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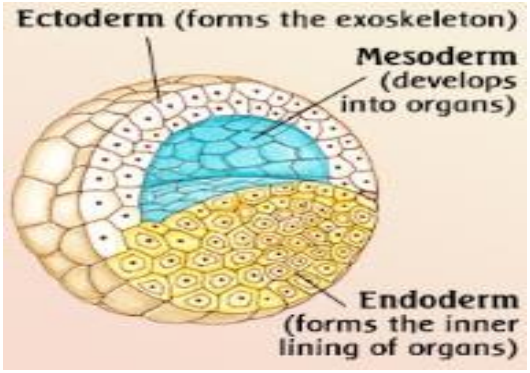
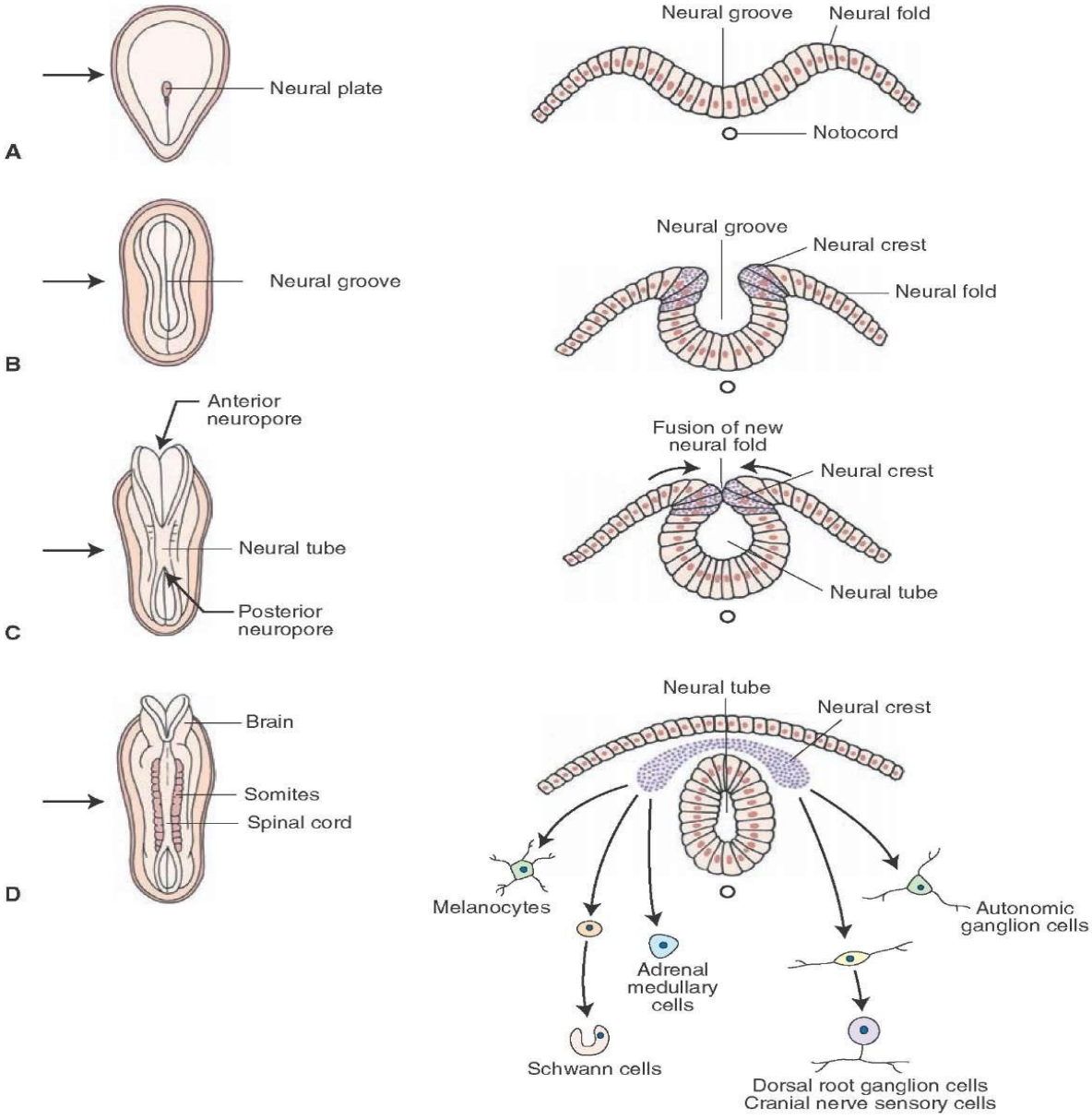
CHAPTER 1

Neurology

Nervous System Development





- There are three germ layers (endoderm, mesoderm, ectoderm) that give rise to all of our tissues and organs through the process of organogenesis during early embryogenesis.

- All nervous system is derived from ectoderm, the part of ectoderm that participate in the development of nervous system is called neuroectoderm.

- Nervous system development (neurulation) go through two steps:

1. Formation of neural plate (neuroectoderm):

- The notochord (mesodermal) induces thickening of the overlying ectoderm through a transcription factor called sonic hedgehog to form the neural plate (neuroectoderm).

- Notochord becomes nucleus pulposus of intervertebral disc in adults.

2. Formation of neural tube & neural crest:

- The midportion of neural plate invaginates forming a neural groove with two neural folds, then the lateral edge of neural folds fuse together to from the neural tube.

- Neural crest forms at the edges of each neural folds and after fusion of the neural fold, it will be dorsolateral and outside the neural tube to be able to migrate throughout the embryo where they settle and differentiate.

- After neuralation is completed, neural tube and neural crest are seperated from the overlying ectoderm and become invested in mesoderm.

- Neural tube → CNS neurons, ependymal cells (inner lining of ventricles, make CSF), oligodendrocytes, astrocytes.

- Neural crest → PNS neurons, Schwann cells, glia, melanocytes, adrenal medulla.

- Mesoderm → Microglia (like Macrophages).

Neural tube Defects

- The middle part of neural tube closes at day 23.

- The rostral (cranial) neuropore closes at day 25.

- The caudal neuropore closes at day 27.

- Filure of fusion of the neural tube during the 4th week of fetal development results in open neural tube defects → persistent connection between amniotic cavity and spinal canal.

- Associated with maternal diabetes and folate deficiency.

- Neural tube defects (NTDs) are divided into anterior and posterior:

A. Anterior NTDs:

- Occur when anterior (cranial) neuropore fails to close.

- Example: Anencephaly.

B. Posterior NTDs:

- They are more common and occur when the posterior (caudal) neuropore fail to close.

- Example: Spina bifida with myeloschisis.

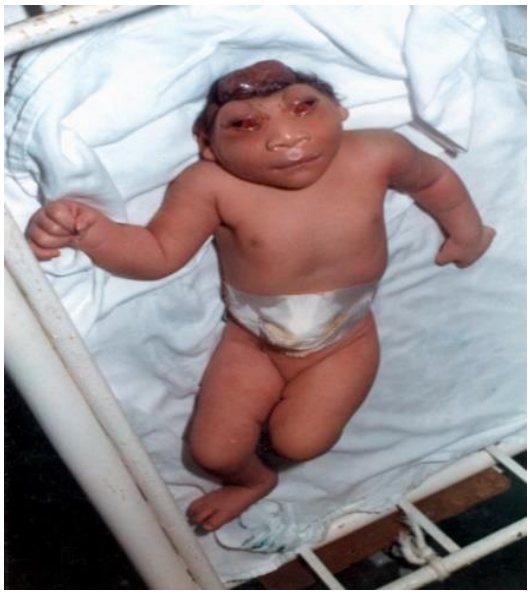
Forebrain anomalies

A. Anencephaly (no brain):

- Failure of rostral (cranial) neuropore to close → brain doesn't develop (no forebrain, open calvarium) → no swallowing reflex → polyhydramnios as a complication.

- Incompatible with life.

- Elevated alpha-feto protein and acetyl choline esterase in pregnancy.



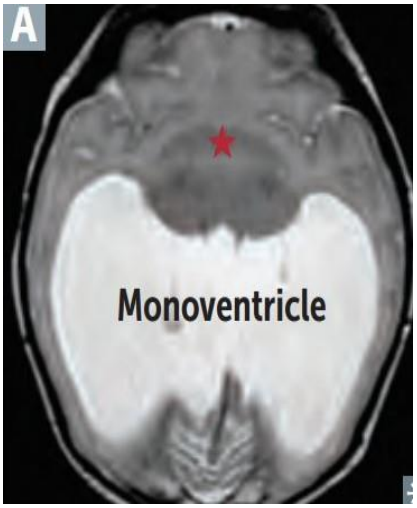
B. Holoprosencephaly:

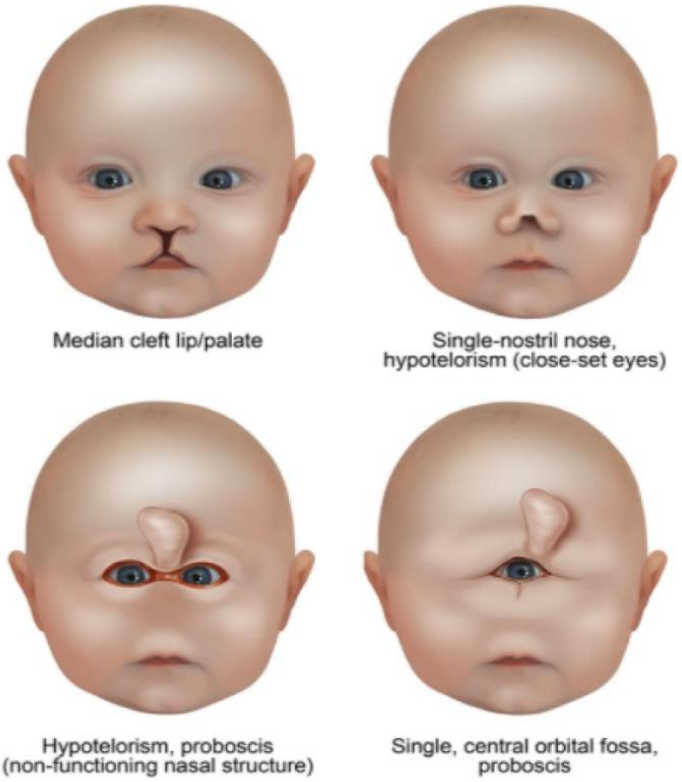
- Failure of the embryonic forebrain (prosencephalon) to separate into 2 cerebral hemispheres.

- May be related to mutations in sonic hedgehog signaling pathway.

- Associated with other midline defects. Moderate form has cleft lip/palate; most severe form results in cyclopia. It is an example of a developmental field defect, which is when an initial embryonic disturbance leads to multiple malformations by disrupting the development of adjacent tissues and structures within a particular region.

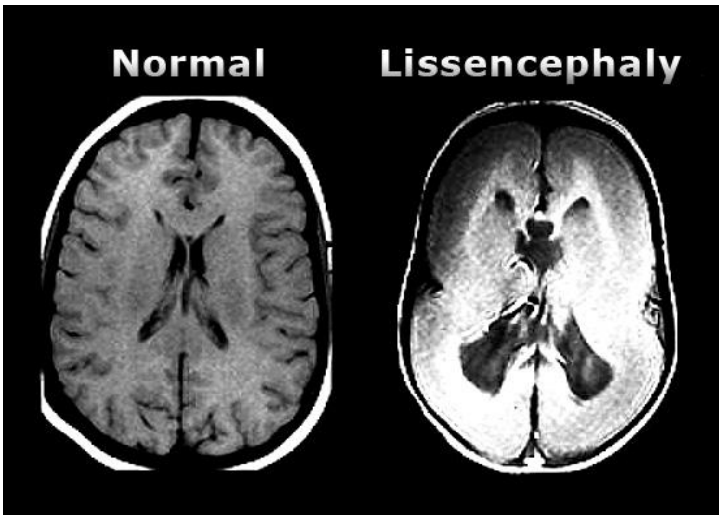
- Associated with patau's syndrome (trisomy 13), severe fetal alcohol syndrome.
- MRI reveals monoventricle and fusion of basal ganglia (star in the figure).





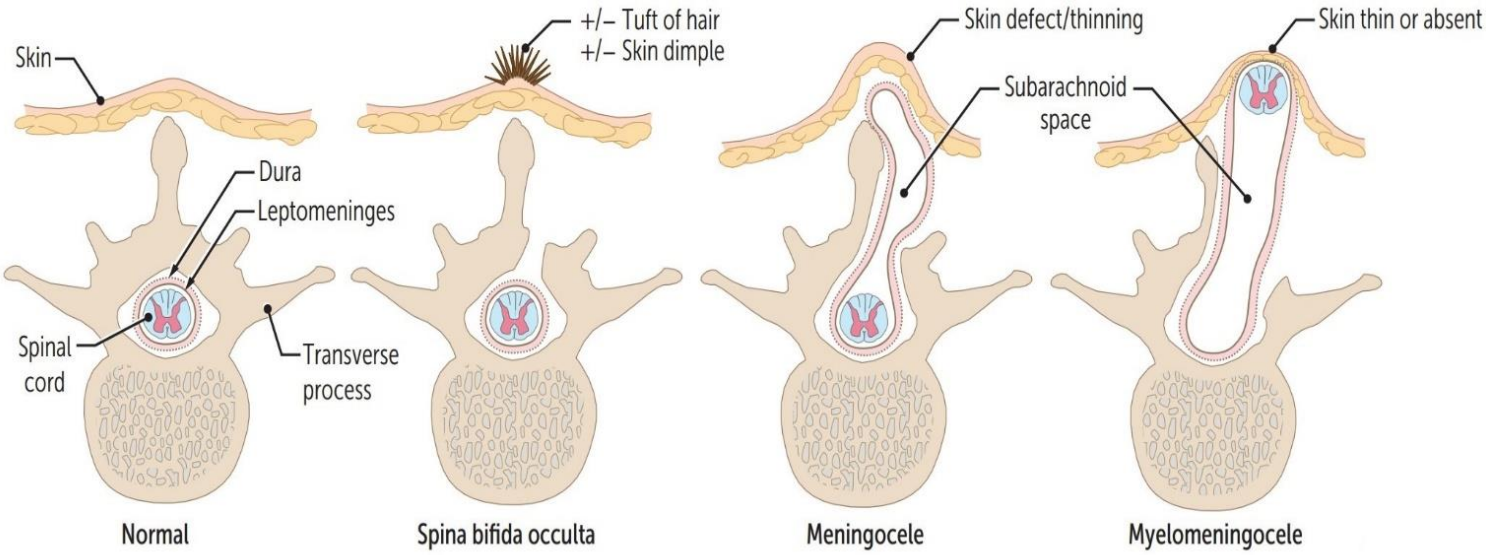
C. Lissencephaly:

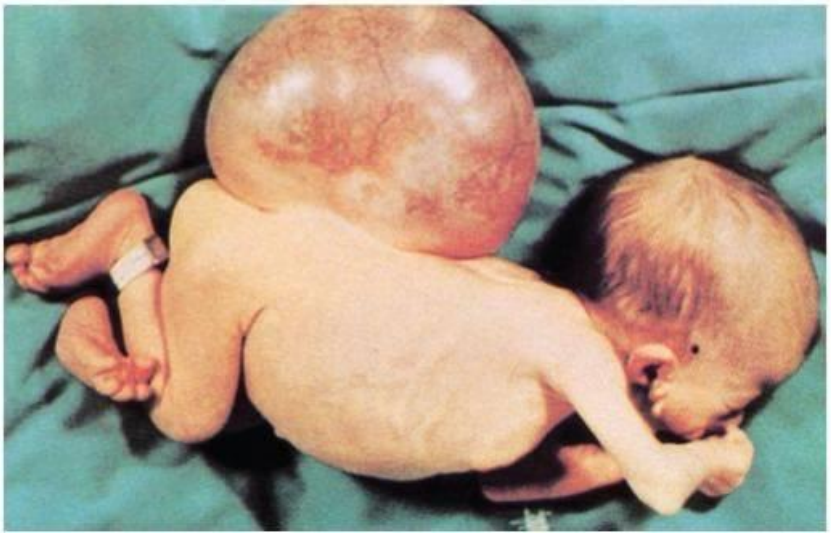
- Failure of neuronal migration resulting in a "smooth brain" that lacks sulci and gyri.
- May be associated with microcephaly, ventriculomegaly.



Spina bifida

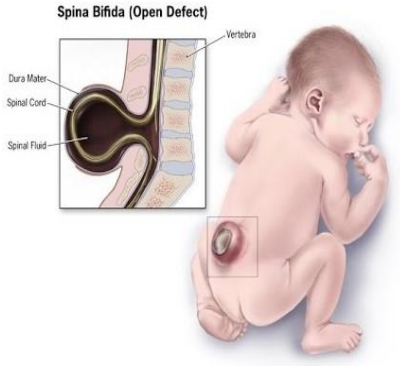
- After closure of neural tube, it induces bone to form vertebral arches (spinous processes).
- Spina bifida develops either due to failure of neural tube to form vertebral arches (spina bifida occulta, spina bifida cystica) or due to failure of closure of neural tube (spina bifida with myeloschisis).





1. Spina bifida occulta (hidden)

- Vertebrae fail to form around spinal cord (missing spinous processes).
- Mildest form.
- More common in lumbar and sacral vertebrae.
- Missed with prenatal ultrasound (so it's occulta).
- Asymptomatic with tuft of hair over the defect.
- No cyst.
- Normal AFP level (not open NTDs and the defect is covered with mesoderm that form normal skin with tuft of hair over it).



2. Spina bifida cystica

- Cyst like protrusion at the site of the defect (missing spinous processes).
- If the cyst contains only CSF lined by dura and arachnoid (Herniation of meninges only), it is called → meningocele.
- If the cyst contains CSF and displaced spinal cord lined by dura and arachnoid (Herniation of meninges and spinal cord), it is called → meningomyelocele (seen with Arnold Chiari type 2).
- There is elevated AFP in both of them, why? - The cyst will prevent separation of neural tube from the overlying neuroectoderm, so AFP will be leaked out to amniotic fluid.
- No elevated acetyl choline esterase, why? - Because this is not an open neural tube defect, it is just failure of neural tube to induce vertebral arches (spinous processes) formation.
- Meningomyelocele is more severe than meningocele, because the displaced spinal cord may stretch lumbosacral spinal nerves → sensory loss and lower limb weakness.

3. Spina bifida with myeloschisis

- Failure of caudal neuropore to close (open neural tube defect).
- Exposed, unfused neural tissue without skin/meningeal covering.
- Rarest but the severest form of spina bifida.
- Increase in both AFP and Acetyl choline esterase because it's an open neural tube defect.

❖ N.B:

- Failure of closure of neural tube (either rostral or caudal) is associated with increased alpha-feto protein and acetyl choline esterase in amniotic fluid or maternal serum.
- Alpha-feto protein isn't specific for open neural tube defects, why? - Because alpha-feto protein is elevated in any body wall defect either dorsal body wall defect (open neural tube defects) or ventral body wall defect (omphalocel and gastrschisis). On the other hand, acetyl choline esterase is specific for neural tube defects (elevated with open neural defects only).
- Studies have proved that folate supplementation during early pregnancy decreases the incidence of neural tube defects. Valproate is teratogenic because it inhibits intestinal folic acid absorption → increasing the risk of neural tube defects. Methotrexate and other folic acid antagonists adversely affect rapidly dividing cells (epithelial cells, stem cells, neural tube cells) by limiting the production of precursors essential to DNA synthesis and repair.

Posterior fossa malformations

1. Arnold chiari malformation:

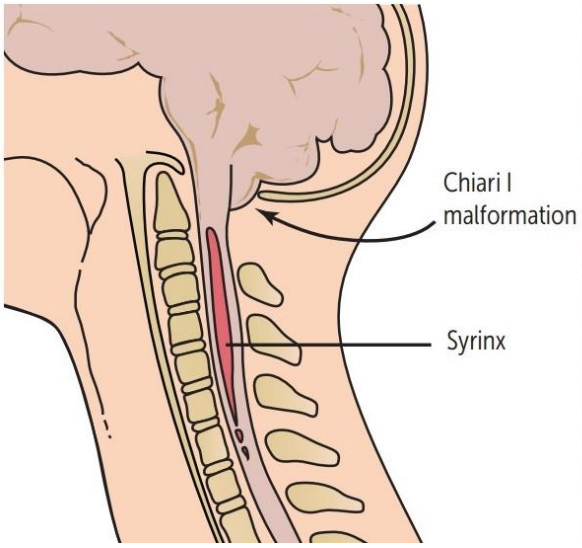
- Cause:

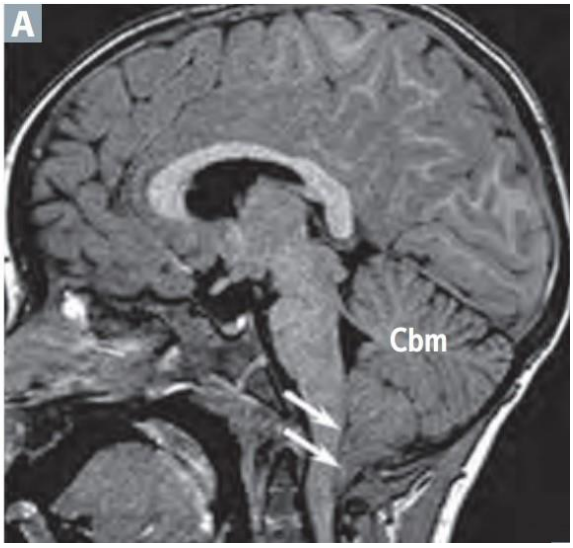
- Downward displacement of certain parts of cerebellum through foramen magnum.

- Types:

A. Type 1 (most common):

- Downward displacement of cerebellar tonsils through the foramen magnum (1 structure).
- Usually asymptomatic in childhood, manifests in adulthood with headaches and cerebellar symptoms.
- Associated with spinal cavitations (syringomyelia).





B. Type 2:

- Downward displacement of cerebellar vermis and tonsils (2 structures) through foramen magnum → aqueductal stenosis → noncommunicating hydrocephalus.

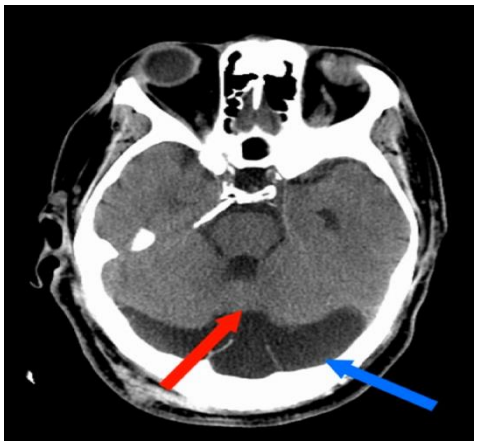
- Frequent association with lumbosacral meningomyelocele.

- More severe than Chiari I, usually presents early in life.

2- Dandy walker malformation:

- Agenesis of cerebellar vermis (red arrow) leads to cystic enlargement of 4th ventricle (blue arrow) that fills the enlarged posterior fossa.

- Failure of foramina of Luschka and Magendie to open → Associated with noncommunicating hydrocephalus, spina bifida.

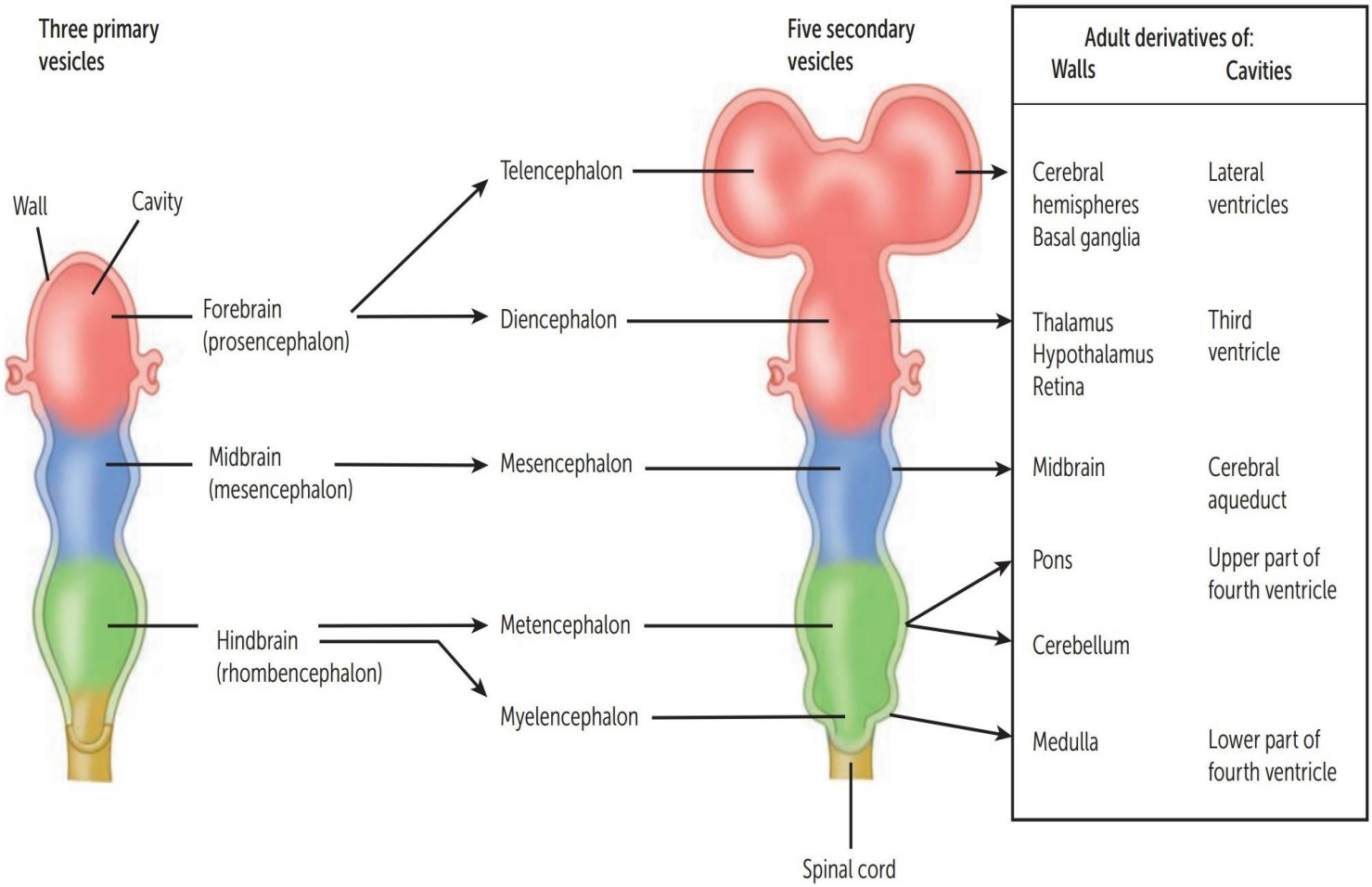


❖ N.B:

- Arnold chiari type 2 and dandy walker may present with noncommunicating hydrocephalus.

Regional specification of developing brain

Telencephalon is the 1st part. Diencephalon is the 2nd part. The rest are arranged alphabetically mesencephalon, metencephalon, myelencephalon.



- I had a question in my exam including this picture, the case was about thalamus, and the question was which secondary vesicle that will develop this part?
  - Answer: Diencephalon.

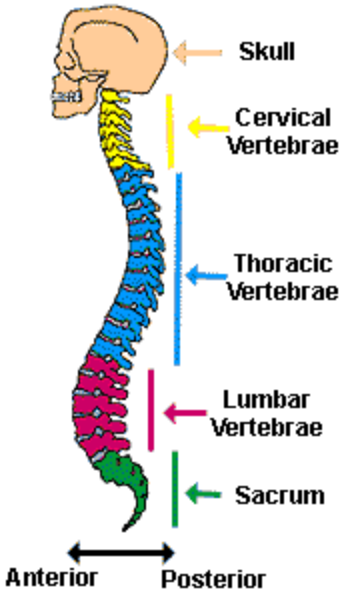
CHAPTER 2

Neuroanatomy

- The central nervous system is formed of 2 main parts:

1) Intracranial part:
a. Cerebral cortex.
b. Brain stem.
c. Cerebellum.

2) Spinal part:
a. Spinal cord.
b. Cauda equina.



A. Spinal cord

- It lies in the vertebral canal and ends at the lower border of 1st lumbar vertebra (the space between L1 & L2).

- It is formed of gray matter (containing the cell bodies of the neurons) surrounded by white matter (containing the axons of the neurons that form the ascending and descending nerve fibers arranged into tracts or fasciculi).

- In a transverse section, the gray matter resembles the letter H or butterfly shape (2 anterior and 2 posterior horns).

Spinal nerves

- There are 31 pairs of spinal nerves arise segmentally from the spinal cord (8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccygeal).

- Each spinal nerve is formed from the combination of nerve fibers from its dorsal and ventral roots (mixed), the dorsal root is the afferent sensory root and carries sensory information to the brain while the ventral root is the efferent motor root and carries motor information from the brain.

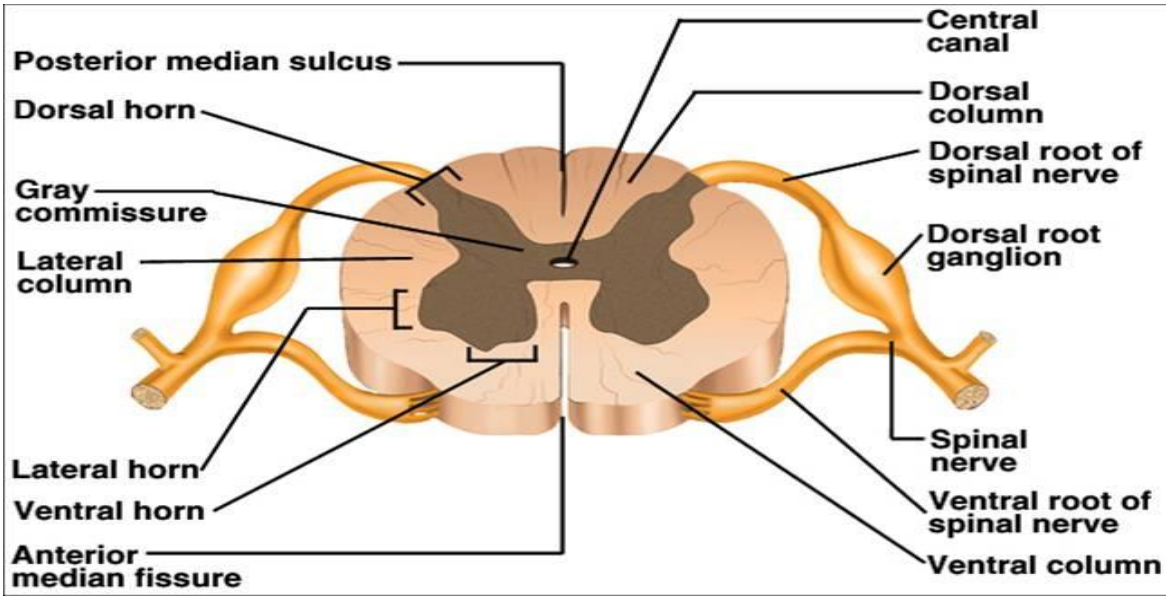
- Areas of spinal cord that innervate limbs ("C5-T1 forming brachial plexus" innervate upper limb and "L2-S2 forming lumbosacral plexus" innervate lower limb) have large ventral horn because there are a lot of skeletal muscles in limbs that need to be innervated by motor neurons in ventral horn.

1. Gray matter (containing the cell bodies of the neurons) is formed of:
   - Dorsal horn (sensory).
   - Ventral horn (motor).
   - Lateral horn (T1-L2) contains preganglionic sympathetic neuron cell.

2. White matter (containing the axons of the neurons that form the ascending and descending nerve fibers arranged into tracts or fasciculi)

5. The dorsal root:
   - The dorsal root is the afferent sensory root and carries sensory information to the brain.

6. The ventral root:
   - The ventral root is the efferent motor root and carries motor information from the brain.



3. Ventral horn:
   - Ventral horn contains cell bodies of motor neurons and the axons of theses neurons form the ventral root.
   - There are two types of motor neurons in ventral horn (alpha motor neuron and gamma motor neuron).
   - Alpha motor neuron makes skeletal muscle contract.
   - N.B: Renshaw cells have feedback inhibition on alpha motor neurons to prevent continuous firing of skeletal muscles → no spasm, that's why when Renshaw cells affected in tetanus by tetanospasmin (neurotoxin) → it causes spasm, lockjaw and opisthotonos (arching of the back due to severe spasm of the back's muscles).

4. Dorsal horn: it receives several types of sensory information from the body, including fine touch, proprioception and vibration. This information is sent from receptors of the skin, bones and joints through sensory neurons (dorsal root) whose cell bodies lie in the dorsal root ganglion.

Motor system

- Voluntary innervation of skeletal muscle:

- For a voluntary muscle to move, it should receive a nerve impulse passing through 2 main neurons:
  1- Upper motor neuron (UMN).

  2- Lower motor neuron (LMN).

1- Upper motor neuron (lateral corticospinal tract, pyramidal tract):

- The voluntary motor impulse originates mainly in the large pyramidal cells (Betz cells) of the motor area (area 4) and to a lesser extend in the cells of the premotor area (area 6).

- The axons of these cells descend in the depth of the cerebral hemisphere in the corona radiata to pass in the internal capsule (genu & posterior limb) and continue their descend in the midbrain, pons and medulla.

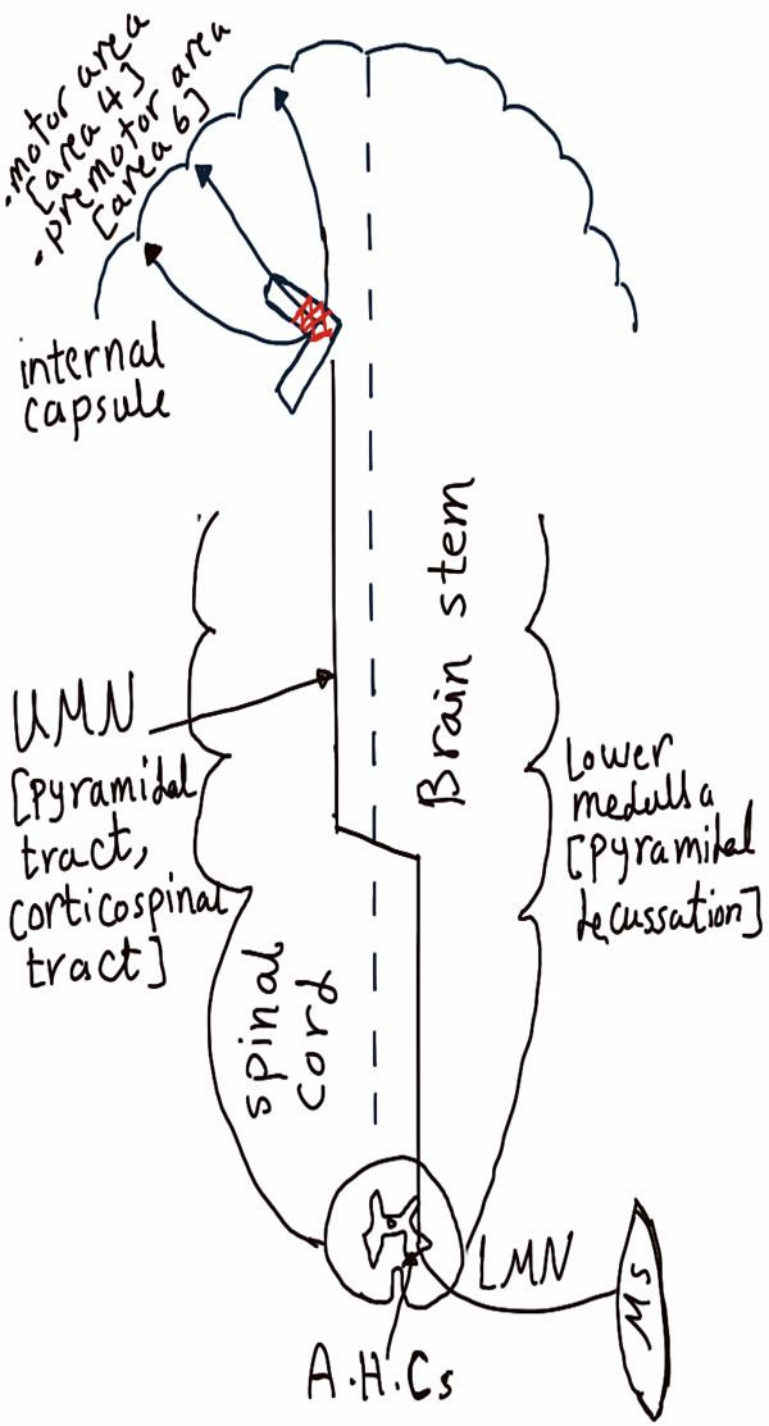
- In the lower medulla, the fibers of corticospinal tract decussate to descend in the white matter of the opposite side of the spinal cord.

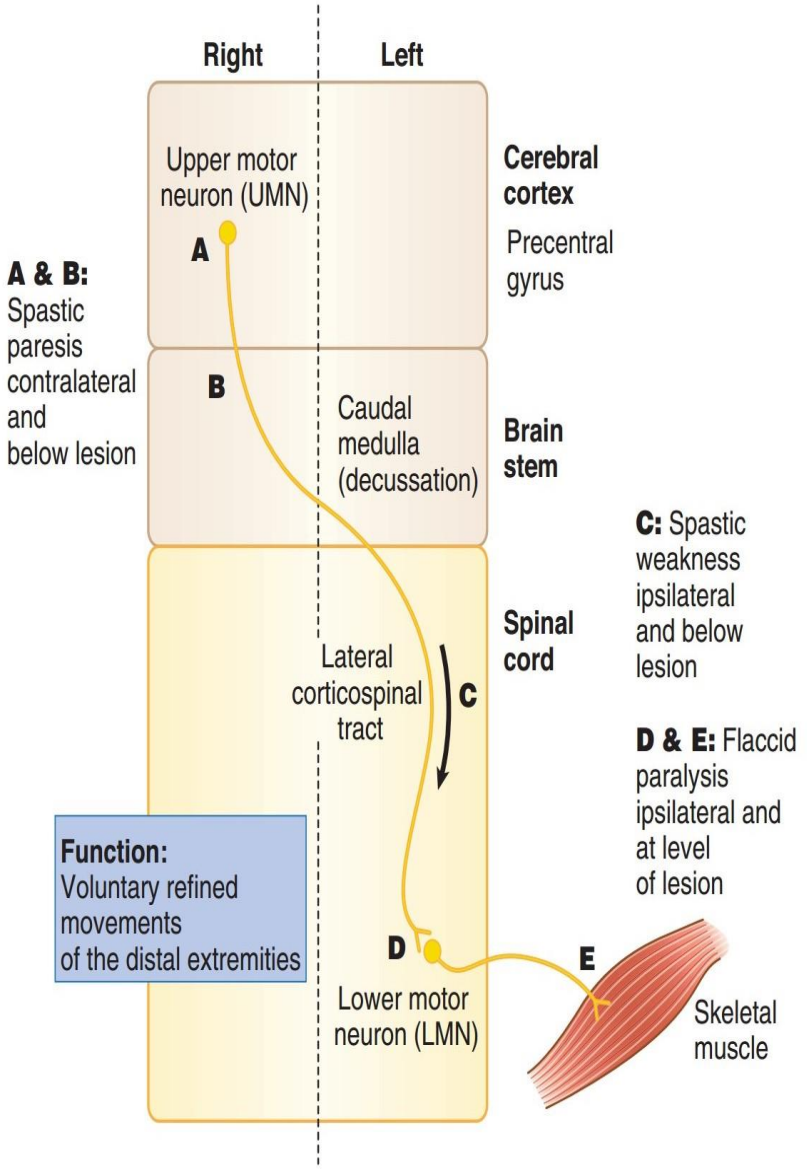
- This pathway starting from the cells of the cortex down to the spinal cord is known as the pyramidal tract or lateral corticospinal tract.

- The corticospinal tract descends the full length of the brain stem in the lateral part of the white matter and as it descends, axons leave the tract and enter the gray matter of the ventral horn to synapse on lower motor neuron.

- The fibers of the pyramidal tract terminate at different levels of the AHCs of the spinal cord.

- In the brain stem, some of the descending pyramidal fibers separate to supply the motor nuclei of the cranial nerves of both sides except the lower 1/2 of the facial nucleus & the hypoglossal nucleus which are supplied only from the contralateral pyramidal tract, these fibers are known as corticobulbar as they don't reach the spinal cord.





UMN (Pyramidal Tract)

2- Lower motor neuron (LMN):

- AHCs: they are a special type of nerve cells situated in the anterior horns of the H shaped grey matter of the spinal cord. They receive the voluntary motor impulse from the pyramidal tract. Their axons exit from the spinal cord as the anterior roots.

- NB: The motor nuclei of the cranial nerves are similar in function to the AHCs as they form the cell bodies of the LMN of the cranial nerves, thus lesion of a cranial nerve nuclei, like lesion of an AHC is a LMN lesion.

- Peripheral motor nerve: carrying the motor impulse from AHCs to the voluntary muscle.

▪ Lesions of UMN (corticospinal tract):

- Above the pyramidal decussation → weakness is seen in muscles on the contralateral side of the body below the level of the lesion.

- Below the pyramidal decussation → ipsilateral muscle weakness below the level of the lesion.

- UMNL always below the level due to deprivation of LMN below the level of the lesion from UMN innervation.

▪ Lesions of LMN:

- A lesion to any part of a lower motor neuron will result in an ipsilateral muscle weakness at the level of the lesion.

▪ Any lesion of the motor system (either UMN or LMN) in spinal cord will result in ipsilateral muscle weakness (LMN at the level, UMN below the level).

▪ Muscle tone:

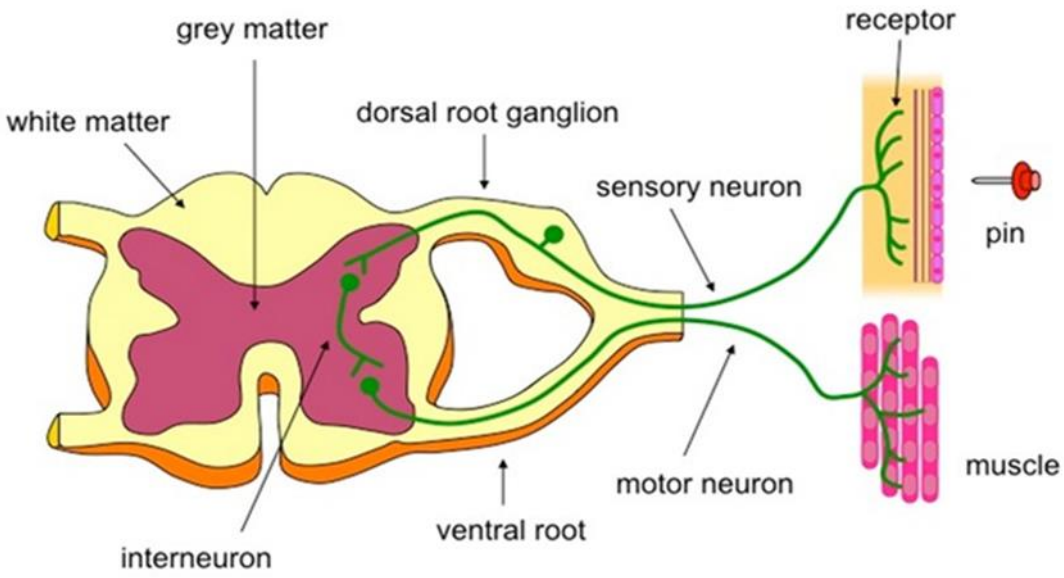
- This is a spontaneous local axon stretch reflex.

- The length of any skeletal muscle is shorter than the distance between its origin & insertion, this puts the muscle in a state of constant slight stretch.

- The stretch stimulates some muscle spindles which send excitatory impulses through the afferent sensory nerve & the dorsal root to the AHCs.

- The excited AHCs send motor impulses through the anterior root & the efferent motor nerve to the muscle.

- This result in continuous reflex sub-tetanic contraction of the muscle, this constitutes the muscle tone which is important for the nourishment of the muscles & the posture of the body.



- The muscle tone receives higher control, mainly inhibitory, through the pyramidal & extrapyramidal systems, therefore:
  - Loss of inhibition of the intact reflex arc leading to increased muscle tone (hypertonia) below the level of the lesion with no wasting of the muscle.
  - Hypertonia in pyramidal tract lesion (UMNL) is called spasticity, but hypertonia in extrapyramidal lesion (basal ganglia lesion) is called rigidity (we will talk about it later in parkinsonism).
  - Interruption of the reflex arc due to LMNL leading to decreased muscle tone (flaccidity) at the level of the lesion, with wasting of the muscles.

Reflex innervation of skeletal muscle:

- This is an induced local axon stretch reflex.
- It is induced by tapping the tendon of the muscle with a hammer. This tap stretches the muscle with synchronous stimulation of all muscle spindles (sensory receptor in skeletal muscle stretch reflexes) & the activation of the local axon reflex (as in muscle tone), resulting in a brief contraction of the muscle.
- The pyramidal system also exerts an inhibitory effect on this stretch reflex, therefore:

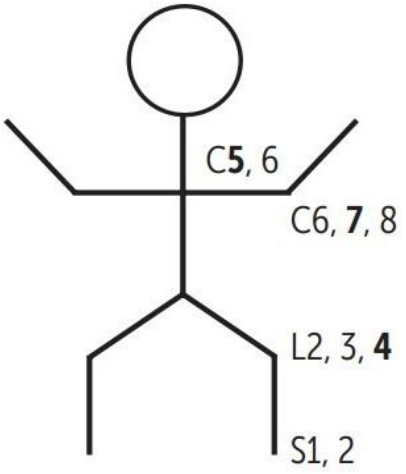
A. UMNL: results in exaggeration of deep reflexes (hyperreflexia) below the level of the lesion.

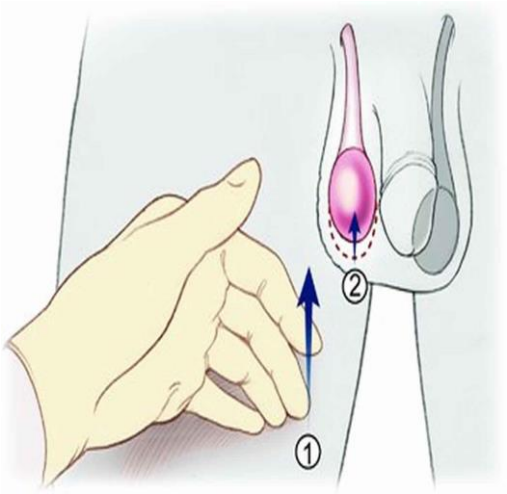
B. LMNL: results in diminution of deep reflexes (hyporeflexia) at the level of the lesion.

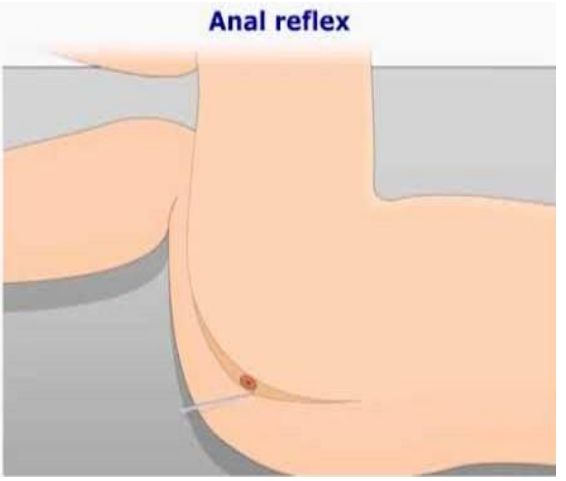
Clinical reflexes:

- Afferent limb: muscle sensory neuron (muscle spindle).
- Efferent limb: lower motor neuron.

- Examples:
  - Achilles reflex → S1, S2.
  - Patellar reflex → L2-L4.
  - Biceps and brachioradialis reflexes → C5, C6.
  - Triceps reflex → C6, C7, C8.
  - Cremasteric reflex → L1, L2.
  - Anal wink reflex (the reflexive contraction of the external anal sphincter upon stroking of the skin around the anus) → S3, S4.







GRADING OF REFLEXES

Grade	Reflexes	What it means
0	Absent	Lower motor neuron lesion
1+	Present but depressed	Normal but may indicate neuropathy
2+	Present / brisk	Normal
3+	Very brisk or increased	Maybe normal but may indicate UMN lesion
4+	Clonus	UMN lesion

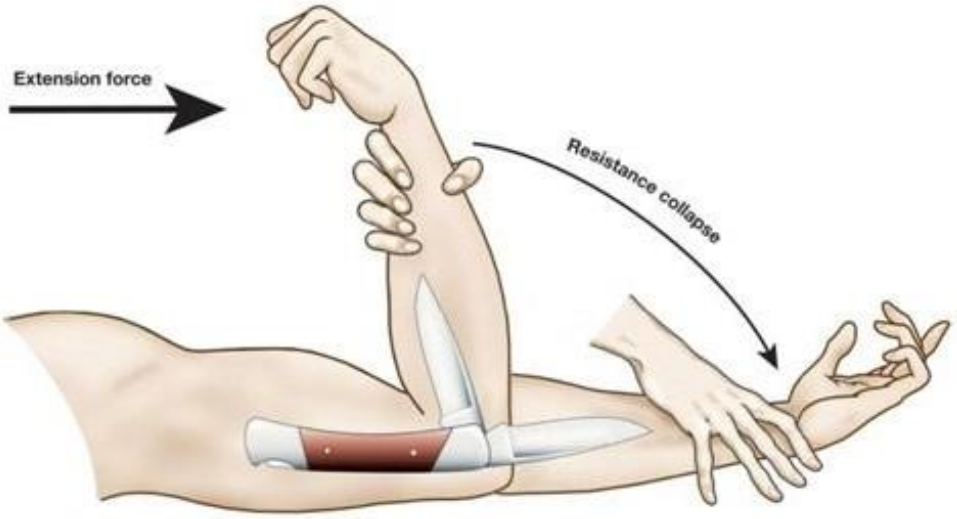
- A lesion to either an upper or a lower motor neuron produces weakness in the ability to voluntarily contract skeletal muscles, so how can you distinguish between these two lesions?

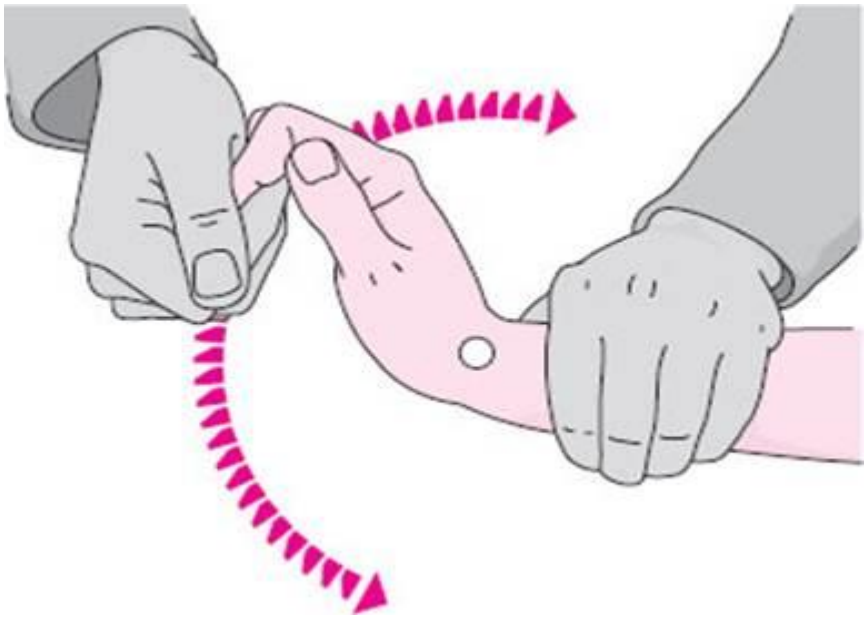
Upper motor neuron lesion (UMNL)

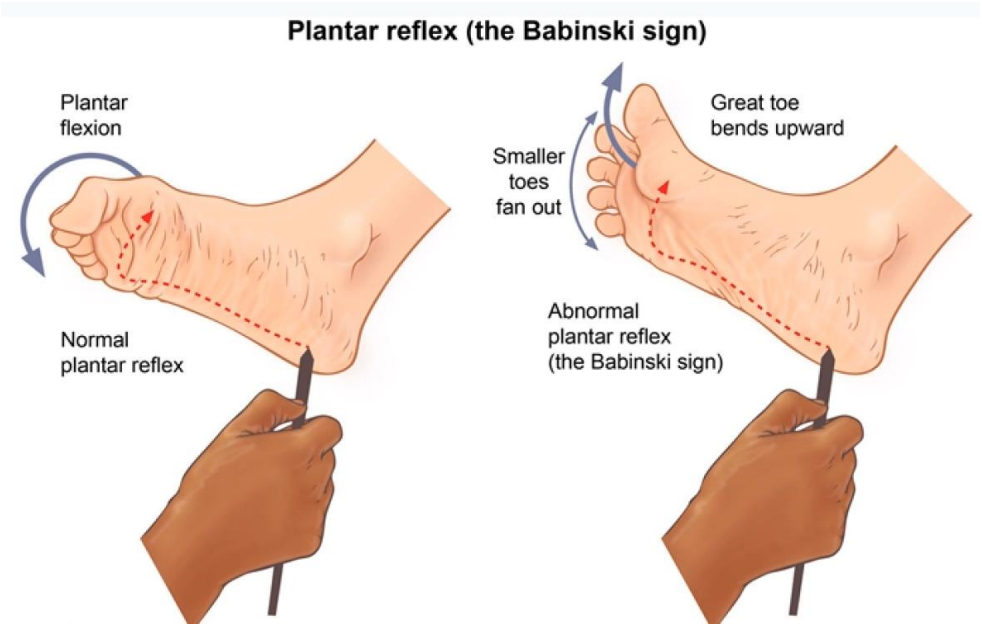
1. Spastic paralysis or weakness (clasp knife spasticity, initial resistance to passive extension followed by sudden release of resistance).
2. Hyperreflexia (brisk DTRs), why spastic and hyperreflexia? Because UMN has a net overall inhibitory effect on muscle stretch reflex (which is responsible for muscle tone and deep reflexes), so in UMNL there is hypertonia (spasticity, clasp knife type) and hyperreflexia.
3. No muscle wasting & if present it is late due to disuse atrophy.
4. Absent fasciculation.
5. + Babinski sign (dorsiflexion of the big toe and fanning of the other toes). Babinski (planter) reflex is a primitive reflex in infants, normally disappear within 1st year of life, so the presence of this reflex in adults signify a UMNL.
6. UMNL will result in spastic paralysis that may be ipsilateral (anywhere in the spinal cord will result in an ipsilateral lesion) or contralateral (anywhere above the decussation of the pyramids will result in contralateral lesion)
7. UMNL always below the level due to deprivation of LMN below the level of the lesion from UMN innervation.

Lower motor neuron lesion (LMNL)

1. Flaccid paralysis or weakness.
2. Hypo or areflexia, why flaccid and areflexia?? Because LMN form the efferent (motor) component of the stretch reflex (which is responsible for muscle tone and deep reflexes), so in LMNL there is hypotonia (flaccidity) and areflexia.
3. Early and marked muscle wasting due to loss of muscle tone.
4. Fasciculation (twitches or contractions of groups of muscle fibers that may produce a twitch visible on the skin) may be present due to irritation of AHCs.
5. Normal planter response.
6. LMNL will result in flaccid paralysis that is always ipsilateral (no crossing) and at the level of the lesion only (because the LMN at other different levels are intact).


Extension force
Resistance collapse




Plantar reflex (the Babinski sign)
Plantar flexion
Normal plantar reflex
Smaller toes fan out
Great toe bends upward
Abnormal plantar reflex (the Babinski sign)

B. Sensory system

- All somatic sensation passes through 3 order neurons from sensory receptors to reach the cortical sensory area of the opposite side:

- The cell bodies of 1st order neuron is always in the dorsal root ganglion.

- The cell of 2nd order neuron varies according to the type of sensation. The axons of the 2nd neuron crosses in the midline and is carried in a tract in the CNS.

- The cell of 3rd order neuron is the thalamus of the opposite side. The axons of the 3rd neuron project to primary somatosensory cortex.

1. Dorsal column – medial lemniscal pathway:

- Carries sensory information for fine touch, proprioception (joint position sensation), vibratory and pressure sensation.

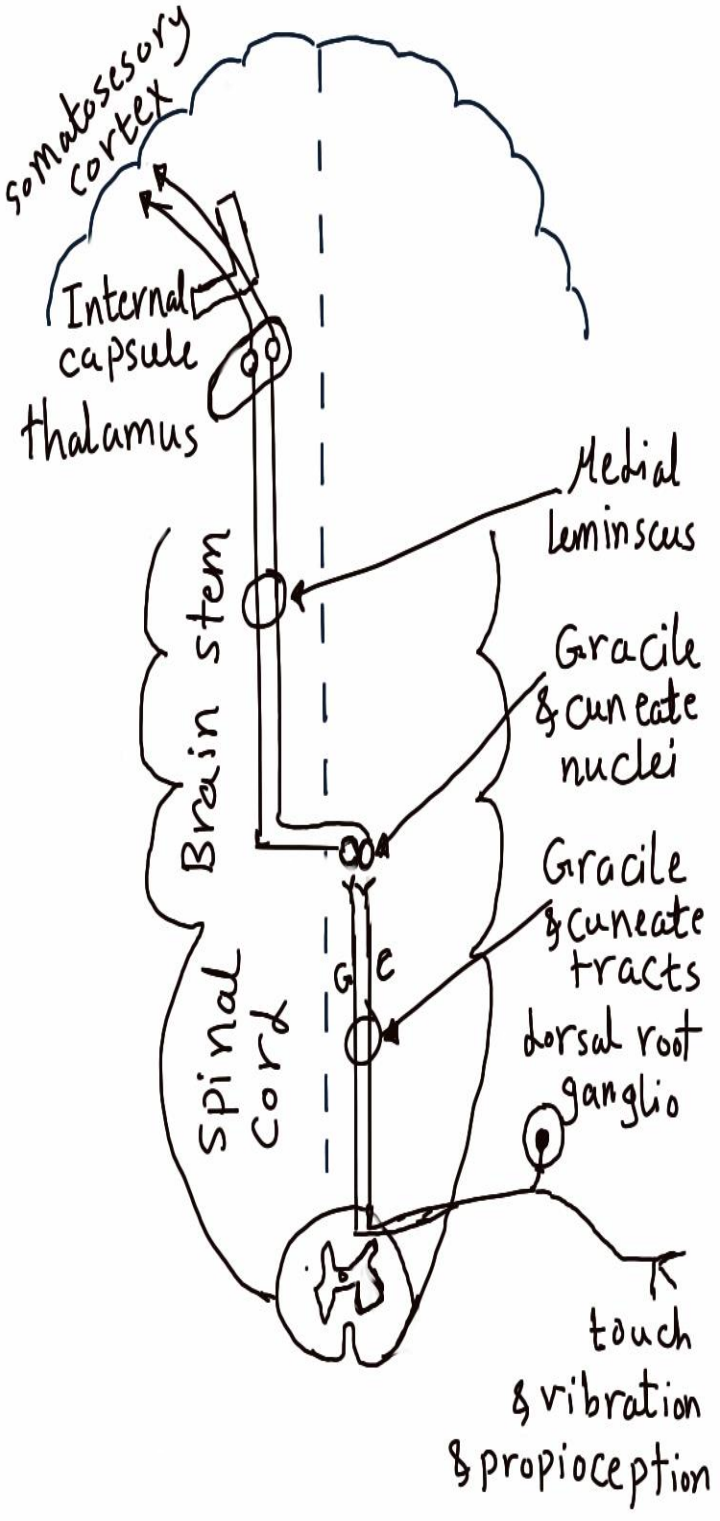
- The 1st order neuron: is the cell of the dorsal root ganglion which enter the spinal cord through dorsal root fibers, then the axons of the 1st order neuron ascend in the gracile & cuneate tracts within the dorsal column of the same side to relay in the gracile & cuneate nuclei in the medulla:

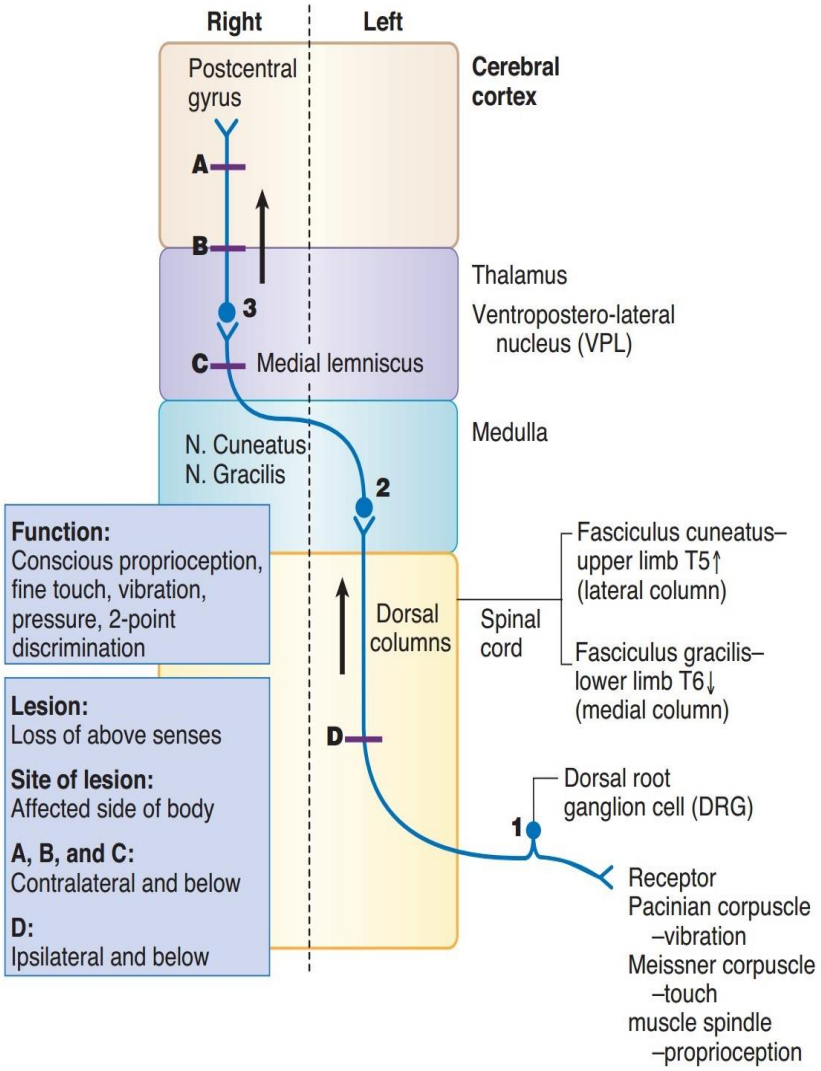
- Gracile tract: carries fibers from lower 1/2 of body and lies medially (Below T7).
- Cuneate tract: carries fibers from upper 1/2 of body and lies laterally (Above T7).

- The 2nd order neuron: from the cell of the gracile & cuneate nuclei in the lower medulla, the axons of the 2nd neuron crosses to the opposite side and ascend through the brain stem in the medial lemniscus. Fibers of the medial lemniscus terminate on the cells of the ventral posterolateral (VPL) nucleus of the thalamus.

- The 3rd order neuron: start in the cells of the ventral posterolateral (VPL) nucleus of the thalamus, then its axons pass through the posterior limb of the internal capsule conducting the impulse to the cortical sensory area in the parietal lobe.

- Lesion of the dorsal column - medial lemniscus pathway in any part along the entire length of the spinal cord will result in ipsilateral loss of vibratory and proprioceptive sensation and below the lesion, while lesion in brain stem or above (after the 2nd order neuron crosses) will result in contralateral loss below the level of the lesion.





Dorsal column - Medial Lemniscus Pathway

2. Anterolateral (spinothalamic tract) pathway:

- Lateral spinothalamic → carry pain and temperature sensation.
- Anterior spinothalamic → carry crude touch and pressure sensation.
- The 1st order neuron: is the cell of the dorsal root ganglion which enter the spinal cord through dorsal root fibers, the axons of the 1st order neuron ascend a couple of segments forming Lissauer's tract and relays (synapse) in the dorsal horn of the grey matter.
- The 2nd order neuron: its cell bodies are located in the dorsal horn of the grey matter (spinal cord), the axons of the 2nd neuron crosses to the opposite side through the ventral white commissure just below the central canal of the spinal cord and coalesce to form the spinothalamic tract, the axons ascend the entire length of the spinal cord through spinothalamic tract then in brain stem to terminate on the cells of the ventral posterolateral (VPL) nucleus of the thalamus.
- The 3rd order neuron: start in the cells of the ventral posterolateral (VPL) nucleus of the thalamus, then its axons pass through the posterior limb of the internal capsule conducting the impulse to the cortical sensory area in the parietal lobe.

- Lesions of spinothalamic tract in the spinal cord or brain stem will result in contralateral loss of pain and temperature because the 2nd order neuron crosses almost as soon as it enters the spinal cord.

- After going through all spinal cord neural pathways, you should know:

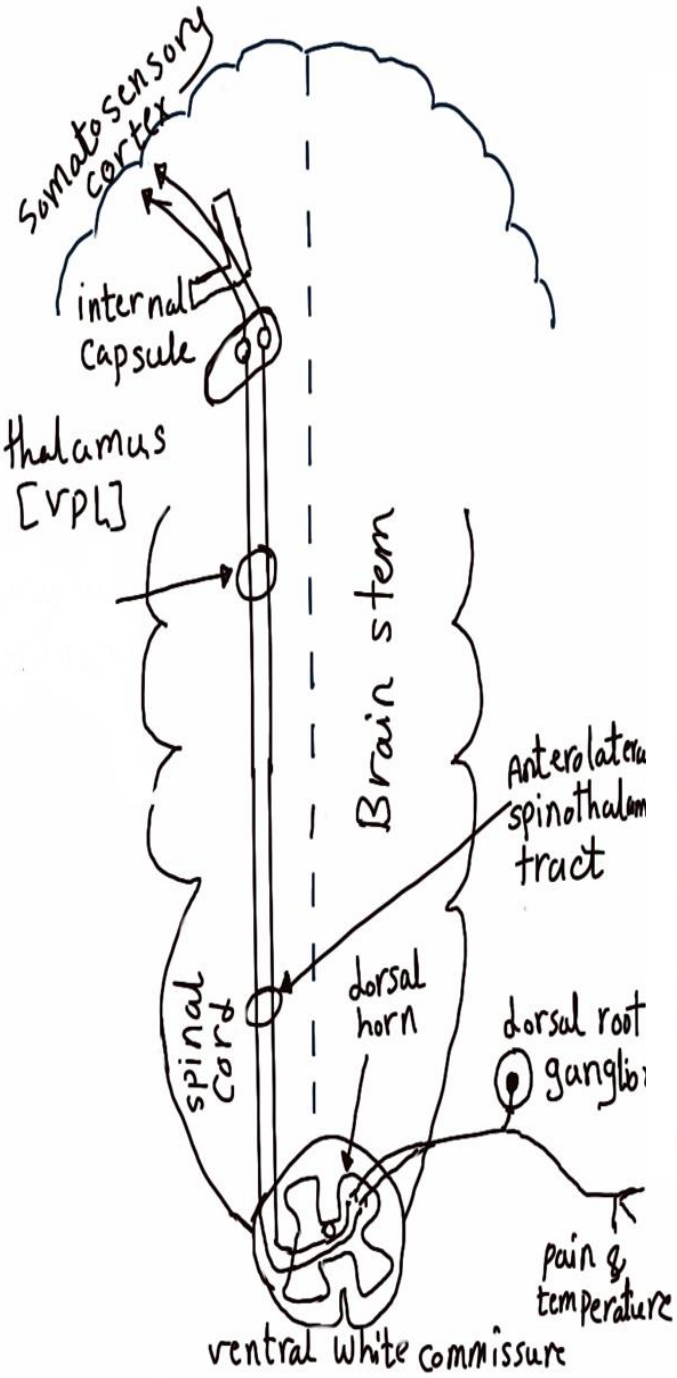
A. Any lesion along the entire length of the spinal cord will result in 2 ipsilateral sign and 1 contralateral sign.

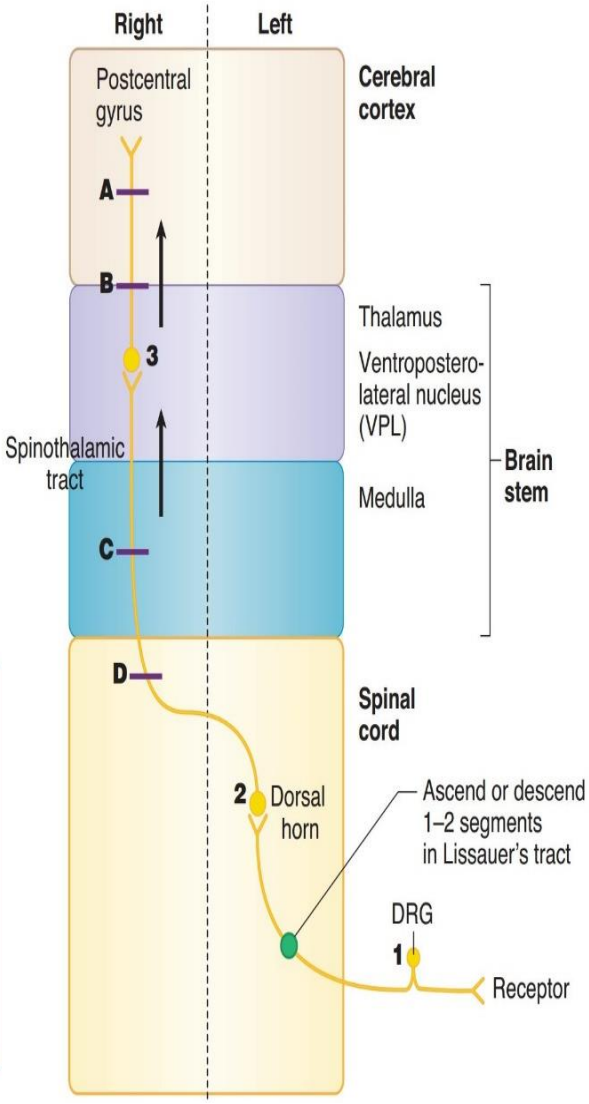
B. 2 ipsilateral:

- Ipsilateral motor signs (UMNL signs below the lesion and LMNL signs at the level of the lesion).
- Ipsilateral loss of vibratory and proprioceptive sensations below the level of the lesion.

C. 1 contralateral:

- Contralateral loss of pain and temperature below the lesion.



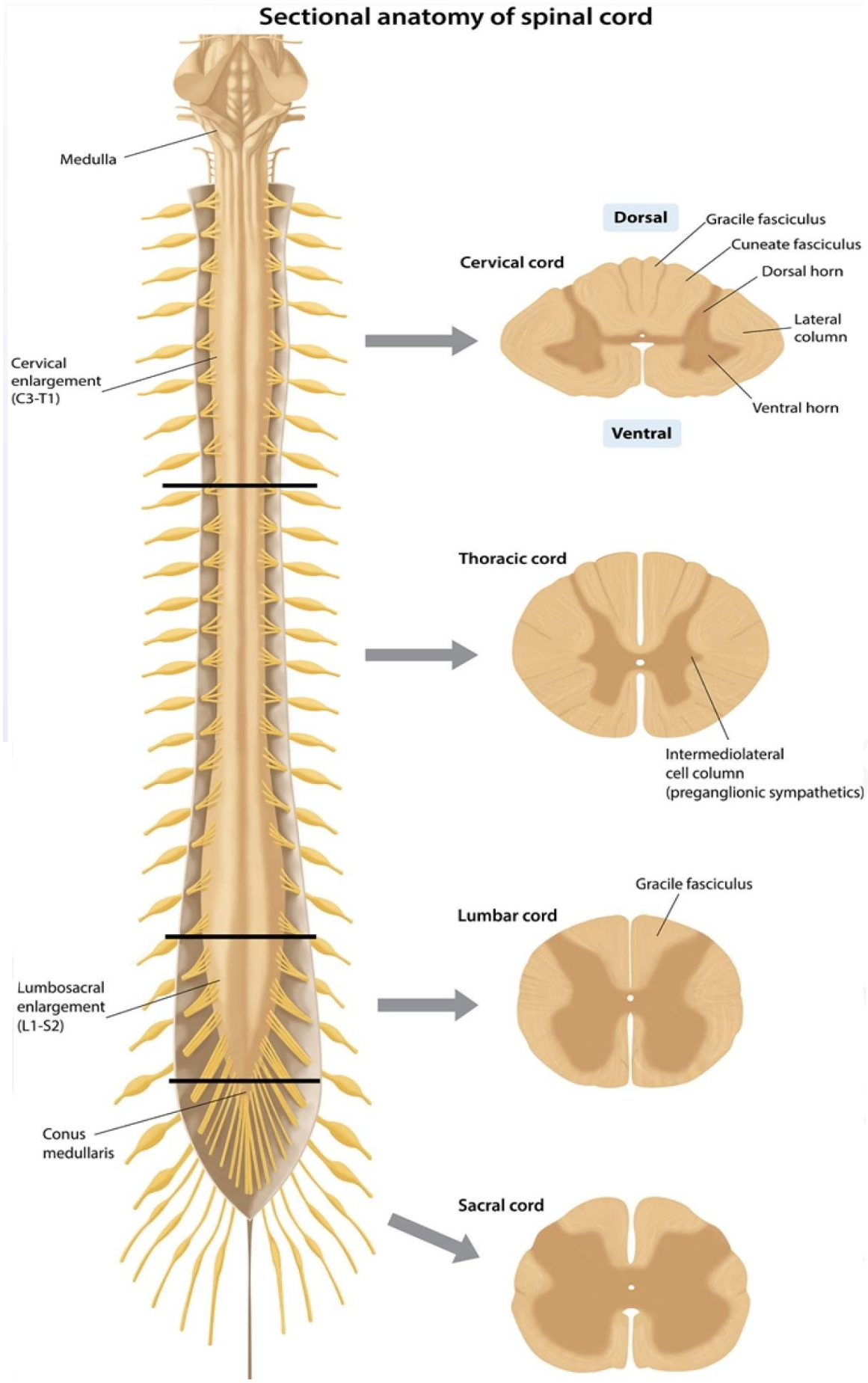


Lesion:
Anesthesia (loss of pain and temperature sensations)

Site of lesion:
Affected side of body

A, B, C, and D:
Contralateral below the lesion; tract intact rostral to the lesion

Spinothalamic Pathway


Sectional anatomy of spinal cord
Medulla
Cervical enlargement (C3-T1)
Lumbosacral enlargement (L1-S2)
Conus medullaris
Cervical cord
Dorsal
Gracile fasciculus
Cuneate fasciculus
Dorsal horn
Lateral column
Ventral horn
Ventral
Thoracic cord
Intermediolateral cell column (preganglionic sympathetics)
Lumbar cord
Gracile fasciculus
Sacral cord

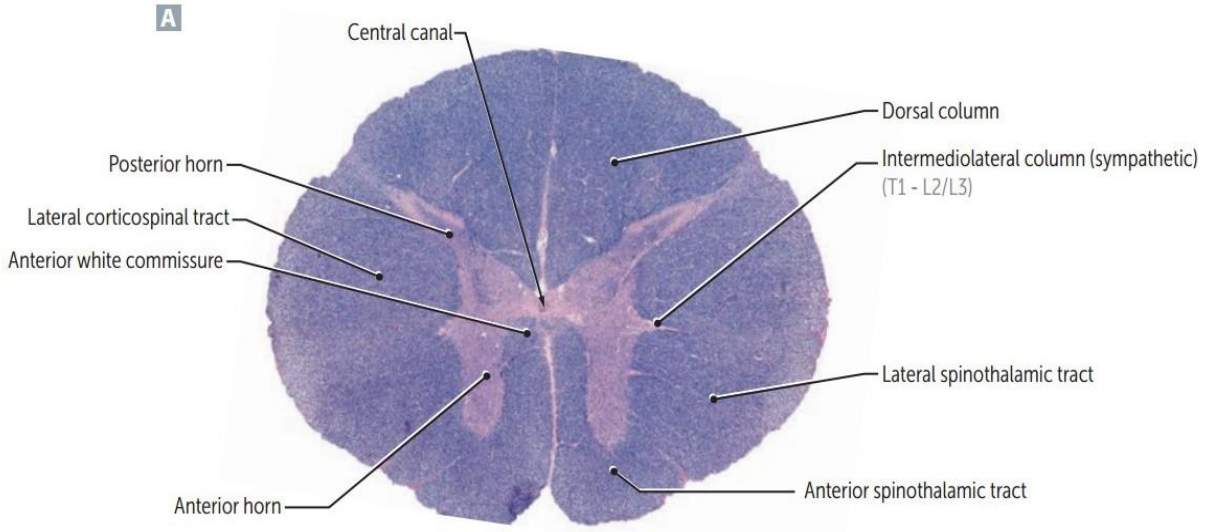
Sectional anatomy of the spinal cord

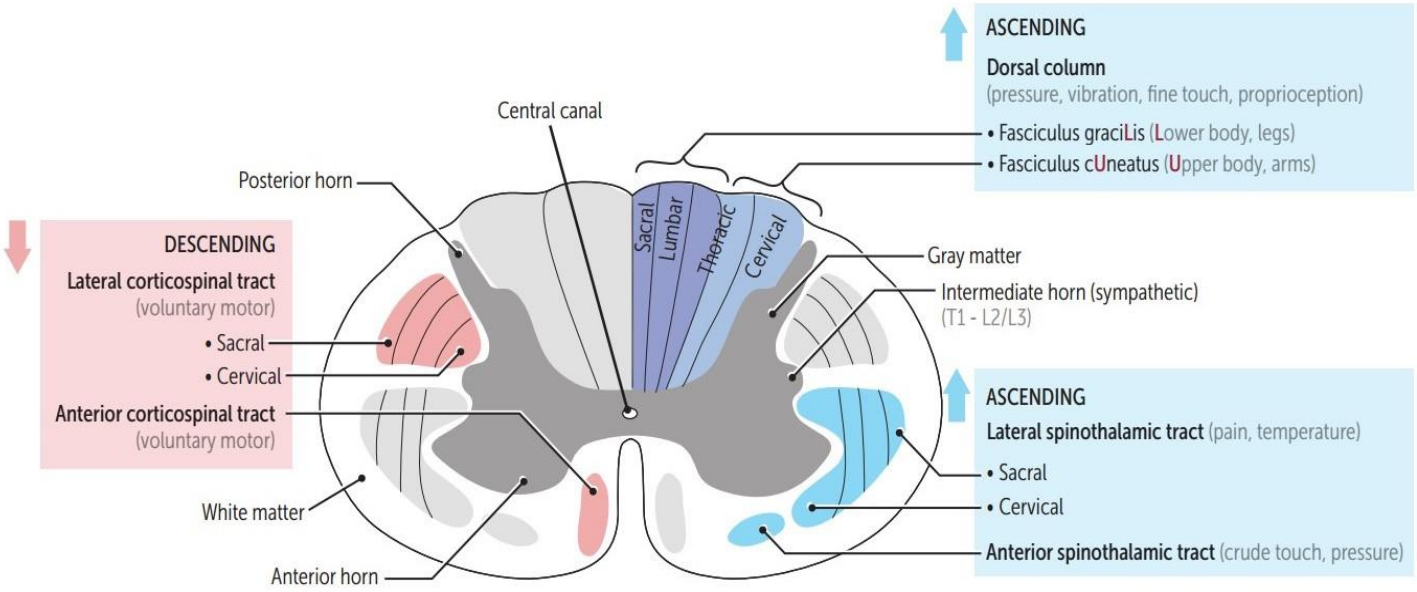
- General features that aid in localizing a transverse spinal cord section include:

1. Moving rostrally, spinal levels have increasing amounts of white matter, decreasing amounts of gray matter, and are more oval-shaped.
2. Lower cervical ($C_5 – T_1$) and lumbosacral regions ($L_2 – S_2$) have large ventral horns as these areas innervate the muscles of the arms and legs, respectively.
3. Thoracic and early lumbar sections contain lateral gray matter horns (intermediolateral cell columns), which are made up of sympathetic preganglionic neurons.
4. Gracile and cuneate fasciculi are present above the T7 spinal level, whereas only the gracile fasciculus is present below this level.

Spinal cord and associated tracts

Legs (Lumbosacral) are Lateral in Lateral corticospinal, spinothalamic tracts. Thoracic spinal cord section in A.
Dorsal columns are organized as you are, with hands at sides. "Arms outside, legs inside."





Oculosympathatic pathway

- Oculosympathatic pathway is like any sensory pathway has 3 order neurons:

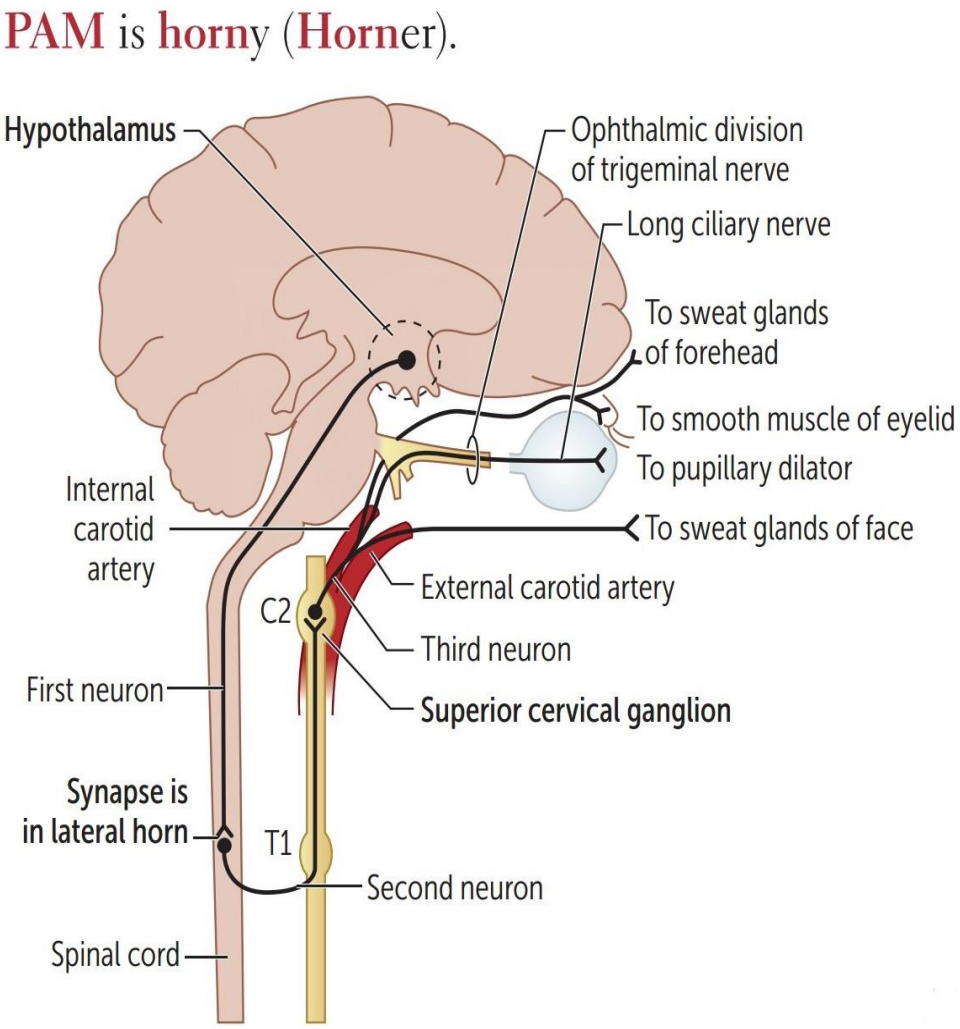
- 1st order neuron: descending hypothalamic fibers, its axons project to the spinal cord to relay in the lateral horn of T1 segment of the spinal cord.

- 2nd order neuron: lateral horn of T1 segment of the spinal cord, its axons project to superior cervical ganglion.

- 3rd order neuron: superior cervical ganglion, its axons (postganglionic fibers):
  - Travel along the internal carotid artery to the orbit and innervate the dilator pupillae muscle → mydriasis, and the superior tarsal muscle within the upper eyelid → elevation of the upper eyelid.

  - Some postganglionic sympathetic fibers travel along the external carotid artery are responsible for facial sweating.

- Any interruption of this pathway leads to ipsilateral Horner's syndrome (Horner's syndrome is always ipsilateral).



- Horner's syndrome is classically characterized by the presence of ipsilateral:

1. Ptosis (drooping of upper eyelid): due to denervation of the sympathetically controlled muller muscle of the upper eyelid.

2. Anhydrosis (impaired sweating): due to loss of sympathetic innervation of the facial sweat gland.

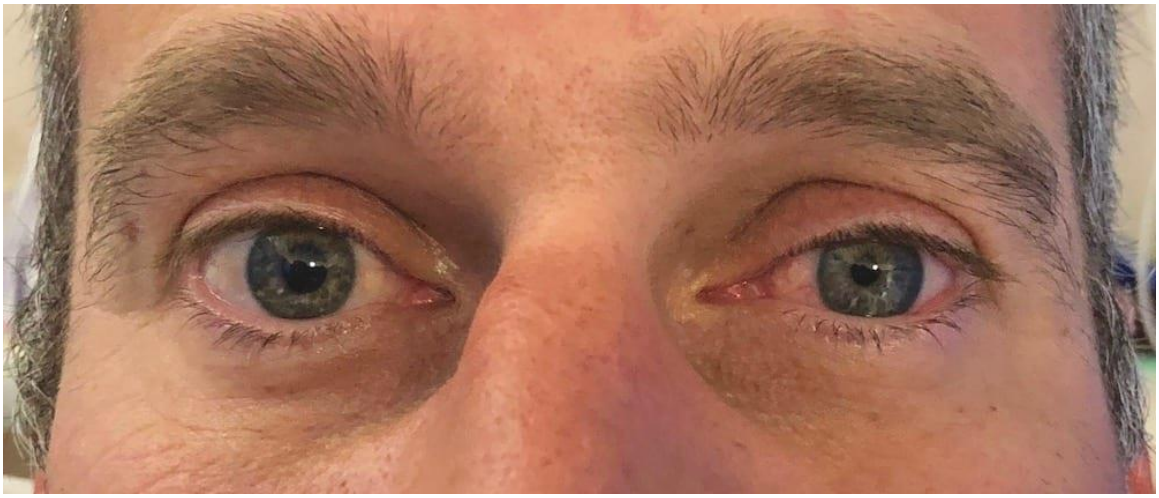
3. Miosis (constricted pupil): because of interruption of the sympathetic fibers to the dilator pupillae muscle, which leads to unopposed parasympathetic action.

