جامعة الملك سعود
King Saud University

Pathology
Teamwork 438

Lecture 5&6: Cerebrovascular accidents

objectives

- Explain the concepts of brain “Hypoxia”, “Ischemia” and “Infarction”.

- Understand the pathogenesis of thrombotic and embolic stroke and be able to identify clinical risk factors.

- Identify the causes and consequences of subarachnoid and intracerebral hemorrhage.

- Build a list of the different causes that can lead to cerebrovascular accident

Black: Original content
Red: Important
Blue: Only found in boys slides

Dark orange: Doctor notes
Grey: Extra/Robbins
Pink: Only found in girls slides

Reviewed by Razan AlRabah & Ibrahim AlBakhiti

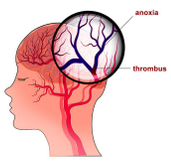
Editing file

Lecture Content

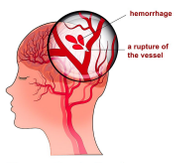
- Global cerebral ischemia
- Focal cerebral ischemia

- Intracranial hemorrhage
- Subarachnoid hemorrhage

Ischemia



Ischemic Stroke



Hemorrhagic Stroke

Hemorrhage

Cerebrovascular Diseases

Vascular diseases

Hypertensive

- Vasculitis
- Primary angiitis
- Vascular malformation

- Slit hemorrhage
- Lacunar infarcts
- Acute hypertensive encephalopathy
- Massive intracerebral hemorrhage

Cerebrovascular Diseases

- It is the broad category of brain disorders caused by pathologic processes involving blood vessels.
- The three main **pathogenic mechanisms** are:

1. **Thrombotic occlusion**
2. **Embolic occlusion**
3. **Vascular rupture**

- Cerebrovascular disease is the third leading cause of death (after heart disease and cancer) in the developed world or the United States.
- It is also the most prevalent neurological disorder in terms of both morbidity and mortality

Recall..

Hypoxia: Deficiency in the amount of **oxygen** reaching the tissues.
Ischemia: An **inadequate blood supply** to an organ or part of the body.
Infarction: Obstruction of the blood supply to an organ or region of tissue, causing **local death of the tissue.**

The brain may be deprived of oxygen by:

Functional hypoxia

- Low partial pressure of oxygen.
  - E.g: high altitude
- Impaired oxygen-carrying capacity.
  - E.g: severe anemia & Carbon monoxide poisoning
- Inhibition of oxygen use by tissue.
  - E.g: Cyanide poisoning.

Ischemia

- Transient or permanent.
- Due to tissue hypoperfusion caused by:
  - **Hypotension.**
  - Vascular rupture.
  - Both.

Stroke

- It is the **clinical term** for a disease with **acute** onset of a **neurologic deficit** as the result of vascular lesions:
  - Hemorrhage accompanies **rupture of the vessels** and leads to direct tissue damage → secondary ischemic injury.
  - Loss of blood supply: (embolism & thrombosis) have similar consequences for the brain:
    - Loss of O_2 & metabolic substrates resulting in → infarction or ischemic injury of regions supplied by the affected vessel.

1 Embolic Stroke

- Intravascular solid, liquid, or gaseous mass that is carried by the blood to a site distant from its point of origin.
- **More common** than thrombotic

Sources of emboli include

1. **Cardiac mural thrombi**[1] (frequent):
   a. Myocardial infarct
   b. Valvular disease
   c. Atrial fibrillation
2. **Paradoxical emboli**, particularly in children with cardiac anomalies (e.g. patent foramen ovale).
3. **Arteries**; (often atheromatous plaques within the carotid arteries or the aortic arch).
4. **Emboli associated with cardiac surgery**
5. **Emboli of other material** (tumor, fat, or air).

Site of emboli

- The territory of distribution of the **middle cerebral arteries** is most frequently affected, since it is parallel with the internal carotid artery.
- Emboli tend to lodge where vessels branch or at stenotic areas caused by atherosclerosis.

