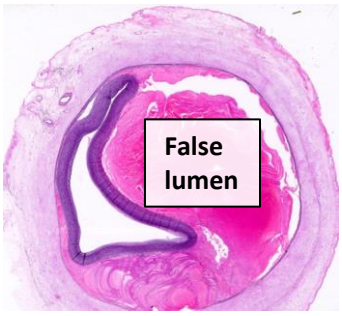


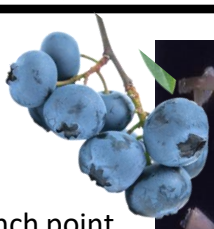
# Arterial Dissection

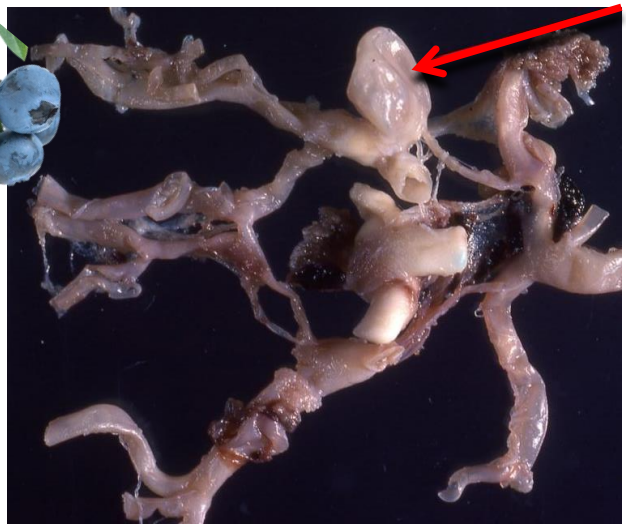
**<u>Disruption of vessel lumen</u>**→ blood can enter "false lumen" and dissect between layers or rupture. Frequently caused by trauma, but can be sporadic.

*<u>Common CNS sites</u>:* carotid/vertebral arteries. Often younger adults, due to trauma.




# Saccular (Berry) Aneurysm





Rupture is the most frequent cause of clinically significant subarachnoid hemorrhage (SAH).

Vast majority are found near major arterial branch point in the anterior circulation of the Circle of Willis.

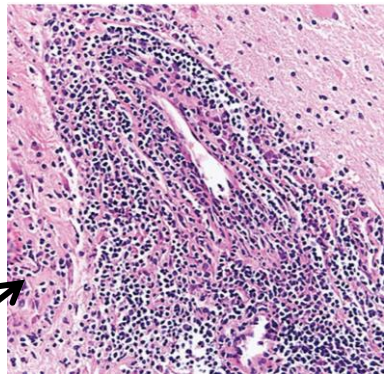
Mostly "sporadic," but associated with AD Polycystic Kidney Disease. Develop during life due to vessel defect.

Bigger lesions→ higher risk of rupture

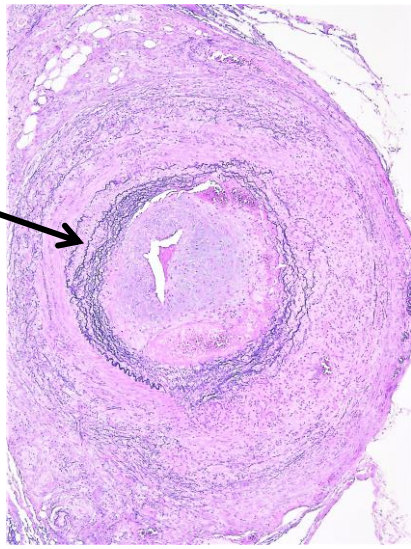
# Vasculitis

**Inflammation of the blood vessels→ luminal narrowing → cerebral infarcts/ischemia.**

Can be infectious, usually due to syphilis or tuberculosis.
Can also be primary/autoimmune (see vascular notes for more extensive discussion)



***<u>Primary angiitis of the CNS</u>***: inflammatory disorder that involves and destroys small and medium-sized vessels with chronic inflammation, giant cells, and granulomas *<u>exclusively</u>* in the CNS. Often requires a biopsy for diagnosis, but given patchiness of process, a negative biopsy does note exclude the diagnosis.



***<u>Giant cell (Temporal) Arteritis:</u>*** Usually impacts aorta and/or its major branches, with a predilection for the branches of the carotid and vertebral arteries, especially the <u>temporal artery</u>. Onset usually *<u>after</u>* age 50. Involvement of ophthalmic artery can cause *<u>permanent blindness</u>*, so considered a medical *emergency* requiring prompt Dx and treatment with corticosteroids. Histologically see <u>lymphohistiocytic inflammation</u> of vessel wall with frequent <u>granulomas/giant cells</u>. <u>Fragmentation of internal elastic lamina</u> (IEL; best seen on EVG stain). Patchy→ so get lots of levels and an EVG in biopsies.