- Associated with lesions along the sympathetic chain:

- 1st neuron: pontine hemorrhage, lateral medullary syndrome, spinal cord lesion above T1 (Brown-Séquard syndrome, late-stage syringomyelia)

- 2nd neuron: stellate ganglion compression by Pancoast tumor.

- 3rd neuron: carotid dissection (painful)



Spinal cord lesions

- Any lesion of spinal cord will present with ipsilateral signs except spinothalamic tract lesion that will present with contralateral loss of pain and temperature.

1- Brown sequard syndrome:

- Cause:

- Hemisection of the spinal cord, most probably due to tumor compressing on one side of spinal cord.

- Findings:

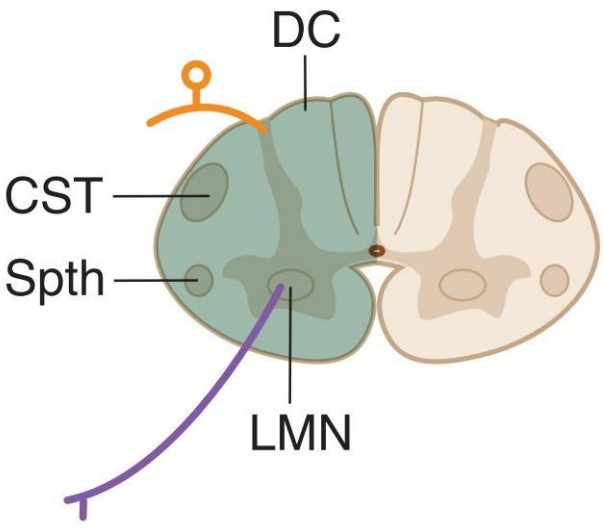
A. At the level of the lesion:

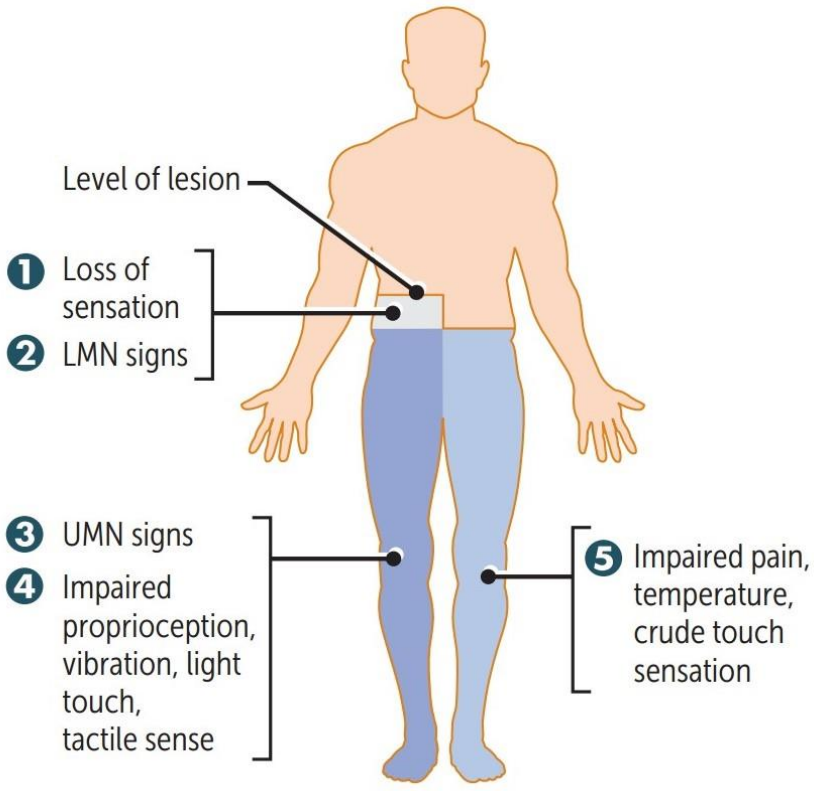
1- Ipsilateral localized LMNL of the muscles supplied by the affected segment.
2- Ipsilateral loss of all sensations in the area supplied by the dorsal roots of the affected segment.

B. Below the level of the lesion:

1- Ipsilateral UMN signs below level of lesion (due to corticospinal tract lesion).
2- Ipsilateral loss of tactile, vibration, proprioception sense below level of lesion (due to dorsal column damage).
3- Contralateral pain and temperature loss below level of lesion (due to spinothalamic tract damage).

C. If the lesion occurs above T_1, patient may present with ipsilateral Horner syndrome due to lesion of oculosympathatic pathway.





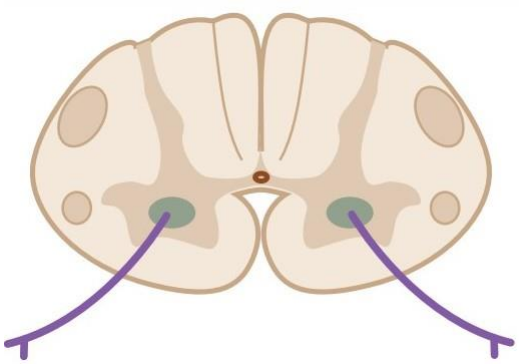
2- Poliomyelitis:

- Cause:

- Acquired disease Caused by poliovirus (Enterovirus, feco-oral transmission) → replicate in oropharynx and small intestine → blood stream → CNS.
- Poliovirus causes selective bilateral destruction of LMN in the ventral horn (irreversible, but in Guillain–Barré there is only demyelination, so it's reversible)

- Findings:

- LMNL signs: Flaccid paralysis, hypotonia, hyporeflexia, fasciculation, muscle atrophy. Respiratory muscle involvement leads to respiratory failure.
- Signs of infection: Malaise, headache, fever, nausea.
- CSF finding: ++ WBCs, slight + of protein with no change in glucose level.



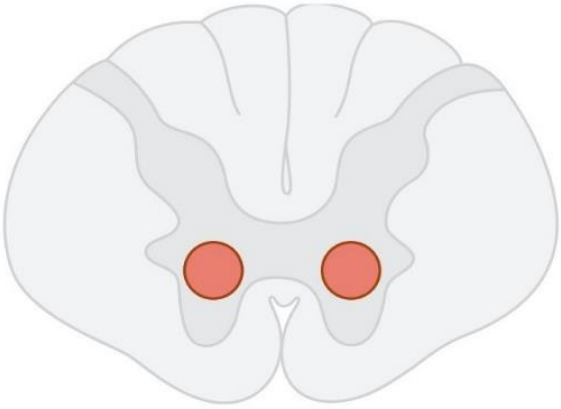
3- Spinal muscular atrophy (Werding – Hoffman disease):

- Cause:

- Autosomal recessive disease.
- Congenital degeneration of anterior horns of spinal cord.
- Infantile poliomyelitis (floppy baby).

- Findings:

- LMNL signs.
- Median age of death of 7 months.



4- Tabes dorsalis:

- Cause:

- Late stage manifestation of neurosyphilis (3ry syphilis, syphilis is a spirochetal infection)
- It's caused by bilateral degeneration of the dorsal roots and dorsal column.
- Common at lumbar cord level.

- Findings:

- It's common at lumbar cord level, so the most common tract to be affected in dorsal column is gracilis fasciculus that carry proprioception from lower limbs → altered sensation of vibratory sense and proprioception (inability of the cortex to sense or feel the legs in space).

- Degeneration of dorsal root → sensory ataxia (inability of the cerebellum to sense or feel the legs due to deprivation of cerebellum from its proprioceptive input because dorsal roots send axons to Clark's nucleus of spinocerebellar pathway) → wide based gait.

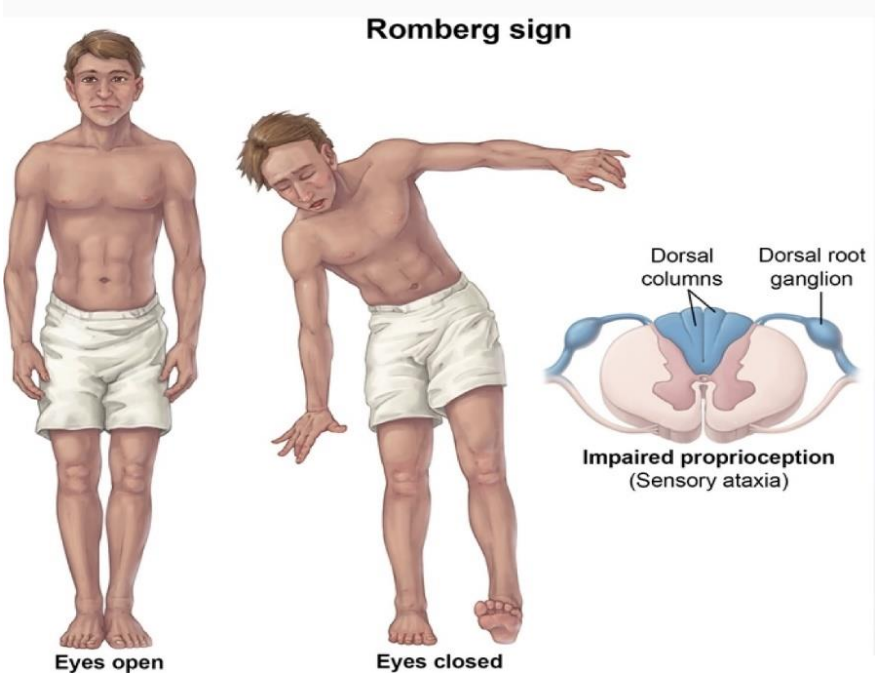
- + Romberg sign:
  - Tested by asking the patient to place his feet together, if the patient can keep his balance with eyes open but sways with the eye closed → + Romberg sign.
  - He keeps his balance with eyes open because interruption of proprioceptive input carried by dorsal column can be compensated by visual input to cerebellum (sensory ataxia), therefore if the patient has balance problems and tend to sway with eyes open, this is indicative of cerebellar damage (cerebellar ataxia).

- Shooting pain that may last minutes or hours (due to demyelinated pain & temperature dorsal roots).

- Absence of DTRs (Deep tendon reflexes) due to demyelination of dorsal roots which are the afferent fibers of the muscle stretch reflex).

- Argyll Robertson pupil:
  - Bilateral small pupils that reduce in size when the patient focuses on a near object (they accommodate), but do not constrict when exposed to bright light (they do not react to light) due to demyelination of pretectal area in midbrain (initiate pupillary light reflex).
  - Accommodate but doesn't react "prostitute's pupil ".

- Charcot joint:
  - A progressive degenerative disease of the joints caused by nerve damage resulting in the loss of ability to feel pain in the joint and instability of the joint.
  - Loss of the protective sensation of pain is what leads to the disintegration of the joint and often leads to deformity in the joint.



5- Amyotrophic lateral sclerosis (lou Gehrig's disease):

- Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease.

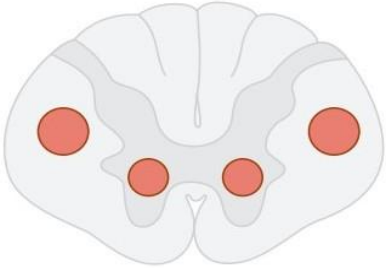
- The disease manifests in middle-aged people and has a progressive course.

- Cause & Findings:

- Pure motor system disease that affect both upper and lower motor neuron bilaterally with no sensory deficits.
- Can be caused by defect in superoxide dismutase 1.
- Damage to motor neurons of the anterior horns → LMN lesion, and demyelination of the corticospinal tracts → UMN lesion). The result is denervation atrophy of the muscles (amyotrophy).
- No sensory or bowel/bladder deficits.

- Qs. Why there is flaccid paralysis of upper limb and spastic paralysis in lower limb? - Because ALS is more common in cervical cord levels (so the patient will present with LMNL signs at the level of the lesion → flaccid paralysis of upper limb, and UMNL below the level → spastic paralysis in lower limbs.

- Most patients die within 5 years of diagnosis. Respiratory complications (such as aspiration pneumonia) are the most common cause of death. Riluzole treatment modestly increase survival by decreasing glutamate release.



6- Anterior spinal artery (ASA) occlusion:

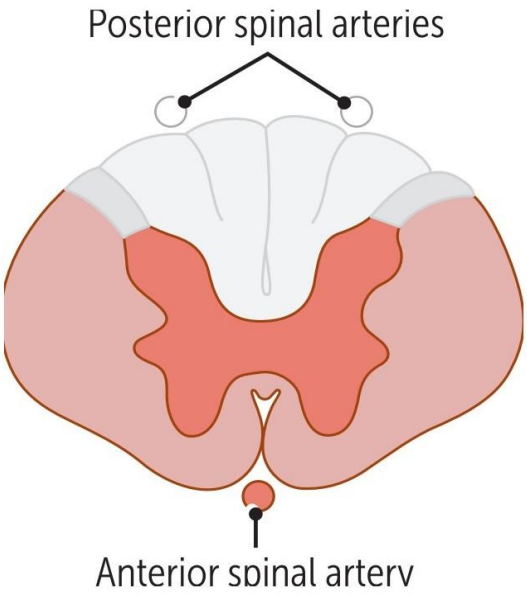
- Cause:

- Occlusion of the ASA interrupts blood supply to the ventrolateral parts of the spinal cord.
- Can be caused by aortic aneurysm repair.

- Findings:

- The same as ALS (bilateral UMN & LMN lesion) but with sensory loss (loss of pain & temperature due to affection of spinothalamic tract).

- Dorsal column is spared (supplied by posterior spinal artery).



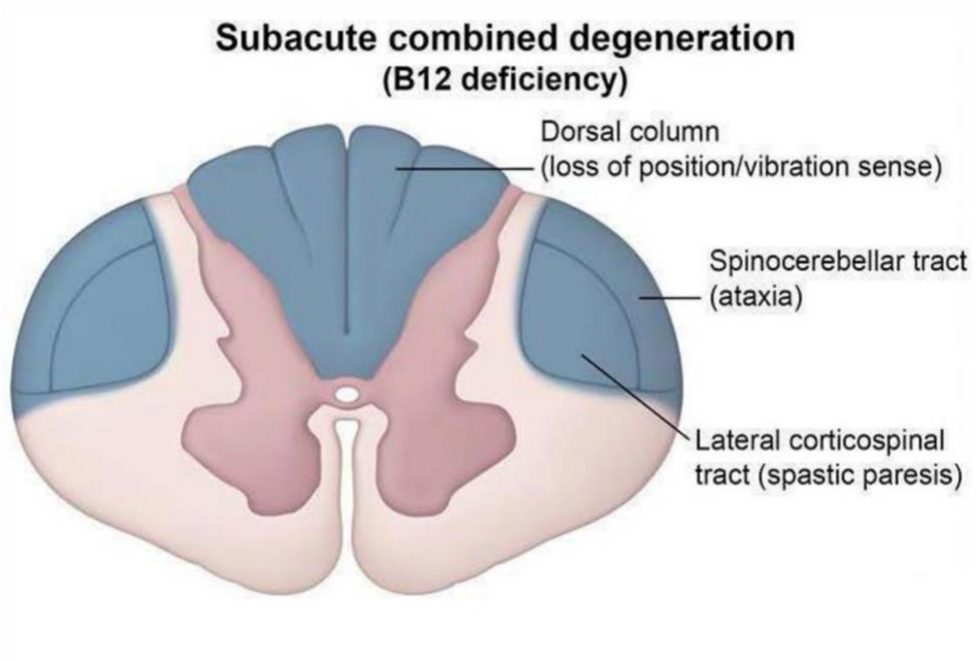
7- Subacute combined degeneration (SCD):

- Cause and findings:

- Combined refers to degeneration of both the ascending (dorsal column) and descending (corticospinal tract) pathway together with peripheral nerves.

- Vitamin B12 deficiency → accumulation of methylmalonic acid (which is toxic to myelin sheath) → patchy demyelination of:
  - Spinocerebellar tracts → Ataxic gait.
  - Corticospinal tract (UMNL Signs).
  - Dorsal columns (impaired vibratory and proprioception sensation).

- Key in the case: megaloblastic anemia + neurological abnormalities = vitamin B12 Deficiency.



8- Syringomyelia:

- Cause and findings:

- Syrinx (cavitation) of the spinal canal that expands and damages anterior white commissure of spinothalamic tract (2nd neuron), usually in the cervical spinal cord → chronic bilateral loss of pain and temperature sensation in cape-like distribution (in the hands and forearm) → dissociated anesthesia (anesthesia of upper limb while lower limb examination is unremarkable).

- Key in the case: frequent burns in both of her hands while cooking or while picking up her cup of tea or coffee.

- Seen with Chiari I malformation.

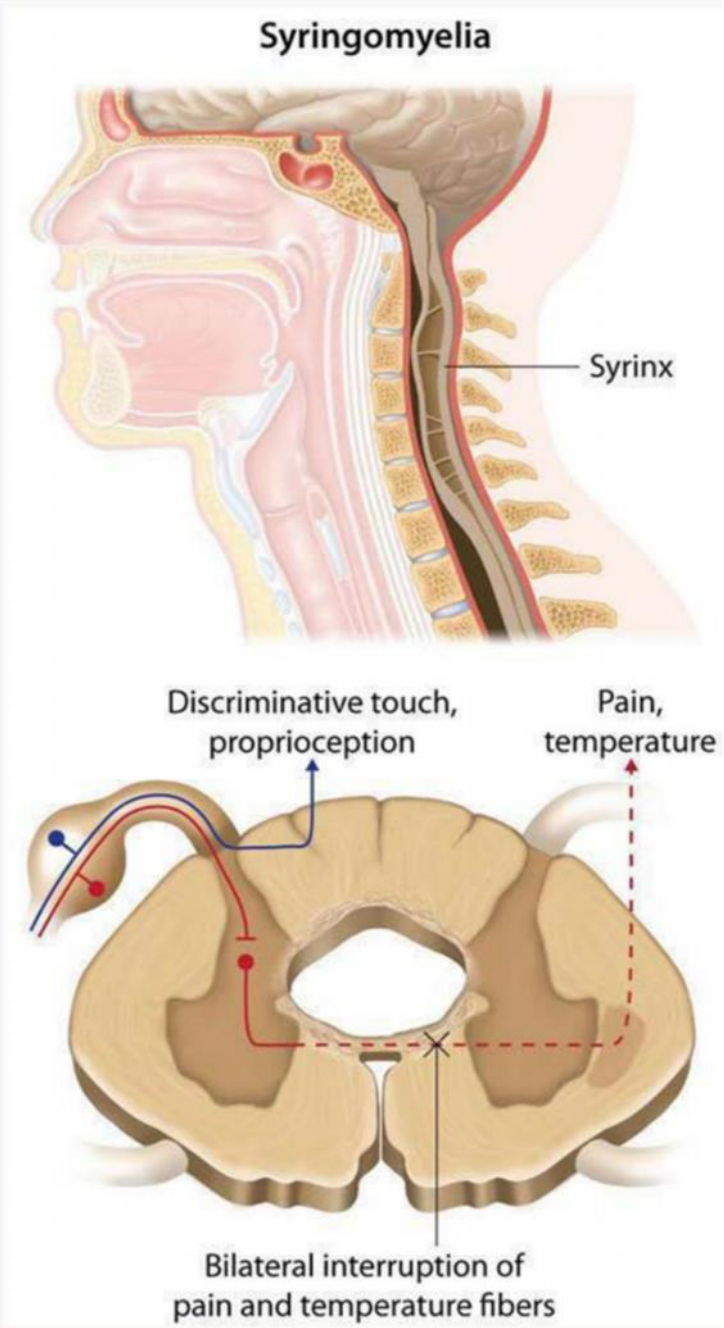
- As the disease progresses, cavitation can expand and affect adjacent portions of spinal cord:

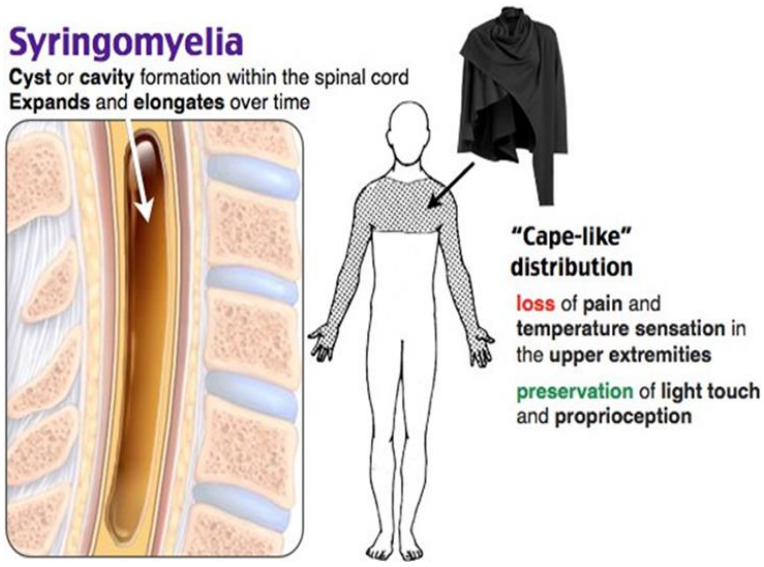
1. Ventral horn cells (LMN) → flaccid paralysis and hyporeflexia of the upper limb muscles.

2. Lateral corticospinal tract (UMN) → spastic paralysis and hyperreflexia of the lower limb (below the level of the lesion).

3. Descending hypothalamic fibers (innervating preganglionic sympathetic neurons) → Horner syndrome (always ipsilateral).

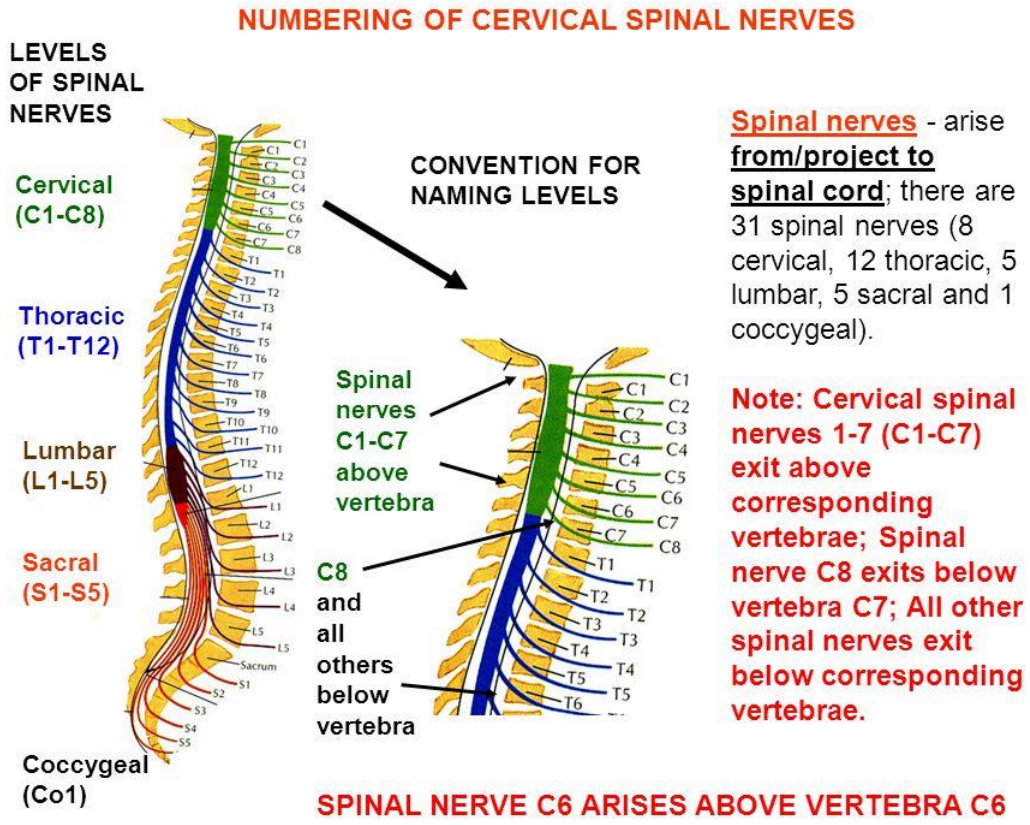
4. Scoliosis can occur due to paresis of paravertebral muscles.


Syringomyelia
Syrinx
Discriminative touch, proprioception
Pain, temperature
Bilateral interruption of pain and temperature fibers


Syringomyelia
Cyst or cavity formation within the spinal cord
Expands and elongates over time
"Cape-like" distribution
loss of pain and temperature sensation in the upper extremities
preservation of light touch and proprioception

B. Cauda Equina

- There are 31 pairs of spinal nerves: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccygeal.
- The vertebral column consists of 33 vertebrae: 7 cervical, 12 thoracic, and 5 lumbar followed by the sacrum (5 fused sacral vertebrae) and the coccyx (4 frequently fused coccygeal vertebrae).
- Nerves C1–C7 exit above the corresponding vertebrae. C8 spinal nerve exits below C7 and above T1. All other nerves exit below (C3 exits above the 3rd cervical vertebra; L2 exits below the 2nd lumbar vertebra).

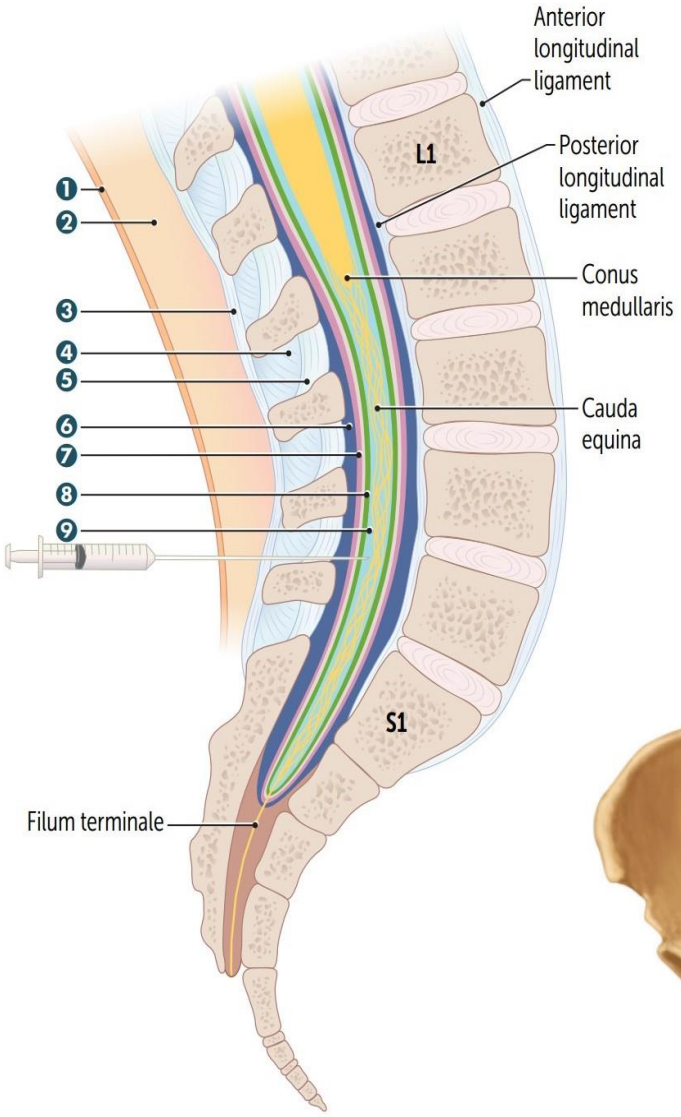


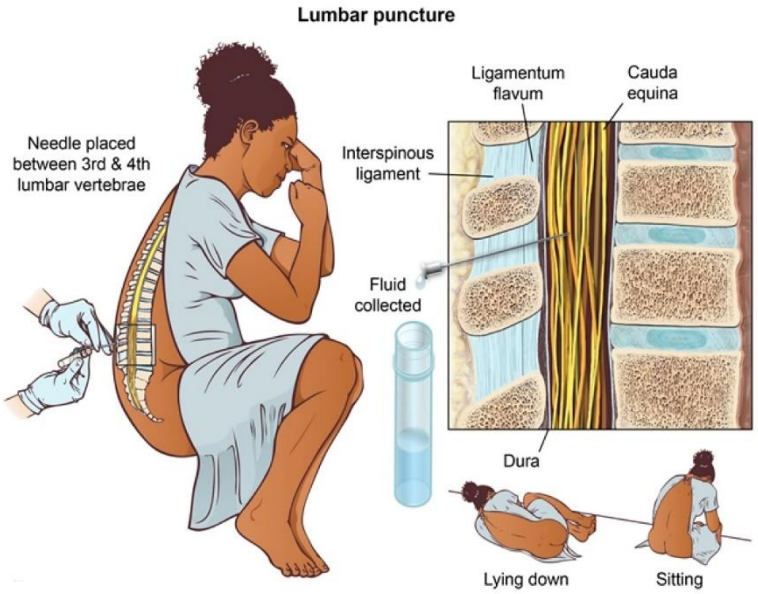
- During intrauterine life, the rate of growth of bones is faster than the rate of growth of the soft tissue, so at birth the vertebral column (bones) is longer than the spinal cord (soft tissue).
- Normally the lower most end of the spinal cord is at the level of the lower border of the first lumbar vertebra or the upper border of the second vertebra (at the junction between the first and second lumbar vertebrae), that's why lumbar puncture (done to obtain a sample of CSF) is usually performed between L3,4 OR L4,5) to avoid injury of the spinal cord.
- Goal of lumbar puncture is to obtain sample of CSF without damaging spinal cord. To keep the cord alive, keep the spinal needle between L3 and L5.

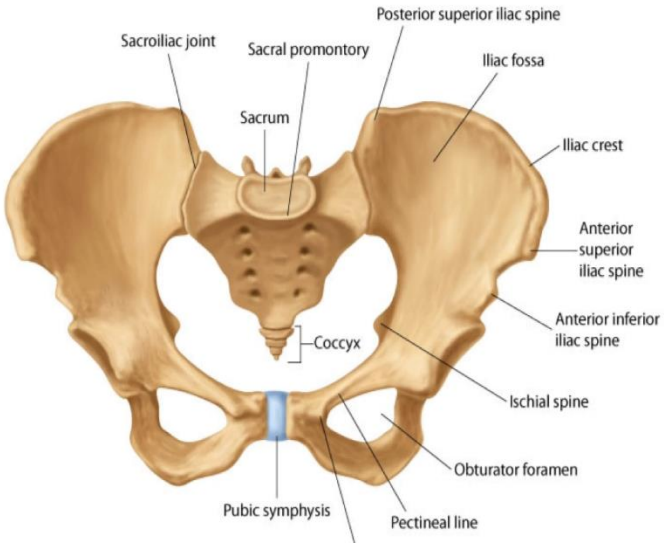
- The L4 vertebral body lies on a line drawn between the highest points of the iliac crests, which can be visually identified and confirmed by palpation.

- <u>Needle passes through:</u>

1. Skin.
2. Fascia and fat.
3. Supraspinous ligament.
4. Interspinous ligament.
5. Ligamentum flavum.
6. Epidural space (epidural anesthesia needle stops here).
7. Dura mater.
8. Arachnoid mater.
9. Subarachnoid space (CSF collection occurs here).







- From the endpoint of spinal cord downwards, the spinal canal is not empty, it is filled by the collection of the lumbosacral roots which descend in this space to escape through their corresponding intervertebral foramina (horse tail).

- This collection of lumbosacral roots in the lower part of vertebral canal is known anatomically as the Cauda Equina. The lowermost three segments of the spinal cord (S3,4,5) are known anatomically as the Conus Medullaris. The above four segments (L4,5 & S1,2) are known anatomically as the Epiconus.

- So, the Cauda Equina consists of nerve roots while the conus and epiconus form part of the spinal cord.

Cauda Equina Syndrome

- Causes:

- Compression of the spinal nerve roots of the Cauda Equina by:

1. Tumors (primary or secondary).

2. Disk herniation.

3. Pott's disease of lumbar vertebrae.

- Findings:

- The Cauda Equina nerve roots provide the sensory and motor innervation of most of the lower back, lower extremities, the pelvic floor and the sphincters, so, its compression will result in:

1- Motor manifestation:

- Motor weakness or paralysis of one or both lower limb of LMN nature and the weakness will affect the muscles supplied by the affected root.

- Loss of ankle reflex (affected S1)

- Loss of ano-cutaneous reflex (affected S3,4).

2- Sensory manifestation:

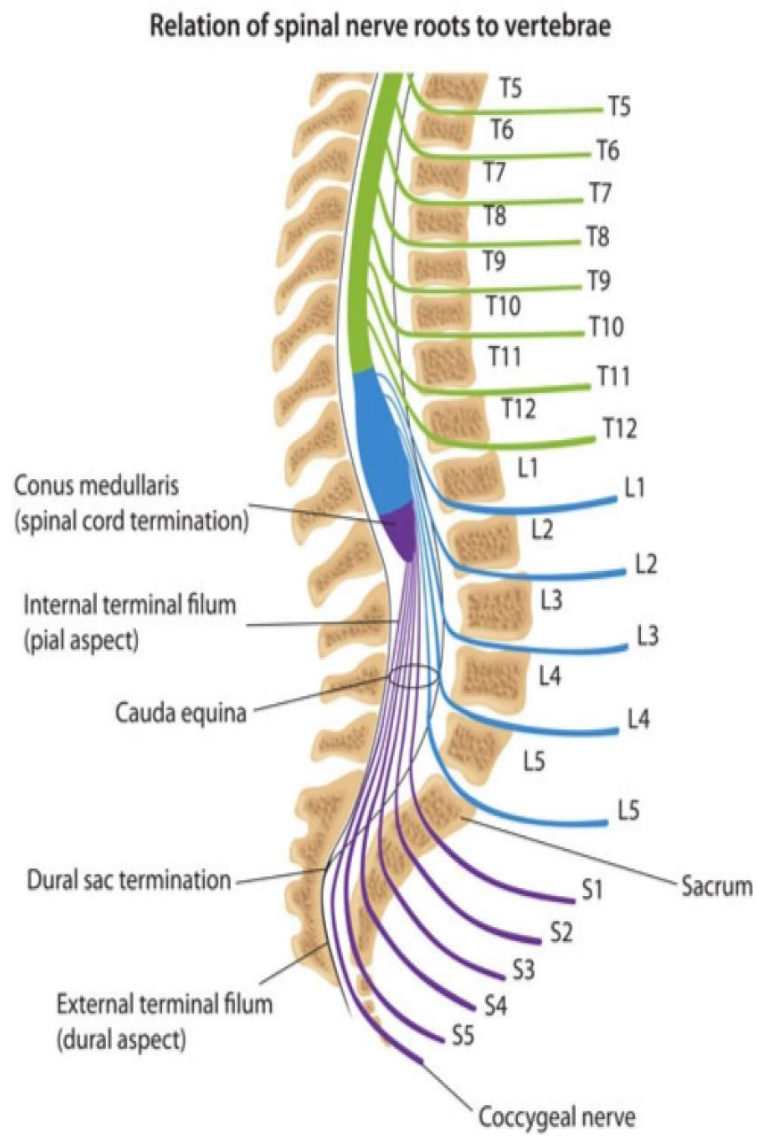
- Radicular pain radiating to one or both legs according to the affected root.

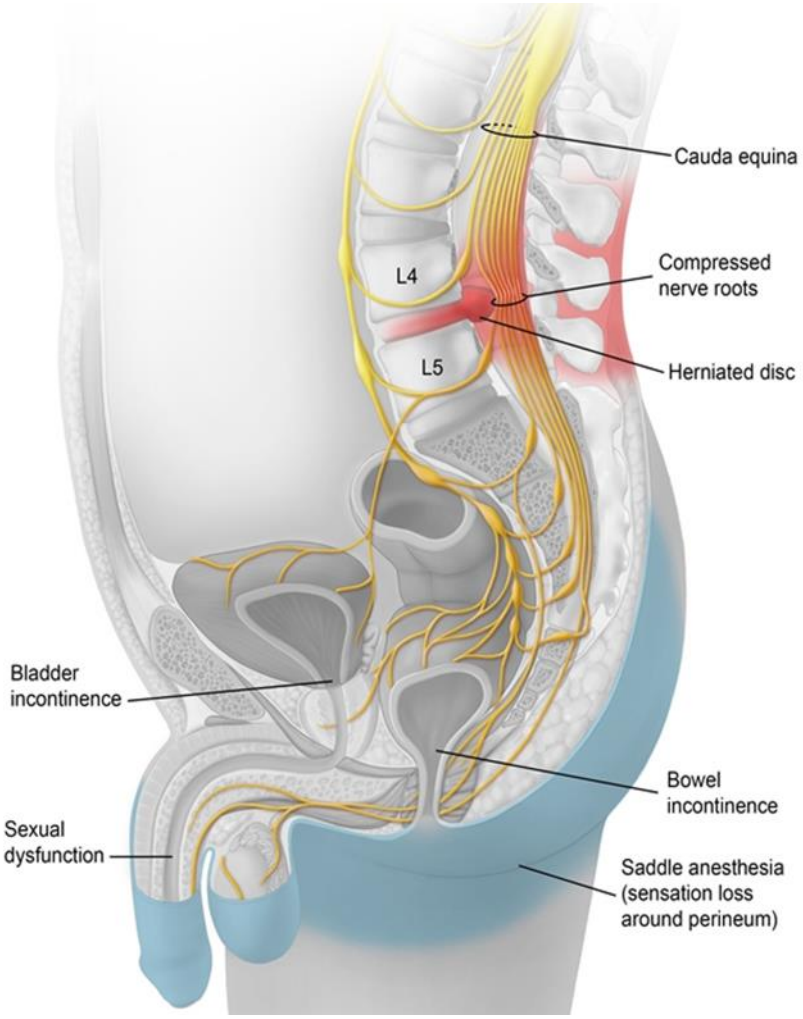
- Saddle anesthesia: Lesion involving S2,3,4 → impairment of pudendal nerve that innervate the perineum → Saddle Anesthesia.

3- Autonomic manifestation:

- Bowl, bladder sphincteric, and sexual dysfunction due to affection of S2,3,4 (Roots of innervation of the sphincters).

- SO, affection of S2,3,4 nerve roots will result in loss of ano-cutaneous reflex, saddle anesthesia, bowl and bladder sphincteric dysfunction which are characteristic for Cauda Equina syndrome.

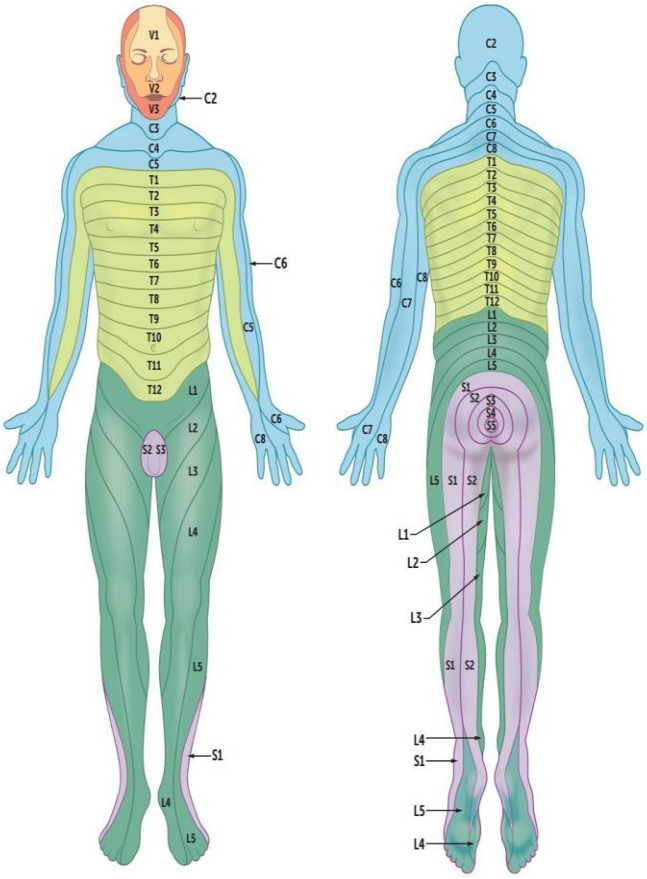

Relation of spinal nerve roots to vertebrae
T5
T6
T7
T8
T9
T10
T11
T12
L1
L2
L3
L4
L5
S1
S2
S3
S4
S5
Conus medullaris
(spinal cord termination)
Internal terminal filum
(pial aspect)
Cauda equina
Dural sac termination
External terminal filum
(dural aspect)
Sacrum
Coccygeal nerve


Cauda equina
L4
Compressed
nerve roots
L5
Herniated disc
Bladder
incontinence
Bowel
incontinence
Sexual
dysfunction
Saddle anesthesia
(sensation loss
around perineum)

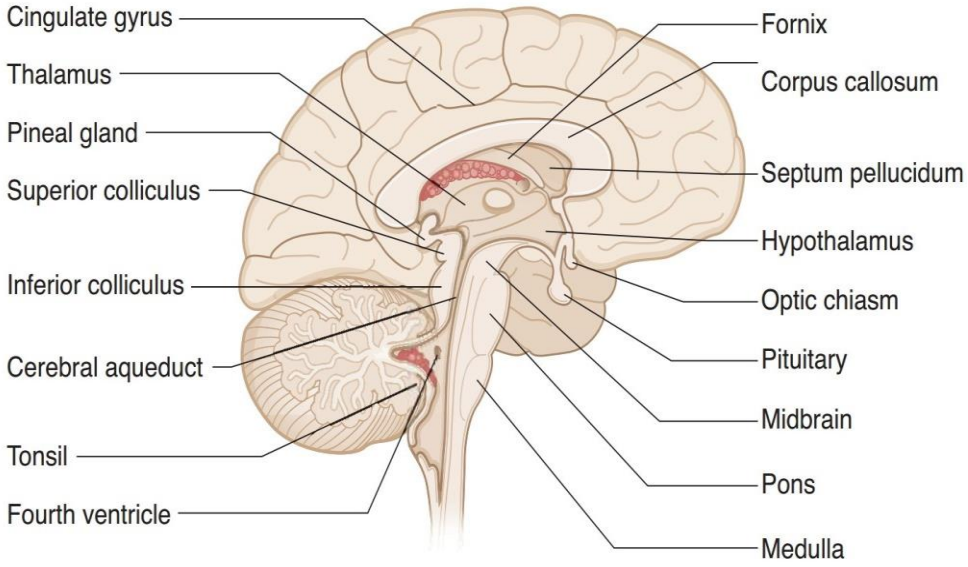
- Dermatomes: an area of skin supplied by sensory neurons from a single spinal cord level (may be distributed to more than one spinal cord level).

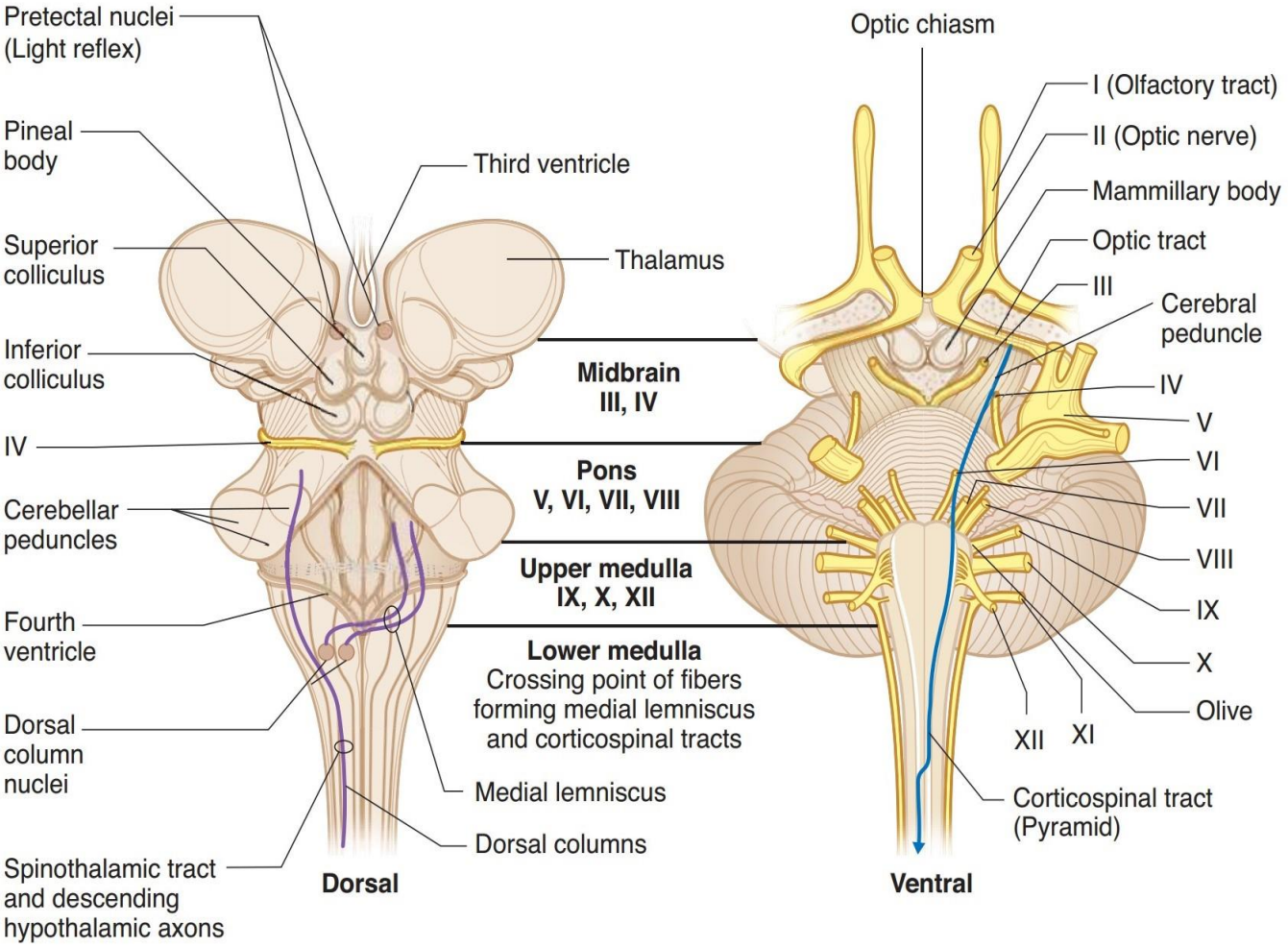
Landmark dermatomes

DERMATOME	CHARACTERISTICS
C2	Posterior half of skull
C3	High turtleneck shirt Diaphragm and gallbladder pain referred to the right shoulder via phrenic nerve C3, 4, 5 keeps the diaphragm alive
C4	Low-collar shirt
C6	Includes thumbs Thumbs up sign on left hand looks like a 6
T4	At the nipple T4 at the teat pore
T7	At the xiphoid process 7 letters in xiphoid
T10	At the umbilicus (belly butten) Point of referred pain in early appendicitis
L1	At the Inguinal Ligament
L4	Includes the kneecaps Down on ALL 4's
S2, S3, S4	Sensation of penile and anal zones S2, 3, 4 keep the penis off the floor



Brain stem


Cingulate gyrus
Thalamus
Pineal gland
Superior colliculus
Inferior colliculus
Cerebral aqueduct
Tonsil
Fourth ventricle
Fornix
Corpus callosum
Septum pellucidum
Hypothalamus
Optic chiasm
Pituitary
Midbrain
Pons
Medulla


Pretectal nuclei (Light reflex)
Pineal body
Superior colliculus
Inferior colliculus
IV
Cerebellar peduncles
Fourth ventricle
Dorsal column nuclei
Spinothalamic tract and descending hypothalamic axons
Third ventricle
Thalamus
Midbrain III, IV
Pons V, VI, VII, VIII
Upper medulla IX, X, XII
Lower medulla
Crossing point of fibers forming medial lemniscus and corticospinal tracts
Medial lemniscus
Dorsal columns
Dorsal
Optic chiasm
I (Olfactory tract)
II (Optic nerve)
Mammillary body
Optic tract
III
Cerebral peduncle
IV
V
VI
VII
VIII
IX
X
Olive
XII
XI
Corticospinal tract (Pyramid)
Ventral

- Brain stem is formed of:

1. Midbrain.
2. Pons.
3. Medulla.

- Course of neural systems in brain stem:

1. Pyramidal system:

- Lesion of Corticospinal tract (pyramidal tract) in brain stem will results in contralateral spastic weakness or paralysis below the level of the lesion (crosses at lower medulla).

2. Dorsal column - medial lemniscus pathway:

- Lesion of medial lemniscus anywhere in the brain stem will result in contralateral loss of vibratory and proprioceptive sensation below the level of the lesion (crosses at lower medulla).

3. Spinothalamic pathway:

- lesion of spinothalamic tract anywhere in the brain stem will result in contralateral loss of pain and temperature below the level of the lesion (crosses at anterior white commissure in spinal cord).

- So, any lesion of the neural system in brain stem will result in contralateral signs and symptoms below the level of the lesion.

- In brain stem cut section:

A. Neural system:

1- Corticospinal and corticobulbar tracts are always Medial.

2- Spinothalamic tract and descending hypothalamic fibers are always Lateral.

3- Medial lemniscus changes its position as it goes through brain stem from Medial to Lateral.

❖ N.B:

1. Medial brain stem has a different vascular blood supply from the Lateral part, and this is of clinical importance, because this means corticospinal tract (medial) & spinothalamic tract and descending hypothalamic fibers (lateral) will not be affected together in brain stem vascular occlusion (medial brain stem syndromes or lateral brain stem syndromes).

2. Descending hypothalamic fibers accompany spinothalamic tract in brain stem on their way to synapse with preganglionic sympathetic neurons (lateral horn of T1), So, any lesion of spinothalamic tract may also affect the descending hypothalamic fibers in brain stem → ipsilateral Horner's syndrome (Horner's syndrome is always ipsilateral).

B. Cranial Nerves:

- 9 cranial nerves are entering or exiting at brain stem levels (from 3rd to 12th cranial nerves except 11th cranial nerve which arise from the cervical spinal cord):

- The first 2 cranial nerves are entering above the brain stem level.
- 2 Cranial nerves arise from the Midbrain → III, IV.
- 4 Cranial nerves arise from the Pons → V, VI, VII, VIII.
- 3 Cranial nerves arise from the Medulla → IX, X, XII.

- The purely Motor cranial nerves (III, IV, VI, XII) are entering or exiting from the Medial part of brain stem.

- Pure sensory and Mixed cranial nerves (V, VII, IX, X) are entering or exiting from the lateral part of brain stem.

- Mixed cranial nerves have motor and sensory components.

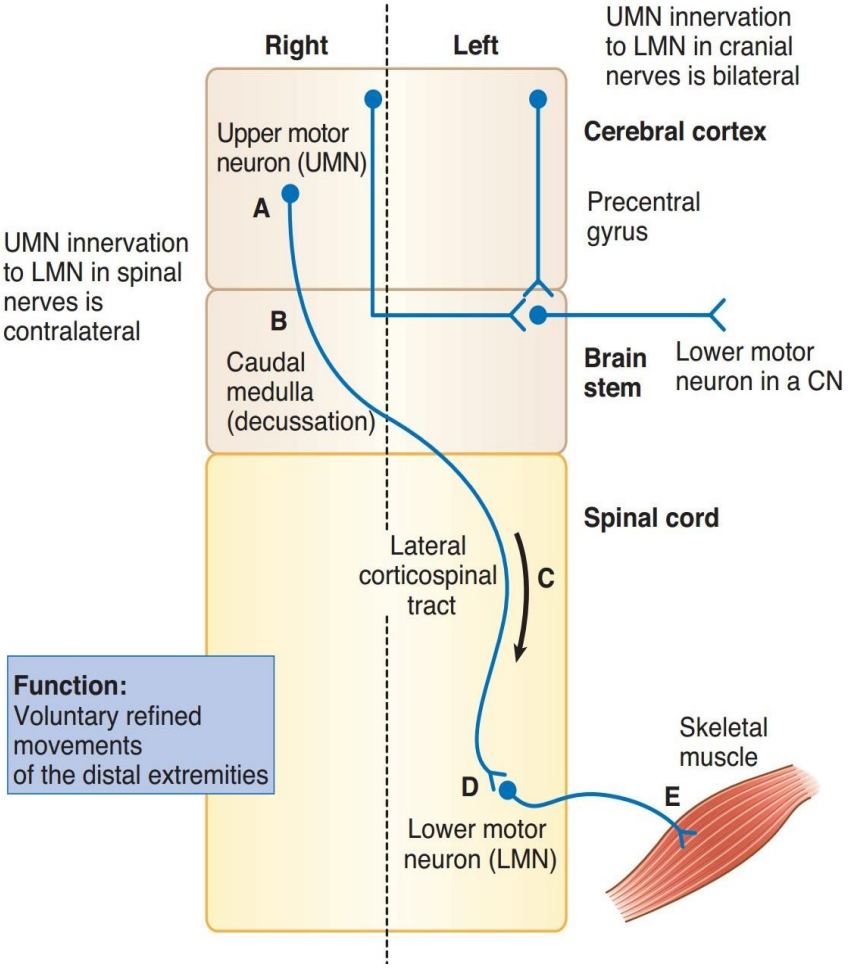
- Corticobulbar Innervation of Cranial Nerve Nuclei:

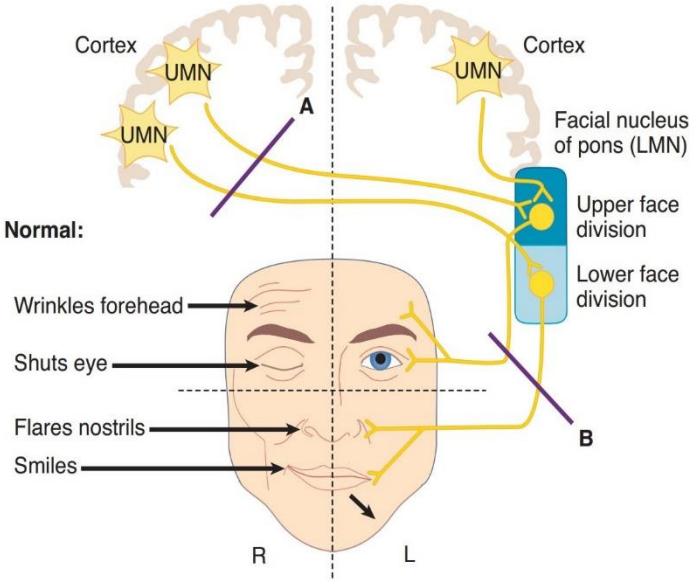
- Corticobulbar fibers serve as the source of upper motoneuron innervation of lower motoneurons in cranial nerve nuclei.

- Corticobulbar fibers arise in the motor cortex and influence lower motoneurons in all brain stem nuclei that innervate skeletal muscles. This includes:
  - Muscles of mastication (CN V).
  - Muscles of facial expression (CN VII).
  - Palate, pharynx, and larynx (CN X).
  - Tongue (CN XII).
  - Sternocleidomastoid and trapezius muscles (CN XI).

- The corticobulbar innervation of cranial nerve lower motoneurons is predominantly bilateral. Each lower motoneuron in a cranial nerve nucleus receives input from corticobulbar axons arising from both the right and the left cerebral cortex (bilateral innervation) except the lower 1/2 of the facial nucleus & the hypoglossal nucleus which are supplied only from the contralateral side (unilateral innervation).

- The lesion of motor nuclei or the cranial nerves is of LMNL type.





- Anatomical landmarks of the brain stem cut section:

1- Midbrain (III, IV):

- There is a small circular canal (cerebral aqueduct of sylvius) that will present in the middle of all midbrain cut sections.

A. Upper Midbrain (III):

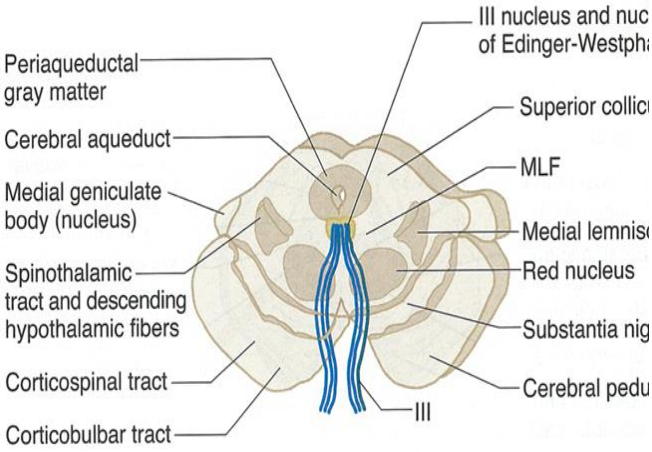
- Above:
  - Cerebral aqueduct of sylvius underneath superior colliculus.

- Below:
  - Cerebral peduncle and corticospinal tract descending through it.
  - Oculomotor nerve (purely Motor) exiting Medially near midline.

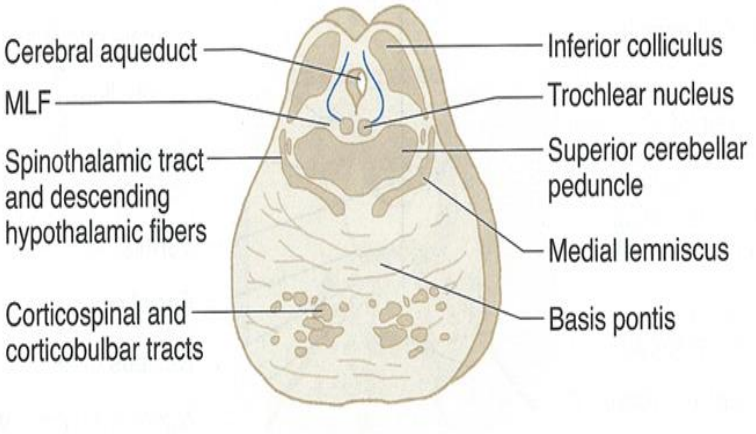
B. Lower midbrain (IV):

- Above: Cerebral aqueduct of sylvius underneath inferior colliculus.

- Below:
  - No cerebral peduncle anymore, but corticospinal tract still descending with corticobulbar tracts.
  - Trochlear nerve (purely Motor) exiting Medially near midline.



Upper Midbrain (CN III)



Lower Midbrain (CN IV)

C. Pons (V , VI , VII , VIII):

- There is a wide space (4th ventricle) that present in the middle of all midbrain cut sections.

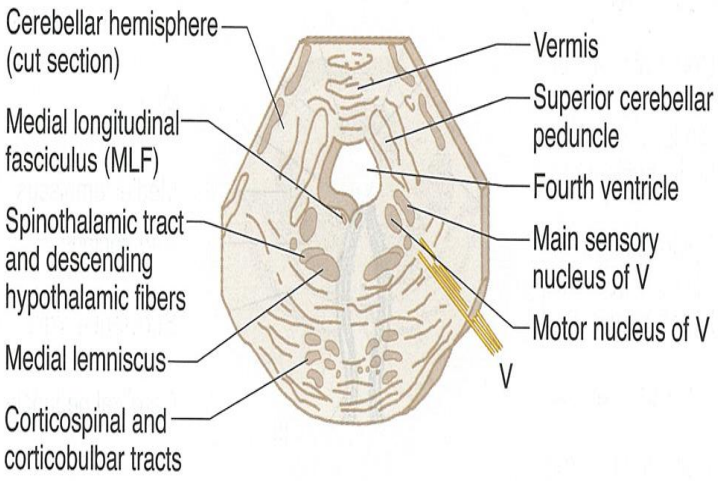
A. Middle Pons (V): Trigeminal nerve (mixed) has motor nucleus for mastication and main sensory nucleus for facial touch.

B. Lower pons (VI, VII):

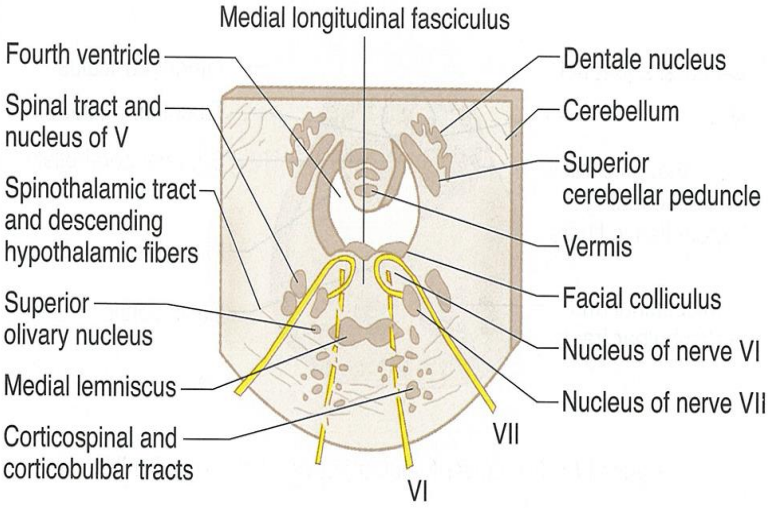
- Because VI cranial nerve is purely Motor, so, it lies in the Medial part of lower pons.
- But VII cranial nerve is mixed nerve, so it lies laterally.

❖ N.B:

- The fibers of facial nerve loops over the abducens nucleus as they leave the facial nucleus, that's why a lesion of abducens nucleus will also injure the facial nerve fibers that is looping over it (question in my exam that pointed at abducens nucleus and asked what will happen if there is a lesion at the pointed area, and the correct answer was one of the signs of facial nerve lesion).



Middle pons (CN V)



Lower pons (CN VI, VII)

C. Medulla (IX, X, XII):

A. Open Medulla (upper medulla):

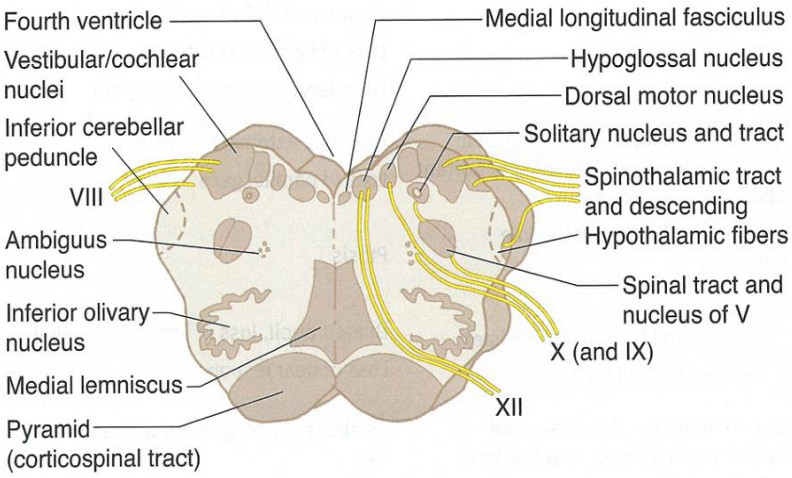
- The most common site of brain stem to develop brain stem vascular syndromes.

- Below:

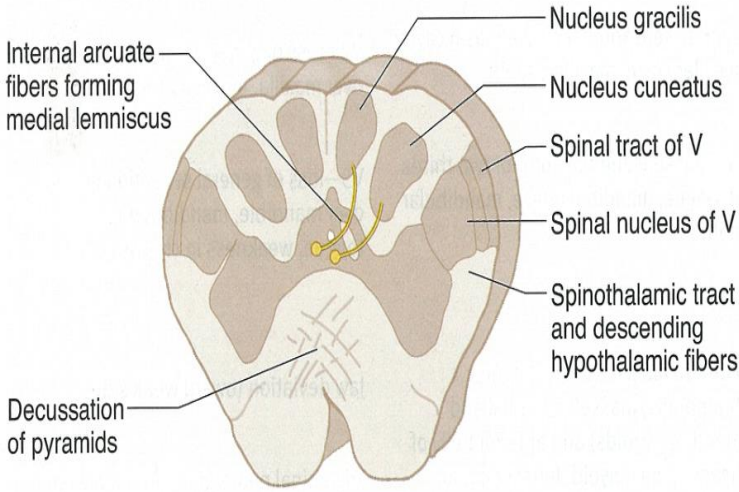
- Highly convoluted nucleus taking the shape of worm (inferior olivary nucleus).
- Because XII is purely Motor, so it lies in the Medial part of upper medulla.
- But IX, X cranial nerves are mixed nerves, so they lie laterally in upper medulla.

B. Closed medulla (lower medulla):

- It is the level of crossing of two neural systems (corticospinal tract & axons of gracile and cuneate nuclei crossing to form medial lemniscus).



Open Medulla (CN IX, X, XII)



Closed Medulla (Decussation)

Cranial Nerves

1- Cranial Nerve I (Olfactory Nerve):

- Type: Sensory.
- Function: Smells.
- Results of lesions: Anosmia.
- Only cranial nerve without thalamic relay to cortex.

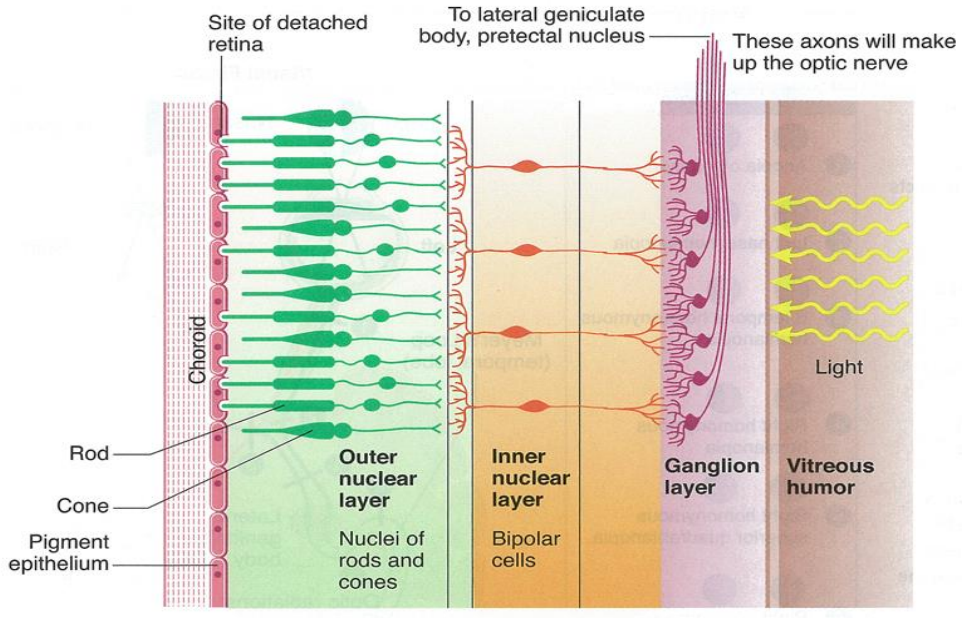
2- Cranial Nerve II (Optic Nerve):

- Type: Sensory.
- Function: Sight.
- Results of lesions:

- Visual field deficits (Anopsia).
- Loss of light reflex.

❖ Visual processing:

- Light must pass through the cornea, aqueous humor, pupil, lens, and vitreous humor before reaching the retina.
- It must then pass through the layers of the retina to reach the photoreceptive layer of rods and cones (rods for night vision & cones for light vision).



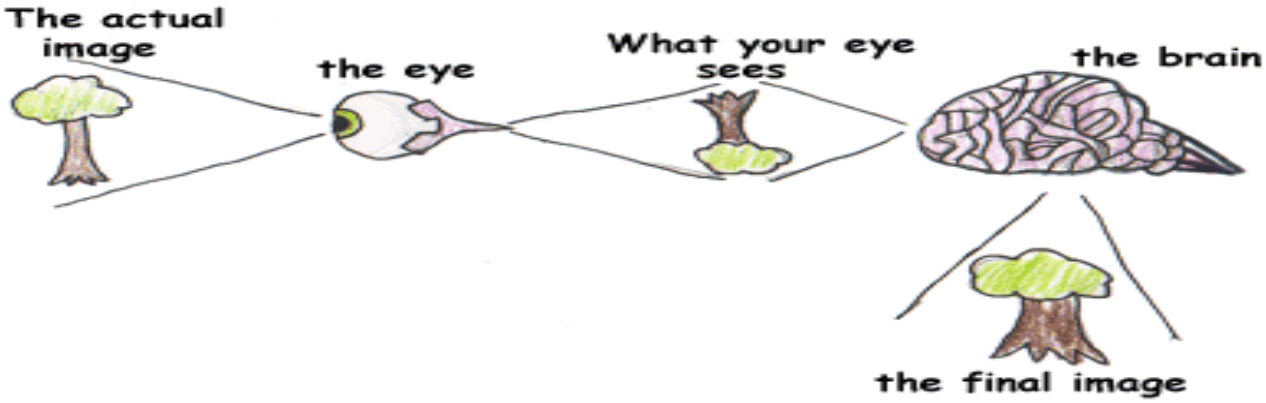
- Visual pathway is like any sensory pathway needs 3 order neurons to deliver visual information from photoreceptors to the primary visual cortex to process visual information:

- 1st order neuron: rods and cones have synaptic contacts on Bipolar cells.
- 2nd order neuron: axons of bipolar cells project to ganglion cells.
  - Axons of ganglion cells converge at the optic disc to form the optic nerve, which enters the cranial cavity through the optic foramen.
  - At the optic disc, these axons acquire a myelin sheath from the oligodendrocytes of the central nervous system.

Qs - What about crossing?

- Before we talk about crossing, you need to know that:

- Like a camera, the lens inverts the image of the visual field on the retina to be upside-down and left-right reversed, so the nasal (medial) retina receives information from the temporal visual field, and the temporal (lateral) retina receives information from the nasal visual field.
- At the optic chiasm, 60 % of the optic nerve fibers from the nasal half of each retina cross and project into the contralateral optic tract.
- Fibers from the temporal retina don't cross at the chiasm and instead pass into the ipsilateral optic tract.
- SO, the optic tract contains remixed optic nerve fibers from the temporal part of the ipsilateral retina and fibers from the nasal part of the contralateral retina.



Qs - What about upper and lower retina?

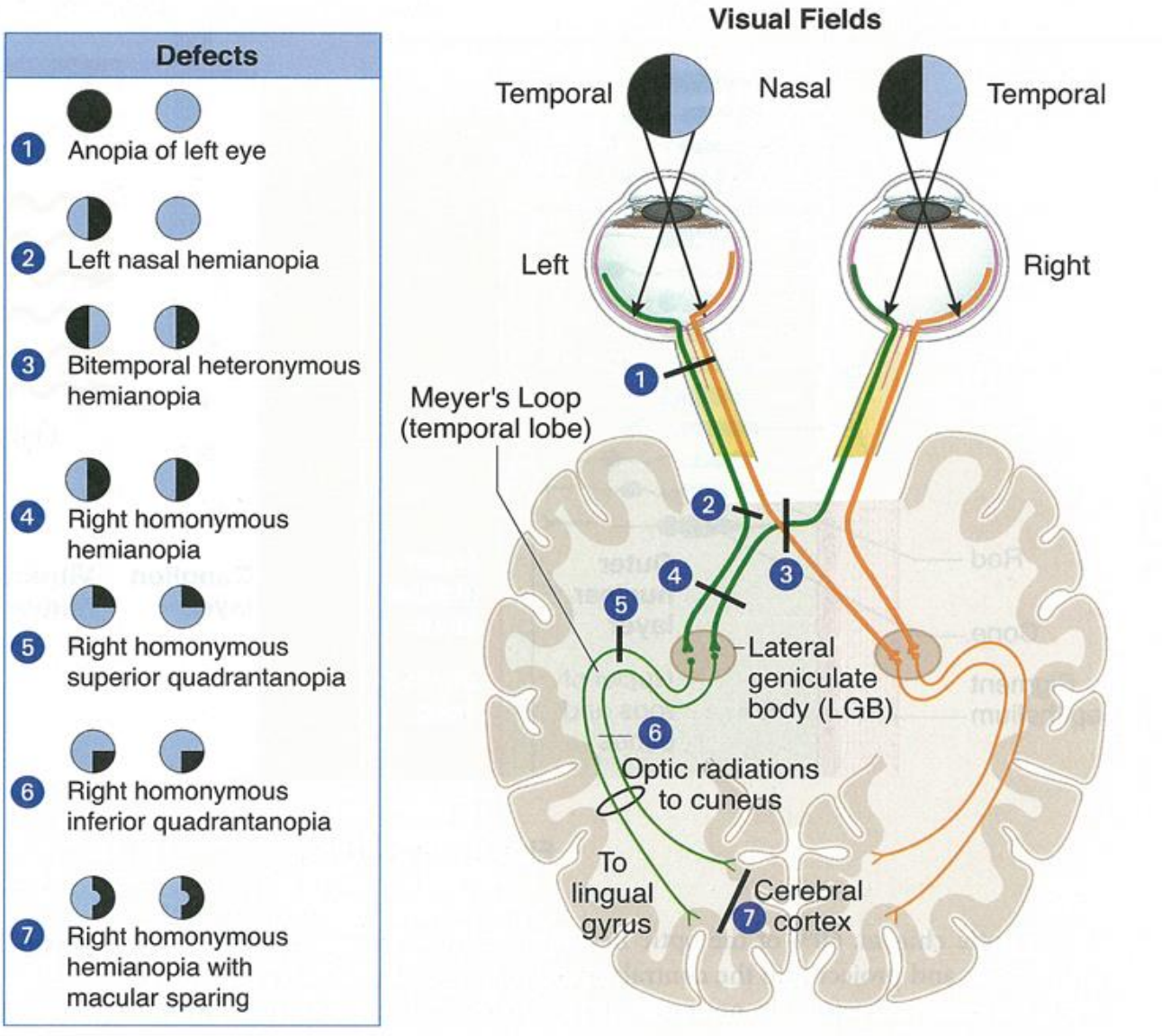
- Memorize the Lower retina " rule of L" and the opposite in upper retina.
- Visual information from Lower retina (that receive information from the upper visual field) courses in → Lateral fibers of the visual radiation (Meyer's Loop) through → temporal lobe to reach → the Lingual gyrus.
- Visual information from upper retina (that receives information from the lower visual field) courses in → medial fibers of the visual radiation through → parietal lobe to reach → cuneus gyrus.

- 3rd order neuron: most fibers in the optic tract project to the Lateral geniculate nucleus of the thalamus (Lateral for Light), then thalamus projects to primary visual cortex for processing visual information.

- After visual processing in primary visual cortex, the brain adjusts the inversion of the visual field that happened on the retina by the lens, SO we see the world in its correct orientation.

- Optic tract fibers also project to the pretectal area for the light reflex, to the superior colliculi for reflex gaze, and to the suprachiasmatic nucleus of the hypothalamus for circadian rhythms.

❖ Visual field defects:



A- Lesions in front of optic chiasm (1, 2) → the visual field deficits are monocular and ipsilateral:

1- Complete lesion of left optic nerve → Anopsia of left eye.

- Ex: optic neuritis, central retinal artery occlusion.

2- Lesion that compresses the outside (temporal fibers) of the left optic nerve → left nasal hemianopia.

- Ex: internal carotid artery aneurysm.

B- Lesions at the optic chiasm (3) → the visual field deficits are binocular (because it affects optic nerve fibers of both eyes), bitemporal (because we only compressing retinal nasal fibers that are representing temporal hemifield information), and heteronymous (different, Right side of one eye and the left side of the other):

3- Lesion at the optic chiasm → Bitemporal heteronymous hemianopia.

- Ex: Tumors that compresses optic chiasm (pituitary adenoma, craniopharyngioma).

C- Lesions after optic chiasm (4, 5, 6) → the visual field deficits are binocular (affect nerve fibers of both eyes), homonymous (at the same sides of both eyes), and contralateral (visual field deficits are contralateral to the side of the lesion). Light reflex is suppressed in lesion at 4 (because Optic tract fibers also project to the pretectal area for the light reflex), intact at 5, 6:

4- lesion of the left optic tract → right homonymous hemianopia & suppressed light reflex.

D. (5, 6) are lesions of either the lateral or the medial fibers of the visual radiation, so, it's lesion of half of the fibers that is coming from the optic tract which means you expect the visual deficits in (5, 6) lesion to be half of the hemianopia which is (quadrantanopia), but the difference between 5 and 6 is which quarter of the visual field will be affected (superior or inferior):

5- Lesion of the left lateral fibers of the visual radiation (left Meyer's loop) → right homonymous superior quadrantanopia (slice of pie on the contralateral sky).

- Ex: Middle cerebral artery occlusion.

6- Lesion of the left medial fibers of the visual radiation → right homonymous inferior quadrantanopia (slice of pie on the contralateral floor).

- Ex: posterior cerebral artery occlusion.

7- lesion of the left visual cortex → right homonymous hemianopia with macular sparing, why? Because macula has dual blood supply from both posterior cerebral artery and middle cerebral artery. In posterior cerebral artery occlusion, visual cortex is still supplied by collaterals from middle cerebral artery.

❖ N.B:

1. It is called visual field defect, so, we are describing the defect in the visual filed vision, not the lesion of the retina!

2. Optic nerve is the only cranial nerve to be affected in multiple sclerosis, why?

- Because multiple sclerosis is an autoimmune inflammation and demyelination of CNS (against oligodendrocytes) and the only cranial nerve that isn't part of PNS is CN II and is considered part of CNS (myelinated by oligodendrocytes not Schwann cells) and its demyelination in Multiple sclerosis cause optic neuritis.

Pupillary Light Reflex

- Cranial nerve reflexes as light, blink and gag reflexes have an afferent limb (sensory) and efferent limb (motor), unique feature to the cranial nerve reflexes which is very valuable to their testing is that in each of those reflexes, when you stimulate sensory limb of corresponding cranial nerve, the motor response generated under normal conditions will be bilateral.

- When light is directed into an eye, it stimulates retinal photoreceptors and results in impulses carried in the optic nerve to → the pretectal area (upper midbrain), cells in the pretectal area send axons to → the Edinger-Westphal nuclei (parasympathetic nucleus of the oculomotor nerve) on both sides, then Edinger-Westphal nucleus gives rise to preganglionic parasympathetic fibers that pass in → the third cranial nerve (oculomotor nerve) to → the ciliary ganglion → short ciliary nerves → sphincter pupillae muscles → constriction of both pupils.

- N.B: Because cells in the pretectal area supply both Edinger-Westphal nuclei, shining light into one eye results in constriction of both the ipsilateral pupil (direct light reflex) and contralateral pupil (consensual light reflex).

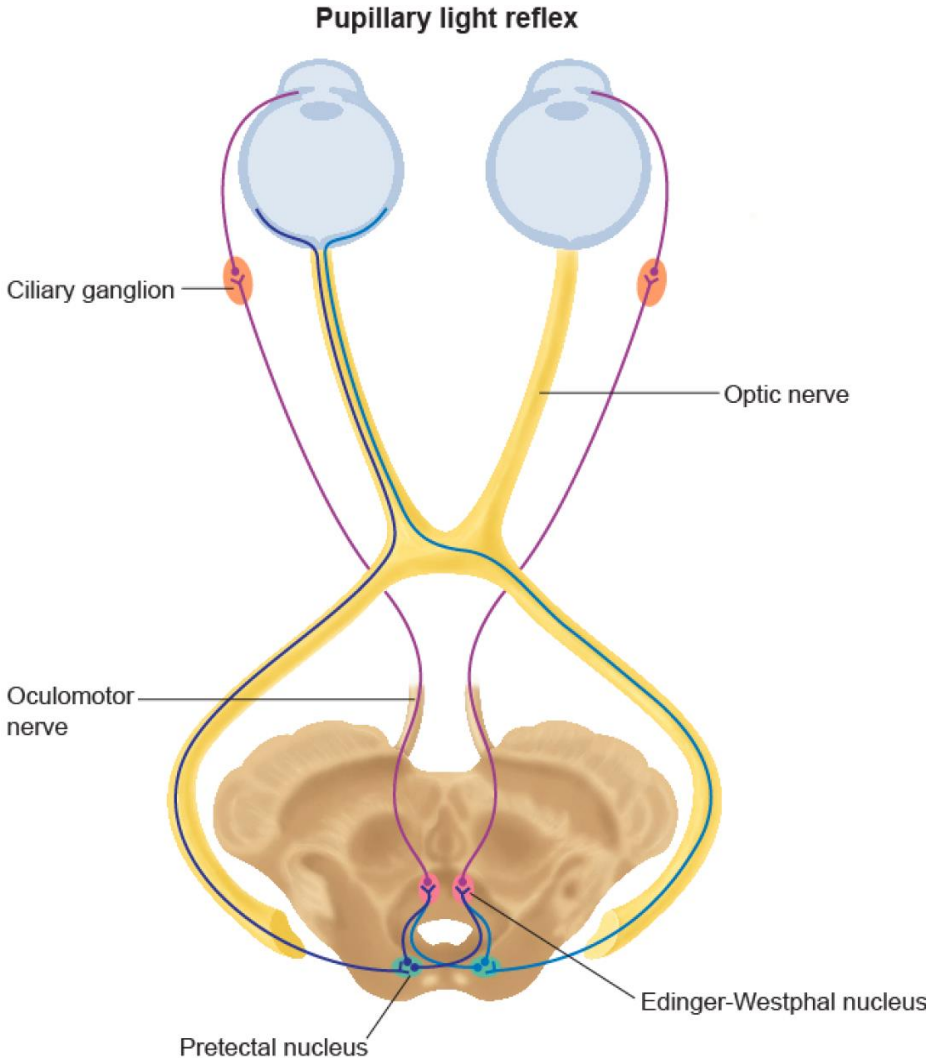
❖ Marcus gunn pupil (Relative Afferent pupillary Defect):

- Cause:

- Lesion of afferent limb of pupillary light reflex (optic neuritis) in multiple sclerosis (intact oculomotor nerve, because multiple sclerosis is an autoimmune disease against oligodendrocytes, and oculomotor nerve is myelinated by Schwann cells).

- Findings:

- Diagnosis is made with swinging flashlight test.
- Shining light in normal eye → both pupils constricts normally.
- Shining light in the eye with optic nerve lesion → both pupils paradoxically dilate (apparent dilatation of both pupils because stimulus carried through that affected CN II is not transmitted).



3. Cranial Nerve III (Oculomotor nerve):

- The oculomotor nerve (III), trochlear nerve (IV), and abducens nerve (VI) coordinate eye movement.

- Type: motor.

- Function and results of lesions:

1. Innervates all extraocular muscles (EXCEPT SO4 & LR6) as superior rectus (SR), inferior rectus (IR), medial rectus (MR) and inferior oblique (IO).

- The action of the ocular muscles innervated by oculomotor nerves is elevation and adduction of the eye (up and in), and the most important action is adduction, so, lesion of oculomotor nerve will result in → down and out eye position (diplopia & external strabismus).

2. Innervates levator palpebrae superioris that elevate the superior (upper) eyelid so, lesion of oculomotor nerve will result in → ptosis (drooping of the eyelid).

3. Innervates sphincter papillae muscle which constricts pupil (miosis), so, lesion of oculomotor nerve will result in → mydriasis & loss of light reflex.

4. Innervates ciliary muscle, which is responsible for accommodation, so, lesion of oculomotor nerve will result in → loss of accommodation (near response).

Accommodation-Convergence Reaction (Near Response)

- It occurs when an individual attempt to focus on a nearby object after looking at a distant object.

- <u>The oculomotor nerve carries the efferent fibers from the Accommodation-Convergence reaction, which consists of 3 components:</u>

1. Accommodation: parasympathetic fibers contract the ciliary muscle, which relaxes suspensory ligaments that increases the curvature of the lens needed for near vision.

2. Convergence: results from contraction of both medial rectus muscles, which pull the eyes to look toward the nose. This allows the image of the near object to focus on the same part of the retina in each eye.

3. Pupillary constriction (miosis): parasympathetic fibers contract the pupillary sphincter muscle → miosis.

- Argyl Robertson pupil:

- Both direct and consensual light reflexes are lost, but the Accommodation-Convergence Reaction remains intact due to lesion of the pretectal nucleus that is responsible for light reflex.

- This type of pupil is often seen in cases of tabes dorsalis (late cases of neurosyphilis), however, it is sometimes seen in patients with pineal tumor (due to compression on pretectal nucleus by the tumor).

- Adie's pupil: is considered a unilateral Argyl Robertson pupil (the affected pupil reacts sluggishly to light, but better to accommodation) due to lesion of ciliary ganglion on the same side of the lesion.

- SO, in bilateral Argyl Robertson pupil, the problem in pretectal nucleus (tabes dosalis)
  But in unilateral Argyl Robertson pupil, the problem in ciliary ganglion (Adies pupil).

- CN III damage:

- CN III has both Motor (Middle) and Parasympathetic (Peripheral) components.

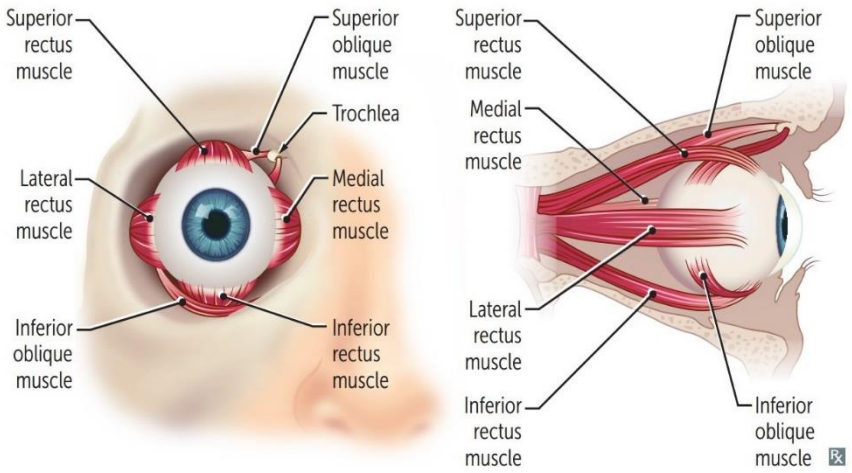
- Common causes include:

  - Ischemia → pupil sparing (motor fibers affected more than parasympathetic fibers).
  - Uncal herniation.
  - Posterior Communicating aneurysm.
  - Cavernous sinus thrombosis.
  - Midbrain stroke.