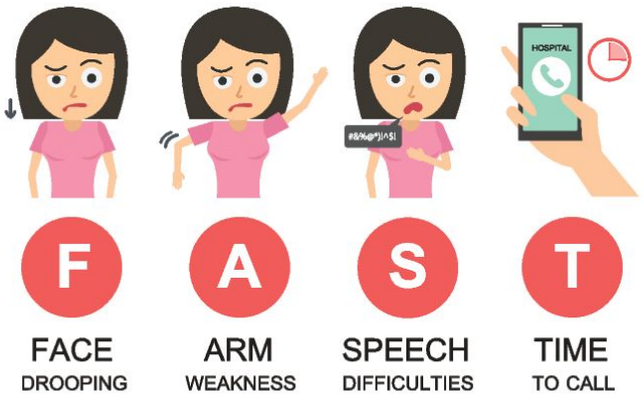
2 Thrombotic Stroke

- The majority of thrombotic occlusions causing cerebral infarctions are due to **atherosclerosis.**
- The most common sites of primary thrombosis:
  1. **The carotid bifurcation.**
  2. **The origin of the middle cerebral artery.**
  3. **At either end of the basilar artery.**
- Thrombotic occlusions usually are superimposed on atherosclerotic plaques[2], accompanied by anterograde extension, fragmentation, and distal embolization.

1- Mural thrombi are thrombi that adhere to the wall of a blood vessel and occur in large vessels.
2- usually areas of stenosis.

Clinical Presentation Of Stroke

- Stroke can be asymptomatic or painless, symptoms depend on:
  - **Which part of the brain** is injured.
  - **Severity.**
- If the brain damage sustained has been slight, there is usually complete recovery, but most survivors of stroke require extensive **rehabilitation.**
- It is very important to recognize the **warning signs** of stroke and to get immediate medical attention if they occur.



1 Sudden.

2 Sometimes people have a **headache.**

3 The most common is **weakness or paralysis of one side** of the body with partial or complete loss of voluntary movement or sensation in a leg or arm.

4 **Speech problems** and weak face muscles, causing drooling.

5 **Numbness or tingling** is very common.

6 Can affect balance, vision, swallowing, breathing and even unconsciousness. Due to involvement of the base of the brain (brainstem).

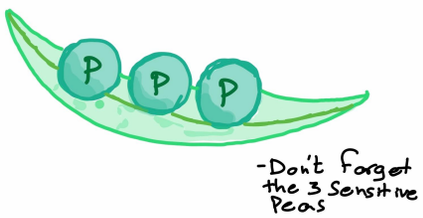
7 In cases of severe brain damage, there may be deep coma, paralysis of one side of the body, and loss of speech, followed by death or permanent neurological disturbances after recovery.

Global Cerebral Ischemia

- **Widespread** ischemic/hypoxic injury occurs when there is a generalized reduction of cerebral perfusion (all the brain), usually systolic pressures less than 50 mmHg.
- **Causes include:**
  - Cardiac arrest
  - Severe hypotension or shock
- **The clinical outcome** varies with the severity and duration of the insult.
  - **Mild**→ transient postischemic confusional state, with eventual complete recovery.
  - **Severe** global cerebral ischemia → widespread neuronal death occurs, irrespective of regional vulnerability.
- If the patient survives the severe form, he could suffer either:

Persistent vegetative state	Respirator brain
• **Severely neurologically impaired** • Deeply **comatose**. It means that the person can't do the routine function by himself like chewing, or urination.	Meet the clinical criteria for "**brain death**" including evidence of: a. Diffuse cortical injury (**isoelectric** or flat electroencephalogram EEG) b. Brain stem damage, including absent reflexes and respiratory drive. When patients with this irreversible form of injury are maintained on mechanical ventilation, the brain gradually undergoes an **autolytic process.**

- **Sensitivity to ischemia:**
  - Neurons are much more sensitive to hypoxia than are glial cells.
- **The most susceptible to ischemia of short duration are:**
  - **P**yramidal cells of the hippocampus
  - **P**yramidal cells of the neocortex
  - **P**urkinje cells of the cerebellum.

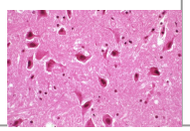


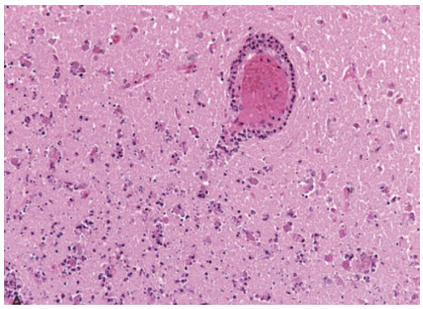
Persistent: غيبوبة
Respirator: ميت دماغي