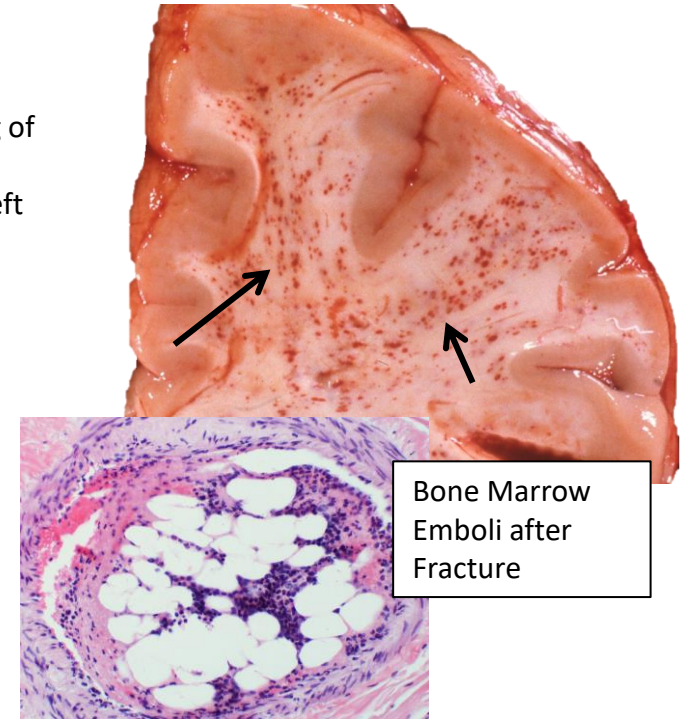
# Embolism

*Many possible types of emboli:*
**Blood clot**—most common. Often from heart in setting of Atrial fibrillation, valvular disease, or post-MI. Can get "paradoxical" emboli from deep veins if there is right-left shunting in the heart.

**Fat**—often after bone fracture (with marrow embolization), can lead to "shower embolization" with widespread white matter hemorrhagic lesions (→).

**Tissue**
**Foreign material**

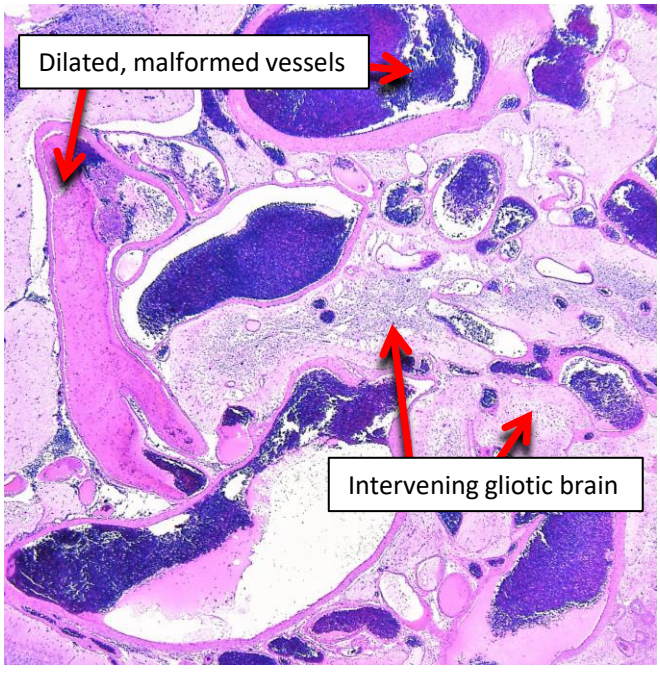
Usually goes to middle cerebral artery stopping at a branch or area of stenosis.



Bone Marrow Emboli after Fracture

# Vascular Malformations

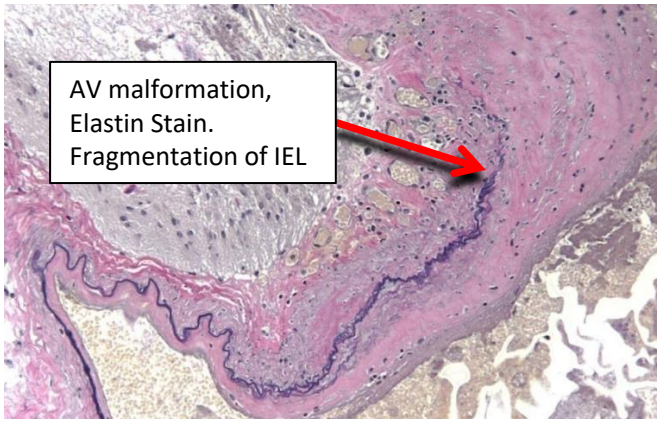
**Arteriovenous malformation**: Network of tangled vasculature channels with prominent, pulsatile, AV shunting (high blood flow). Enlarged vessels, including arteries with duplication or fragmentation of internal elastic lamina (IEL) and vessels with replacement of media by hyalinized connective tissue, separated by gliotic tissue. Involve brain ± subarachnoid space. Risk of **rupture**, often signs of prior hemorrhage. Usually, young men presenting with seizure and bleed.




**Cavernous malformation**: Large, distended vascular channels with thin, collagenized walls without intervening nervous tissue. Low flow without AV shunting. Most common in cerebellum.
Risk of hemorrhage.

**Capillary telangiectasia**: Microscopic foci of dilated, thin-waled vascular channels separate by relatively normal brain parenchyma and occurring most frequently in the pons. Lower risk.

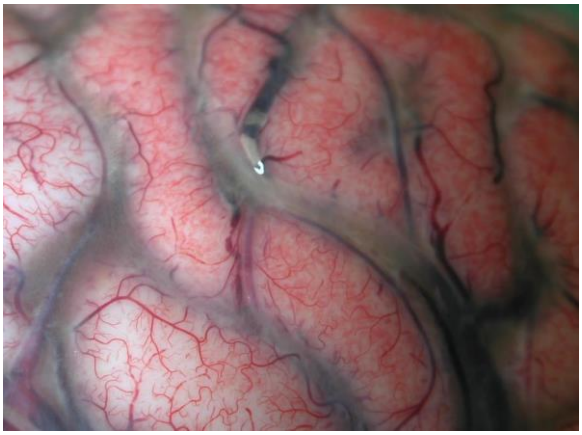
**Venous angioma**: Aggregates of ectatic venous channels.



