Pathology Revision of CNS Block (Final)

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5.6- Cerebrovascular Accidents:

Two types:

1-Embolic or Thrombotic (Ischemic Stroke) (85%):

Embolic stroke.	Thrombotic stroke.
more common than thrombosis. Usually involve **middle cerebral arteries.** **Sources of emboli include:** Cardiac mural thrombi[1] (more frequent) and arteries (Carotid Arteries). **Emboli of other material:** (tumor,air, or **fat due to fracture**)	Thrombotic occlusions causing cerebral infarctions are due to **atherosclerosis** **Most common sites of primary thrombosis:** **a- The carotid bifurcation** b- The origin of the middle cerebral artery c- At either end of the basilar artery **Subsequent areas affected:** **a+b**: superolateral surface of cerebral hemisphere leading to *contralateral weakness and sensory loss of face,arm,& hand,* *visual field cut, & aphasia.* **c:** posterior cerebral artery will be affected leading to *visual disturbances (contralateral homonymous hemianopia mainly & memory impairment.*)

2-Hemorrhage (15%):

Intracerebral hemorrhage.	Subarachnoid Hemorrhage.
take time to develop, secondary to: ● **Hypertension and diseases lead vascular wall injury** (e.g. vasculitis). ● **Sturecal lesion such as: Arteriovenous malformation** and cavernous malformation. ● **Intraparenchymal tumor.**	**The patient has very severe headache suddenly ,** These sometimes leading to: **obstruction of CSF flow as** or **distribution of CSF resorption** Which result **Hydrocephalus.** the prognosis worsens with each episode of bleeding. **Causes:** ● **Rupture of a saccular (berry) aneurysm (The most frequent) → Anterior communicating artery (most common site near major arterial branch point followed by middle cerebral artery.) →** aneurysms greater than **10 mm have high risk of bleeding** (so it is related to size.) **→ may give ear murmure as a symptom.** ● **Trauma** **In the healing phase of subarachnoid hemorrhage, shows:** ● Meningeal fibrosis > epilepsy. ● Scarring

[1] Mural thrombi are thrombi that adhere to the wall of a blood vessel and occur in large vessels.

Global Cerebral Ischemia.

Widespread, Majors etiologies:

- **Acute decrease in blood flow (severe hypotension or shock and cardiac arrest).**
- Low perfusion **(atherosclerosis)**
- Chronic hypoxia.
- Repeated hypoglycemia (insulinoma[2]).

The clinical outcome:

1- Mild: complete recovery (transient postischemic confusional state.)

2- Severe: undergo either : Persistent vegetative state or Respirator brain → "flat" on EEG. brain gradually undergoes an autolytic process.

Gross: wide gyri and narrowed sulci > brain swollen and cut surface shows poor demarcation between gray and white matter.

Most susceptible to ischemia are:

- **Pyramidal cells of the Sommer sector (CA1) of the hippocampus.**
- **Purkinje cells of the cerebellum.**
- **Pyramidal neurons in the neocortex.**

Microscopically, infarction shows:		
Early changes	**Subacute changes**	**Repair**
12 to 24 hours after the insult	24 hours to 2 weeks	after 2 weeks
Red neurons. **(Doesn't appear before 12 hours.)** nuclear pyknosis & karyorrhexis.	- neutrophils. - macrophages. - vascular proliferation and reactive gliosis.	Removal of all necrotic tissue and gliosis. (more gliosis and less inflammation.)

Focal Cerebral Ischemia. *the symptoms depend on the site.*

result from arterial occlusion > partial **infarction.** Infarct **is modified by collateral flow** such as:

- The major source of **collateral** flow is the **circle of Willis.**
- **Cortical-leptomeningeal anastomoses.**

No collateral flow for the deep penetrating vessels supplying :

- **Hypothalamus → if affected → endocrine lesion.**
- **Basal ganglia → if affected → Parkinson's like symptoms.**
- **Deep white matter → if affected → MS like symptoms.**

[2] Presence of insulin in blood.

