SAQs

{ ومن لم يذق مرّ التعلُّمِ ساعةً.. تجرع ذلَّ الجهل طوال حياتهِ }

References: Team Work + Pathoma.

Cell injury

- **Markers of CNS injury:**
  - Red Neuron.
  - Intra cellular inclusions.
  - Dystrophic neurites
- **Markers of Axonal injury:**
  - **Axonal injury:**
    - Spheroids.
    - Disruption of axonal transport.
    - Central chromatolysis.
  - **Diffuse axonal injury:**
    - Wide, asymmetric distribution of axonal swelling.
    - 50% of patients develop coma.
- **Cerebral Edema:**
  - **Vasogenic:**
    - The integrity of the normal blood-brain barrier is disrupted, allowing fluid to shift from the vascular compartment into the extracellular spaces of the brain.
  - **Cytotoxic:**
    - An increase in intracellular fluid secondary to neuronal and glial cell membrane injury, as might follow generalized hypoxic-ischemic insult or after exposure to some toxin.
- **Astrocyte injury and repair:**
  - Gliosis.
  - Nucleus enlarges and vesicular.
  - Nucleolus is prominent.
  - **Gemistocytic astrocyte:**
    - Scant cytoplasm expands to a bright pink.
    - Numerous stouts.
    - Ramifying processes
  - **Fibrillary astrocytes:**
    - Less distinct cytoplasm and appear more fibrillar .

- **Oligodendrocytes in Injury and Repair:**
  - Produce myelin.
  - **Progressive multifocal leukoencephalopathy:**
    - Viral inclusions can be seen in oligodendrocytes, with a smudgy, homogeneous-appearing enlarged nucleus.

- **Ependymal cells in Injury and Repair:**
  - Line the ventricular system and the central canal of the spinal cord.
  - Cytomegalovirus (CMV), can produce extensive ependymal injury, with typical viral inclusions.

- **Microglia in Injury and Repair:**
  - **Microglia:**
  - Bone marrow-derived cells.
  - Function as the phagocytes of the CNS.
  - When activated, they proliferate and become more evident.
  - Elongated nuclei (*rod cells*) in neurosyphilis or other infections.

- **Markers for peripheral nerve injury:**
  - **Axonal neuropathy:**
    - Directly injured axon.
    - Wallerian degeneration.
    - Decrease in the density of axons.
  - **Segmental demyelination:**
    - Damage to Schwann cells or myelin
    - Individual myelin internode.

- **Corpora Amylacea:**
  Small hyaline masses of unknown significance found in the prostate gland, pulmonary alveoli and neuroglia.

CNS Tumors

- **Basic Principles:**
  - Can be metastatic (50%) or primary (50%)
  - **Metastatic tumors** characteristically present as multiple, well-circumscribed lesions at the gray-white junction.
    - Lung, breast, and kidney are common sources.
  - **Primary tumors** are classified according to cell type of origin (e.g., astrocytes, meningothelial cells, ependymal cells, oligodendrocytes, or neuroectoderm).
    - In adults, primary tumors are usually supratentorial.
    - Most common tumors in adults are glioblastoma multiform, meningioma, and schwannoma.
    - In children, primary tumors are usually infratentorial.
  - Most common tumors in children are **pilocytic astrocytoma**, **ependymoma**, and **medulloblastoma**.
  - Primary malignant CNS tumors are locally destructive, but **rarely metastasize.**
- **Glioblastoma Multiform (GBM):**
  - **Malignant**, high-grade tumor of astrocytes
  - Most common primary malignant CNS tumor in adults
  - Usually arises in the **cerebral hemisphere;** characteristically crosses the corpus callosum ('butterfly' lesion)
  - Characterized by regions of **necrosis** surrounded by tumor cells (pseudopalisading) and endothelial cell proliferation; tumor cells are GFAP positive.
  - Poor prognosis.

- **Meningioma:**
    - Benign tumor of arachnoid cells.
    - **Most common** benign CNS tumor in adults.
    - More commonly seen **in women**; rare in children.
    - May present as seizures; tumor compresses, but does not invade, the cortex.
    - Imaging reveals a round mass attached to the dura.
    - Histology shows a **whorled pattern; psammoma bodies may be present.**
- **Schwannoma:**
    - Benign tumor of Schwann cells.
    - Involves cranial or spinal nerves; within the cranium, most frequently involves cranial nerve VIII at the cerebellopontine angle (presents as loss of hearing and tinnitus).
    - Tumor cells are S-100 positive.
    - Bilateral tumors are seen in neurofibromatosis type 2.
- **Oligodendroglioma:**
    - Malignant tumor of **oligodendrocytes.**
    - Imaging reveals a **calcified** tumor in the white matter, usually involving the **frontal lobe**; may present with seizures
    - 'Fried-egg' appearance of cells on biopsy.