# Infectious

Given blood brain barrier, host defenses are less effective in clearing CNS infections. Infections can get to the brain hematogenously, through direct implantation, through local extension, or along peripheral nerves.

## Meningitis



Meningitis = inflammation of the leptomeninges and CSF within the subarachnoid space.
Meningoencephalitis = meningitis + inflammation of brain

### Acute Pyogenic (Bacterial) Meningitis

Most common bacterial infection of CNS.
High mortality. Much of the damage is actually due to the immune response.

Present with signs of infection (fever) and meningeal irritation (headache, nuchal rigidity, photophobia)

CSF: Increased pressure and protein. Low glucose. Cloudy/purulent with lots of PMNs.

Micro: **PMNs fill subarachnoid space**

Can cause venous thrombosis→ infarct
Can cause scaring fibrosis→ hydrocephalus

Treat with antibiotics (for infection) and steroids (for scarring/inflammation).

***Bacteria depends on age*:**
**Neonate**: E. Coli, Group-B strep.,
**Kid/Teen**: N. Meningitidis, Strep. Pneumoniae,
**Adult**: Strep. Pneumoniae, N. Meningitidis, Listeria,

H. influenzae was formerly an important pathogen, but vaccination has been very successful

### Aseptic (viral) Meningitis

Caused by viral infection ("aseptic" is a misnomer)
Less severe/fulminant course than bacterial.

CSF: Lymphocyte pleocytosis, mild increase in protein/pressure. Normal glucose.

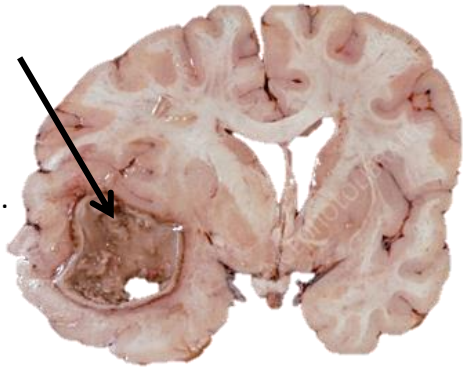
Usually self-limited and treated supportively.

***Common viral agents:***
Enteroviruses (e.g., Coxsackievirus), HSV, West Nile virus.

In most cases, no specific agent is identified!

## Abscess

Second most common CNS bacterial infection
Often unifocal. Often immunosuppressed.
High mortality. Increased intracranial pressure.

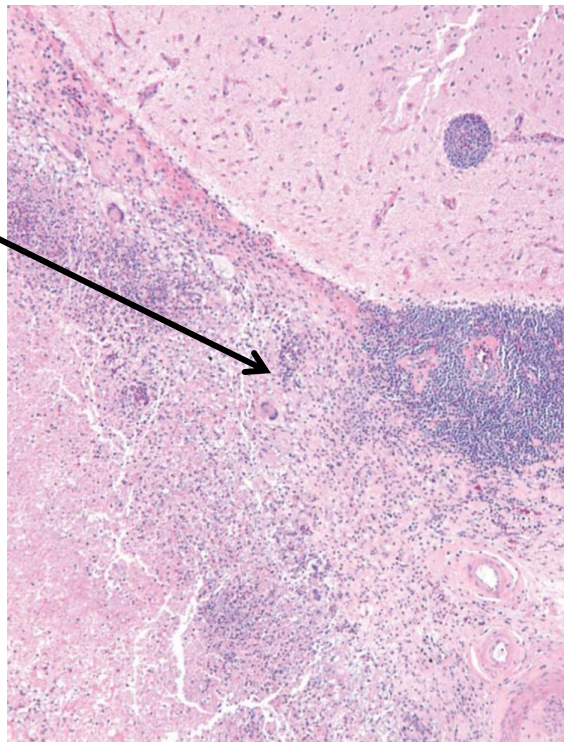


Can gain access through direct spread (otitis, sinusitis, trauma) or emboli.
Can be monomicrobial or polymicrobial, Aggressive to indolent.

Discrete lesions with liquefactive necrosis. Surrounded by gliosis with granulation tissue and neovascularization.

On CT: Ring enhancing lesion surrounded by edema (similar to GBM)

# Chronic Bacterial Meningoencephalitis



***Mycobacterium tuberculosis***

May be part of systemic disease or solitary.

Diffuse meningoencephalitis with chronic inflammation and macrophages and granulomas in subarachnoid space. Often worse around base of brain.

Arteries can show obliterative endarteritis.

*Tuberculoma*: circumscribed mass → causes mass effect

Organisms visible on AFB stain.

Present with headache, malaise, confusion.
CSF: only moderate pleocytosis (scattered lymphs, monocytes, PMNs), Increased protein, Normalish glucose.

Serious complications: arachnoid fibrosis→ hydrocephalus; obliterative endarteritis → infarcts

***Treponema pallidum* (Neurosyphilis)**

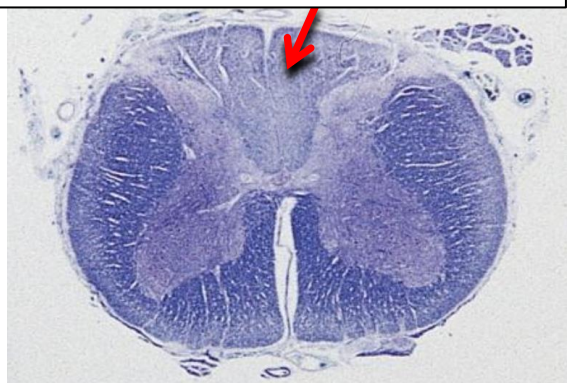
Tertiary stage syphilis, only about ~10% of untreated cases.

