Lecture Five + Six

Pathogenesis and Risk Factor of

Cerebrovascular Accidents

432 ***Pathology*** *Team*

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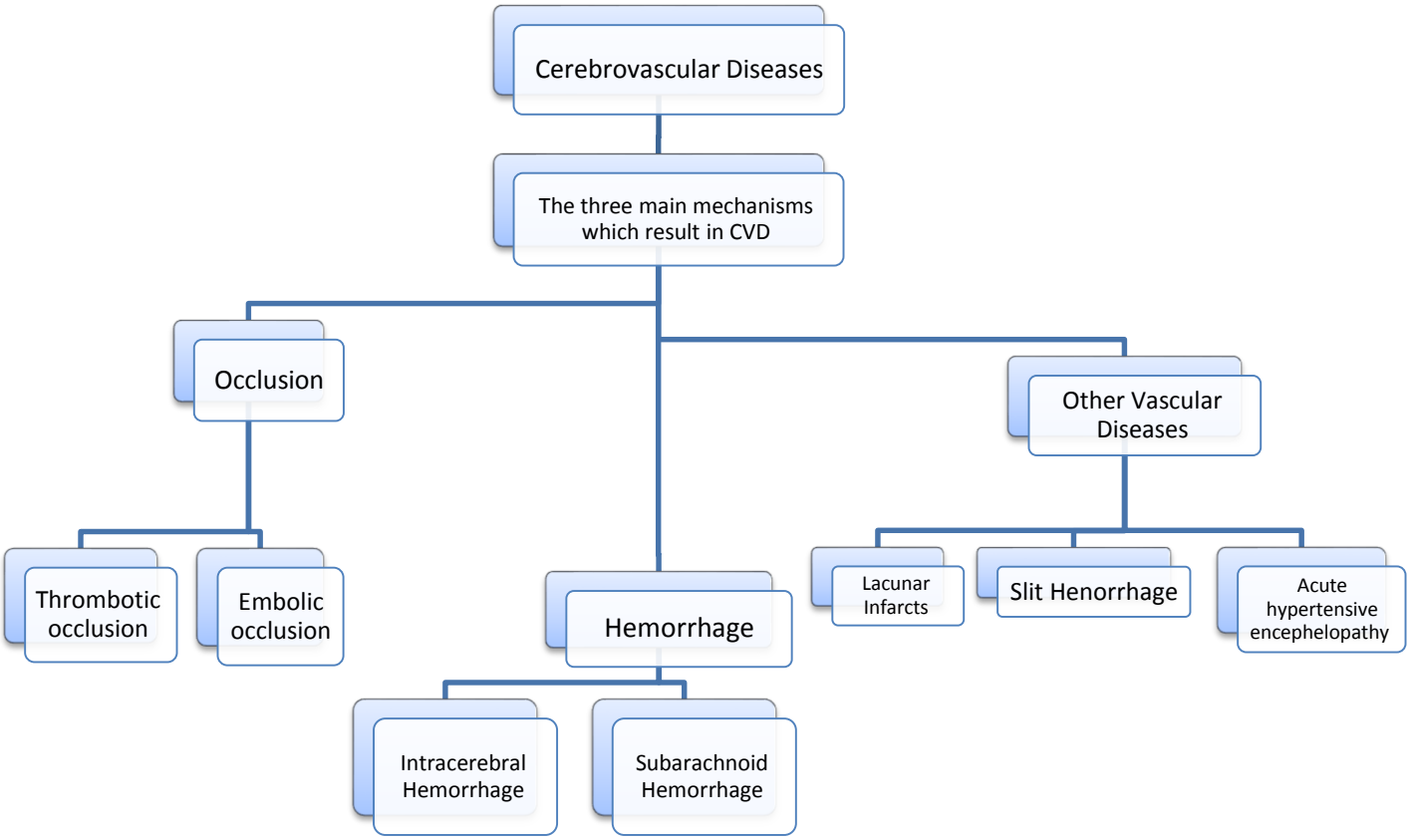
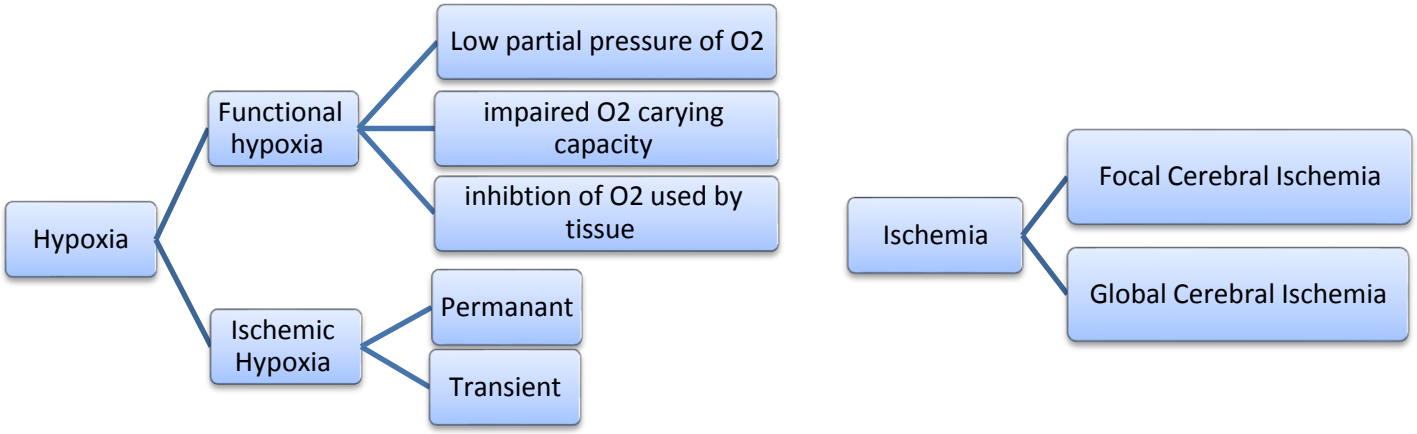
CNS Block