Global Cerebral Ischemia

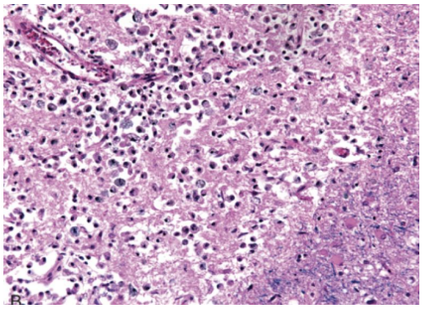
Gross pathology:

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

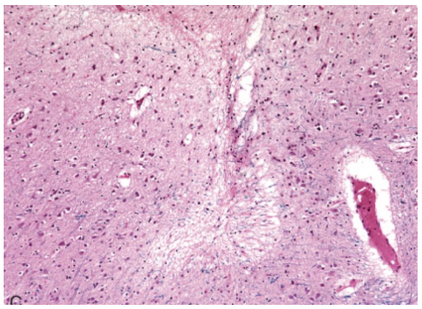
Microscopic pathology		
Early changes	**Subacute changes**	**Repair**
12 to 24 hours[1]	24 hours to 2 weeks	After 2 weeks
Red neurons, characterized initially by: - Microvacuolization. - Cytoplasmic eosinophilia. - Nuclear pyknosis. - Karyorrhexis. Similar changes occur later in glial cells. 	- The reaction to tissue damage begins with **infiltration by neutrophils**. - Necrosis of tissue, **influx of macrophages**, vascular proliferation (angiogenesis) and reactive gliosis.	- Removal of all necrotic tissue. - Loss of organized CNS structure. - Gliosis.



1 Infiltration of a cerebral infarction by **neutrophils** begins at the edges of the lesion where the vascular supply is intact.



2 By day 10, an area of infarction shows the **presence of macrophages** and surrounding reactive gliosis.



3 Old intracortical infarcts are seen as areas of tissue loss with a modest amount of **residual gliosis.**

1- Before 12 hours you might see nothing.

Focal Cerebral Ischemia

- **What causes focal cerebral ischemia?**
  Cerebral arterial occlusion leads to focal ischemia first, then to an infarction in the distribution of the compromised vessels.
- The **size**, **location**, and **shape** of the infarct and the extent of tissue damage that results are determined by modifying variables, most importantly the **adequacy of collateral flow**[1]**:**
  - The **major source** of collateral flow: **circle of Willis (**base of the brain**).**
  - **Partial** collateralization is also provided over the surface of the brain through **cortical-leptomeningeal anastomoses.**
  - There is **little** if any collateral flow for the deep penetrating vessels supplying structures such as:
    - ➔ **Thalamus**
    - ➔ **Basal ganglia**
    - ➔ **Deep white matter**
- Infarcts can be divided into two groups based on their macroscopic and corresponding radiologic appearance:

Infracts

Non-hemorrhagic	Hemorrhagic
Result from acute vascular **occlusions.**	Result from **reperfusion** of ischemic tissue, either through: - Collaterals - Dissolution of emboli Often produce multiple, sometimes confluent petechial hemorrhages

1- The three organs that have dual blood supply: lungs, brain and gut.

Focal Cerebral Ischemia

Gross pathology: (non-hemorrhagic)

First 6 hours	48 hours	2-10 days	10 days - 3 Weeks
- Irreversible injury, little can be observed. - Tissue is unchanged in appearance.	- Tissue becomes **pale**, **soft**, and **swollen**. - The corticomedullary junction becomes indistinct.	Brain becomes **gelatinous** and **friable**, and the boundary between normal and abnormal tissue becomes **more distinct** as edema resolves in the adjacent tissue that has survived.	Tissue **liquefies**, eventually leaving a **fluid-filled cavity** lined by dark grey tissue → gradually expands as dead tissue is removed.

Microscopic pathology: (non-hemorrhagic)

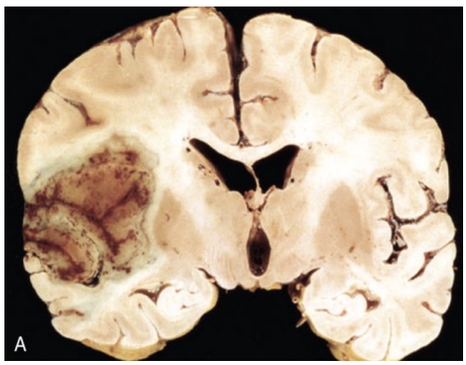
After the first 12 hours	48 hours	2-3 weeks	After several months
- **Red neurons** and both cytotoxic and vasogenic edema predominate. - Loss of the usual characteristics of white and gray matter structures. - Endothelial and glial cells, mainly astrocytes, swell. - Myelinated fibers begin to disintegrate[1].	**Neutrophil emigration**, Followed by mononuclear phagocytic cells.	- **Macrophages** containing myelin breakdown products or blood may persist in the lesion for months to years. - As the process of phagocytosis and liquefaction proceeds, **astrocytes** at the edges of the lesion progressively enlarge, divide, and develop a prominent network of protoplasmic extensions.	- 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.