Meningovascular neurosyphilis: Chronic meningitis of the base of the brain. Distinctive perivascular inflammation with lots of plasma cells.

Paretic neurosyphilis: Insidious, progressive mental deficits with altered mood → dementia.

Tabes dorsalis: damage of the secondary nerves in the dorsal roots → impaired proprioception & pain perception → ataxia & injury

Tabes dorsalis: Destruction of posterior columns of spinal cord

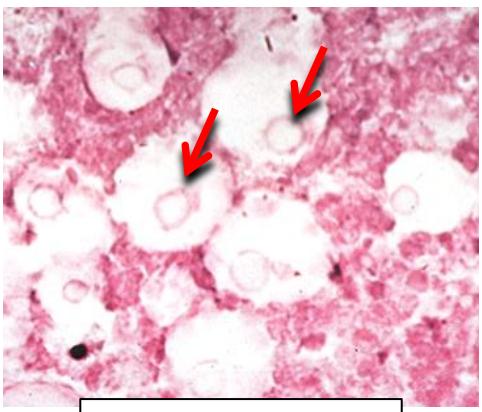


# Fungal infections

Mostly seen in immunocompromised setting.
Usually in the setting of widespread hematogenous dissemination.

Cryptococcal meningitis is a common opportunistic infection in the setting of HIV/AIDS. Mucoid-encapsulated “soap bubble” yeasts with pleomorphic sizes.

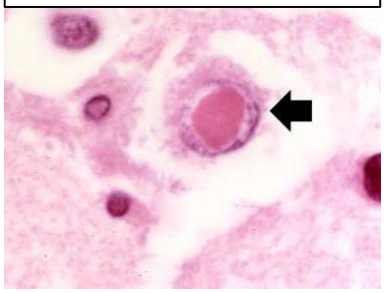
Can also have infections by Candida, Mucor, and Aspergillis (as well as other endemic fungi, like Histoplasma)



Cryptococcal meningitis

# Viral Encephalitis

HSV: Cowdry type A inclusion



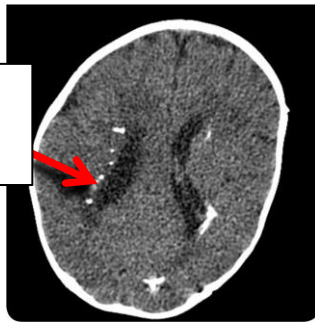
**Herpes Simplex Virus (HSV)**

Most common in children and young adults (HSV-1).
Neonates can get during vaginal delivery if mom has active primary HSV-2.
Can be acute/fulminant or subacute.
Disease focused on temporal lobes. Necrosis and hemorrhage.
Can see Cowdry type A inclusions in neurons and glia.

**Varicella-Zoster Virus (Herpes Zoster)**

Primary varicella infection = "Chickenpox" → then virus enters latent phase in dorsal root ganglia → reactivation leads to vesicular painful rash in nerve dermatomal distribution ("Shingles"). Usually self-limited.
Rarely causes overt CNS disease.

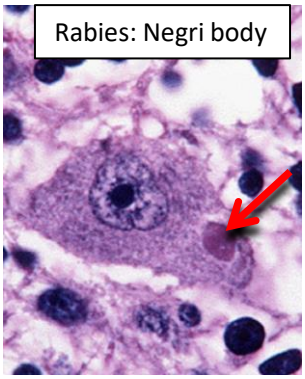
Periventricular calcifications in congenital CMV



**Cytomegalovirus (CMV)**

CNS infection seen in fetuses and immunosuppressed.
In utero infection → periventricular necrosis and calcifications, microcephaly.
Immunosuppressed→ subacute panencephalitis with CMV inclusions.

Rabies: Negri body

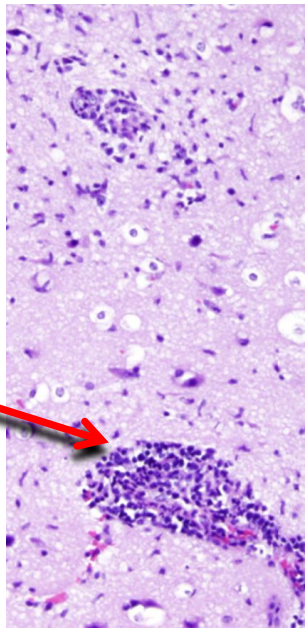


**Rabies**

Severe encephalitis transmitted by bite from infected mammal.
Virus ascends from wound site along peripheral nerves (slowly, over 1-3 months).
Negri bodies: pathognomonic cytoplasmic oval, pink inclusions in neurons (viral inclusions). Widespread neuronal degeneration.
Symptoms: CNS excitability, pharyngeal muscle contraction→ foaming at the mouth and hydrophobia.

**Polio**

Mostly eliminated by vaccination.
In non-immunized: gastroenteritis → small fraction of patients it invades CNS → inflammation of anterior horn motor neurons of spinal cord → flaccid paralysis.



**Arthropod-Borne Viral Encephalitis (Arboviruses)**

Causes epidemic encephalitis in tropical regions
E.g., West Nile virus, Western Equine virus
Lymphocytic meningoencephalitis with a tendency to be worse perivascularly.
Microglia form aggregates around necrosis→ microglial nodules.