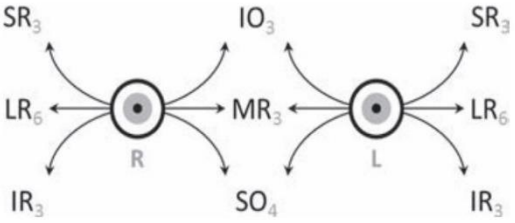
- Motor output to extraocular muscles → affected primarily by vascular disease (diabetes mellitus) due to ↓ diffusion of oxygen and nutrients to the interior fibers from compromised vasculature that resides on outside of nerve. Signs: ptosis, "down-and-out" gaze.

- Parasympathetic output: fibers on the periphery are first affected by compression (PCom aneurysm, uncal herniation). Signs: diminished or absent pupillary light reflex, "blown pupil" often with "down-and-out" gaze.

Ocular motility



CN VI innervates the Lateral Rectus.
CN IV innervates the Superior Oblique.
CN III innervates the Rest.
The "chemical formula" $LR_6SO_4R_3$.



Obliques go Opposite (left SO and IO tested with patient looking right).
IOU: IO tested looking Up.

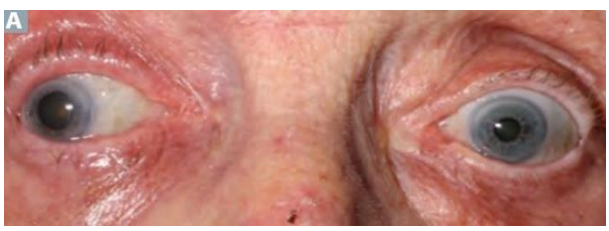
5. Cranial Nerve IV (Trochlear Nerve, SO4):

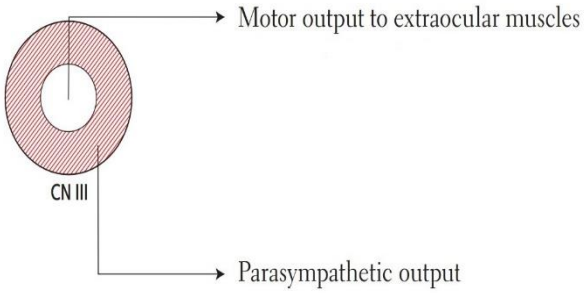
- Type: motor.

- Function and results of lesions:

- Innervate only one extraocular muscle, superior oblique (SO4) which causes the eye to intort (internally rotate) and depress while adducted, so, lesion of trochlear nerve will result in diplopia (double vision) only when the patient looking downwards (going downstairs or reading), this diplopia is called vertical diplopia because injury to the trochlear nerve cause weakness of downward eye movement.

- The affected eye drifts upward relative to the normal eye, due to the unopposed actions of the remaining extraocular muscles, so, this patient sees two visual fields (one from each eye), separated vertically (vertical diplopia).



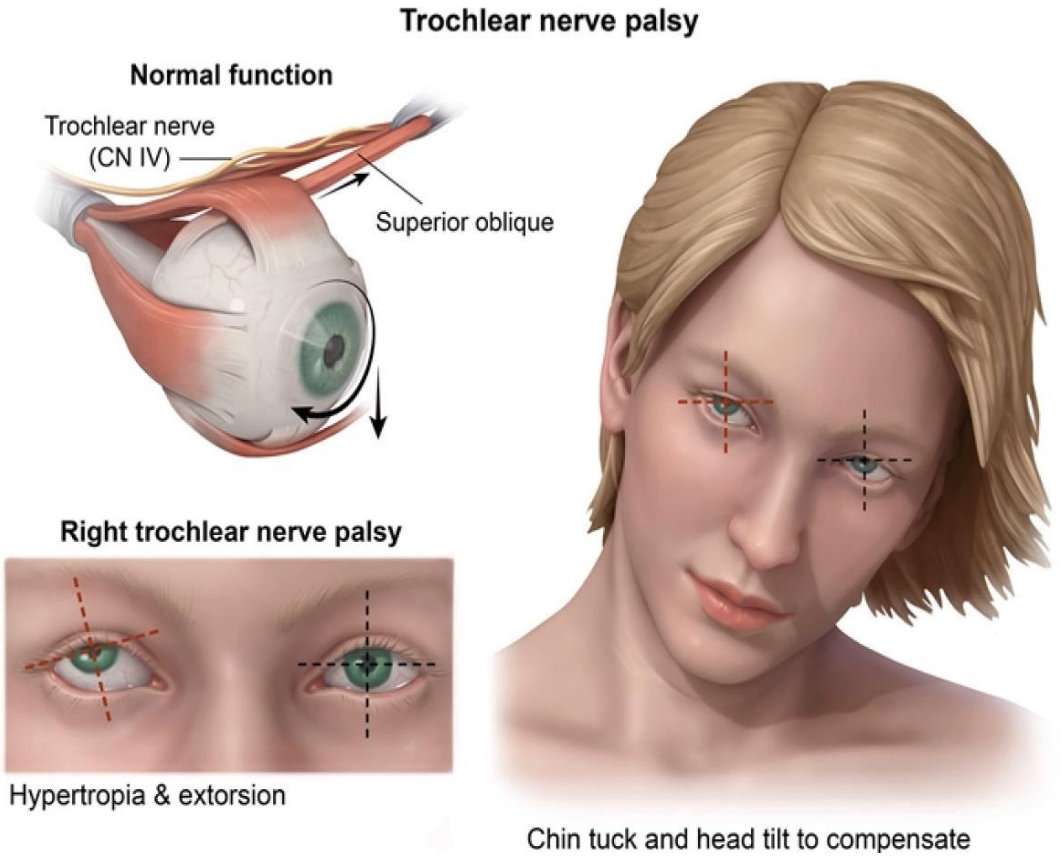


- CN IV damage:

- Pupil is higher in the affected eye.

- Characteristic head tilt to contralateral/unaffected side to compensate for lack of intortion in affected eye.

- Can't see the floor with CN IV damage.



6. Cranial Nerve V (Trigiminal Nerve):

- Type: mixed.

- Function and results of lesions:

- It is formed of sensory and motor divisions:

A. The sensory division:

- It conducts sensations from the face (except the angle of the mandible supplied by C2), the anterior 2/3 of the tongue and the buccal cavity to the sensory nuclei of trigeminal nerve in pons.

- It is formed of 3 branches, the ophthalmic (V1), maxillary (V2) and mandibular (V3) branches which enter the cranial cavity respectively through the Superior orbital fissure, the foramen Rotundum and the foramen Ovale (Divisions of CN V exit owing to Standing Room Only).

1- Ophthalmic (V1):

- Carry general sensation (touch, pain and temperature) of forehead, scalp and cornea, so, lesion of ophthalmic branch will result in → loss of general sensation in skin of forehead and scalp.

- It is the afferent (sensory) limb of blinking reflex, so, its lesion will result in loss of blinking reflex.

Corneal Reflex (Blink reflex)

- The goal of this reflex is to protect both eyes by reflexively closing both of them when only one is touched.

- When you touch the cornea or conjunctiva by apiece of cotton, afferent impulses from the conjunctiva or cornea travel in the ophthalmic branch of trigeminal nerve (V1) to the sensory nucleus of the trigeminal nerve.

- This then projects to the motor nucleus of facial nerve of both eyes. The facial nerve supplies the orbicularis oculi muscles, leading to closure of the eyelids and a blink action.

- Afferent: V1. Efferent: VII of both eyes.

2- Maxillary (V2):

- Carry general sensation of palate, nasal cavity, maxillary face and maxillary teeth, so, lesion of maxillary branch will result in → loss of general sensation in skin over maxilla and maxillary teeth.

3- Mandibular (V3):

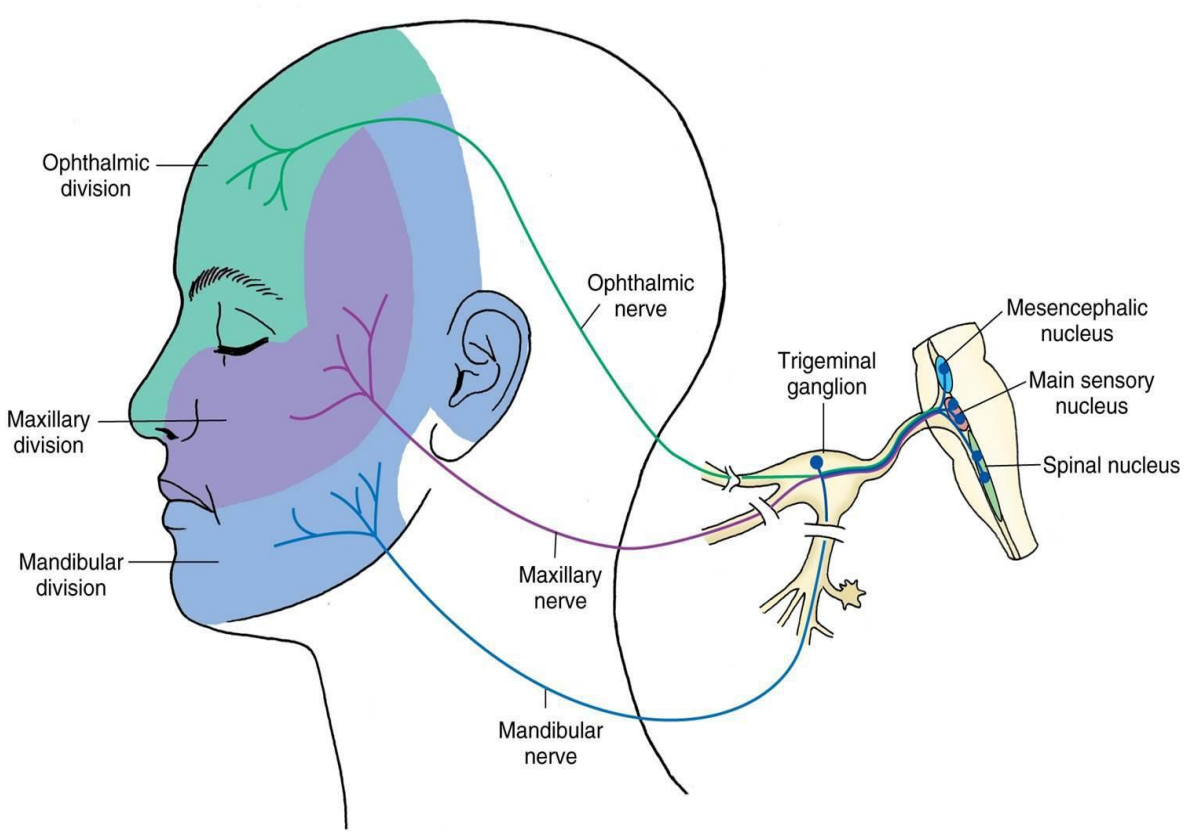
- Carry general sensation of anterior two thirds of tongue, mandibular face and mandibular teeth, so, lesion of mandibular branch will result in loss of general sensation in skin over mandible, mandibular teeth and tongue.

- There are three sensory trigeminal nuclei:

- The mesencephalic nucleus → receives information about proprioception of the face (the feeling of position of the muscles).

- The chief (main) sensory nucleus → receives information about touch and vibratory sensation of the face.

- The spinal trigeminal nucleus → receives information about pain and temperature of the ipsilateral face, so, its lesion will result in loss of pain & temperature of the ipsilateral face.



Trigeminal neuralgia

- Severe attacks of unilateral pain along one or more of the sensory branches of the trigeminal nerve, usually the maxillary or mandibular branches.
- It usually affects middle age, more commonly females.
- The exact cause is unknown but there are certain predisposing factors as compression of the trigeminal nerve rootlets at their entry to the brain stem by aberrant loops of the cerebellar arteries.
- The attacks are precipitated by movement of the jaw as laughing, brushing of the teeth, mastication and last several days or weeks.
- In-between attacks the patient is completely free.
- Treatment: the drug of choice is Carbamazepine.
- Key in the case: unilateral facial pain, the patient describes the pain as "a knife stabbing my face".

B. The motor division:

- It starts in the motor nucleus in the pons to supply the muscles of the jaw as:

- The muscles of mastication (teMporalis, Masseter, Medial and lateral pterygoids).
- Anterior belly of digastric.
- Mylohyoid.
- Tensor tympani & tensor palati.

- 3 muscles close jaw: Masseter, teMporalis, Medial pterygoid. M's Munch.

- 1 opens: Lateral pterygoid. Lateral Lowers (when speaking of pterygoids with respect to jaw motion).

- "It takes more muscle to keep your mouth shut".

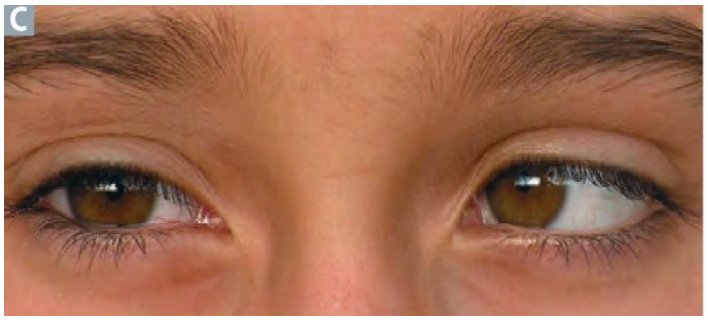
- SO, the lesion of motor division of trigeminal nerve will result in → deviation of the jaw to the side of the lesion, why? - Due to the unopposed action of the pterygoid muscles of the healthy side.

7. Cranial Nerve VI (Abducens Nerve, LR6):

- Type: motor.

- Function and results of lesions:

- Innervate only one extraocular muscle, lateral rectus (LR6) which abduct the eyeball, so, lesion of abducens nerve will result in (diplopia & internal strabismus)



8. Cranial Nerve VII (Facial nerve):

- Type: mixed.

- Function and results of lesions:

- The facial nerve is a mixed nerve, as it contains motor, sensory and autonomic fibers.

A. The motor part:

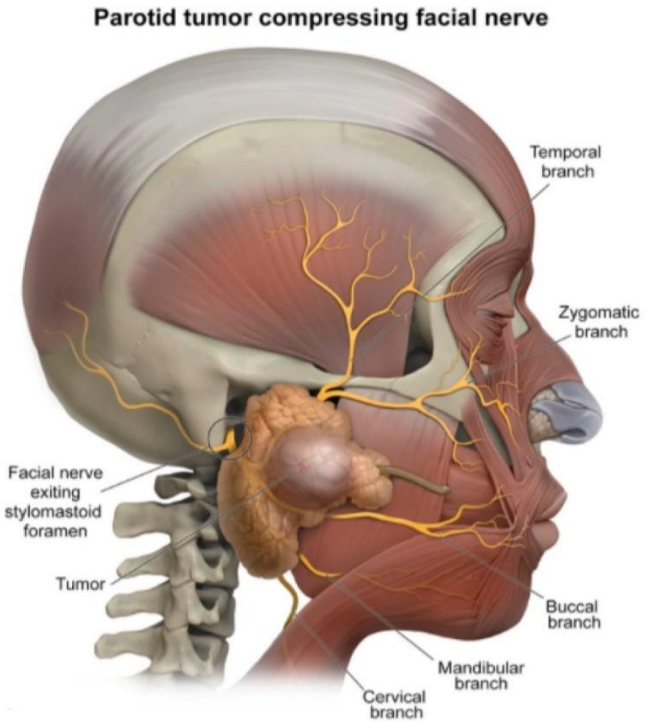
- Supplies the muscles of facial expression as well as 4 other muscles:
  - Platysma.
  - Stapedius (protects inner ear from loud sounds).
  - Stylohyoid.
  - Posterior belly of the digastric muscle.

B. The sensory part: receives taste sensations from the anterior 2/3 of the tongue.

C. The autonomic part: supplies the lacrimal gland as well as the submaxillary and sublingual salivary glands.

❖ N.B:

- The facial nerve courses through the parotid gland, but doesn't innervate it, so it's liable for injury in parotid surgery or compression by parotid gland tumors (usually malignant).



❖ Facial nerve lesions:

- Upper motor innervation of spinal nerves is contralateral (from the opposite side then crosses in lower medulla) and is called corticospinal tract.

- Lower motor neuron innervation of spinal nerves (from anterior horn cells of spinal cord up to the peripheral nerves) is always ipsilateral.

- But upper motor innervation of cranial nerves is bilateral (from both sides) and is called corticobulbar tract except the lower half of facial nucleus and hypoglossal nucleus.

- If there is a lesion of one of the corticobulbar tracts (one side), there will not be any deficit of most cranial nerves, why? - Because enough cortical information from the intact corticobulbar tract of the opposite side still able to innervate the motor nuclei of most cranial nerves except the lower half of facial and hypoglossal nuclei.

- Lower motor neuron innervation of cranial nerves (from motor nuclei of cranial nerves up to the cranial nerves) is always ipsilateral.

- Lesion A: Lesion of all upper motor neurons of facial nerve will result in → contralateral lower face weakness (muscles of the nose and mouth), but upper face is intact (muscles of forehead and eyelid) because it's bilaterally innervated (corticobulbar tracts of both sides).

- Lesion B: Lesion of all lower motor neurons of facial nerve (lesion of facial nucleus or facial nerve fibers) will result in → ipsilateral complete facial palsy (Bell's palsy).

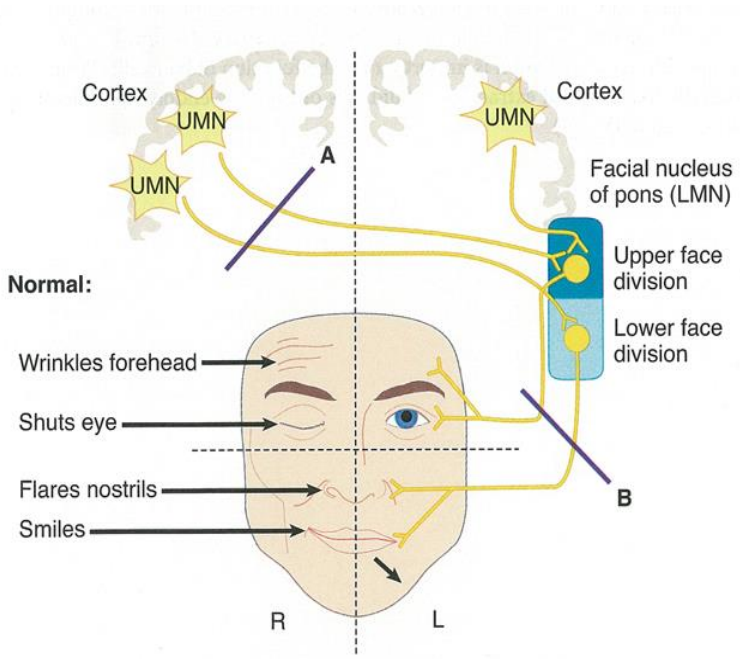
- In addition to unilateral facial paralysis, patient with Bell's palsy may experience decreased tearing, hyperacusis, and loss of taste sensation over the anterior 2/3 of the tongue.

- In UMN lesion facial paralysis (contralateral lower face), there is:

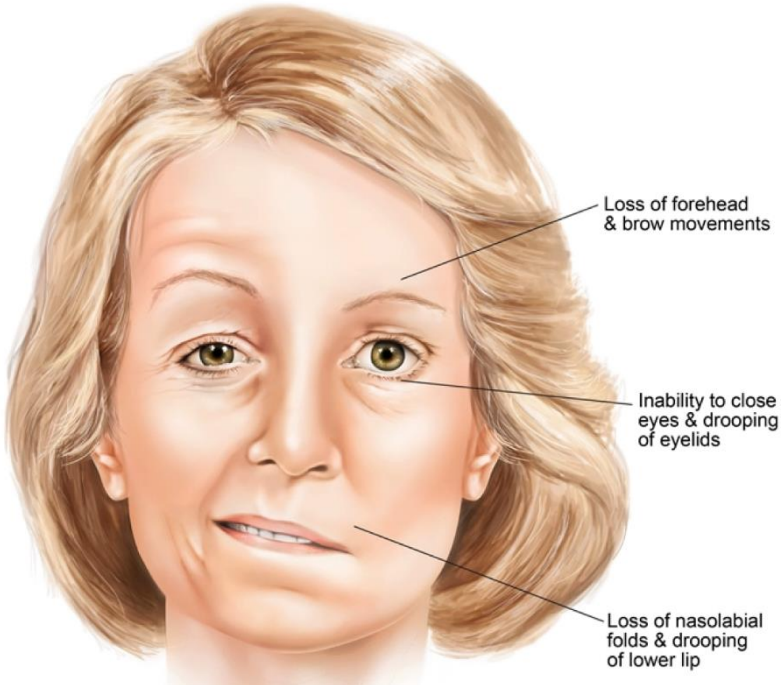
- Obliteration of the nasolabial fold.
- Drooping of the angel of the mouth with dribbling of the saliva.
- Accumulation of food behind the cheek.
- Inability to below the cheek.
- Inability to show the teeth properly.

- In LMN facial paralysis (ipsilateral complete facial paralysis) there are in addition:

- Inability to raise the eyebrows with absence of wrinkles of the forehead
- Inability to close the eye.



Peripheral facial palsy



9. Cranial Nerve VIII (Vestibulochochlear Nerve):

- Type: sensory.

- Function and results of lesions:

- The nerve is composed of two divisions:

A. Cochlear Division:

- Each ear consists of 3 components:

- 2 air filled spaces (the external ear and the middle ear).
- The fluid filled spaces of the inner ear.

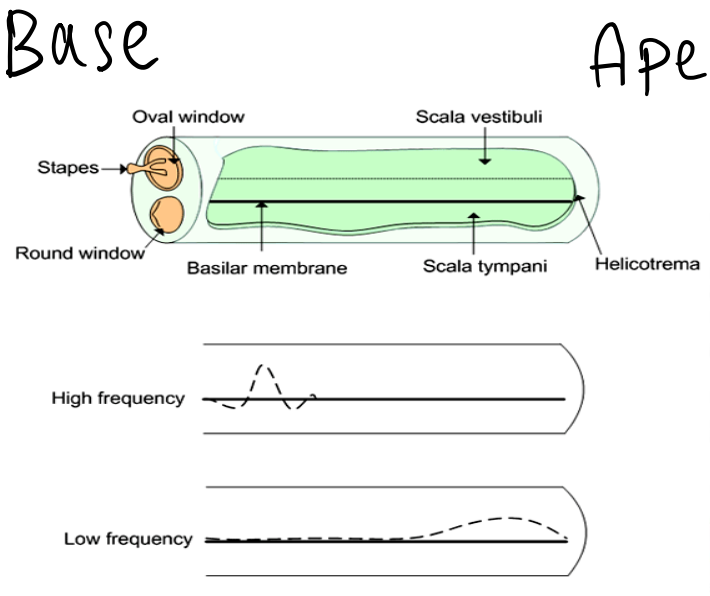
- The external ear:

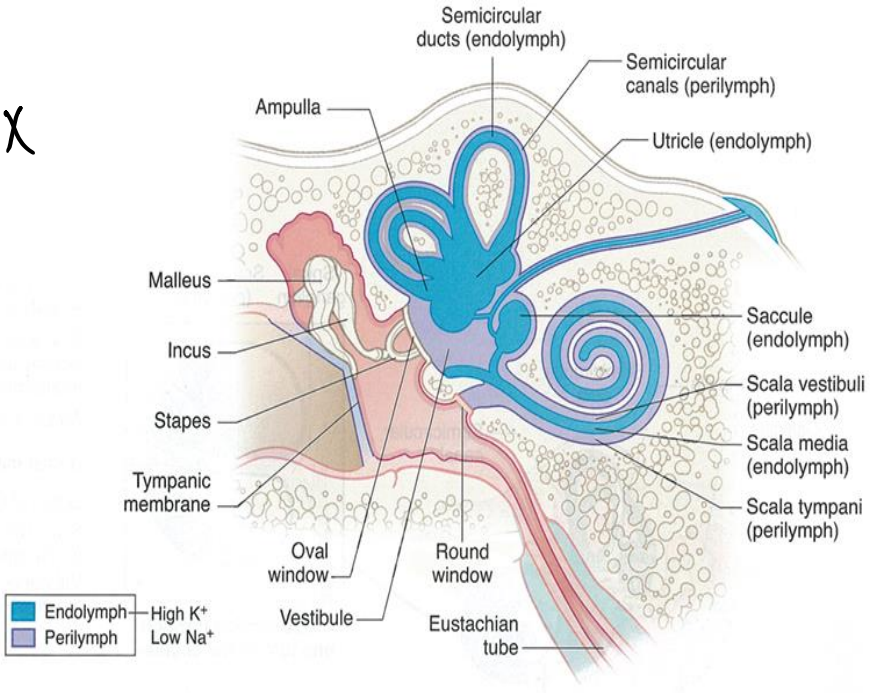
- The external ear includes the ear pinna and the external auditory meatus, which extends to the tympanic membrane.

- Sound waves travel through the external auditory meatus and cause the tympanic membrane to vibrate.

- Movement of the tympanic membrane causes vibration of the ossicles in the middle ear (malleus, incus and stapes).

- These auditory ossicles amplify the vibration received by the tympanic membrane and transmit them to the fluid of the inner ear.





- The inner ear:

- It is a fluid-filled site encased in bone that houses the cochlea which is responsible for hearing, the semicircular canals, and the vestibule (utricle and saccule) which are responsible for balance and motion.

- The cochlea is a cone-shaped spiraling structure. The cochlea is composed of three spiraling fluid-filled ducts known as the Scala vestibuli, the Scala media, and the Scala tympani.

- The Scala media lies between the Scala vestibuli and the Scala tympani. Both the Scala vestibuli and the Scala tympani are filled with perilymph, while the Scala media is filled with endolymph.

- The Scala media is separated from the Scala tympani by the basilar membrane. The Scala media is also unique in that it houses the organ of Corti. The organ of Corti is the specific site where sound is transduced into the nervous system.

- Sound transduction:

- First, Sound reaches the middle ear by vibrating the tympanic membrane.

- The vibration is transferred to → the oval window by the ossicles. Vibration of the oval window causes → movement of the perilymph in the scala vestibuli, which is transmitted to → the scala tympani.

- Perilymph movement in the scala tympani, in turn, causes → the basilar membrane to vibrate.

- Vibration of the basilar membrane causes → bending of the cilia of the hair cells. Hair cell bending causes → oscillating hyperpolarization and depolarization → creating nervous impulse from sound.

- Low frequency sound is best detected at the apex of the cochlea near the helicotrema. The helicotrema is the site where the scala vestibuli and the scala tympani meet.

- High frequency sound is best detected at the base of the cochlea near the oval and round windows.

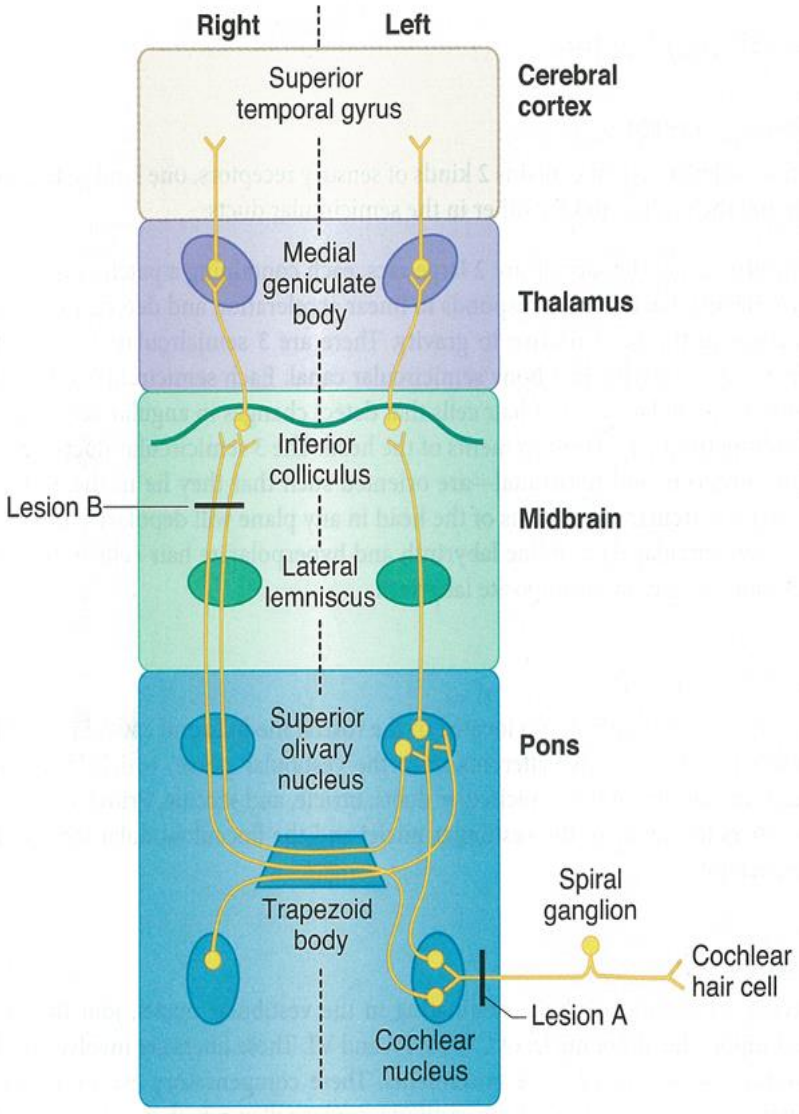
- Tympanic membrane (external ear) and Ossicles (middle ear) function is to amplify (conduct) sound through the air. That's why any lesion of external (wax accumulation) or middle ear (otitis media, otosclerosis) → cause conductive hearing loss. But lesion of hair cells in the inner ear or cranial nerve VIII will result in → sensorineural hearing loss.

- Otosclerosis is abnormal growth of bone near the middle ear → conductive hearing loss.

- Noise-induced hearing loss results from trauma to the stereociliated hair cells of the organ of Corti. The acoustic reflex normally dampens the effects of loud noise by causing the stapedius and tensor tympani muscles to contract, which lessens the responsiveness of the ossicles to sound. However, prolonged noise exposure can cause distortion or fracture of the stereocilia due to shearing forces against the tectorial membrane. High-frequency hearing is lost first, regardless of the frequency of the sound causing the damage. Key in the case: hearing loss in a rock musician who has spent a lot of time in his

studio recently. Sudden extremely loud noises can produce hearing loss due to tympanic membrane rupture.

- Sound processing:



- Function of auditory pathway:

1- Hearing:

- Hearing by delivering auditory information from receptors (cochlear hair cells) to the primary auditory cortex to process auditory information.

2- Localize the source of the sound in the space.

- Auditory pathway is like any sensory pathway needs 3 order neurons to deliver auditory information from receptors (cochlear hair cells) to the primary auditory cortex to process auditory information:

- 1st order neuron:
  - Spiral ganglion which is a bipolar cell. It contains cell bodies whose peripheral axons innervate auditory hair cells of the organ of Corti. The central axons from these bipolar cells form the cochlear part of the eighth cranial nerve.
  - All the axons in the cochlear part of the eighth cranial nerve enter the pontomedullary junction and synapse in the cochlear nucleus.

- 2nd order neuron:
  - Cochlear nucleus, some of the cochlear nuclei axons cross through the trapezoid body to innervate the contralateral superior olivary nucleus.
  - Axons of cells in the cochlear nuclei bilaterally innervate the superior olivary nuclei in the pons.

- The superior olivary nuclei are the first auditory nuclei to receive bilateral input from both ears (some from the ipsilateral cochlear nucleus and some from the contralateral cochlear nucleus) and use it to localize sound sources (1st site of sound localization).

- SO, Superior olivary nucleus and anything above it will participate in both hearing and sound localization.

- The lateral lemniscus carries auditory input from the superior olivary nuclei to the inferior colliculus of the midbrain.

- Each lateral lemniscus carries information derived from both ears, however, input from the contralateral ear predominates.

- The inferior colliculus sends auditory information to the Medial geniculate body (MGB) of the thalamus (Music).

- From the MGB, the auditory radiation projects to the primary auditory cortex.

- Lesions causing hearing loss:

A. Lesions before trapezoid body (site of crossing):

- Lesion of cochlear part of the eighth cranial nerve or cochlear nucleus → profound sensorineural hearing loss which will be unilateral (affect one side), ipsilateral (hearing loss will be at the same side of the lesion) because there still no crossing.

B. Lesions after trapezoid body:

- Lesion of the superior olivary nucleus, lateral lemniscus, inferior colliculus, medial geniculate body or primary auditory cortex → slight sensorineural hearing loss which will be bilateral (both sides) and decreased ability to localize sounds.

- SO, in a nutshell:
  - Profound hearing loss in one ear → lesion before trapezoid body.
  - Slight bilateral hearing loss and decreased ability to localize sound → lesion after trapezoid body.

Hearing Loss

- Hearing loss is classified as either conductive (obstruction of external sound vibrations to the inner ear) or sensorineural (involving the inner ear, cochlea, or auditory nerve)

- The Rinne and Weber tests can be used to help determine the type of hearing loss.

- Air-conducted sound is normally louder and heard longer than bone-conducted sound.

A. Weber test:

- It is performed by placing a vibrating tuning fork on the middle of forehead equidistant from both ears. The vibration is normally heard equally in both ears, if the vibration heard louder in 1 ear, it indicates an abnormal test.

- Conductive hearing loss causes lateralization to the affected ear as the conduction deficits masks the ambient noise in the room, allowing the vibration to be better heard.

- In contrast, sensorineural hearing loss causes lateralization to the unaffected ear as the unimpaired inner ear can better sense the vibration.

B. Rinne test:

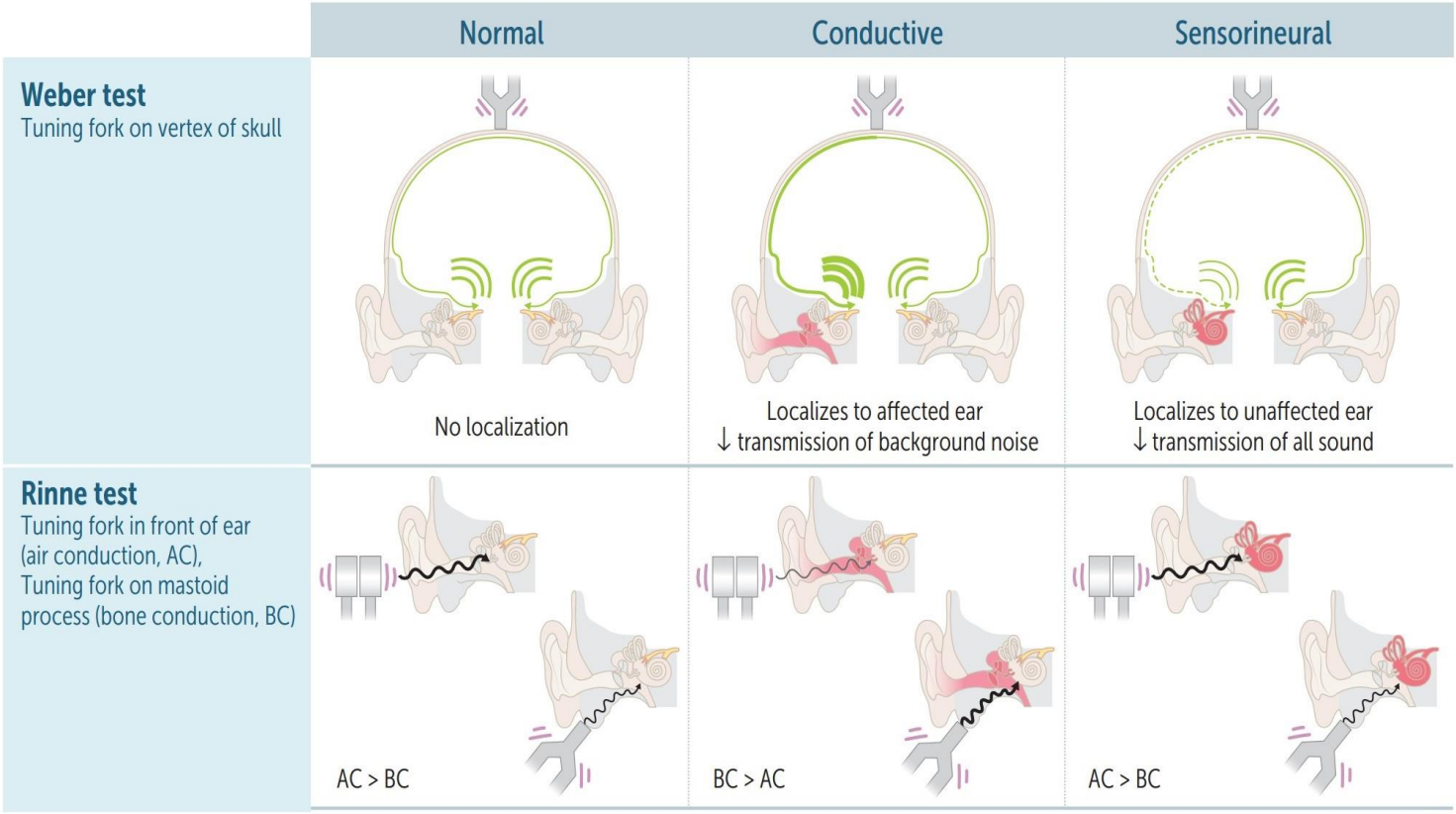
- Compares the perceived sound produced by a vibrating tuning fork when the stem is placed on the mastoid bone (bone conduction) VS. when it held near the external auditory meatus (air conduction).

- The Rinne test is considered positive (normal) if the sound is heard best at the external auditory meatus and negative (abnormal) if the patient hears the vibration better at the mastoid.

- An abnormal Rinne test suggests conductive hearing loss.

- SO, in a nutshell:
- In Conductive hearing loss (bone conduction > air conduction): there is abnormal Rinne test (in affected ear) and weber test localizes to affected ear.

- In Sensorineural hearing loss (air conduction > bone conduction): there is normal Rinne test and weber test localizes to unaffected ear.



Cholesteatoma

- It is overgrowth of desquamated keratin debris within middle ear space → may erode ossicles & mastoid air cells → conductive hearing loss.
- Often presents with painless otorrhea.

Presbycusis

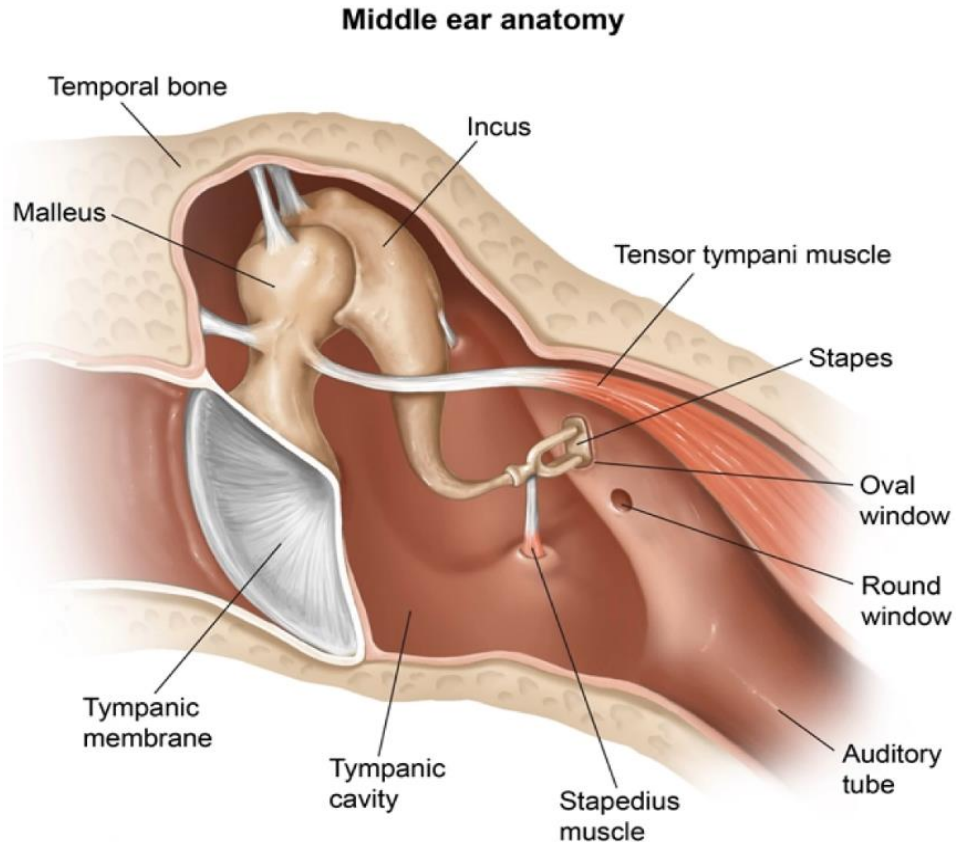
- Presbycusis (presby "elder" + akousis "hearing").
- Age related bilateral/symmetric sensorineural hearing loss mostly to high pitched sounds due to loss of hair cells at the base of the chochlea (preserved low-frequency hearing at apex).

Hyperacusis

- Increased sensitivity to loud sounds due lesion of the facial nerve in the brain stem (weakness of the stapedius muscle that protects inner ear from loud sounds).
- The stapedius muscle functions to stabilize the stapes; paralysis of the muscle (secondary to an injury or lesion to the facial nerve) causes the stapes to oscillate more widely, producing hyperacusis.

- Patients will typically complain of increased sensitivity to everyday sounds (eg, shutting doors, ringing phones, traffic) and will often withdraw socially as a result.

- Treatment consists of retraining (or sound) therapy using broadband noise ("white noise").



B. Vestibular part:

- The vestibular system contains 2 kinds of sensory receptors, one kind in the utricle and the saccule and the other in the semicircular ducts.

- The utricle and saccule respond to linear acceleration and detects positional changes in the head relative to gravity.

- The three semicircular ducts respond to angular acceleration and deceleration of the head.

- Vestibulo-ocular Reflex:

- Is the way that your brain moves your eyes to keep them focused on the stimulus of interest when there is a change in your head position.

- When you turn your head horizontally, there is a compensatory eye movement represent the afferent limb of the vestibule-ocular reflex, which enables the eye to remain focused on the target of interest during movement of the head.

- When you turn your head to the right side, it causes the endolymph to flow in the semicircular duct and stimulate hair cells of the right ear → increasing the firing rate of the vestibular nerve which project these information to the right vestibular nuclei in brain stem.

- These nuclei then send axons to the left abducens nucleus and by way of the medial longitudinal fasciculus to the right oculomotor nucleus.

- MLF is heavily myelinated fiber bundle (high speed conductivity) which compensate for the long distance between the vestibular nuclei and oculomotor nucleus.

- The right oculomotor nerve → the right medial rectus → adducts the right eye.

- The left abducens nerve → the left lateral rectus → abducts the left eye.

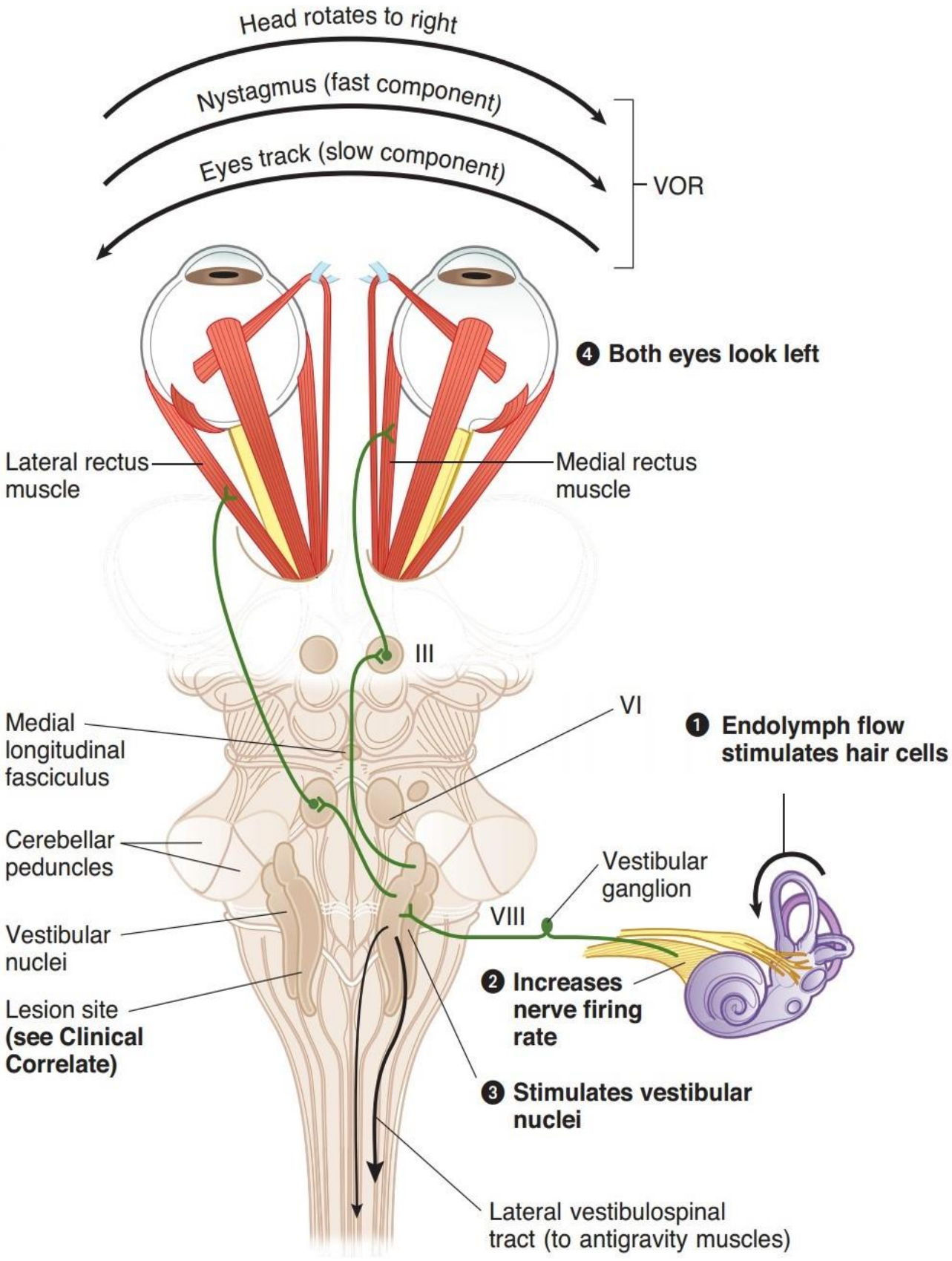
- The net effect of stimulating these nuclei is that both eyes will look to the left.

▪ Lesion of vestibular system will result in:

- Imbalance (Because vestibular nuclei also send information to the flocculonodular lobe of the cerebellum).

- Vertigo and dizziness.

- Nystagmus.


Head rotates to right
Nystagmus (fast component)
Eyes track (slow component)
VOR
4 Both eyes look left
Lateral rectus muscle
Medial rectus muscle
III
VI
Medial longitudinal fasciculus
Cerebellar peduncles
Vestibular nuclei
Lesion site (see Clinical Correlate)
1 Endolymph flow stimulates hair cells
Vestibular ganglion
VIII
2 Increases nerve firing rate
3 Stimulates vestibular nuclei
Lateral vestibulospinal tract (to antigravity muscles)

- Vestibular evoked nystagmus (in vestibular nerve or nucleus lesion):

- Vestibular Nystagmus is a rhythmic oscillation of the eyes with a slow deviation of the eyes toward the lesion and a fast correction back to the opposite side.

- If the left vestibular nerve or nuclei are lesioned, then the right vestibular nuclei are unopposed and act as if they have been stimulated (as if the head turned to this side) → causing both eyes to look slowly to the left → This is the slow phase of a pathologic vestibular nystagmus.

- And because the head didn't move, the cortex responds by moving both eyes quickly back to the right (the opposite side) → This is the fast phase of a pathologic vestibular nystagmus (The corrective fast phase is always away from the side of the lesion).

- Tests for Nystagmus:

- The integrity of the vestibulo-occular reflex can be an indicator of brain stem integrity and still connected to the cerebral cortex in comatose patients.

- To test this reflex, a vestibular system is induced by performing a caloric test in which an examiner introduces warm or cool water into an external auditory meatus.

- A mnemonic which summarizes the direction of the fast phase of vestibular nystagmus in a caloric test is COWS (Cold Opposite, Warm Same):

  - Cold water irrigation of ear → nystagmus to Opposite side (mimics a lesion).

  - Warm water irrigation of ear → nystagmus to Same side.

  - If there is no fast correction phase, this means there is a lesion of cerebral cortex.

  - Introduction of cool water into the external ear mimics a lesion, it inhibits the semicircular duct activity on the same side, and the opposite vestibular nuclei moves the eyes slowly toward the cool-water ear. The corrective or fast phase of the nystagmus moves the eyes quickly away from the ear where the cool water was introduced.

  - Introduction of warm water into the external ear stimulates the semicircular activity and the opposite of what happened in cool water occurs.

Vertigo

- Vertigo is a false sensation of movement (the sensation of movement in the absence of actual movement). Acutely, these episodes are commonly associated with nausea and vomiting.

- Etiology:

- Central vertigo describes vertigo caused by lesions affecting the vestibular structures in the brainstem and cerebellum.

- Peripheral vertigo describes vertigo caused by lesions affecting the inner ear and cranial nerve VIII (vestibulocochlear nerve).

1. Central vertigo:

- History and neurologic examination often help localize the lesion; patient with vascular risk factors, acute-onset headache, and gait instability likely has central etiology from stroke or hemorrhage.

- Central vertigo is caused by any cerebellar or brain-stem tumor, bleed, or ischemia.

- Because vertigo may indicate an underlying stroke or hemorrhage, patients require urgent noncontrast CT scan of the head if they have >1 of the following:

✓ Prominent stroke risk factors (hyperlipidemia, hypertension, diabetes mellitus).
✓ New-onset headache.
✓ Neurologic signs/symptoms.

2. Peripheral vertigo:

- Once you have determined that the patient has peripheral vertigo, there is a wide differential diagnosis that should be considered:

A. Benign paroxysmal positional vertigo (BPPV):

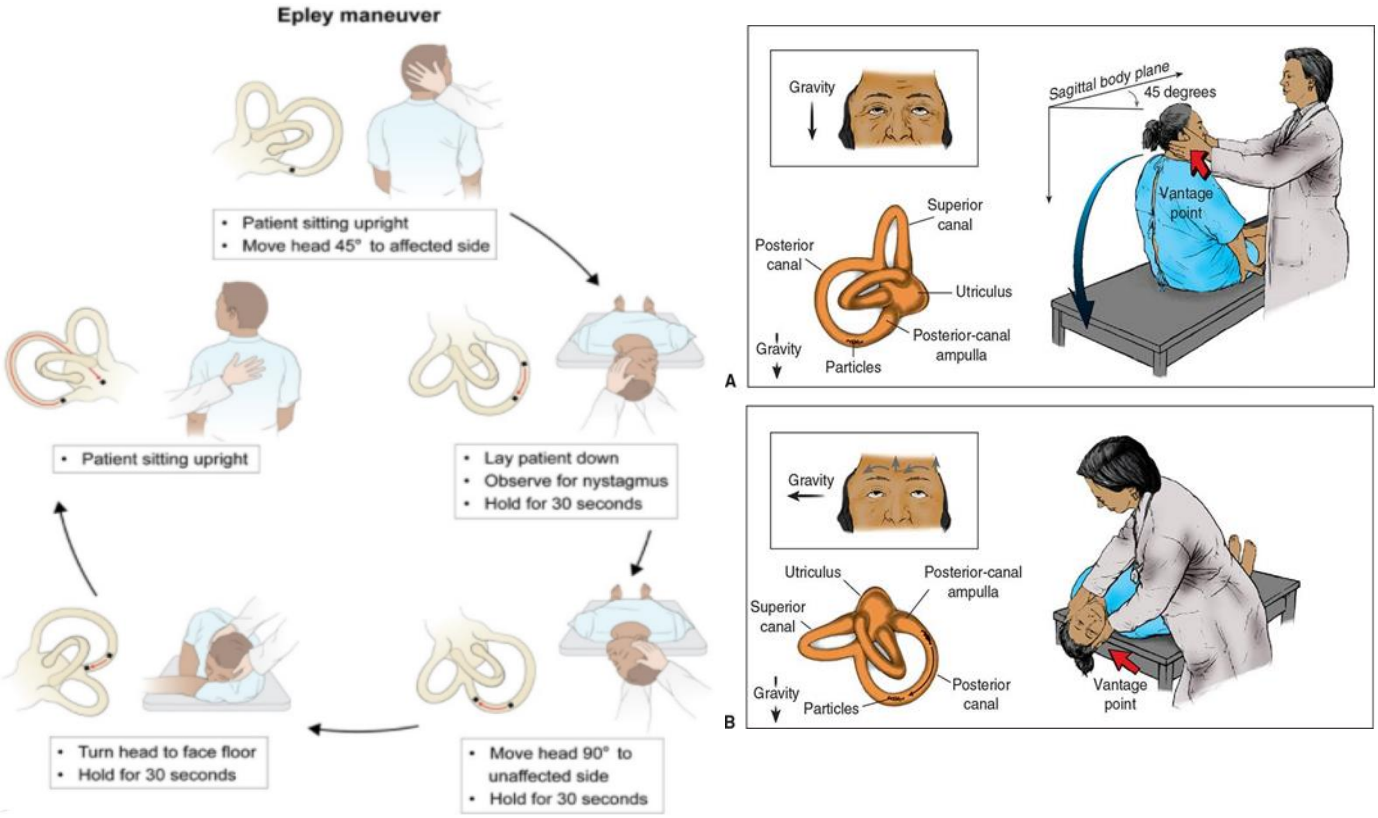
- Benign paroxysmal positional vertigo is the most common cause of vertigo.

- It is due to crystalline deposits (canaliths) in the semicircular canals that disrupt the normal flow of fluid in the vestibular system.

- This leads to contradictory signaling from the corresponding canals on each side, which is interpreted as a spinning/vertigo sensation.

- The Dix-Hallpike maneuver can help diagnose BPPV: vertigo and nystagmus are triggered as the patient quickly lies back into a supine position with the head rotated 45 degrees.

- BPPV resolves spontaneously in most cases but can recur months or years later. Symptoms can be relieved with the canalith repositioning maneuver (Epley maneuver).



B. Ménière disease:

- A disorder of the inner ear characterized by an increased volume of endolymph due to defective absorption of endolymph.

- The resultant distension of the endolymphatic system causes damage to both the vestibular and cochlear components of the inner ear.

- Meniere's disease is characterized by the triad of tinnitus, vertigo, and sensorineural hearing loss:

✓ Tinnitus → refers to ringing in the affected ear, often accompanied by a feeling of fullness.
✓ Vertigo → It is a sensation of motion when no motion is present or an exaggerated sense of motion for a given bodily movement.
✓ Sensorineural hearing loss.

C. Labyrinthitis:

- Viral or post-viral inflammation of the vestibular nerve. presents with sudden onset of severe vertigo that lasts for several days with hearing loss and tinnitus. The disease frequently follows an upper respiratory tract infection.

- Voluntary horizontal conjugate gaze:

- The eyeballs move together in conjugate gaze.

- The ocular muscles function to move and position both eyes as a unit so that an image falls on a corresponding spot on the retina of each eye. The slightest weakness in the movements of one eye causes diplopia, the presence of a double image, indicating that the image has been shifted to a different position on the retina of the affected side.

- Horizontal gaze is controlled by interconnected gaze centers:

A. One control center is in the frontal lobe (the frontal eye field). This area acts as a center for contralateral horizontal gaze.
B. In the brainstem (pons) there is a second gaze center, known as the paramedian pontine reticular information (PPRF), this is a center for ipsilateral horizontal gaze.

- When PPRF is activated by neurons in the frontal eye field, it sends axons to synapse with cell bodies in the abducens nucleus. It also sends axons that cross immediately and course in the contralateral MLF to reach the contralateral oculomotor nucleus.

- For both eyes to look to the right in horizontal gaze, the right abducens nerve and the right lateral rectus muscle must be active to abduct the right eye, and the left oculomotor nerve and the left medial rectus muscle must be active to adduct the left eye. The net effect is that both eyes will look to the right.

- In the brain stem, the abducens and oculomotor nuclei are interconnected by the fibers in the medial longitudinal fasciculus that permit conjugate gaze, either when the target moves or when the head moves, through their connections to gaze centers and the vestibular system.

- MLF: adduct an eye during horizontal gaze by connecting the abducens and oculomotor nuclei together.

- Because MLF is highly myelinated fiber bundle, it is affected in Multiple Sclerosis leading to internuclear ophthalmoplegia (internuclear because MLF lies between 2 nuclei, abducent and oculomotor nuclei).

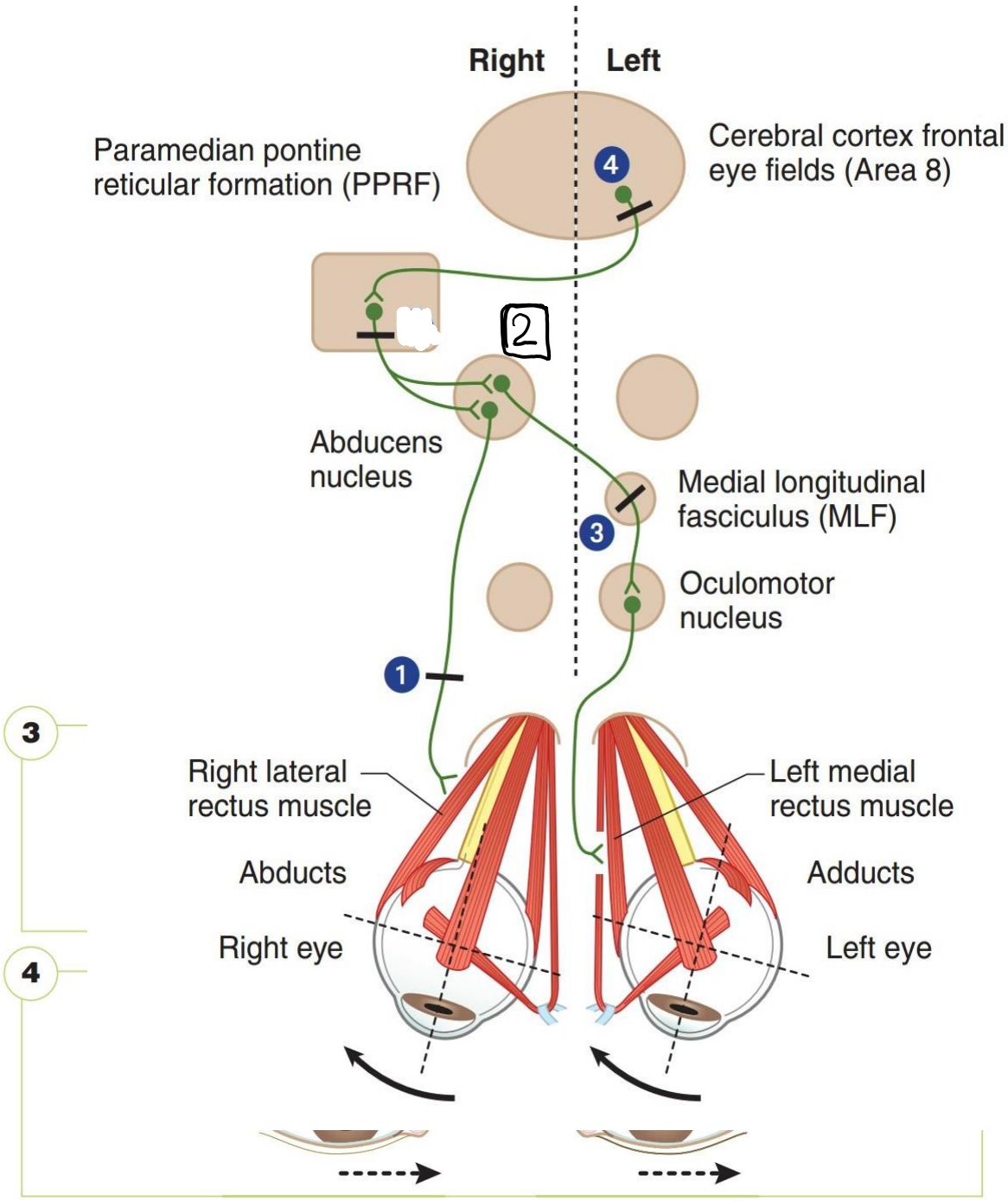
- In internuclear ophthalmoplegia there is No adduction in conjugate lateral gaze although there is intact oculomotor nerve.

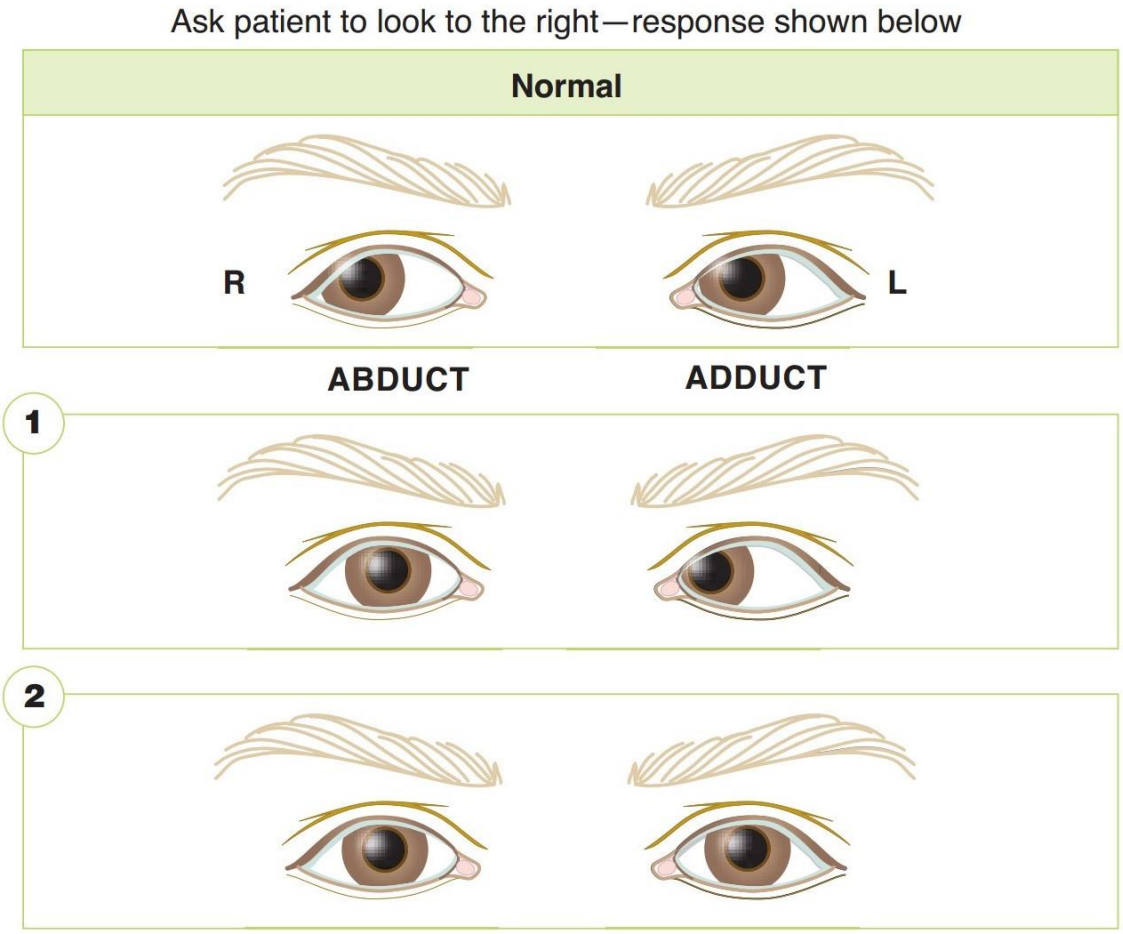
❖ Qs- How to differentiate between MLF lesion and oculomotor nerve lesion?

- In oculomotor nerve lesion, there is also ptosis & dilated pupil and loss of accommodation.

- In MLF lesion, I can't adduct the eye in horizontal eye gaze but there is intact convergence in accommodations, because this is the function of oculomotor nerve, not MLF.

- The corticobulbar fibers that innervate all cranial nerves lies just near frontal eye field so, lesion of frontal eye field in the cortex may affect also corticobulbar tract (contralateral lower face weakness), also there may be lesion of pyramidal tract (contralateral upper limb weakness).





- Abnormalities in horizontal gaze:

Lesion location	Results
1- Right abducens nerve	Right eye cannot look right (abduct)
2- Right abducens nucleus	- Neither eye can look right (lateral gaze paralysis). - Complete right facial paralysis (because the fibers of facial nerve loops over the abducent nucleus as they leave the facial nucleus).
3- Left MLF (pons)	Internuclear ophthalmoplegia: left eye cannot look right but convergence is intact.
4- Left cerebral cortex	Neither eye can look right but slow drift to left, may be seen with right lower face weakness and right upper limb weakness

9. Cranial Nerve IX (Glossopharyngeal Nerve):

- Type: mixed.

- Function and results of lesions:

- Glossopharyngeal Nerve is a mixed nerve carrying motor, sensory and autonomic fibers:

A. Motor fibers: to stylopharyngeus muscle.

B. Sensory fibers: to all sensation of posterior one-third of the tongue (General sensation & Taste sensation), inner surface of tympanic membrane, Eustachian tube, tonsillar region, and upper pharynx.

C. Autonomic fibers: to parotid gland.

- It is also an afferent (sensory) limb of the gag reflex.

- SO, lesion of Glossopharyngeal Nerve will result in loss of all sensation of posterior one-third of the tongue and loss of gag reflex.

10. Cranial Nerve X (Vagus Nerve):

- Type: mixed.

- Function and results of lesions:

- Vagus Nerve is a mixed nerve carrying motor, sensory and autonomic (parasympathetic fibers):

A. Motor fibers to:

- All muscles of the larynx.
- Muscles of the palate except tensor palati (V).
- Muscles of the pharynx for swallowing except stylopharyngeus (IX).

B. Sensory fibers: from the thoracic & abdominal viscera.

C. Autonomic (parasympathetic) fibers: to the heart, the GIT glands in foregut and midgut.

- SO, lesion of Vagus nerve result in:

- Nasal speech & nasal regurgitation.
- Hoarseness.
- Dysphagia & palatal droop.
- Uvula pointing away from affected side because weak side collapses and uvula points away.
- Loss of gag reflex (efferent limb). Loss of cough reflex.

Gag reflex (pharyngeal reflex)

- The goal of this reflex is to prevent something from entering the throat except as a part of normal swallowing and helps prevent chocking.
- This reflex is evoked by touching the soft palate, which stimulates sensory fibers of the glossopharyngeal nerve, the net results is simultaneous bilateral contraction of muscles of the palate (elevates), pharynx (constricts), and larynx (closes).
- SO, Afferent: IX, Efferent: X Bilaterally.
- N.B: The case may mention that there is deviation of the uvula on the right side for example to give you a hint that there is a left Vagus nerve lesion, so, don't be confused when you see deviation of the uvula in a case of patient with lost Gag reflex!

- Vagal Nuclei:

- Nucleus Solitarius (Sensory) → Receives visceral Sensory information (taste, baroreceptors, gut distension).

- Nucleus aMbiguus (Motor) → Motor innervation of pharynx, larynx, upper esophagus (swallowing, palate elevation).

- Dorsal motor nucleus → Sends autonomic (parasympathetic) fibers to heart, lungs, upper GIT.

❖ N.B:

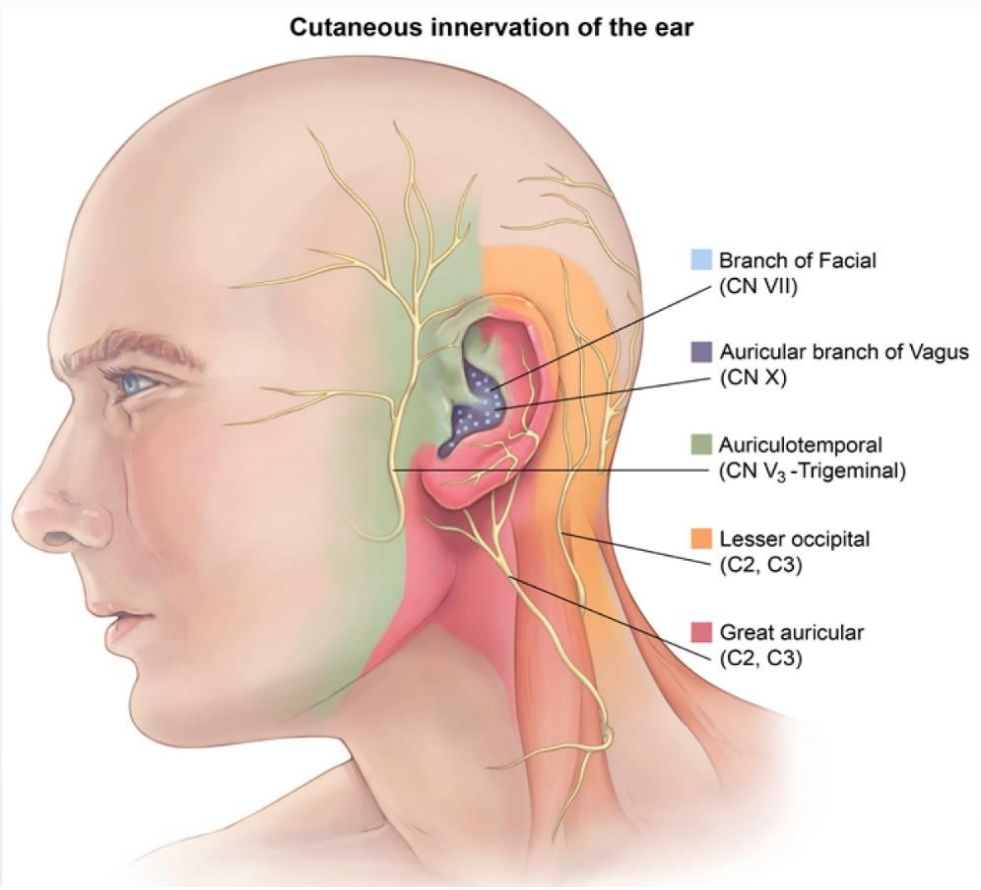
1. Bulbar palsy (The bulb is an archaic term for the medulla oblongata): occurs due to lower motor neuron lesion (mostly at the nuclear level) of the cranial nerves IX, X, XI, XII → impairment of function of the cranial nerves IX, X, XI, XII.

- In contrast, pseudobulbar palsy: occurs due to upper motor neuron lesion (bilateral corticobulbar tract lesion, because cranial nerves nuclei receive bilateral innervation due to multiple or recurrent stroke)) of cranial nerves IX, X, XI, XII → impairment of function of the cranial nerves IX, X, XI, XI.
- Both of them present with bulbar symptoms:

- Dysphagia.
- Dysarthria.
- Dysphonia.
- Nasal regurgitation.

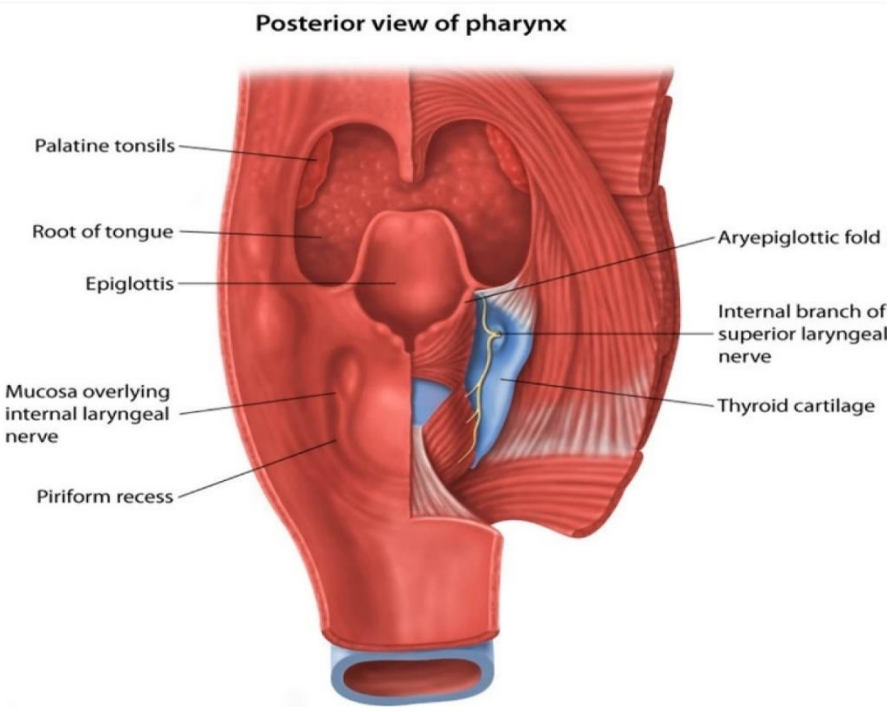
- Lower motor neuron signs (atrophy and fasciculations of the tongue, absent gag reflex) differentiate bulbar palsy from pseudobulbar palsy, which presents with upper motor neuron signs (spastic tongue, exaggerated gag, and jaw jerk reflexes).

2. The vagus nerve provides some cutaneous sensation to the posterior external auditory canal via its small auricular branch. Inspection of the patient by inserting an otoscope speculum into the external auditory meatus in close contact with its posterior wall → a vasovagal syncope will result leading to a decrease in blood pressure and heart rate.



3. The internal laryngeal nerve (branch of superior laryngeal nerve) mediates the afferent limb of the cough reflex above the vocal cords.

- Foreign bodies (chicken or fish bones) can become lodged in the piriform recess and may cause damage to the nerve, impairing the cough reflex.



11. Cranial Nerve VI (Accessory Nerve):

- Type: motor.

- Function and results of lesions:

- It is a purely motor nerve that supplies 2 muscles:
  - Sternomastoid that rotate the head to the opposite side, so, lesion of Accessory nerve will result in → weakness in turning head to opposite side.
  - Trapezius that elevate the shoulder, so, lesion of Accessory nerve will result in → shoulder droop.

12. Cranial Nerve VII (Hypoglossal Nerve):

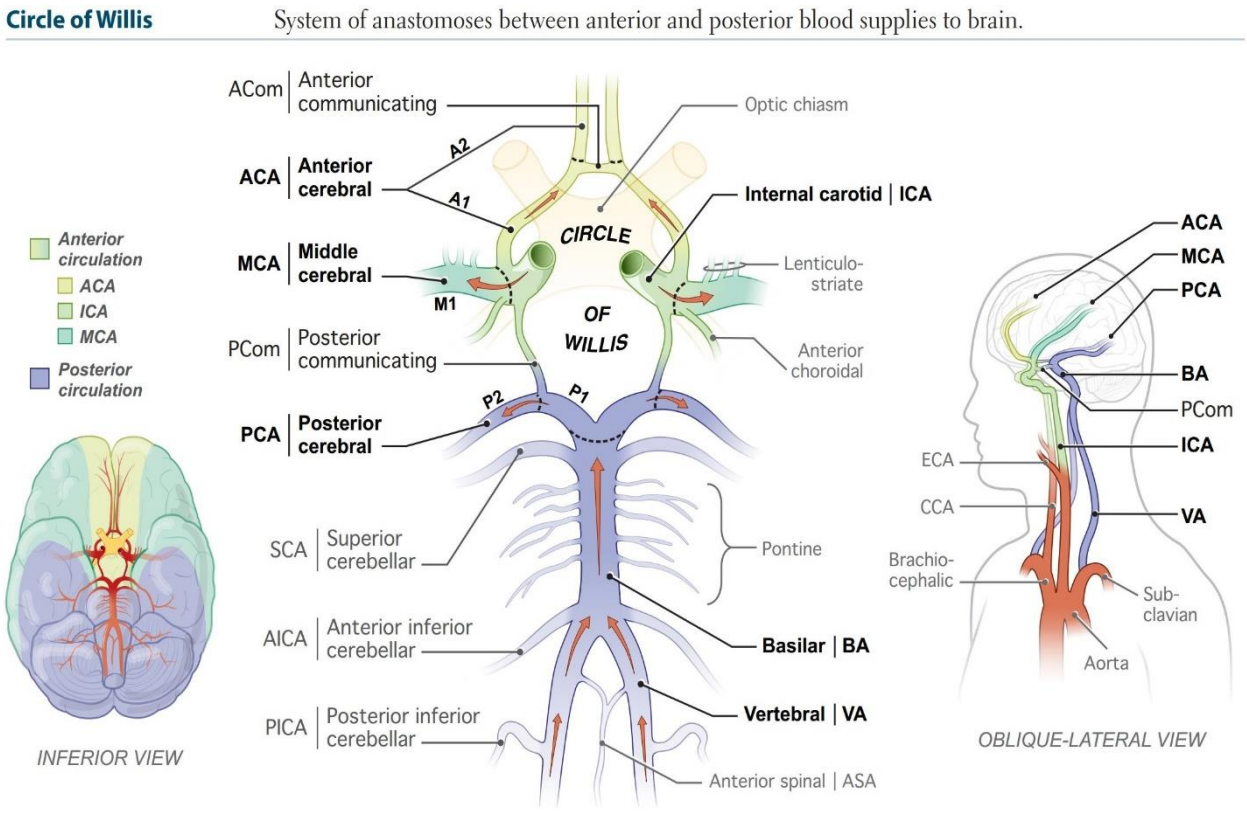
- Type: motor.

- Function and results of lesions:

- It is a purely motor nerve that supplies all muscles of the tongue except palatoglossus (X), so, its lesion will result in → deviation of the tongue toward the side of the lesion on protrusion (tongue licks the lesion) due to weakened tongue muscles on affected side.

Brain stem vascular syndromes

- The medial brain stem has a different vascular blood supply than the lateral brain stem.



1- Blood supply of the medulla:

- 2 vertebral arteries pass upwards through the vertebral foramina to enter the cranial cavity through the foramen magnum and runs upwards on each side of the medulla.

- Branches of the vertebral artery include:

- Anterior spinal artery (ASA) → supplies the ventromedial part of the medulla.
- Posterior inferior cerebellar artery (PICA) → supplies the dorsolateral part of the medulla.

2- Blood supply of the pons:

- Both vertebral arteries meet at the lower border of the pons to form one midline single artery, the basilar artery, which runs upwards on the ventral surface of the pons then divides into its two terminal branches the posterior cerebral arteries.

- Branches of the basilar arteries:

- Paramedian arteries (near the midline) → supplies the medial pons.
- Superior cerebellar artery → supplies lateral part of rostral pons (upper pons).
- Anterior inferior cerebellar artery (AICA) → supplies lateral part of the caudal pons (lower pons).

3- Blood supply of the midbrain:

- At the rostral end of the midbrain, the basilar artery divides into a pair of posterior cerebral arteries.

- Branches of the posterior cerebral artery: different branches supply medial and lateral midbrain.

❖ SO, in A nutshell:

- Branches of vertebral artery:

- ASA → medial medulla.
- PICA → lateral medulla.

- Branches of basilar artery:

- Paramedian → medial pons.
- Superior cerebellar → lateral part of upper pons.
- AICA → lateral part of lower pons.
- Posterior cerebral branches → different branches supply the medial and lateral midbrain.

❖ Some rules in brain stem vascular syndromes:

- It is uncommon to injure parts of the brain stem without involving one or more cranial nerves or affecting one or more of the descending or ascending long tracts.

- The cranial nerve lesion will localize the lesion to:

- Midbrain (CN III, IV).
- Upper Pons (CN V), Lower pons (CN VI, VII, VIII).
- Upper medulla (CN IX, X, XII).

- Lesions in the brain stem to any of the long tracts except for the descending hypothalamic fibers will result in a contralateral deficit.

- Lesion to the descending hypothalamic fibers that results in Horner syndrome is always seen ipsilateral to the side of the lesion.

❖ Qs - What you expect in brain stem vascular syndrome?

- A combination between a contralateral long tract sign with a cranial nerve sign.

1. Medial medullary syndrome (A):

- Cause: occlusion of the vertebral artery or the anterior spinal artery (ASA).

- Findings:

- Corticospinal tract → contralateral spastic paresis.

- Medial lemniscus → contralateral loss of touch, vibration and proprioception.

- XII Nucleus/fibers → ipsilateral flaccid paralysis of tongue with tongue deviation to the side of the lesion on protrusion.

2. Lateral medullary (Wallenberg) syndrome (B):

- Cause: occlusion of the posterior inferior cerebellar artery (PICA) or vascular dissection of the vertebral artery.

- Findings:

- Spinothalamic tract → contralateral loss of pain & temperature of the body.

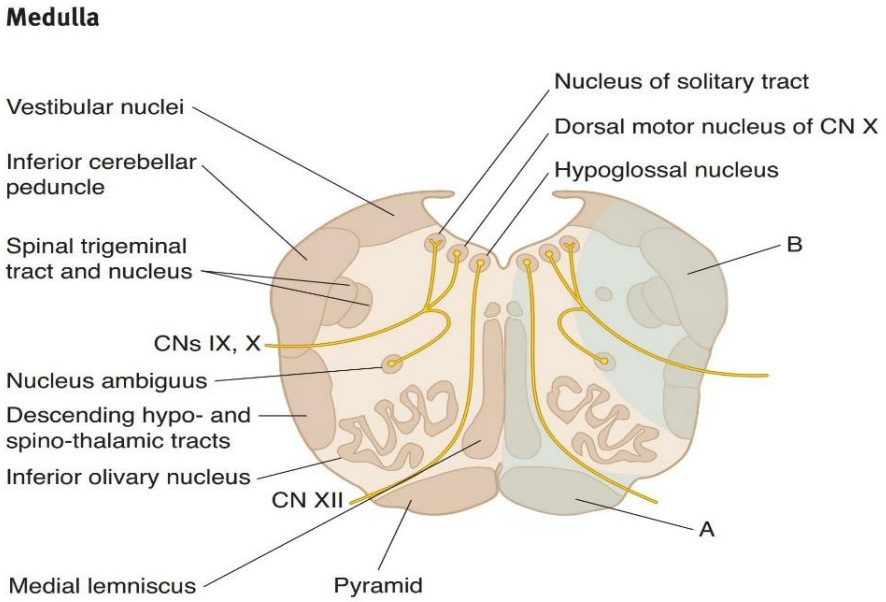
- Descending hypothalamic fibers → ipsilateral Horner syndrome.

- Inferior cerebellar peduncle → ipsilateral limb ataxia.

- Lesions of the glossopharyngeal nerve result in a diminished or absent gag reflex.

- Nucleus aMbiguous (X) → ipsilateral paralysis of larynx, pharynx, palate → dysarthria, dysphagia, loss of gag reflex. Nucleus ambiguus effects are specific to PICA lesions.

- Spinal nucleus of V CN → ipsilateral pain and temperature of the face.



3. Medial pontine syndrome:

- Cause: occlusion of the paramedian branches of Basilar arteries.

- Findings:

- Corticospinal tract → contralateral spastic paresis.

- Medial lemniscus → contralateral loss of touch & position and vibratory sensation.

- Fibers of VI CN → medial strabismus and diplobia.

4. Lateral pontine syndrome:

- Cause: occlusion of anterior inferior cerebellar artery (AICA). Also supplies middle and inferior cerebellar peduncles (part of cerebellum).

- Findings:

- Spinothalamic tract → contralateral loss of pain & temperature of the body.

- Descending hypothalamic fibers → ipsilateral Horner syndrome.

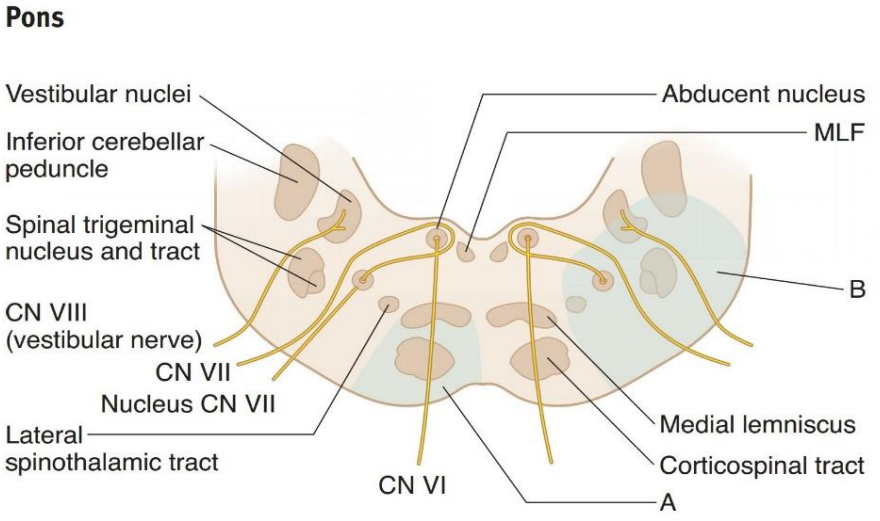
- Middle cerebellar peduncle → ipsilateral ataxia.

- Spinal nucleus & tract of V CN → ipsilateral loss of pain & temperature of the face.

- Facial nucleus & fibers of VII CN → ipsilateral facial paralysis (LMN lesion vs UMN lesion in cortical stroke), ipsilateral loss of taste (anterior two third of tongue), lacrimation, salivation, corneal reflex, and hyperacusis. Facial nucleus effects are specific to AICA lesions.

- Vestibular nuclei of VIII CN → vertigo, nausea & vomiting, and nystagmus.

- Cochlear nucleus & fibers of VIII CN → ipsilateral hearing loss.



5. Medial midbrain syndrome:

- Cause: occlusion of posterior cerebral arteries branches.

- Findings:

- Corticospinal tract → contralateral spastic paresis of the body.

- Corticobulbar tract → contralateral paresis of lower face.