Non hemorrhagic :

Gross

First 6 hours	After 48 hours	2 to 10 days	10 days to 3 weeks
Unchanged	**pale**, soft, and swollen,	gelatinous and friable, & boundary between normal and abnormal tissue becomes more distinct due to edema	the tissue liquefies, fluid leaving.

Microscopic examination

First 12 hours	Until 48 hours	2 to 3 weeks	After several months
● **Red neurons** and both type of edema. ● Endothelial and glial cells, mainly astrocytes, swell,	**neutrophil emigration.**	● **Macrophages** containing myelin bs. ● astrocytes at the edges of the lesion progressively enlarge, divide, and develop a prominent network of protoplasmic extensions. ● **Gliosis is very prominent.**	● **Striking astrocytic nuclear (start to disappear.)** and cytoplasmic enlargement regress in cortex. ● The pia and arachnoid are not affected and do not contribute to **the healing process (Gliosis) why ? → scarring → epilepsy.**

Hemorrhagic: same as non hemorrhagic but with hemorrhage.

Watershed infarcts :

border zone between the ACA and MCA distribution is at great risk → damage produces band of necrosis.

Hypertensive Cerebrovascular Disease.

Hypertension causes:

- hypertension affects deep penetrating arteries and arterioles → supply basal ganglia + deep white matter.
- **hyaline arteriolar sclerosis in arterioles - Charcot-Bouchard microaneurysms -**
- **Lacunar infarcts:** Consist of small cavities formed by degeneration of brain tissue with scattered *lipid-laden macrophages* surrounding gliosis. commonly in deep grey matter (basal ganglia + thalamus.)
- **Slit hemorrhages:** slitlike cavity surrounded by brownish discoloration (we see the pigment from macrophages eating iron from blood.)
- **Acute hypertensive encephalopathy;** Petechiae and **fibrinoid necrosis** of arterioles in the gray and white matter
- **Massive hypertensive intracerebral hemorrhage**

Vasculitis.

infectious arteritis , usually occurs in setting of immunosuppression or it could be primary angiitis in both cases we give immunosuppressive treatment and steroids.

7-Neurodegenerative Diseases:

- Cellular degeneration of neurons in the brain cause symptoms depend on the pattern of involvement of the brain
- **Dementia:** The development of memory impairment and other cognitive deficits with preservation of a normal level of consciousness.
- Dementia is not part of normal aging.

Major causes of dementia:

Primary Neurodegenerative Disorders	Alzheimer disease, Lewy body dementia, Huntington disease
Infections	Prion-associated disorders, HIV, Progressive multifocal leukoencephalopathy
Vascular and Traumatic Diseases	Multi-infarct, Global hypoxic-ischemic brain injury, Chronic subdural hematomas
Metabolic and Nutritional Diseases	Thiamine deficiency (Wernicke-Korsakoff syndrome)
Miscellaneous	Brain tumors, Neuronal storage diseases, Toxic injury (e.g. mercury)

Alzheimer Disease.

- Most common cause of dementia[3] in the elderly.
- **Symptoms:** Progressive disorientation, Memory loss, Aphasia, disability at end stage.
- Death usually occurs from **intercurrent pneumonia.**
- Increasing incidence with age.
- **Clinical** assessment and modern **radiologic** methods allows **accurate diagnosis** in 80% to 90% of cases.
- Most cases are **sporadic** & at least 5% to 10% are **familial.**

Sporadic Alzheimer	Familial Alzheimer
1. **ε 4 (ApoE4)**, (30%), and is thought to both **increase the risk** and ***lower*** **the age** of onset of the disease. 2. ***SORL1***[4] → **late-onset** Alzheimer disease.	**accumulation of a peptide (β amyloid, or A β)**

Pathogenesis:

- **Amyloid precursor protein (APP)** cut by **β -site** APP-cleaving enzyme and **γ -secretase** to generate **A β .**
- Accumulation of A β has several effects on neurons and neuronal function:
  - Small aggregates → **alter neurotransmission**, **toxic to neurons** and **synaptic endings**
  - Larger deposits → form of **plaques** → neuronal death, elicit a local inflammatory response.
- **Presence of A β also leads neurons to hyperphosphorylate the microtubule binding protein "tau" → Tau** aggregates into tangles around nucleus → neuronal dysfunction and cell death.