**Progressive Multifocal Leukoencephaly (PML)**

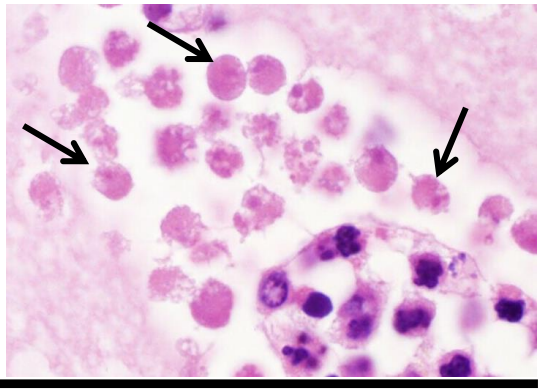
Caused by JC polyomavirus, which preferentially infects oligodendrocytes→ demyelination. Occurs in immunosuppressed patients almost exclusively, often from virus reactivation.

# Amebic infections

***Naelgleria* species**: Rapidly fatal necrotizing encephalitis. Acquired through nose from swimming in fresh water.

***Acanthamoeba***: chronic granulomatous meningitis.

Amoeba can resemble macrophages and other host cells with pale nuclei and are highlighted by PAS and GMS stains and confirmed by IF or molecular methods usually.



# Neurocysticercosis

Most common CNS parasitic infection.
Usually present with seizures.
Acquired by fecal contamination of food by eggs of the **pork tapeworm**, *Taenia solium*.
Larvae form thin-walled cysts throughout the CNS, including the brain.
In US, most patients are immigrants or travelers.
Eventually, cysts die and calcify.

Viable cyst wall: three layers
Outer: Wavy, eosinophilic cuticle
Middle: Cellular with small dark nuclei
Inner: Loose fibrils of reticular layer

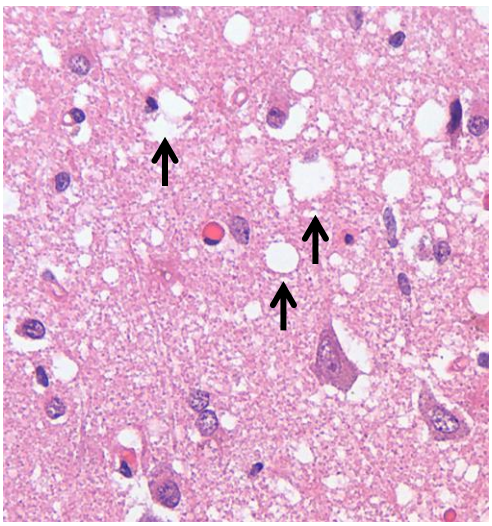
Scolex (mouth part)

# Prions

**Abnormal forms of cellular proteins** that cause transmissible neurodegenerative disorders: protein conformational change from α-helix form to abnormal β-pleated sheet form → resistant to degeneration→ accumulates→ progressive dementia → fatal.

<u>Cruetzfeld-Jakob Disease (CJD)</u>: most common Prion disease. Usually sporadic.

**Spongiform changes**: microscopic vacuoles (→) in neuropil and in some neurons. No inflammation.

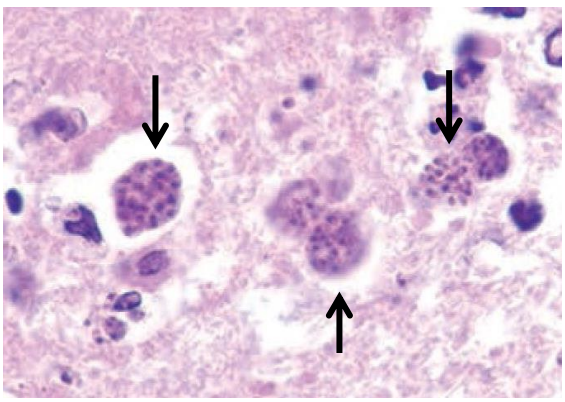


# Toxoplasmosis

Protozoan opportunistic infection, usually in HIV/AIDS.
Infected by ingesting oocytes in cat feces.

Subacute symptoms. Multiple ring-enhancing lesions.
Brain abscess in cortex. Tachyzoites and Bradyzoites seen at periphery of necrotic foci.

In non-immunosuppressed, can get congenital infection in fetus from mother.



# Are these glial cells ***reactive*** or ***neoplastic***?

**Gliosis** = ***reactive*** **changes of glial cells in response to injury.** Includes both proliferation and hypertrophy.

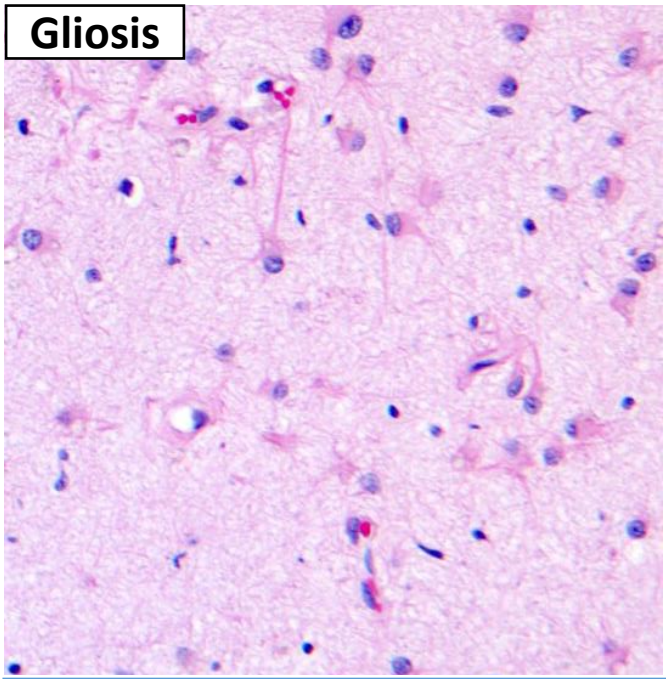
This <u>can histologically mimic a tumor</u> and pose a diagnostic dilemma, especially intraoperatively. This is particularly troublesome as gliosis can be found adjacent to tumors or as part of reactive process that can mimic tumors radiographically.