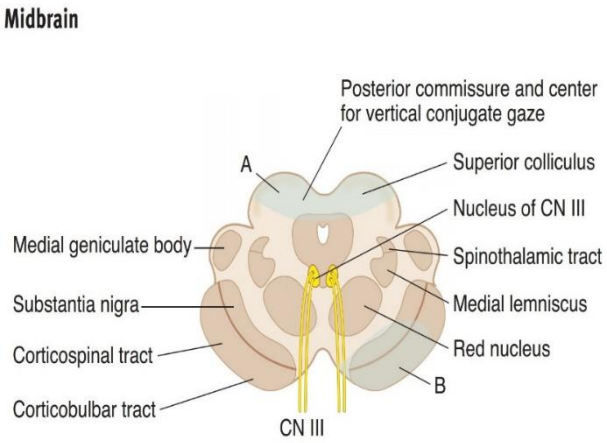
- Fibers of III CN → ipsilateral oculomotor palsy (lateral strabismus, dilated pupil, and ptosis).

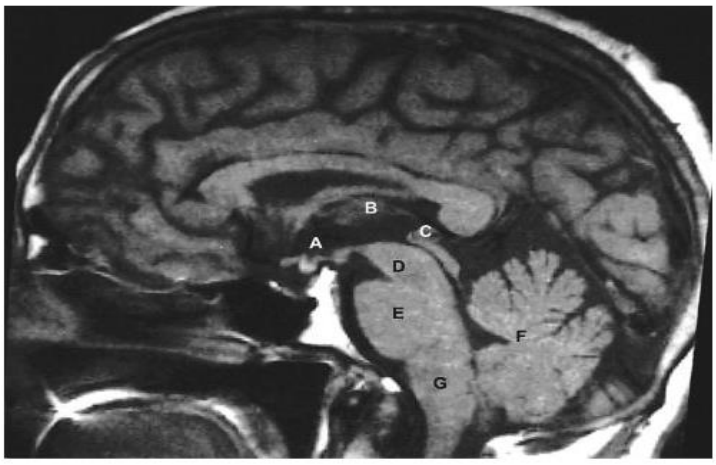
6. Dorsal midbrain (parinaud) syndrome:

- Cause: tumor in pineal region (Germinoma, malignant tumor thought to originate from embryonic germ cells).

- Findings:

- Compression by the tumor on:
  - Superior colliculus (responsible for upward gaze, eye looking up and down without movement of your head) → paralysis of upward gaze.
  - Pretectal area → pupillary reflex abnormalities, and light-near dissociation (pupils that react to accommodation but not to light).
  - Cerebral aqueduct of sylvius → noncommunicating hydrocephalus (papilledema, headache, and vomiting).
- It may present with Precocious puberty: it is caused by B-Hcg production. Precocious puberty is presented in males with growth of facial and pubic hair along with enlarged genitalia in a boy younger than 9 years old. For girls, it presents with appearance of secondary sexual characteristics before age 7.





A: Suprasellar region, B: Thalamus, C: pineal gland, D: Midbrain, E: Pons, G: Medulla, F: Cerebellum.

Cranial nerves and vessel pathway

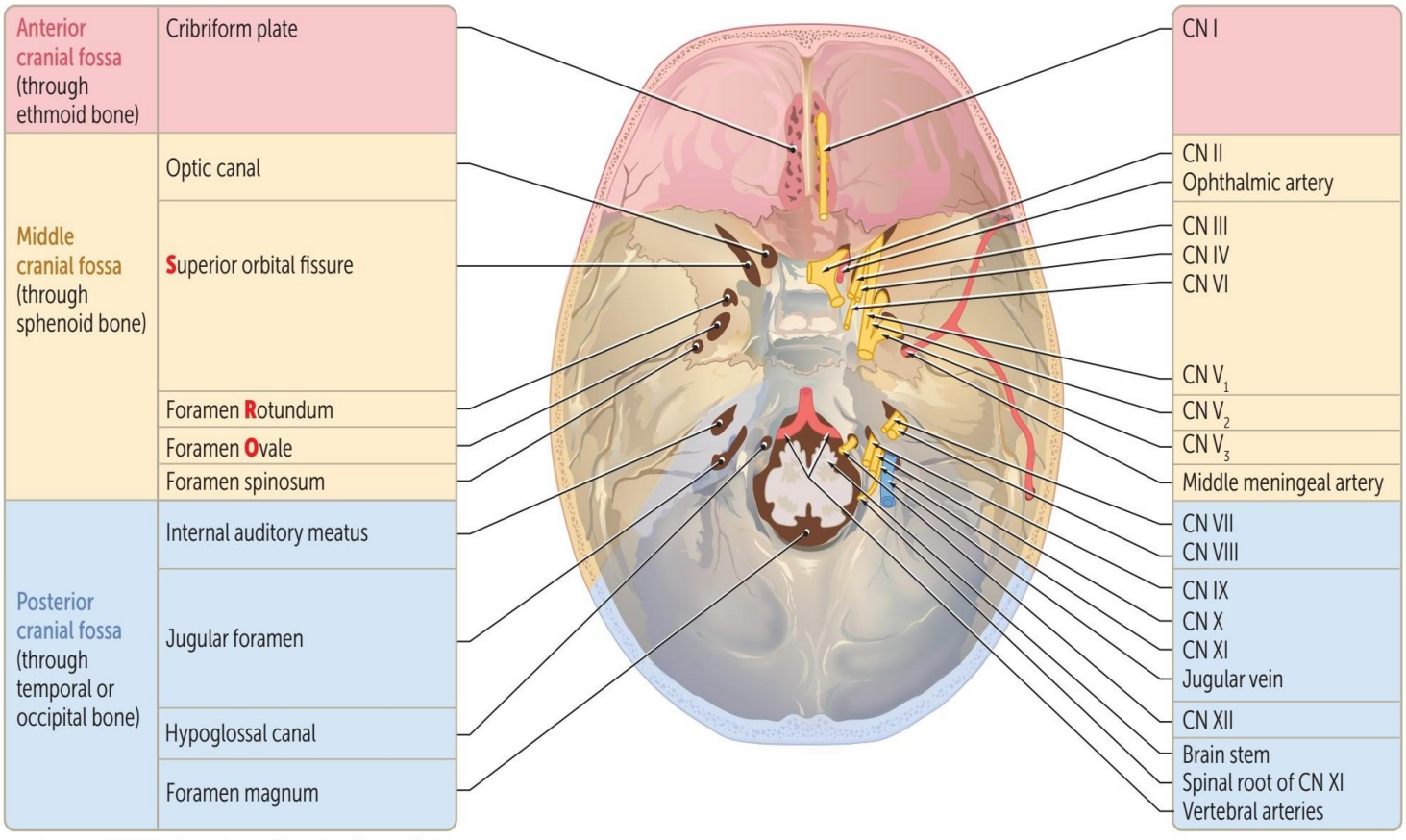
- Cribriform plate (CN I)

- Middle cranial fossa (CN II - VI) through sphenoid bone:

- Optic canal (CN II, ophthalmic artery, central retinal vein).
- Superior orbital fissure (CN III, IV, VI, V1, ophthalmic vein, sympathetic fibers).
- Foramen Rotundum (CN V2).
- Foramen Ovale (CN V3).
- Foramen spinosum (middle meningeal artery).
- Divisions of CN V exit owing to Standing Room Only.

- Posterior cranial fossa (CN VII - XII) through temporal or occipital bone:

- Internal auditory meatus (CN VII, VIII).
- Jugular foramen (CN IX, X, XI, jugular vein).
- Hypoglossal canal (CN XII).
- Foramen magnum (spinal roots of CN XI, brain stem, vertebral arteries).



Divisions of CN V exit owing to Standing Room Only

Jugular foramen (Vernet) syndrome

- Passing through the jugular foramen are cranial nerves (CN) IX, X, and XI.

- Lesions of the jugular foramen (due to tumors as metastasis to bone, trauma, or infection) can result in jugular foramen (Vernet) syndrome, which is characterized by CN IX. X, and XI dysfunction (Symptoms are related to the nerve affected):

- Loss of taste from the posterior 1/3 of the tongue (CN IX)
- Loss of gag reflex (CN IX, X).
- Dysphagia (CN IX, X).
- Dysphonia/hoarseness (CN X).
- Soft palate drop with deviation of the uvula toward the contralateral side (CN X).
- Sternocleidomastoid and trapezius muscle paresis (CN XI).

Cranial nerve reflexes

Reflex	Afferent	Efferent
Corneal	V1	VII (orbicularis oculi)
Lacrimation	V1	VII
Jaw reflex	V3 (sensory – muscle spindle from masseter)	V3 (Motor – Masseter)
Pupillary	II	III
Gag	IX	X
Cough	X	X

Common cranial nerve lesions

Common cranial nerve lesions	Results
CN V motor lesion	Jaw deviates toward side of lesion due to unopposed force from the opposite pterygoid muscle.
CN X lesion	Uvula deviates away from side of lesion. Weak side collapses and uvula points away.
CN XI lesion	Weakness turning head to contralateral side of lesion (sternocleidomastoid). Because the left SCM contracts to help turn the head to the right. Shoulder droop on side of lesion (trapezius)
CN XII lesion	Tongue deviates toward side of lesion (lick your tongue) due to weakened tongue muscles on affected side.

Innervation of the tongue

- Innervation of the tongue is complex, as there are motor, general sensory and gustatory (taste) components:

1- Motor innervation:

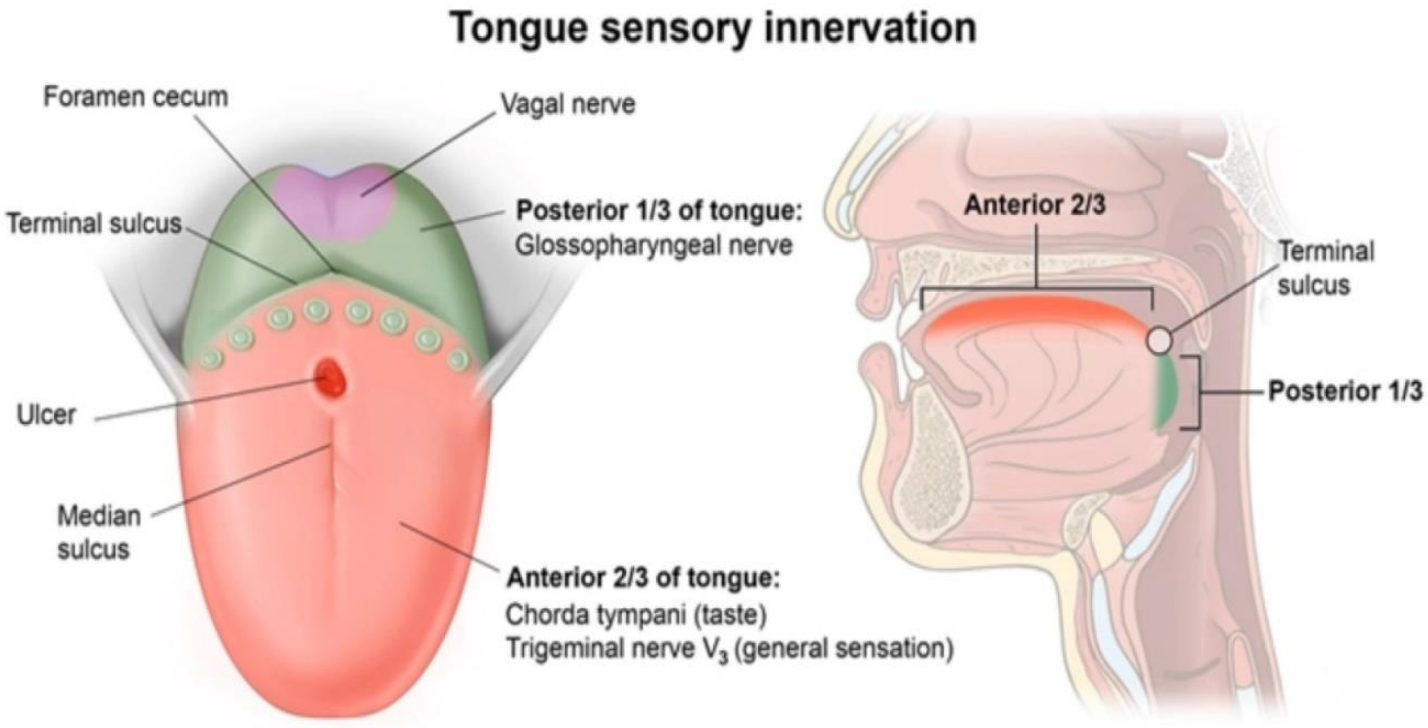
- Motor innervation of the tongue is provided by the hypoglossal nerve (CN XII) with the exception of the palatoglossus muscle, which is innervated by the vagus nerve (CN X).

2- General sensory:

- General sensory innervation of the tongue (including touch, pain, pressure and temperature sensation) is provided by:
  - Anterior 2/3 of the tongue → mandibular branch of trigeminal nerve (CN V3).
  - Posterior 1/3 of the tongue → glossopharyngeal nerve (CN IX).
  - Posterior area of the tongue root → Vagus nerve (CN X).

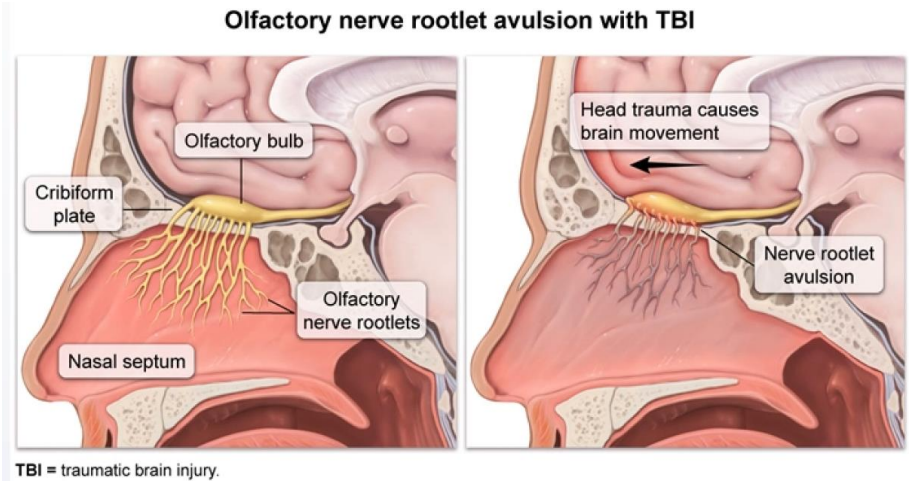
3- Gustatory innervation (taste buds):

- Anterior 2/3 of the tongue → chorda tympani branch of facial nerve (CN VII).
- Posterior 1/3 of the tongue → glossopharyngeal nerve (CN IX).
- Posterior area of the tongue root → Vagus nerve (CN X).



❖ N.B:

- Smell occurs when odorants bind to nasal chemoreceptors that relay signals via the olfactory nerve through the cribriform plate to the olfactory bulb, which then projects to the primary olfactory cortex in the medial temporal lobe.
- Head trauma can tear olfactory nerve rootlets as they cross the cribriform plate, causing anosmia. Acceleration-deceleration forces during head trauma can lead to avulsion of the olfactory nerve rootlets as they transverse the cribriform plate, resulting in anosmia. The flavor of food and beverages is dependent on smell and taste, with smell being the most important contributing factor. Consequently, patients with loss of smell often describe problems with taste.
- Anosmia is often associated with ageusia (loss of taste).



Cavernous sinus

- Collection of venous sinuses on either side of pituitary gland.
- Blood from eye and superficial cortex → cavernous sinus → internal jugular vein.
- Nerves that control extraocular muscles (CN III, IV, VI) + V1 and occasionally V2 + cavernous portion of internal carotid artery + postganglionic sympathetic pupillary fibers en route to orbit, all pass through cavernous sinus.

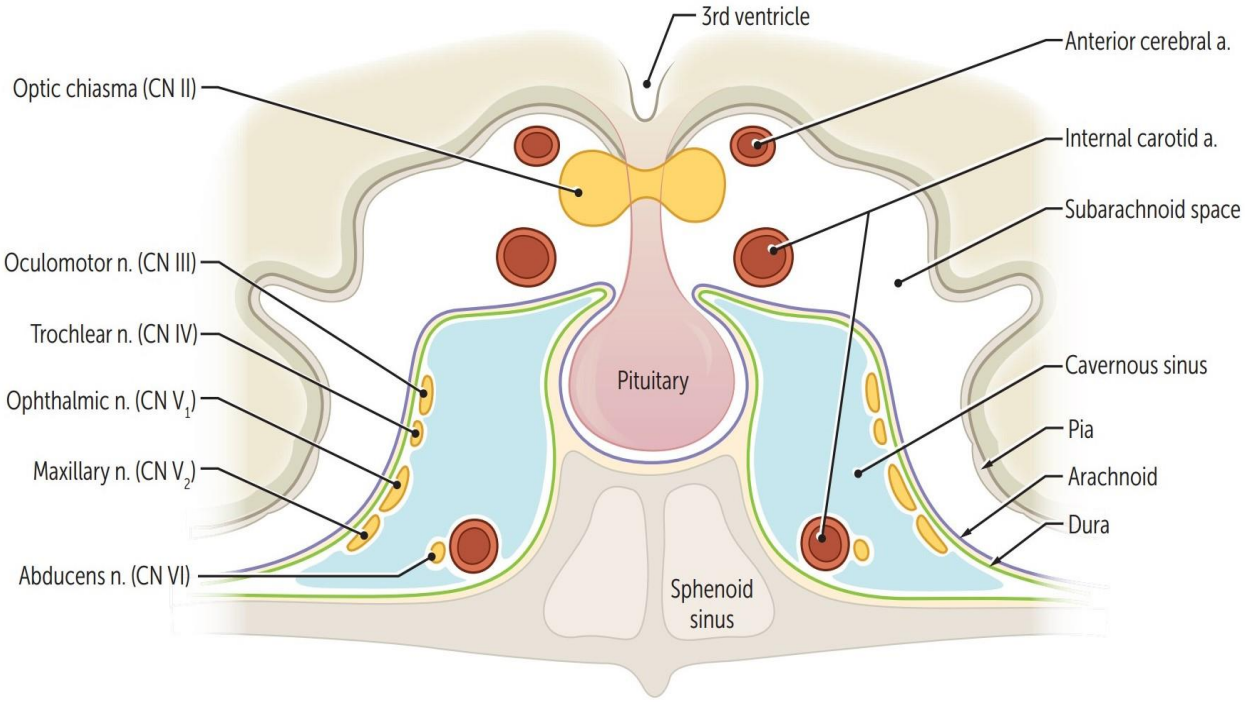
1. Cavernous sinus syndrome:

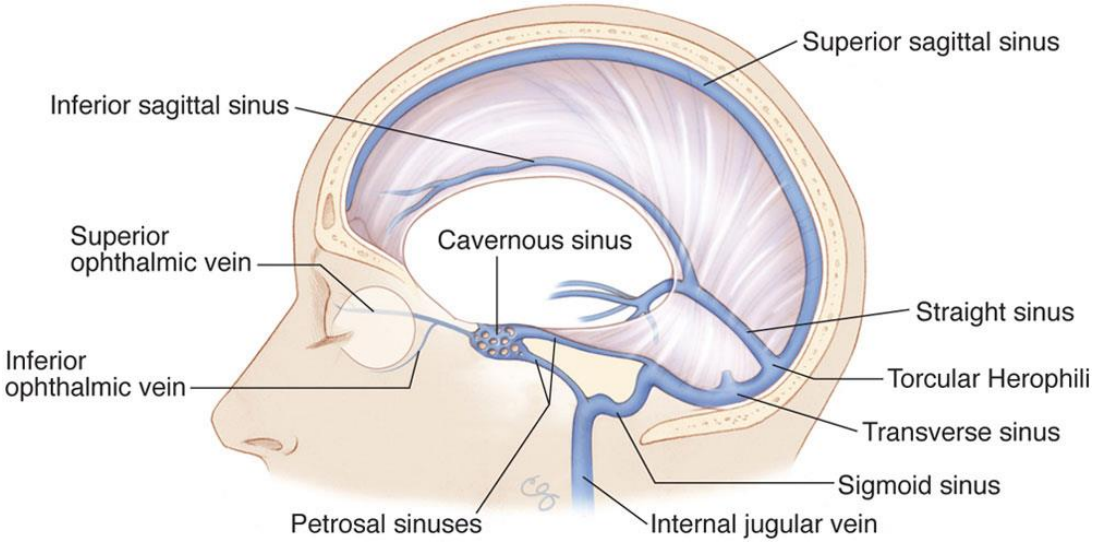
- Causes:

- Pituitary tumor mass effect.
- Cavernous sinus thrombosis (formation of a blood clot within the cavernous sinus, the cause is usually from a spreading infection in the nose, sinuses, ears, or teeth. Staphylococcus aureus and Streptococcus are often the associated bacteria).
- Because of its connections with the facial vein via the superior ophthalmic vein, it is possible to get infections in the cavernous sinus from an external facial injury within the danger area of the face. In patients with thrombophlebitis of the facial vein, pieces of the clot may break off and enter the cavernous sinus, forming a cavernous sinus thrombosis.

- Findings:
  - Present with variable ophthalmoplegia, ↓ corneal sensation, occasional decrease in maxillary sensation, and Horner syndrome.

  - CN VI and internal carotid artery are most susceptible to injury because they are more medial.

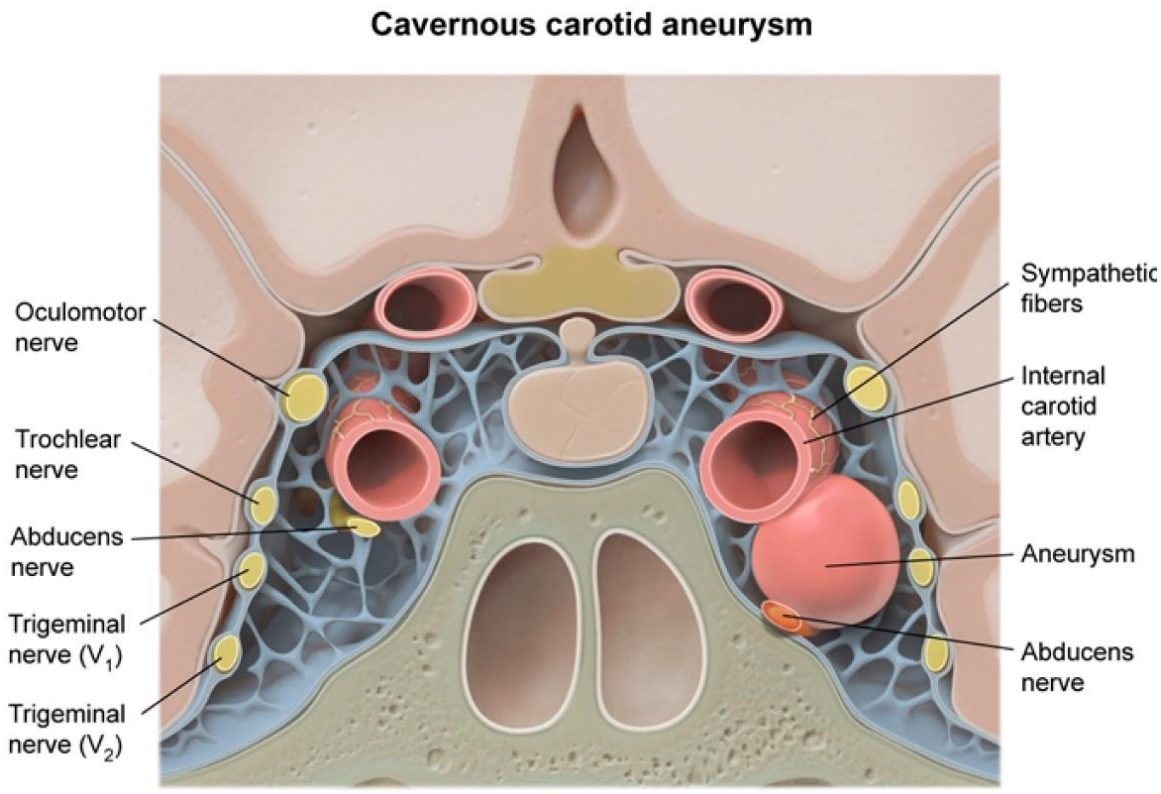




2. Cavernous carotid aneurysm:

- An expanding aneurysm in the cavernous portion of the internal carotid artery (ICA) is most likely to initially cause headache and diplopia (ipsilateral lateral rectus weakness) due to compressing or stretching of the abducens nerve (CN VI) as it runs next to the ICA in the cavernous sinus.

- Other commonly affected nerves include the oculomotor nerve (CN III), trochlear nerve (CN IV), and the V1 and V2 branches of the trigeminal nerve (CN V).



Cerebellum

- The cerebellum is derived from the metencephalon.

- It is located dorsal to the pons and the medulla and the fourth ventricle is found between the cerebellum and the dorsal aspect of the pons.

- Function:

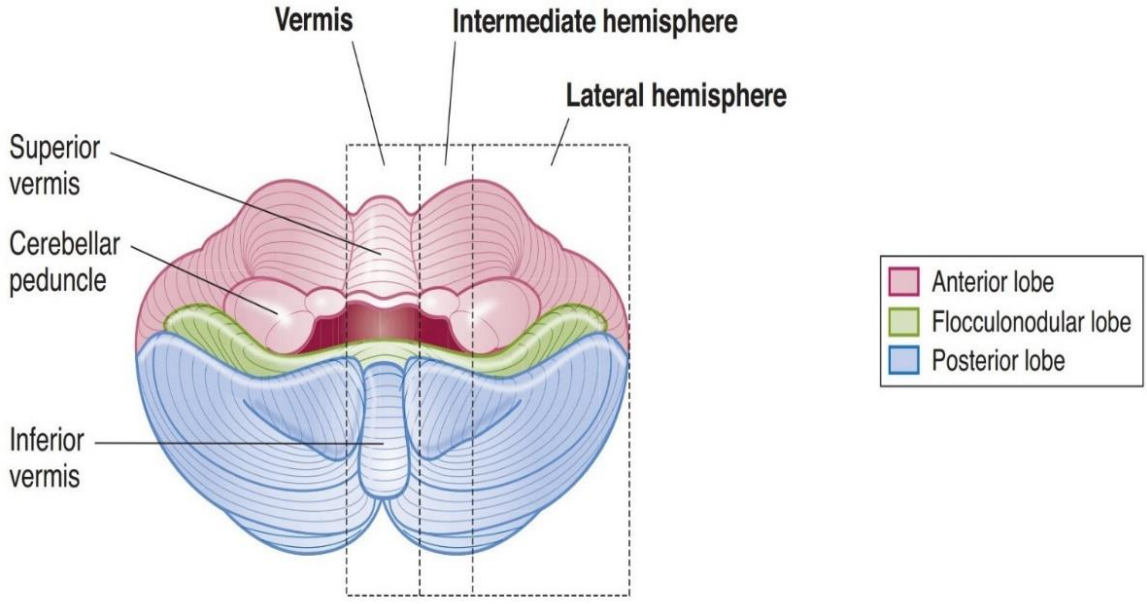
- The main function of the cerebellum is to promote smooth execution of skeletal muscle contractions.
- It has also a role in motor planning and is involved in control of balance and eye movement.

- Both of cerebellum and basal ganglia mediate their effect by influencing the upper motor neuron. The basal ganglia is responsible for getting the movement started (initiate skeletal muscle contraction), but the cerebellum is responsible for promoting smooth execution of skeletal muscle contraction.

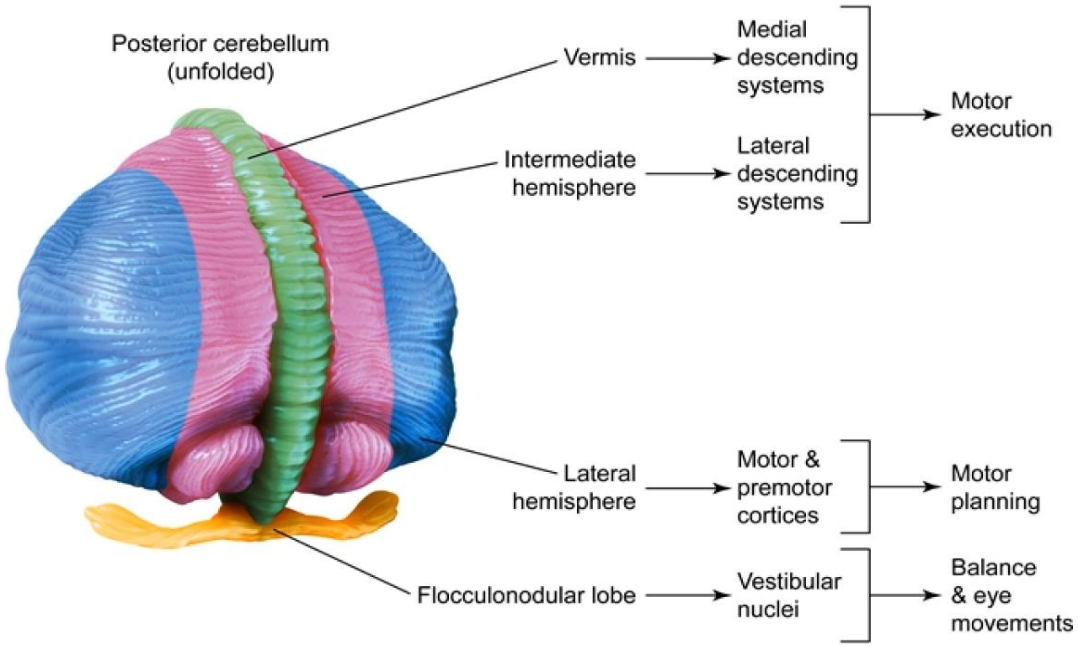
- The cerebellum consists of a midline vermis and 2 lateral cerebellar hemispheres.

- The topographic organization of the cerebellum indicates that:

- The vermis → controls the axial and proximal musculature of the limbs.
- The intermediate part of cerebellar hemisphere → controls distal musculature of the limbs.
- The lateral part of cerebellar hemisphere → is involved in motor planning.
- The flocculonodular lobe → involved in control of balance and eye movement.



Functional anatomy of the cerebellum



- Cerebellar peduncles:

- Cerebellar peduncles are the parts that connects cerebellum to the brain stem. There are 6 cerebellar peduncles, 3 on the left and 3 on the right which include, superior cerebellar peduncle, middle cerebellar peduncle and inferior cerebellar peduncle.

- Major input to the cerebellum travels in → the inferior cerebellar peduncle (ICP) and middle cerebellar peduncle (MCP):
  - Input form contralateral cortex via middle cerebellar peduncle.
  - Input from ipsilateral proprioceptive information via inferior cerebellar peduncle from spinal cord.

- Major outflow from the cerebellum travels in → the superior cerebellar peduncle (SCP).

- How the cerebellum smoothen and modulate skeletal muscle contraction:

- The cerebellar cortex is formed of 3 cell layers: the molecular layer, the purkinje layer and the granule cell layer.

- The purkinje layer is the middle and most important layer of the cerebellar cortex.

- All of the inputs to the cerebellum are directed toward influencing the firing of purkinje cells, and only axons of purkinje cells leave the cerebellar cortex.

- All of the outflow of the cerebellar cortex is inhibitory (using GABA neurotransmitter) and all of the input to the cerebellar cortex is excitatory (using glutamate neurotransmitter).

- The excitatory input enters the cerebellum in the form of climbing fibers and mossy fibers.

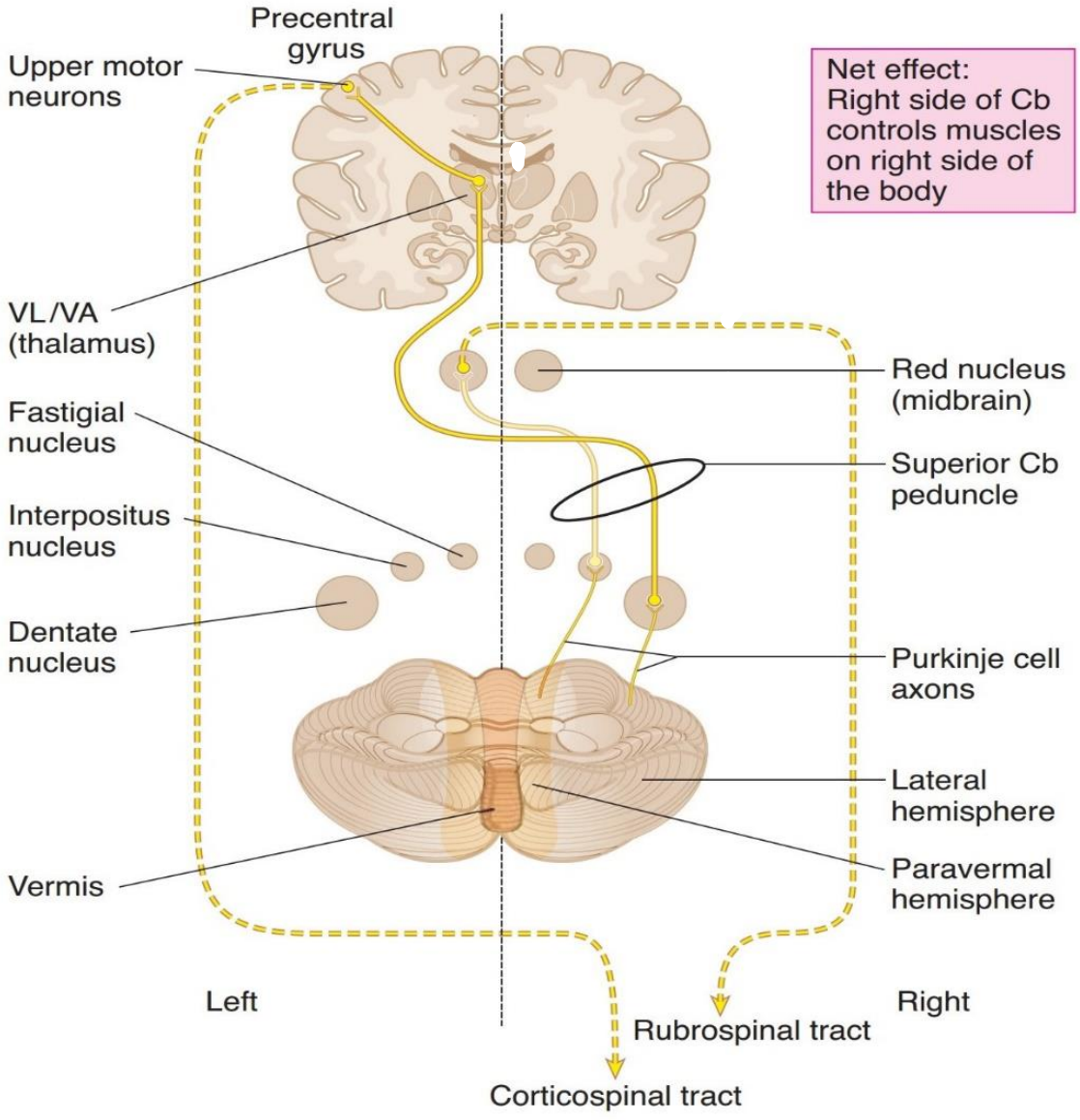
- Purkinje cell axons project to and inhibit the deep cerebellar nuclei.

- The neurotransmitter that is used by purkinje cells is GABA which is an inhibitory neurotransmitter, that's why the entire outflow of the cerebellum is inhibitory and this makes sense because the main function of the cerebellum is smoothening or modulating the skeletal muscle contraction by inhibition of the UMN through the purkinje cells of the cerebellum.

- There are four deep cerebellar nuclei, from Lateral → Medial: Dentate, Emboliform, Globose, and Fastigial " Don't Eat Greasy Foods ", the most important of them is the dentate nucleus.

- Axons from the dentate nucleus leave through the superior cerebellar peduncle, cross the midline, and terminate in the ventrolateral (VL) nucleus of the thalamus.

- The VL nucleus of the thalamus projects to primary motor cortex to inhibit the upper motor neurons (corticospinal and corticobulbar tracts) to smoothen and modulate skeletal muscle contraction.



- Spinocerebellar tract pathway:

- Carry unconscious proprioceptive input from muscle spindle and Golgi tendon organ to the cerebellum, where this information is used to help monitor and modulate movements.

- It enters the spinal cord through dorsal root fibers to relay in the dorsal root ganglion, then ascends to project sensory information about unconscious proprioception to the ipsilateral cerebellum via the inferior cerebellar peduncle (No crossing).

Cerebellar lesions

- Qs- where do you expect the symptoms associated with cerebellar lesions will be?

- It will be ipsilateral, why? - Because there is double crossing!

- The major outflow of the cerebellum projects to the contralateral motor cortex by crossing through the superior cerebellar peduncle, then the corticospinal fibers cross on their way to the spinal cord by crossing through lower medulla.

- SO, unilateral lesions of the cerebellum will result in ipsilateral symptoms (toward the side of the lesion).

1- Lateral lesions (lesions that include the hemisphere):

- The lateral part of the cerebellar hemisphere controls the lateral musculature of the limbs, SO, lesion of the lateral hemisphere will result in:

- Gait: Propensity to fall toward injured side (ipsilateral ataxic gait).

- Speech: Scanning speech, patient divide words into syllables due to asynergy of the muscles responsible for speech.

- Intention Tremors (tremors with an intended movement):
  - Tremors mean when they perform a voluntary movement, they can't execute it smoothly.
  - Intention means tremors with movement and absent at rest.

- Dysmetria: inability to stop movement at the proper place.

- Dysdiadochokinesia: reduced ability to perform alternating movements, such as pronation and supination of the forearm.

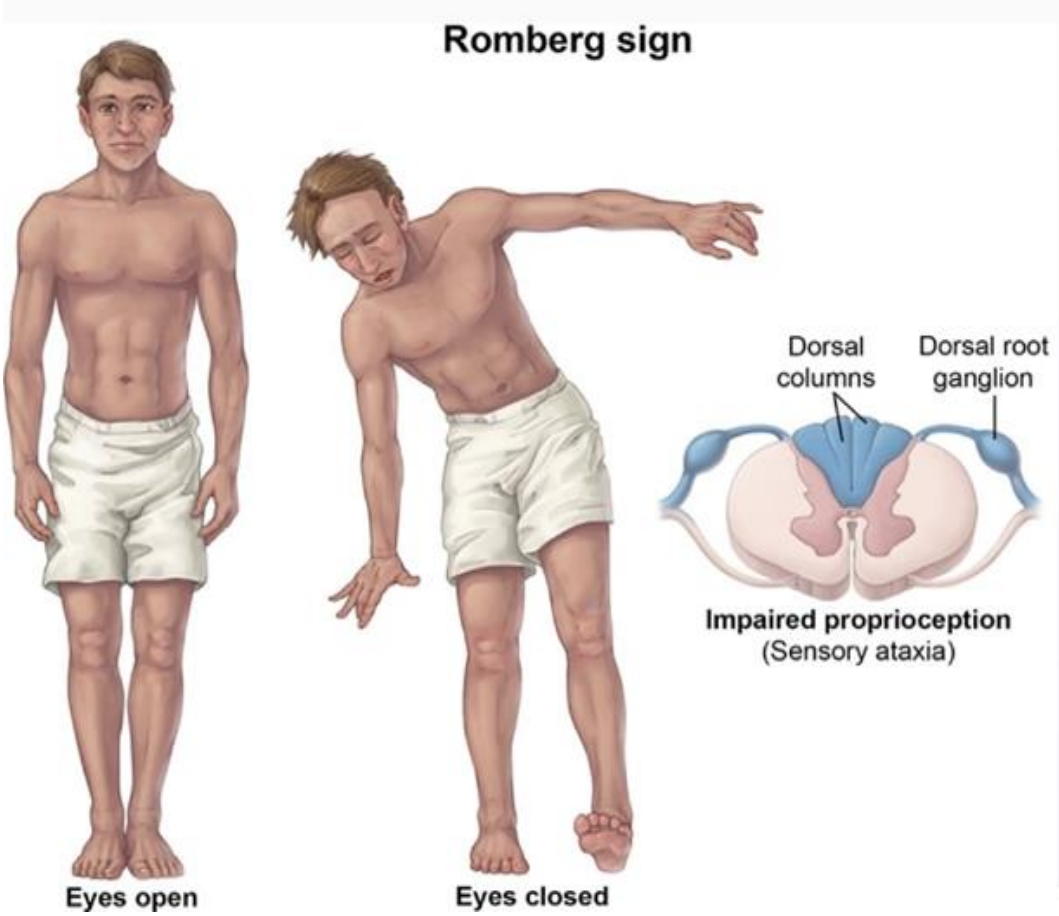
- Nystagmus:
  - The function of cerebellum is to keep your eyes fixed on the target of the interest during horizontal gaze.
  - SO, in cerebellar lesion, the eyes may pass the target of interest or stop too soon and then oscillate a few times before they settle on the target.

2- Medial lesions (lesions that include the vermis):

- The vermis controls the axial and proximal musculature of the limbs, So, lesion of the vermis will result in truncal ataxia (wide-based cerebellar ataxic gait).

- Qs- How to differentiate ataxic gait in patient with vermal lesion from those with a lesion of the dorsal column?

- By Romberg sign:
  - In cerebellar lesions → patients will sway or lose their balance with their eyes open or close.
  - In dorsal column lesion → patients sway with their eyes closed only (+ Romberg sign).



Friedreich Ataxia

- Cause:

- One of the hereditary ataxic disorders.

- Autosomal recessive trinucleotide repeat disorder (expansion of the GAA triplet repeat) on chromosome 9 in gene that codes frataxin protein (mitochondrial protein that is important in electron transport chain) → decrease in its expression (low frataxin level) → excess oxygen free radicals → progressive damage to the nervous system.

- Findings:

- Degeneration of pyramidal tract → muscle weakness in the arms and legs.

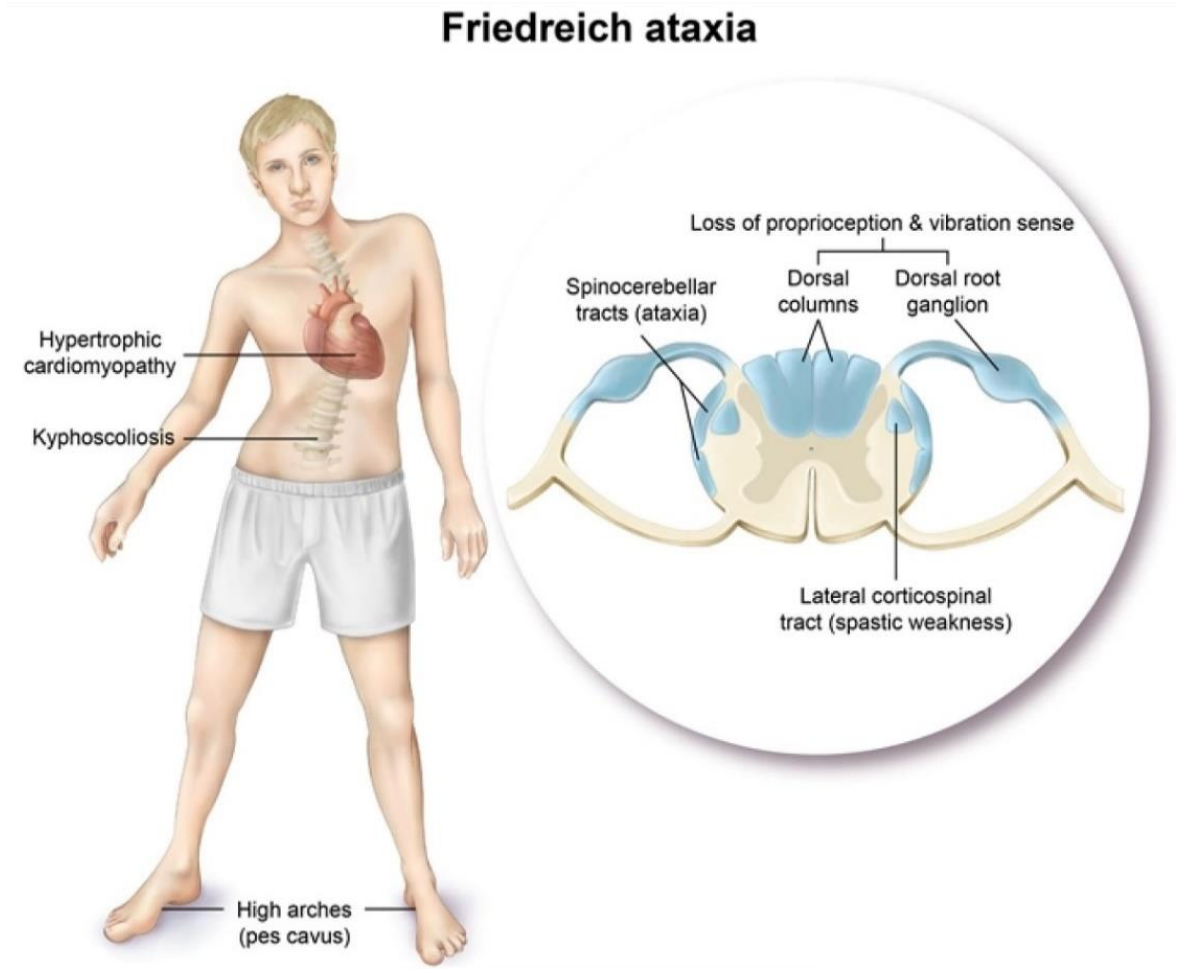
- Degeneration of spinocerebellar tract → gait ataxia, staggering gait, frequent fall, nystagmus and dysarthria (slurred speech).

- Degeneration of dorsal column → loss of vibratory and proprioception sense.

- Degeneration of peripheral nerves → loss of deep tendon reflexes

- Skeletal deformities → kyphoscoliosis, pes cavus, and hammer toes.

- Associated with diabetes mellitus and hypertrophic cardiomyopathy (cause of death).



Friedreich ataxia	
Genetics	• Autosomal recessive • Loss-of-function, trinucleotide repeat (GAA) in *frataxin* gene
Clinical features	• Neurologic deficits ◦ Cerebellar ataxia ◦ Dysarthria ◦ Loss of vibration and/or position sense ◦ Absent deep tendon reflexes • Hypertrophic cardiomyopathy • Skeletal deformities (eg, scoliosis) • Diabetes mellitus
Prognosis	• Mean survival age 30-40 • Mortality due to cardiac dysfunction (eg, arrhythmia, congestive heart failure)

❖ N.B:

- Vitamin E primarily serves to protect fatty acids from oxidation. As a result, vitamin E deficiency predisposes those cell membranes with high fatty acid content to oxidative injury.
- The cells that are most susceptible to increased oxidation in vitamin E deficiency are erythrocytes → hemolytic anemia and neurons with long axons, specifically, spinocerebellar tract, dorsal column of spinal cord and peripheral nerves.
- That's why vitamin E deficiency symptoms closely mimic Friedreich ataxia because many of the same areas of the CNS are affected.

Basal Ganglia

- Function: initiate skeletal muscle contraction.
- Striatum = putamen (motor) + Caudate (cognitive).
- Lentiform = putamen + globus pallidus.
- The basal ganglia receive excitatory inputs from large areas of cerebral cortex, then project back to the motor cortex after a relay in the ventrolateral nucleus of the thalamus (motor nucleus of the thalamus).
- The basal ganglia, motor cortex and the ventrolateral nucleus of the thalamus are interconnected together to form 2 parallel but antagonistic circuits known as the direct and indirect pathways.
- Both pathways use a process known as "disinhibition" to mediate their effects, whereby one population of inhibitory neurons inhibits a second population of inhibitory neuron utilizing 2 GABA neurons in series.
- The net effect of disinhibition (inhibition of the inhibitory) is excitation.

1- Direct pathway (excitatory):

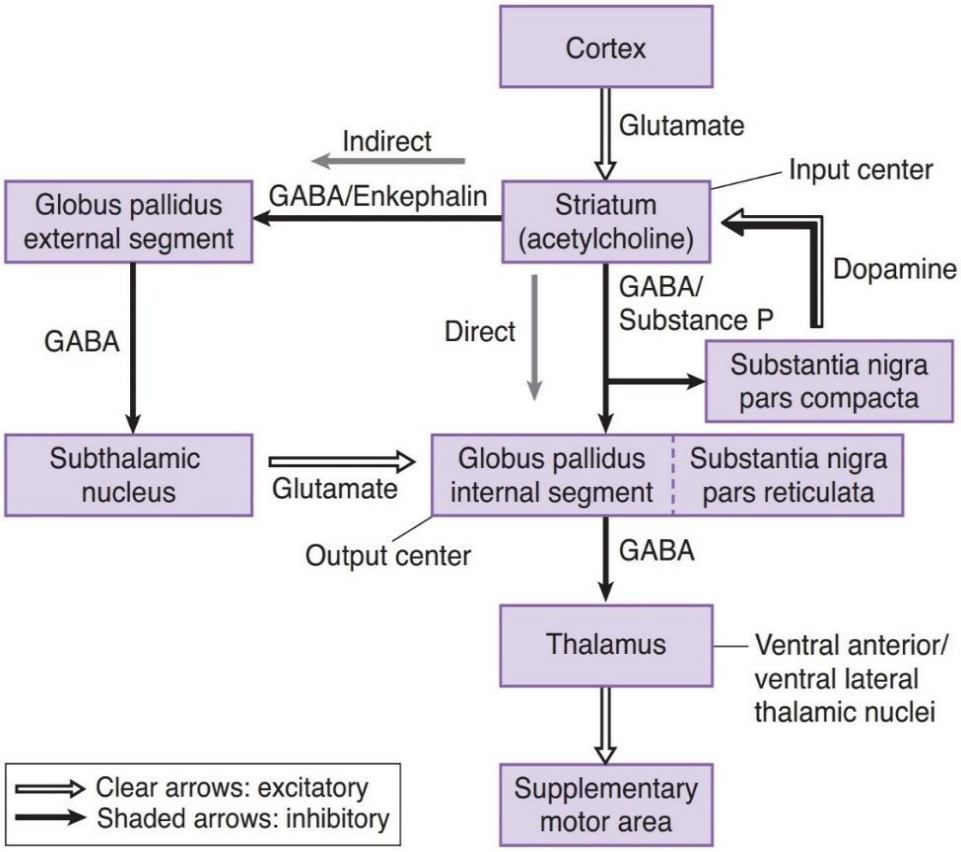
- Excitatory input from the cerebral cortex (glutamate) projects to → striatal neurons in the caudate and putamen nuclei (inhibitory neuron, use GABA) project to → Globus pallidus internal segment (inhibitory neuron, use GABA) → the GABA axons of the internal segment of Globus pallidus project to → thalamus which is disinhibited (inhibition of the inhibitory, So the net effect is excitation), then the thalamic input excites → the motor cortex.

❖ SO, the net effect of the disinhibition in the direct pathway results in an increased level of cortical excitation and the initiation of movement.

2- Indirect pathway (inhibitory):

- Excitatory input from the cerebral cortex (glutamate) projects to → striatal neurons in the caudate and putamen nuclei (inhibitory neuron, use GABA) project to → Globus pallidus external segment (inhibitory neuron , use GABA) → the GABA axons of the external segment of Globus pallidus project to → subthalamic nucleus which is disinhibited (excited) , the subthalamic nucleus excites inhibitory GABA neurons in the internal segment of the Globus pallidus which inhibits the thalamus, then the thalamic input inhibit → the motor cortex.

❖ SO, the net effect of the disinhibition in the indirect pathway results in a decreased level of cortical excitation → suppression of unwanted movement.



- <u>In addition to the GABA neurons, 2 other neurons of chemically significant neurons enhance the effects of the direct or indirect pathways:</u>

1- Dopaminergic neurons in the substania nigra which project to striatum. The effect of dopamine drives the direct pathway increasing cortical excitation. Dopamine excites the direct pathway through D_1 receptors and inhibits the indirect pathway through D_2 receptors.

2- Cholinergic neurons found within the striatum have the opposite effect. Acetyl choline (ACH) drives the indirect pathway, decreasing cortical excitation.

- <u>Direct pathway (excitatory)</u>:
- Excites or Drive motor cortex.
- Promotes initiation of movement.
- Enhanced by Dopamine.

- <u>Indirect pathway (inhibitory)</u>:
- Inhibits motor cortex.
- Suppresses unwanted movement.
- Enhanced by ACH.

❖ N.B: Unlike the cerebellum, the outflow of the basal ganglia doesn't cross to the other side, it projects to the motor cortex of the same side.

- Qs - Where do you expect the signs of right basal ganglia lesion will be?
- It will influence the initiation of movement on the contralateral side. Because the Right basal ganglia projects to the right motor cortex that innervates the left side of the body because corticospinal tract (UMN) crosses in lower medulla.

Basal Ganglia Lesions

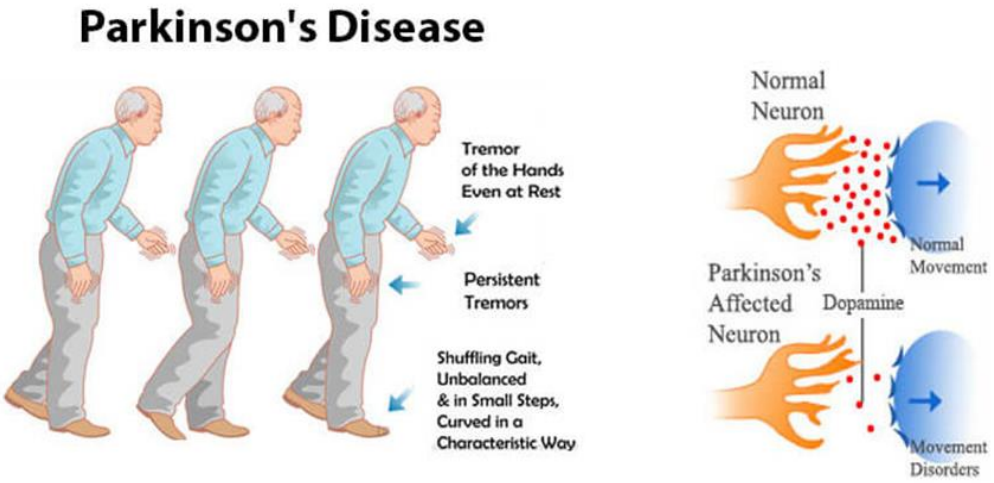
1- Parkinson disease:

- Cause:
- Loss of pigmented dopaminergic neurons from substantia nigra (that drives the direct pathway) → underactive motor cortex.

- Findings:
- Parkinson TRAPS your body and mask your face (expressionless):
  - Tremors (pill-rolling resting tremors vs. intention tremors in cerebellar lesions).
  - Rigidity (cogwheel).
  - Akinesia or bradykinesia.
  - Postural instability.
  - Shuffling gate.

- Lewy bodies: intracytoplasmic eosinophilic inclusions, contain alpha synuclein.

- MPTP, a contaminant in illegal drugs, is metabolized to MPP+, which is toxic to substantia nigra which causes permanent symptoms of Parkinson's disease.



- Patients with medically intractable symptoms of Parkinson disease may benefit from high-frequency deep brain stimulation of the globus pallidus internus or subthalamic nucleus as it promotes thalamo-cortical disinhibition with improved mobility.

2- Huntington disease:

- Onset:

- Between ages 20 and 50.

- Cause:

- Autosomal dominant trinucleotide repeat disorder on chromosome 4 (CAG) which codes for huntingtin protein → degeneration of GABAnergic neurons in neostriatum (mainly caudate nucleus) → leading to atrophy of caudate nucleus → enlargement of the frontal horns of the lateral ventricles.

- Huntington disease is considered an indirect pathway lesion because the degeneration of GABAnergic neurons affects mainly the indirect pathway that is supposed to suppress unwanted movement, So, the findings of Huntington disease are mainly in the form of purposeless involuntary movement as:

- Chorea (sudden, jerky, purposeless movement).
- Athetosis (writhing, snake like movement).
- Personality changes.
- Aggression, depression and dementia.

- Disease show anticipation and genetic imprinting.

- ↑ Dopamine, ↓ GABA and ACH. Caudate loses ACh and GABA.

- Loss of GABA containing neurons leads to decreased GABA in the brain, this is the most characteristic biochemical feature of Huntington disease.

3- Wilson disease (hepatolenticular degeneration):

- Cause:

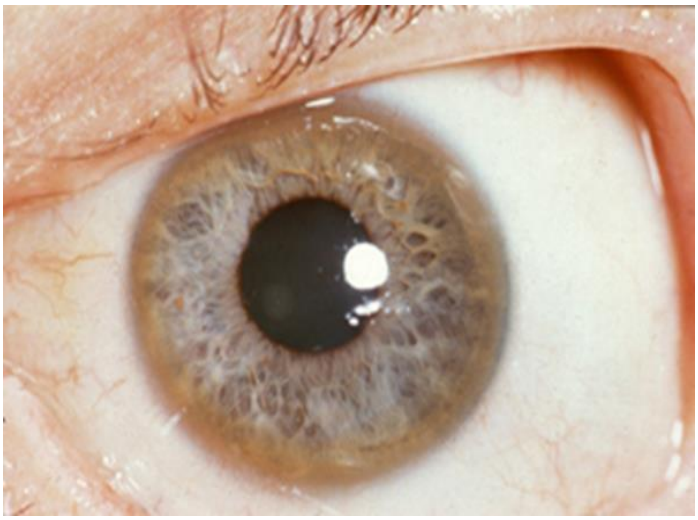
- Autosomal recessive defect in copper transport → accumulation of copper in liver, basal ganglia and eye.

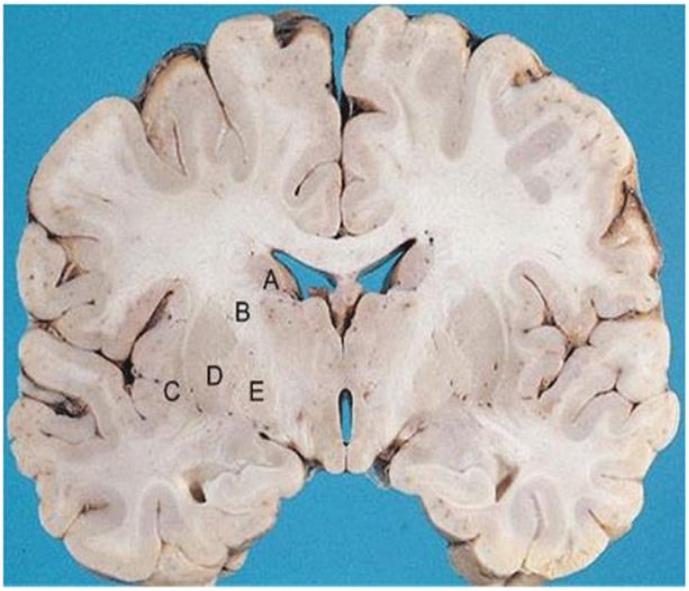
- Findings:

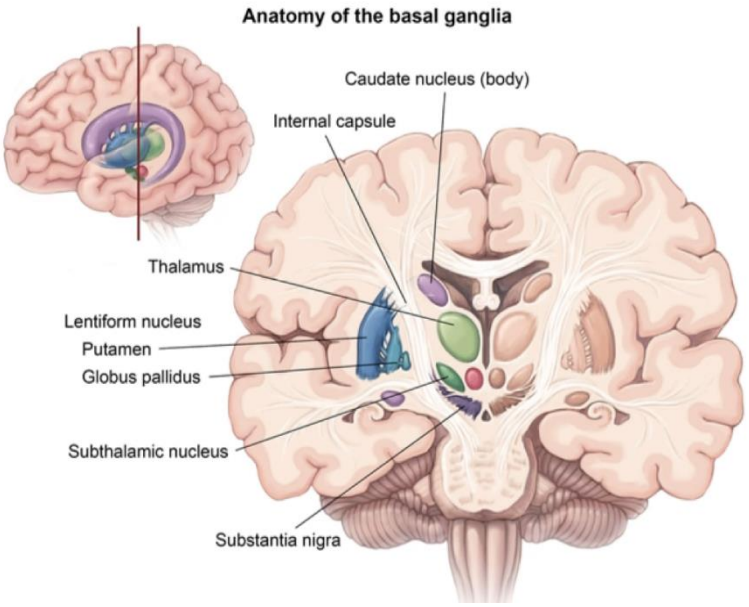
- Accumulation of copper in:

  - Liver → fatty change, hepatitis and cirrhosis.
  - Basal ganglia → cystic degeneration of the putamen → one or both pathways (direct & indirect) may be involved, So, the findings are combination of either parkinsonian dyskinesia or Huntington chorea with other neuropsychiatric symptoms.
  - Eye → accumulation of copper in Descemet's membrane (edges of the cornea) producing Kayser-Fleischer ring (pathognomonic).

- Treatment: penicillamine (acts as a chelator).







A - Caudate nucleus B - Internal capsule C - Insula D - the putamen E - the Globus pallidus

- The caudate is atrophied in Huntington's disease, but in Wilson's disease there is cystic degeneration of the putamen.

4- Hemibalsmus:

- Cause:

- Damage of the subthalamic nucleus which play an important role in the modulation of basal ganglia output, most commonly from a lacunar stroke (usually have a long history of hypertension).

- Findings:

- Contralateral Wild, flinging movement of limbs.

Types of tremors

- Intension tremors: in cerebellar lesions.
- Resting pill rolling tremors: in basal ganglia lesions as Parkinson disease.
- Essential tremors:

- It is the most common diagnosed movement disorder.
- Essential tremor is believed to be inherited in an autosomal dominant fashion, So, it is sometimes also referred to as familial tremor.
- Patients experience a slowly progressive symmetric postural and/or kinetic tremor that most commonly affects the upper extremities.
- Patients commonly report that their symptoms improve with alcohol consumption.
- First line treatment is the nonspecific beta blockers as propranolol.

Diencephalon

1- Thalamus:

- Serves as a major sensory relay for information that ultimately reaches the neocortex. Motor control areas (basal ganglia & cerebellum) also synapse in the thalamus before reaching the cortex.

NUCLEUS	INPUT	INFO	DESTINATION	MNEMONIC
Ventral Postero-Lateral Nucleus (VPL)	Spinothalamic and dorsal column/medial lemniscus	Vibration, Pain, Pressure, Proprioception, Light touch, temperature	Primary somatosensory cortex.	
Ventral Postero-Medial nucleus (VPM)	Trigeminal and gustatory pathway.	Face sensation, taste.	Primary somatosensory cortex.	Makeup goes on the face
Lateral Geniculate nucleus (LGN)	CN II	Vision	Calcarine sulcus	Lateral for Light
Medial geniculate nucleus (MGN)	Superior olive and inferior colliculus of tectum.	Hearing	Auditory cortex of temporal lobe	Medial for Music
Ventral lateral Nucleus (VL)	Basal ganglia & cerebellum.	Motor	Motor cortex	

Thalamic syndrome

- Cause:

- A vascular lesion of the thalamus, such as ischemic or hemorrhagic stroke → damage to the thalamic sensory nuclei (VPL and VPM) → total sensory loss on the contralateral side of the body and face (pure hemisensory loss).

- Findings:

- Total sensory loss on the contralateral side of the body (face and body).

- The thalamic ventral posterior lateral nucleus (receives input from the spinothalamic tract and dorsal columns) and ventral posterior medial nucleus (receives input from the trigeminal pathway) send somatosensory projections to the cortex via thalamocortical fibers.

- Several weeks to months following the stroke, sensory deficits can improve; however, some patients develop thalamic pain syndrome. This condition is characterized by severe paroxysmal burning pain over the affected area and is classically exacerbated by light touch (allodynia).

2- Hypothalamus:

- Maintains homeostasis by regulating Thirst and water balance, controlling Adenohypophysis (anterior pituitary) and Neurohypophysis (posterior pituitary) release of hormones produced in the hypothalamus, and regulating Hunger, Autonomic nervous system, Temperature, and Sexual urges (TAN HATS).

Hypothalamic nuclei	Function	Lesion	MNEMONIC
Lateral nucleus	Feeding center	- Anorexia, failure to thrive. - Inhibited by leptin.	Lateral injury makes you Lean.
VentroMedial nucleus	Satiety center	- Lesion as in craniopharyngioma → Hyperphagia, obesity. - Stimulated by leptin.	VentroMedial injury makes you Very Massive.
Anterior nucleus	Cooling, stimulate the parasympathetic nervous system.	Hyperthermia	A/C = Anterior Cooling.
Posterior nucleus	Heating, stimulate the sympathetic nervous system.	Poikliothermia (hypothermia)	Heating controlled by Posterior nucleus ("Hot Pot").
Supra-optic and paraventricular	Synthesize ADH and oxytocin.	Diabetes insipidus: characterized by polydipsia and polyuria.	
Suprachiasmatic nucleus	Regulates circadian rhythms by receiving direct visual input		SCN is a Sun-Censing Nucleus.
Arcuate	Produces hypothalamic releasing and inhibiting factors that regulates anterior pituitary gland, has neurons that produce dopamine (prolactin inhibiting factor)		
Preoptic area	Thermoregulation, sexual behavior, Releases GnRH. Failure of GnRH-producing neurons to migrate from olfactory pit → Kallmann syndrome.		

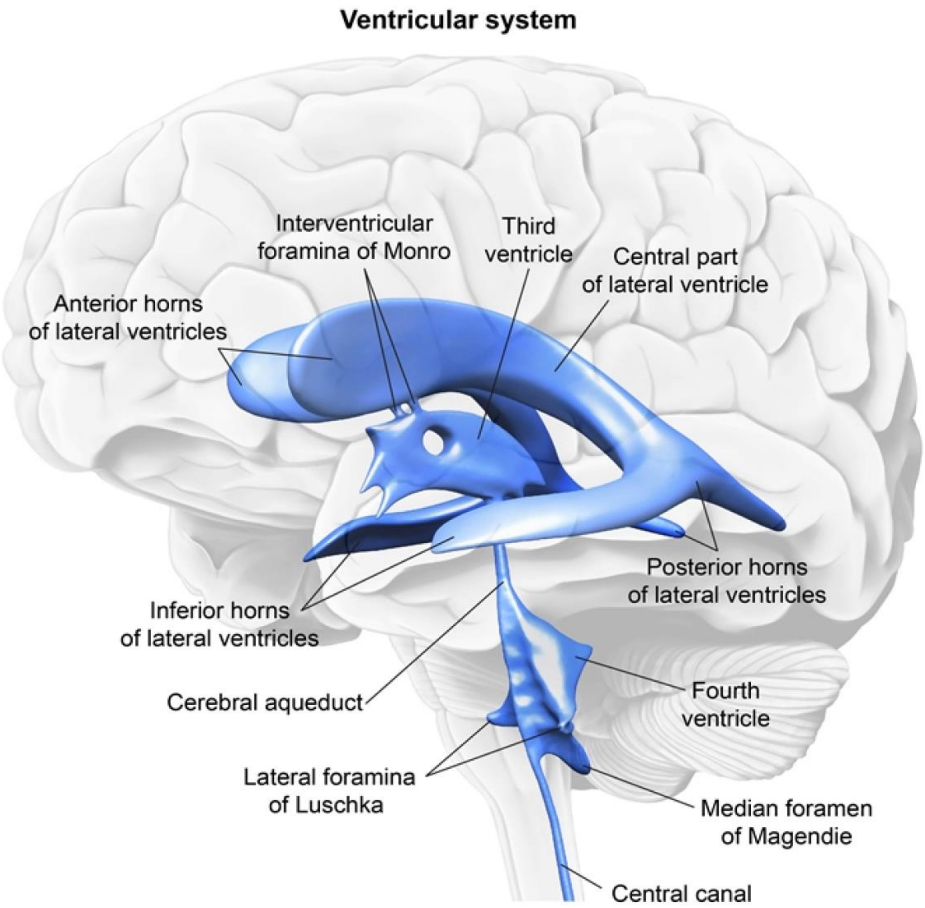
3- Subthalamus:

- The subthalamic nucleus is involved in the indirect pathway of basal ganglia, its lesion → hemiballismus (contralateral flinging movement of one or both extremities).

4- Epithalamus:

- Consists of the pineal body and the habenular nuclei.
- The pineal body secretes melatonin (has a sleep inducing properties) into blood stream.
- Environmental light regulates the activity of the pineal gland through a retinal-suprachiasmatic-pineal pathway.
- Pineal tumor (pinealoma): see before in dorsal midbrain syndrome.

Ventricular System



- Choroid plexus (contains choroid epithelial cells and is in the lateral, third, and fourth ventricles) secretes CSF into all ventricles.

- <u>There are 4 interconnected ventricles in the brain (2 lateral ventricles, a third ventricle, and a fourth ventricle):</u>

- Lateral ventricles →3rd ventricle via right and left interventricular foramina of monro.
- 3rd ventricle → 4th ventricle via cerebral aqueduct of sylvius.
- 4th ventricle → subarachnoid space via:
  - 2 Foramina of Lushka = Lateral.
  - Foramina of Magendi = Medial.

- CSF is reabsorbed by arachnoid granulation and then drains into Dural venous sinuses.

- Dural venous sinuses are large venous channels that run through the dura. It drains blood from cerebral veins and receive CSF from arachnoid granulations, then empty into internal jugular vein.

Hydrocephalus

- Definition:

- Excess volume and/or pressure of CSF → Dilated ventricles.

- Types:

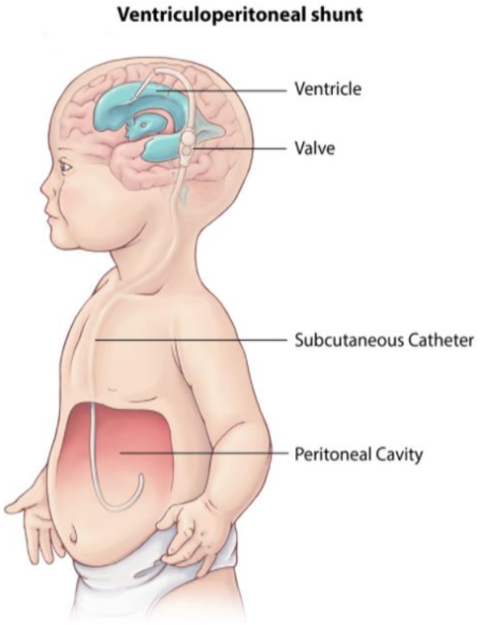
1- Noncommunicating (Obstructive) hydrocephalus:

- Cause: Obstruction of flow of CSF within ventricles, most commonly occurs at narrow points as foramen of monrow or cerebral aqueduct of sylvius due to tumor or scarring (post-hemorrhage, post infection as meningitis) or CNS malformation.

- Findings:

- Obstruction at the level of the cerebral aqueduct causes increased pressure and ventricular dilatation proximal to the site of obstruction.

- In patient with cerebral aqueduct stenosis, there is increased pressure and ventricular dilatation in lateral and third ventricles, but the fourth ventricle is normal sized as it's distal to obstruction.



2- Communicating hydrocephalus:

- Cause:

- It usually results from impaired CSF absorption by the arachnoid granulation (no drainage) as a sequela of meningeal infection (tuberculosis, meningitis) or subarachnoid/intraventricular hemorrhage.

- Rarely it occurs due to increased production of CSF caused by papilloma of the choroid plexus.

- Findings: It presents with global ventricular dilatation and increased intracranial pressure (ICP) without significant blockage to CSF flow within the brain or brainstem.

3- Normal pressur hydrocephalus:

- Cause:

- It is considered to be a form of communicating hydrocephalus where impaired absorption of CSF is compensated by shrinkage of the brain (the enlarged ventricles press the cortex against the skull).

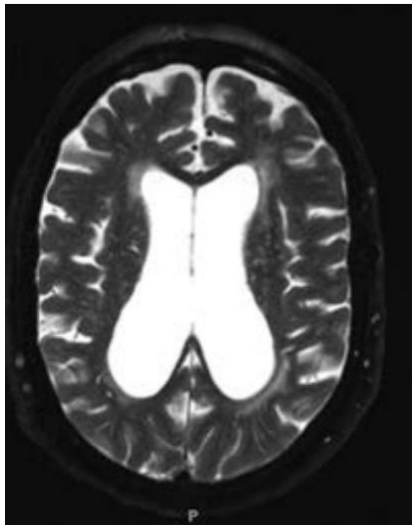
- Findings:

- It presents with enlarged ventricles in the setting of normal ICP (shrinkage of the brain gives more space to the increase in volume → no increase in pressure).

- The dilated ventricles cause disruption of the periventricular white matter (corona radiate) that carries cortical afferent and efferent fibers and produces triad of:
  - Urinary incontinence → wet.
  - Apraxic (magnetic) gait → wobbly.
  - Dementia → wacky.

- Bladder control is influenced by bilateral descending cortical fibers to inhibit the sacral micturition center. Disruption (stretching) of the periventricular area by the distended ventricles → loos of cortical inhibition on the sacral micturition center → development of urge incontinence.

- Symptoms potentially reversible with CSF drainage via lumbar puncture or shunt placement.



4- Hydrocephalus ex vacuo:

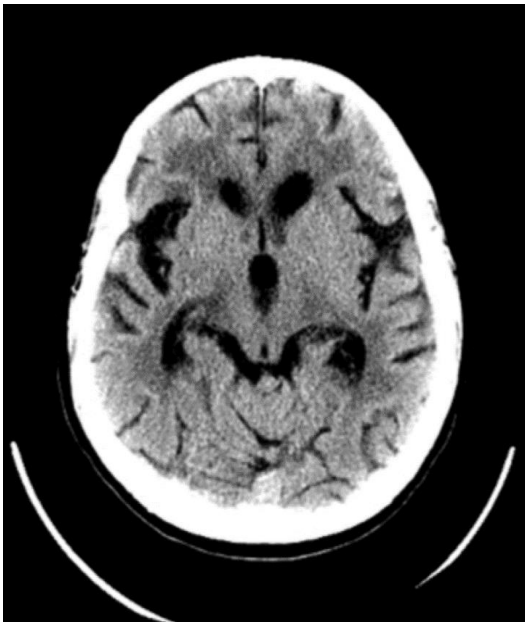
- Cause:

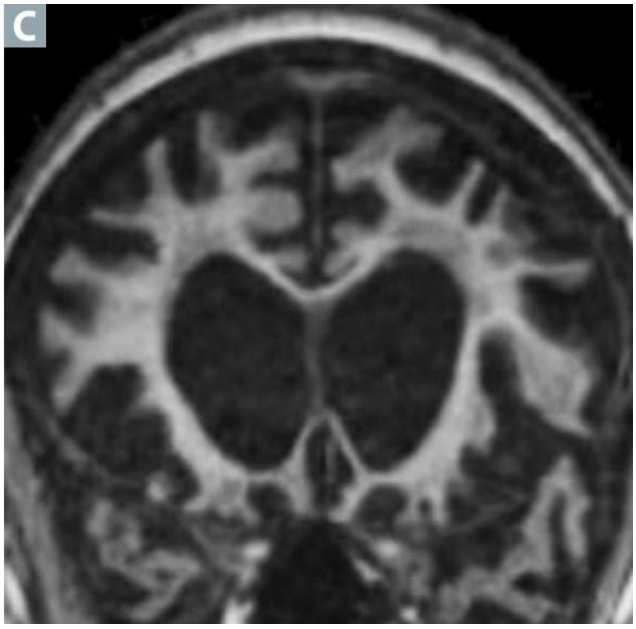
- It occurs most often in elderly patients with dementia.

- It is associated with diseases with diffuse cerebral atrophy as dementia (Alzheimer, pick's disease) or advanced HIV disease.

- Findings:

- It presents with enlarged ventricles with normal ICP secondary to cortical atrophy.





❖ N.B:

1. Hydrocephalus in early infancy (before the closure of the fontanels and sutures) typically presents with macrocephaly (head circumference greater than 2 standard deviations above the mean of gender and age).

2. Long term sequelae of hydrocephalus include lower extremity spasticity and hyperreflexia due to stretching of the periventricular pyramidal tract.

Pseudotumor cerebri

- Also called idiopathic intracranial hypertension.

- <u>Cause:</u>

- Pseudotumor cerebri is idiopathic but the pathology may involve impaired absorption of CSF by the arachnoid villi.

- Risk factors include female sex, Tetracyclines, Obesity, vitamin A excess, Danazol (female TOAD).

- <u>Findings:</u>

- Suspect pseudotumor cerebri in a young obese female with a headache that is suggestive of brain tumor but with normal neuroimaging and elevated CSF pressure (pseudotumor).

- Neurological signs are usually absent except for papilledema, diplopia (usually from CN VI palsy) with no mental status changes.

- Treatment:

- Start with medical treatment as weight reduction and acetazolamide (decreases CSF production) if weight reduction fails.

- When medical treatment fails or visual field defects are progressive → repeated lumbar puncture to relieve symptoms, also shunting or optic nerve sheath fenestration may be done to prevent blindness which is the most significant complication of this otherwise benign disorder.

❖ N.B:

- Lumbar puncture is contraindicated in space occupying lesions as brain tumors or brain abscess because there is markedly elevated intracranial pressure and sudden relieve of pressure by doing lumbar puncture → brain herniation.

Cerebral cortex

- It is formed of 2 cerebral hemispheres, connected to each other by the corpus callosum and to the upper part of the brain stem by the 2 cerebral peduncles.

- The surface of each hemisphere is divided into 4 lobes:

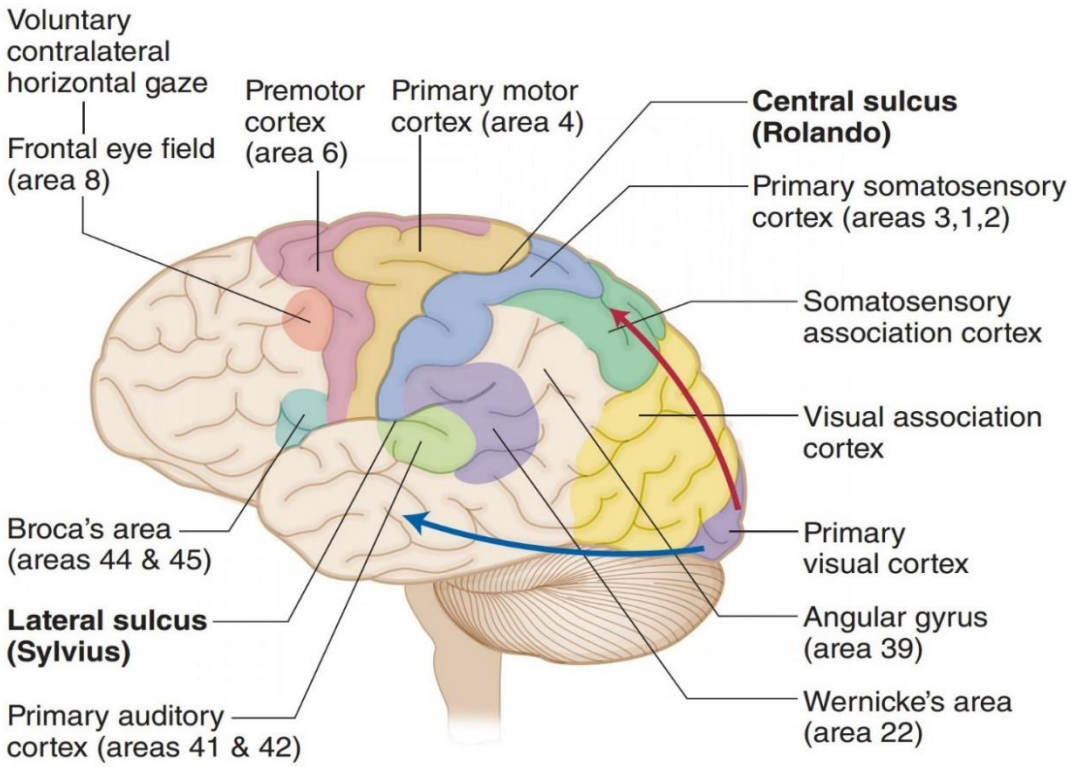
1- Frontal.
2- Parietal.
3- Temporal.
4- Occipital.

- The surface of cerebral cortex is highly convoluted with the bulges, referred to as gyri, and the spaces separating the gyri, called sulci.

- These lobes are separated from each other by sulci (fissures):

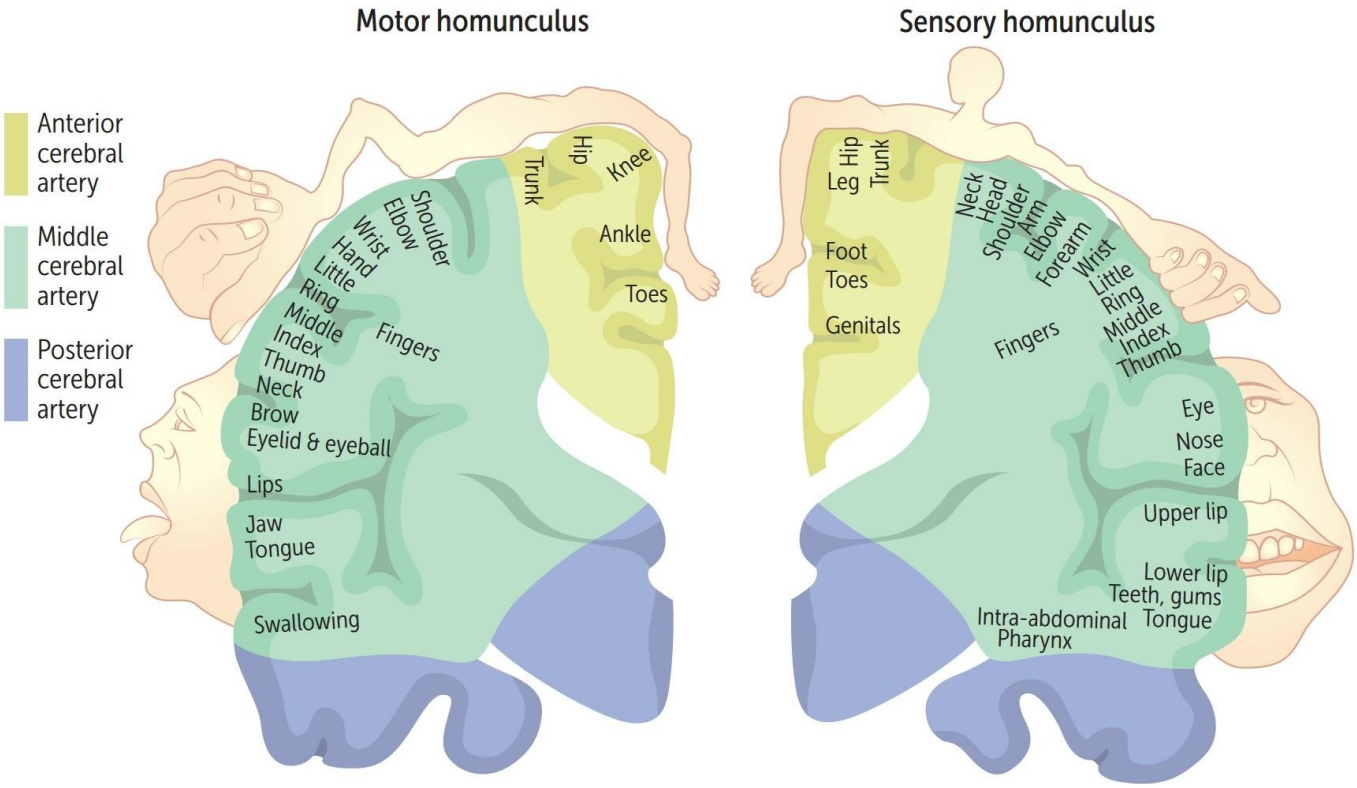
- On the lateral aspect of cerebral hemisphere:
  - The central sulcus separates the frontal from the parietal lobes.
  - The lateral sulcus (Sylvius)) separates the frontal & parietal lobes from the temporal lobe.

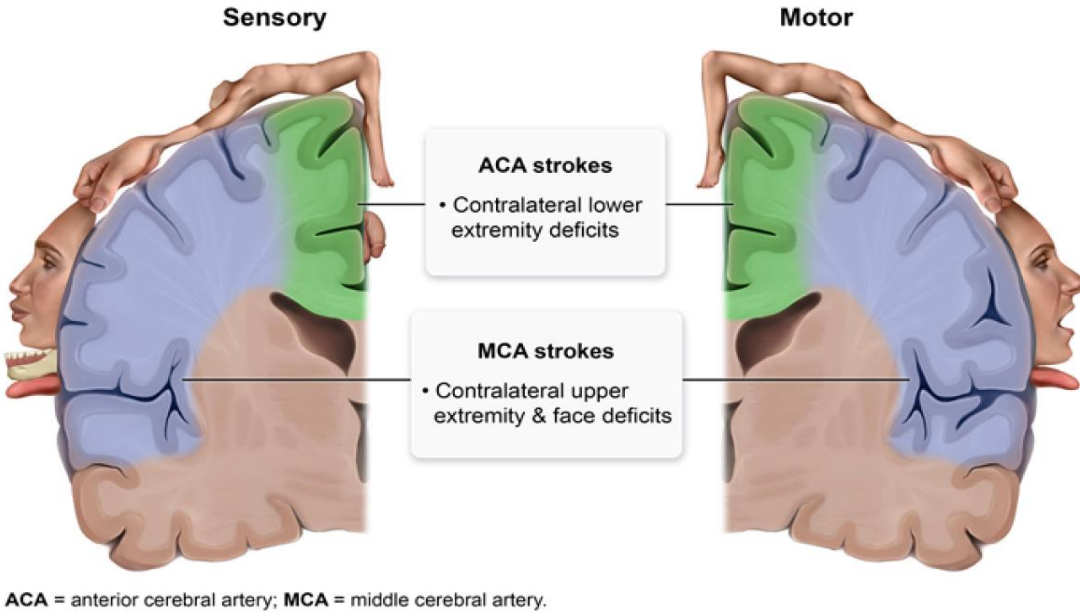
- On the medial aspect of cerebral hemisphere:
  - The cingulate sulcus separates the frontal and parietal lobes from the cingulate gyrus.
  - The parieto-occipital sulcus separates the parietal lobe from the occipital lobe.



- Homunculus of the cerebral cortex:

- Our body is represented in the primary motor cortex (portion of the human brain responsible for the processing and integration of motor information) and the primary somatosensory cortex (portion of the human brain responsible for the processing and integration of sensory information) upside down , the head is represented on the lateral aspect of hemisphere then the regions for the neck, upper limb, and trunk. But On the medial aspect of the hemisphere the representation for the pelvis and lower limb.





ACA = anterior cerebral artery; **MCA** = middle cerebral artery.