Color Index: female notes are in purple. Male notes are in Blue. Red is important. Orange is explanation.

Cerebrovascular Diseases

Mind Map:





Terminology

Terminology:

NOTE: Make sure you understand the terms below very well because they are the bases of this lecture

Thrombosis:
Is the formation of a blood clot inside a blood vessel, obstructing the flow of blood through the circulatory system. It could be due to injury of the blood vessels or in certain conditions.

Embolism:
A clot that breaks free and begins to travel around the body. Not necessarily a detachment of blood clot (thromboembolism), it can be fat embolism, air embolism, cholesterol embolism, foreign body embolism (like a bullet).

Hemorrhage:
Is the loss of blood or blood escaping from the circulatory system either internally or externally. It accompanies the rupture of the blood vessels and leads to direct tissue damage and secondary Ischemia. Examples of hemorrhage in CVD: subarachnoid and intracerebral hemorrhage.

Hypoxia:
Deprived adequate supply of Oxygen to the body or to a region inside the body (for example here the brain) and it can be caused by many reasons.

Ischemia:
Is a restriction in blood supply to tissues, causing a shortage of oxygen and glucose needed for cellular metabolism to keep the tissue alive, specially the brain and heart since they are very aerobic which means that they count on O2 to generate ATP. If Ischemia is very severe it can lead to Infarction.

Infarction:
Tissue death (NECROSIS) caused by local lack of oxygen due to complete obstruction of the blood supply. In the Brain we have Cerebral Infarction and the type of necrosis is Liquefactive Necrosis.

NOTE:

- All what have been typed in RED have been mentioned by Dr. Hala during the lecture and the details will be discussed within the slides.

- You have to link the cellular changes of the Neurons in the brain with the cerebrovascular injury, so remember what we took in the previous lecture.

Introduction

The brain may be deprived of oxygen by any of several mechanisms:

1)Functional hypoxia, in:

- Low partial pressure of oxygen (ex, high altitude)
- Impaired oxygen-carrying capacity (ex, severe Anemia, Thalassemia, Carbon monoxide poisoning)
- Inhibition of oxygen use by tissue (ex, Cyanide poisoning).

2) Ischemia (which lead to hypoxia), either transient or permanent:

Due to tissue hypoperfusion, which can be caused by:

- Hypotension
- Vascular obstruction
- or both

Notes

Cyanide poisoning: when the quantity of oxygen reaching the cells is normal, but the cells are unable to use the oxygen effectively, due to disabled oxidative phosphorylation enzymes.

Carbon monoxide poisoning: Carbon monoxide competes with oxygen for binding sites on hemoglobin molecules. And since carbon monoxide binds tighter than oxygen, it can prevent the carriage of oxygen. Example: smoking cigarettes over a period of time.

Partial pressure of gases: Gases dissolve, diffuse, and react according to their partial pressures.

Silent stroke: Asymptomatic and have more long lasting neurological dysfunction than TIA

Cerebrovascular Diseases

Cerebrovascular Disease is the third leading cause of death (after heart disease and cancer) in the United States.