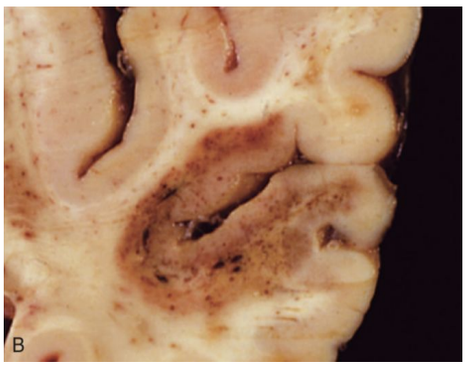
Microscopic pathology: (hemorrhagic infarct)

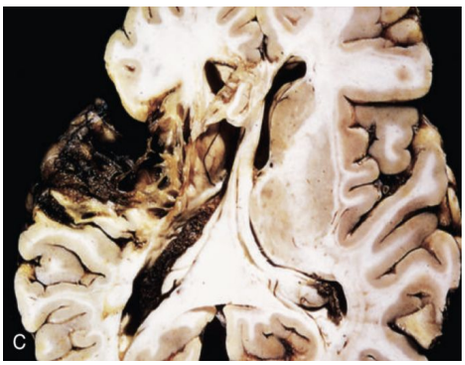
- It parallels ischemic infarction with the addition of:
  - Blood extravasation and resorption.
- If the person is receiving anticoagulant treatment, may be associated with extensive intracerebral hematomas.

1- Break up into small parts.

Focal Cerebral Ischemia







Found in girls slides:

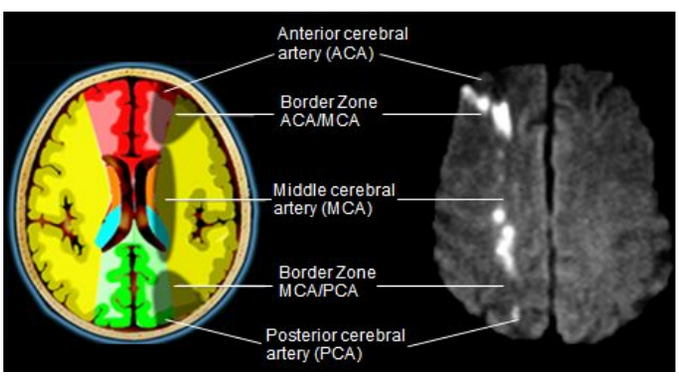
A. **Hemorrhagic or red infarction:** Section of the brain showing a large discolored focally hemorrhagic region in the left middle cerebral artery distribution.

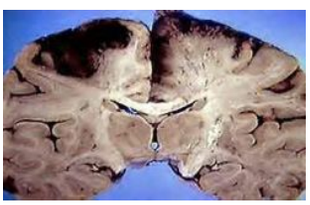
B. An infarct with **punctate hemorrhages**, consistent with ischemia-reperfusion injury[1], is present in the temporal lobe.

C. **Non-hemorrhagic:** Old cystic infarct shows destruction of cortex and surrounding gliosis.

Border zone (watershed) infracts

- Wedge-shaped areas of infraction that occur in those regions of the brain and spinal cord that lie at the most distal fields of arterial perfusion.
- It is usually seen after **hypotensive episodes.**
- In the cerebral hemispheres, the border zone between the anterior and the middle cerebral artery distributions is at greatest risk.
- Damage to this region produces a band of necrosis over the cerebral convexity a few centimeters lateral to the interhemispheric fissure.