Anatomy of cerebral cortex

Frontal lobe

- A large area of the frontal cortex in front of the central sulcus is related to the control of movements, primarily on the opposite side of the body. These areas include:

1- Primary motor (area 4) and premotor (area 6) cortex:

- The primary motor cortex is in the precentral gyrus, immediately anterior to the central sulcus.
- It contains an orderly skeletal motor map of the contralateral side of the body.
- The muscles of the head are represented on the lateral aspect of hemisphere then the regions for the neck, upper limb, and trunk.
- On the medial aspect of the hemisphere is the motor representation for the pelvis and lower limb.
- Deficits after lesion:

- Contralateral spastic paresis (region depends on area of homunculus affected).

2- Frontal eye field (area 8):

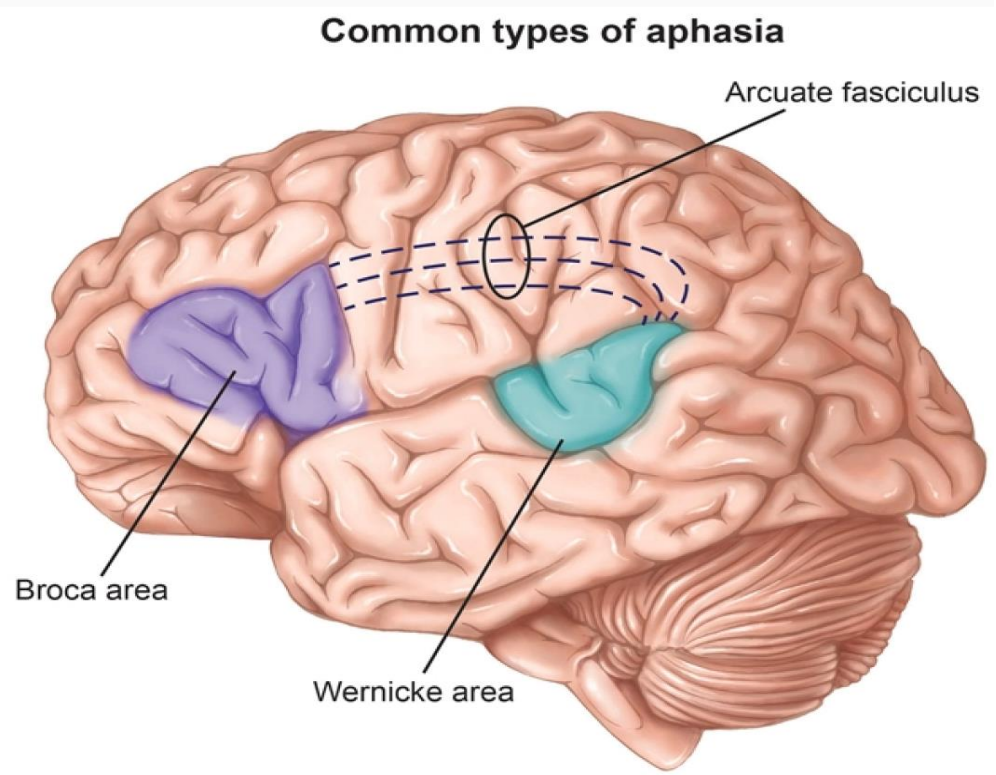
- Lies in front of the motor cortex
- It is the center for contralateral horizontal gaze.
- Deficits after lesion:

- Inability to make voluntary eye movement toward the contralateral side.
- Because the activity of the intact frontal eye field in the opposite cortex would also be unopposed after such a lesion, the result is conjugate slow deviation of the eyes toward the side of the lesion.

3- Prefrontal cortex:

- The prefrontal cortex is located in front of the premotor area and represents about a quarter of the entire cerebral cortex in the human brain.
- This area is involved in organizing and planning the intellectual and emotional aspects of behavior.
- Deficits after lesion:

- Lesions in the prefrontal area produce what is called the frontal lobe syndrome.
- Frontal lobe syndrome: symptoms can include poor judgment, difficulty concentrating and problem solving, apathy (severe emotional indifference), inappropriate social behavior and the emergence of infantile suckling or grasp reflexes that are suppressed in adults (disinhibtion).



4- Broca's area:

- The left hemisphere is considered to be the hemisphere that is dominant for language.

- There are three language centers on the lateral aspect of the left hemisphere in the vascular territory of the left middle cerebral artery:

1- Broca's area (frontal lobe).
2- Wernicke area (temporal lobe).
3- Angular gyrus (parietal lobe, Its significance is in transferring visual information to Wernicke's area, in order to make meaning out of visually perceived words).

- Aphasia is a higher-order inability to speak (language deficit).

- Dysarthria is a motor inability to speak (articulation deficit).

- The ability to write is usually also affected in a similar way (agraphia) in all aphasias, although the hand used for writing can be used normally in all other tasks.

- Broca's area in the left or dominant hemisphere is the center for motor speech (make motor plan to say something).

- The middle cerebral artery supplies Broca's area (superior division) and Wernicke's area (inferior division).

- Deficits after lesion:

- Broca's (Expressive, non-fluent) aphasia → difficulty in piecing together words to produce expressive speech with impaired repetition and intact comprehension (can understand written and spoken language but say almost nothing).

- Agraphia.

- Patients are aware of and frustrated by their problem (because of their lack of the ability to verbalize their thoughts orally or in writing).

- The damage often extends posteriorly into the primary motor cortex and might be combined with a contralateral facial and arm weakness.

Parietal lobe

- The parietal lobe begins just posterior to the central sulcus with the postcentral gyrus.

1- Primary somatosensory cortex (area 3, 1, 2):

- Lies in the postcentral gyrus.

- Like primary motor cortex, there is similar somatotopic representation of the body upside-down, with head, neck, upper limb and trunk represented on the lateral aspect of the hemisphere, and pelvis and lower limb represented medially.

- Function: perception of cortical sensation from the opposite half of the body.

- Deficits after lesion:

- Contralateral loss of all somatic sensations (region depends on area of homunculus affected).

2- Posterior parietal association cortex:

- Just posterior to the somatosensory areas, including:

A. Superior parietal lobule (area 5, 7):

- Function:

- The superior parietal lobule is involved with spatial orientation, receives a visual input as well as sensory input and integrate them which is important for the formation of body image, awareness of the body and its position in space.

- Deficits after lesion:

- Apraxia (disruption of the patterning and execution of learned motor movement) which reflect a lack of understanding how to organize the performance of a pattern of movement (what should be done first, the next..).
- Astereognosia (inability to recognize objects by touch) due to impaired integration of visual and somatosensory input.

❖ Hemispatial neglect syndrome (asomatognosia):

▪ Cause:

- Widespread lesions in the nondominant right parietal lobe → impaired integration of visual and somatosensory information which is important for the formation of body image and awareness of the body and its position in space.

▪ Findings:

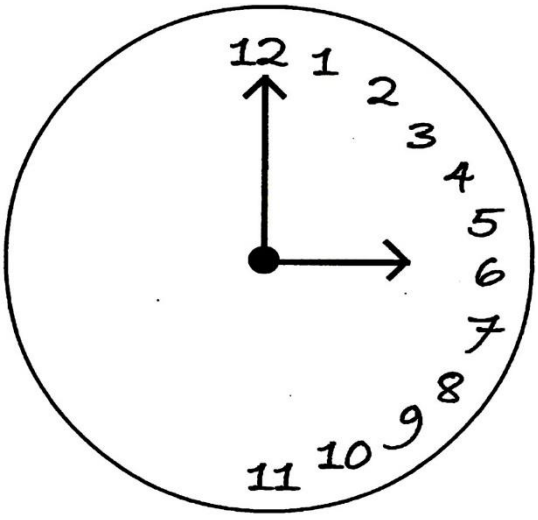
- Unawareness or neglect of the contralateral half of the body.

- Patients will have no visual deficits, so they can see, but deny the existence of things in the left visual field.

- Patients may deny that the left arm or left leg belongs to them when the affected limb is passively brought into their field of vision.

- Patients may shave only the right side of their face, comb the right side of their hair, and ignore the subject located in the left side of a space.

- Asking a patient to fill in the numbers of a clock is a typical test that is used to detect hemi-neglect syndrome.



B. Inferior parietal lobule (areas 39, 40):

▪ Function:

- Inferior parietal lobule has been involved in the perception of emotions in facial stimuli, interpretation of sensory information concerned with language, mathematical operations, and body image.

▪ Deficits of lesion:

- This constellation of deficits constitutes grestmann syndrome and underscores the role of this cortical area in the integration of how children begin to count, add, and subtract using their fingers.

❖ Gerstmann syndrome:

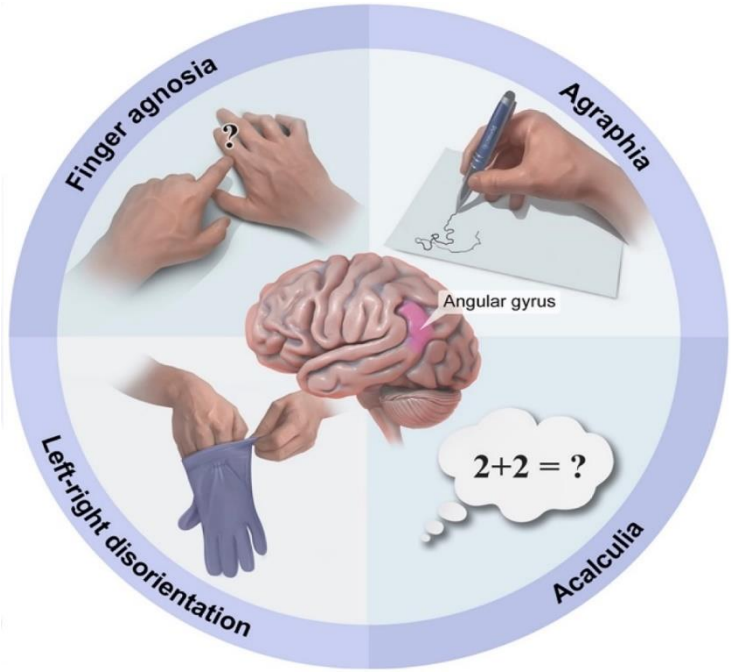
▪ Cause:

- The lesion is confined to the angular gyrus in the dominant parietal lobe.

- The angular gyrus is part of the parietal association cortex, an area that integrates multisensory (visual, tactile, verbal) information to comprehend events and solve problems. Specifically, it is important for semantic processing, word reading and comprehension, and number processing.

▪ Findings:

- Alexia: loss of ability to comprehend written language.
- Agraphia.
- But spoken language may be understood.
- Alexia with agraphia in pure angular gyrus lesions is often seen with 3 other unique symptoms:
  - Acalculia (loss of the ability to perform simple mathematical tasks).
  - Finger Agnosia (inability to recognize one's fingers).
  - Right – left disorientation.



Temporal lobe

1- Primary auditory cortex (areas 41, 42):

▪ Function: auditory sensory area.

▪ Deficits after lesion:

- Slight hearing loss, never deafness as hearing is bilaterally represented.

2- Auditory associative area (area 22):

- Function: recognition & recall of sounds.

- Deficits after lesion:

- Auditory agnosia: the patient hears but doesn't understand (recognize) what he hears.

3- Wernicke's area:

- Function: it is the cortical region that function in language comprehension.

- Wernicke's (Fluent) aphasia:

  - Cause: lesion in Wernicke's area in the temporal lobe or in the parietal lobe.

  - Findings: Patient cannot understand any form of language, speech is fast and fluent, but not comprehensible (word salad) with poor repetition.

❖ Qs - why there is poor repetition although the motor speech center (Broca's area) is contact?

- Because to repeat something you need to:

1- Understand it (Wernicke's area).
2- Make motor plan to say it (broca's area).
3- Connect broca's area with Wernicke's area (arcuate fasciculus).

- A stroke to Wernicke's area will also knocks out part of the arcuate fasciculus (impaired comprehension and no repetition).

❖ Other types of aphasia:

1- Conduction aphasia:

- Cause: Lesion affecting the arcuate fasciculus that connects Wernicke's areas in the temporal and parietal lobe with broca's area in the frontal lobe.

- Findings:

- Fluent speech, intact comprehension but poor repetition with many word-finding pauses.

- This is an example of disconnect syndrome in which the deficit represents an inability to send information from one cortical area to another.

2- Global aphasia:

- Cause: Broca's, Wernicke's areas, and arcuate fasciculus are affected.

- Findings:

- Nonfluent aphasia with impaired comprehension and poor repetition.

3- Transcortical motor aphasia:

- Cause:

- There is a stroke knocking out frontal lobe around Broca's area, but Broca's area and the arcuate fasciculus are spared.

- Findings:

- Nonfluent aphasia with good comprehension and intact repetition.

4- Transcortical sensory aphasia:

- Cause:

- There is a stroke knocking out temporal lobe around Wernicke area, but Wernicke area and the arcuate fasciculus are spared.

- Findings:

- Poor comprehension with fluent speech and intact repetition.

5- Mixed transcortical aphasia:

- Cause:

- Broca's and Wernicke areas and arcuate fasciculus remain intact; surrounding watershed areas affected.

- Findings:

- Nonfluent speech, poor comprehension, and intact repetition.

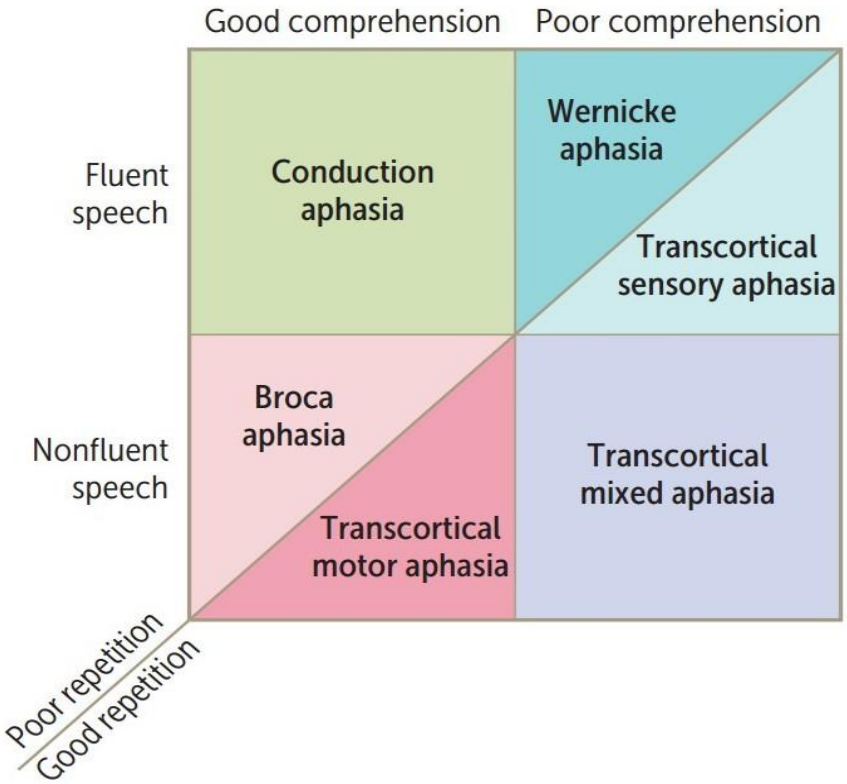
❖ You will notice that in all types of transcortical aphasias, there is always sparing of arcuate fasciculus → intact repetition.

❖ Aphasia in anutshell:

- Broca's (motor) aphasia → nonfluent, good comprehension, poor repetition.
  Vs.
- Transcortical motor aphasia → nonfluent, good comprehension, good repetition.

- Wernicke's (sensory) aphasia → fluent, poor comprehension, poor repetition.
  Vs
- Transcortical sensory aphasia → fluent, poor comprehension, good repetition.

- Conduction aphasia → fluent, good comprehension, poor repetition.
  Vs
- Global aphasia → nonfluent, poor comprehension, poor repetition.


Good comprehension
Poor comprehension
Fluent speech
Nonfluent speech
Conduction aphasia
Wernicke aphasia
Transcortical sensory aphasia
Broca aphasia
Transcortical motor aphasia
Transcortical mixed aphasia
Poor repetition
Good repetition

Occipital lobe

1- Primary visual cortex (area 17):

- Function: perception of visual images.

- Deficits of lesion:

- Usually due to occlusion of a branch of posterior cerebral artery.

- A unilateral lesion inside area 17 results in a contralateral homonymous hemianopia with macular sparing (because of dual blood supply from both the posterior and middle cerebral arteries).

2- Visual associative area (areas 18, 19):

- Function: integrate complex visual input from both hemispheres for visual processing.

❖ Alexia Without Agraphia:

- A principal "higher-order" deficit associated with occipital lobe damage is alexia without agraphia (or pure word blindness).

- The patients are unable to read at all. However, they are able to write. This is another example of a disconnect syndrome in which information from the occipital lobe is not available to the parietal or frontal lobes to either understand or express what has been seen.

- The cause of the syndrome is usually an occlusion of the left posterior cerebral artery (dominant hemisphere) that affects not only the anterior part of the occipital lobe but the splenium of the corpus callosum.

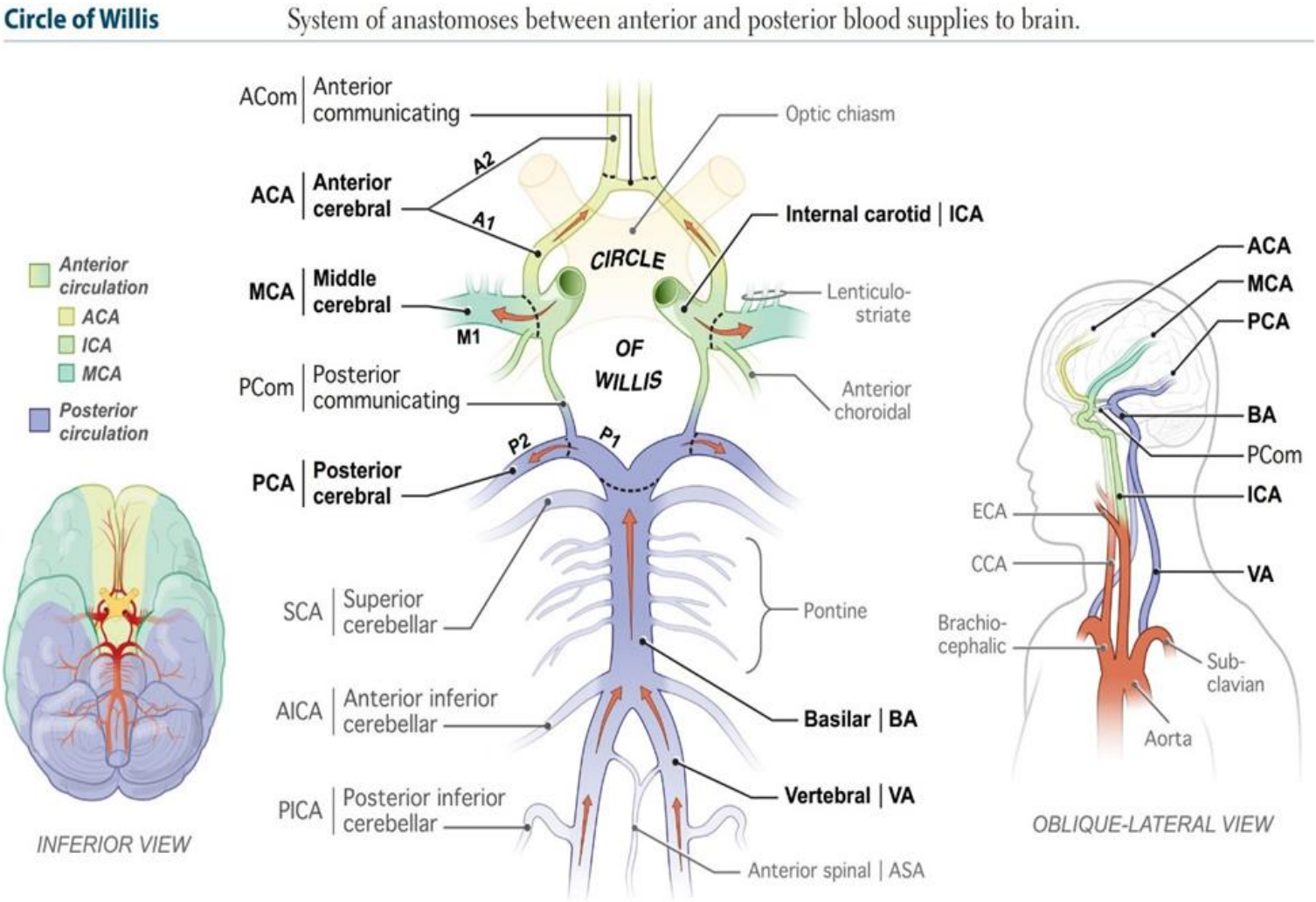
- Involvement of the left occipital cortex results in a right homonymous hemianopsia with macular sparing. Involvement of the splenium of the corpus callosum prevents visual information from the intact right occipital cortex from reaching language comprehension centers in the left hemisphere.

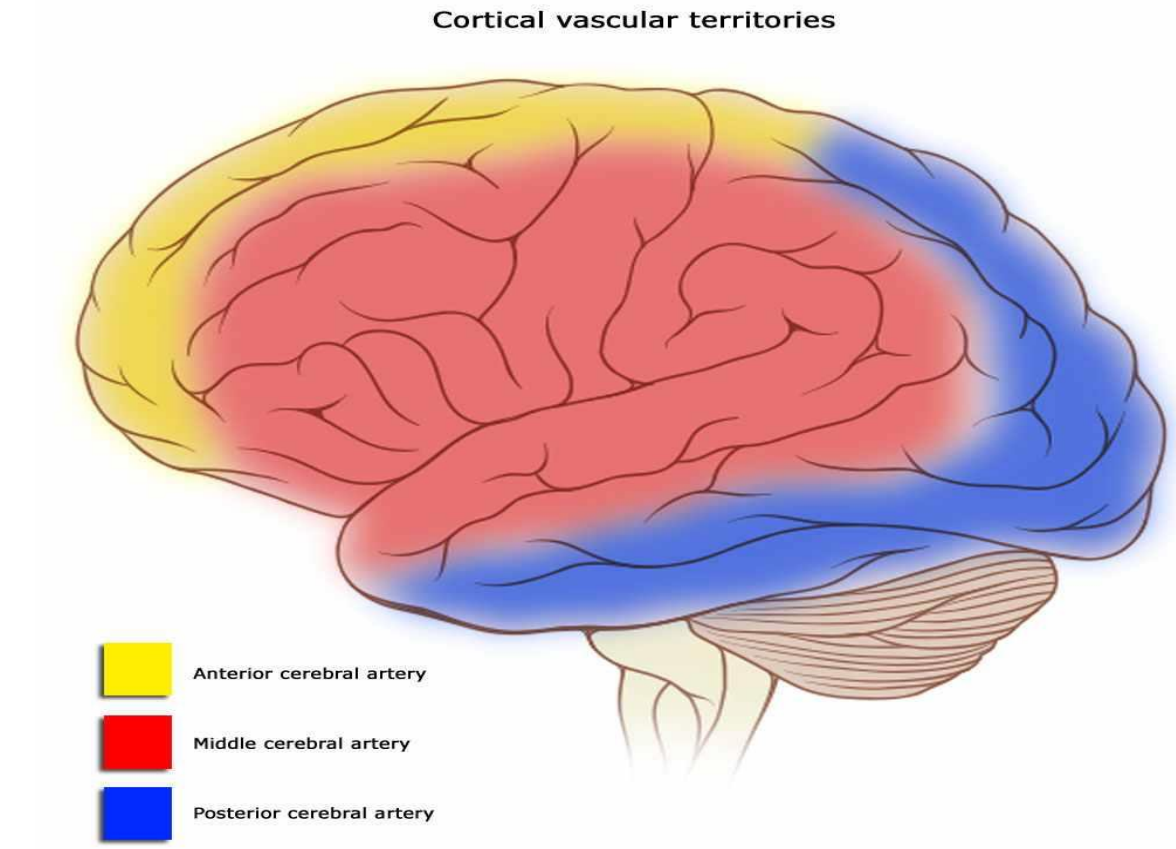
Blood supply of the cerebral cortex

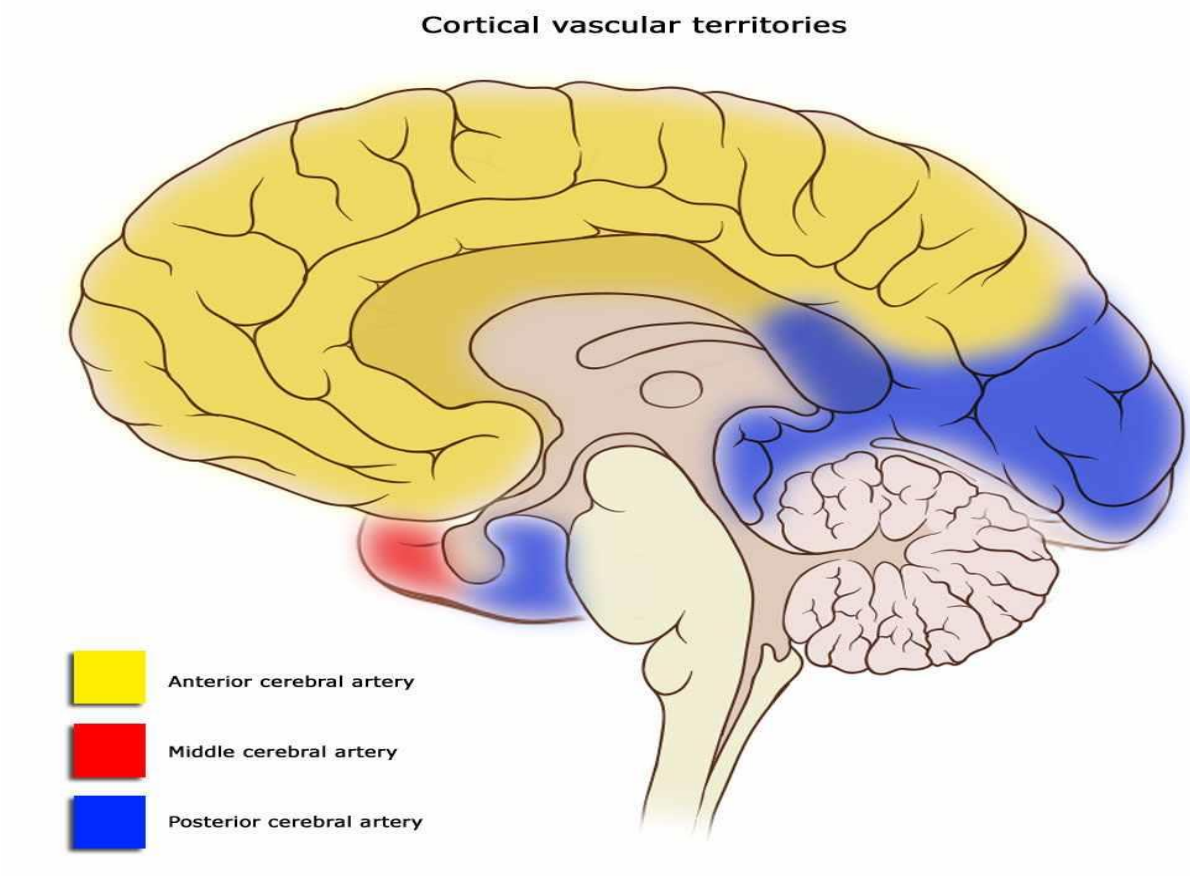
- <u>The blood reaches the brain through two systems of blood vessels:</u>

1- The carotid system (Anterior circulation).

2- The vertebral system (Posterior circulation).




Cortical vascular territories
Anterior cerebral artery
Middle cerebral artery
Posterior cerebral artery


Cortical vascular territories
Anterior cerebral artery
Middle cerebral artery
Posterior cerebral artery

1- The carotid system (Anterior circulation):

- Each internal carotid artery enters the cranial cavity through the carotid foramen and canal to the cavernous sinus where it lies lateral to optic chiasma.

- The artery in the sinus gives off three small branches:

- The ophthalmic artery.
- The anterior choroidal artery.
- The posterior communicating artery.

- The internal carotid artery then divides into its two terminal branches → the middle and anterior cerebral arteries.

A. The middle cerebral artery supplies:

- The lateral surface of the frontal, parietal, and upper temporal lobes.

- The posterior limb and genu of internal capsule (Lenticulostriate branch of middle cerebral artery).

- Temporal lobe (Wernicke area); frontal lobe (Broca's area).

- The lateral fibers of visual radiation as they emerge from the lateral geniculate nucleus of the thalamus and course in Meyer's loop.

- Occlusion of the middle cerebral artery:

  - Spastic paresis of the contralateral lower face and upper limb.

  - Anesthesia of the contralateral face and upper limb.

  - An aphasia (Broca's, Wernicke, or conduction) may be seen when branches of left middle cerebral artery are affected.

  - Left sided neglect may be seen with a blockage of branches of the right middle cerebral artery to the right parietal lobe.

  - Contralateral superior quadrantanopia may be seen with a blockage of the branches that supply Meyer's loop fibers in the temporal lobe.

B. The anterior cerebral artery supplies:

- Medial surface of frontal and parietal lobes.

- Anterior limb of anterior capsule.

- Occlusion of anterior cerebral artery will results in:

  - Spastic paresis of the contralateral lower limb.

- Anesthesia of the contralateral lower limb.

- Urinary incontinence may be present (usually occurs only with bilateral damage).

2- The vertebral system (Posterior circulation):

- 2 vertebral arteries pass upwards through the vertebral foramina to enter the cranial cavity through the foramen magnum and runs upwards on each side of the medulla.

- Both vertebral arteries meet at the lower border of the pons to form one midline single artery, the basilar artery, which runs upwards on the ventral surface of the pons then divides into its two terminal branches the posterior cerebral arteries.

- Each posterior cerebral artery supplies:

- The occipital and temporal cortex on the inferior and lateral surface of the hemisphere

- The occipital lobe and posterior two-thirds of the temporal lobe on the medial surface of the hemisphere.

- Occlusion of the posterior cerebral artery will result in:

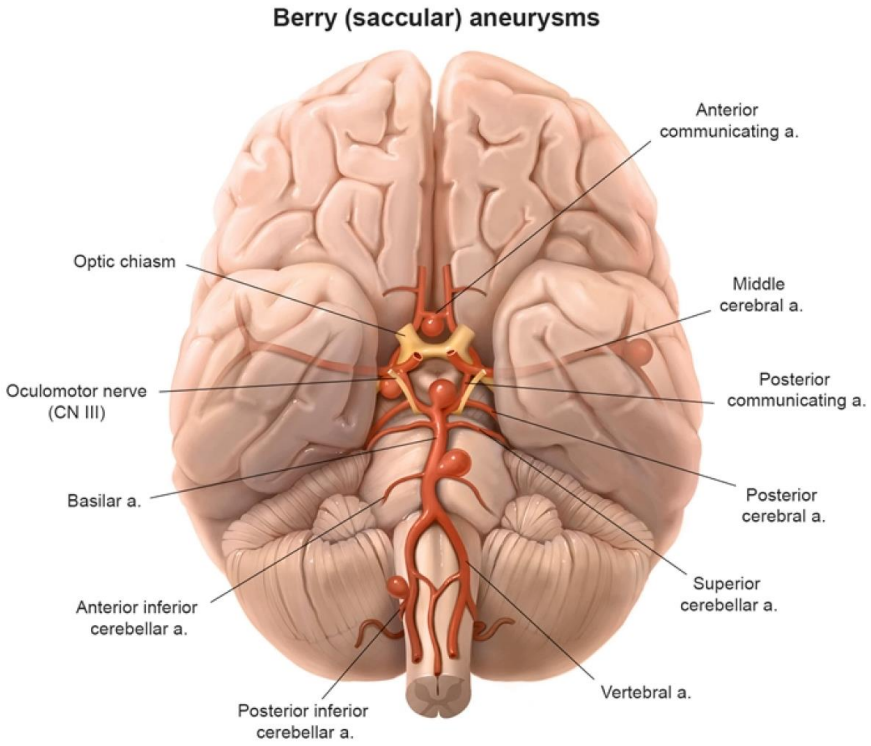
- Contralateral homonymous hemianopia with macular sparing.

- Alexia without agraphia (dominant hemisphere).

❖ Circle of Willis:

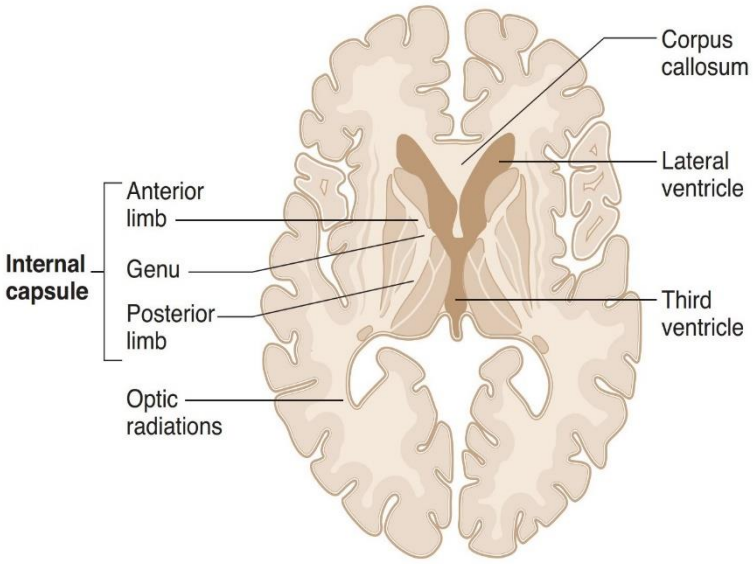
- Both anterior cerebral arteries are connected together by the anterior communicating artery. Also, the internal carotid artery of each side is connected to the posterior cerebral artery of the same side by the posterior communicating artery. In this way, the circle of Willis is formed where the two carotid arteries communicate with each other and with the vertebra-basilar system.

- The most common aneurysm site in the circle of Willis is where the anterior communicating artery joins an anterior cerebral artery.



Blood supply of internal capsule

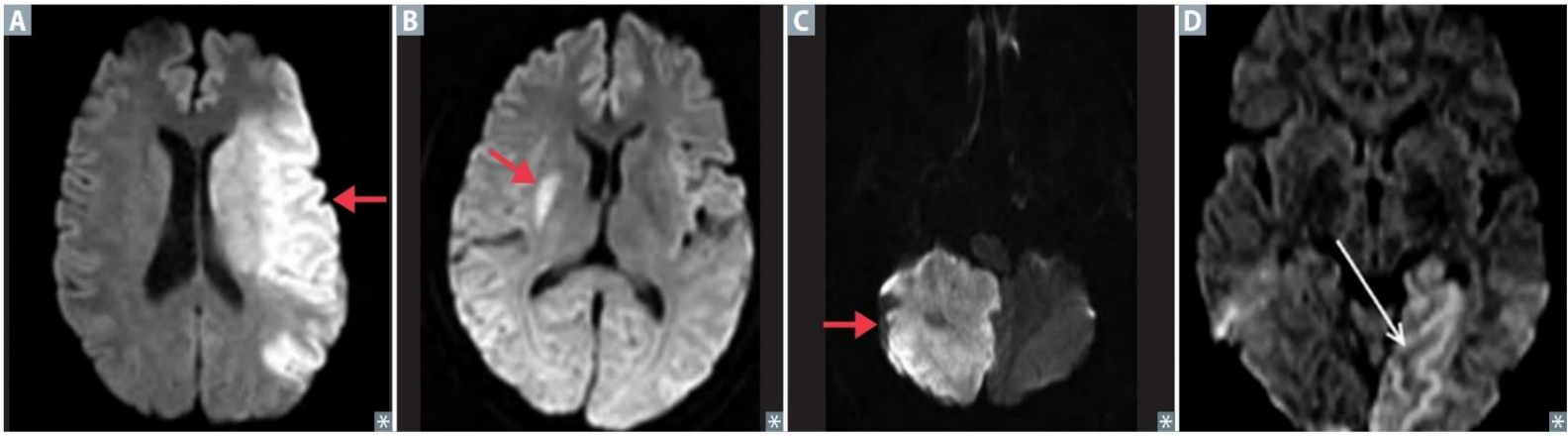
Internal capsule	Arterial supply	Tracts
Anterior limb	Medial striate branch of anterior cerebral artery	Thalamocortical
Genu	Lenticulostriate branch of middle cerebral artery	Corticobulbar
Posterior limb	Lenticulostriate branch of middle cerebral artery	Corticospinal, all somatosensory thalamocortical projections



Effects of strokes

ARTERY	AREA OF LESION	SYMPTOMS	NOTES
Anterior circulation			
Middle cerebral artery	Motor and sensory cortices A—upper limb and face. Temporal lobe (Wernicke area); frontal lobe (Broca area).	Contralateral paralysis and sensory loss—face and upper limb. Aphasia if in dominant (usually left) hemisphere. Hemineglect if lesion affects nondominant (usually right) hemisphere.	Wernicke aphasia is associated with right superior quadrant visual field defect due to temporal lobe involvement.
Anterior cerebral artery	Motor and sensory cortices—lower limb.	Contralateral paralysis and sensory loss—lower limb, urinary incontinence.	
Lenticulostriate artery	Striatum, internal capsule.	Contralateral paralysis. Absence of cortical signs (eg, neglect, aphasia, visual field loss).	Pure motor stroke. Common location of lacunar infarcts B, due to hyaline arteriosclerosis (lipohyalinosis) 2° to unmanaged hypertension.
Posterior circulation			
Anterior spinal artery	Lateral corticospinal tract. Medial lemniscus. Caudal medulla—hypoglossal nerve.	Contralateral paralysis—upper and lower limbs. ↓ contralateral proprioception. Ipsilateral hypoglossal dysfunction (tongue deviates ipsilaterally).	Medial medullary syndrome—caused by infarct of paramedian branches of ASA and/or vertebral arteries.
Posterior inferior cerebellar artery	Lateral medulla: Nucleus ambiguus (CN IX, X, XI) Vestibular nuclei Lateral spinothalamic tract, spinal trigeminal nucleus Sympathetic fibers Inferior cerebellar peduncle	 Dysphagia, hoarseness, ↓ gag reflex, hiccups. Vomiting, vertigo, nystagmus ↓ pain and temperature sensation from contralateral body, ipsilateral face. Ipsilateral Horner syndrome. Ipsilateral ataxia, dysmetria.	Lateral medullary (Wallenberg) syndrome. Nucleus ambiguus effects are specific to PICA lesions C. "Don't pick a (PICA) horse (hoarseness) that can't eat (dysphagia)." Also supplies inferior cerebellar peduncle (part of cerebellum).
Anterior inferior cerebellar artery	Lateral pons: Facial nucleus Vestibular nuclei Spinothalamic tract, spinal trigeminal nucleus Sympathetic fibers Middle and inferior cerebellar peduncles Labyrinthine artery	 Paralysis of face (LMN lesion vs UMN lesion in cortical stroke), ↓ lacrimation, ↓ salivation, ↓ taste from anterior 2/3 of tongue. Vomiting, vertigo, nystagmus ↓ pain and temperature sensation from contralateral body, ipsilateral face. Ipsilateral Horner syndrome. Ipsilateral ataxia, dysmetria. Ipsilateral sensorineural deafness, vertigo.	Lateral pontine syndrome. Facial nucleus effects are specific to AICA lesions. "Facial droop means AICA's pooped." Also supplies middle and inferior cerebellar peduncles (part of cerebellum).

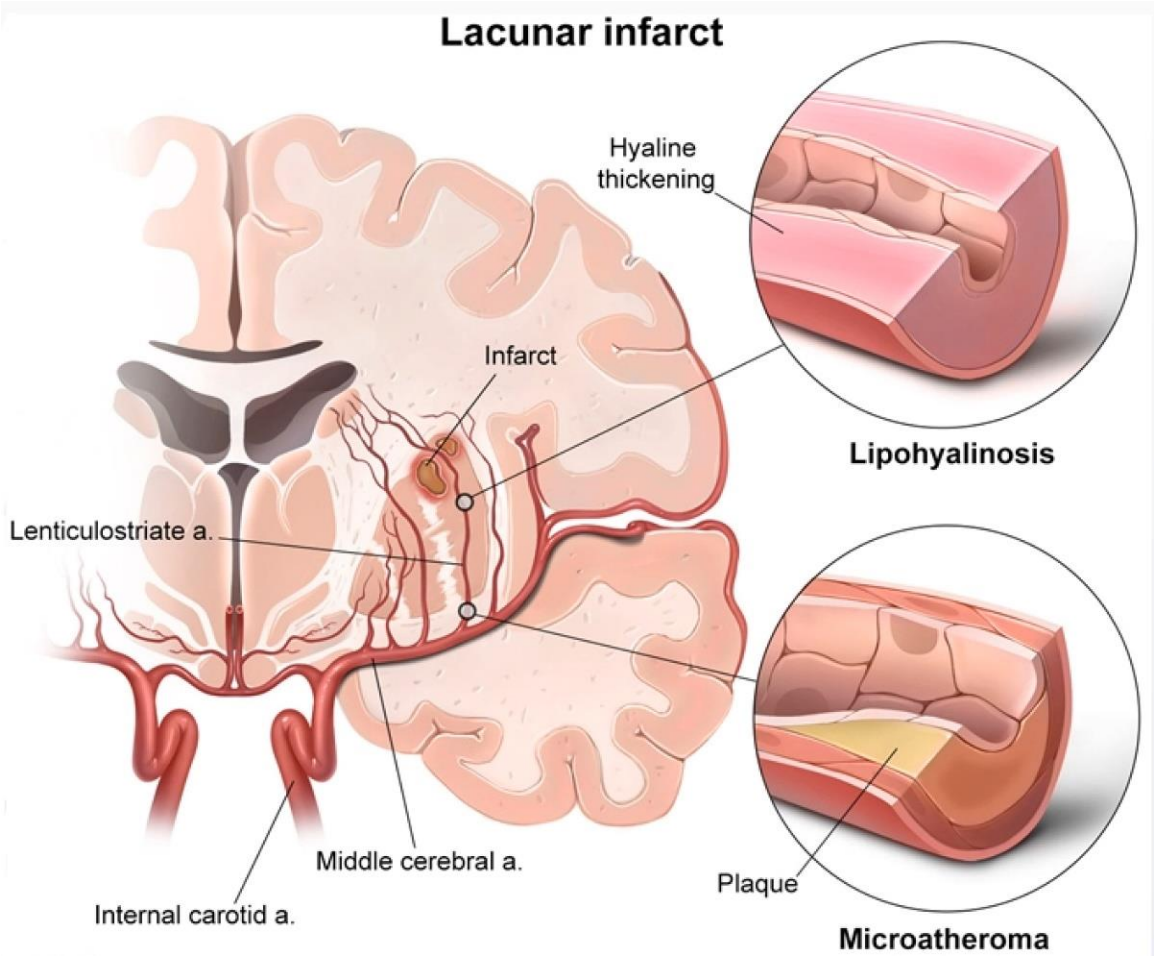
ARTERY	AREA OF LESION	SYMPTOMS	NOTES
Basilar artery	Pons, medulla, lower midbrain.	RAS spared, therefore preserved consciousness.	Locked-in syndrome (locked in the basement).
	Corticospinal and corticobulbar tracts.	Quadriplegia; loss of voluntary facial, mouth, and tongue movements.	
	Ocular cranial nerve nuclei, paramedian pontine reticular formation.	Loss of horizontal, but not vertical, eye movements.	
Posterior cerebral artery	Occipital lobe D.	Contralateral hemianopia with macular sparing; alexia without agraphia (dominant hemisphere).	



❖ N.B:

1. Lacunar strokes occur due to microatheroma formation and lipohyalinosis in the small penetrating arteries of the brain.

- In a few weeks, Astrocytes proliferate on the site of the injury and form a glial scar (cystic space surrounded by scar tissue). These small cavitary spaces are filled with CSF, that's why it's called lacunes (latin: lake).
- They often affect the internal capsule and result in pure motor hemiparesis.
- Hypertension, hyperlipidemia, diabetes, and smoking are major risk factors.
- Lacunar infarcts are most commonly associated with chronic hypertension, which leads to arteriolar sclerosis and occlusion of deep penetrating branches of the major cerebral arteries.
- Acute unilateral motor weakness without sensory deficits or higher cortical dysfunction (pure motor hemiparesis) Is suggestive of a lacunar stroke affecting the posterior limb of the internal capsule.
- Lacunar stroke of the posterolateral thalamus typically presents with sudden-onset contralateral sensory loss involving all sensory modalities (pure sensory stroke).



2. Patients with an internal capsule stroke commonly have pure motor weakness affecting the contralateral arm, leg, and lower face.
   - Contralateral spasticity or increased tone, hyperreflexia, and a positive Babinski sign are also present.

Limbic system

- Function of the limbic system:

1- Smelling: Olfactory information reaches the cerebral cortex (temporal lobe) and limbic system (amygdala) without thalamic relay.
2- Sex drive.
3- Memory/learning.
4- Behavior and emotions.

- Limbic structures:

- Limbic structures are found on the medial aspect of the cerebral hemisphere, the major components are:
  - Hippocampus → important in memory and learning.
  - Amygdala → attaches an emotional significance to a stimulus and helps to imprint the emotional response in memory.
  - The limbic system includes other cortical (cingulate gyrus) and dincephalic (mammillary body) structures.

Limbic System lesions

1- Anterograde amnesia:

- Cause:

- Bilateral damage to the medial temporal lobes including the hippocampus.

- Findings:

- Results in a profound loss of the ability to acquire new information.

2- Korsakoff-syndrome:

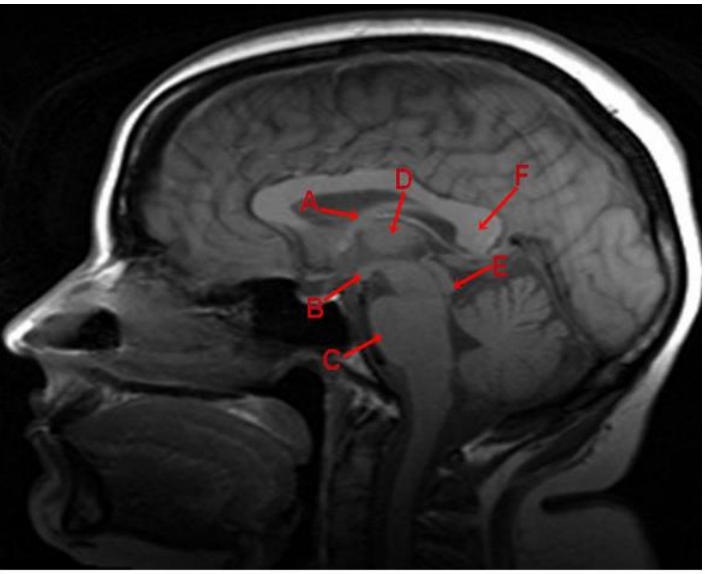
- Cause:

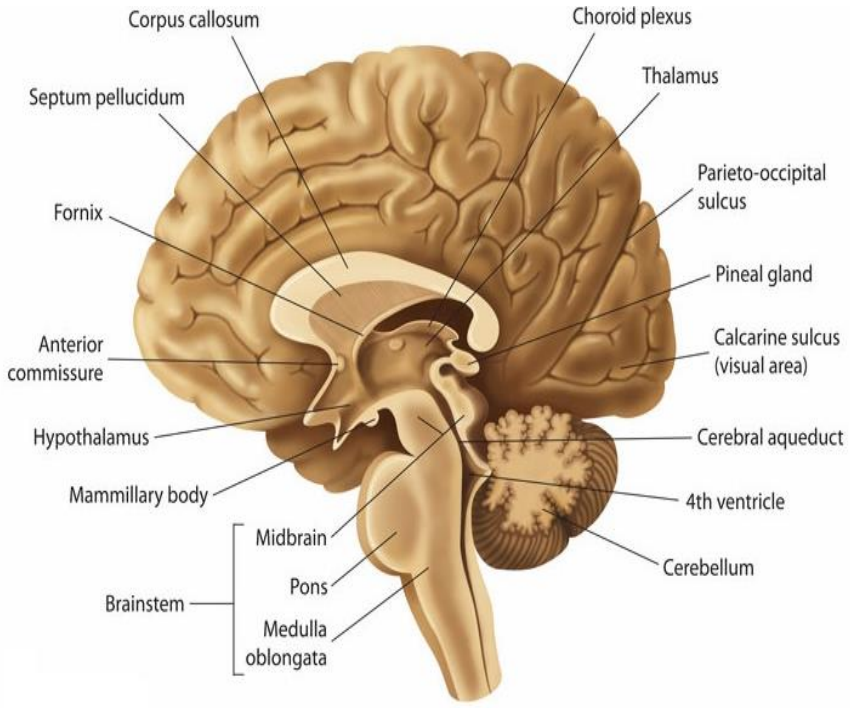
- It is seen mainly in alcoholics who have a thiamine deficiency.

- Thiamine is a key coenzyme for pyruvate dehydrogenase, which is involved in glucose metabolism.

- Thiamine deficiency results in the brain's inability to properly metabolize glucose and turn it into energy.

- The structure in the brain that most frequently undergoes hemorrhagic necrosis in the setting of thiamine deficiency is the mammillary body.





A. The fornix, B. Mammillary body, C. The basis pontis, D. The dorsal thalamus, E. The inferior colliculus, F. The splenium of corpus callosum.

- In korsakoff syndrome there is hemorrhagic necrosis of mammillary bodies due to thiamine deficiency.

- Findings:

- The mammillary body is part of the papez circuit, which is a neural pathway of the limbic system that is involved in the cortical control of emotion and memory.

- Confusion, Ataxia, Ophthalmoplegia form the triad of Wernicke encephalopathy

- The chronic effects of thiamine deficiency lead to Korsakoff syndrome which is characterized by anterograde and retrograde amnesia, confabulation (they fill the memory gap with a fabricated story that themselves believe to be true), apathy and lack of insight.

- The memory loss in Korsakoff syndrome is permanent.

- Treatment: intravenous thiamine supplementation. Giving dextrose without prior thiamine can precipitate a Wernicke encephalopathy

3- Kluver-bucy syndrome:

- Cause: Bilateral lesion of the amygdala.

- Findings: Disinhibited behavior (hyperphagia, hypersexuality, hyperorality).

❖ In a nutshell:

- Bilateral lesion of Hippocampus → Anterograde Amnesia.
- Bilateral lesion of Amygdala → Kluver-bucy syndrome.
- Hemorrhagic necrosis of mammillary bodies in thiamine deficiency → Korsakoff syndrome.

❖ N.B:

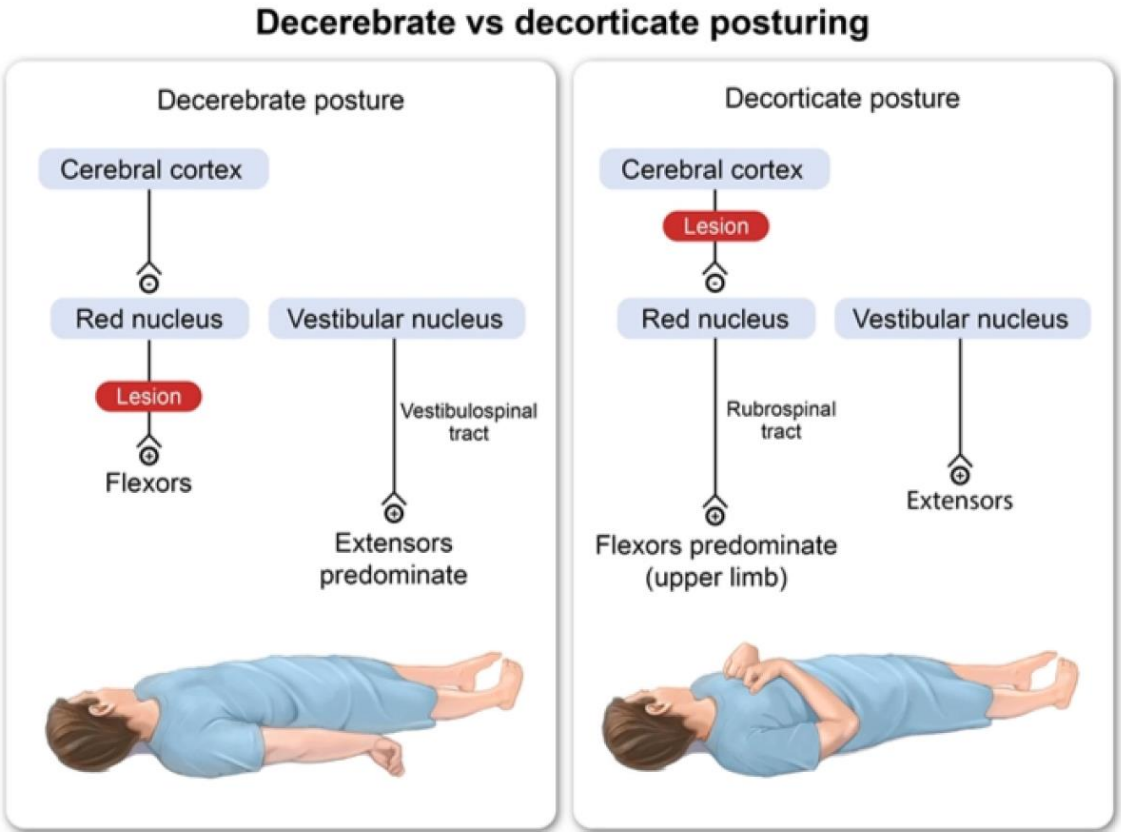
- Reticular activating system is a part of the brainstem that plays an important role in sleep, alertness and consciousness, SO, its lesion will result in reduced level of arousal and wakefulness (Coma).

Common brain lesions

AREA OF LESION	CONSEQUENCE	EXAMPLES/COMMENTS
Frontal lobe	Disinhibition and deficits in concentration, orientation, judgment; may have reemergence of primitive reflexes	
Frontal eye fields	Destructive lesions (eg, MCA stroke): eyes look toward brain lesion (ie, away from side of hemiplegia)	
Paramedian pontine reticular formation	Eyes look away from brain lesion (ie, toward side of hemiplegia)	
Medial longitudinal fasciculus	Internuclear ophthalmoplegia (impaired adduction of ipsilateral eye; nystagmus of contralateral eye with abduction)	Multiple sclerosis
Dominant parietal cortex	Agraphia, acalculia, finger agnosia, left-right disorientation	Gerstmann syndrome
Nondominant parietal cortex	Agnosia of the contralateral side of the world	Hemispatial neglect syndrome
Hippocampus (bilateral)	Anterograde amnesia—inability to make new memories	
Basal ganglia	May result in tremor at rest, chorea, athetosis	Parkinson disease, Huntington disease, Wilson disease
Subthalamic nucleus	Contralateral hemiballismus	
Mammillary bodies (bilateral)	Wernicke-Korsakoff syndrome—Confusion, Ataxia, Nystagmus, Ophthalmoplegia, memory loss (anterograde and retrograde amnesia), confabulation, personality changes	Wernicke problems come in a CAN O' beer and other conditions associated with thiamine deficiency
Amygdala (bilateral)	Klüver-Bucy syndrome—disinhibited behavior (eg, hyperphagia, hypersexuality, hyperorality)	HSV-1 encephalitis
Dorsal midbrain	Parinaud syndrome—vertical gaze palsy, pupillary light-near dissociation, lid retraction, convergence-retraction nystagmus	Stroke, hydrocephalus, pinealoma
Reticular activating system (midbrain)	Reduced levels of arousal and wakefulness	Coma
Cerebellar hemisphere	Intention tremor, limb ataxia, loss of balance; damage to cerebellum → ipsilateral deficits; fall toward side of lesion	Cerebellar hemispheres are laterally located—affect lateral limbs
Cerebellar vermis	Truncal ataxia (wide-based, "drunken sailor" gait), nystagmus	Vermis is centrally located—affects central body Degeneration associated with chronic alcohol use
Red nucleus (midbrain)	Decorticate (flexor) posturing—lesion above red nucleus, presents with flexion of upper extremities and extension of lower extremities Decerebrate (extensor) posturing—lesion at or below red nucleus, presents with extension of upper and lower extremities	Worse prognosis with decerebrate posturing In decorticate posturing, your hands are near the cor (heart)

❖ N.B:

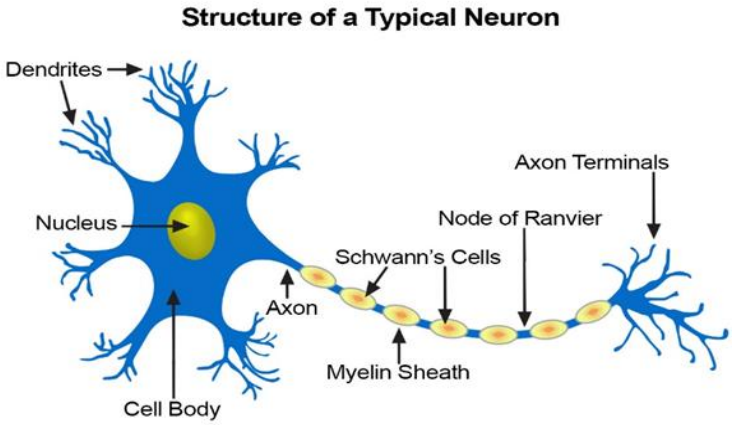
- Damage to the brainstem at or below the level of the red nucleus (midbrain tegmentum, pons) usually causes decerebrate (extensor) posturing due to loss of descending excitation to the upper limb flexors (via the rubrospinal tract) and extensor predominance (due to unopposed vestibulospinal tract output).
- In contrast, damage to neural structures above the red nucleus (cerebral hemispheres, internal capsule) typically results in decorticate (flexor) posturing due to loss of descending inhibition of the red nucleus and subsequent hyperactivity of upper limb flexors (Note: The vestibulospinal tract originates from vestibular nuclei at the pontomedullary junction and does not receive significant descending cortical inhibition.)

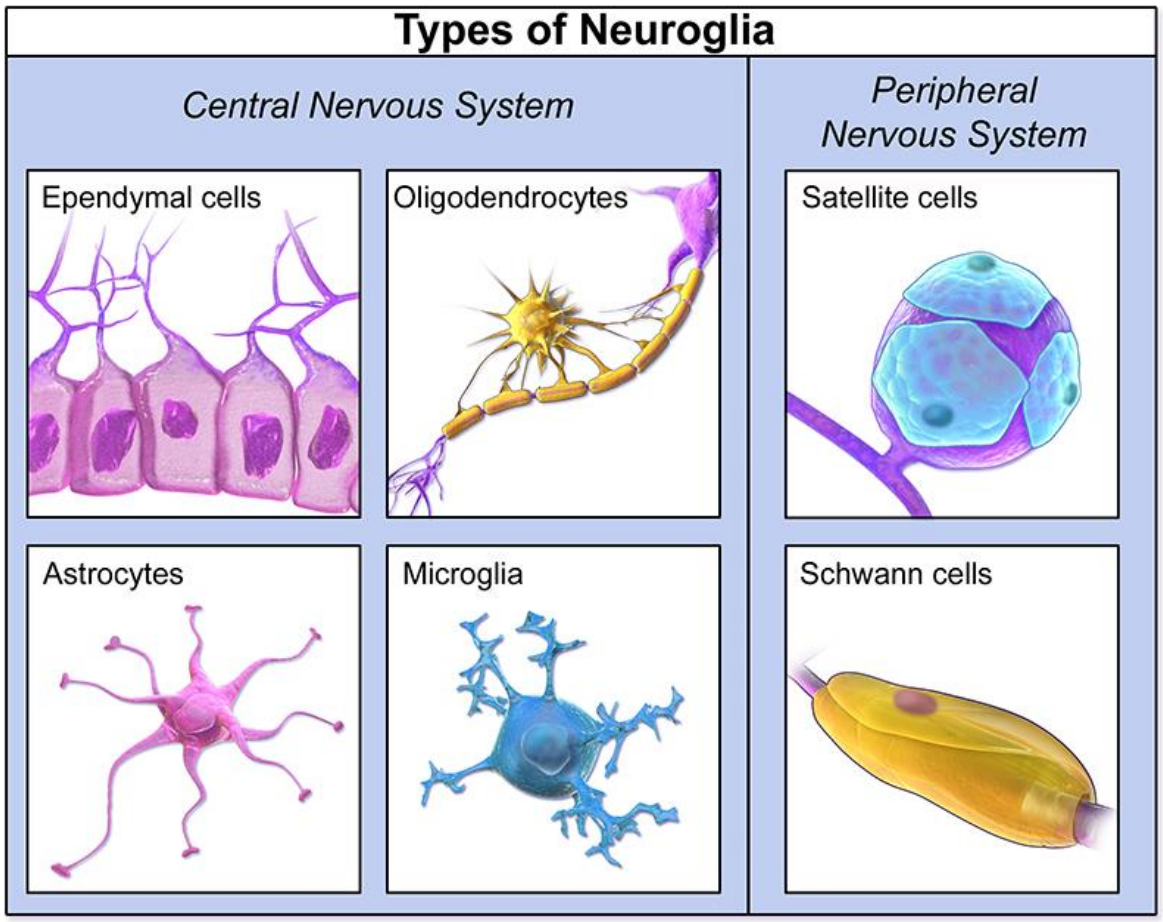


CHAPTER 3

Physiology

- There are two main type of cells that make up the nervous system → neurons and glial cells.
- There are four major types of glial cells in the CNS → astrocytes, oligodendrocytes, microglia and ependymal cells.
- There are also two types of glial cells in the PNS → Schwann cells and satellite cells.
- Glial cells are also called neuroglia. Unlike neurons, glial cells do not conduct nerve electrical signals. They instead serve to protect and nourish the neurons. Neurons depend on glial cells to grow, nourish themselves, and establish effective synapses.





Neurons

- Signal-transmitting cells of the nervous system.
- Permanent cells → do not divide in adulthood.
- Signal-relaying cells with dendrites (receive input), cell bodies, and axons (send output).
- Cell bodies and dendrites can be seen on Nissl staining (stains RER). RER is not present in the axon.
- Neuron markers → neurofilament protein, synaptophysin.

Astrocytes

- Most common glial cell type in CNS.
- Functions:
  - Physical support, repair.
  - Extracellular K buffer.
  - Removal of excess neurotransmitter.
  - Component of blood-brain barrier.
  - Glycogen fuel reserve buffer.
- Derived from neuroectoderm.
- Astrocyte marker → GFAP (glial fibrillary acid protein).
- Reactive gliosis in response to neural injury.

Microglia

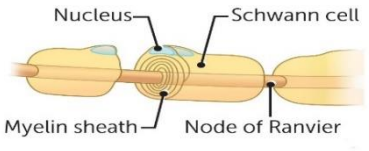
- Phagocytic scavenger cells of CNS (mesodermal, mononuclear origin).
- Activation in response to tissue damage → release of inflammatory mediators (nitric oxide, glutamate).
- HIV can persist in the brain via microglia. HIV-infected microglia fuse to form multinucleated giant cells in CNS seen in HIV-associated dementia.

Ependymal cells

- Ciliated simple columnar glial cells line the ventricles and central canal of spinal cord.
- Apical surfaces are covered in cilia (which circulate CSF) and microvilli (which help with CSF absorption).
- Specialized ependymal cells (choroid plexus) produce CSF.

❖ N.B:

- The axons of neurons are wrapped by electrically insulating material called myelin sheath which increases the conduction velocity of signals transmitted in the axons by the saltatory conduction of action potential at the nodes of Ranvier where there is high concentration of Na channels.
- Schwann cells myelinate the axons of the Peripheral Nervous System, whereas Oligodendrocytes myelinate the axons of the Central Nervous System.
- Myelination ↑ Length constant (space constant): A measure of how long the depolarization signal can propagate. Demyelination → ↓ length constant due to increased charge dissipation along a nerve axon.
- Myelination ↓ Time constant: Lower time constants allow quicker changes in membrane potential, thus increasing axonal conduction speed. Demyelination would increase the time constant and lead to slower impulse conduction.



Schwann cells

- Myelinate axons of neurons in PNS.
- Derived from neural crest.
- Each Schwann cell myelinates only 1 PNS axon.
- May be injured in Guillain-Barre syndrome.
- Acoustic Neuroma: type of schwannoma typically located in internal acoustic meatus (CN VIII), if bilateral, strongly associated with neurofibromatosis type 2.

Oligodendroglia

- Myelinate axons of neurons in CNS.
- Derived from neuroectoderm.
- Each oligodendrocyte can myelinate many axons.
- Injured in multiple sclerosis, progressive multifocal leukoencephalopathy (PML), leukodystrophy.

- The peripheral nervous system refers to parts of the nervous system outside the brain and spinal cord. It includes the cranial nerves, spinal nerves and their roots and branches, peripheral nerves, and neuromuscular junctions.

- The cranial nerves are components of the peripheral nervous system, with the exception of cranial nerve II (the optic nerve), which is not a true peripheral nerve but a neural tract of the diencephalon connecting the retina with the lateral geniculate nucleus, hence both the optic nerve and the retina are part of the central nervous system (CNS), so, all cranial nerves are myelinated by Schwann cells except optic nerve is myelinated by oligodendrocytes.

Wallerian Degeneration

- Occurs in the segment of axon that has lost connection with the cell body due to trauma.

- Such injury causes specific changes in both the proximal and distal segments of the axon, as well as the neuronal body.

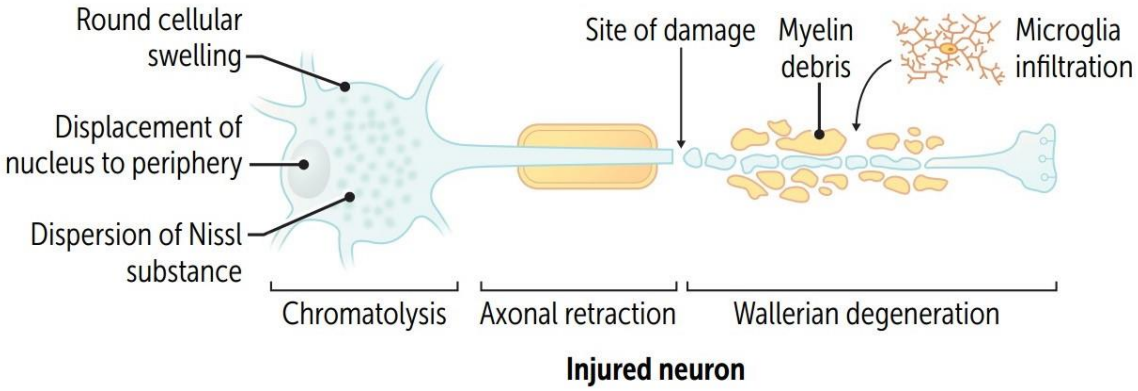
- First, swelling and irregularity are noted in the distal segment of the axon. Within a week the axon is destroyed, and its fragments are digested by macrophages.

- Similar degenerative changes occur in the segment of axon that lies proximal to the injury.

- The changes seen in the neuronal body after the axon is severed are called axonal reaction:

- The cell body shows signs of cellular edema. It becomes swollen and rounded, with the nucleus displaced to the periphery.

- Nissel substance become fine, granular and dispersed throughout the cytoplasm (central chromatolysis). These changes reflect an increased synthesis of protein by the cells in order to regenerate the severed axon.



- In the peripheral nervous system:

- Schwann cells sense the axonal degeneration and begin to degrade their myelin and secrete cytokines and chemokines that recruit macrophages.

- This allows effective clearance of myelin debris which, along with trophic factor secretion by Schwann cells, stimulates formation of a growth cone from the stump of the proximal axon and facilitates nerve regeneration.

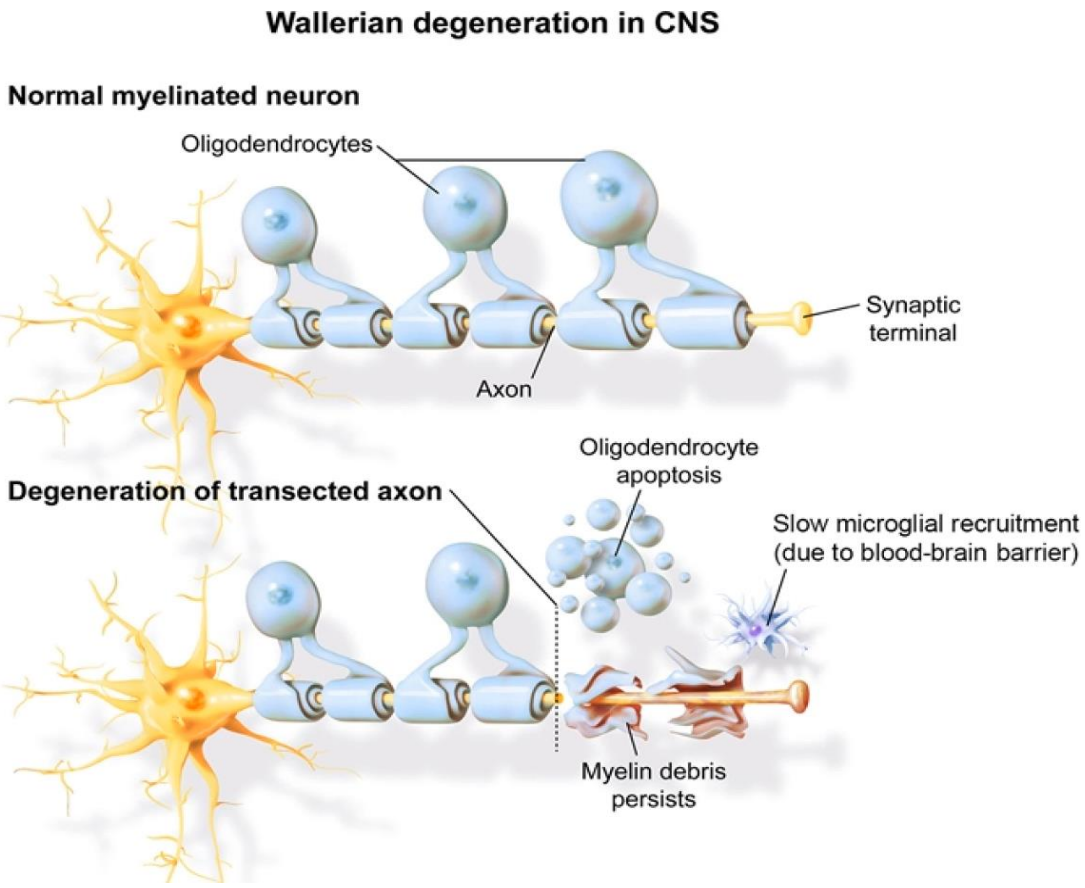
- In the central nervous system:

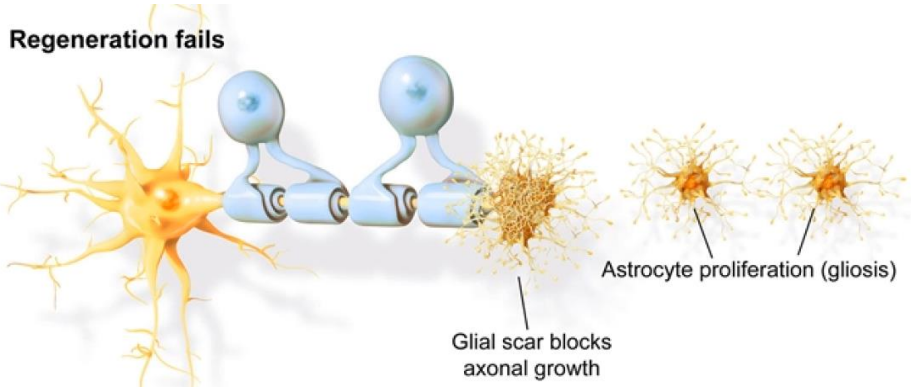
- Phagocytic macrophages/microglia are recruited more slowly because of the blood-brain barrier.

- Myelin-producing oligodendrocytes also become inactive or undergo apoptosis and do not assist with phagocytosis.

- This slows removal of the myelin debris, which can persist for years in the degenerating tracts and suppress axonal growth via myelin-associated inhibitory factors.

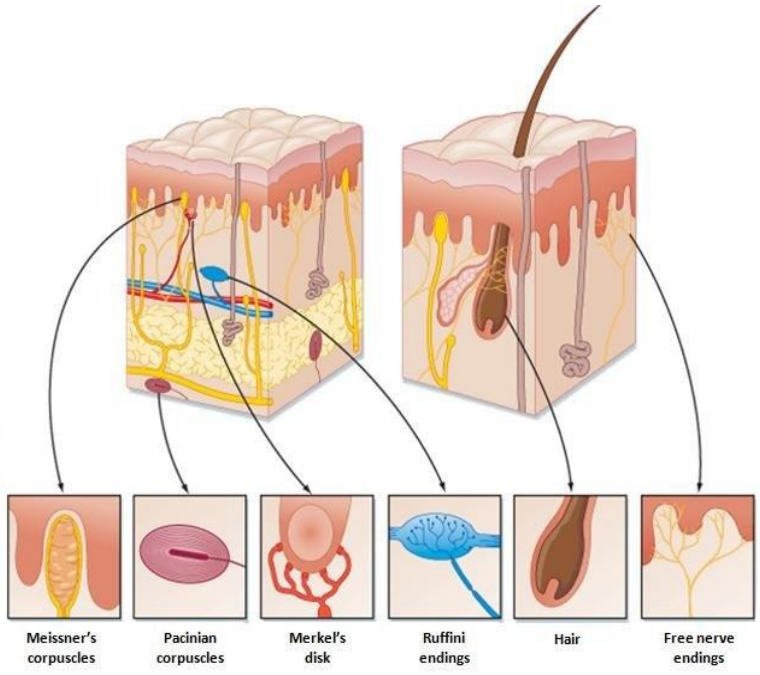
- Astrocytes also release inhibitory molecules and proliferate in the weeks to months following injury, forming a glial scar that acts as a barrier to axon regeneration.





Sensory receptors

Receptor type	Sensory neuron fiber type	Location	Senses
Free nerve endings	Aδ → fast, myelinated fibers C → slow, unmyelinated A Delta plane is fast, but a taxC is slow.	All skin, epidermis, some viscera	Pain, temperature
Meissner corpuscles	Large, myelinated fibers; adapt quickly	Glabrous (hairless) skin	Fine/light touch, position sense, low-frequency vibration
Merkel discs	Large, myelinated fibers; adapt slowly (continuous firing)	Finger tips, superficial skin	Deep static touch (shapes, edges), position sense
Pacinian corpuscles	Large, myelinated fibers; adapt quickly	Deep skin layers, ligaments, joints	Pressure, High-frequency vibration
Ruffini corpuscles	Dendritic endings with capsule; adapt slowly	Finger tips, joints	Pressure, slippage of objects along surface of skin, joint angle change



Neurotransmitter changes with disease

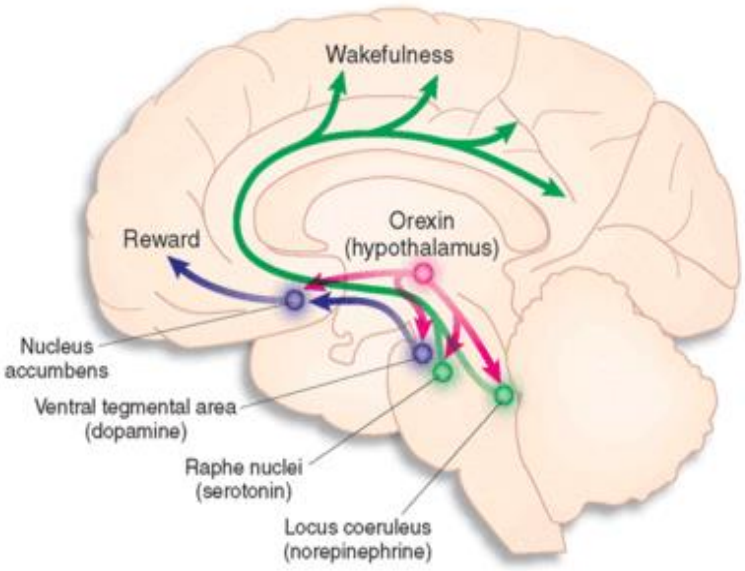
Neurotransmitter	Location of synthesis	Anexity	Depression	Schitzophrenia	Alzheimer disease	Huntigton disease	Parkinson disease
Acetylcholine	Basal nucleus of Meynert				↓	↓	↑
Dopamine	Ventral tegmentum, SNc		↓	↑		↑	↓
GABA	Nucleus accumbens	↓				↓	
Norepinephrine	Locus ceruleus (pons)	↑	↓				
Serotonin	Raphe nuclei (medulla, pons)	↓	↓				↓

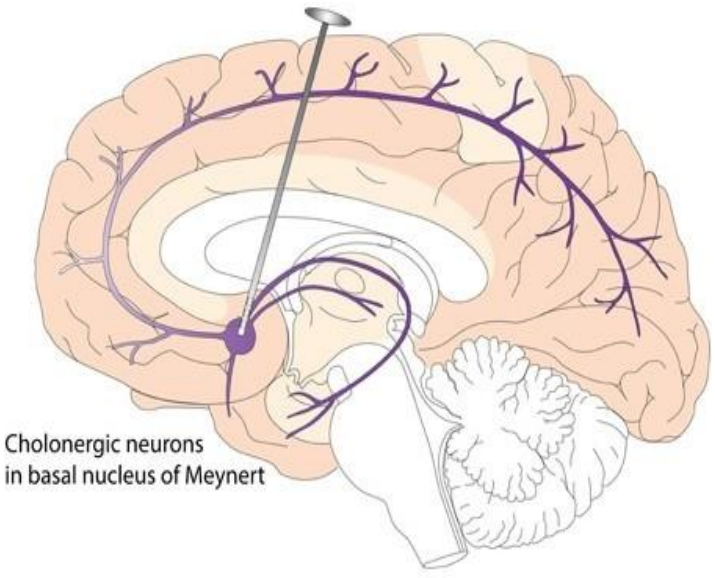
❖ N.B:

1. The locus ceruleus is a paired brainstem nucleus located in the posterior rostral pons near the lateral floor of the fourth ventricle and functions as the principal site for norepinephrine synthesis in the brain.

2. Serotonin-releasing neurons in the central nervous system (CNS) are located in the raphe nuclei.

- These neurons disseminate widely to synapse on numerous structures in the CNS.
- Antidepressants such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants inhibit serotonin reuptake at these synapses.





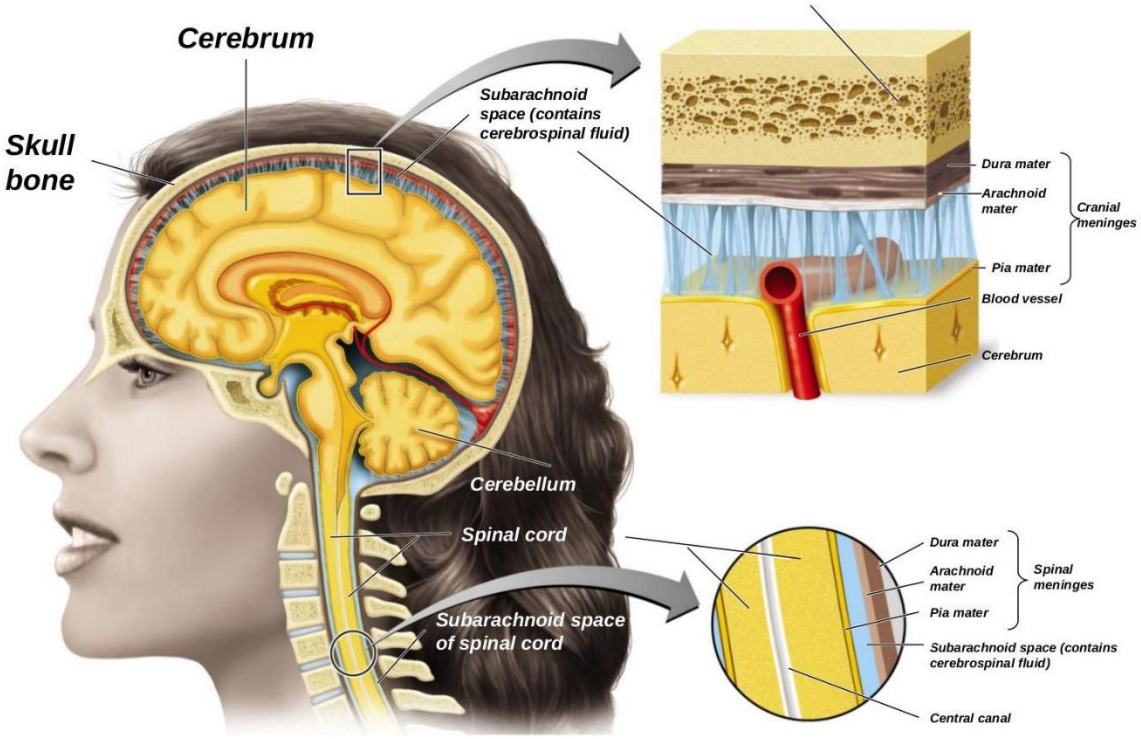
Meninges

- Three membranes that surround and protect the brain and spinal cord:

- Dura mater: thick outer layer closest to skull. Derived from mesoderm.

- Arachnoid mater: middle layer, contains web-like connections. Derived from neural crest.

- Pia mater: thin, fibrous inner layer that firmly adheres to brain and spinal cord. Derived from neural crest.



Blood-brain barrier

- Prevents circulating blood substances (bacteria, drugs) from reaching the CSF/CNS.

- Formed by 3 structures:
  - Tight junctions between nonfenestrated capillary endothelial cells.
  - Basement membrane.
  - Astrocyte foot processes.

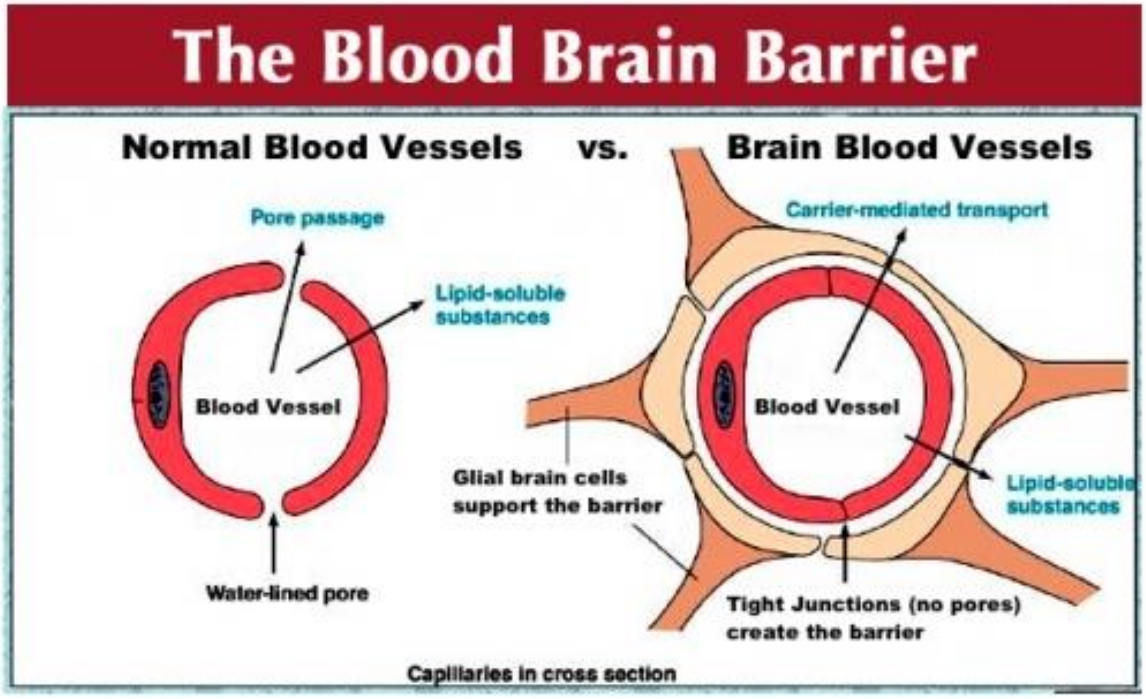
- Glucose and amino acids cross slowly by carrier-mediated transport mechanisms.

- Nonpolar/lipid-soluble substances cross rapidly via diffusion.

- Circumventricular organs with fenestrated capillaries and no blood-brain barrier allow molecules in blood to affect brain function:

- Area postrema → vomiting after chemotherapy.
- OVLT [organum vasculosum lamina terminalis] → osmoreceptors.
- Neurosecretory products to enter circulation (neurohypophysis) → ADH release.

- Infarction and/or neoplasm destroys endothelial cell tight junctions → vasogenic edema.



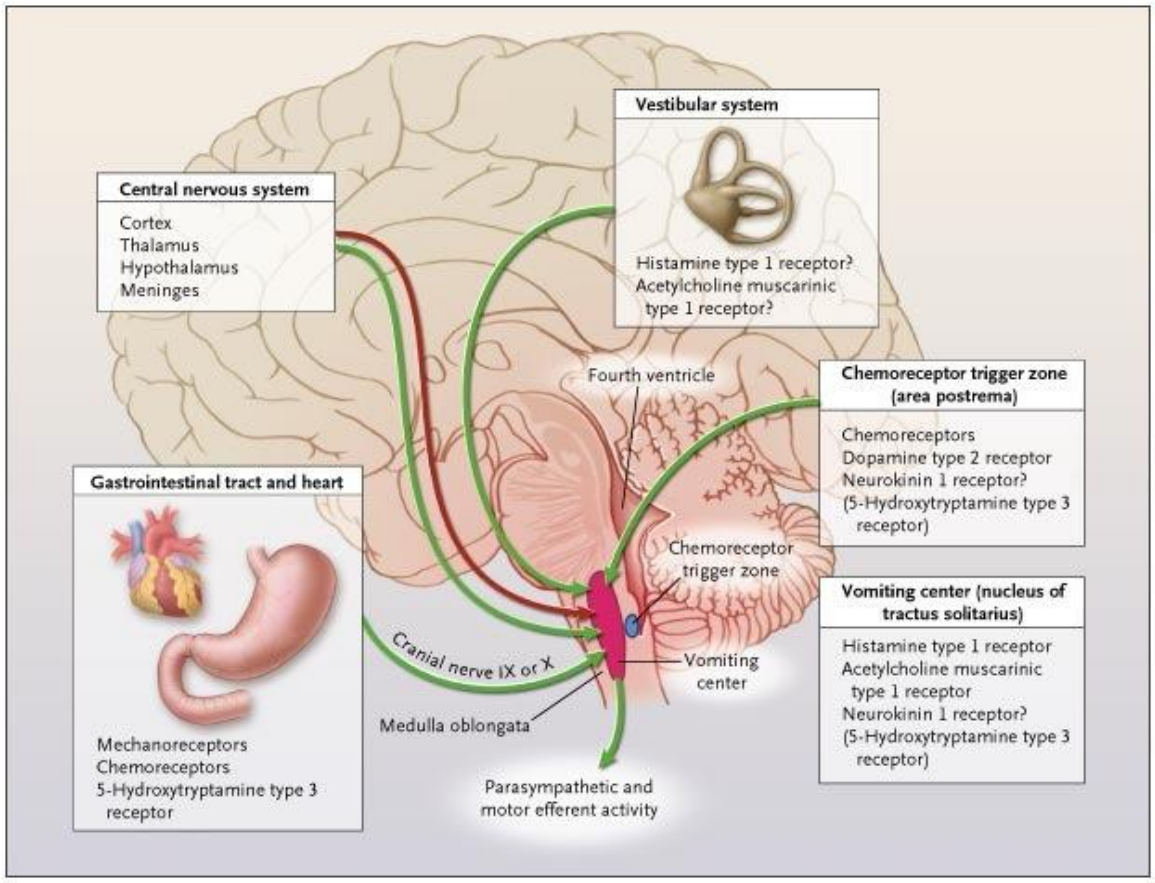
Vomiting center

- Coordinated by nucleus tractus solitarius (NTS) in the medulla, which receives information from the chemoreceptor trigger zone (CTZ, located within area postrema of the dorsal medulla near the fourth ventricle), GI tract (via vagus nerve), vestibular system, and CNS.