It is also the most prevalent neurologic disorder in terms of both morbidity and mortality rates.

Stroke

It is the clinical term for a disease with acute onset of a neurologic deficit as the result of vascular lesions (blood vessels), either hemorrhage or loss of blood supply (by embolus or thrombus occlusion).

Thrombotic and embolic stroke:

Overall, embolic infarctions are more common.

Sources of emboli include:

- Cardiac mural thrombi (frequent) (Myocardial infarct, valvular disease, atrial fibrillation)
- Arteries (Atheromatous plaques within the carotid arteries).
- Paradoxical emboli (it is a Passage of a clot (thrombus) from a vein to an artery)
- Emboli associated with cardiac surgery.
- Emboli of other material (tumor, fat, or air).

The majority of thrombotic occlusions causing cerebral infarctions are due to atherosclerosis.

Atherosclerotic stenosis can develop on top of a superimposed thrombosis, accompanied by anterograde extension, fragmentation, and distal embolization or the other way around: Atherosclerotic plaque in an artery → Stenosis + Endothelial cells injury → Decreases blood flow + Hypercoagulability complement → Formation of blood clot (thrombus)

NOTE:
- Must differentiate between a thrombus and hemorrhage stroke because each one has a specific treatment
- First thing you do is CT scan when a patient come from an accident to role out hemorrhage
- When a patient come with a "sudden" severe headache you must think of a stroke yet it can be asymptomatic as well

The most common sites of primary thrombosis:

- The carotid bifurcation.
- The origin of the middle cerebral artery.
- Either end of the basilar artery.

The territory of distribution of the middle cerebral arteries is most frequently affected by embolic infarction

WHY? Because it arises from the internal carotid and continues STRAIGHT UP (without going left or right) into the lateral sulcus, so it has a higher chance of getting blocked by any embolus detached from the heart valves.

Clinical presentation

- Depends on which part of the brain is injured, and how severely it is injured.
- Sometimes people with stroke have a headache, but stroke can also be completely painless (at the beginning Asymptomatic).
- It is very important to recognize the warning signs (ex, elderly people and a person feels dizzy) of stroke and to get immediate medical attention if they occur (cause it can be prevented).
- If the brain damage sustained has been slight, there is usually complete recovery, but most survivors of stroke require extensive rehabilitation (ex,TIA)

Symptoms:

- Sudden (ACUTE not CHRONIC for weeks or months)
- Weakness or paralysis of one side of the body, opposite of the affected side of brain (most common)
- Speech problems, and weak face muscles causing drooling.
- Numbness or tingling (also very common)
- Base of the brain: problems in balance, vision, swallowing, breathing and even unconsciousness.
- Deep coma, paralysis of one side of the body, and loss of speech, followed by death or permanent neurological disturbances after recovery (in cases of severe brain damage).

REMEMBER:

- **The most likely artery to be occluded** in the brain is the middle cerebral artery which supplies most parts of the brain.
- Atherosclerosis risk factors: Hypertension, Diabetes, unhealthy cholesterol level, overweight and obesity, smoking, age.
- Uncontrolled diabetes causes damage to blood vessels and make them more prone to damage from atherosclerosis and hypertension.

Ischemia

1- Global Cerebral Ischemia:

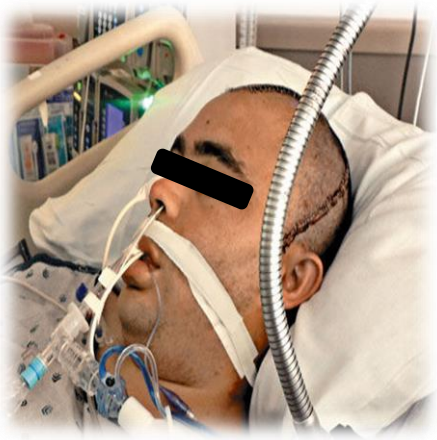
Widespread ischemic/hypoxic injury occurs when there is a generalized reduction of cerebral perfusion, usually below systolic pressures of less than 50mmHg.

Causes include:

- Cardiac arrest
- Severe hypotension or shock (Hypovolemic shock)

The clinical outcome varies with the severity of the insult:
If mild → may be only a transient post-ischemic confusional state, with eventual complete recovery.

In severe global cerebral ischemia→ widespread neuronal death, irrespective of regional vulnerability, occurs (like the states below):



1- **Persistent vegetative state:** (A wakeful unconscious state that lasts longer than a few weeks is referred to as a persistent vegetative state Individuals who survive in this state often remain severely impaired neurologically and deeply comatose).