Early reactive astrocytosis→ hypertrophy with enlarged cytoplasm/processes and open chromatin with prominent nucleoli (abundant astrocyte cytoplasm is almost always pathologic!)

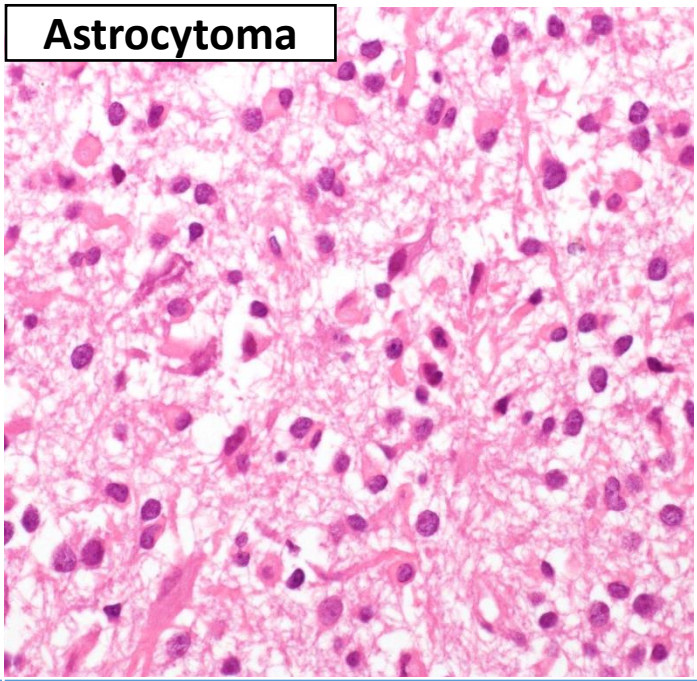
Longer term reactive astrocytosis → astrocytes become ***gemistocytic*** (large amounts of brightly eosinophilic eccentric cytoplasm) Warning: some tumors can appear gemistocytic too!!

Chronic reactive astrocytosis → often seen around slow-growing lesions → more fibrillar with long astrocytic processes and Rosenthal fibers → *"piloid gliosis" (as it resembles a pilocytic astrocytoma)*

**Gliosis**



**Astrocytoma**

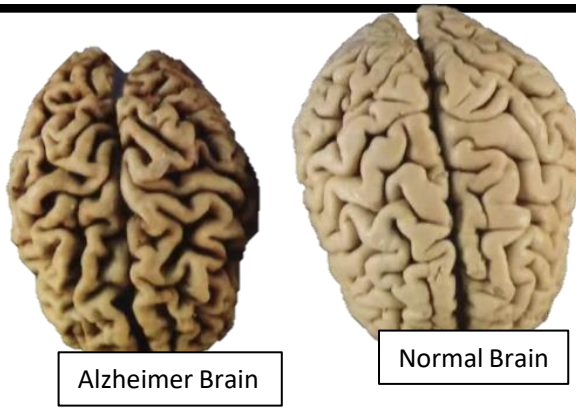


| Gliosis | Glioma |
|---|---|
| Euchromatic, round/ovoid nuclei<br>Often single prominent nucleolus | Large, hyperchromatic, irregular (astrocytoma) to round nuclei (oligodendroglioma) |
| Evenly spaced astrocytes | Clustering of astrocytes, Hypercellular, Satellitosis |
| Abundant eosinophilic cytoplasm | "Naked" nuclei |
| Astrocytes with variable atypia | Uniform atypia (monomorphic) |
| No mitotic activity | Possible mitoses |
| Uncommon to see microcystic change | Microcystic changes more common |
| Radially oriented fibrillary processes | Necrosis and/or microvascular proliferation (usually in high grades) |
| Other reactive changes, such as inflammation, macrophages, etc… | Demonstratable mutation (e.g., IDH1, ATRX, etc…) |

# Degenerative

In general, diseases of **gray matter** with progressive, selective **loss of neurons** with associated secondary changes in white matter.
*Common theme*: presence of **protein aggregates that are resistant to degradation** through the ubiquitin-proteasome system → inclusions

## Alzheimer Disease *"AD"*

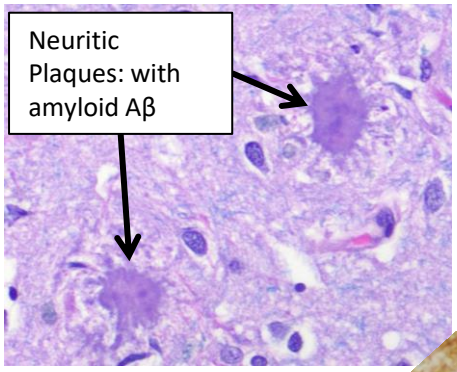



**Most common cause of dementia in the elderly**.
Impacts cerebral cortex.
Slow, but relentless loss of cognitive function.

Gross: **Cortical atrophy**, with widening of the sulci.
Ventricular enlargement due to loss of brain volume.