- CTZ and adjacent vomiting center nuclei receive input from 5 major receptors: muscarinic (M1), dopamine (D2), histamine (H1), serotonin (5-HT3), and neurokinin (NK-1) receptors.

- 5-HT_3, D_2, and NK-1 antagonists used to treat chemotherapy-induced vomiting.

- H_1 and M_1 antagonists treat motion sickness; H1 antagonists treat hyperemesis gravidarum.



Dopaminergic pathways

- There are 4 major dopaminergic pathways in the brain (mesolimbic, mesocortical, tuberoinfundibular, nigrostriatal).

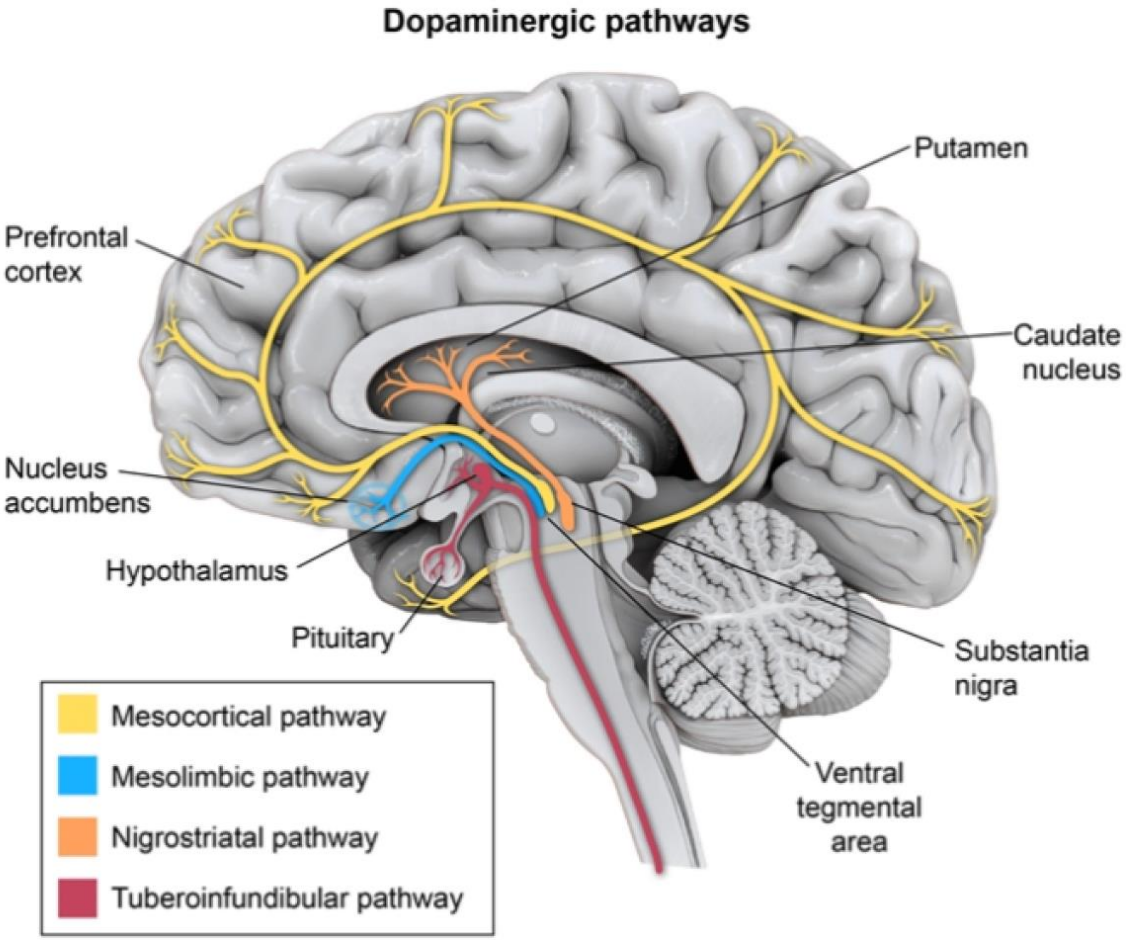
Pathway	Symptoms of altered activity	Notes
Mesocortical	↓ activity → "negative" symptoms (anergia, apathy, lack of spontaneity)	Antipsychotic drugs have limited effect
Mesolimbic	↑ activity → "positive" symptoms (delusions, hallucinations, disorganized thoughts)	1° therapeutic target of antipsychotic drugs → ↓ positive symptoms (in schizophrenia)
Nigrostriatal	↓ activity → extrapyramidal symptoms (dystonia, akathisia, parkinsonism, tardive dyskinesia)	Major dopaminergic pathway in brain. Significantly affected by movement disorders and antipsychotic drugs
Tuberoinfundibular	↓ activity → ↑ prolactin → ↓ libido, sexual dysfunction, galactorrhea, gynecomastia (in men)	

- Dopamine hyperactivity in the mesolimbic pathway is associated with positive psychotic symptoms (hallucinations, delusions).

- The side effects of antipsychotic therapy are largely caused by D_2 receptor blockade in other dopaminergic pathways.

- The tuberoinfundibular pathway connects the hypothalamus to the pituitary gland and is responsible for the tonic inhibition of prolactin secretion. Neurons in the arcuate nucleus of the hypothalamus secrete dopamine, which binds to D2 receptors on pituitary lactotrophs, resulting in decreased prolactin secretion from the anterior pituitary gland.

- Antipsychotics can interrupt the tuberoinfundibular pathway, causing increased blood prolactin levels (hyperprolactinemia), which may lead to galactorrhea (milky nipple discharge unrelated to pregnancy/breastfeeding) and menstrual irregularities (amenorrhea).

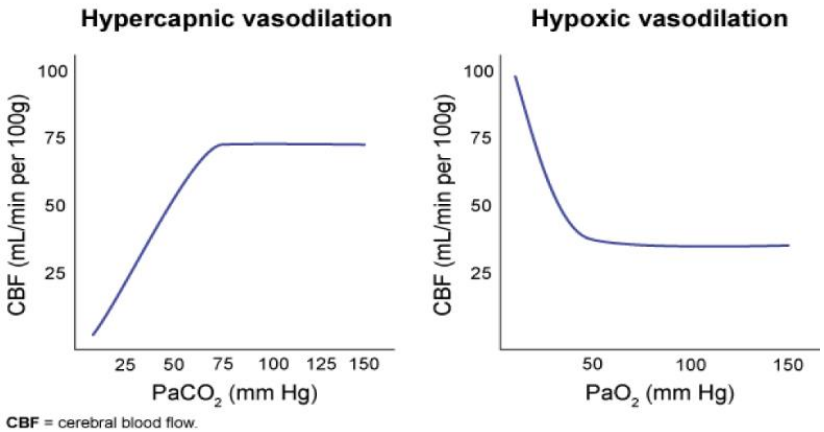


Regulation of cerebral perfusion

- Brain perfusion relies on tight regulation.

$$CPP = MAP - ICP$$

- Cerebral perfusion pressure (CPP) relies on a pressure gradient between mean arterial pressure (MAP) and intracranial pressure (ICP).
- Intracranial pressure (ICP) is determined by the volume of brain parenchyma (80%), blood (12%), and CSF (8%) within a rigid cranial vault.
- Cerebral perfusion is primarily driven by PCO_2 (the most important regulator of cerebral perfusion).
- In hypercapnia (right graph), there is increase in CO_2 → which will cause vasodilatation of the cerebral vessels → ↑ cerebral blood flow → ↑ cerebral perfusion.
- That's why therapeutic hyperventilation may be used in acute cerebral edema (stroke, trauma) to ↓ intracranial pressure (ICP), How? - Therapeutic Hyperventilation → ↓ PCO_2 → vasoconstriction of cerebral vessels → ↓ cerebral blood flow → ↓ cerebral blood volume, and ICP and help prevent brain herniation.
- In panic attacks, there is hyperventilation (↓ PCO_2) → ↓ cerebral blood flow, which explains fainting in panic attacks.
- PO_2 (left graph) also modulates perfusion in severe hypoxia (only when $PO_2 < 50$ mmHg), because in brain or any other organs except the lung, when you have ischemic condition there is increase in perfusion to this ischemic area.
- CPP = MAP – ICP, if there is ↓ MAP or ↑ ICP there will be decrease in intracranial perfusion pressure.
- If CPP = 0, this means there is no cerebral perfusion → brain death.



CBF = cerebral blood flow.

CHAPTER 4

Pathology

Neurodegenerative disorders

- Definition: ↓ in cognitive ability, memory, or function with intact consciousness.

- Must rule out depression as cause of dementia (pseudodementia). Other reversible causes of dementia: hypothyroidism, vitamin B12 deficiency, neurosyphilis, normal pressure hydrocephalus.

1- Alzheimer disease:

- It is a neurodegenerative disorder that presents with progressive memory loss.

- The most common cause of dementia and usually affects people > 60 years old:

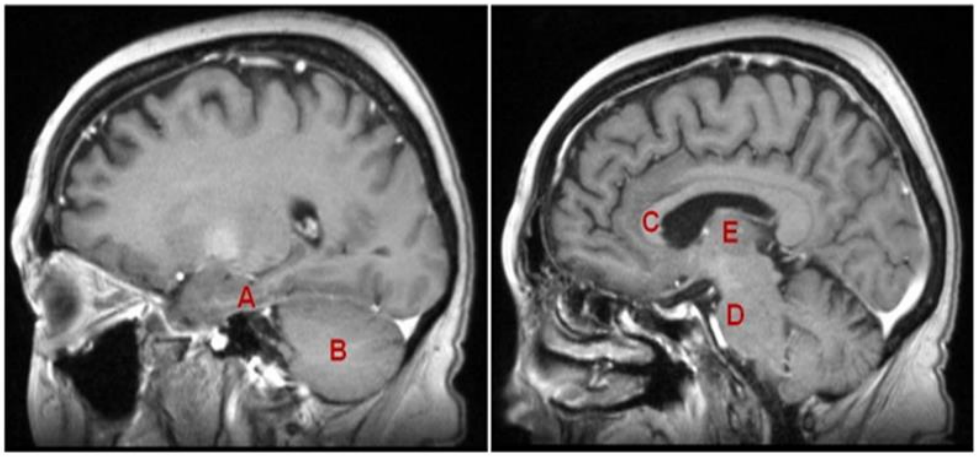
- Early → language deficits (word-finding difficulty).
- Later → impairment in executive function and associated behavioral abnormalities become more pronounced, patients can have trouble performing everyday functions (shopping, cooking).

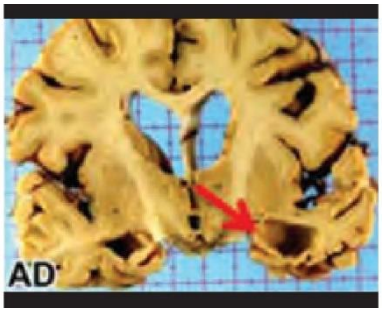
- Key in the case:

- Above 60 years old patient brought by the daughter or her husband with memory troubles.

Clinical features of Alzheimer disease	
Early findings	• Anterograde memory loss (ie, immediate recall affected, distant memories preserved) • Visuospatial deficits (eg, lost in own neighborhood) • Language difficulties (eg, difficulty finding words) • Cognitive impairment with progressive decline
Late findings	• Neuropsychiatric (eg, hallucinations, wandering) • Dyspraxia (eg, difficulty performing learned motor tasks) • Lack of insight regarding deficits • Noncognitive neurologic deficits (eg, pyramidal & extrapyramidal motor, myoclonus, seizures) • Urinary incontinence

- Advanced Alzheimer's disease is associated with diffuse brain atrophy. Hippocampal atrophy is evident even in the early stages of the disease and can be detected by brain MRI.





A. The Hippocampus, B. The Cerebellum, C. The Corpus callosum, D. pons, E. Thalamus

- The hippocampus (A) is the area of the brain demonstrating the greatest degree of atrophy in Alzheimer's disease.

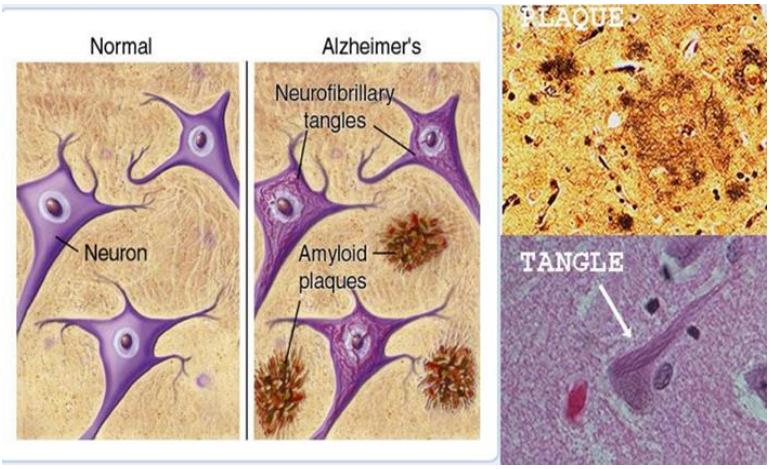
- Characteristic pathologic changes associated with Alzheimer's dementia involve accumulation of intracellular neurofibrillary tangles and extracellular AB amyloid plaques:

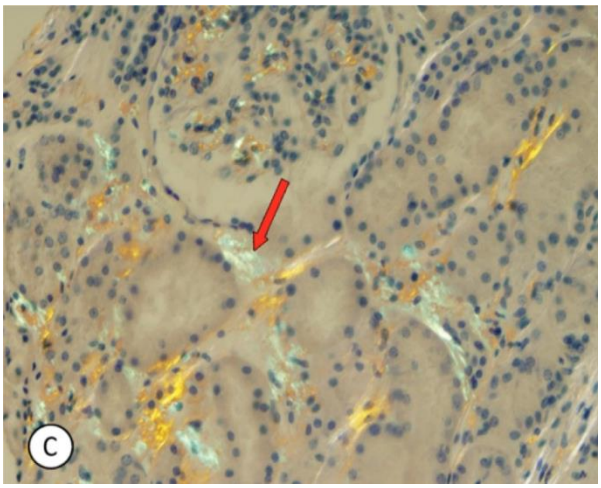
- Neurofibrillary tangles are composed of tau protein, a primary component of intracellular microtubules. In Alzheimer disease, tau protein is disturbed and hyperphosphorylated, causing microtubule structures to collapse into "tangles" that contribute to global neuronal dysfunction. Number of tangles correlates with degree of dementia.

- AB amyloid is an abnormal fragment of amyloid precursor protein (APP), which is normally involved in synaptic formation and repair. In Alzheimer disease, the protein is not properly cleared and forms amyloid fragments, these then harden into insoluble plaques and accumulate in brain tissue (senile plaques), and vessel wall (amyloid angiopathy → ↑ Risk of spontaneous lobar hemorrhage, particularly in the elderly. The most common sites of hemorrhage include the occipital and parietal lobes).

- All amyloids form extracellular deposits that stain with Congo red. When seen under polarized light, it gives → apple-green birefringence. Congo red staining of brain samples reveals patchy amyloid deposits.

- There is an important biochemical abnormality noted in Alzheimer disease patients which is a decrease in acetylcholine level. This occurs due to the deficiency of choline Acetyltransferase (a transferase enzyme responsible for the synthesis of the neurotransmitter acetylcholine). The decline in acetylcholine levels is most notable in basal nucleus of meynert (participates in memory & cognition) and hippocampus (responsible for formation of new memories).





- Down syndrome patients have an ↑ risk of developing Alzheimer, why? - The association of down syndrome and Alzheimer disease may be explained by the fact that the APP gene is located on chromosome 21. Cleavage of APP (amyloid precursor protein) forms AB amyloid, which is the substance that accumulates in brain tissue and vessel walls. Trisomy of 21 means that three copies of the APP gene are present. More APP is therefore produced in down syndrome, facilitating accelerated accumulation of amyloid and Alzheimer like changes.

- Alzheimer disease has a strong genetic predisposition. According to age when symptoms begin, Alzheimer disease can be classified as early or late.

- The following three mutation sites have been associated with early onset familial Alzheimer disease (onset < 60 years old):

1- Amyloid precursor protein (APP) gene on chromosome 21.
2- Presenilin 1 gene on chromosome 14.
3- Presenilin 2 gene on chromosome 1.

- Both APP and presenilin gene mutations are thought to promote the production of AB amyloid.

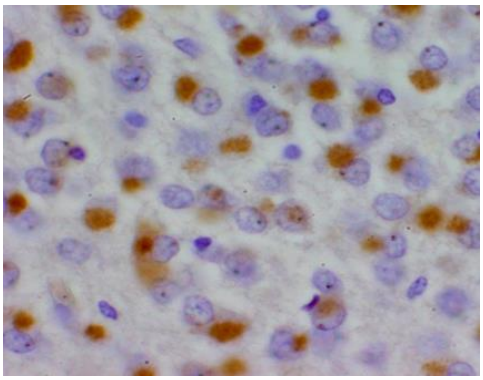
- Sporadic Alzheimer disease is associated with the apolipoprotein E4 genotype. It is thought that the Apo E4 protein may be involved in the formation of senile plaques. But ApoE2 ↓ Risk.

2- Frontotemporal dementia (pick's disease):

- It is associated with pronounced atrophy of frontal lobe that eventually progress to include the temporal lobes, that's why it's called (frontotemporal disease).

- Because frontal lobe includes the motor cortex, Broca's speech area, frontal eye fields, and the prefrontal cortex → The disease manifest initially with change in personality, social behavior (prefornal cortex lesion), language abnormalities (broca's area lesion) that progress over time to a more global dementia with obvious neurocognitive deficits.

- Pick's bodies: cytoplasmic inclusions of hyperphosphorylated microtubule associated tau protein.



- When evaluating a patient with dementia, frontotemporal dementia should be differentiated from the more common Alzheimer disease:

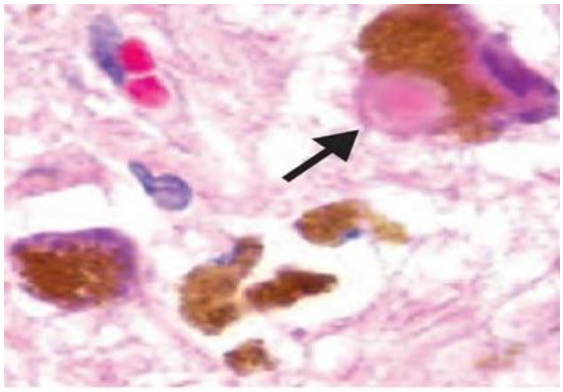
Criteria	Frontotemporal dementia	Alzheimer disease
Macroscopic examination	Pronounced atrophy of frontal & temporal lobes	Mild to moderate generalized brain atrophy
Onset	Early (50S, 60S)	60S or older
Microscopic features	Pick's bodies	Senile plaques Amyloid angiopathy Neurofibrillary tangles
Initial symptoms	Personality & behavioral changes (apathy and inappropriate social behavior)	Impairments involving recent memory
Genetic basis	Autosomal dominant in 20 – 40 % of cases	Chromosome 21 (APP gene) Apolipoprotein E4

3- Lewy body dementia:

- Initially dementia and visual hallucinations (haLewycinations) followed by parkinsonian features.

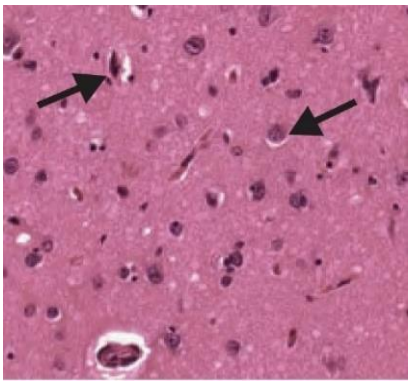
- At autopsy, Lewy bodies (eosinophilic intracytoplasmic inclusions representing accumulations of alpha synuclein protein, primarily in cortex) are a pathologic finding, but also present in Parkinson's disease. The key distinction between these two conditions is the early appearance of dementia in Lewy body disease and of early motor symptoms in Parkinson's disease.

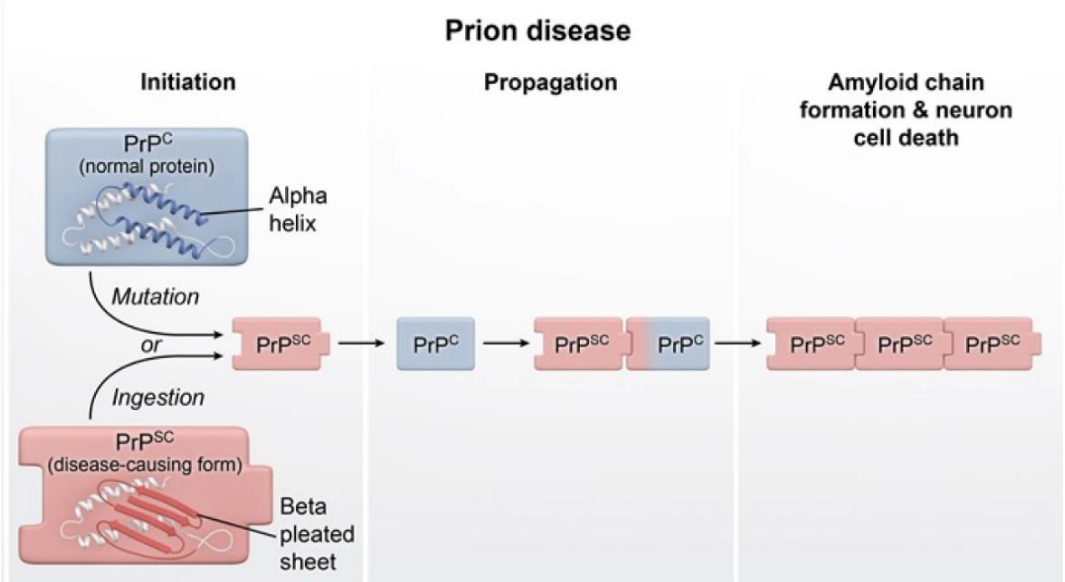
- Called Lewy body dementia if cognitive and motor symptom onset < 1 year apart, otherwise considered dementia 2° to Parkinson disease.



4- Creutzfeldt-jakob disease:

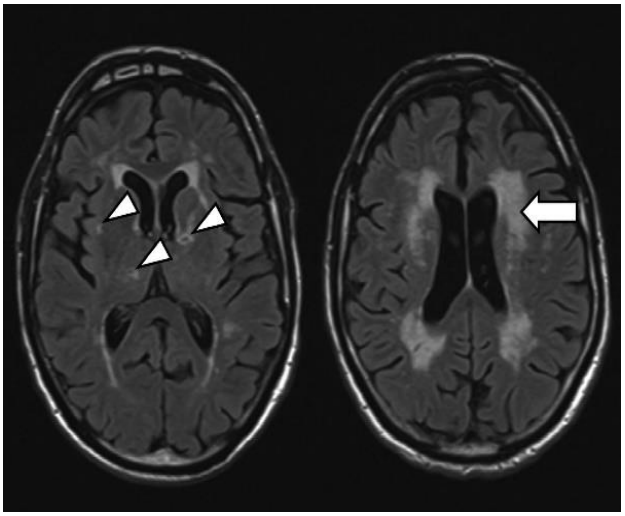
- Rapidly progressive (weeks to months) dementia with myoclonus (startle myoclonus).
- It is an example of prion disease in humans.
- Prion protein (PrP) is normally found in neurons and has an α-helical structure. If the conversion of α-helix into β-Pleated sheet occurs, the protein becomes resistant to proteases → accumulation of this abnormal protein in gray matter → prion disease.
- In Creutzfeldt-Jakob disease, the affected gray matter undergoes spongiform change → vacuoles form within the cytoplasm of neurons without inflammatory changes, later they grow bigger and form cysts resembling spongiform, that's why Creutzfeldt-Jakob disease is also called → spongiform encephalopathy due to spongiform transformation of the gray matter.
- Commonly see periodic sharp waves on EEG and ↑ 14-3-3 protein in CSF.
- Prion disease in humans → Creutzfeldt-Jakob disease, in cows → mad cow disease.





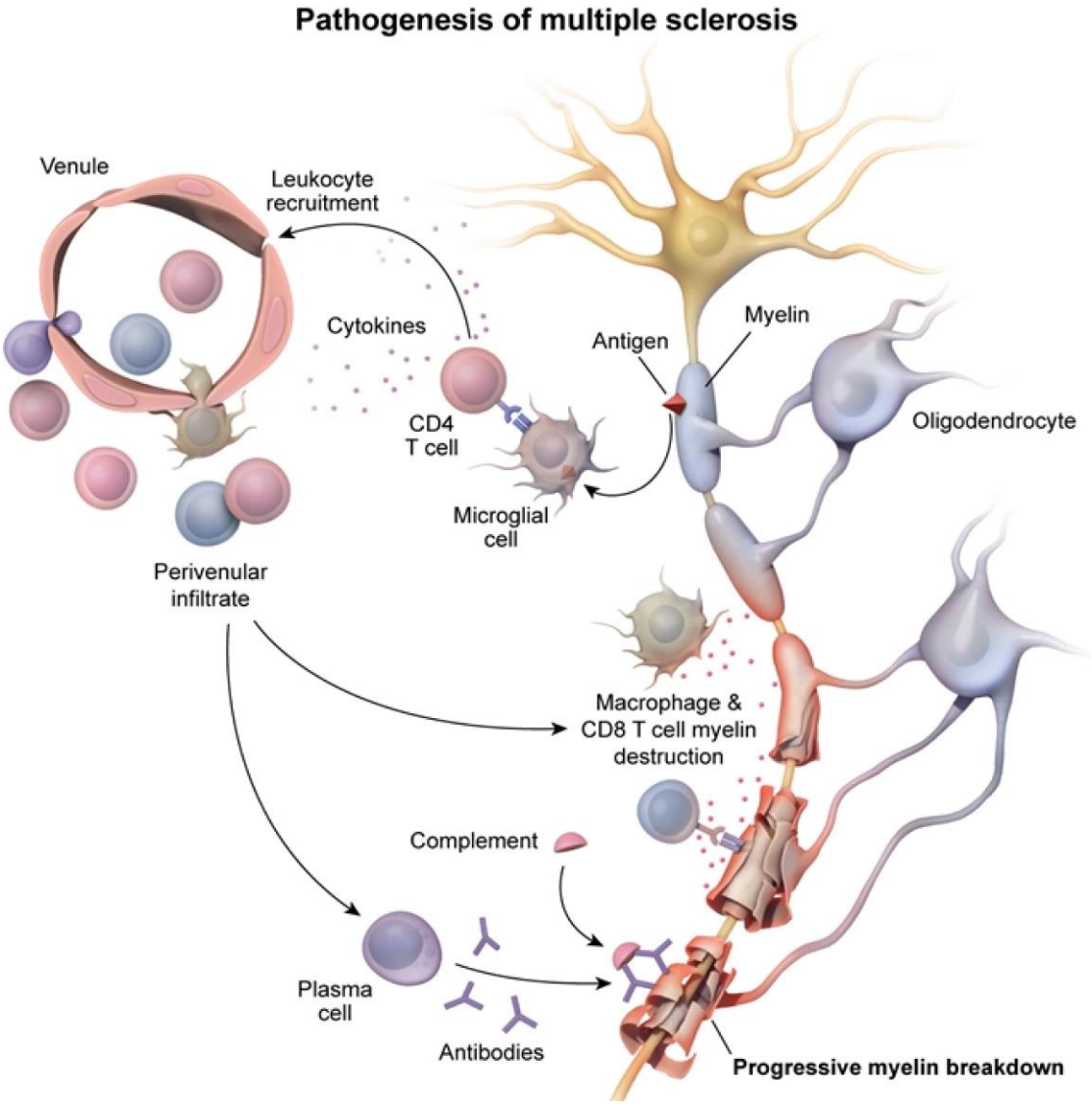
5- Vascular dementia:

- Result of multiple arterial infarcts and/or chronic ischemia.
- Step-wise decline in cognitive ability with late-onset memory impairment.
- 2nd most common cause of dementia in elderly.
- MRI or CT shows multiple cortical and/or subcortical infarcts.



Demyelinating Diseases

- It is a chronic autoimmune demyelinating disease affecting the white matter of the central nervous system (brain and spinal cord).
- Most often affects women in their 20s and 30s.
- The disease course is highly variable and is characterized by relapses and remissions that occur over many years.
- It should be suspected in a patient with neurological deficits that cannot be explained by a single lesion.
- Affected areas demonstrate myelin breakdown (demyelination), the demyelination of axons impairs saltatory conduction down the axon which results in → slowing of neuronal signal transmission.



- Pathogenesis:

- Active MS plaques are characterized by perivenular inflammatory infiltrates made up primarily of autoreactive T lymphocytes and macrophages directed against myelin components.

- Extensive inflammation damages the blood-brain barrier, increasing inflammatory cell recruitment into the CNS (with the vessel wall remaining intact, unlike in CNS vasculitis).

- Infiltrating macrophages containing myelin debris are seen throughout the lesion, and recruitment of B lymphocytes to the perivascular spaces leads to the formation of myelin-specific antibodies.

- Patchy demyelination occurs, and while axons are typically spared, significant or prolonged disease may result in neuron death. Residual chronic findings include hypertrophy and hyperplasia of astrocytes (glial scarring).

- The clinical presentation of MS reflects the involvement of different sites within the CNS. Some common initial symptoms include:

1- Optic neuritis:

- Painful unilateral visual loss associated with Marcus Gunn pupil.

- Marcus Gunn pupil (Relative Afferent Pupillary Defect).

- Cause:

- Lesion of afferent limb of pupillary light reflex (optic nerve) in multiple sclerosis (intact oculomotor nerve, because multiple sclerosis is an autoimmune disease against oligodendrocytes, and oculomotor nerve is myelinated by Schwann cells).

- Findings:

- Diagnosis is made with swinging flashlight test:
  - Shining light in normal eye → both pupils constricts normally.
  - Shining light in the eye with optic nerve lesion → both pupils paradoxically dilate (apparent dilatation of both pupils because stimulus carried through that CN II is weaker).

2- Internuclear ophthalmoplegia:

- Impaired eye adduction during lateral gaze due to demyelination of the medial longitudinal fasciculus.

- MLF function: adduct an eye during horizontal gaze by connecting the abducens and oculomotor nuclei together.

- Because MLF is highly myelinated fiber bundle, it is affected in MS leading to internuclear ophthalmoplegia (internuclear because MLF lies between 2 nuclei, abducent and oculomotor nuclei).

- In internuclear ophthalmoplegia there is No adduction in conjugate lateral gaze although there is intact oculomotor nerve.

- Qs- How to differentiate between MLF lesion and oculomotor nerve lesion?

- In oculomotor nerve lesion, there is also ptosis & dilated pupil and loss of accommodation.

- In MLF lesion, i can't adduct the eye in horizontal eye gaze but there is intact bilateral adduction (convergence) in accommodations, because this is the function of oculomotor nerve, not MLF.

3- Brain stem and Cerebellar dysfunction: includes intension tremor, scanning speech, ataxia, vertigo and nystagmus.

4- Sensory and motor symptoms: includes hemiparesis, spasticity, hemisesensory loss, bowel and bladder dysfunction.

- Fatigue is the most non-specific symptom of MS. Patients may feel particularly fatigued after taking hot shower or after strenuous activity in heated environments, why? - This is due to decreased axonal transmission associated with increased heat.

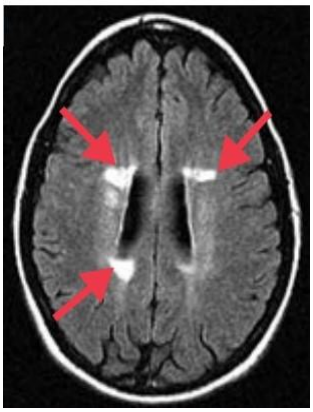
- Charcot classic triad of MS is a SIN:
  - Scanning speech.
  - Intention tremor.
  - Incontinence.
  - Internuclear ophthalmoplegia.
  - Nystagmus.

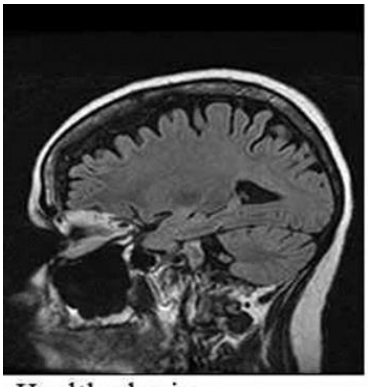
- Lab Findings:

- Oligoclonal bands (increased concentration of gamma globulin in CSF) on protein electrophoresis are diagnostic.

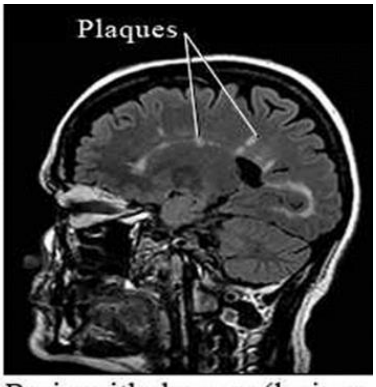
- MRI is a gold standard: MRI findings in MS typically include white matter lesions scattered throughout the brain and/or spinal cord with a predilection for the subcortical periventricular regions.

- These plaques are due to loss of myelin sheath and depletion of oligodendrocytes.





Healthy brain



Brain with damage (lesions or plaques) caused by MS

- Treatment:

- Stop relapses and slow progression with disease-modifying therapies (β interferon, glatiramer, natalizumab).

- Treat acute flares with IV steroids.

- Symptomatic treatment for:
  - Neurologic bladder (catheterization, muscarinic antagonists).
  - Spasticity (Baclofen, GABA receptor agonist).
  - Pain (TCAs, anticonvulsants).

Guillan-Barre syndrome

- Autoimmune disease associated with infections (campylobacter jejuni, viral infection) that contain ganglioside like substance in their lipopolysaccharide layer (Molecular Mimicry).

- Antibodies formed against this substance cross-react with the ganglioside components of myelin → segmental demyelination and endoneural inflammatory infiltrate are seen on the light microscopy of motor fibers, sensory fibers, peripheral nerves.

- It is strongly associated with campylobacter jejuni infection, viruses [Zika])

- It manifests with symmetric ascending muscle weakness that starts after recovery of respiratory or gastrointestinal infection.

- Muscle weakness is accompanied by the disappearance of deep tendon reflexes (areflexia)

- Symmetric ascending muscle weakness + loss of reflexes starts after recovery of respiratory or gastrointestinal infection → GBS.

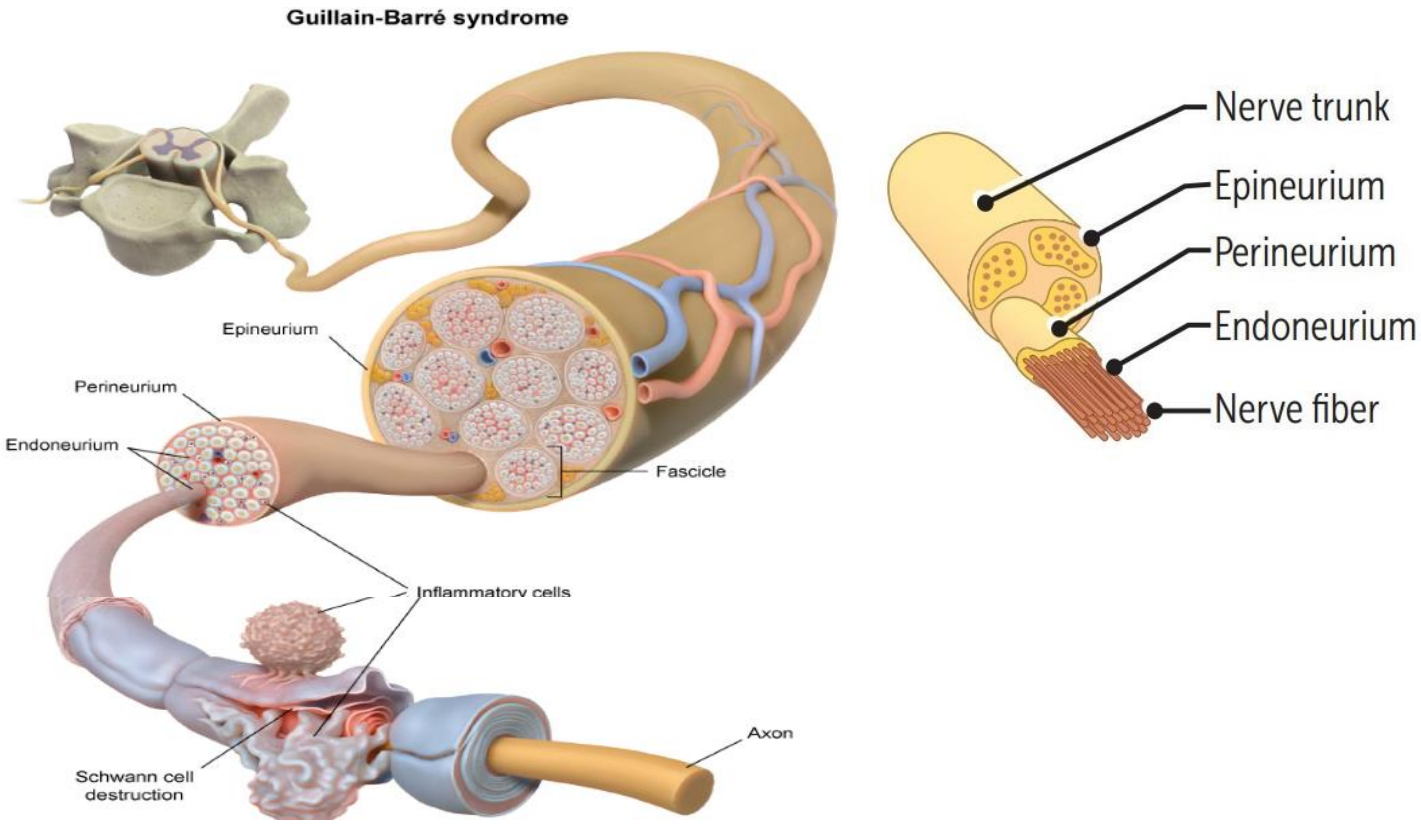
- Paralysis may ascend to the cranial nerves (especially CN VII) → Bell's palsy in 50 % of cases (usually bilateral).
- Paralysis of respiratory muscles is fatal without supportive care (phrenic nerve involvement).

- May present with autonomic deregulation (cardiac irregularities, hypertension, hypotension).

- Almost all patients survive, the majority recover completely after weeks to months.

- Findings: ↑ CSF protein with normal cell count (albuminocytologic dissociation), ↑ protein may cause papilledema.

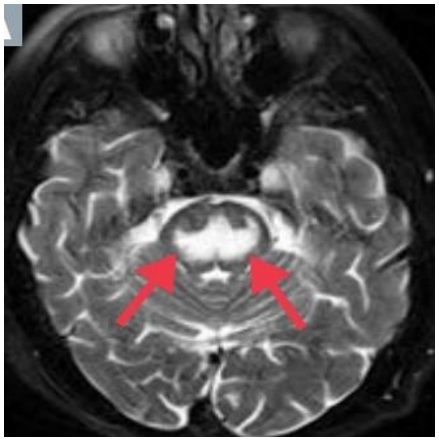
- Treatment: Plasmapheresis or IV immunoglobulin, and Respiratory support is critical until recovery.

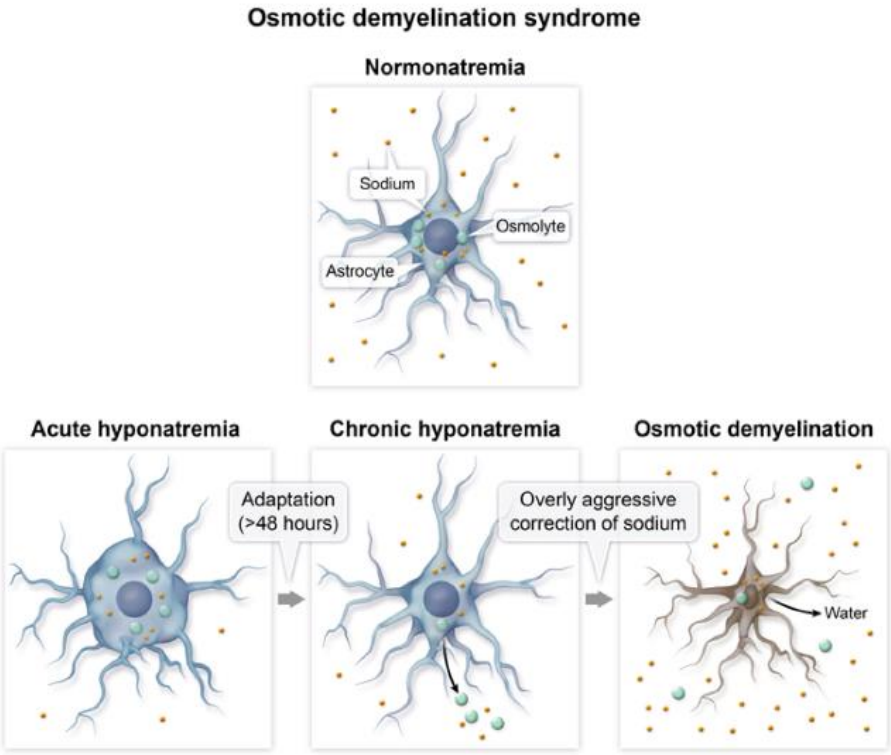


Other demyelinating and dysmyelinating diseases

1. Osmotic demyelination syndrome:

- Also called central pontine myelinolysis.
- It results from rapid correction of chronic hyponatremia → Osmotic demyelination of the axons in the central part of the pons.
- A rapid increase in extracellular tonicity (due to aggressive saline hydration) quickly draws water out of central nervous system cells → resulting in uncontrolled cell shrinkage leads to degeneration of astrocytes (crucial for myelin maintenance) and oligodendrocytes.
- Demyelination typically affects the pons, but can also occur at extrapontine sites (basal ganglia and cerebral white matter).
- The typical clinical features include quadriplegia (due to demyelination of corticospinal tracts) and pseudobulbar palsy (due to demyelination of the corticobulbar tracts of CN IX, X, XI).
- Patients with involvement of the bilateral pons may develop locked in syndrome with near-total paralysis and aphasia but with intact cognitive abilities, blinking, and vertical eye movements.





- Correcting serum Na too fast:

- "From low to high, your pons will die" (osmotic demyelination syndrome).

- "From high to low, your brains will blow" (cerebral edema/herniation).

2. Acute disseminated (postinfectious) encephalomyelitis:

- Multifocal periventricular inflammation and demyelination after infection (commonly measles or varicella zoster virus) or certain vaccinations (rabies, smallpox).

- Presents with rapidly progressive multifocal neurologic symptoms, altered mental status.

- Subacute sclerosing panencephalitis:

- It is a rare complication of measles infection (RNA virus).

- It occurs in children who appear to have recovered from measles infection several years earlier.

- Certain type of measles virus is missing an antigen (M protein), the missing antigen causes → failure of the measles virus to be cleared by the immune system and allow its persistence in the CNS, this retained virus causes → inflammation, demyelination, gliosis in many cerebral areas.

- It presents with gradual progressive psychoneurological deterioration consisting of personality change, seizures, myoclonus, spasticity, and coma.

3. HSV 1 encephalitis:

- The most common cause of sporadic encephalitis.
- It results from the reactivation of latent virus (Herps simplex virus type 1) in the trigeminal ganglion.
- Temporal lobe involvement is characteristic of HSV 1 encephalitis.
- The most common early symptoms of acute encephalitis are headache and fever, mental status changes and seizures may follow.
- Specific symptoms of herpetic encephalitis are related to HSV1 Predilection for temporal lobe, including aphasia (damage of speech area), olfactory hallucination (olfactory cortex involvement), and personality change (amygdala damage).
- Macroscopic brain examination reveals edema and hemorrhagic necrosis of the temporal lobes.
- EEG can reveal focal temporal abnormalities.

4. Progressive multifocal leukoencephalopathy (PML):

- Demyelination of CNS due to destruction of oligodendrocytes.
- It occurs due to reactivation of the JC virus (a polyomavirus).
- It occurs in severely immunocompromised patients, such as those with AIDS, lymphoma, or leukemia.
- PML causes progressive dementia, motor deficits, and visual impairment.
- Rapidly progressive, usually fatal.
- Risk associated with natalizumab, rituximab (decrease immunity).

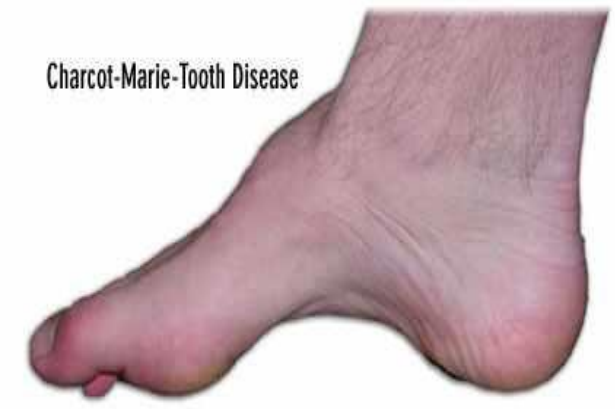
5. Charcot-Marie-Tooth disease:

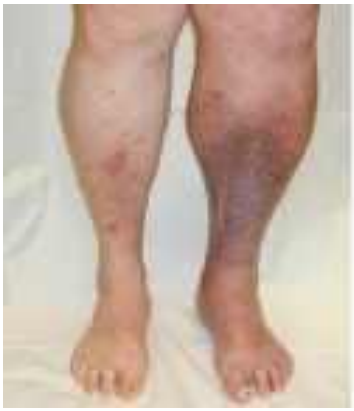
- Also known as hereditary motor and sensory neuropathy (HMSN).
- Autosomal dominant disease. It is caused by mutation of the genes responsible for myelin synthesis. Abnormal myelin synthesis leads to decreased nerve conduction velocity.
- <u>It presents with loss of both motor and sensory innervation leading to:</u>

- Distal weakness and sensory loss.
- Wasting in the legs. The legs look like inverted champagne bottles.
- Decreased deep tendon reflexes.
- Weakness of foot dorsiflexion (foot drop) due to involvement of the common peroneal nerve.

- Food deformity with a high arch is common (pes cavus, hammer toe).
- Tremors.

▪ No treatment.



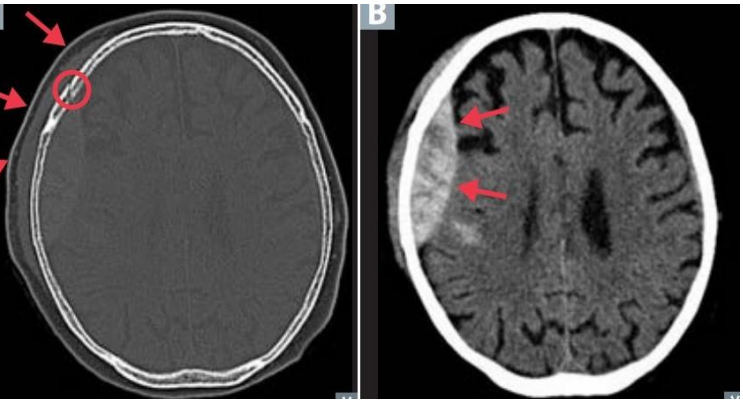


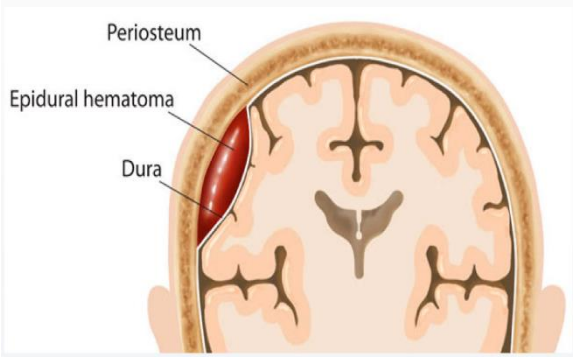
6. Krabbe disease: (Biochemistry book, Lysosomal storage disease section).
7. Metachromatic leukodystrophy: (Biochemistry book, Lysosomal storage disease section).
8. Adrenoleukodystrophy: (Biochemistry book, Peroxisomal diseases section).

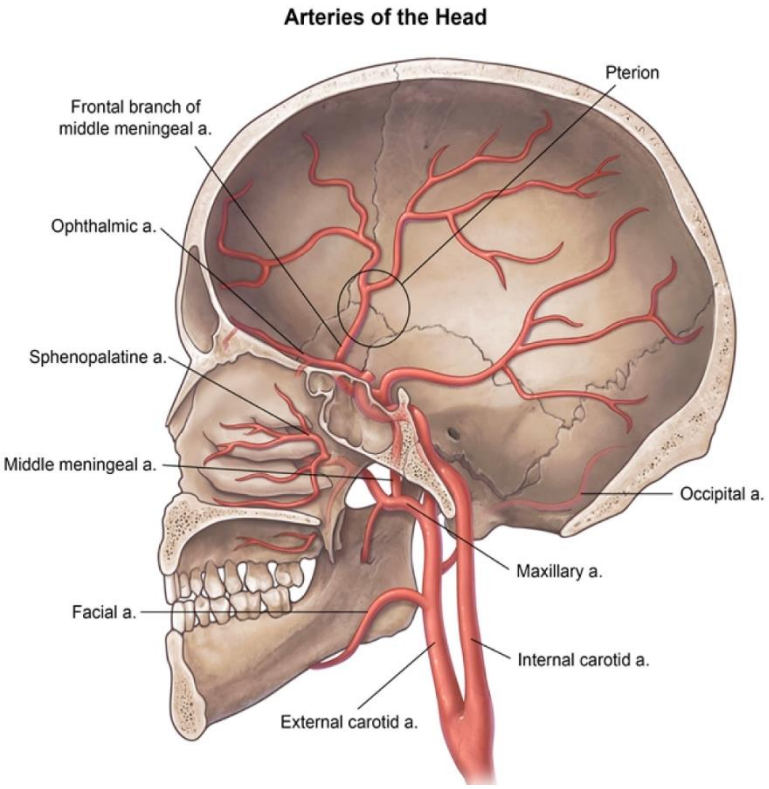
Intracranial hemorrhage

Epidural hematoma

- It is an accumulation of blood between the skull bone and dura mater.
- The majority of cases are associated with fracture of the temporal bone and subsequent rupture or tear of the middle meningeal artery (branch of Maxillary artery).
- The clinical presentation of epidural hematoma is characteristic. The patient may lose consciousness at the time of impact → Then quickly regains consciousness, and feels well for a few hours after the injury. This transient period of wellbeing is called a lucid interval. It is followed by a quick decline in mental function that can progress into a coma and death.
- The neurologic deterioration after lucid interval is due to Rapid expansion of hematoma under systemic arterial pressure → ↑ intracranial pressure → leading to herniation and death.
- CT without contrast is diagnostic and reveals: hyperdense biconvex mass located between the brain and the skull not crossing suture lines.
- The index of suspicion for epidural hematoma should be high, as this condition is life-threatening.



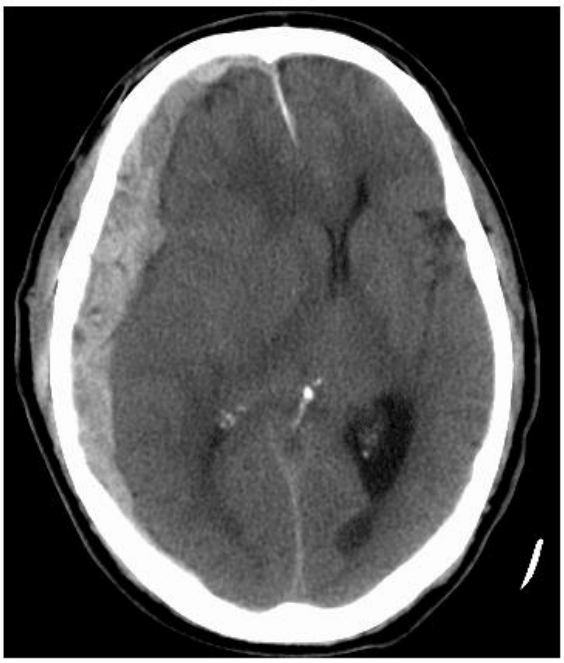


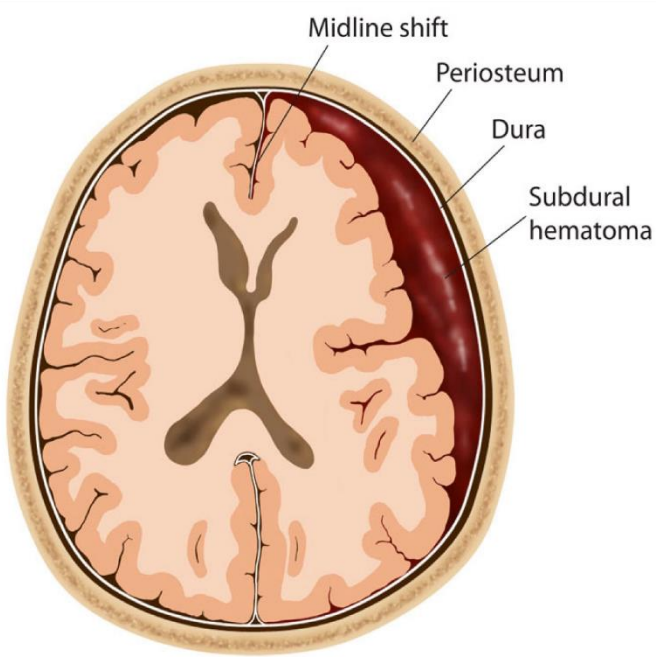


Subdural hematoma

- It is an accumulation of blood between the dura mater and arachnoid.
- Often occurs as a result of acceleration - deceleration injury (blunt trauma as fall or motor vehicle accident, shaken baby).
- But more common in elderly individuals or alcoholics after a minor trauma, this increased incidence is explained by age-related brain atrophy → the distance from the skull to the brain surface increases → cortical bridging veins (which carry blood from the cortex to the venous sinuses) are under more tension and rupture more easily → accumulation of blood between the dura mater and arachnoid, as the hematoma expands → it raises the intracranial pressure and compresses the brain.
- But venous bleeding is relatively slow (low pressure in veins), which explains the gradual onset of symptoms in subdural hematoma.
- Patients complain of gradually worsening headache and slow decline in mental function.
- Herniation and death may occur.
- <u>On CT scan: subdural hematoma is seen as:</u>

- Crescent-shaped hemorrhage that crosses suture lines.
- Midline shift.



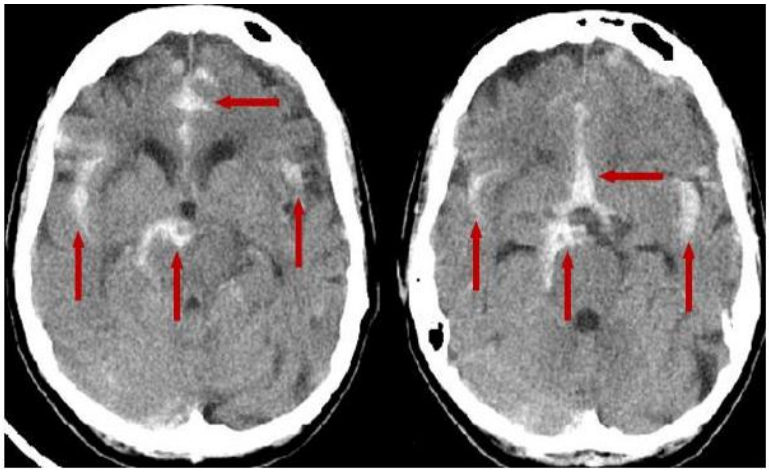


Subarachnoid hemorrhage (SAH)

- It is a life-threatening condition.
- It occurs due to trauma or rupture of saccular (berry) aneurysm or arteriovenous malformation.
- SAH manifests with the abrupt onset of severe headache, the patient describes it as "the worst headache in my life".
- Confusion, fever, and nuchal rigidity may also be present.
- Complications:

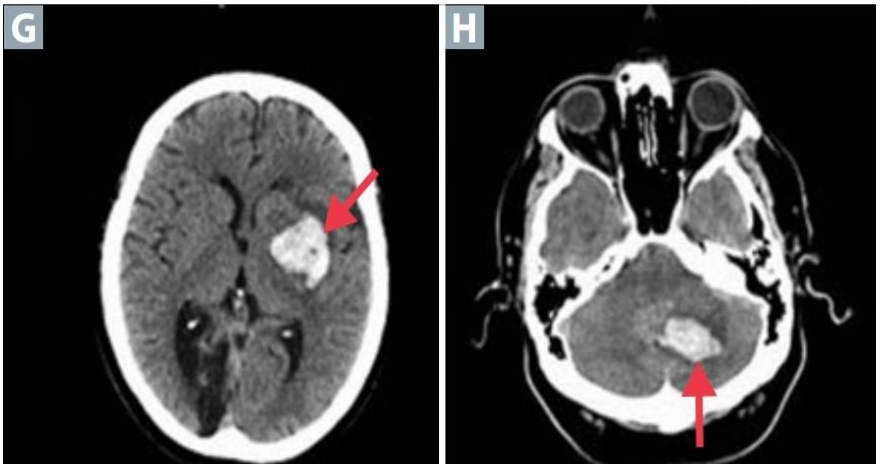
- If the patient survives initial subarachnoid hemorrhage, a number of complications may occur:
  - More than half of the patients develop secondary arterial vasospasm in the vessels surrounding the ruptured aneurysm most probably due to impaired brain autoregulation, this vasospasm causes → cerebral ischemia, which presents as new-onset confusion and focal neurological deficits 4-12 days after the initial insult. Nimodipine, a selective calcium channel blocker, is often prescribed to prevent this vasospasm.
  - ↑ risk of developing communicating and/or obstructive hydrocephalus.

- CT scan without contrast reveals blood in the basal cisterns, but fails to show vasospasm.
- Lumbar puncture reveals gross blood or xanthochromia (yellow discoloration of CSF).



Intraparenchymal (hypertensive) hemorrhage

- Hypertension is the most common cause of intraparenchymal hemorrhage.
- Increased blood pressure → induces hyaline arteriosclerosis of the tiny arterioles, most commonly in basal ganglia and internal capsule → the vascular wall weakens and become prone to dilatation, expansion of these arterioles forms → Charcot-Bouchard microaneurysms → rupture of these microaneurysms → intraparenchymal hemorrhage.
- Hypertensive hemorrhages (Charcot-Bouchard microaneurysm) most often occur in putamen of basal ganglia (lenticulostriate vessels G), followed by thalamus, pons, and cerebellum H.
- Also seen with amyloid angiopathy (recurrent lobar hemorrhagic stroke in elderly), vasculitis, neoplasm, and 2º to reperfusion injury in ischemic stroke.

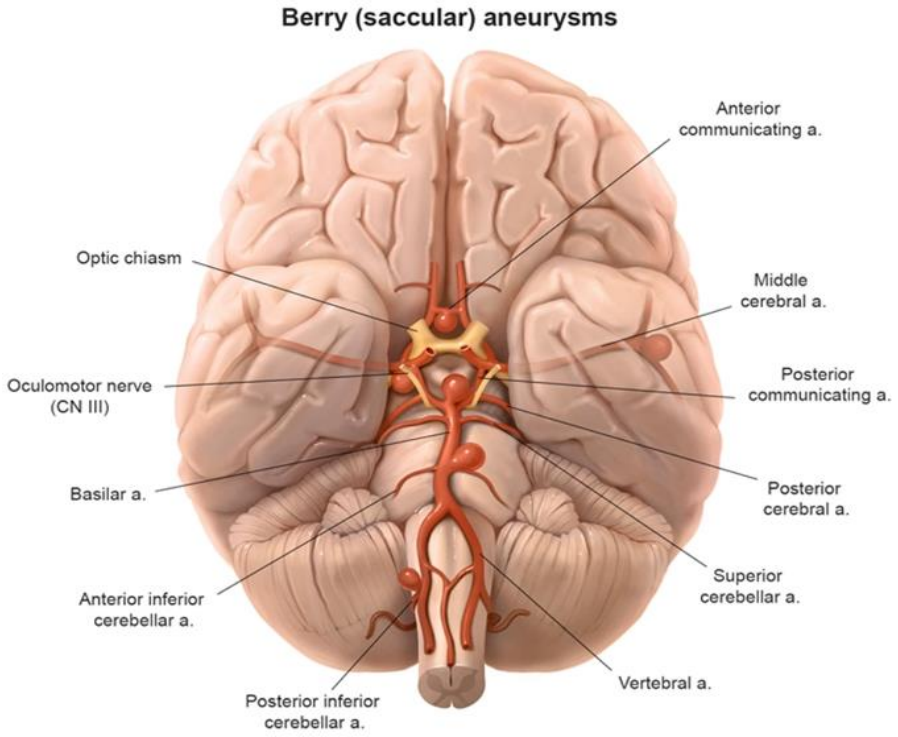


Type of hemorrhage	Epidural hematoma	Subdural hematoma	Subarachnoid hemorrhage
Blood vessel involved	Middle meningeal artery	Bridging cortical veins	Saccular (berry aneurysms) or arteriovenous malformation
Location	Between the skull and the dura	Between the dura and arachnoid	Between the arachnoid and pia mater
Clinical manifestation	Lucid interval, followed by Loss of consciousness	Gradual onset of headache and confusion	Severe headache "the worst headache of my life", fever, nuchal rigidity.
Presentation on CT scan	Biconvex hematoma	Crescent-shaped hematoma	Blood in the basal cisterns

Saccular (Berry) aneurysm

- Aneurysms are abnormal dilation of an artery due to weakening of vessel wall.
- The most common cause of SAH.
- These aneurysms usually occur at the circle of Willis, with the anterior communicating artery being the most common site (junction of ACom and ACA).
- Berry aneurysms are associated with Ehler-Danlos syndrome, marfan syndrome, and autosomal dominant polycystic disease.
- Other risk factors: advanced age, hypertension, smoking, race (↑ risk in African-Americans).
- Usually clinically silent until rupture (most common complication) → subarachnoid hemorrhage ("worst headache of my life" or "thunderclap headache") → focal neurologic deficits.
- Can also cause symptoms via direct compression of surrounding structures by growing aneurysm:

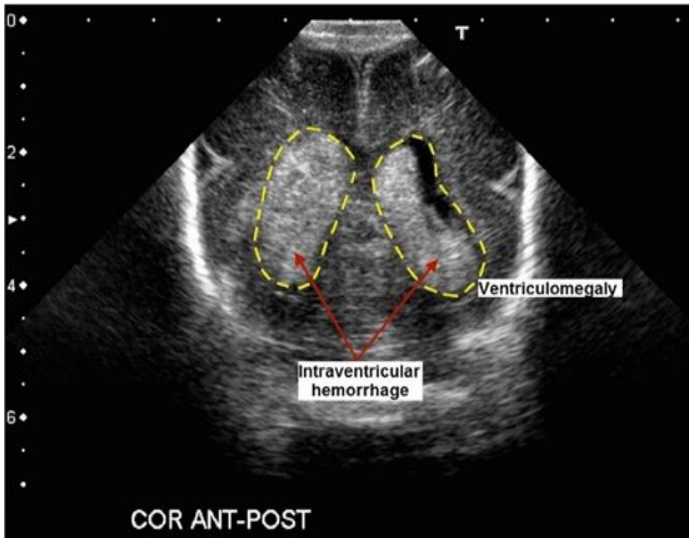
- ACom → compression of optic chiasm (bitemporal hemianopia) → visual acuity deficits; rupture → ischemia in ACA distribution → contralateral lower extremity hemiparesis, sensory deficits.
- PCom → compression of ipsilateral CN III → mydriasis ("blown pupil"); may also see ptosis, "down and out" eye.

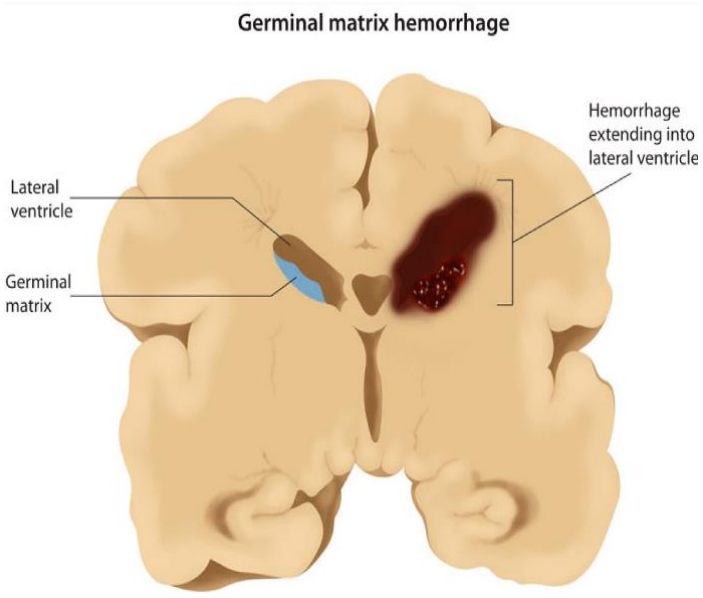


	Charcot-Bouchard microaneurysms	Berry (saccular) aneurysms
Associated systemic disease	Hypertension	ADPKD, Marfan, Ehler-Danlos syndrome
Location	Small arteries that perfuse the basal ganglia and internal capsule.	Circle of wills, anterior and posterior communicating arteries
Result of rupture	Intracerebral hemorrhage in the areas of basal ganglia & internal capsule.	Subarachnoid hemorrhage
Symptoms of rupture	Sudden onset of focal deficits	Sudden onset headache and altered level of consciousness are more prominent than focal neurologic symptoms

Neonatal intraventricular hemorrhage

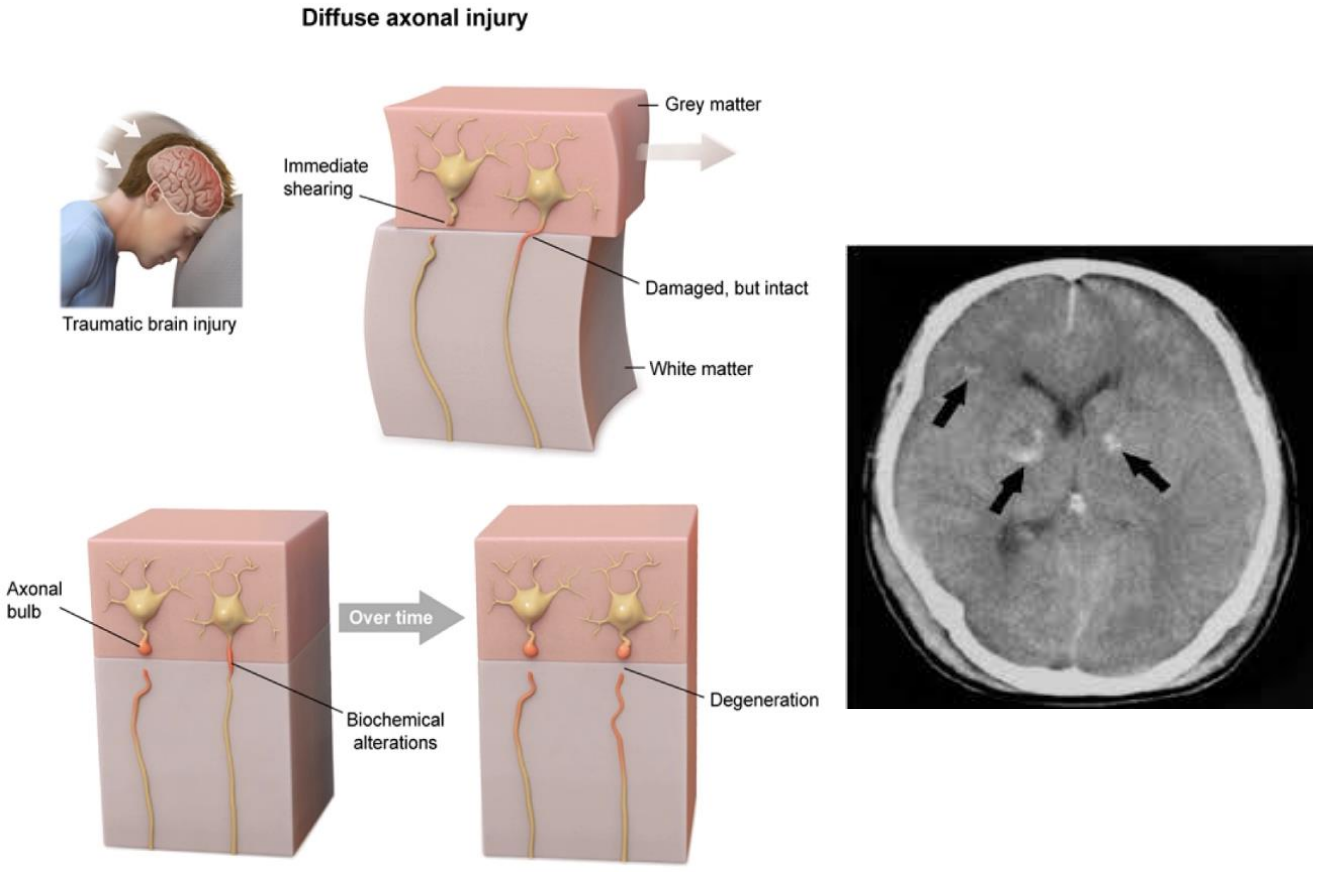
- Bleeding into ventricles.
- Increased risk in premature and low-birth-weight infants. Studies have shown that the incidence of IVH is inversely proportional to birth weight (the lower the birth weight, the greater the likelihood of IVH).
- Originates in germinal matrix, a highly vascularized layer within the subventricular zone.
- The susceptibility is due to capillary fragility of the subependymal germinal matrix and immature autoregulation of cerebral blood flow. Exposure to vascular perfusion injuries have also been associated with IVH.
- Can present with altered level of consciousness, bulging fontanelle, hypotension, seizures, coma.





Diffuse axonal injury

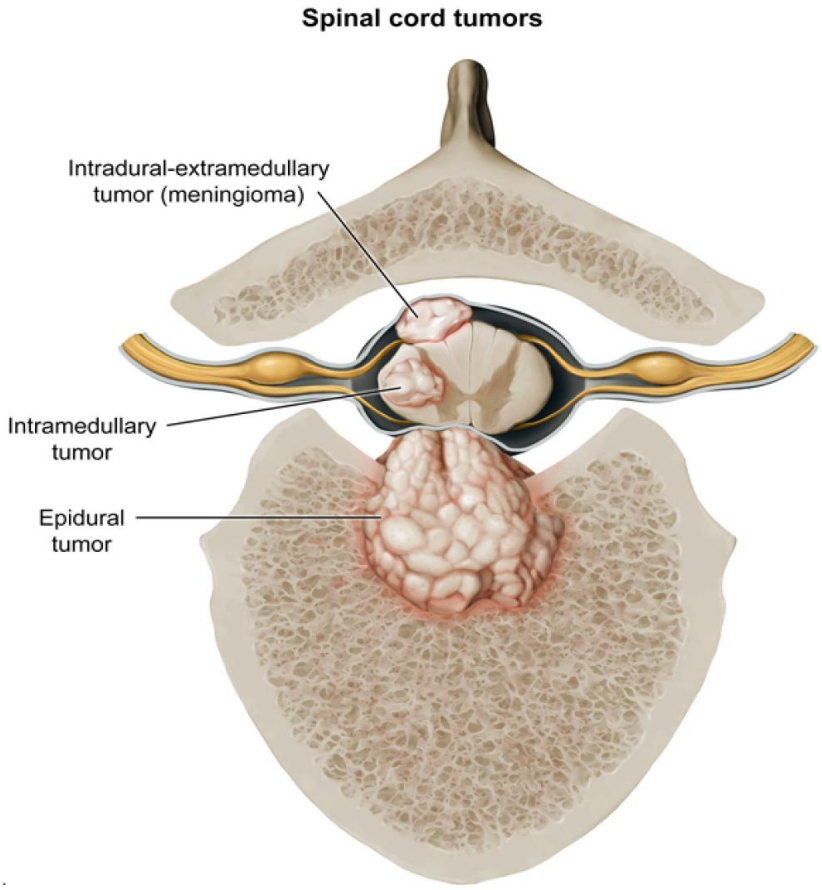
- Diffuse axonal injury is the most significant cause of morbidity in patients with traumatic brain injuries.
- It is frequently due to traumatic deceleration injury and results in vegetative state.
- Sudden acceleration-deceleration impact produces rotational forces that affect the brain areas where the density difference is the maximum, thus most of the diffuse axonal injury occur at gray white matter junction.
- Transfer of force can result in immediate shearing of the white matter tracts or induce secondary biochemical changes leading to degradation of the axonal cytoskeleton with subsequent axon breakage.
- Normal axonal transport is inhibited, leading to accumulation of axonally transported proteins (amyloid precursor, alpha-synuclein) within axonal swellings at the point of injury (axonal bulb formation).
- Presentation varies based on the extent of injury; most patients are comatose (Glasgow Coma Score <8); however, those with very mild DAI may have only concussive symptoms (headache, amnesia).
- CT scan characteristically shows numerous minute punctate hemorrhages with blurring of grey white interface. However, MRI is more sensitive than CT scan for diagnosing diffuse axonal injury.



❖ N.B:

1. Neoplastic spinal cord compression most commonly results from local extension of vertebral metastases into the epidural space.

- Presenting symptoms typically include severe back pain (typically worse at night), motor weakness, and/or sensory deficits.
- Urinary and fecal retention or incontinence are common late- stage findings.



2. Paraneoplastic syndromes can occur due to the production of hormone-like substances from tumor cells.

- They can also result from immune reactions against tumor cells that cross-react with normal cells, causing dysfunction and/or damage to healthy organs and tissues.
- Neurologic paraneoplastic syndromes (paraneoplastic cerebellar degeneration) are an autoimmune phenomenon.

Strokes

- Definition:

- Stroke is the sudden onset of a neurological deficit from the death of brain tissue.

- Stroke is the third most common cause of death in the United States.

- Etiology:

- Stroke is caused by a sudden blockage in the flow of blood to the brain in 85% of cases and by bleeding in 15% of cases.

1- Hemorrhagic stroke:

- Intracerebral bleeding, often due to hypertension, anticoagulation, cancer (abnormal vessels can bleed).

- May be 2° to ischemic stroke followed by reperfusion (vessel fragility).

- Basal ganglia are most common site of intracerebral hemorrhage.

2- Ischemic stroke:

A. Thrombotic:

- Due to a clot forming directly at site of infarction (commonly the MCA) usually over an atherosclerotic plaque.

B. Embolic:

- Embolus from another part of the body obstructs vessel.

- Can affect multiple vascular territories.

- Examples: atrial fibrillation, DVT with patent foramen ovale.

C. Hypoxic (Global cerebral ischemia):

- Also called hypoxic-ischemic-encephalopathy.

- It results from systemic hypoperfusion (cardiovascular surgeries, extensive myocardial infarction, cardiac arrest) → rapid cessation of cerebral blood flow → Global cerebral ischemia.

- If brain perfusion restored rapidly → no irreversible damage to the brain occurs, such patient may experience transient confusion before a complete recovery.

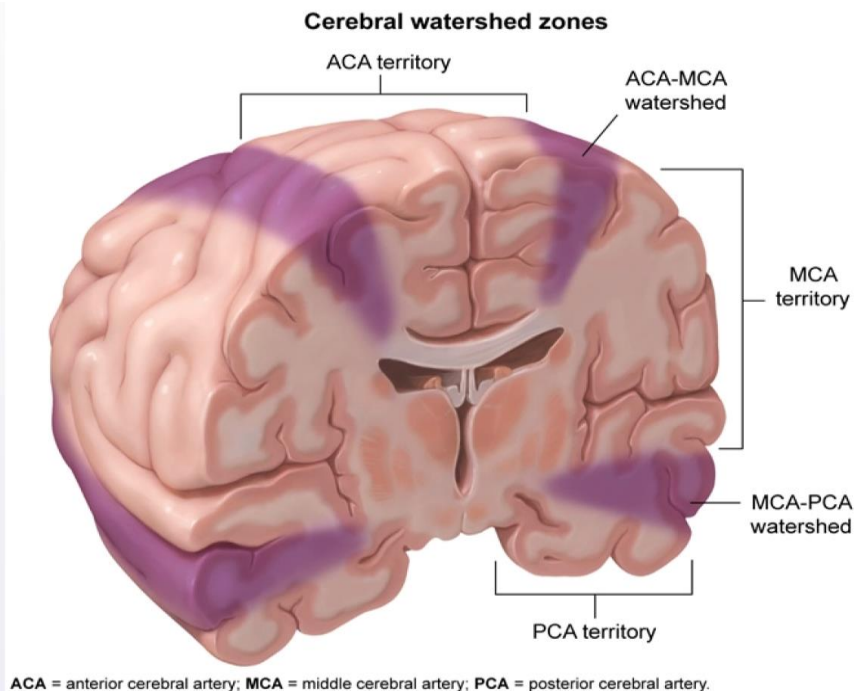
- If ischemia lasts longer than five minutes → causes irreversible damage to neurons.

- Some areas of brain are markedly more susceptible to ischemia than others, and these areas are damaged first.

- The cells most vulnerable to ischemia are the hippocampus, neocortex, purkinje cells of the cerebellum and watershed areas ("vulnerable hippos need pure water").

- The hippocampus is the first area to be damaged during global cerebral ischemia. Ischemic hypoxia "hippocampus is most vulnerable".

- If ischemia is more profound, necrosis of the areas supplied by the most distal branches of the cerebral arteries can occur (between the zones of perfusion of the anterior, middle and posterior cerebral arteries), and is termed watershed infarction (bilateral wedge-shaped strips of necrosis over the cerebral convexity, parallel and adjacent to the interhemispheric fissure).

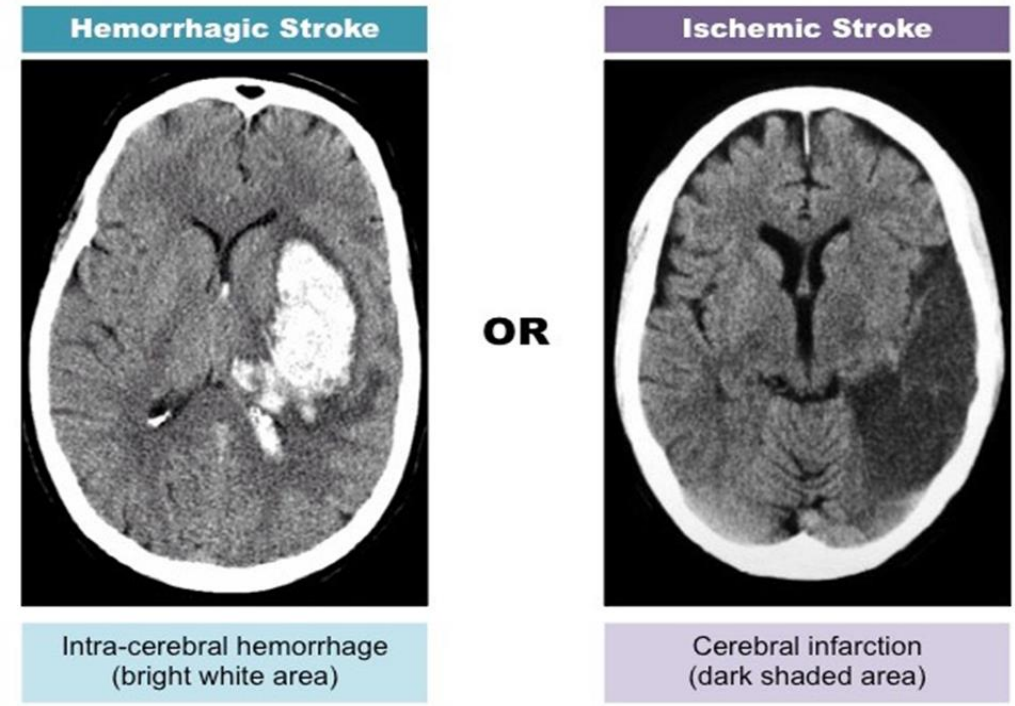


- Stroke imaging:

- The best initial test in any kind of stroke is a CT scan of the head without contrast. The most accurate test is an MRI.

- CT scan is done first, not because it is the most sensitive test for stroke, but in order to exclude hemorrhage as a cause of the stroke prior to initiating treatment (before tPA can be given, it worsens the case in hemorrhagic stroke).

- Hemorrhagic strokes appear immediately on non-contrast CT as white hyperdense regions in the brain parenchyma whereas many ischemic strokes do not become evident (hypodense) until 6–24 hr. Diffusion-weighted MRI can detect ischemia within 3–30 min.



- Treatment of ischemic stroke:

- Tissue plasminogen activator (tPA, if within 3- 4.5 hrs. of onset and no hemorrhage/risk of hemorrhage) and/or thrombectomy (if large artery occlusion).

- Reduce risk with medical therapy (aspirin or clopidogrel).

- Optimum control of blood pressure, blood sugars, lipids.

- Treat conditions that ↑ risk (atrial fibrillation, carotid artery stenosis).

❖ Ischemic stroke results in liquefactive necrosis:

- Although lethal ischemic injury in most organs results in coagulative necrosis of parenchymal cells, in the brain such injury produces a focus of liquefactive necrosis (lysosomal digestion of the brain tissue) within 10 days of infarction.

- Microglia are the phagocytic scavenger cells of CNS, activated in response to tissue damage

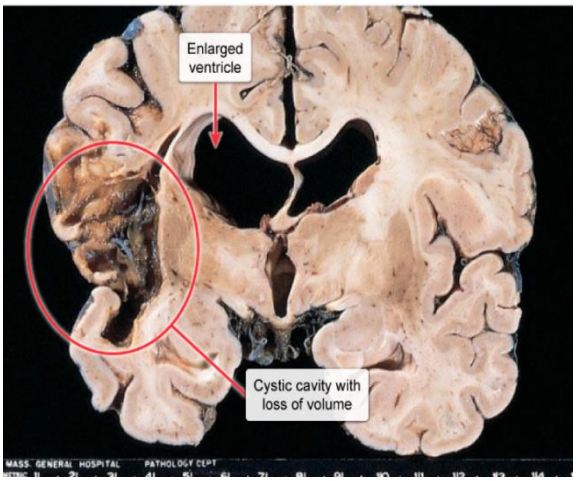
- A neuron that is responding to irreversible injury is called a “red neuron".

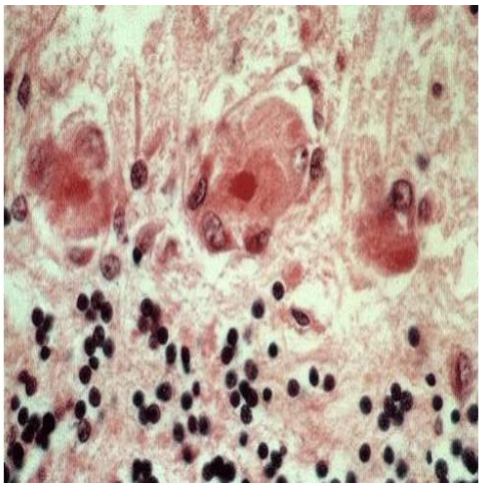
- Characteristic changes become evident 12-24 hours after the injurious event and include:

- Shrinkage of the cell body, eosinophilia of the cytoplasm, pyknosis (shrinking) of the nucleus, and loss of nissel substance followed by death of the neuron.

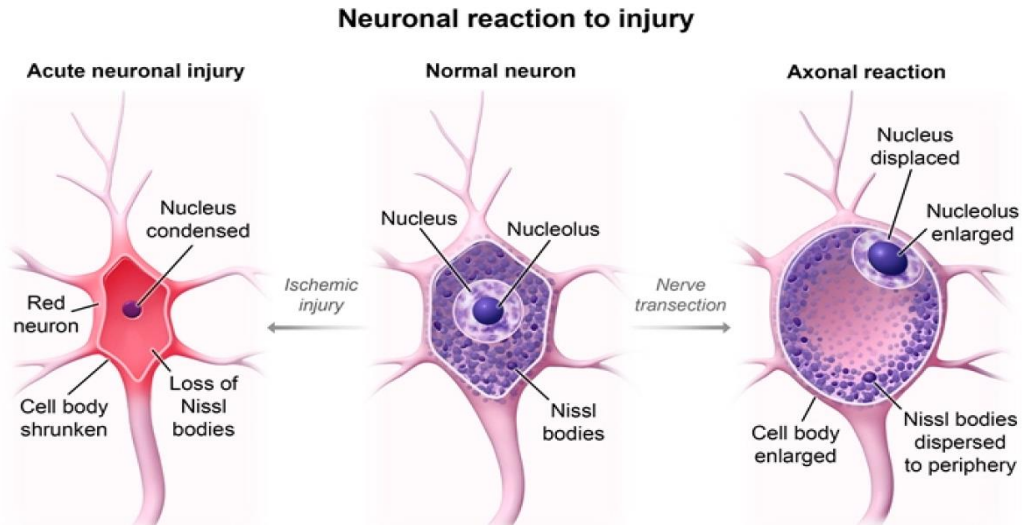
- Astrocytes proliferate (Glial hyperplasia) on the site of the injury and form a glial scar (Gliosis).