2- **Respirator brain:** brain death, (isoelectric, or "flat" electroencephalogram) and brain stem damage, including absent reflexes and respiratory drive.

Autolytic process: when patients with this pervasive form of injury are maintained on mechanical ventilation, the brain gradually undergoes an autolytic process (Autolysis is more commonly known as self-digestion)

Sensitivity to ischemia:

Neurons are **much more sensitive** to hypoxia than the glial cells (glial cells are more resistant)

The most susceptible to ischemia of short duration are: (First to be affected):

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

Gross pathology:

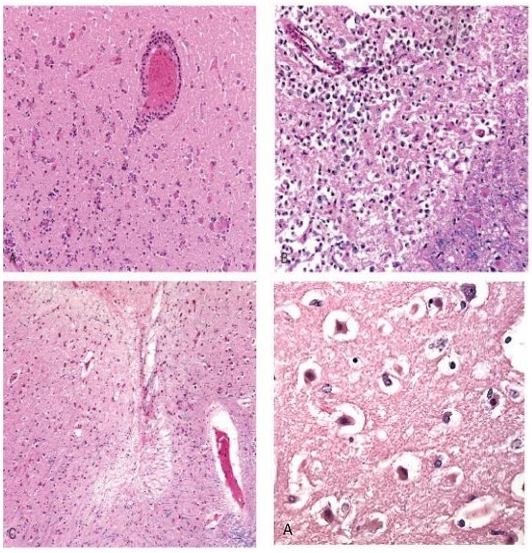
- The brain is swollen, with wide gyri and narrowed sulci
- The cut surface shows poor demarcation between gray and white matter

(Disrupted Blood brain barrier, and when you make a cut you can't differentiate between the white and grey matter)

Histopathology: The histopathologic changes that accompany irreversible ischemic injury are grouped into 3 categories:

1- Early changes:

- **Red neurons**. (**1st sign** of ischemia or Stroke)
- Infiltration by neutrophils (12 to 24 hours after the insult red neurons, characterized initially by microvacuolization → cytoplasmic eosinophilia, and later nuclear pyknosis and karyorrhexis).



2- Subacute changes:

- Necrosis of tissue
- Reactive gliosis (24 hours to 2 weeks The reaction to tissue damage begins with infiltration by neutrophils Necrosis of tissue, influx of macrophages, vascular proliferation and reactive gliosis)

3- Repair

- Pseudo laminar necrosis.

  (After 2 weeks removal of all necrotic tissue, loss of organized CNS structure and gliosis)

2- Focal Cerebral Ischemia:

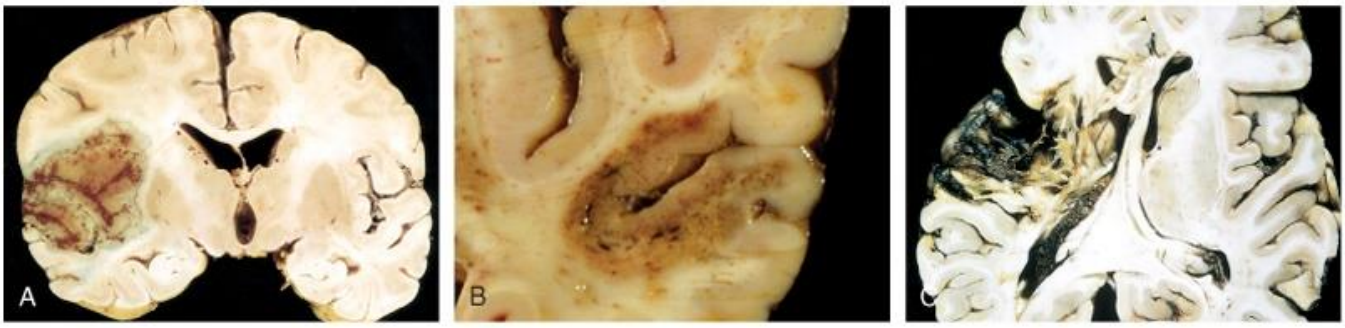
- Cerebral arterial occlusion → focal ischemia
- The size, location, and shape of the infarct are determined by modifying variables, most importantly the adequacy of collateral flow:
  - Circle of Willis
  - Cortical-leptomeningeal anastomoses
  - In contrast, there is little if any collateral flow for the deep penetrating vessels supplying structures such as:
    - **Thalamus**
    - **Basal ganglia**
    - **Deep white matter**

    (Areas which are less ***irrigated*** are prone to get infarcted)

Gross pathology:

Non-hemorrhagic infarct:

- **First 6 hours:** the tissue is in unchanged in appearance.
- **By 48 hours:** pale, soft, and swollen- corticomedullary junction indistinct.
- **From 2 to 10 days:** gelatinous and friable-boundaries distinct- edema subsides.
- **From 10 days to 3 weeks:** liquefaction.