- Alzheimer disease occurs in almost all patients with **trisomy 21 (Down syndrome)**.

[3] Dementia is a general term for a decline in mental ability severe enough to interfere with daily life.
[4] is a protein that in humans is encoded by the SORL1 gene.

Gross	Microscopic	
	Plaques (extracellular)	**Neurofibrillary tangles (intracellular)**
- Cortical atrophy with widening of the cerebral sulci (frontal, temporal, and parietal lobes) - **Hydrocephalus ex vacuo.**	- Paired helical filaments, basophilic, fibrillary. - encircle the nucleus. - Found in entorhinal cortex. - Contain **tau** protein. - Not specific for Alzheimer's.	- Focal, spherical, dilated, tortuous, silver-staining neuritic processes with central amyloid core contains **Aβ**. - *Found in hippocampus, amygdala, neocortex.* - ***diffuse plaques:*** Aβ deposits without surrounding neuritic reaction.

- For pathohistology we use Silver staining methods & immunohistochemistry.

Parkinsonism: Syndrome,which is made from group of symptoms. Mostly caused by *Parkinson disease.*
Lewy bodies: Single or multiple, intracytoplasmic filaments composed of α-synuclein.

Parkinson's Disease:

- 6-8 decades.
- Men more than woman.
- Mostly sporadic.
- α-synuclein[5] mutations cause autosomal dominant PD.
- genetic loci for Parkinson's disease:
  - **Parkin** (an E3 ubiquitin ligase)
  - **UCHL-1** (enzyme involved in recycling of ubiquitin)

Gross	Microscopic
Pallor of the substantia nigra and locus ceruleus	- Loss of the pigmented, neurons - Gliosis. - **Lewy bodies.**

- 10% to 15% of individuals with Parkinson disease **develop dementia**
- **Treatment:** L-DOPA.
- **Prognosis:** Death is usually the result of intercurrent infection or trauma from frequent falls.

[5] a protein that is abundant in the human brain>> mainly at the tips of (neurons) in the presynaptic terminals.

8-Congenital Malformation & Hydrocephalus:

- CNS malformations can lead to to mental retardation, cerebral palsy, or neural tube defects.
- Prenatal or perinatal insults may either cause: Failure of normal CNS development or Tissue destruction.
- CNS malformation can be caused by mutations affecting molecules in pathways of neuronal and glial: Development, Migration, Connection.
- Additionally, some toxic compounds and infectious agents are known to have teratogenic effects.

Forbrain Malformation		
1-Megalencephaly	**2-Microencephaly**	**3-Lissencephaly(agyria)**
The volume of brain may be abnormally large.	brain is small and usually associated with a small head (more common). It can occur due to: 1-Chromosome abnormalities. 2-Fetal alcohol syndrome. 3- (HIV-1) infection. acquired in utero -All causes are associated with a decreased number of neurons destined for the cerebral cortex.	Is characterized by an absence of normal gyration leading to a smooth-surfaced brain. The cortex is abnormally thickened and is usually only four-layered.

Neural Tube Defects		
-they are Most frequent CNS malformations. - Can be detected by elevated α-fetoprotein in amniotic fluid		
1-Myelomeningocele	**2-Anencephaly**	**3-Encephalocele**
an extension of CNS tissue through a defect in the vertebral column involving (Spinal cord + Meninges) • occur most commonly in the lumbosacral region	a malformation of the anterior end of the neural tube, with absence of the brain and top of skull.	diverticulum of malformed CNS tissue extending through a defect in the cranium it most often involves the occipital region or the posterior fossa

Posterior Fossa Anomalies.

- **The most common malformations in this region of the brain result in either misplaced or absent cerebellum.**
- **Typically, these are associated with hydrocephalus.**

The Arnold-Chiari malformation type II.