- Eventually, the infarcted central nervous system tissue is replaced with a cystic space surrounded by a dense astroglial scar (gliosis).



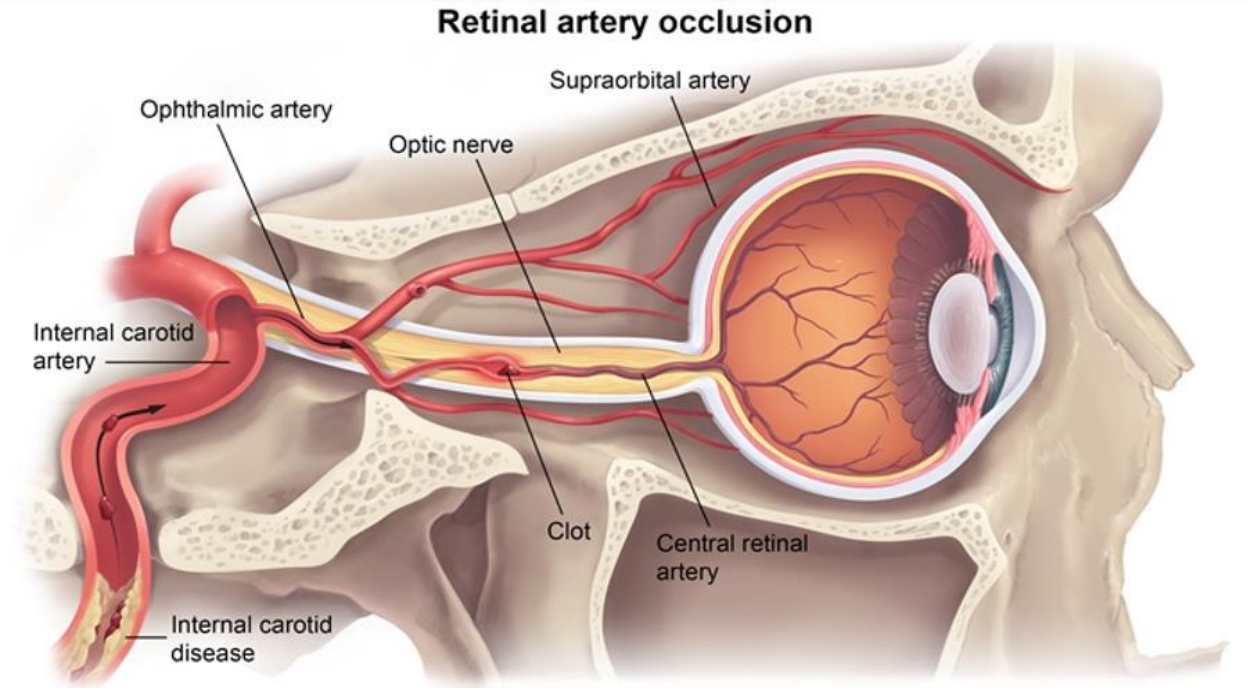


Time after the injury	Microscopic changes	Macroscopic changes
12-24 hrs.	Red neurons (eosinophilic cytoplasm, pyknotic nuclei, loss of Nissl substance)	
24-72 hrs.	Necrosis and neutrophilic infiltration	
3-5 days	Macrophage infiltration and phagocytize the fragments of neurons, myelin, and necrotic debris (which explains the abundance of lipids in the cytoplasm of microglia after staining in the area of neuronal death)	
1-2 weeks	Reactive gliosis around the necrotic area	Liquefactive necrosis
>2 weeks	Astrocyte hypertrophy and proliferation → Glial scar	Cystic area surrounded by gliosis



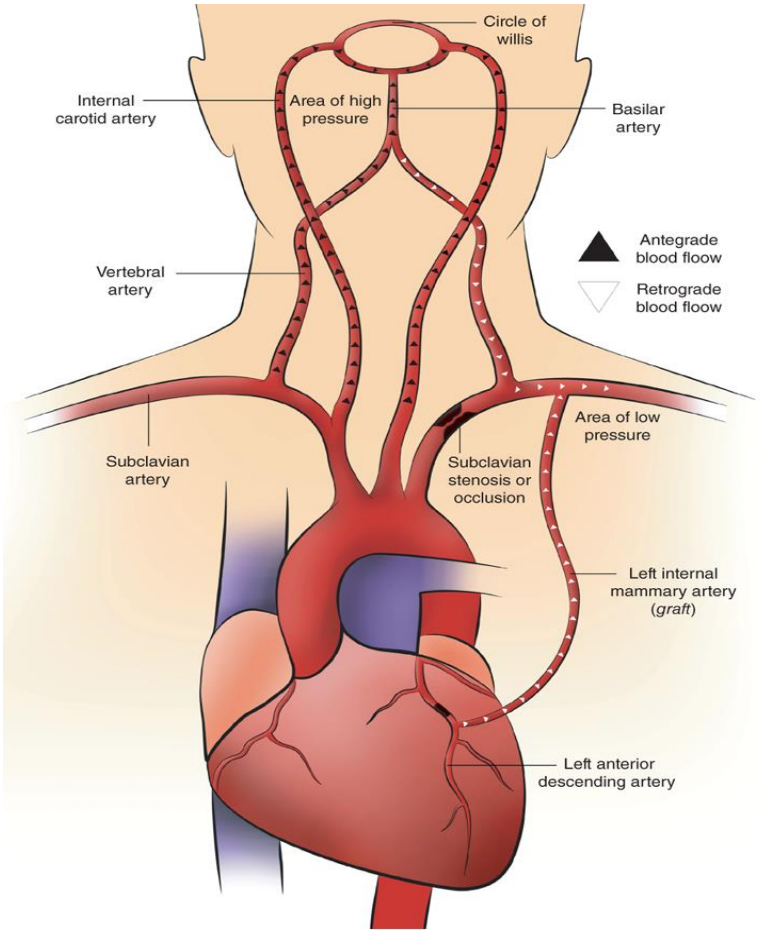
Transient ischemic attack (TIA)

- Brief, reversible episode of focal neurologic dysfunction without acute infarction (⊖ MRI), with the majority resolving in < 15 minutes deficits due to focal ischemia.
- TIAs present exactly the same as stroke, except that symptoms last less than 24 hours and resolve completely.
- Cases may present with transient loss of vision in one eye, known as amurosis fugax due to occlusion of ophthalmic artery (the first branch of carotid artery) → Retinal artery occlusion by embolus from dislodged atheromatous plaque in the carotid artery.
- TIAs are always caused by emboli or thrombosis. TIAs are never due to hemorrhage, hemorrhage do not resolve in 24 hours.



Subclavian steal syndrome

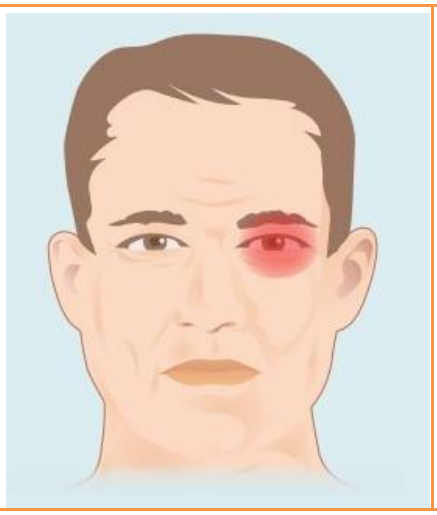
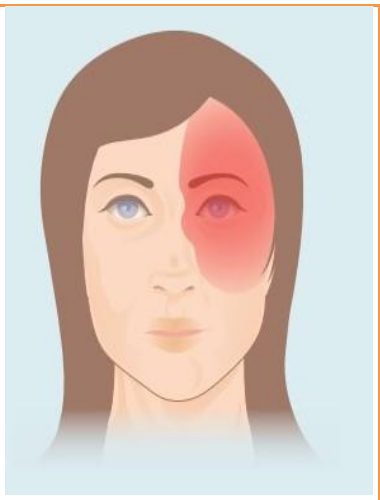
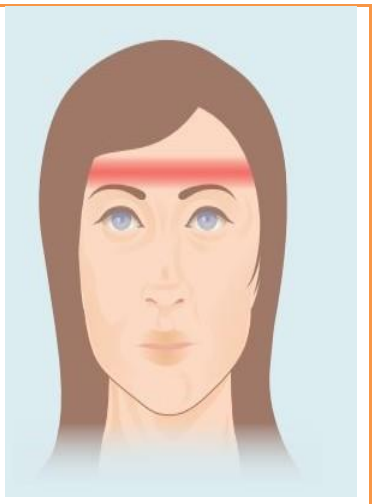
- Subclavian steal syndrome is rare but fascinating (medical school professors love it, thus it is likely to appear on exams).
- An arteriosclerotic stenotic plaque at the origin of the subclavian (proximal to the take-off of the vertebral arteries) allows enough blood supply to reach the arm for normal activity, but does not allow enough to meet higher demands when the arm is exercised.
- When that happens, the arm sucks blood away from the brain by reversing the flow in the vertebral.
- Clinically the patient describes claudication of the arm (coldness, tingling, muscle pain) and posterior neurologic signs (visual symptoms, equilibrium problems) when the arm is exercised.
- The lowered distal subclavian arterial pressure leads to reversal in blood flow ("steal") from the contralateral vertebral artery to the ipsilateral vertebral artery, away from the brainstem.
- Duplex scanning is diagnostic when it shows reversal of flow.
- Bypass surgery is curative.



Differentiating headaches

- Brain tissues itself is not sensitive to pain as it lacks pain receptors. Rather, the pain is caused by disturbance of the pain sensitive structures as meninges, cranial nerves, or extracranial structures.
- More common in females, except cluster headaches.

Classification	Cluster	Migraine	Tension
Sex predilection	Male > Female	Female > Male	Female > Male
Family history	No	Often present	No
Localization	Unilateral (behind one eye)	Unilateral	Bilateral (band like pattern around head)
Onset	During sleep	Variable	Under stress
Duration	15 min - 3 hrs. Repetitive	4 - 72 hrs.	> 30 min (typically 4 -6 hrs) Constant
Description	▪ Excruciating periorbital pain with lacrimation and rhinorrhea. ▪ May induce Horner syndrome. ▪ Repetitive brief headache. ▪ Often patients will have a pain-free interval of about a year between each series of attacks.	▪ Pulsating pain with nausea, photophobia, or phonophobia. ▪ May have "aura". ▪ Due to irritation of CN V, meninges, or blood vessels (release of substance P, calcitonin gene related peptide, vasoactive peptides)	▪ Steady pain. ▪ No photophobia or phonophobia. ▪ No aura. ▪ Do not typically limit patient's ability to perform daily functions.
Treatment	▪ Acute: sumatriptan, 100% O2 ▪ Prophylaxis: verapamil	▪ Acute: NSAIDs, triptans, dihydroergotamine ▪ Prophylaxis: lifestyle changes (sleep, exercise, diet), β-blockers, amitriptyline, topiramate, valproate, botulinum toxin injections. ▪ POUND: Pulsatile, One-day duration, Unilateral, Nausea, Disabling	▪ Acute: analgesics, NSAIDs, acetaminophen ▪ Prophylaxis: TCAs (amitriptyline), Behavioral therapy

- Other causes:

- Subarachnoid hemorrhage: "the worst headache in my life ".
- Meningitis.
- Hydrocephalus.
- Neoplasia.
- Arteritis.

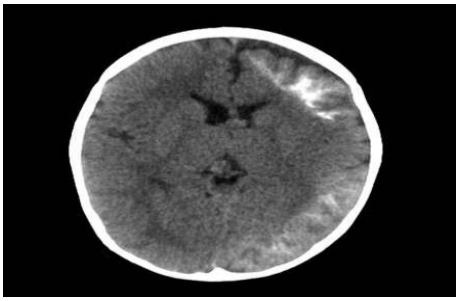
Fever vs heat stroke

	Fever	Heat stroke
Pathophysiology	Cytokine activation during inflammation (infection)	Inability of body to dissipate heat (exertion)
Temperature	Usually < 40 °C	Usually > 40 °C
Complications	Febrile seizure (benign, usually self-limiting)	CNS dysfunction (confusion), end-organ damage, acute respiratory distress syndrome, rhabdomyolysis
Management	Acetaminophen or ibuprofen for comfort (does not prevent future febrile seizures), antibiotic therapy if indicated	Rapid external cooling, rehydration and electrolyte correction

Neurocutaneous disorders

Sturge-Weber syndrome

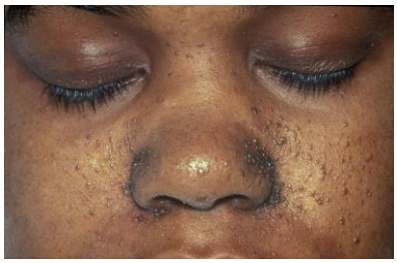
- A rare congenital non-inherited (sporadic) neurocutaneous disorder.
- Developmental anomaly of neural crest derivatives (mesoderm, ectoderm) due to activating mutation of GNAQ gene.
- It is characterized by the presence of cutaneous facial angiomas affecting small (capillary-sized) blood vessels on one side of the body → port wine stain of the face (nevus flammeus, a non-neoplastic Birthmark in the ophthalmic (V1) and maxillary (V2) distributions of the trigeminal nerve) as well as ipsilateral leptomeningeal angiomas → seizures / epilepsy , intellectual disability
- Episcleral hemangioma → ↑ intraocular pressure → early onset glaucoma.
- Skull radiograph may show characteristic "tram – track" calcification.
- SSTURGGE-Weber: Sporadic (occur by chance, not inherited), port wine Stain, Tram track calcification, Unilateral, Retardation (intellectual disability), Glaucoma, GNAQ gene, Epilepsy.

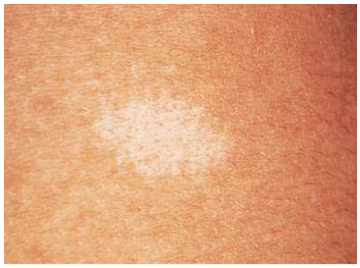


Tuberous sclerosis

- It is an autosomal dominant disorder due to mutation of either of two tumor suppressor genes TSC1, TSC2 which code for the protein hamartin and tuberin respectively.
- It is characterized by cortical tubers (means swelling in Latin) and subependymal hamartomas in the brain → seizures and mental retardation.
- Cardiac rhabdomyomas, facial angiofibromas, and leaf shaped patches of skin lacking pigment (ash leaf patches) can occur as well.
- Renal angiomyolipomas are associated with tuberous sclerosis. Renal (angio – myo – lipoma) is a benign tumor composed of blood vessels, smooth muscle, and fat. These tumors can be diagnosed with an

abdominal CT scan, as the density of fat is less than that of water. In patients with bilateral renal angiomyolipomas, the incidence of tuberous sclerosis is 80 -90 %.





Neurofibromatosis type 1 (Von Recklinghausen disease)

- It is an autosomal dominant disorder (100% penetrance). It occurs due to a mutation of the tumor suppressor gene NF1 located on the chromosome 17 (17 letters in "von Recklinghausen".

- The presentation of NF1 is highly variable, all or none of the following symptoms may be present in any individual who suffers from NF1:

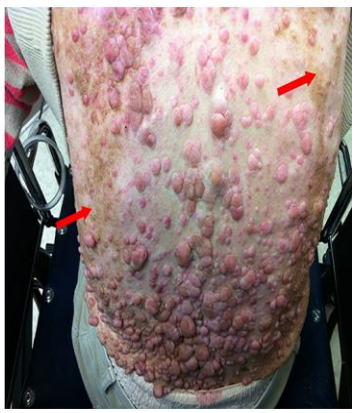
- Skin: café au lait spots are hyperpigmented lesions with either smooth or irregular borders.

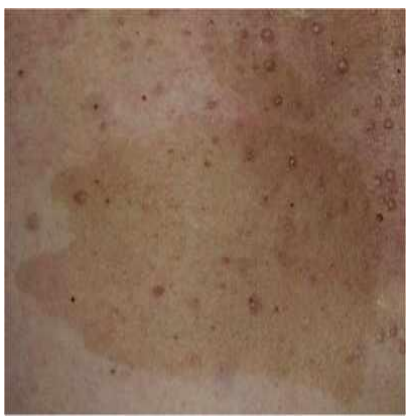
- Neurofibromas: short sessile or pedunculated lesions that vary in size comprised mostly of Schwann cells. They are commonly multiple and distributed throughout the body.

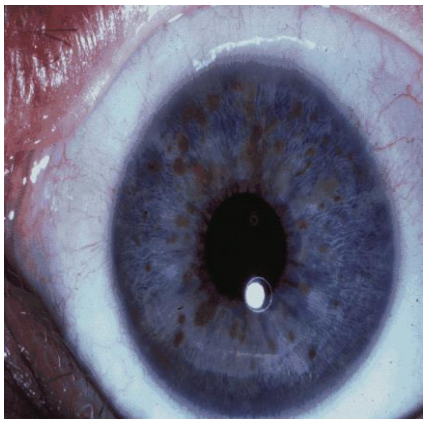
- Eye: optic nerve gliomas may occur and cause visual loss. Lisch nodules are pigmented hamartomas of the iris and are asymptomatic.

- Bony abnormalities: include sphenoid dysplasia, congenital pseudoarthrosis, and scoliosis.

- Other associated tumors: meningiomas, gliomas, pheochromocytomas.







Neurofibromatosis type II

- It is an autosomal dominant disorder.
- Mutation in NF2 tumor suppressor gene (merlin) on chromosome 22.
- Bilateral vestibular schwannomas, juvenile cataracts, meningiomas, ependymomas.
- NF2 affects 2 ears, 2 eyes.

Von Hippel-Lindau disease

- A rare autosomal dominant condition due to mutation of the tumor suppressor gene VHL on chromosome 3 (VHL = 3 letters).
- It is characterized by the presence of:

- Capillary hemangioblastoma (high vascularity with hyperchromatic nuclei) in the retina, brain stem, cerebellum, and spinal cord + cavernous hemangiomas in skin, mucosa and organs.

- Patients are also at increased risk for pheochromocytoma and renal cell carcinoma, which can be bilateral.
- Patients with both sporadic and hereditary (associated with Von Hippel Lindau disease) renal cell carcinomas are found to have deletions of the VHL gene on chromosome 3p.

❖ In a nutshell:

- If you found in the case a disorder that involves the musculocutaneous system (muscle and skin lesion) and nervous system (neurological lesion), it is most probably a neurocutaneous disorder, try to find a key in the case to know which type of neurocutaneous disorder is the case talking about?

- Sturge weber syndrome → port wine stain (nevus flammus), leptomeningeal angioma.
- Tuberous sclerosis → ash leaf patches, Renal angiomyolipoma, seizures, mental retardation.
- Neurofibromatosis → type 1: café au lait, neurofibromas, lisch nodules.
- Von Hibbel Lindau → capillary hemangioblastoma, cavernous hemangioma, bilateral renal cell carcinoma, Pheochromocytoma.

Adult primary brain tumors

- Half of all brain and spinal cord tumors are metastatic. The most frequent primary CNS tumors are glioblastoma multiforme and meningioma.

- Presenting symptoms vary depending on tumor location:

- Supratentorial tumor classically presents with seizures, weakness, and sensory changes.

- Posterior fossa tumor typically presents with cerebellar dysfunction (ataxia, dysmetria).

- Signs of increased intracranial pressure (early-morning headache/vomiting, papilledema) can occur as the tumor enlarges, regardless of tumor location.

1. Glioblastoma multiforme (grade IV astrocytoma):

- Astrocytomas originates from astrocytes, immunoreactivity for glial fibrillary acidic protein (GFAP) with ill-defined pattern of growth.

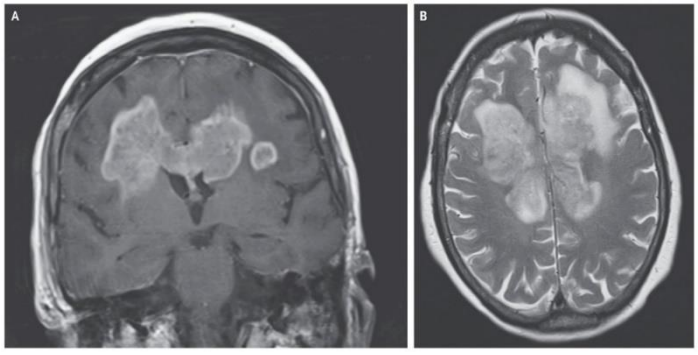
- Grading of astrocytomas is important for both prognosis and treatment. There are 4 grades of astrocytomas based on nuclear atypia (pleomorphism), mitosis, necrosis and vascular endothelial hyperplasia.

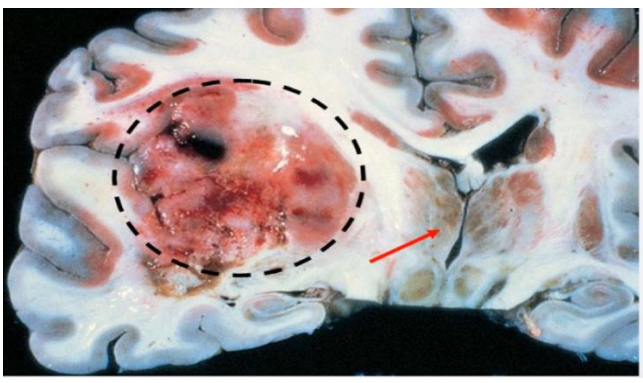
- Grade 4 astrocytoma is the most common CNS primary malignancy in adults and the worst grade of astrocytoma (most common and most lethal ~ 1-year median survival).

- Most cases are associated with oncogenic mutations that increase epidermal growth factor receptor expression on the tumor cells, leading to increased transduction of growth signals that promote cellular survival and proliferation.

- The most common location is white matter of cerebral (A) hemisphere which can cross corpus callosum to the other cerebral hemisphere resembling butterfly shape, that's why it's called butterfly glioma.

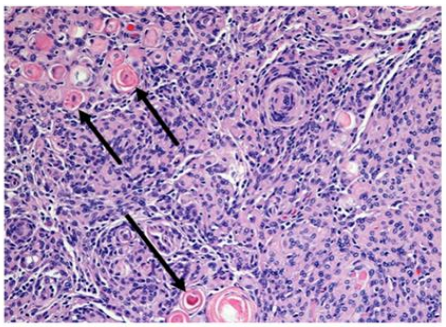
- The characteristic histopathological features are an area of necrosis surrounded by rows of neoplastic cells "pseudopalisading necrosis" (B).

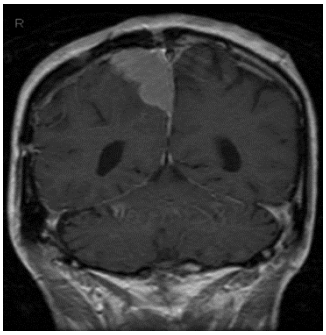




2. Meningioma:

- The second most common primary CNS tumor in adults (Slowly growing, well circumscribed and benign tumors).
- Meningiomas arise from cells of the arachnoid cells (external to brain parenchyma) and may have a dural attachment "tail" (C).
- Most often occurs in convexities of hemispheres and parasagittal region.
- Often asymptomatic, may present with seizure or focal neurologic signs due to compression of adjacent brain structures.
- Histology: spindle cells concentrically arranged in a whorled pattern (D), Psammoma bodies (a core of dense calcification with surrounding collagen-fiber bundles) are characteristic of meningiomas.





3. Hemangioblastoma:

- Most often cerebellar (E).
- Blood vessel origin.
- Associated with von Hippel-Lindau syndrome when found with retinal angiomas. Can produce erythropoietin → 2° polycythemia.
- Histology: closely arranged, thin-walled capillaries with minimal intervening parenchyma (F).

4. Schwannoma:

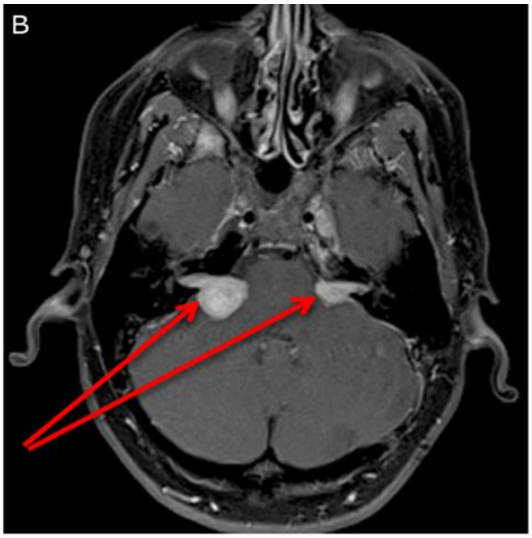
- Tumor of the peripheral nervous system that arise from schwann cells (H).
- Cranial nerves are covered by schwann cells; therefore, schwannomas can arise from any cranial nerve, except CN II.
- The most common site of intracranial schwannomas is the cerebellopontine angle (G) involving CNs V, VII, and VIII, but often localized to CN VIII in internal acoustic meatus → tinnitus, vertigo, and sensorineural hearing loss.

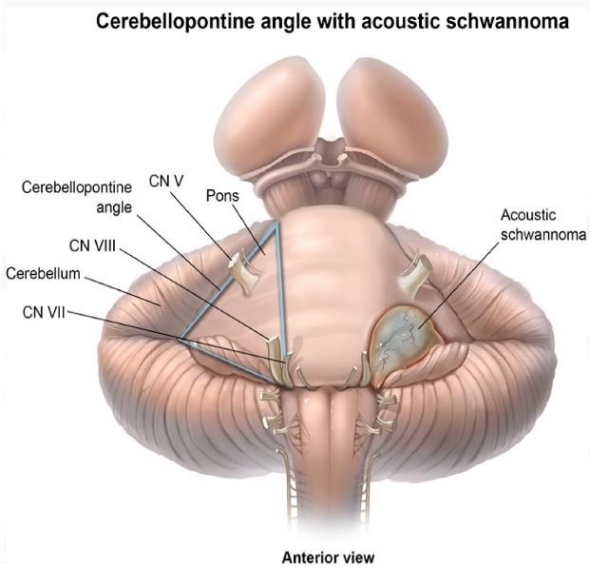
- Schwannomas in this particular location are also called acoustic neuromas. Bilateral acoustic neuroma is found in neurofibromatosis type 2. NF-2 differs from NF-1 in that it causes fewer cutaneous manifestations and presents with central nervous system involvement.

- Schwannomas are universally S-100 Positive (marker for tumors derived from neural crest).

❖ N.B:

- Melanoma are also S-100 Positive because both melanocytes and schwann cells are derived from the neural crest.





5. Oligodendroglioma:

- It is a glioma of oliodendroglial origin.

- Typically, in the white matter of frontal lobe (I).

- It often manifests with seizures.

- Histology: round nuclei with clear cytoplasm “fried egg cells" (J).

- Chicken wire capillary pattern.

- Oligodendrogliomas are slow growing tumors that allow long survival but they tend to recur after surgery.

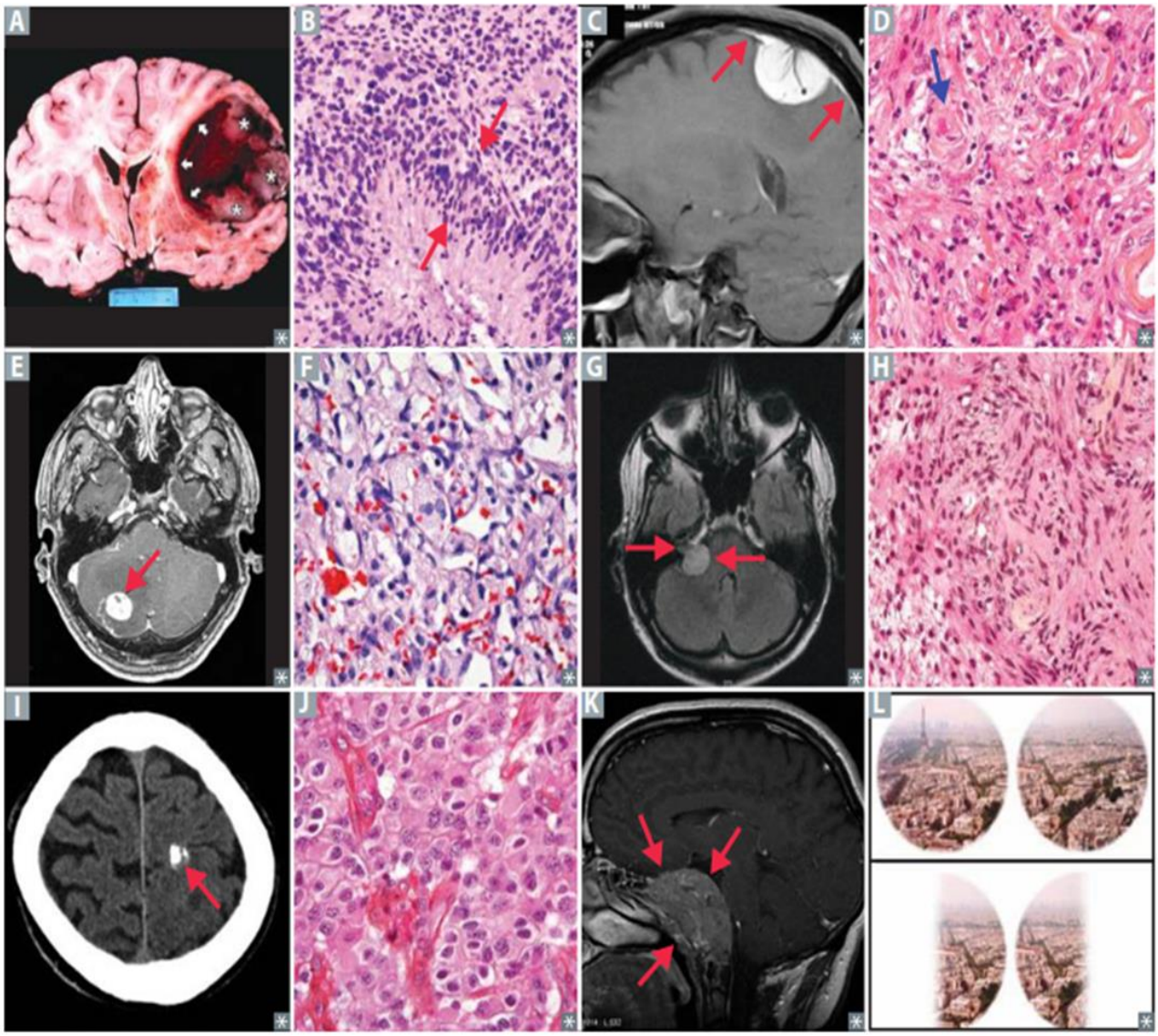
6. Pituitary adenoma:

- It is the most common cause of bitemporal hemianopia (loss of peripheral vision leading to difficulty in driving for example) which is caused by pressure on the central part of optic chiasm by the tumor (L).

- Pituitary tumors can also secrete hormones, prolactinomas (K) are the most common adenoma (excess prolactin) → amenorrhea and galactorrhea.

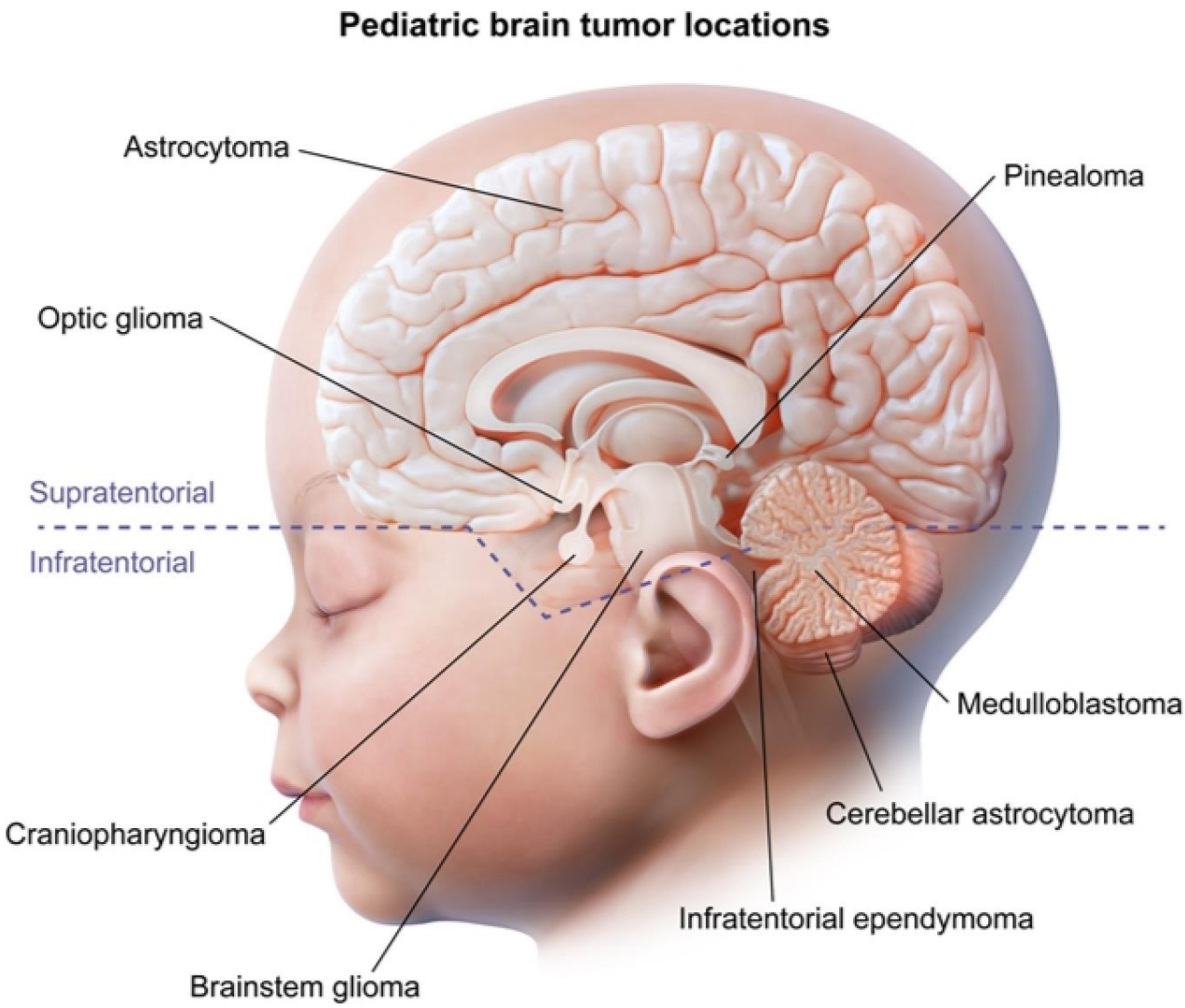
❖ N.B:

- Primary CNS lymphoma is the most frequent CNS tumor in immunosuppressed patients, such as those suffering from AIDS. These tumors arise from B cells and are universally associated with Epstein Barr Virus.
- The clinical presentation is nonspecific. Mental status changes, seizures or progressive neurological deficits may occur. They are high grade tumors with a poor prognosis.



Childhood primary brain tumors

- In the pediatric population, central nervous system (CNS) tumors are the most common solid tumors and the second most common malignancies after leukemias.
- Low-grade astrocytoma, particularly pilocytic astrocytoma, is the most common brain tumor in children.
- In children, most primary brain tumors arise infratentorially, craniopharyngiomas being an important exception.
- Most common type of benign pediatric primary brain tumor: pilocytic astrocytoma.
- Most common malignant pediatric primary brain tumor: medulloblastoma.



1. Pilocytic (low-grade) astrocytoma:

- It is a grade 1 pilocytic astrocytoma.
- The most common primary brain tumor in children. Benign tumor with a good prognosis.
- Usually arise in posterior fossa (cerebellum) (A).
- Microscopically: pilocytic astrocytomas are well differentiated neoplasms comprised of spindle cells with hair-like glial processes (pilo means hair) that are associated with microcysts, that's why it's called pilocystic astrocytoma. These cells are mixed with Rosenthal fibers and granular eosinophilic bodies (B).
- May be supratentorial.
- Key in the case: A cystic tumor in the cerebellum of a child is most likely a pilocytic astrocytoma.

2. Medulloblastoma:

- The second most common brain tunor of childhood. Most common malignant brain tumor in childhood.
- A form of primitive neuroectodermal tumors (PNET).
- It is located in the cerebellum (C). The cerebellar vermis is the most common location of medulloblastoma → truncal ataxia.
- The tumor may compress 4th ventricle → noncommunicating hydrocephalus.
- Medulloblastomas are undifferentiated and aggressive tumors with poor prognosis.
- Histology: Homer wright rosettes, small blue cells (D). It consists of sheets of small cells with deeply basophilic nuclei and scant cytoplasm with abundant mitosis.

3. Ependymoma:

- The third most common brain neoplasm in children.
- Ependymal cell origin. Most commonly found in 4th ventricle (E). Can cause hydrocephalus. Poor prognosis.
- On microscopic examination, tumor cells are organized around the lumen of the ventricle and small vessels resembling rosettes "Perivascular Rosettes" (F).

4. Craniopharyngioma:

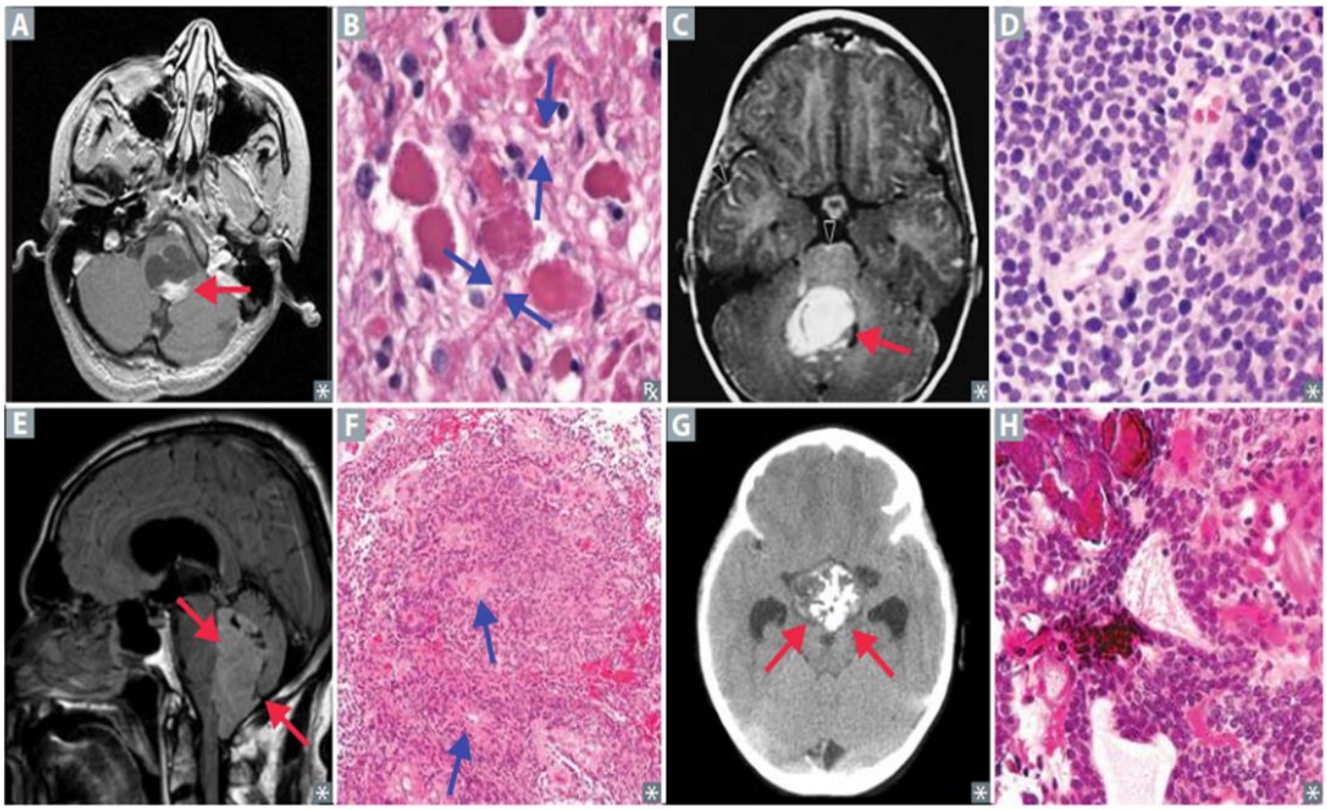
- Benign childhood tumor, may be confused with pituitary adenoma (both can cause bitemporal hemianopia).
- Most common childhood supratentorial tumor.
- Derived from remnants of Rathke pouch.
- Histology: Calcification is common “tooth enamel like " (G, H)

5. Pinealoma:

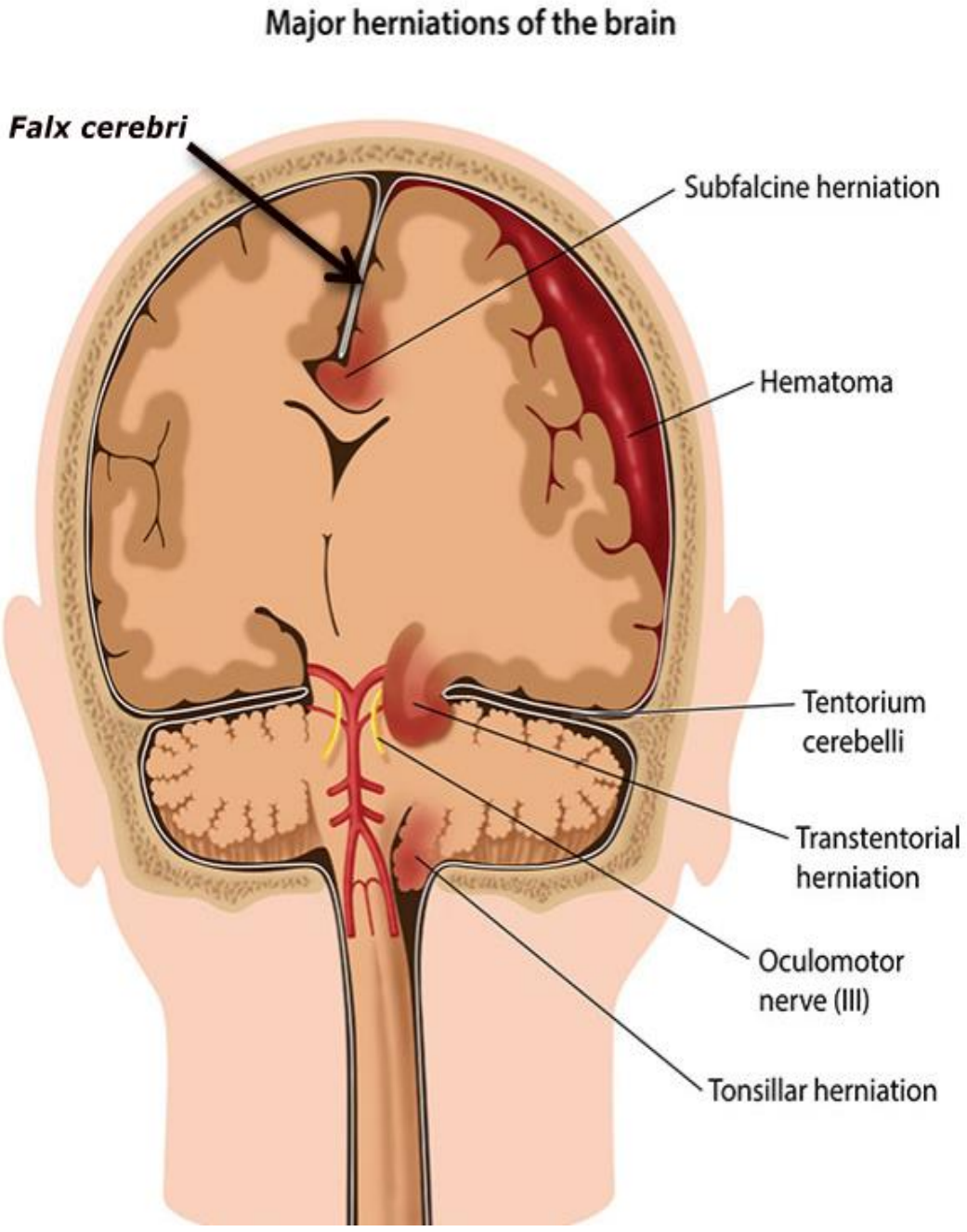
- Tumor of pineal gland.
- Can cause Parinaud syndrome (discussed before in dorsal midbrain syndrome) precocious puberty in males (hCG production).

❖ N.B:

- Synaptophysin is a protein found in the presynaptic vesicles of neurons, neuroendocrine and neuroectodermal cells. CNS tumors of neuronal origin frequently stain positively for synaptophysin on immunohistology.
- Neoplasms of glial origin (astrocytomas, meningioma, pituitary adenoma, ependymomas, and oligodendrogliomas) stain for Glial Fibrillary Acidic Protein (GFAP).



Herniation syndromes



- The cranial vault is limited by the rigid cranial bones and divided into compartments by the dural folds (falx cerebri and tentorium cerebelli).

- There is no room for brain expansion in the event of a brain edema, tumor, or hemorrhage. As a result, portions of the brain can protrude through the openings in the falx cerebri or through the foramen magnum. This process is called herniation.

1. Cingulate (subfalcine) herniation under falx cerebri:

- The cingulate gyrus herniates under the falx cerebri, potentially compressing the anterior cerebral artery.

2. Downward transtentorial (central) herniation:

- Caudal displacement of brain stem → rupture of paramedian basilar artery branches → Duret hemorrhages.

- Usually fatal.

3. Transtentorial (Uncal) herniation:

- Occurs when the medial temporal lobe (uncus) herniates through the gap between the crus cerebri and the tentorium.

- The most common cause of transtentorial herniation is an ipsilateral mass lesion (brain tumor, subdural or epidural hematoma, and intracerebral hemorrhage).

- This mass causes an increase in supratentorial pressure on the side of the lesion → forces the ipsilateral uncus to herniate through the gap between the crus cerebri and the tentorium (uncal herniation)

- As a result, the following structures may become compressed:

A. Ipsilateral oculomotor nerve (CN III) compression:

- Down and out position of the ipsilateral eye.
- Dilated pupil.
- Ptosis.

B. Ipsilateral posterior cerebral artery compression: Contralateral homonymous hemianopia with macular sparing.

C. Contralateral cerebral peduncle compression against the tentorium may occur → contralateral corticocerebral tract lesion → ipsilateral hemiparesis (ipsilateral to the side of herniation).

D. Brain stem hemorrhage (Duret hemorrhage) may occur in the pons and midbrain due to stretching and rupture of basilar artery, which is usually fatal.

4. Cerebellar tonsillar herniation into the foramen magnum:

- The cerebellar tonsils displace through the foramen magnum and compress the medulla → cardiorespiratory arrest may occur.

Diabetic Neuropathy

- Peripheral neuropathy is a common complication of diabetes mellitus.

- It occurs in both type 1 and 2 diabetes, and is associated with poor glycemic control and/or long duration of the disease.

- The most important mechanisms of the development of diabetic neuropathy are the following:

1. Non-enzymatic glycosylation of proteins leads to increased thickness, hyalinization, and narrowing of the walls of the arteries (Endoneural arteriole hyalinization). These changes lead to diabetic microangiopathy of endoneural arterioles → ischemic nerve damage.

2. Intracellular hyperglycemia occurs in peripheral nerves. Accumulating glucose is converted into sorbitol and fructose by aldose reductase. Sorbitol increases cell osmolarity and facilitates water influx into the cell. The result is osmotic damage to axons and Schwann cells.

- The most common types of diabetic neuropathy are:

Type of neuropathy	Symptoms
Distal symmetric polyneuropathy	- Sensory: paresthesia (tingling, numbness), intense burning pain, loss of pain -temperature - vibration - position sensation. - Motor (commonly in combination with sensory symptoms): weakness, atrophy, decreased DTR. - Both motor and sensory deficits are symmetric and bilateral, involving feet and hands in "stocking and glove" distribution.
Autonomic polyneuropathy	- GIT: Gastroparesis, constipation. - Cardiovascular: orthostatic hypotension. - Urinary: overflow incontinence, neurogenic bladder. - Sexual: erectile and ejaculatory abnormalities.
Mononeuropathy	- Cranial mononeuropathy: oculomotor (III), Facial (VII), and optic (II). - Somatic mononeuropathy: commonly bilateral involvement of the median nerve, ulnar and common peroneal nerves.

Diabetic ophthalmoplegia

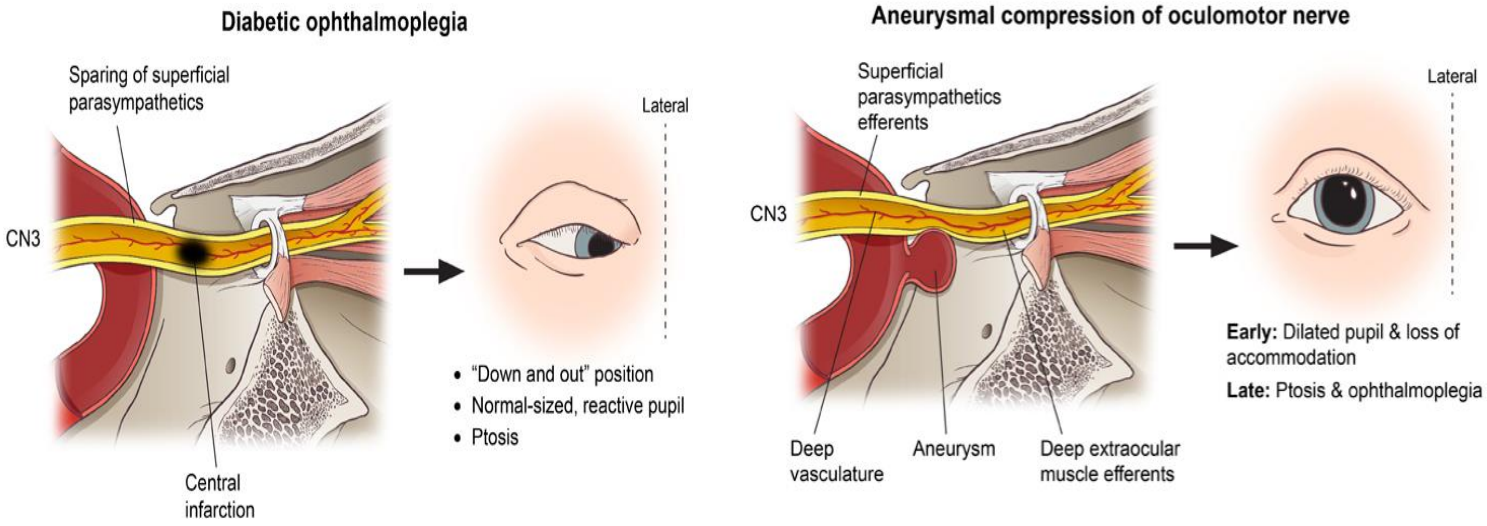
- The clinical features of diabetic neuropathy vary considerably depending on the pattern of nerve involvement, which can be broadly divided into polyneuropathy, mononeuropathy, and autonomic neuropathy.

- Mononeuropathies can also be further subdivided into cranial and peripheral types.

- All ocular motor nerves (III, IV, VI) can be affected in diabetes but unilateral cranial nerve III involvement is most common.

- Cranial nerve III has 2 components:

- The somatic component that innervates the extraocular muscles is located centrally.
- The autonomic component responsible for pupillary constriction and accommodation is located in the periphery.



- Diabetic ophthalmoplegia is caused by predominantly central nerve ischemia, which affects the central somatic nerve fibers but spares peripheral parasympathetic fibers, So, Symptoms of diabetic ophthalmoplegia include: ptosis, down and out gaze, but normal sized reactive pupil (normal light and accommodation reflexes).

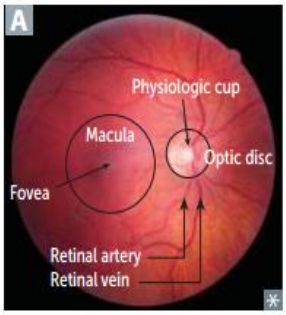
- In berry aneurysm, early the aneurysm compresses the peripheral parasympathetic nerve fibers and later compresses the central somatic nerve fibers of cranial nerve III, So, Symptoms of aneurysmal compression of cranial nerve III include:

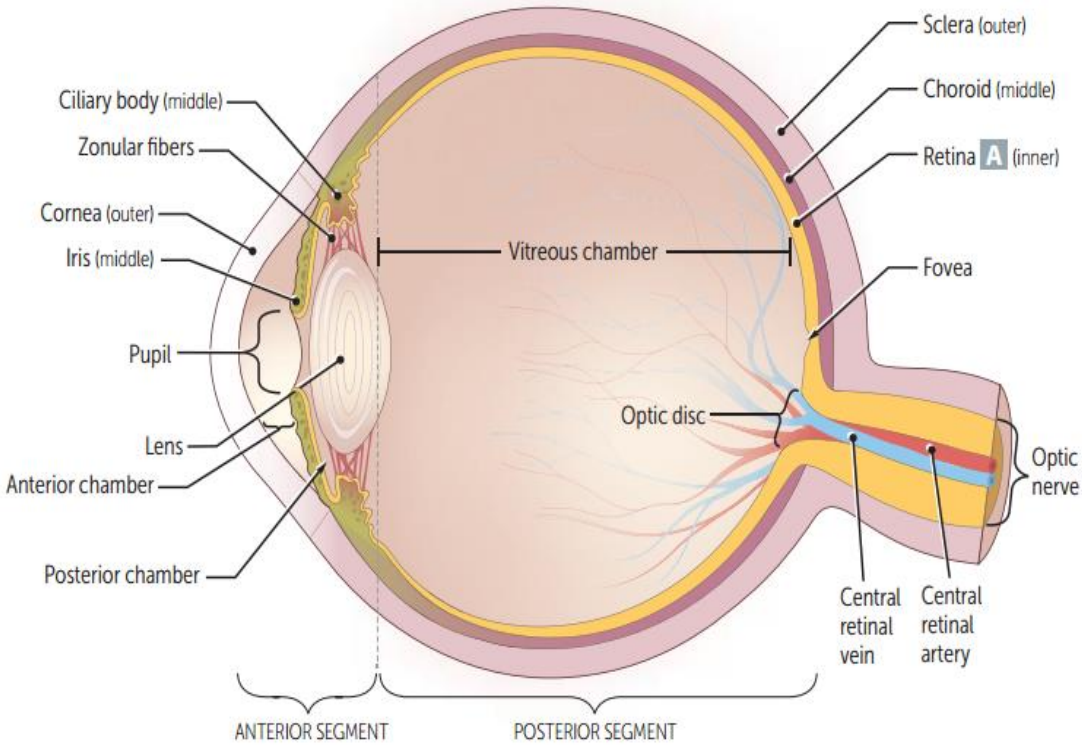
- Early → dilated pupil and loss of accommodation.
- Late → ptosis and ophthalmoplegia.

CHAPTER 5

Ophthalmology

Normal eye





Conjunctivitis

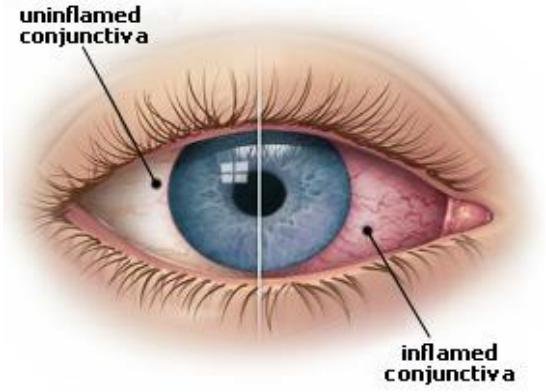
- Inflammation of the conjunctiva → red eye.

- Causes:

- Bacterial: pus; treat with antibiotics.

- Viral: most common, often adenovirus; sparse mucous discharge, swollen preauricular node, ↑ lacrimation; self-resolving.

- Allergic: Allergic conjunctivitis is an acute hypersensitivity reaction that is caused by environmental exposure to allergens. It is characterized by intense itching, hyperemia, tearing, conjunctival edema and eyelid edema.



Refractive errors

- Common cause of impaired vision, correctable with glasses:

1. Hyperopia:

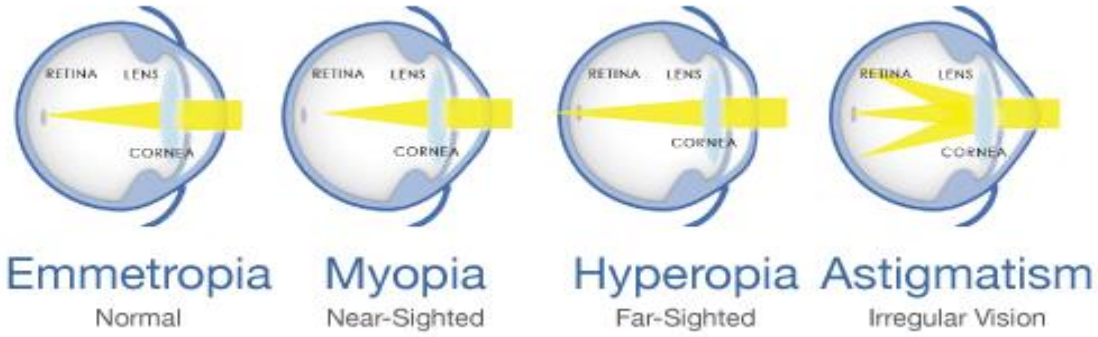
- Also known as "farsightedness".
- Eye too short for refractive power of cornea and lens → light focused behind retina.
- Correct with convex (converging) lenses.

2. Myopia:

- Also known as "nearsightedness".
- Eye too long for refractive power of cornea and lens → light focused in front of retina.
- Correct with concave (diverging) lens.

3. Astigmatism:

- Abnormal curvature of cornea → different refractive power at different axes.
- Correct with cylindrical lens.

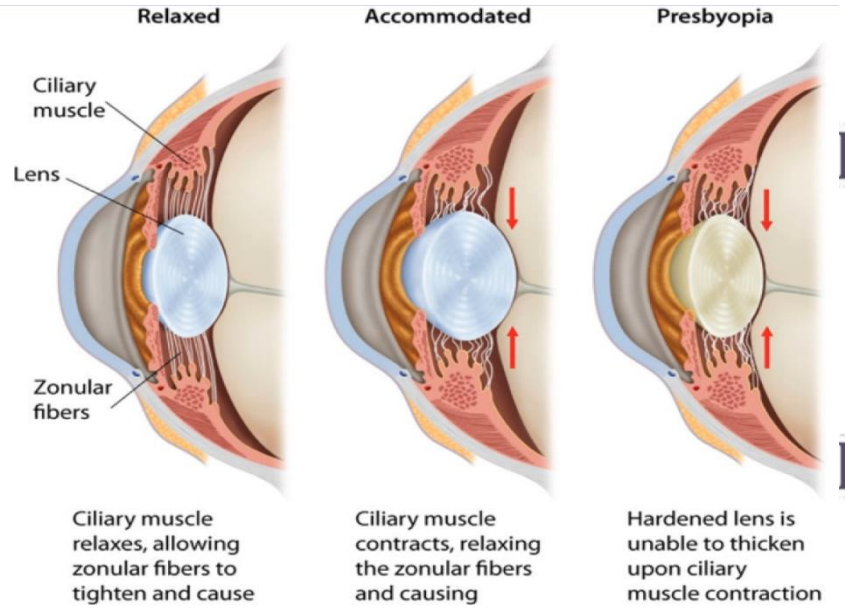


Presbyopia

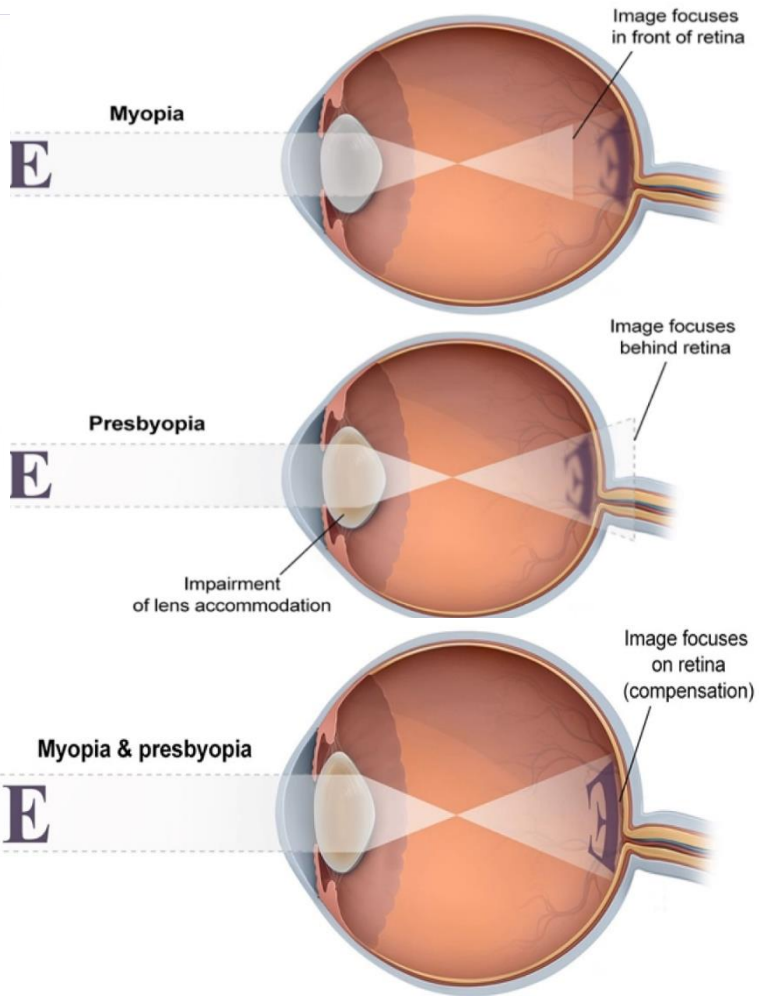
- Aging-related impaired accommodation (focusing on near objects), primarily due to ↓ lens elasticity, changes in lens curvature, ↓ strength of the ciliary muscle.
- This decrease in elasticity prohibits accommodation of the lens, which is required in order to focus on near objects.
- The tendency of patients to hold reading material at a further distance is classic for presbyopia. Patients often need "reading glasses" (magnifiers).

❖ N.B:

- Normally, in accommodation, when focusing on near objects (reading), ciliary muscle contraction relaxes the zonular fibers, allowing the lens to become more convex so the image focuses on the retina.
- Starting around age 40-50, almost all individuals develop an inability to focus on near objects. In this condition, called presbyopia, progressive denaturation of lens proteins and changes in lens curvature cause the lens to become less elastic and lose its accommodating power.
- This causes the image of near objects to focus behind the retina. Conversely, in myopia (increased eye axial length), the image focuses in front of the retina. Therefore, presbyopia can compensate for myopia by displacing the image backward, so that it focuses on the retina.
- Patients with mild myopia often note improvement with age as presbyopia develops. In patients without myopia, presbyopia manifests with difficulty reading fine print and the need to hold objects farther in order to see them clearly.



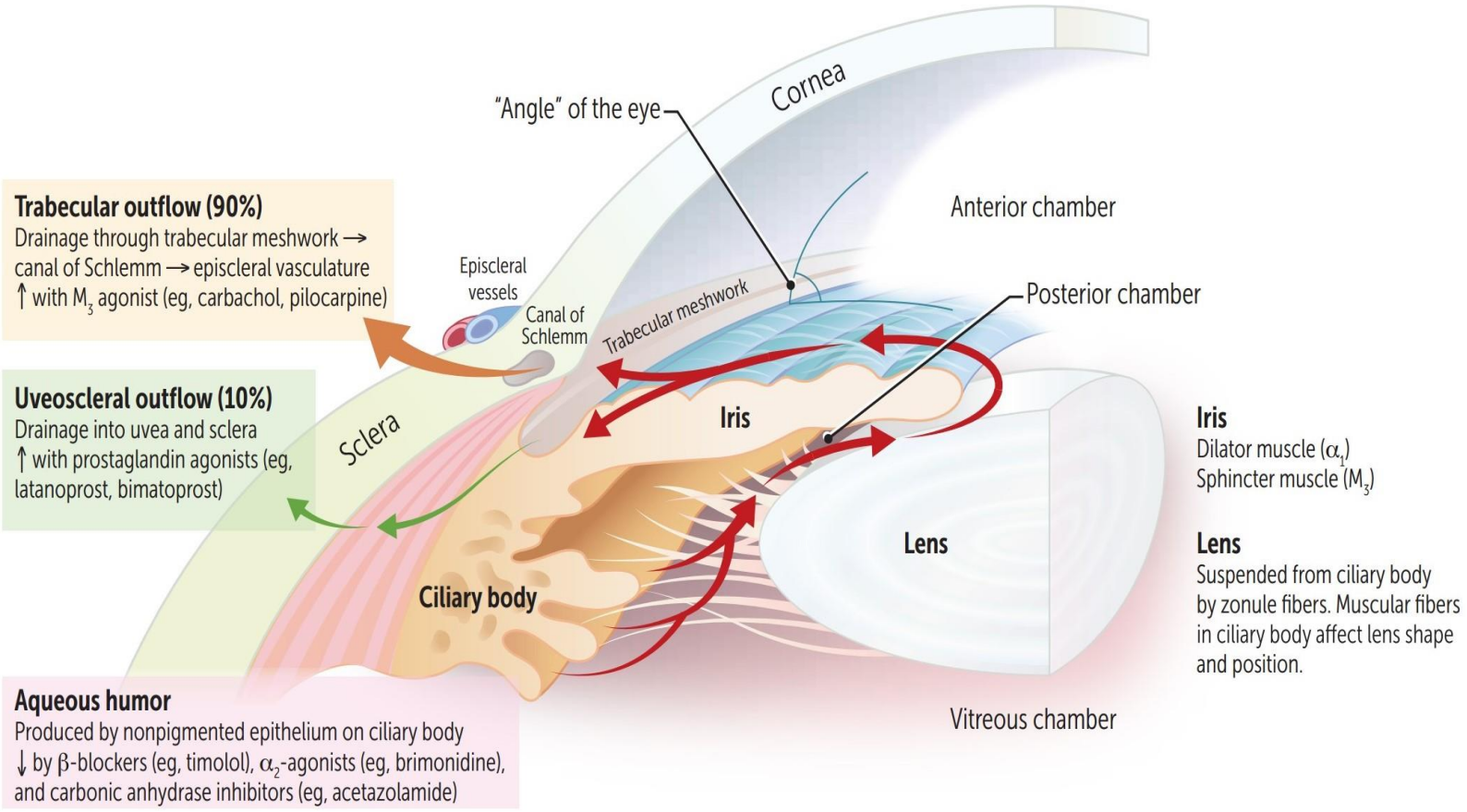
Interaction between presbyopia & myopia



Cataract

- Painless, often bilateral, opacification of lens, often resulting in ↓ vision.
- Acquired risk factors: ↑ age, smoking, excessive alcohol use, excessive sunlight, prolonged corticosteroid use, diabetes mellitus, trauma, infection;
- Congenital risk factors: classic galactosemia, galactokinase deficiency, trisomies (13, 18, 21), ToRCHeS infections (rubella), Marfan syndrome, Alport syndrome, myotonic dystrophy, neurofibromatosis 2.

A cataract is an opacity of the normally clear lens which may develop as a result of aging, metabolic disorders, trauma or heredity



Glaucoma

- Optic disc atrophy with characteristic cupping (thinning of outer rim of optic nerve head [B] versus normal [A]), usually with elevated intraocular pressure (IOP) and progressive peripheral visual field loss.

1- Open angle:

- Associated with ↑ age, African-American race, family history.
- Painless, more common in U.S.
- It is generally asymptomatic in the initial stages, followed by a gradual loss of peripheral vision over a period of years, and eventual tunnel vision.
- Primary: cause unclear.
- Secondary: blocked trabecular meshwork from WBCs (uveitis), RBCs (vitreous hemorrhage), retinal elements (retinal detachment).

2- Closed/narrow angle:

- Primary:

- Enlargement or forward movement of lens against central iris (pupil margin) → obstruction of normal aqueous flow through pupil → fluid builds up behind iris, pushing peripheral iris against cornea [C] and impeding flow through trabecular meshwork.

- Secondary:

- Hypoxia from retinal disease (diabetes mellitus, vein occlusion) induces vasoproliferation in iris that contracts angle.

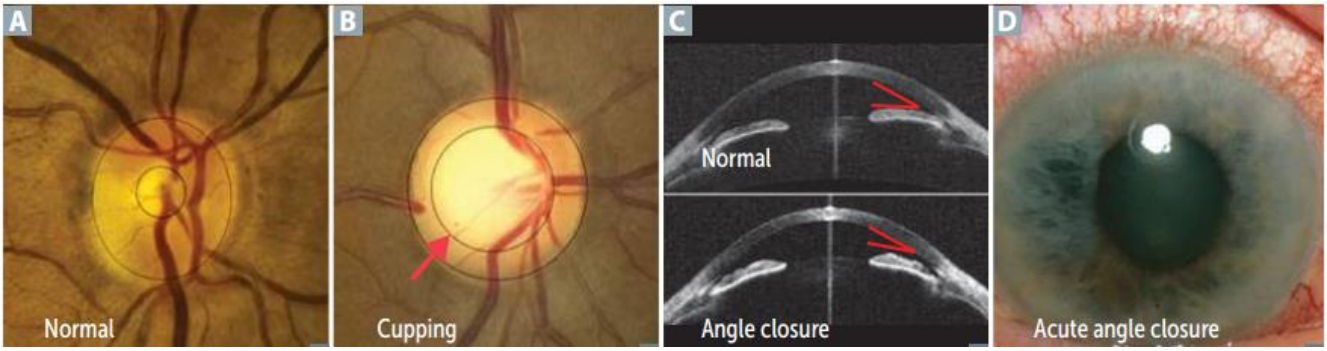
- Closed angel glaucoma can be acute or chronic:

A. Chronic closure: often asymptomatic with damage to optic nerve and peripheral vision.

B. Acute closure:

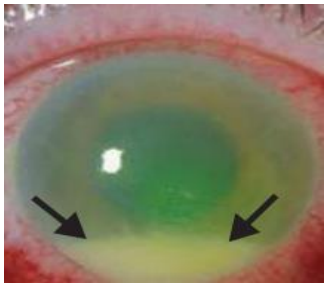
- True ophthalmic emergency.
- ↑ IOP pushes iris forward → angle closes abruptly.
- Very painful, red eye [D], sudden vision loss, halos around lights, rock-hard eye, frontal headache.
- It usually occurs following pupillary dilation, which may occur in darkened movie theaters, during times of stress, or due to drug intake.
- Mydriatic agents contraindicated.

- It is important to distinguish acute angle closure glaucoma from migraine, cluster headache, temporal arteritis, and keratoconjunctivitis because failure to correctly diagnose this disease can lead to blindness.



Uveitis

- Inflammation of uvea (iritis aka anterior uveitis, choroiditis aka posterior uveitis).
- May have hypopyon (accumulation of pus in anterior chamber) or conjunctival redness.
- Associated with systemic inflammatory disorders (sarcoidosis, rheumatoid arthritis, juvenile idiopathic arthritis, HLA-B27–associated conditions).



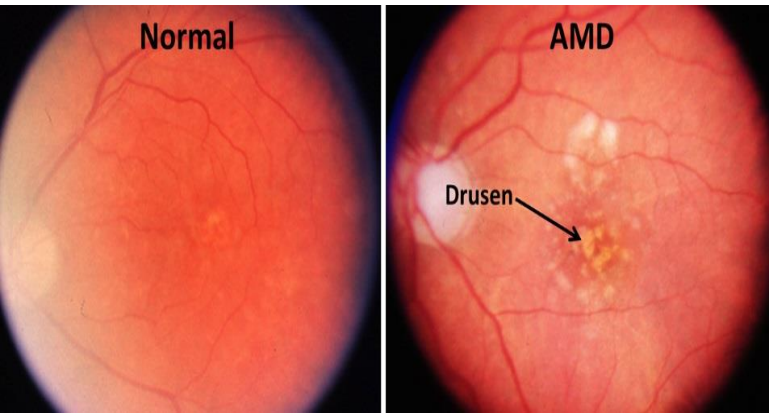
Age-related macular degeneration

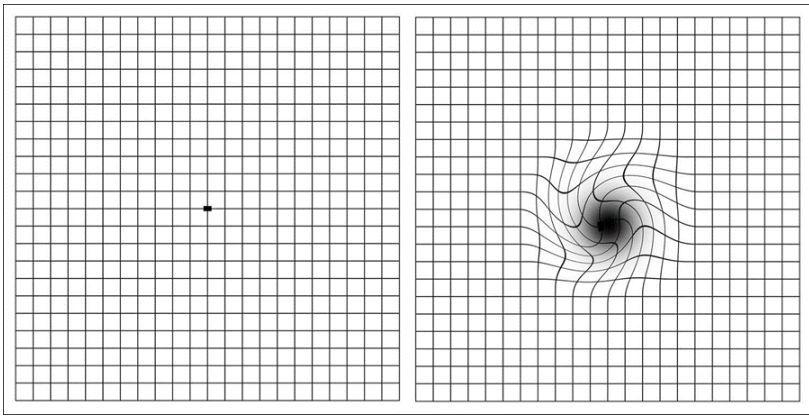
- Degeneration of macula (central area of retina).
- Causes distortion (metamorphopsia) and eventual loss of central vision (scotomas).
- One of the earliest findings in macular degeneration is distortion of straight lines such that they appear wavy.
- Patients may be asymptomatic, but others complain of visual problems in either one or both eyes. Driving and reading are often some of the first activities that are affected since they require fine visual acuity, which is provided primarily by the macula.

- Types:

- Dry (nonexudative, > 80%):
  - Deposition of yellowish extracellular material in and beneath Bruch membrane and retinal pigment epithelium (Drusen) with gradual ↓ in vision.
  - Prevent progression with multivitamin and antioxidant supplements.

- Wet (exudative, 10–15%):
  - Rapid loss of vision due to bleeding 2° to choroidal neovascularization.
  - Treat with anti-VEGF (vascular endothelial growth factor) injections (ranibizumab) or laser.





❖ N.B:

- The term scotoma refers to any visual defect surrounded by a relatively unimpaired field of vision (discrete area of altered vision surrounded by zones of normal vision).
- Scotomas occur due to pathologic processes that involve parts of the retina or optic nerve. Examples of such processes include demyelinating diseases such as multiple sclerosis, diabetic retinopathy and retinitis pigmentosa.
- Pathologic processes that involve the entire optic nerve lead to monocular blindness.
- The macula is a yellowish spot approximately 1.5 mm in diameter located near the center of the retina. It is characterized histologically by the presence of densely packed cones, few overlying cells and no blood vessels. Each macular cone synapses to a single bipolar cell, which, in turn, synapses to a single ganglion cell. Due to this arrangement the visual acuity in the macula, and particularly the fovea, is greater than in any other area of the retina.
- Lesions of the macula cause central scotomas.

Diabetic retinopathy

- Retinal damage due to chronic hyperglycemia induced microvascular injury.

- It occurs in both insulin dependent and non-insulin dependent diabetes mellites.

- Diabetic retinopathy is the leading cause of blindness in the USA.

- The prevalence of DR is proportionate to the duration of diabetes and severity of hyperglycemia over time; tight control of diabetes is associated with a lower long-term risk of DR.

- Two types:

A. Nonproliferative (early disease):

- The earliest morphologic changes include pericyte degeneration (Cells that wrap and support retinal capillaries) →Microaneurysms due to degeneration → Rupture → dot-blot hemorrhages.

- Damaged capillaries leak blood → lipids and fluid seep into retina → Hard exudates and macular edema.

- Ischemic injury to the retina, which manifests as cotton-wool spots.

- Treatment: blood sugar control.

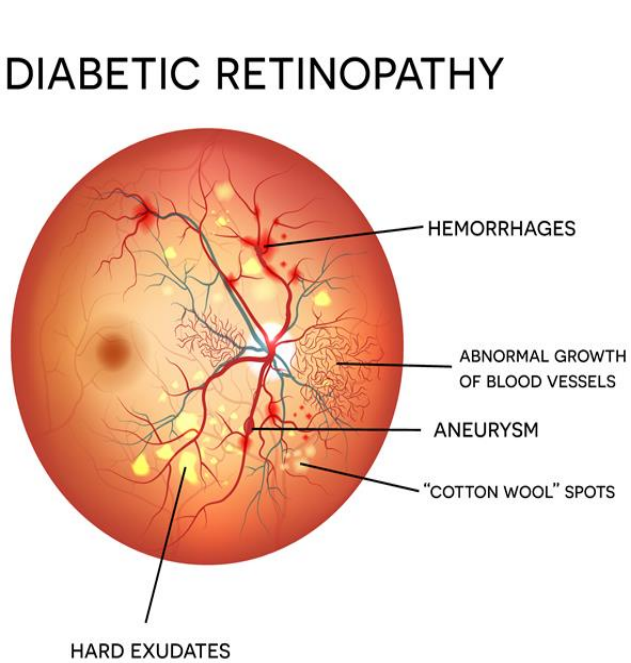
B. Proliferative (advanced disease):

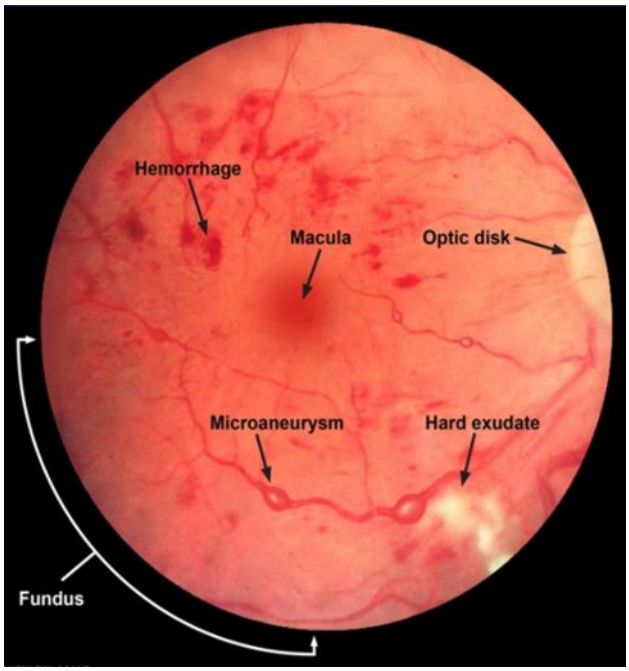
- Progressive retinal ischemia stimulates production of angiogenic factors (vascular endothelial growth factor), leading to formation of new retinal vessels (neovascularization).

- The new vessels are fragile and often extend into the adjacent vitreous.

- Traction from the vitreous can cause detachment of the retina or laceration of the vessels, leading to acute hemorrhage and vision loss.

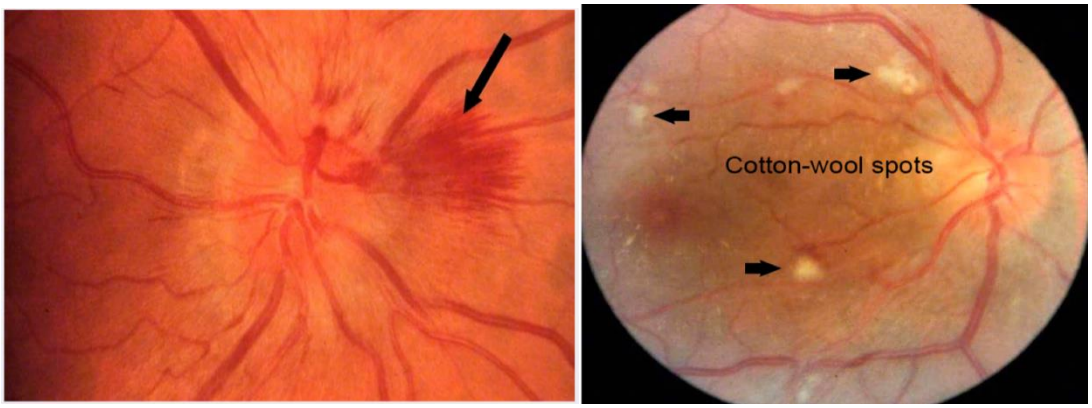
- Treatment: peripheral retinal photocoagulation, anti-VEGF (bevacizumab).





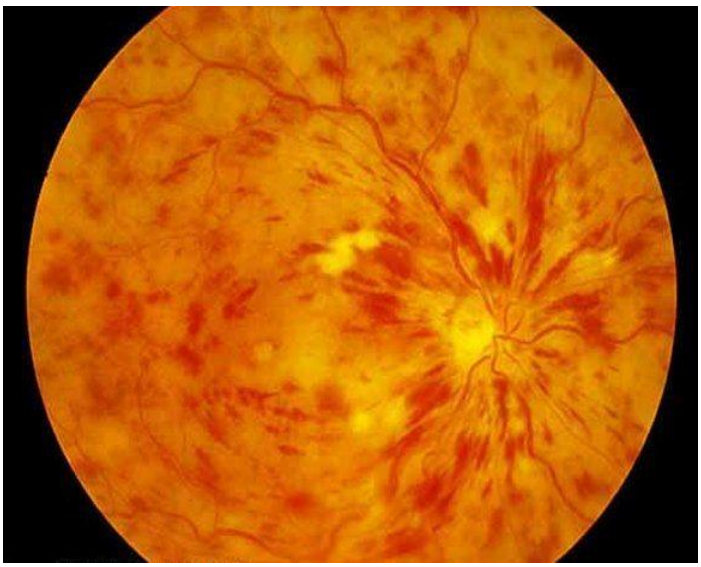
Hypertensive retinopathy

- Retinal damage due to chronic uncontrolled HTN.
- Hypertensive retinal hemorrhage typically causes painless, unilateral visual disturbances, ranging from mild obscuration without loss of visual acuity to permanent blindness.
- Severe hypertension in retinal precapillary arterioles causes endothelial disruption, leakage of plasma into the arteriolar wall, and fibrinous necrosis. The necrotic vessels can then bleed into the nerve fiber layers, causing dot- and flame-shaped hemorrhages.
- Diagnosis of hypertensive retinal hemorrhage is usually confirmed by direct ophthalmoscopic evaluation. Other findings of hypertensive retinopathy include thickening of the arteriolar walls ("copper or silver wiring"), compression of the associated veins (arteriovenous nicking), and small, white foci of retinal ischemia (cotton-wool spots).
- Associated with ↑ risk of stroke, CAD, kidney disease.



Central Retinal vein occlusion

- Patients with central retinal vein occlusion usually present with subacute monocular visual loss, but it is typically not quite as acute as the vision loss seen in patients with central retinal artery occlusion.
- CRVO is associated with coagulopathy, hyperviscosity, chronic glaucoma and atherosclerotic risk factors (including age, diabetes, and hypertension).
- The characteristic changes on funduscopic examination are sometimes referred to as the "blood and thunder" appearance and include optic disk swelling, retinal hemorrhage, dilated veins, and cotton wool spots.
- No treatment is particularly effective, but some patients may have partial recovery of vision within the first three months.

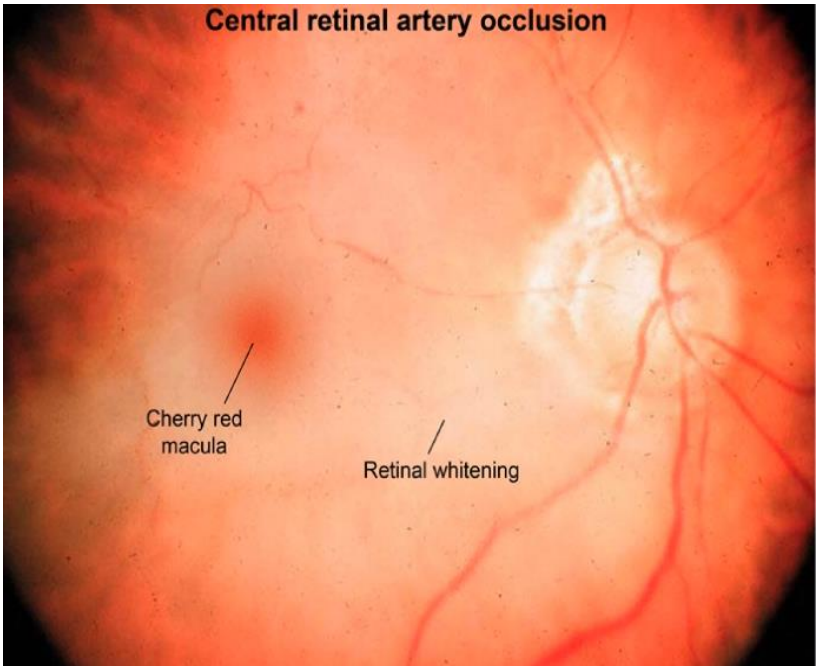


Central retinal artery occlusion

- Acute and painless monocular vision loss is characteristic of central retinal artery occlusion (CRAO). The vision loss includes the entire visual field and is often permanent.

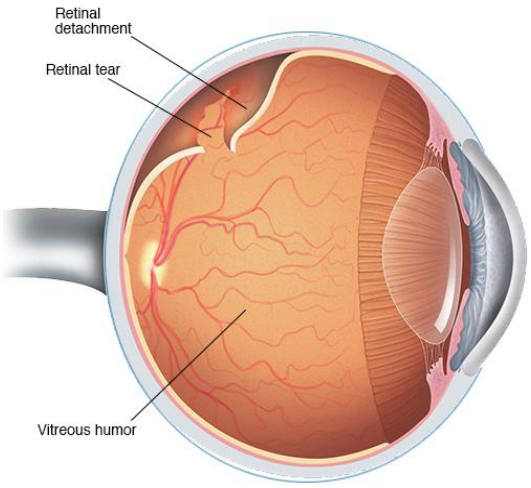
- Specific fundoscopic findings include a pale retina and cherry red macula. These findings are explained by the fact that the macula has a separate blood supply from the choroid artery, while the rest of retina is supplied by the central retinal artery.