Histopathology:

The tissue reaction follows a characteristic sequence:

1- After the first 12 hours:

- Red neurons and edema
- Endothelial and glial cells, mainly astrocytes, swell, and myelinated fibers begin to disintegrate.

2- Until 48 hours: neutrophilic emigration, mononuclear phagocytic cells in the ensuing **2 to 3 weeks,** Macrophages **months to years**.

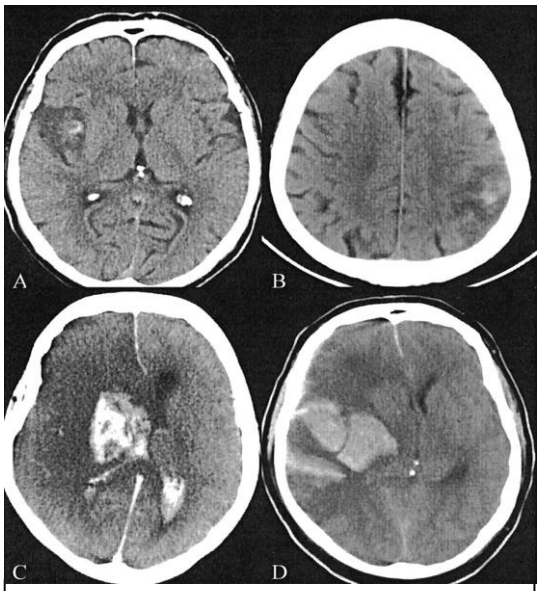
3- Gliosis.

4- After several months:

- The striking astrocytic nuclear and cytoplasmic enlargement recedes.
- In the wall of the cavity, astrocyte processes form a dense feltwork of glial fibers admixed with new capillaries and a few perivascular connective tissue fibers.
- In the cerebral cortex the cavity is delimited from the meninges and subarachnoid space by a gliotic layer of tissue, derived from the molecular layer of cortex.
- The Pia and Arachnoid are not affected and do not contribute to the healing process.

Microscopic findings

The microscopic picture and evolution of **hemorrhagic infarction** shows parallel ischemic infarction, with the addition of blood extravasation and resorption. In persons receiving anticoagulant treatment (treatment from thrombosis), hemorrhagic infarcts may be associated with extensive intracerebral hematomas (*see picture A*).