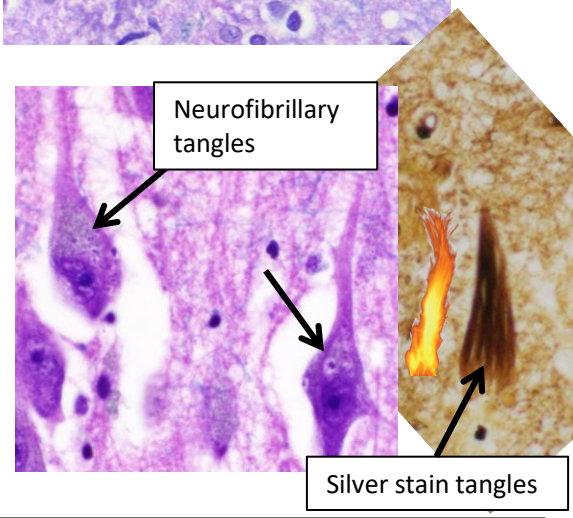
Micro: **Neuritic (senile) plaques**: spherical collections of dilated, tortuous, neuritic processes (dystrophic dendrites), often around an amyloid core, which may have a clear halo.

The main plaque component of the amyloid core is **Aβ**, which is derived from APP (Amyloid Precursor Protein) and can be identified with special IHC.
***Deposition of Aβ is the fundamental abnormality in AD.***




**Neurofibrillary tangles**: bundles of filaments in the cytoplasm of the neuron that displace or encircle the nucleus. Best seen on silver or IHC stains.
Can resemble "flames."

A major component of tangles is **tau** protein. Tangles are not specific and are seen in other diseases.
*(Think: **T**angle = **t**au)*

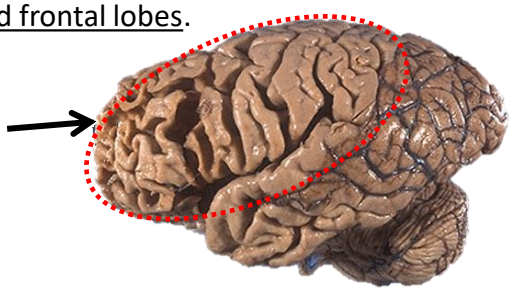



Accompanied by cerebral amyloid angiopathy (see vascular section).

## Frontotemporal Dementias *"FTDs"*

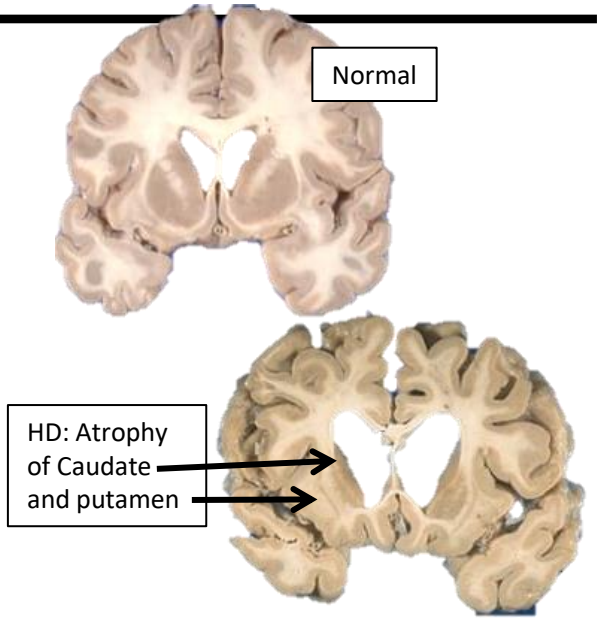
Group of disorders with shared clinical features of progressive deterioration of language and changes in personality corresponding to degeneration of the temporal and frontal lobes.

**Pick Disease (Lobar atrophy):** usually sporadic.
Pronounced asymmetric atrophy of frontal and temporal lobes.



Other FTDs are strongly genetic. Some include the accumulation of tau protein.

# Huntington Disease



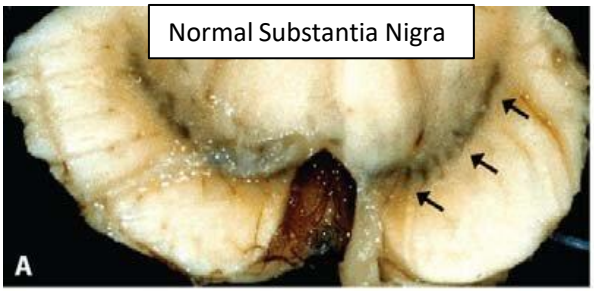

**Autosomal Dominant**.
Dementia and Progressive movement disorder (Chorea: Jerky, hyperkinetic movement of all parts of the body)

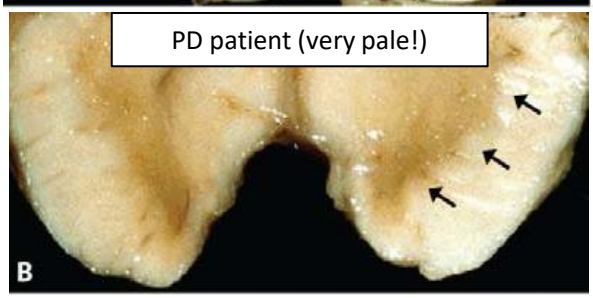
Gross: **Atrophy of caudate nucleus** (and to a lesser extent the putamen)
Degeneration of striatal neurons.

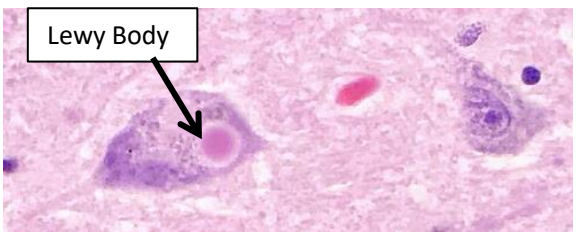
Genetics: Prototype for trinucleotide repeat expansion of HD gene locus. More repeats→ earlier disease onset.