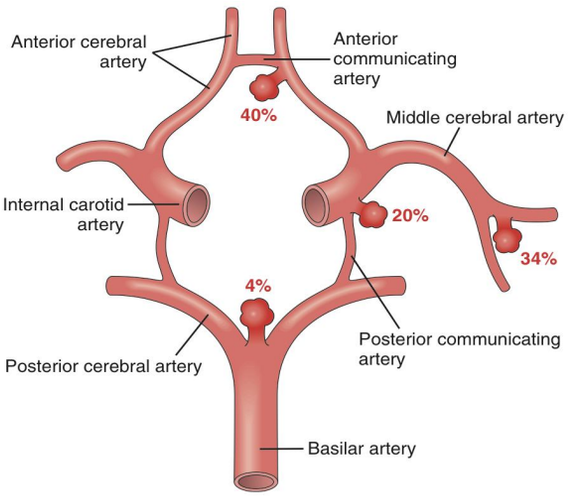




1- Outer areas are spared due to anastomosis → Subcortical necrosis

Subarachnoid Hemorrhage

- Bleeding into the subarachnoid space.



Common sites of saccular aneurysms.

The most common site is branching point of **anterior communicating artery**

Causes:

- **Rupture of a saccular (berry) aneurysm**[1] (the most frequent clinically significant nontraumatic cause)
- Vascular malformation.
- Trauma.
- Rupture of an intracerebral hemorrhage into the ventricular system.
- Hematologic disturbances (e.g. coagulopathies).
- Tumors.

Incidence:

- Between 25-50% of individuals die from the first rupture, although those who survive typically improve and recover consciousness within minutes.
- **Multiple aneurysm** exist in 20-30% of cases. Although they are sometimes referred to as congenital, they are not present at birth but **develop over time** because of underlying defect in the vessels media.

Prognosis

- The prognosis worsens with each episode of bleeding.

Location

- About 90% of saccular aneurysm occur in the **anterior circulation** near major arterial branch points.

Symptoms

- Patient stricken with sudden, excruciating **headache** (described as "the worst headache I've ever had") and rapidly **lose consciousness.**

1- Media layer of a blood vessel fails to develop at the branching points leading to weakness of the wall and cause saccular outpouching which is called Berry aneurysm and eventually → rupture.

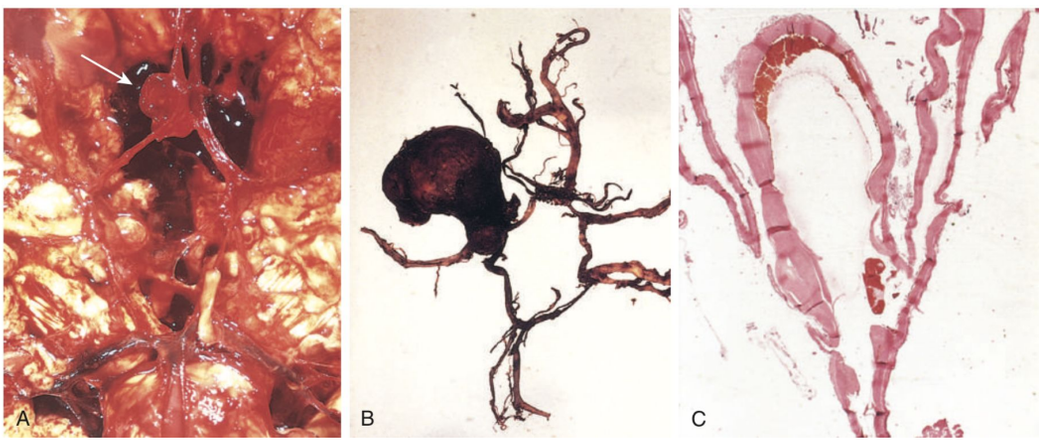
Subarachnoid Hemorrhage Cont.

Risk factors

- Rupture can occur at any time, but in about one-third of cases it is associated with acute increase in **intracranial pressure,** such as with straining at stool or sexual orgasms.
- The probability of aneurysm rupture increases with the **size** of the lesion; an aneurysm greater than 10mm has a roughly 50% risk of bleeding per year.
- In the early period after a subarachnoid hemorrhage, there is a risk of additional ischemic injury from **vasospasm** involving other vessels.

After injury

- **Recurrent bleeding** is common in survivors, currently it is not possible to predict which individuals will have recurrences of bleeding.
- In the healing phase **meningeal fibrosis** and **scarring** occur, sometimes leading to **obstruction of CSF flow** as well as interruption of the normal pathways of **CSF resorption** leading to **hydrocephalus.**



A. View of the base of the brain, dissected to show the circle of Willis with an aneurysm of the anterior cerebral artery (arrow).
B. The circle of Willis is dissected to show a large aneurysm.
C. Section through a saccular aneurysm showing the hyalinized fibrous vessel wall. H&E stain.