- **Pilocytic Astrocytoma**
  - Benign tumor of **astrocytes**
  - Most common CNS tumor in **children**; usually arises in the **cerebellum**
  - Imaging reveals a cystic lesion with a mural nodule.
  - Biopsy shows Rosenthal fibers (thick eosinophilic processes of astrocytes) and eosinophilic granular bodies; tumor cells are GFAP positive.
- **Medulloblastoma:**
  - Malignant tumor derived from the granular cells of the cerebellum (neuroectoderm)
  - Usually arises in children.
  - Histology reveals small, round blue cells; Homer-Wright rosettes may be present.
  - Poor prognosis; tumor grows rapidly and spreads via CSF.
  - Metastasis to the cauda cquina is termed 'drop metastasis.'
- **Ependymoma:**
  - Malignant tumor of ependymal cells; usually seen in children.
  - Most commonly arises in the 4th ventricle; may present with hydrocephalus.
  - Perivascular pseudorosettes are a characteristic finding on biopsy.

Multiple Sclerosis

- Autoimmune destruction of CNS myelin and oligodendrocytes 1.
- Most common chronic CNS disease of young adults (20-30 years of age); more commonly seen in women
- Associated with **HLA-DR2**
- More commonly seen in regions **away from the equator**
- Presents with relapsing neurologic deficits with periods of remission (multiple lesions in time and space). Clinical features include l. Blurred vision in one eye (optic nerve)
- Vertigo and scanning speech mimicking alcohol intoxication **(brainstem)**
- Internuclear ophthalmoplegia (medial longitudinal fasciculus)
- **Hemiparesis** or **unilateral loss of sensation** (cerebral white matter, usually periventricular)
- Lower extremity loss of sensation or weakness (spinal cord)
- Bowel, bladder, and sexual dysfunction (autonomic nervous system)
- Diagnosis is made by **MRI and lumbar puncture.**
- MRI reveals **plaques** (areas of white matter demyelination).
- Lumbar puncture shows increased lymphocytes, increased immunoglobulins with oligoclonal IgG bands on high resolution electrophoresis, and myelin basic protein.
- Gross examination shows **gray-appearing plaques** in the white matter.
- Treatment of acute attacks includes **high-dose steroids**.
- Long-term treatment with **interferon beta** slows progression of disease.

Cerebrovascular Disease

- **Basic Principles:**
  - **Neurologic deficit** due to cerebrovascular compromise; major cause of morbidity and mortality
  - Due to ischemia (85% of cases) or hemorrhage (15% of cases)
  - Neurons are dependent on serum glucose as an essential energy source and are particularly susceptible to ischemia (undergo necrosis within 3-5 minutes).

- **Global Cerebral Ischemia:**
  - Global ischemia to the brain
  - Major etiologies:
    - Low perfusion (e.g., atherosclerosis)
    - Acute decrease in blood flow (e.g., cardiogenic shock)
    - Chronic hypoxia (e.g., anemia)
    - Repeated episodes of hypoglycemia (e.g., insulinoma)
  - Clinical features are based on duration and magnitude of the insult.
  - Mild global ischemia results in transient confusion with prompt recovery.
  - **Severe global ischemia** results in diffuse necrosis; survival leads to a 'vegetative state.'
  - Moderate global ischemia leads to infarcts in watershed areas (e.g., area lying between regions fed by the anterior and middle cerebral artery) and damage to highly vulnerable regions such as:
    - Pyramidal neurons of the cerebral cortex (layers 3, 5, and 6)-leads to laminar necrosis.

- Pyramidal neurons of the hippocampus -important in long-term memory.
- Purkinje layer of the cerebellum-integrates sensory perception with motor control.

- **Ischemic Stroke:**
  - Regional ischemia to the brain that results in focal neurologic deficits lasting > 24 hours. If symptoms last < 24 hours, the event is termed a transient ischemic attack
  - Subtypes include thrombotic, embolic, and lacunar strokes.
  - **Thrombotic stroke** is due to rupture of an atherosclerotic plaque.
    - Atherosclerosis usually develops at branch points (e.g., bifurcation of internal carotid and middle cerebral artery in the circle of Willis).
    - Results in a pale infarct at the periphery of the cortex
  - **Embolic stroke** is due to thromboemboli.
    - Most common source of emboli is the left side of the heart (e.g., atrial fibrillation).
    - Usually involves the middle cerebral artery
    - Results in a hemorrhagic infarct at the periphery of the cortex
  - **Lacunar stroke** occurs secondary to hyaline arteriolosclerosis, a complication of hypertension.
    - Most commonly involves lenticulostriate vessels, resulting in small cystic areas of infarction

- Involvement of the internal capsule leads to a pure motor stroke.
- Involvement of the thalamus leads to a pure sensory stroke.