Picture A

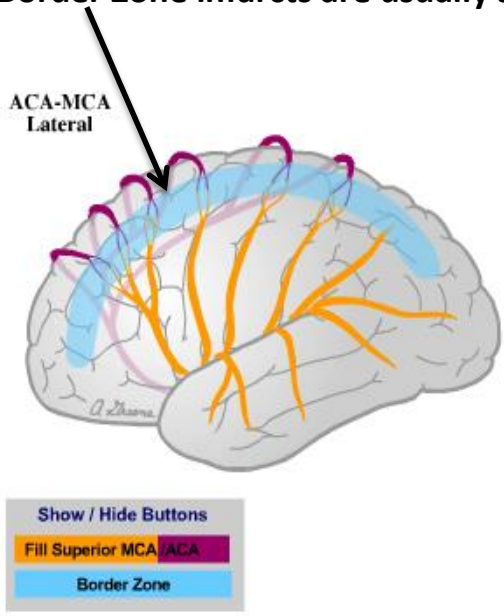
3- Border zone ("watershed") infarcts

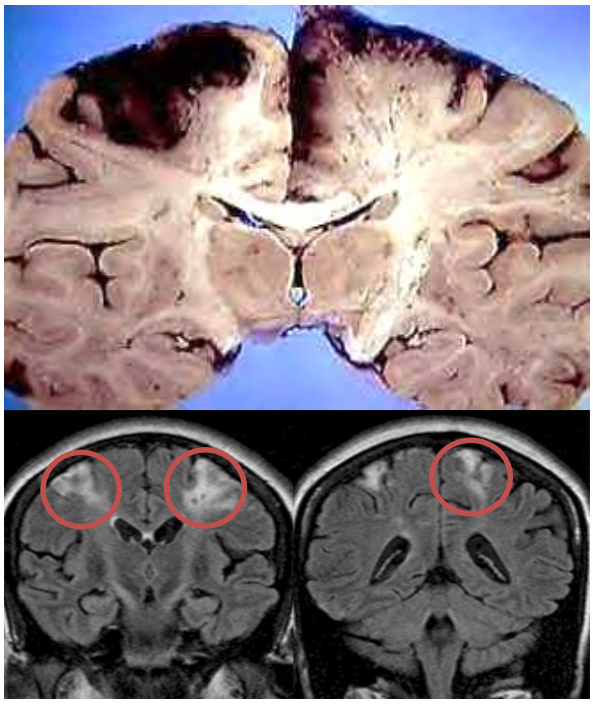
Wedge-shaped areas of infarction that occur in those regions of the brain and spinal cord that lie at the most distal fields of arterial perfusion.

Site of greatest risk: in cerebral hemispheres the border zone between anterior and middle cerebral arteries is the site of greatest risk. Why? Because this area is the least irrigated so more prone to infarction.

Site of necrosis: Over the cerebral convexity a few centimeters lateral to the interhemispheric fissure.

Border Zone infarcts are usually seen after hypotensive episodes





Helpful video "Watershed stroke": https://www.youtube.com/watch?v=Ii9ygvAf5a8

Intracranial Hemorrhages

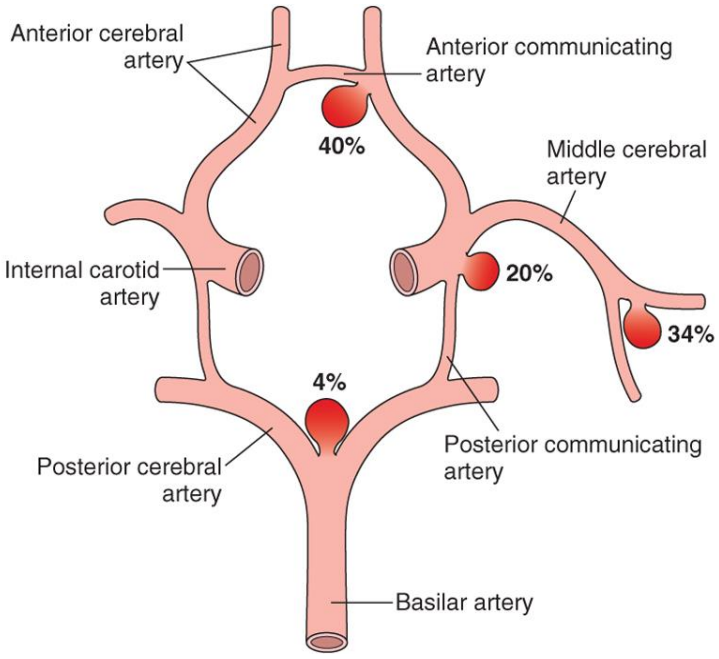
1- Intracerebral Hemorrhages:

Hemorrhages within the brain (intracerebral) can occur secondary to:

- Hypertension because it increases the impact of blood flow on blood vessels leading to aneurysm which may rupture and lead to hemorrhage.
- Vascular wall injury (e.g. Vasculitis), it can be caused by:
  a) Immune disorders especially SLE, treated by steroids.
  b) Infections, such as: syphilis, TB, and Brucellosis which can affect the brain and blood vessels and cause granulomatous inflammation of blood vessels and lead them to rupture causing hemorrhage. Treated by antibiotics.
- Arteriovenous malformation: Congenital anomaly, a tuft of blood vessles (arteries + capillaries + veins) that proliferate in the brain and may bleed for an unknown cause.

- An intraparenchymal tumor because tumors lead to Angiogenesis (endothelial cell proliferation) which may burst causing hemorrhage

Hemorrhages associated with the dura (in either subdural or epidural spaces) make up a pattern associated with trauma.



Most common sites of aneurysm: 40%:

- Anterior communicating artery
- Anterior cerebral artery

Patients with Aneurysm sometimes hear murmurs in their ears and get headaches.

Why patients with Aneurysm hear murmurs in their ears? Due to the blood flow inside the sacs (blood flow causes turbulence inside the sacs)

2- Subarachnoid Hemorrhages (In CSF Area):

Subarachnoid Hemorrhages are secondary to:

- Rupture of a saccular (berry) aneurysm.
- Vascular malformation
- Trauma
- Rupture of an intracerebral hemorrhage into the ventricular system
- Hematologic disturbances
- Tumors

> ***REMEMBER:*** Patients with subarachnoid hemorrhage have:
> 1. **Severe headaches** 2. Increased intracranial pressure.