Relentlessly progressive to death (~15 yrs)

# Parkinson / Lewy Body Dementia




"***Parkinsonism***" is a clinical syndrome characterized by diminished facial expressions, stooped posture, tremor, rigidity, bradykinesia, etc..

Parkinsonism is seen in a number of conditions that all result in the common **damage to nigrostriatal dopaminergic system.**

A diagnosis of **Parkinson Disease (PD)** is made in some one with Parkinsonism in the absence of other etiologies.

Gross: **Pallor of the substantia nigra**.
Micro: Loss of pigmented, catecholaminergic neurons, associated with gliosis.

**Lewy bodies** may be found in some remaining neurons: single or multiple cytoplasmic, eosinophilic, rounded inclusions that often have a dense center with a pale halo. Composed of α-synuclein. Can also be found in basal nucleus.

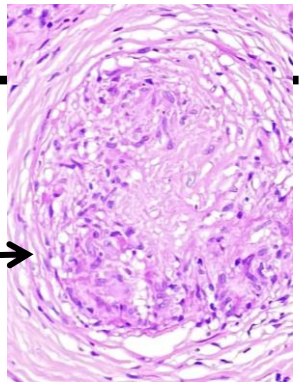
Additional clinical features: Autonomic dysfunction
Cognitive dysfunction—characteristically includes hallucinations and prominent frontal signs (personality changes). Can see PD histologic changes (Lewy Bodies) in the cortex

# Central Pontine Myelinolysis

**Loss of myelin** with relative preservation of axons and neuronal cell bodies in **Pons**. No inflammation.
Associated with **rapid correction of hyponatremia** (but can see in sever other electrolyte abnormalities).
Rapidly evolving quadriplegia

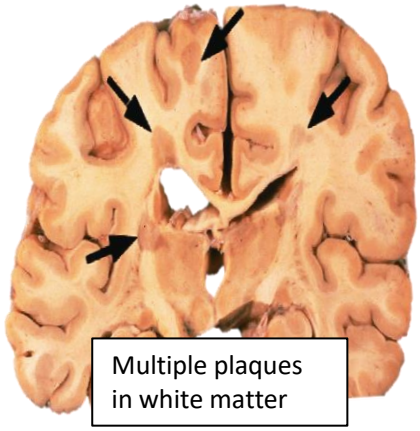
# Idiopathic/Autoimmune

## Sarcoidosis



Inflammatory disorder of unknown etiology that can impact any part of the body.
CNS symptoms correspond with site of disease. Most common is cranial neuropathy.
**Non-necrotizing granulomatous inflammation**. Often near vessels.
Elevated serum Angiotensin Converting Enzyme (ACE).
Diagnosis of exclusion→ Always get Bug stains! (at least AFB & GMS)

## Multiple Sclerosis *"MS"*



Multiple plaques in white matter

**Autoimmune**. Most common **demyelinating disorder**.
Distinct episodes of neurologic deficits, separated in time, attributable to white matter lesions that are separated in space.

*Demyelination* = damage to myelin, with relative preservation of axons → without myelin insulation, nerves can't carry electrical impulses well.

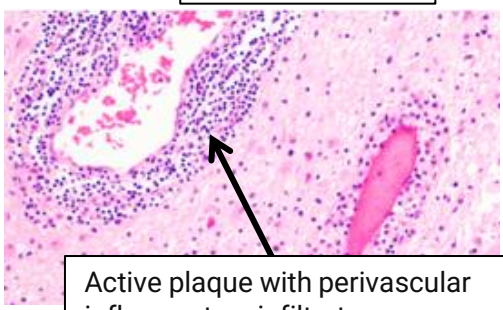
**Relapsing and remitting episodes** with neurologic defects, followed by gradual, partial recovery→ slow, steady decline.

Impacts optic nerve→ unilateral vision impairment
Spinal cord lesions→ motor/sensory impairment

Most commonly **younger women** (rare in kids and >50yrs).

Autoimmune response against myelin sheath involves both gene and environmental factors.

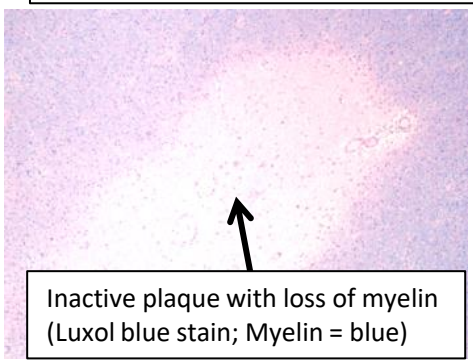
Gross: Multiple, well-circumscribed, gray-tan, irregularly-shaped plaques in white matter. (Seen on MRI)



Active plaque with perivascular inflammatory infiltrates

Micro: Active plaque: abundant macrophages actively digesting myelin lipid. Inflammatory cells, mostly around vessels. Axons preserved.

Inactive plaque: Little/no myelin. Reduced oligodendrocytes. Gliosis. Fewer axons.



Inactive plaque with loss of myelin (Luxol blue stain; Myelin = blue)

CSF: IgG levels increased with **oligoclonal IgG bands** (indicative of B cell clones, thought to be self-reactive B cells)

## Rasmussen encephalitis

Progressive disorder with seizures, decline, hemispheric atrophy, and hemiparesis.
Thought to be autoimmune. Usually kids < 15 yrs old.
Histology resembles viral encephalitis: Perivascular chronic inflammation with neuronal degeneration, gliosis, and microglial nodules.