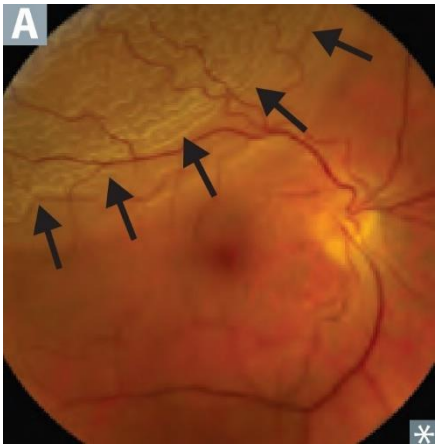
- The central retinal artery is a branch of the ophthalmic artery, which arises from the internal carotid artery. Embolism is the most common cause of central artery occlusion; predisposing conditions include atrial fibrillation and carotid artery stenosis.



Retinal detachment

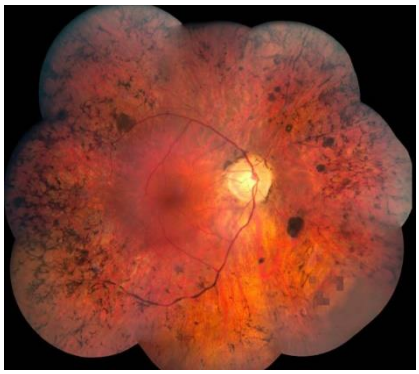
- Separation of neurosensory layer of retina (photoreceptor layer with rods and cones) from outermost pigmented epithelium (normally shields excess light, supports retina) → degeneration of photoreceptors → vision loss.
- May be 2° to retinal breaks, diabetic traction, inflammatory effusions.
- Visualized on fundoscopy as crinkling of retinal tissue and changes in vessel direction.
- Breaks more common in patients with high myopia and/or history of head trauma. Often preceded by posterior vitreous detachment ("flashes" and "floaters") and eventual monocular loss of vision like a "curtain drawn down."
- Surgical emergency.





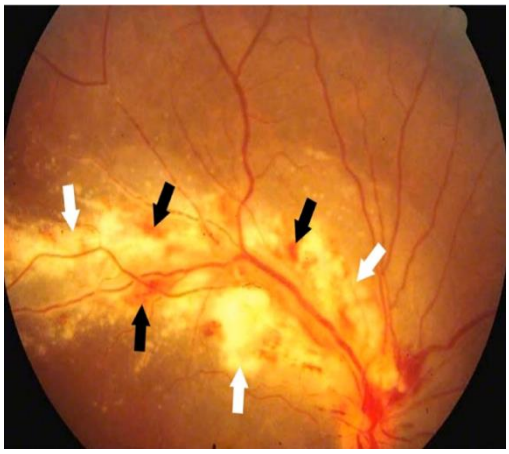
Retinitis pigmentosa

- Inherited retinal degeneration.
- Painless, progressive vision loss beginning with night blindness (rods affected first).
- Bone spicule-shaped deposits around macula.



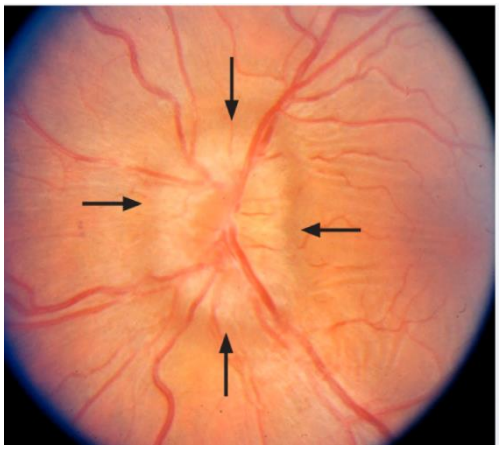
Retinitis

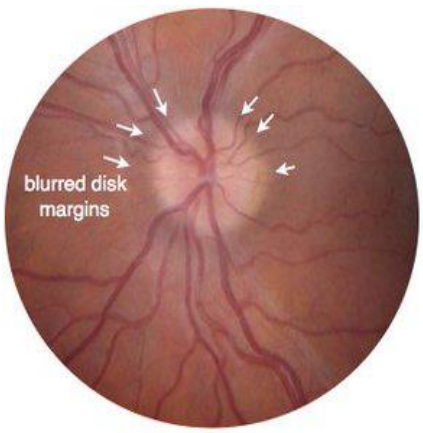
- Retinal edema and necrosis leading to scar.
- Often viral (CMV, HSV, HZV).
- Cytomegalovirus retinitis is the most common cause of ocular disease in patients with untreated AIDS who have CD4 counts <50/mm^3. Diagnosis is made by funduscopy, which typically reveals yellow-white, fluffy retinal lesions near the retinal vessels with associated hemorrhage. Treatment with ganciclovir is required to prevent blindness.



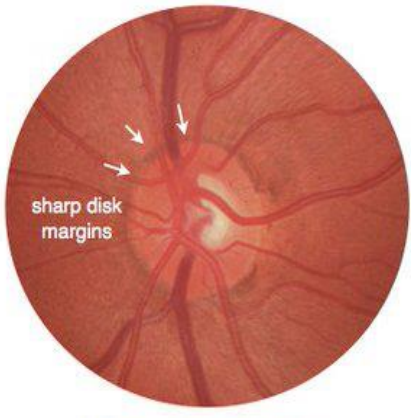
Papilledema

- Optic disc swelling (usually bilateral) due to ↑ ICP (2° to mass effect).
- Increased intracranial pressure is transmitted through the cerebrospinal fluid in the subarachnoid space, which is continuous with the optic nerve sheath.
- This buildup of pressure compresses the optic nerves externally, which in turn impairs axoplasmic flow within the optic nerves, causing bilateral optic disc edema (papilledema). Compared to normal funduscopy, patients with papilledema have elevation of the optic disc with blurred disc margins (black arrows).





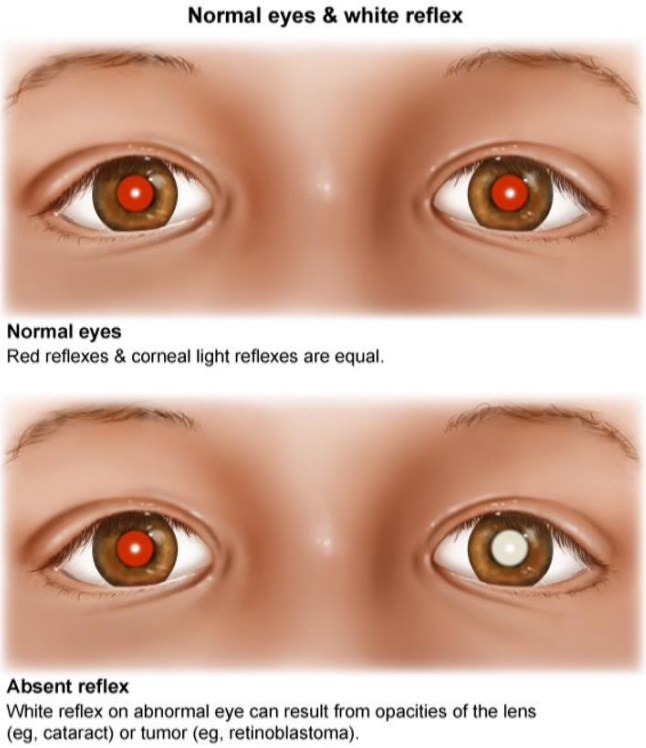
Papilledema

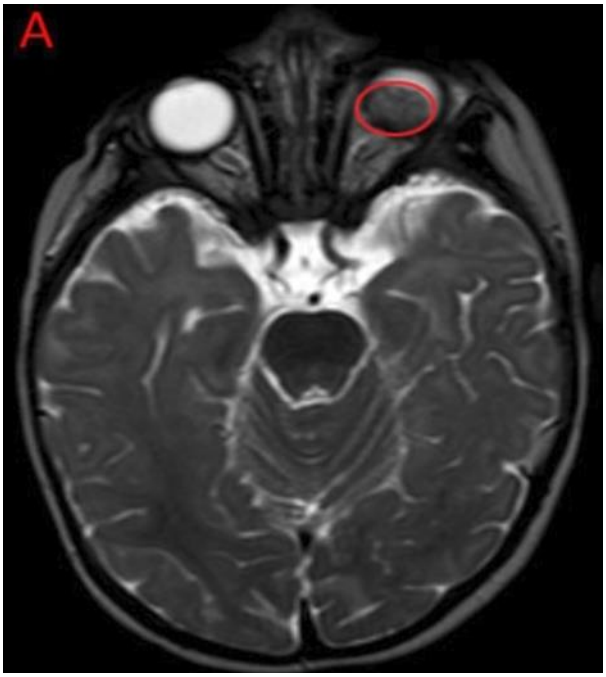


Normal Optic Disk

Leukocoria

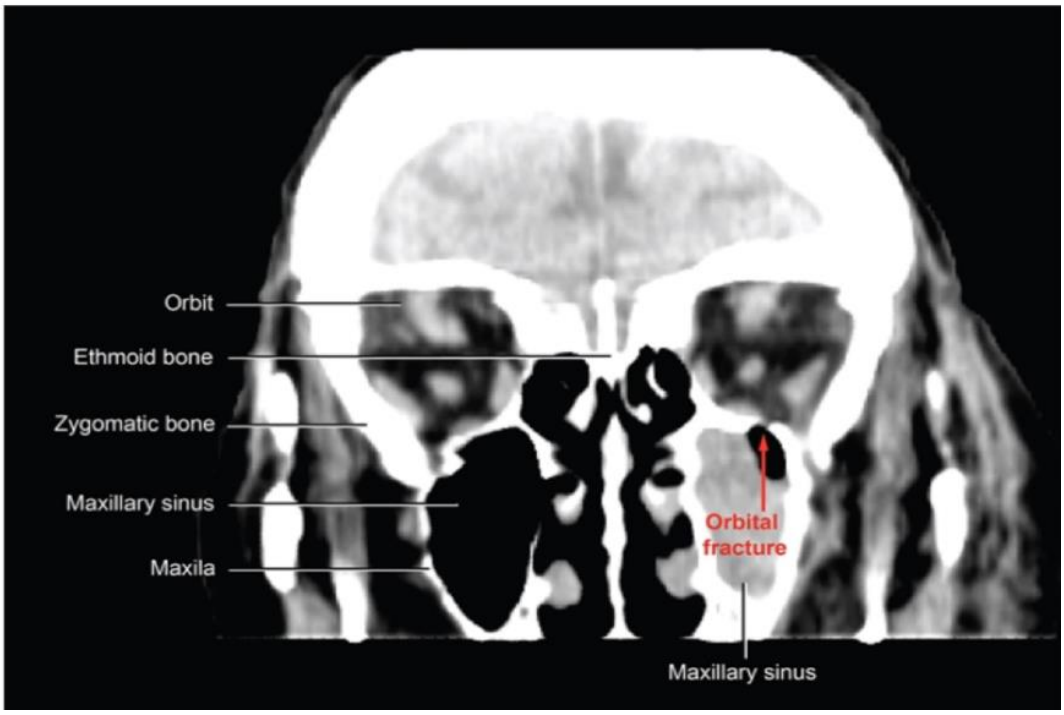
- Loss (whitening) of the red reflex.
- Important causes in children include retinoblastoma, congenital cataract, toxocariasis.
- Familial retinoblastoma occurs as a result of mutations of each of the two Rb genes ("two hits"). These patients have an increased risk of secondary tumors, especially osteosarcomas, later in life.
- Every case of leukocoria in children is considered a retinoblastoma, until proven otherwise; therefore, such cases should be promptly referred to an ophthalmologist. The diagnosis is highly suspected with US or CT scan findings of a mass with calcifications.





❖ N.B:

- The orbit is bound superiorly by the thick orbital plate of the frontal bone and laterally by the thick bone of the zygoma and greater and lesser sphenoid wings.
- In contrast, the orbital floor is composed of a very thin layer of bone that separates the orbit from the air-filled maxillary sinus. Similarly, the orbit's medial wall is composed of the thin ethmoid and lacrimal bones, which separate it from the ethmoid air cells.
- Blunt trauma to the eye causes a rapid increase in pressure that typically does not rupture the globe but is transmitted posteriorly into the orbit.
- The weakest plates of bone in the orbit, the medial and inferior walls, are common sites of fracture. Fracture is typically evident on radiographic imaging, and fluid (blood) or herniation of the orbital contents can often be visualized in the adjacent normally air-filled sinuses.


Orbit
Ethmoid bone
Zygomatic bone
Maxillary sinus
Maxila
Orbital fracture
Maxillary sinus

CHAPTER 6

Pharmacology

Opioid Analgesic

- Drugs:

- Morphine, fentanyl, codeine, loperamide, methadone, mepridine, dextromethorphan, diphenoxylate, pentazocine.

- Mechanism of action:

- Endogenous opiate peptides represented by endorphin, enkephalin, and dynorphin.

- Opioid analgesics act as agonists at opioid receptors (μ = β-endorphin, δ = enkephalin, κ = dynorphin) to modulate synaptic transmission.

- They act by presynaptic and postsynaptic inhibition through G_i coupling:
  - Presynaptic receptors → ↓ Ca influx → ↓ substance P release (pain neurotransmitter).
  - Postsynaptic receptors → ↑ K efflux → membrane hyperpolarization.

- Clinical use:

1. Full agonist opioids (morphine, heroin, meperidine, methadone, codeine, fentanyl):

A. Morphine:

- It is a prototype μ agonist.

- ↑ pain tolerance and ↓ perception and reaction to pain → Analgesia.

- Cough suppression → antitussive action.

B. Codeine:

- It is a prodrug that is converted by the cytochrome P450 into morphine (its active form), So, cytochrome P450 inducers will increase its active form and may lead to toxicity.

- Analgesia, Cough suppression.

C. Methadone (long acting opioid drug): used in maintenance of opiate addiction.

D. Meperidine:

- Metabolized by cytochrome P450 → normeperidine (a serotonin reuptake inhibitor), normeperidine may cause serotonin syndrome.

- Analgesia.

- Also, antimuscarinic action (has the opposite of morphine's smooth muscle effect), So, no miosis, no spasm of GI / GU/ Gallbladder, and tachycardia.

2. Partial agonist opioids:

- Buprenorphine: alone act as agonist, but do not give it to a patient on a full agonist → it will act as antagonist → precipitation of withdrawal.

3. Mixed agonist – antagonist opioid:

A. Nalbuphine, pentazocine:

- κ agonist and μ antagonist.
- Analgesia for moderate to severe pain.
- Because of its weak antagonistic effects, it can cause withdrawal symptoms in patients who are dependent or tolerant to morphine or other opioids.

B. Butorphanol:

- κ-opioid receptor agonist and μ-opioid receptor partial agonist, produces analgesia.
- Severe pain (migraine, labor).
- Causes less respiratory depression than full opioid agonists.
- Can cause opioid withdrawal symptoms if patient is also taking full opioid agonist (competition for opioid receptors).
- Overdose not easily reversed with naloxone.

4. Opioid antagonist:

- Naloxone: IV, Reversal for respiratory depression.
- Naltrexone: per oral, ↓ craving for alcohol and used in opiate addiction.

5. Opiate related drugs with specific indications:

- Loperamide, Diphenoxylate: treatment of diarrhea.
- Dextromethorphan: treatment of cough.

▪ Side effects of opioids:

- Sedation.
- Respiratory depression: ↓ response to ↑ PCO_2, so don't give O_2 in morphine toxicity, but give naloxone.

- Cardiovascular: minimal effects on heart, but cause vasodilatation due to histamine release → cerebral vessel VD → increased cerebral blood flow → ↑ ICP (avoid in head trauma).

- Nausea and vomiting: stimulation of the chemoreceptor trigger zone (CTZ) in the area postrema.

- Smooth muscle:
  - GIT → ↓ peristalsis → constipation (heroin abusers use a lot of laxatives).
  - GUT → urinary retention.
  - Biliary (sphincter of Oddi spasm) → ↑ intrabiliary pressure.
  - Pupil → miosis (except meperidine → mydriasis).

- Additive CNS depression with other drugs.

▪ Contraindications and cautions for opioids:

- Head injury → possible increased intracranial pressure.

- Pulmonary dysfunction (except pulmonary edema) → cause respiratory depression.

- Hepatic/renal dysfunction → possible accumulation.

- Pregnancy → possible neonatal depression or dependence except meperidine.

▪ Toxicity:

- Acute toxicity causes a classic triad: Pinpoint pupil, Respiratory depression, Coma.

▪ Management of acute toxicity:

- Supportive treatment + IV naloxone.

▪ Symptoms of withdrawal:

- Muscle cramps and CNS originating pain.

- Lacrimation, rhinorrhea, and salivation.

- Anxiety and sweating.

- Yawning.

❖ N.B:

1. The use of opioids can lead to development of tolerance or a decrease in opioid effectiveness and physiological response with continued use.

- The mechanism of acute opioid tolerance is still uncertain but is postulated to involve phosphorylation of opioid receptors by protein kinase. Chronic tolerance may involve increased adenylyl cyclase activity or nitric oxide levels.
- In the case of morphine, the neurotransmitter glutamate has also been shown to interact with opioid pathways to modulate morphine tolerance.
- Glutamate is an excitatory neurotransmitter that binds and activates NAMDA receptors. NMDA receptors activation can cause increased phosphorylation of opioid receptors and increased nitric oxide levels which ultimately leads to morphine tolerance.
- In animal studies, NMDA receptors antagonists, like ketamine, block the actions of glutamate and effectively block morphine tolerance.

2. Tolerance to the different side effects of opioids is expected to occur. However, tolerance to constipation and miosis does not readily occur.

Tramadol

- Mechanism of action:

- Very weak opioid agonist, also inhibits 5-HT and norepinephrine reuptake (works on multiple neurotransmitters "tram it all" in with tramadol).

- Clinical use:

- Chronic pain.

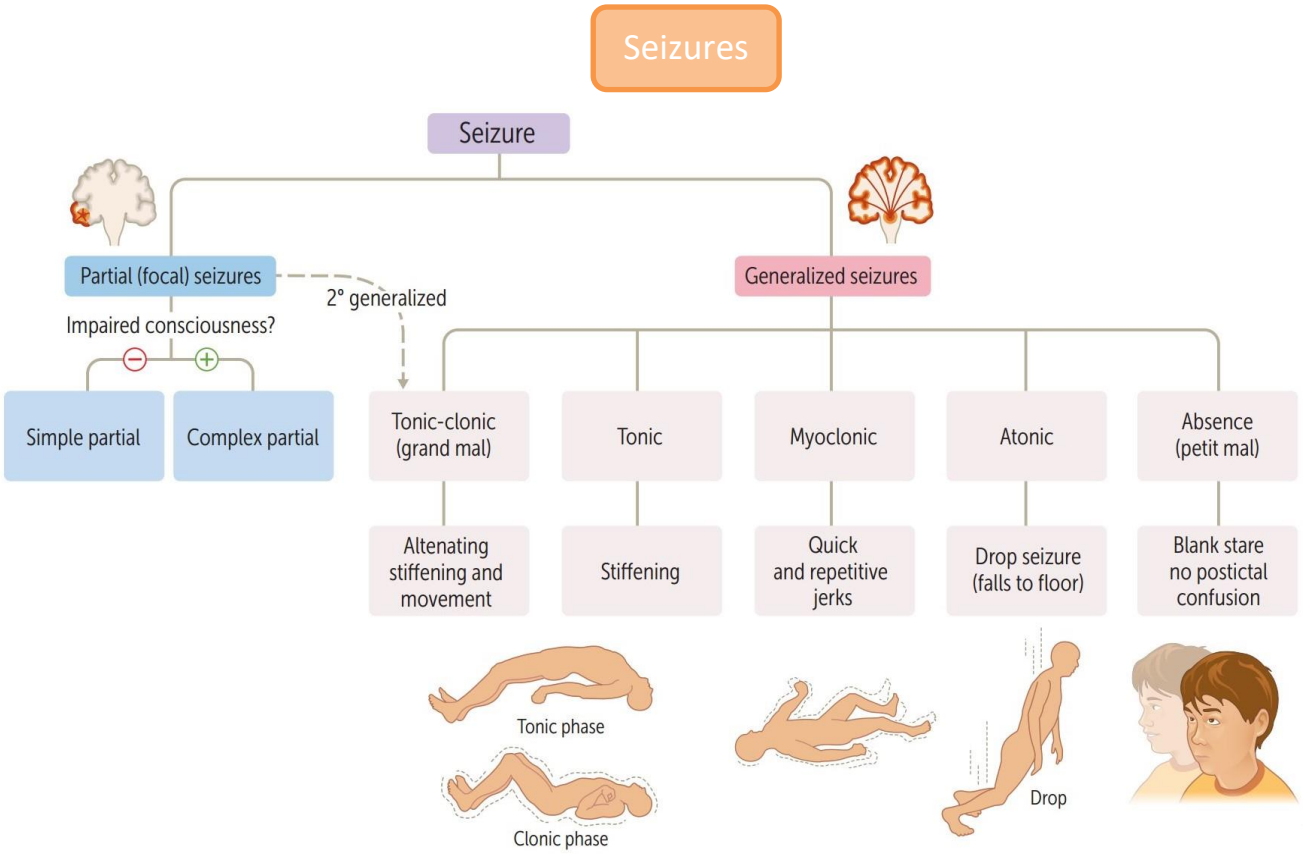
- Toxicity:

- Similar to opioids.

- Decreases seizure threshold.

- Can cause Serotonin syndrome.

- Tramadol is a Slight opioid agonist, and a Serotonin and norepinephrine reuptake inhibitor. It is used for Stubborn pain, but can lower Seizure threshold, and may cause Serotonin Syndrome.



- Seizures is characterized by synchronized, high-frequency neuronal firing:
- Seizures that involve a localized part of the brain are called → partial.
- Seizures that involve the whole of the brain are called → generalized.
- Secondary generalization: may be used to describe a partial seizure that later spreads to the whole cortex and become generalized.
- A simple seizure means that there is no associated impairment of consciousness during or after the event.
- A complex seizure, to the contrary, are characterized by loss of memory during the event and postictal state.
- Epilepsy is a disorder of recurrent seizures (febrile seizures are not epilepsy).
- Causes of seizures by age:
  - Children: genetic, infection (febrile), trauma, congenital, metabolic.
  - Adults: tumor, trauma, stroke, infection.
  - Elderly: stroke, tumor, trauma, metabolic, infection.

- Types:

1- Partial seizures:

A. Simple partial:

- One body part is involved (partial, localized area of the brain involved), no loss of consciousness and no postictal confusion (simple).

B. Complex partial:

- Almost always from temporal lobe involvement (mood change, illusion, hallucination), impaired consciousness and postictal state are present.

- Drug of choice for both simple partial and complex partial seizures is carbamazepine (1st line).

2- Generalized seizures:

A. Absence (petit mal) seizures:

- Brief episodes of staring, but no postictal confusion.

- Drug of choice: ethosuximide (1st line), valproate (2nd line).

B. Tonic colonic (Grand mal) seizures:

- Generalized tonic extension of the extremities followed by colonic rhythmic movements, loss of consciousness and prolonged postictal confusion are present.

- Drug of choice: phenytoin, carbamazepine, and valproate.

C. Myoclonic seizures:

- Brief arrhythmic jerking movements, last < 1 sec, usually occur in clusters for a few minutes, no loss of consciousness.

- Drug of choice: valproic acid (1st line).

D. Tonic: stiffening.

E. Atonic: "drop" seizures (falls to floor); commonly mistaken for fainting.

Epilepsy drugs

- Seizures results from episodic electrical discharges in cerebral neurons associated with prolonged depolarization, followed by prolonged hyperpolarization.

- The goal of drug management is restoration of normal patterns of electrical activity.

- Mechanism of action of antiepileptic drugs:

1. ↓ axonal conduction by preventing Na influx through fast Na channels: phenytoin, carbamazepine and valproic acid.

2. ↑ inhibitory tone by facilitation of GABA mediated hyperpolarization: barbiturates and benzodiazepines.

3. ↓ excitatory effect of glutamic acid: lamotrigine and topiramate.

4. ↓ presynaptic Ca influx through type T channels in thalamic neurons: ethosuximide.

- Phenytoin, carbamazepine and valproic acid inhibits neuronal high frequency firing by reducing the ability of Na channels to recover from inactivation (blocks voltage gated Na channels in cortical neurons). They stabilize these channels in an inactivated state, therefore, fewer Na channels are available for the propagation of an abnormal action potential).

- Valproate is the 1st line for treatment of absence seizures when associated with tonic colonic or myoclonic seizures.

Phenytoin

- Mechanism of action:

- It blocks voltage gated Na channels in cortical neurons.

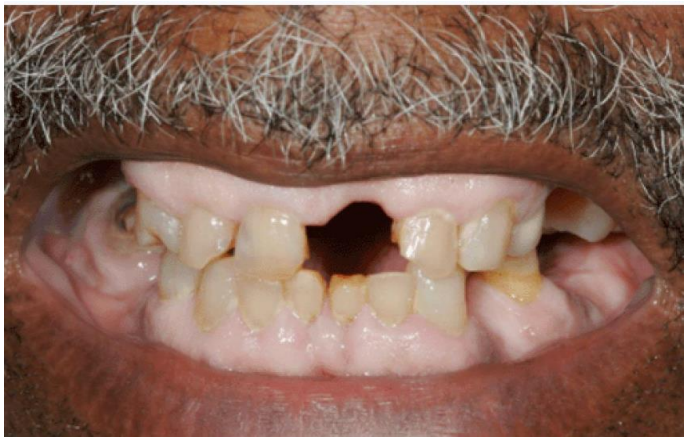
- It stabilizes these channels in an inactivated state, therefore, fewer Na channels are available for the propagation of an abnormal action potential.

- Clinical use:

- Phenytoin is an anticonvulsant effective in the treatment of grand mal (tonic-clonic) seizures, partial seizures, and status epilepticus (fosphenytoin).

- Side effects:

- Phenytoin has a narrow therapeutic index with a number of potential adverse effects:
  - It affects the cerebellum and vestibular system → Ataxia and nystagmus.
  - Gingival hyperplasia is a common side effect and is sometimes reversible when phenytoin is withdrawn. Phenytoin causes increased expression of platelet-derived growth factor (PDGF). When gingival macrophages are exposed to increased amounts of PDGF, they stimulate proliferation of gingival cells and alveolar bone.
  - Undesirable cosmetic effects as hirsutism, coarsening of facial features and acneiform skin rash limit its use.
  - Phenytoin interferes with the metabolism of folic acid and may cause → megaloblastic anemia.
  - Phenytoin induces the P450 cytochrome oxidase system. It increases the metabolism and therefore decreases the blood level of many medications.
  - Interferes with vitamin D metabolism → osteomalacia.
  - If taken during pregnancy, it may cause fetal hydantoin syndrome, cleft lip and palate.
  - It has been also associated with generalized lymphadenopathy.



Carbamazepine

- Mechanism of action:

- It blocks voltage gated Na channels in cortical neurons.

- It stabilizes these channels in an inactivated state, therefore, fewer Na channels are available for the propagation of an abnormal action potential.

- Clinical use:

- It is used for simple and complex partial seizures, generalized tonic-colonic seizures, as a mood stabilizer in bipolar disorder, and it is the 1st line for treatment of trigeminal neuralgia.

- Side effects:

- Bone marrow suppression may lead to anemia, agranulocytosis, and thrombocytopenia, So, Complete blood counts should be monitored periodically.

- It is also hepatotoxic, So, LFTs should be monitored regularly.

- A carbamazepine associated increase in ADH secretion may cause SIADH.

- Teratogenicity: cleft lip and palate & spina bifida.

Sodium valproate (Valproic acid)

- Mechanism of action:

- Multiple mechanisms:

  - It blocks voltage gated Na channels in cortical neurons as phenytoin and carbamazepine. it stabilizes these channels in an inactivated state, therefore, fewer Na channels are available for the propagation of an abnormal action potential.

  - It also increases the concentration of GABA by inhibiting GABA transaminase and blocks T Type Ca channels in thalamic neurons as ethosuximide.

- Clinical use:

- It is the drug of choice for myoclonic seizures.

- It is also used as a mood stabilizer for bipolar disorder.

- Side effects:

- Hepatotoxicity (from toxic metabolites).

- Thrombocytopenia.

- Pancreatitis.

- Alopecia.

- Teratogenicity: spina bifida.

Ethosuximide

- Mechanism of action:
- It blocks T type of calcium channels in thalamic neurons causing hyperpolarization.

- Clinical use:
- It is the drug of choice for treatment of absence seizures.

Benzodiazepines (Diazepam, Lorazepam)

- Mechanism of action:
- Facilitate GABA action by ↑ frequency of Cl channel opening → membrane hyperpolarization.

- Clinical use:
- It is used for the treatment of status epilepticus (Lorazepam).

- It is also used for the treatment for eclampsia seizures (1st line in treatment of eclampsia seizures is $MgSo_4$).

- Side effects: we will talk about them later.

Barbiturates (Phenobarbital)

- Mechanism of action:
- Facilitate GABA action by ↑ duration of Cl channel opening, thus ↓ neuron firing (barbidurates ↑ duration).

- Clinical use:
- It is used for the treatment of status epilepticus.

- Side effects: we will talk about them later.

❖ New anticonvulsants that are used predominantly for the treatment of refractory partial seizures are:

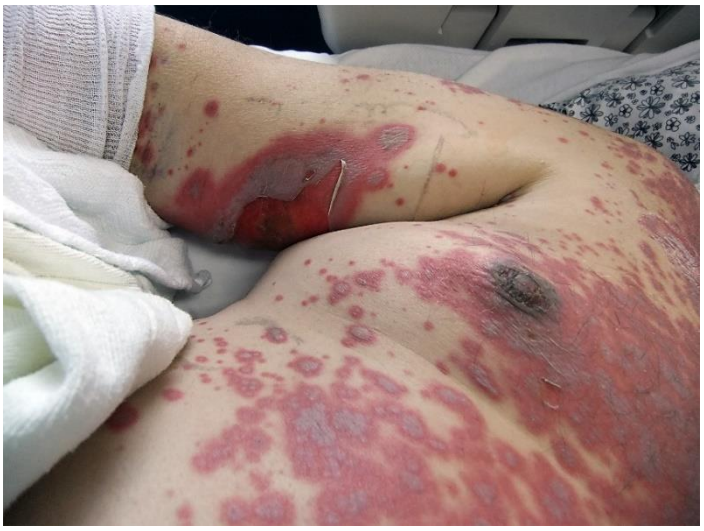
A. Lamotrigine:

- Mechanism of action:
- Block voltage gated Na channels, inhibits the release of glutamate.

- Clinical use:
- It is used mainly for the treatment of refractory partial seizures.
- It is also effective in management of generalized tonic colonic seizures, and in the treatment of bipolar disorder.

- Side effects:

- The newer anticonvulsant drugs have fewer side effects than other anticonvulsants. However, lamotrigine is associated with a potentially life-threatening hypersensitivity reaction (Steven Johnson syndrome) that manifests as a skin rash especially in children which requires discontinuation of the drug immediately.



B. Topiramate: blocks Na channels and enhance the effect of GABA.

C. Tiagabine: inhibitor of GABA intake.

D. Vigabatrin: inhibit GABA transaminase (the enzyme that metabolize GABA) and increase GABA concentration.

E. Gabapentin: increase brain GABA concentration, used also in neuropathic pain (such as post-herpetic neuralgia).

❖ N.B:

1. Avoid abrupt withdrawal of antiepileptic drugs, which may precipitate seizures.

2. Phenytoin, carbamazepine and phenobarbital are cytochrome P450 inducers.

3. Primidone is an antiepileptic that is metabolized to phenobarbital and phenylethylmalonamide (PEMA). All three compounds are active anticonvulsants.

- Primidone causes elevated blood phenobarbital levels.

Status Epilepticus

- Definition:

- Recurrent or continuous generalized tonic colonic seizures that last for ≥ 5 minutes without a return to consciousness.

- It is a life-threatening condition that has a number of systemic effects, including hypertension, tachycardia, cardiac arrhythmia, and lactic acidosis.

- Treatment:

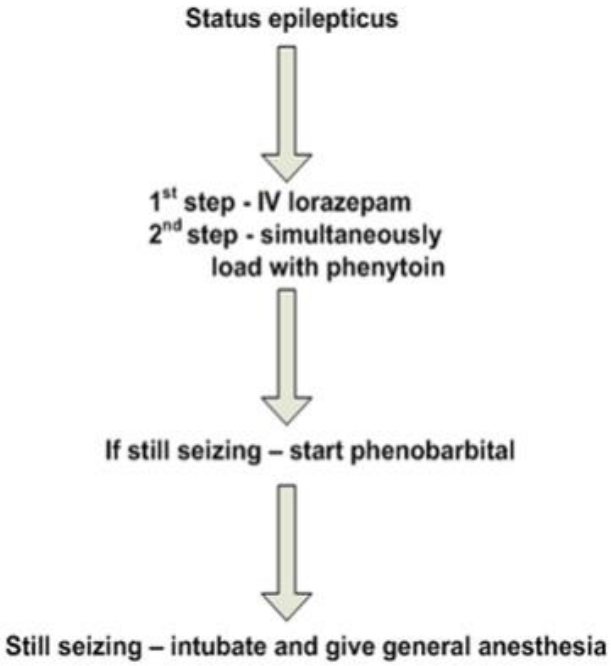
- Treatment of status epilepticus should be started immediately. It consists of the following:

1. Benzodiazepines are the first line drugs for management of status epilepticus. Lorazepam is the drug of choice.

2. Phenytoin (fosphenytoin for parenteral use) is administered simultaneously to prevent the recurrence of seizures. Benzodiazepines are preferred to phenytoin for initial seizure management because benzodiazepines have more rapid onset of action. The onset of action of phenytoin is 15 minutes after IV infusion, but benzodiazepines begin working within a few minutes.

3. If seizures do not stop after benzodiazepines and phenytoin are administered, phenobarbital is indicated.

4. If still seizing intubate and give Midazolam, propofol, or inhaled anesthetics to induce a state of general anesthesia.

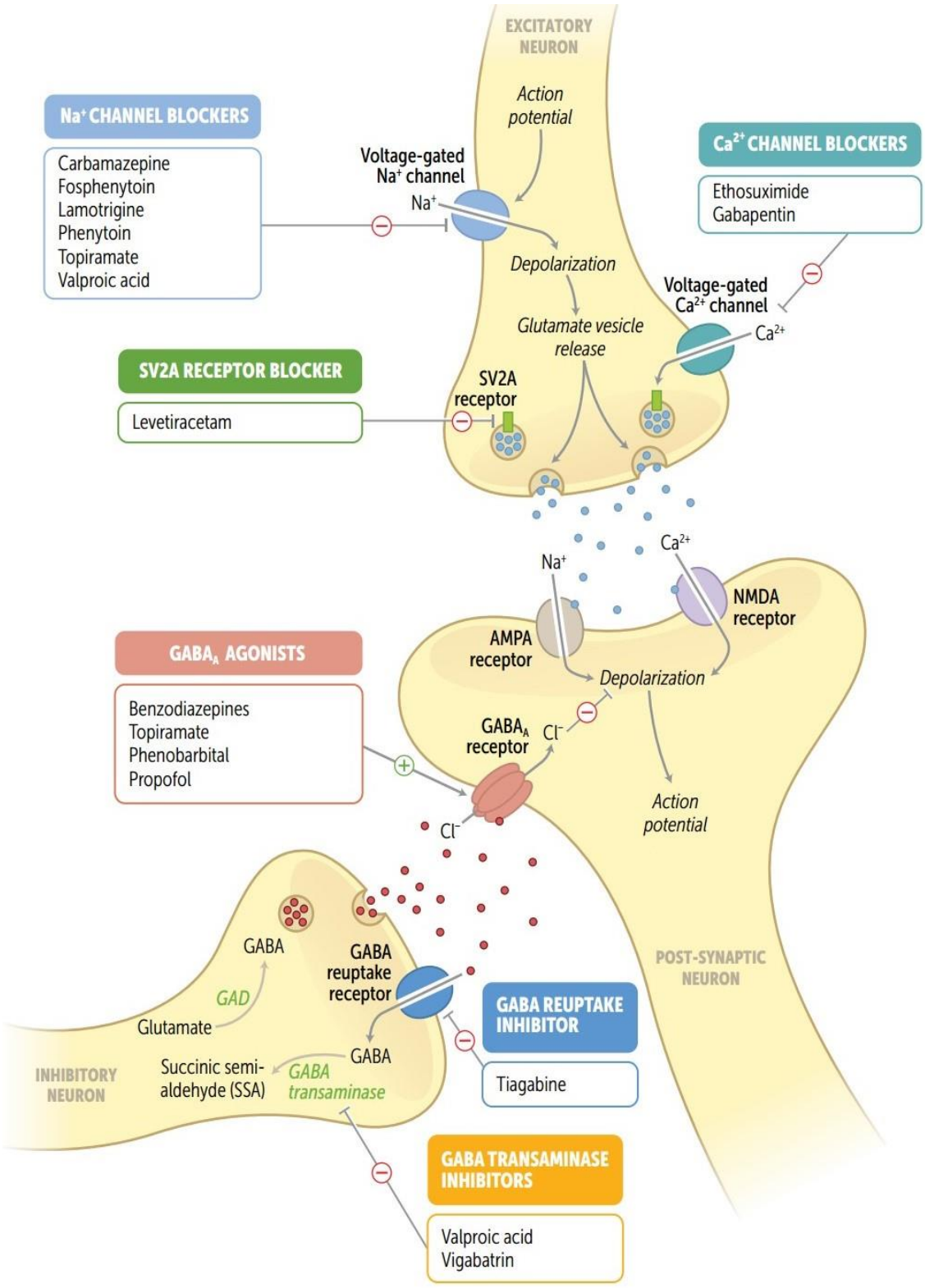


❖ N.B:

- Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare and potentially life-threatening drug reaction typically occurring 2-8 weeks after drug exposure.
- Commonly associated drugs include anticonvulsants (phenytoin, carbamazepine), allopurinol, sulfonamides (sulfasalazine), and antibiotics (minocycline, vancomycin).
- Although the exact mechanism is unknown, it likely involves drug-induced herpesvirus reactivation followed by clonal expansion of T cells that cross- react with the drug.
- Patients typically develop fever, generalized lymphadenopathy, facial edema, and diffuse morbilliform skin rash that can progress to a confluent erythema with follicular accentuation.
- Other affected organs can include the liver (hepatomegaly, jaundice), kidney (acute interstitial nephritis), and lung (cough, dyspnea).
- Laboratory studies usually show eosinophilia, atypical lymphocytosis, and elevated serum alanine transaminase.
- Clinical findings improve over several weeks following withdrawal of the drug.

Sedative – hypnotic – anxiolytic drugs

- Benzodiazepines and barbiturates cause dose dependent CNS depression that extends from sedation to anesthesia to respiratory depression and death.



Barbiturates

- Drugs:

- Phenobarbital, pentobarbital, and thiopental.

- Mechanism of action:

- Facilitate GABA action by ↑ duration of Cl channel opening, thus ↓ neuron firing (barbidurates ↑ duration).

- Clinical use:

- Sedative for anxiety, seizures (phenobarbital), insomnia, induction of anesthesia (thiopental).

- Toxicity:

- Respiratory and cardiovascular depression (can be fatal), CNS depression (can be exacerbated by EtOH use), dependence, drug interactions (induces cytochrome P-450).

- Overdose treatment is supportive (assist respiration and maintain BP).

- Contraindication:

- Contraindicated in porphyrias.

Benzodiazepine

- Drugs:

- Diazepam, lorazepam, triazolam, temazepam, oxazepam, midazolam, chlordiazepoxide, alprazolam.

- Mechanism:

- Facilitate GABA action by ↑ frequency of Cl channel opening →membrane hyperpolarization.

- ↓ REM sleep.

- Act through BZ receptors:
  - BZ_1 mediate sedation.
  - BZ_2 mediate antianxiety and impairment of cognitive functions.

- Most have long half-lives and metabolized by the liver to active metabolites except ATOM: Alprazolam, Triazolam, Oxazepam, and Midazolam are short acting → higher addictive potential.

- Clinical use:

- Anxiety, panic disorder, spasticity, status epilepticus (lorazepam), detoxification (especially alcohol withdrawal, DTs), night terrors, sleepwalking, general anesthetic (amnesia, muscle relaxation), hypnotic (insomnia).

- Lorazepam, Oxazepam, and Temazepam can be used for those with liver disease who drink a LOT due to minimal first-pass metabolism.

▪ Toxicity:

- Dependence, additive CNS depression effects with alcohol and barbiturates (all bind the GABAA receptor).

- Less risk of respiratory depression and coma than with barbiturates.

- Treat overdose with flumazenil (competitive antagonist at GABA benzodiazepine receptor).

❖ N.B:

▪ Benzodiazepines, barbiturates, and EtOH all bind the GABA receptor, which is a ligand-gated Cl channel.
▪ As a class, all benzodiazepines should be excluded from use in conjugation with alcohol, barbiturates, neuroleptics, or 1st generation antihistamines (additive CNS depression).
▪ First generation H1 histamine receptor antagonists, including diphenhydramine and chlorpheniramine cause significant sedation (easily penetrate the BBB and accumulate in CNS), especially when used with other medication that cause CNS depression (as Benzodiazepines).

Nonbenzodiazepine hypnotics

▪ Drugs: Zolpidem, Zaleplon, esZopiclone. "All ZZZs put you to sleep".

▪ Mechanism of action:

- Zolpidem is a short-acting hypnotic agent structurally unrelated to benzodiazepines.

- Despite chemical difference, the mechanism of action of zolpidem and benzodiazepines is similar, both bind to the same portion of the GABA A on the CNS (BZ_1 subtype).

- Effects reversed by flumazenil.

▪ Clinical use:

- Insomnia. It has a rapid onset of action (15 min after administration).

▪ Adverse effects:

- Ataxia, headaches, and confusion.

- It has the following important properties in comparison to benzodiazepines (because they act on BZ_1, not BZ_2, So, it avoids the impairment of cognition side effects of BZ_2):

1. Less potential for tolerance and addiction.
2. No anticonvulsant properties.
3. No muscle relaxing effects.
4. Not used for anesthesia.

Suvorexant

- Mechanism of action:

- Orexin (hypocretin) receptor antagonist.

- Suvorexant is an orexin antagonist.

- Clinical use: Insomnia.

- Adverse effects: CNS depression (somnolence), headache, abnormal sleep-related activities.

- Contraindications:

- Narcolepsy, combination with strong CYP3A4 inhibitors.
- Not recommended in patients with liver disease.
- Limited physical dependence or abuse potential.

Ramelteon

- Mechanism of action:

- Melatonin receptor agonist; binds MT1 and MT2 in suprachiasmatic nucleus.

- Ramelteon is a melatonin receptor agonist.

- Clinical use: Insomnia.

- Adverse effects:

- Dizziness, nausea, fatigue, headache.
- No dependence (not a controlled substance).

General principles of anesthesia

- CNS drugs must be lipid soluble (cross the blood-brain barrier) or be actively transported.
- The onset of anesthesia occurs when a sufficient quantity of anesthetics is transferred to the brain.
- Before gas anesthetics can reach the target organ (brain), they must move through a number of compartments (inhaled air → lungs → blood → brain).
- In blood: solubility of the anesthetic in the blood is called (blood/gas partition coefficient). Higher blood solubility means that more anesthetics must be absorbed by the blood before it can be effectively transferred to other tissues.
- The arteriovenous concentration gradient is the difference between the concentration of a gas anesthetic in arterial and venous blood. The solubility of the anesthetic in the peripheral tissues is a major factor in determining the size of the arteriovenous gradient.
- If tissue solubility is high, a large amount of anesthetic is taken up from the arterial blood, which results in low venous concentration. As a result, saturation of the blood requires further absorption of anesthetic in order to replace that which is absorbed by the peripheral tissues. Because blood saturation takes longer, brain saturation is also delayed and onset of action is slower.
- So, the speed of anesthetic induction is determined by the rate at which the brain tissue take up the agent, which depend on the solubility of the anesthetic in the blood. If an agent has poor blood solubility (low blood/gas partition coefficient), the amount of gas needed to saturate the blood is small and brain saturation occurs quickly. Conversely, highly soluble anesthetics (high blood/gas partition coefficient) are absorbed to a greater degree by the blood, delaying the saturation of the brain.

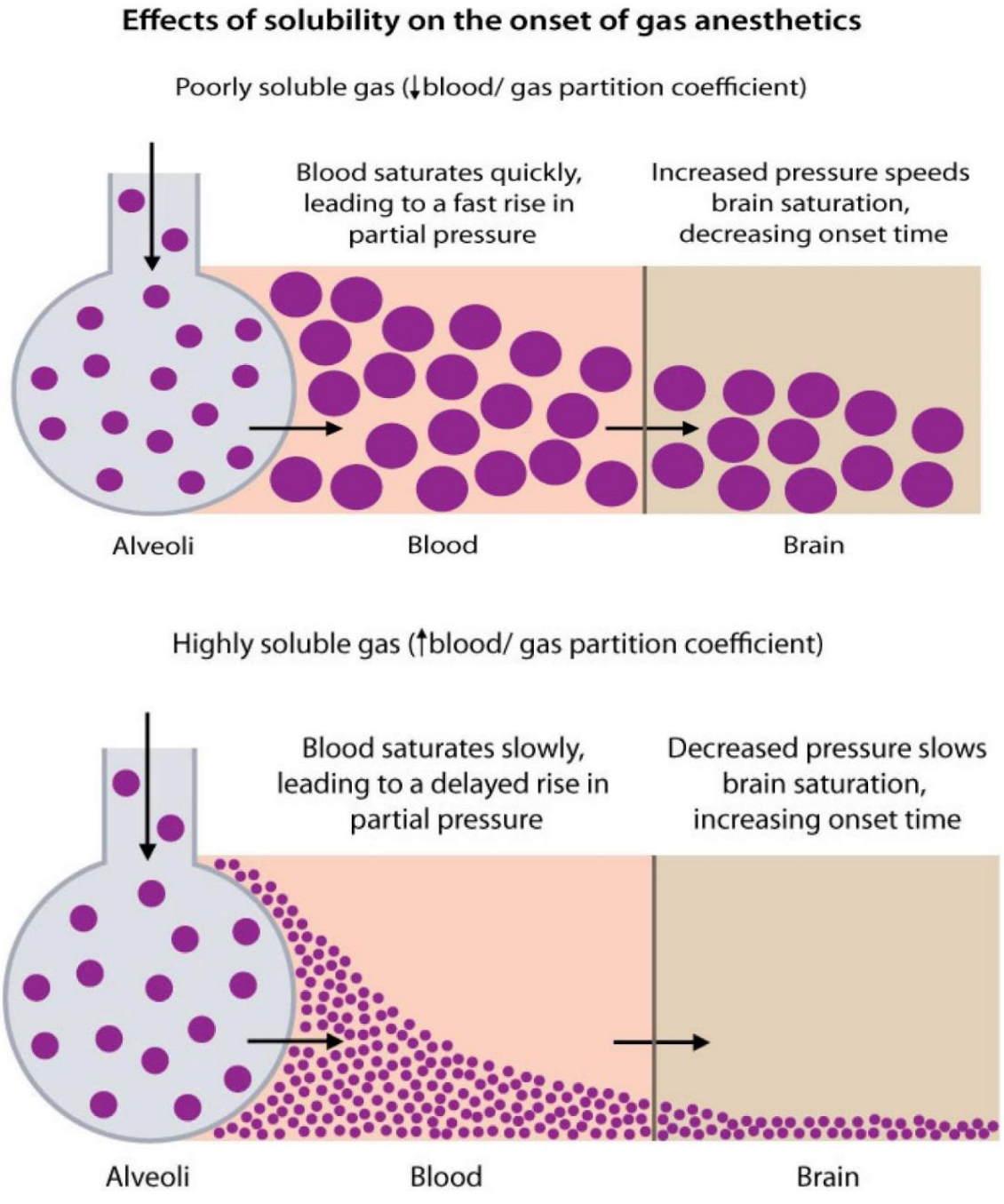
❖ In a nutshell:

- Rates of onset and recovery depend on the blood/gas ratio:
  - The more soluble the anesthetic in the blood, the slower the anesthesia.
  - Anesthetics with high blood/gas ratios are associated with slow onset and slow recovery.
  - Anesthetics with low blood/gas ratios are associated with fast onset and recovery.
  - The rule is: The lower the number of the blood/gas ratio, the faster the onset and recovery.
- MAC= Minimal Alveolar Concentration of inhaled anesthetic required to prevent 50% of subjects from moving in response to noxious stimulus (skin incision). MAC is a measure of potency ED50.
- The potency of the drug depends on the lipid solubility. The more lipid soluble the anesthetic, the lower the MAC and the greater the potency.
- The rule is the lower the MAC value (ED50), the more potent the drug is.

- Examples:

- Nitrous oxide (NO) has ↓ blood and lipid solubility, and thus fast induction and low potency.

- Halothane, in contrast, has ↑ lipid and blood solubility, and thus high potency and slow induction.



Inhaled anesthetics

- General anesthesia cause loss of consciousness, analgesia, amnesia, skeletal muscle relaxation and inhibition of reflexes. This complex of symptoms occurs due to inhibition of electrical activity of neurons.

- Most inhalation anesthetics as barbiturates and benzodiazepines achieve CNS depression by influencing GABA receptors and increasing the inhibitory action of GABA.

- Inhalation anesthetics affect almost all organ systems of the body. Almost all of them increase cerebral blood flow which is undesirable effect as it results in increased ICP. Other important effects are myocardial depression, hypotension, respiratory depression and decreased renal function.

- Drugs: Halothane, enflurane, isoflurane, sevoflurane, methoxyflurane, NO (anes + nitric oxide).

- Mechanism: unknown.

- Toxicity:

- Hepatotoxicity (Halothane), nephrotoxicity (methoxyflurane), proconvulsant (enflurane), expansion of trapped gas in a body cavity (NO).

- Massive hepatic necrosis is a rare but severe complication of halothane exposure. It occurs due to direct liver injury by halothane metabolites and formation of autoantibodies against liver proteins. Light microscopy shows massive centrilobular hepatic necrosis.

- Can cause malignant hyperthermia (halothane).

❖ Malignant hyperthermia:

- Occurs after administration of inhalation anesthetics especially halothane (except NO) or succinylcholine to genetically susceptible individuals.

- Genetic susceptibility may be related to mutations in the genes encoding the ryanodine receptors (calcium channel) of sarcoplasmic reticulum. It releases small amounts of calcium in the cytoplasm of the muscle fiber during muscle contraction.

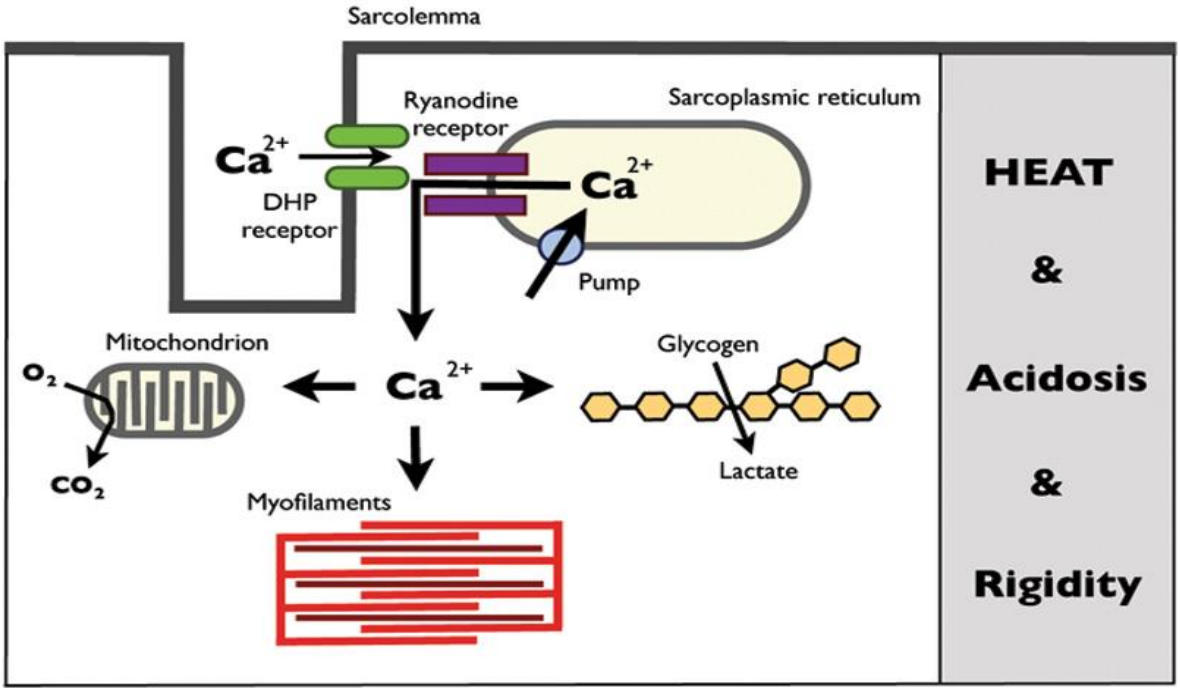
- Abnormal ryanodine receptors release large amount of Ca after exposure to anesthetic → Excess of free Ca in the cytoplasm of muscle fibers stimulates its ATP-dependent reuptake by sarcoplasmic reticulum → Excessive consumption of ATP generates heat, loss of ATP along with high temperature induces → muscle damage (Rhabdomyolysis) → release of potassium, myoglobin, and creatine kinase into circulation.

- Clinically, malignant hyperthermia presents with fever and muscle rigidity soon after surgery under general anesthesia. Tachycardia, hypertension, hyperkalemia, acidosis and myoglobinuria are characteristic.

- Treatment:

- Malignant hyperthermia is a life-threatening condition and should be treated promptly.

- Dantrolene is a muscle relaxant effective in malignant hyperthermia. It acts on ryanodine receptor → prevents further release of Ca into the cytoplasm of muscle fibers.



Intravenous anesthetics

- GABA (gamma-aminobutyric acid) is the main inhibitory neurotransmitter in the central nervous system. There are three types of GABA receptors (GABA A, GABA B, GABA C). Activation of each type of receptor ultimately leads to neuron hyperpolarization (inhibition).

- Benzodiazepines, Barbiturates, and alcohol all bind to different components of the GABA A receptor and facilitate the inhibitory action of GABA in the CNS.

1. Barbiturates (Thiopental):

- Thiopental: high lipid solubility, high potency, rapid entry into brain.

- Used for induction of anesthesia and short surgical procedures.

- In a pharmacological study, Researchers found that awakening from thiopental occurred because the plasma level rapidly declined. The cause of the rapid plasma decay of thiopental was not metabolism of the drug but rather redistribution of the drug to other tissues throughout the body (skeletal muscles and adipose tissue). This rapid clearance leads to recovery from anesthesia.

- Phenobarbital and other barbiturates can induce hepatic microsomal enzymes (cytochrome P450 inducer) → increasing metabolism and clearance of other drugs, decreasing its therapeutic effect.

- No antidote for thiopental.

2. Benzodiazepines (Midazolam):

- Benzodiazepines act by allosterically binding to the GABA A receptor and stimulating the influx of chloride ions into the neurons by increasing the frequency of ion channel opening → neuronal hyperpolarization.

- Midazolam most common drug used for endoscopy and outpatient surgeries, used adjunctively with gaseous anesthetics and narcotics. May cause severe postoperative respiratory depression, ↓ BP, anterograde amnesia.

- Treat overdose with flumazenil.

3. Propofol:

- Used for sedation in ICU, rapid anesthesia induction, short procedures.

- Potentiates GABA A effect.

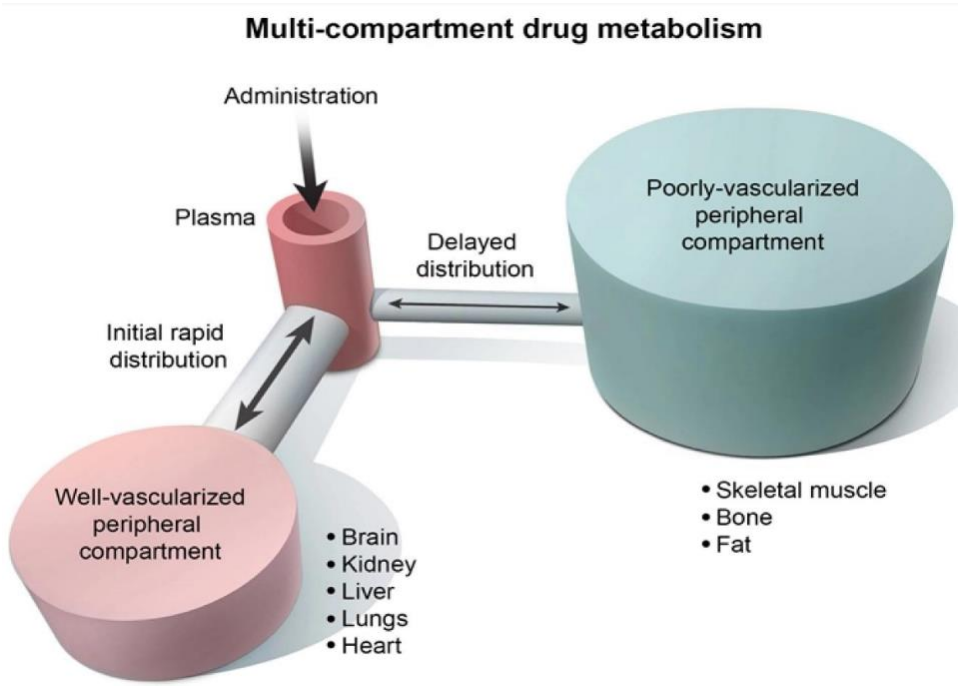
- Less postoperative nausea than thiopental (antiemetic).

4. Arylcyclohexylamines (Ketamine):

- PCP analogs that act as dissociative anesthetics (no sensory input).
- Block NMDA receptors.
- Cardiovascular stimulants.
- Cause disorientation, hallucination, bad dreams.
- ↑ cerebral blood flow.

❖ N.B:

- Drug distribution is not uniform; the rate at which drugs are delivered to target tissues is dependent on several factors, such as regional blood flow and drug characteristics.
- The pharmacokinetic profile of highly lipophilic anesthetic drugs, such as propofol, can be predicted using a multi-compartment model of distribution.
- Following administration of a single intravenous bolus, drug levels are high in the central compartment (plasma).
- However, the drug is quickly distributed to the well-vascularized peripheral compartment (brain, liver, kidneys, lungs) due to the increased lipophilicity of the tissues compared to the blood.
- Overtime, drug redistribution will occur through the central compartment into the poorly vascularized peripheral compartment (skeletal muscle, fat, bone), which has the highest volume of distribution for lipophilic agents.
- Redistribution occurs rapidly with highly lipophilic drugs and is responsible for the short duration of action seen with commonly used anesthetics such as propofol.



Local anesthetics

- Drugs:

- All local anesthetics are caines.

- Esters: procaine, cocaine, tetracaine (esters have just one i in their names) are metabolized by plasma and tissue esterases.

- Amides: lIdocaIne, mepIvacaIne, bupIvacaIne (amIdes have 2 I's in name) are metabolized by liver amidases.

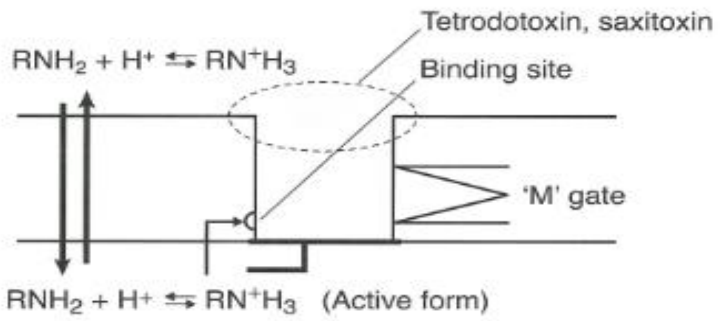
- Mechanism of action:

- Block Na channels by binding to specific receptors on inner portion of channel. Preferentially bind to inactivated Na channels keeping them in this inactive state.

- All local anesthetics are weak bases with pka near 8. So, they will be in 2 forms, ionized and non-ionized. The ionized form is the active form.

- Most ph. of our body is lower than 8 → acidic medium. In acidic medium, there is a lot of H ions, so most of the weak bases drugs in acidic medium will be in the ionized form (active form), and a less amount will be in the non-ionized form. But ionized form of the drug cannot cross the membrane and only non-ionized form can cross the membrane. So, less amount of the local anesthetics (non-ionized form) cross the membrane then converted to the ionized form (active form) that bind to the inactive Na channels keeping them in the inactive state. Every time small amount of the non-ionized form of the drug cross the membrane, some of the ionized drug will become nonionized to set a new equilibrium between the ratio of ionized form and non-ionized form.

- In infected tissue (more acidic medium), alkaline anesthetics are more charged, So you will need more anesthetic and long duration to get anesthetic effect in infected tissues.



- Principle: Can be given with vasoconstrictors (usually epinephrine) to enhance local action: ↓ bleeding, ↑ anesthesia by ↓ systemic concentration.

- Order of nerve blockade:

- Small-diameter fibers > large diameter.

- Myelinated fibers (high firing rate nerve fibers) > unmyelinated fibers.

- Overall, size factor predominates over myelination such that small myelinated fibers > small unmyelinated fibers > large myelinated fibers > large unmyelinated fibers

- Order of loss: (1) pain, (2) temperature, (3) touch, (4) pressure, recovery is in reverse order.

- Clinical use:

- Minor surgical procedures, spinal anesthesia.

- If allergic to esters, give amides.

- Toxicity:

- CNS excitation, severe cardiovascular toxicity (bupivacaine), hypertension, hypotension, arrhythmias (cocaine), methemoglobinemia (benzocaine).

Neuromuscular blocking drugs

- Muscle paralysis in surgery or mechanical ventilation. Selective for motor (vs. autonomic) nicotinic receptor.

- Nicotinic receptors have 5 subunits. Two acetyl choline bind to two alpha subunits in order to open Na channel → depolarization of the muscle. It interacts with N_m receptors at the neuromuscular junction.

1. Depolarizing (non-competitive) nicotinic agonist:

- Drugs:

- Succinylcholine, strong ACh receptor agonist, produces sustained depolarization followed by desensitization and prevents muscle contraction.

- Reversal of blockade:

- Phase I (prolonged depolarization): no antidote. AChE inhibitors may even potentiate phase I.

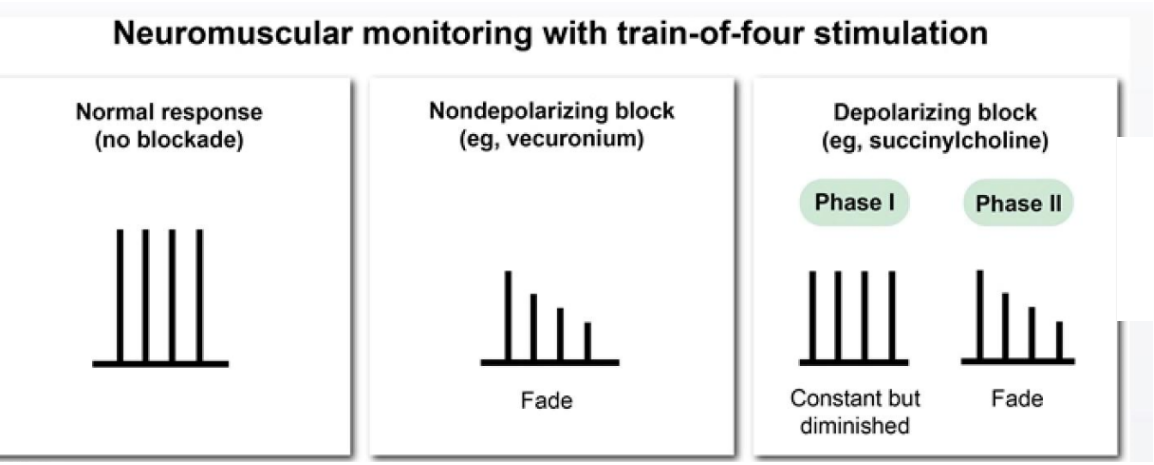
- Phase II: desensitization (receptors are not responsive any more) → no muscle contraction. ACh receptors are available but desensitized. AChE inhibitors may reverse phase II.

- Succinylcholine is actually rapidly hydrolyzed by pseudocholinesterase → short duration.

- There may be a genetic defect leads to atypical pseudocholinesterase → no metabolism of succinylcholine → long recovery and may need ventilator support after the operation.

- Complications:

- Include hypercalcemia, hyperkalemia (it's a Na / K ion channel, and because the succinylcholine keeps the channel in sustained depolarization in phase I → The channel stays open and K leaks out of muscle cells), malignant hyperthermia.



2. Nondepolarizing (competitive) nicotinic antagonists:

- Drugs:

- Tubocurarine, atracurium, mivacurium, pancuronium, vecuronium, rocuronium (nondepolarizing drugs have "curium" or "coronium" suffix), competitive antagonists, compete with ACh for receptors.

- Reversal of blockade:

- Acetyl choline esterase inhibitors as neostigmine (must be given with atropine to prevent muscarinic effects such as bradycardia), edrophonium, and other cholinesterase inhibitors.

❖ N.B:

- Myasthenia gravis (MG) is caused by autoantibodies against postsynaptic nicotinic acetylcholine receptors (AChRs), leading to fewer functional AChRs and fatigable muscle weakness.
- Nondepolarizing neuromuscular blocking agents (vecuronium) are competitive antagonists of AChRs; due to the depletion of receptors, patients with MG are extremely sensitive to these agents and very small doses can induce paralysis and impair airway protection.

Dantrolene

- Mechanism of action:

- Prevents release of Ca from the sarcoplasmic reticulum of skeletal muscle by inhibiting the ryanodine receptor.

- Clinical use:

- Malignant hyperthermia and neuroleptic malignant syndrome (a toxicity of antipsychotic drugs).

Baclofen

- Mechanism of action:

- Inhibits $GABA_B$ receptors at spinal cord level, inducing skeletal muscle relaxation (centrally acting skeletal muscle relaxant).

- Clinical use:

- Muscle spasms or spasticity (acute low back pain).

Cyclobenzaprine

- Mechanism of action:

- Centrally acting skeletal muscle relaxant.
- Structurally related to TCAs, similar anticholinergic side effects.

- Clinical use:

- Muscle spasm.

Tizanidine

- Mechanism of action:

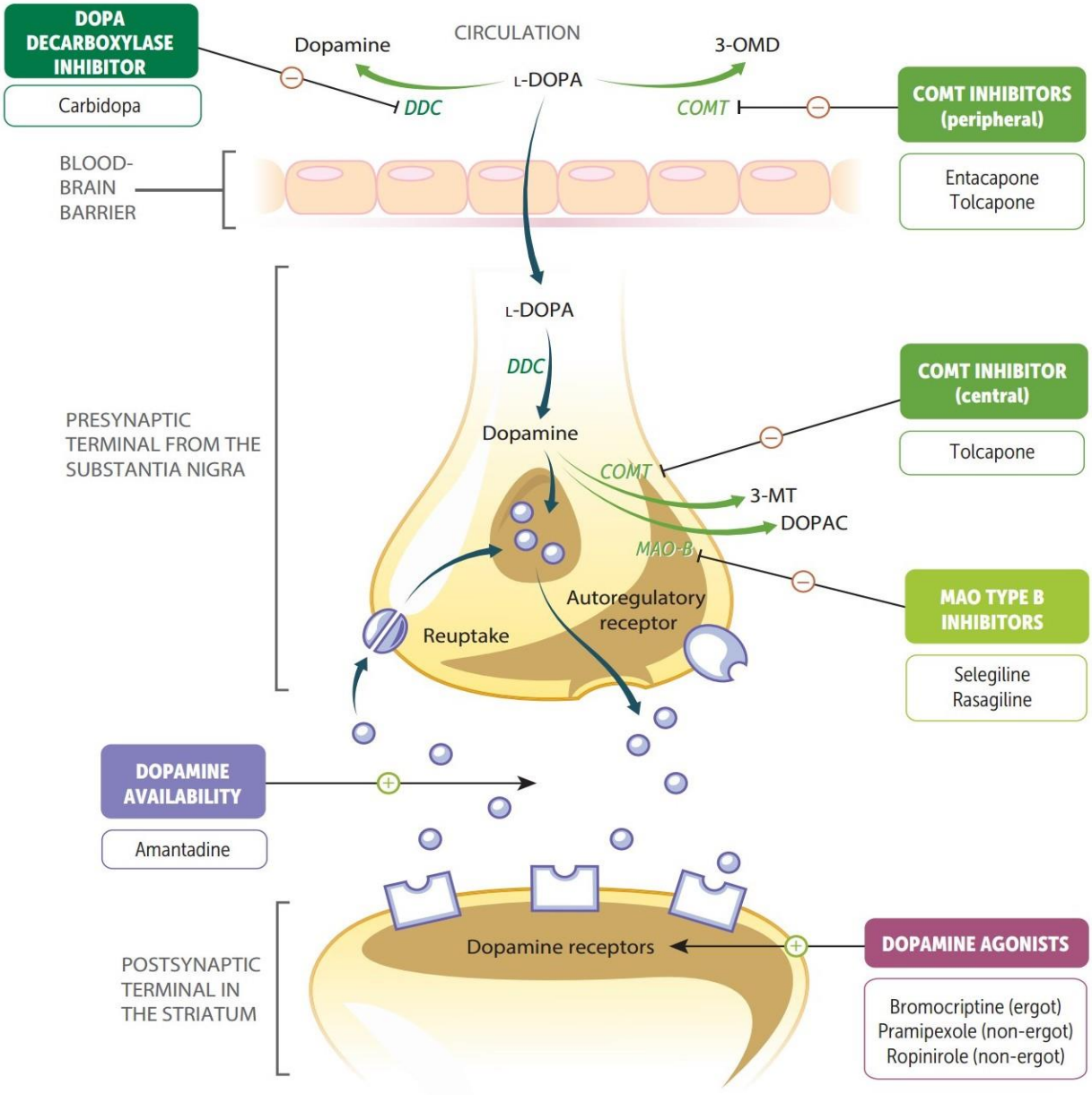
- α_2 agonist, acts centrally.

- Clinical use:

- Muscle spasticity, multiple sclerosis, ALS, cerebral palsy.

Parkinson disease drugs

- Parkinsonism is due to loss of dopaminergic neurons and excess cholinergic activity.



- <u>Parkinson disease drugs are BALSA:</u>

- Bromocriptine.
- Amantadine.
- Levodopa (with carbidopa).
- Selegiline (and COMT inhibitors).
- Antimuscarinic.

1. Dopamine agonists

- Dopamine agonists have a chemical structure similar to the neurotransmitter dopamine and directly stimulate dopamine receptors.

- There are two classes of dopamine agonists:
- Ergot compounds: Bromocriptine and pergolide.
- Non-ergot compounds: pramipexole and ropinirole.

- Dopamine agonists have an important role in the treatment of Parkinson disease because these medications have a long half-life and prolong the effects of levodopa, thus limiting motor fluctuations.

- Bromocriptine also treats hyperprolactinemia.

- Pramipexole and ropinirole are used also in the treatment of restless leg syndrome.

- Side effects: dyskinesia and psychosis.

2. ↑ Dopamine Availability

- Amantadine (↑ dopamine release and ↓ dopamine reuptake), also used as an antiviral against influenza A and rubella.

- Toxicity:
- Peripheral edema, Ataxia, livedo reticularis

3. ↑ L-Dopa Availability

- Mechanism of action:
- Levodopa is the immediate precursor of dopamine, a neurotransmitter that is absent in the Nigrostriatum of patients with Parkinson's disease.

- Dopamine itself cannot be administered directly because it is unable to cross the BBB.

- Levodopa, the precursor of dopamine, however, can cross the BBB.

- Unfortunately, levodopa is rapidly metabolized in the peripheral tissues and only small percentage reaches the brain. Thus, levodopa has tradionally been administered with carbidopa (a peripheral dopa decarboxylase inhibitor) to ↑ the bioavailability of L-dopa in the brain and to limit peripheral side effects (nausea & vomiting).

- Anxiety and agitation are central effects of dopamine and are caused by L-dopa, regardless of whether carbidopa is added to levodopa treatment. In fact, anxiety and agitation can be increased because more dopamine is available to the brain.

- Even with carbidopa, however, only 5-10% of levodopa reaches the brain. Because one of the main enzymes responsible for this peripheral catabolism of levodopa is Catechol-O-Methyl-Transferase (COMT).

- Entacapone is a COMT inhibitor that primarily serves to increase the bioavailability by inhibiting peripheral methylation.

- Tolcapone is another COMT inhibitor that inhibit both peripheral and central methylation. Unlike entacapone, tolcapone has been associated with hepatotoxicity.

▪ Clinical use:
- Parkinson disease.

▪ Side effects:
- Dyskinesia, psychosis and vomiting.

▪ Toxicity:
- Arrhythmias from ↑ peripheral formation of catecholamines. Long-term use can lead to dyskinesia following administration ("on-off" phenomenon), akinesia between doses.

❖ N.B:

1. Most over-the-counter vitamins contain B6. Vitamin B6 supplementation should not be taken by those on levodopa therapy, because B6 increases the peripheral metabolism of levodopa and decreases its effectiveness. The more peripheral conversion of levodopa, the less levodopa enters the CNS.

2. The "on-off" phenomenon:

▪ It is an unpredictable and dose-independent characteristic of advanced Parkinson disease. There is no clear etiology for this phenomenon.

▪ L-dopa is usually administered several times per day. If the L-dopa dosage is high enough to be effective, the patient is in an "on" period. During an "on" period, the patient is mobile and usually feels well. However, during an "off" period, a patient's status may actually be worse than if the patient had taken no L-dopa at all.

▪ It has been found that if the dose is kept constant the "on-off" effect is minimized.

4. Prevent dopamine breakdown

- Agents act centrally (post-BBB) to block breakdown of dopamine → ↑ available dopamine:

- Selegiline blocks conversion of dopamine into 3-MT by selectively inhibiting MAO-B.
- Tolcapone: blocks conversion of dopamine to DOPAC by inhibiting central COMT.

- Mechanism of action: Selectively inhibits MAO-B, which preferentially metabolizes dopamine over norepinephrine and 5-HT, thereby ↑ the availability of dopamine.

- Clinical use: Adjunctive agent to L-dopa in treatment of Parkinson disease.

- Toxicity: May enhance adverse effects of L-dopa.

5. Curb excess cholinergic activity

- Benztropine and trihexyphenidyl (Antimuscarinic, improves tremor and rigidity but has little effect on bradykinesia).

❖ Drug-induced parkinsonism:

- A type of extrapyramidal symptom which is most often due to first-generation antipsychotic medications due to dopamine (D_2) receptor blockade in the nigrostriatal pathway.

- Centrally-acting antimuscarinic drugs (trihexyphenidyl, Benztropine) are the preferred treatment for drug-induced parkinsonism after discontinuing the offending medication.

- Levodopa and dopamine agonists are contraindicated for antipsychotic-induced parkinsonism as they can precipitate psychosis.

Alzheimer drugs

- Current Alzheimer's disease specific therapies include:

1. Enhanced cholinergic neurotransmission.
- Ex: cholinesterase inhibitors (Donepezil).

2. Antioxidants (vitamin E).

3. NMDA receptor antagonists (memantine).

Donepezil, galantamine, rivastigmine, tacrine

- 1st-line treatment.
- Mechanism of action: AChE inhibitors.
- Toxicity: Nausea, dizziness, insomnia.

Memantine

- Mechanism of action:

- NMDA receptor antagonist, it is thought that CNS NMDA-receptor overstimulation by glutamate may contribute to AD symptoms.

- Toxicity:

- Dizziness, confusion, hallucinations.

Huntington disease drugs

- Neurotransmitter changes in Huntington disease: ↓ GABA, ↓ Ach, ↑ dopamine.
- Tetrabenazine: inhibit vesicular monoamine transporter (VMAT), limit dopamine vesicle packaging and release.

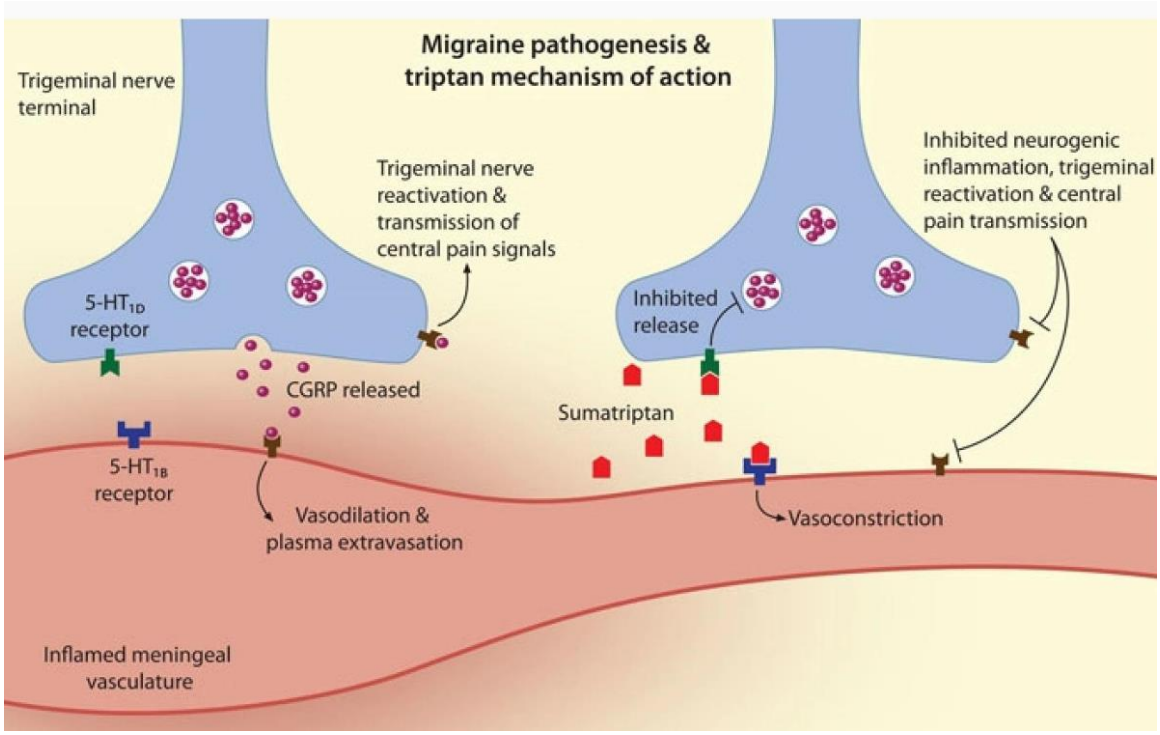
Triptans (Sumatriptan)

- Mechanism of action:

- The pain during migraine is due to activation of trigeminal afferents that innervates the meninges, this causes release of vasoactive neuropeptides, including substance P and calcitonin gene related peptide → neurogenic inflammation due to vasodilatation and plasma protein extravasation.

- 5-HT agonists that directly counter the pathophysiologic mechanism of migraine headaches by inhibiting the release of vasoactive peptides → vasoconstriction and blocking pain pathways in the brain stem.

- They are commonly prescribed as abortive therapy for the outpatient treatment of acute migraines, particularly in patients who are not responsive to analgesics.



- Clinical use:

- Acute migraine, cluster headache attacks.

- Toxicity:

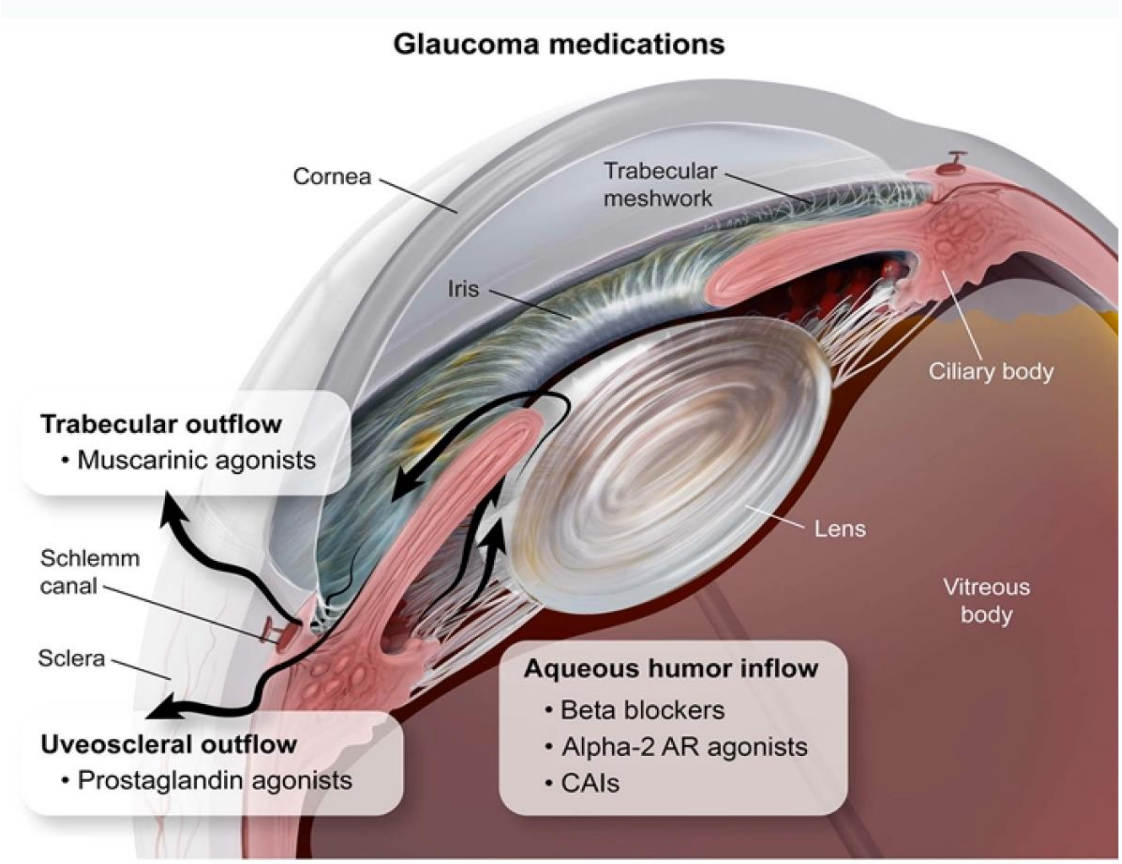
- Coronary vasospasm (contraindicated in patients with CAD or Prinzmetal angina), mild paresthesia, serotonin syndrome (in combination with other 5-HT agonists).

Glaucoma drugs

- Aqueous humor is produced by the epithelial cells of the ciliary body.

- It is excreted into the posterior eye chamber and transferred through the pupil into the anterior eye chamber. The anterior chamber angle (iridocorneal angle) contains a trabecular meshwork through which the aqueous humor diffuses into the Schlemm's canal (scleral venous sinuses). Schlemm's canal drains into episcleral and conjunctival veins.

- Glaucoma is a chronic eye disease characterized by increased intraocular pressure. It develops due to diminished outflow or increased secretion of the aqueous humor.



Alpha-2 AR agonists = alpha-2 adrenergic receptor agonists; **CAIs** = carbonic anhydrase inhibitors.

A. Narrow (Closed) angel glaucoma:

- An acute painful ↑ IOP due to block of canal of Schlemm.

- Antimuscarinic drugs and alpha agonists are contraindicated in closed angle glaucoma → mydriasis → impairment of outflow of aqueous humor.

- Emergency drug management prior to surgery usually involves cholinomimetics, carbonic anhydrase inhibitors and/or mannitol.

B. Open angel glaucoma:

- ↑ IOP due to ↓ reabsorption of aqueous humor → painless vision loss and blindness.

- Treatment of open angle glaucoma includes the use of beta blockers to decrease formation of fluid by ciliary epithelial cells and the use of muscarinic agonists to improve drainage through the canal of Schlemm.

- Both types of glaucoma can ultimately lead to blindness.

- Drugs that cause miosis as cholinomimetics improve outflow drainage, in contrast, drugs that cause mydriasis aggravate closed angel glaucoma.

- The drugs used to treat glaucoma either decrease the production of aqueous humor or increase its outflow.

- Timolol and other non-selective beta blockers work by diminishing the secretion of aqueous humor by the ciliary epithelium.

- Acetazolamide, a carbonic anhydrase inhibitor, also decreases aqueous humor secretion by the ciliary epithelium.

- Prostaglandin (latanoprost) and cholinomimetics (pilocarpine, carbachol) decrease intraocular pressure by increasing the outflow of the aqueous humor.

1. α-agonists (Epinephrine α1, Brimonidine α2)

- Mechanism of action:

- ↓ aqueous humor synthesis via vasoconstriction (epinephrine).

- ↓ aqueous humor synthesis (brimonidine).

- Side effects:

- Mydriasis (α1) do not use in closed-angle glaucoma.

- Blurry vision, ocular hyperemia, foreign body sensation, ocular allergic reactions, ocular pruritus.

2. B blockers (Timolol, betaxolol, carteolol)

- Mechanism of action:

- ↓ aqueous humor synthesis by ciliary epithelium.

- Side effects: No pupillary or vision changes.

3. Diuretics (Acetazolamide)

- Mechanism of action:
- ↓ aqueous humor synthesis via inhibition of carbonic anhydrase.

- Side effects:
- No pupillary or vision changes.

4. Cholinomimetics

A. Direct (pilocarpine, carbachol):

- Mechanism of action:
- ↑ outflow of aqueous humor via contraction of ciliary muscle and opening of trabecular meshwork.

- Use pilocarpine in emergencies very effective at opening meshwork into canal of Schlemm.

B. Indirect (physostigmine, echothiophate):

- Mechanism of action:
- ↑ outflow of aqueous humor via contraction of ciliary muscle and opening of trabecular meshwork.

- Side effects of cholinomimetics:
- Miosis and cyclospasm (contraction of ciliary muscle).

5. Prostaglandin (Latanoprost, PGF2)

- Mechanism of action:
- ↑ outflow of aqueous humor via ↓ resistance of flow through uveoscleral pathway.

- Side effects:
- Darkens color of iris (browning).