How Subarachnoid Hemorrhages occurs:

- Blood under arterial pressure is forced into the subarachnoid space, and individuals are stricken with sudden, excruciating headache (classically described as "the worst headache I've ever had") and rapidly lose consciousness.
- Between 25% and 50% of individuals die with the first rupture, although those who survive typically improve and recover consciousness in minutes.
- Recurring bleeding is common in survivors; it is currently not possible to predict which individuals will have recurrences of bleeding.
- The prognosis worsens with each episode of bleeding.
- About 90% of saccular aneurysms occur in the anterior circulation near major arterial branch points.
- Multiple aneurysms: 20% to 30% of cases are congenital.
- The probability of aneurysm rupture increases with the size of the lesion, such that aneurysms greater than 1 cm have a roughly 50% risk of bleeding per year (factors that promote Aneurysm rupture: Hypertension, size of the sac, straining at stool or sexual activities).
- In the early period after a subarachnoid hemorrhage, there is a risk of additional ischemic injury from vasospasm involving other vessels (vasospasm occurs to decrease blood flow thus decrease hemorrhage).
- In the healing phase of subarachnoid hemorrhage, meningeal fibrosis and scarring occur, sometimes leading to obstruction of CSF flow as well as interruption of the normal pathways of CSF reabsorption (leading to Hydrocephalus).

Hypertensive Cerebrovascular Disease

- Intracerebral hemorrhage (previously mentioned, MOST IMPORTANT)
- Lacunar infarcts (lacuna means empty space)
- Slit hemorrhages (elongated openings)
- Hypertensive encephalopathy

Hypertension: It causes Hyaline sclerosis. Where? In the deep penetrating arteries and arterioles that supply the basal ganglia, white matter, and brainstem

What is hyaline sclerosis? It is a thickening of the walls of arterioles by the deposition of homogeneous pink hyaline material leading to weakening of the walls of arterioles and thus rupture. It is associated with Hypertension, Diabetes Mellitus and aging.

Chronic hypertension: minute aneurysms in vessels that are less than 300 µm in diameter → *Charcot-Bouchard microaneurysms* → rupture

a) Lacunar Infarcts:

- Small cavitary infarcts.
- Deep gray matter (basal ganglia and thalamus), internal capsule, deep white matter, and pons.
- Cavities of tissue loss with scattered lipid-laden macrophages and surrounding gliosis (macrophages filled with lipids because they engulfed brain lipids).
- Silent or cause significant neurologic impairment.

b) Slit hemorrhage:

Rupture of the small-caliber (diameter) penetrating vessels and the development of small hemorrhages

In time, these hemorrhages resorb, leaving behind a slitlike cavity surrounded by brownish discoloration (due to iron from blood)

c) Acute hypertensive encephalopathy:

A clinicopathologic syndrome:

- Diffuse cerebral dysfunction, including headaches, confusion, vomiting, and convulsions, sometimes leading to coma.
- Does not usually remit spontaneously.
- May be associated with an edematous brain, with or without transtentorial or tonsillar herniation.
- Petechiae and fibrinoid necrosis of arterioles in the gray and white matter may be seen microscopically.

REMEMBER:
In chronic hypertension: there's hyaline sclerosis.
In acute hypertensive encephalopathy: there's fibrinoid necrosis.

Vasculitis

Infectious arteritis of small and large vessels:

- Previously in association with syphilis and tuberculosis
- Now more commonly occurs in the setting of immunosuppression and opportunistic infection (such as toxoplasmosis, aspergillosis, and CMV encephalitis) (SLE Causes vasculitis which lead to hemorrhage)

Systemic forms of vasculitis, such as polyarteritis nodosa, may involve cerebral vessels and cause single or multiple infarcts throughout the brain

Primary angitis of the CNS: (unknown cause of inflammation of blood vessels):

- An inflammatory disorder that involves multiple small to medium-sized parenchymal and subarachnoid vessels.
- Affected individuals manifest a diffuse encephalopathic clinical picture, often with cognitive dysfunction.
- Improvement occurs with steroid and immunosuppressive treatment (even though they're not caused by SLE or any immune disorder).

Homework!

1- What are the risk factors of strokes?

There is two types of risk factors for stroke:

- **Controllable**: generally fall into two categories: lifestyle risk factors or medical risk factors.

- **Uncontrollable**: include being over age 55, being male, being African American, Hispanic or Asian/Pacific Islander, or having a family history of stroke or transient ischemic attack (TIA).