- Ischemic stroke results in **liquefactive necrosis**. Eosinophilic change in the cytoplasm of neurons (red neurons) is an early microscopic finding (12 hours after infarction).
- **Coagulative necrosis** (24 hours), infiltration by neutrophils (days l-3) and microglial cells (days 4-7), and granulation tissue (weeks 2-3) then ensue.
- Results in formation of a fluid-filled **cystic space** surrounded by **gliosis.**

- **Intracerebral Hemorrhage:**
  - Bleeding into brain **parenchyma**
  - Classically due to rupture of **Charcot-Bouchard microaneurysms** of the lenticulostriate vessels
    1. Complication of hypertension; treatment of hypertension reduces incidence by half
    2. Basal ganglia is the most common site
  - Presents as severe headache, nausea, vomiting, and eventual coma

- **Subarachnoid Hemorrhage:**

  - Bleeding into the subarachnoid space
  - Presents as a **sudden headache** ("worst headache of my life") with nuchal rigidity
  - Lumbar puncture shows xanthochromia (yellow hue due to bilirubin breakdown).
  - Most frequently (85%) **due to rupture of a berry aneurysm**; other causes include AV malformations and an anticoagulated state.
    - Berry aneurysms are thin-walled saccular outpouchings that lack a media layer, increasing the risk for rupture.
    - Most frequently located in the anterior circle of Willis at branch points of the anterior communicating artery
    - Associated with Marfan syndrome and autosomal dominant polycystic kidney disease

Dementia And Degenerative Disorders

- **Basic Principles:**
  - Characterized by **loss of neurons** within the gray matter; often due to accumulation of protein which damages neurons
  - Degeneration of the cortex leads to **dementia.**
  - Degeneration of the brainstem and basal ganglia **leads to movement disorders.**

- **Alzheimer Disease (Ad):**
  - Degenerative disease of cortex; **most common** cause of dementia
  - Clinical features:
    - Slow-onset memory loss (begins with short-term memory loss and progresses to long-term memory loss) and progressive disorientation
    - **Loss** of learned motor skills and language
    - Changes in **behavior** and **personality**
    - Patients become **mute** and **bed ridden**; infection is a **common** cause of death.
    - Focal neurologic deficits are **not** seen in early disease.
  - Most cases (95%) are **sporadic** and seen in the elderly.
  - Risk **increases** with age (doubles every 5 years after the age of 60).

- Early-onset AD is seen in
  - **Familial** cases- associated with presenilin 1 and presenilin 2 mutations 2.
  - **Down syndrome**- commonly occurs by 40 years of age
- Morphologic features include
  - **Cerebral atrophy** with narrowing of the gyri, widening of the sulci, and dilation of the ventricles
  - **Neuritic plaques**-extracellular core comprised of amyloid with entangled neuritic processes.
    → **AB amyloid** is derived from amyloid precursor protein (APP), which is coded on chromosome 21. APP normally undergoes alpha cleavage; beta cleavage results in amyloid.
    → Amyloid may also **deposit** around vessels, increasing the risk of hemorrhage.
  - **Neurofibrillary tangles**-intracellular aggregates of fibers composed of hyperphosphorylated tau protein
    → Tau is a microtubule-associated protein.
  - Loss of cholinergic neurons in the nucleus basalis of Meynert
- Diagnosis is made by clinical and pathological correlation.
  - Presumptive diagnosis is made clinically after excluding other causes.
  - Confirmed by **histology** at **autopsy** (when possible)

- **Parkinson Disease:**
  - Degenerative loss of **dopaminergic neurons** in the substantia nigra of the basal ganglia
  - Nigrostriatal pathway of basal ganglia uses **dopamine** to initiate movement.
  - Common disorder related to aging; seen in 2% of older adults
  - Unknown etiology; historically, rare cases were related to MPTP exposure (a contaminant in illicit drugs).
  - **Clinical features ('TRAP')**
    - Tremor-pill rolling tremor at rest; disappears with movement
    - Rigidity-cogwheel rigidity in the extremities
    - Akinesia/bradykinesia-slowing of voluntary movement; expressionless face
    - Postural instability and shuffling gait
  - Histology reveals **loss** of **pigmented neurons** in the substantia nigra and round, eosinophilic inclusions of a-synuclein (Lewy bodies, Fig. 17.13C) in affected neurons.
  - Dementia is a **common** feature of late disease.
  - Early-onset dementia is suggestive of **Lewy body dementia**, which is characterized by **dementia**, **hallucinations** and **parkinsonian features**; histology reveals cortical Lewy bodies.