1-A small posterior fossa.
2-A misshapen midline cerebellum.
3-Downward extension of vermis through the foramen magnum.
4-Hydrocephalus.
5-A lumbar Myelomeningocele.

Hydrocephalus.

Hydrocephalus refers to the accumulation of excessive CSF within the ventricular system.

- **Most cases occur as a consequence of impaired flow or impaired resorption of CSF, in rare instances (e.g., tumors of the choroid plexus), overproduction of CSF may be responsible.**

- **When hydrocephalus develops in infancy before closure of the cranial sutures >> there is enlargement of the head.**
- **When hydrocephalus develops after fusion of the sutures (Adults) >> it is associated with expansion of the ventricles and increased intracranial pressure, without a change in head circumference.**

Types of Hydrocephalus	
1-Non-communicating hydrocephalus	**2-communicating hydrocephalus**
obstacle to the flow of CSF within the ventricular system, then a portion of the ventricles enlarges while the remainder does not. **-It is most commonly seen with masses at the foramen of Monro or aqueduct of Sylvius.**	**All of the ventricular system is enlarged.** **the cause is most often reduced reabsorption of CSF.**

causes of hydrocephalus.

1. **Hypersecretion of CSF: e.g. choroid plexus tumor.**
2. **Obstructive hydrocephalus:**

- Obstruction of the foramina of Monro: (colloid cyst).
- Obstruction of the 3rd ventricle: (Pilocytic astrocytoma)
- Obstruction of the aqueduct: (aqueductal stenosis or atresia and posterior fossa tumors)
- Obstruction of the foramina of Luschka Or impairment of flow from the 4th ventricle: (Chiari malformation, meningitis, subarachnoid hemorrhage, posterior fossa tumors).
- Fibrosis of the subarachnoid space (meningitis, subarachnoid hemorrhage, meningeal dissemination of tumors).

Defective filtration of CSF: postulated for low-pressure hydrocephalus.

9-Meningitis:

- **Inflammation in pia,arachnoid and subarachnoid space.**
- **Most common root Hematogenous.**

CSF	Pyogenic Meningitis	Tb Meningitis	Aseptic (enterovirus)	brain abscess (strep./staph)
Appearance	purulent/turbid	fibrin wed (pleocytosis)	clear	-
Predominant cell	polymorphs	Lymphocytes	Lymphocytes	scanty cells
protein	↑	↑	normal	↑
glucose	↓	↓ /normal	normal	normal
symptoms/signs	1-Headache 2-Irritability 3-Neck stiffness	Fibrinous exudate at base of brain	-Meningeal irritation -Fever -Alteration of consciousness → Acute onset without recognizable organism	progressive focal neurological deficit + ↑ ICP
complications	1-Phlebitis → hemorrhage→ infarction 2-Hydrocephalus 3-Septicemia → adrenal gland→ WFS[6]	-	-	-Herniation -Rupture into ventricles or subarachnoid space.
Notes	gram stained or smear can be cultured	-	treatment self-limiting or symptomatically	predisposing condition: 1-acute endocarditis 2-cyanotic CHD 3-bronchiectasis
Site	Pia & arachnoid	subarachnoid at the base the base of brain	Pia & arachnoid	Brain tissue

Brain abscess: (morphology)

-Liquefactive necrosis
-Edematous (astrocytes+inflammatory cells)

Epidural and subdural (fungal or bacterial)

- Epidural associated with osteomyelitis→infection from sinusitis or surgical procedure
- Spinal epidural space → compression→ needs neurological emergency

[6] Waterhouse-friderichsen syndrome

Empyema

Symptoms: febrile, headache, neck stiffness

- infection of skull or are sinus → may spread to subdural→ subdural empyema
- May cause thrombophlebitis → occlusion→ infarction of brain

treatment: surgical drainage *the only residual after recovery Dural thickening

TB

- Tuberculoma intraparenchymal mass→ rupture will cause→ tuberculous meningitis
- Always occur after hematogenous spread from primary pulmonary infection
- Microscopic: shows examination central core of caseous necrosis

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