Controllable Medical Risk Factors	Controllable Lifestyle Risk Factors
High Blood Pressure	Tobacco Use and Smoking
Atrial Fibrillation	Alcohol Use
High Cholesterol	Physical Inactivity
Diabetes	Obesity
Atherosclerosis	
Circulation Problems	

2- What is transient-ischemic attack (TIA)?

A transient ischemic attack (TIA) is like a stroke, producing similar symptoms, but usually lasting only a few minutes and causing no permanent damage. Often called a mini stroke, a transient ischemic attack may be a warning. About 1 in 3 people who have a transient ischemic attack eventually has a stroke, with about half occurring within a year after the transient ischemic attack.

A transient ischemic attack can serve as both a warning and an opportunity, a warning of an impending stroke and an opportunity to take steps to prevent it.

"From Robbins"

Cerebral Amyloid Angiopathy (CAA) is a disease in which amyloidogenic peptides, typically the same ones found in Alzheimer disease, deposit in the walls of medium and small caliber meningeal and cortical vessels. The amyloid confers a rigid, pipelike appearance and stains with Congo red. Amyloid deposition weakens vessel walls and increase the risk of hemorrhage, which differ in distribution from those associated with hypertension. Specifically, CAA-associated hemorrhage often occur in the lobes of the cerebral cortex.

Summary (from Robbins Basic Pathology)

Cerebrovascular Diseases

- **Stroke is the clinical term for acute-onset neuralgic deficits resulting from hemorrhage or obstructive vascular lesions.**
- **Cerebral infarction follows loss of blood supply and can be widespread or focal, or affect regions with the least robust vascular supply (watershred infarcts)**
- **Focal cerebral infarcts are most commonly embolic; with subsequent dissolution of an embolism and reperfusion, a nonhemorrhagic infarct can become hemorrhagic.**
- **Primary intraparenchymal hemorrhages typically are due to either hypertension (most commonly in white matter, deep gray matter, or posterior fossa contents) or cerebral amyloid angiopathy**
- **Spontaneous subarachnoid hemorrhage usually is caused by a structural vascular abnormality, such as an aneurysm or arteriovenous malformation.**

Questions from Pathology Recall book

1/ what are the transient ischemic attacks (TIAs)?

Episodes of focal neurologic defects caused by temporary lack of cerebral blood flow, with complete resolution of deficits.

2/ If TIAs are present, there is increased risk for what?

Increased risk of cerebral infarcts

3/ what are the 2 mechanisms of brain infarction?

Occlusion of the arterial blood supply to the brain from thrombosis, or embolism.

4/ what is the most common cause of vascular thrombosis?

Atherosclerosis plaques in blood vessels. They can rupture and initiate the coagulation cascade.

5/ what is the most common site of embolic occlusion?
Medial cerebral artery.

6/ what are lacunae?
Small healed infarcts that appears grossly as ''pits'' in brain matter.

7/where are the 2 types of hemorrhagic disease?
Intracerebral hemorrhage – Subarachnoid hemorrhage.

8/ what develops as a result of chronic hypertension?
Charcot-Bouchard aneurysm

9/ what increases risk of rupture in cased of aneurysm?
Hypertension

Case 1/ A 42- year-old woman presents to the emergency department at 8 PM, mildly somnolent and complaining of the "worst headache of her life", which began at 6 AM on the same day, awakening her. She took acetaminophen (Tylenol) twice during the day, with some relief. At noon she started to have nausea with vomiting, and by 3 PM she had developed right arm and leg weakness. She denies any head trauma, which of the following is the most likely diagnosis?

A. Epilepsy
B. Hypoglycemia
C. Subarachnoid hemorrhage
D. Transient ischemic attack

Case 2/ A 58-year-old man with a 15-year history of hypertension, a history of smoking two packs of cigarettes a day, and diabetes mellitus experiences the acute onset of weakness and numbness on the left side of his body and an inability to walk. He admits to having a severe headache. His wife reports that during the ride to the emergency center he become lethargic. His blood pressure upon arrival was 192/105 mm Hg. Which of the following is the most likely finding on the initial CT scan of the head?

A. Hemorrhage in the cerebellum (posterior fossa)
B. Hemorrhage in the right cerebral hemisphere
C. Hemorrhage in the left cerebral hemisphere
D. Enlarged cerebral ventricles and prominent gyri

The cases from case files Pathology book

Answers:

- Case 1 / C
- Case 2 / B

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If there is any mistake or feedback please contact us: 432PathologyTeam@gmail.com

432 Pathology Team
*Good Luck ^_^*