Congenital Malformations & Hydrocephalus

- **Hydrocephalus:**
  - An abnormal accumulation of C S F in the ventricles, which in turn may lead to an **increased intracranial pressure (ICP).**
  - Increased CSF resulting in dilated ventricles
  - Can cause dementia in adults; usually idiopathic
  - Presents as triad of urinary incontinence, gait instability, and dementia ("wet, wobbly, and wacky")
  - When **hydrocephalus** develops in infancy **before closure of the cranial sutures** → **enlargement** of the head
  - When Hydrocephalus develops **after fusion of the sutures → expansion of the ventricles and increased intracranial pressure,** without a change in head circumference.
  - **Types of hydrocephalus:**
    - **Noncommunicating hydrocephalus**: If there is an obstacle to the flow of CSF within the ventricular system, then a portion of the ventricles enlarges while the remainder does not.
    - **Communicating hydrocephalus**: all of the ventricular system is enlarged; here the cause is most often reduced resorption of CSF.
  - Lumbar puncture improves symptoms; treatment is ventriculoperitoneal shunting.

- **Congenital Malformations:**
  - The incidence of CNS malformations, giving rise to mental retardation, cerebral palsy, or neural tube defects, is estimated at 1% to 2%
  - The timing of an injury will be reflected in the pattern of malformation
  - Prenatal or perinatal insults may either cause:
    - Failure of normal CNS development
    - Tissue destruction

- **Developmental Anomalies:**
  - **Forebrain Malformations:**
    - The volume of brain in forebrain malformations might be:
      - Abnormally large (*megalencephaly*)
      - Small (*microencephaly*, *more common*, associated with a small head).
    - They can occur in a wide range of clinical settings, including:
      - Chromosome abnormalities
      - Fetal alcohol syndrome
      - Human immunodeficiency virus 1 (HIV-1) infection acquired in utero
    - **Lissencephaly (agyria):**

      Characterized by an absence of normal gyration and a smooth-surfaced brain. In case of more patchy involvement, it's called *pachygyria*

- **Neural Tube Defects:**
  - Arise from incomplete closure of the neural tube
  - Neural plate invaginates early in gestation to form the neural tube, which runs along the cranial-caudal axis of the embryo.
  - The wall of the neural tube forms central nervous system tissue, the hollow lumen forms the ventricles and spinal cord canal, and the neural crest forms the peripheral nervous system
  - Associated with low folate levels prior to conception
  - Detected during prenatal care by elevated alpha-fetoprotein (AFP) levels in the amniotic fluid and maternal blood
  - **Diseases associated:**
    - **Myelomeningocele:** is an extension of CNS tissue through a defect in the vertebral column
    - **Encephalocele:** is a diverticulum of malformed CNS tissue extending through a defect in the cranium.
    - **Anencephaly** is absence of the skull and brain (disruption of the cranial end of the neural tube).

      → Leads to a 'frog-like' appearance of the fetus

      → Results in maternal polyhydramnios since fetal swallowing of amniotic fluid is impaired
- **Arnold-Chiari Malformation (Type II):**
  - Congenital extension of cerebellar tonsils through the foramen magnum
  - Obstruction of CSF flow can result in hydrocephalus.
  - May occur in association with meningomyelocele and syringomyelia

Meningitis

- **Basic Principles**
  - Inflammation of the **leptomeninges** (Pia and arachnoid together)
  - Meninges consist of three layers (dura, arachnoid, and pia) that lie between the brain and the skull.
  - Most commonly due to an **infectious** agent
    - **Group B streptococci**, **E coli**, and **Listeria monocytogenes** (neonates)
    - **N meningitidis** (children and teenagers), **Streptococcus pneumoniae** (adults and elderly), and **H influenza***a* (non-vaccinated infants)
    - **Coxsackievirus** (children; fecal-oral transmission)
    - **Fungi** (immunocompromised individuals)
  - Presents with classic triad of **headache**, **nuchal rigidity**, and **fever**; **photophobia**, **vomiting**, and **altered** mental status may also be present.
  - Diagnosis is made by **lumbar puncture** (sampling of CSF).
  - **CSF findings:**
    - **Bacterial meningitis:** neutrophils with ↓ CSF glucose; gram stain and culture often identify the causative organism.
    - **Viral meningitis:** lymphocytes with normal CSF glucose
    - **Fungal meningitis**: lymphocytes with ↓ CSF glucose
  - Complications are usually seen with bacterial meningitis. l. Death - herniation secondary to cerebral edema 2. Hydrocephalus, hearing loss, and seizures-sequelae related to fibrosis.

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قال صلى الله عليه وسلم: {من سلك طريقًا يلتمس فيه علمًا سهَّل الله له بهِ طريقًا إلى الجنة}

دعواتنا لكم بالتوفيق