Intracranial Hemorrhage

- Hemorrhage within the brain (bleeding into the brain parenchyma)

Causes (can occur secondary to the following):

- **Hypertension.**
- Other forms of vascular wall injury (e.g. vasculitis).
- Arteriovenous malformation and cavernous malfunction.
- Intraparenchymal tumor.
- Cerebral amyloid angiopathy[1]

- Hemorrhage associated with the dura (in either **subdural** or **epidural** space) make up a pattern associated with **trauma**.

Hypertensive Cerebrovascular Disease

Hypertension causes several changes on the brain, including::

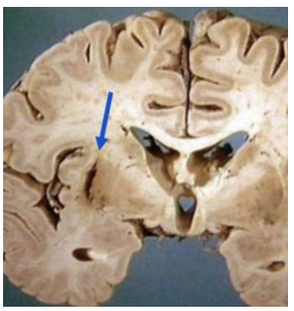
- It affects **deep penetrating arteries** and arterioles supplying the:
  - **Basal ganglia**
  - **Hemispheric white matter**
  - **Brain stem.**
- **Hyaline arteriolar sclerosis in arterioles** → weaker than normal vessels and are more vulnerable to rupture.
- Chronic hypertension is associated with the development of **minute aneurysms** (**charcot bouchard microaneurysms**), in vessels that are less than 300 μm in diameter, which can rupture.

1- Amyloid deposition in the walls of medium and small caliber meningeal and cortical vessels, which weakens vessels wall and increases the risk for hemorrhage.

Hypertensive Cerebrovascular Disease

Effects of hypertension on the brain include:

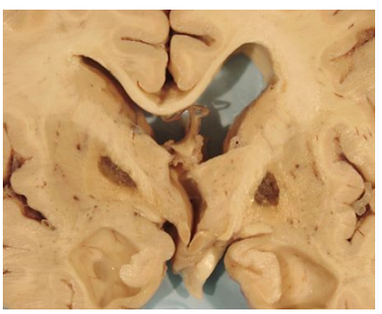
Slit Hemorrhage



- Rupture of the small **caliber penetrating vessels** leads to development of small hemorrhage.
- Hemorrhages resorb, leaving behind a slit like cavity surrounded by brownish discoloration (iron from blood).

Lacunar Infarcts

- Small cavitary infarcts (due to occlusion of small penetrating vessels[1])
- Mostly in **deep grey matter** (basal ganglia and thalamus), internal capsule, deep white matter, and pons.
- Consist of **cavities** formed by degeneration of brain tissue with scattered **lipid laden[2] macrophages** surrounding gliosis.
- Depending on their CNS location, they can either be clinically **silent** or cause **significant neurologic impairment.**

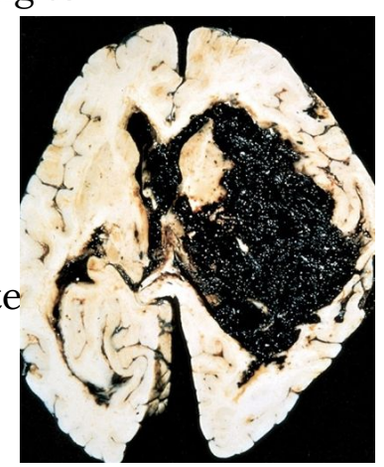


Acute hypertensive encephalopathy

- A **clinicopathologic syndrome**: **Diffuse** cerebral dysfunction, including headaches, **confusion**, vomiting, and convulsions, sometimes leading to coma.
- Does not remit spontaneously
- May be associated with an **edematous brain**, with or without transtentorial or tonsillar herniation.

Microscopically:

- **Petechiae and fibrinoid necrosis of arterioles** in the gray and white matter.



Massive intracerebral hemorrhage

- Massive hypertensive hemorrhage rupturing into the lateral ventricle.

1- Most commonly the lenticulostriate branches of the MCA which can be of thrombotic origin.
2- Source of the lipids is myelin

Vascular Diseases

Vasculitis

- Infectious arteritis of **small and large** vessels:
  - Previously associated with **syphilis** and **tuberculosis.**
  - Now occurs more in the setting of **immunosuppression** and **opportunistic infection** (such as toxoplasmosis, aspergillosis, and CMV encephalitis).
- Systemic forms of vasculitis, such as **polyarteritis nodosa**, may involve **cerebral vessels** and cause single or multiple infarcts throughout the brain.

Primary angiitis of the CNS

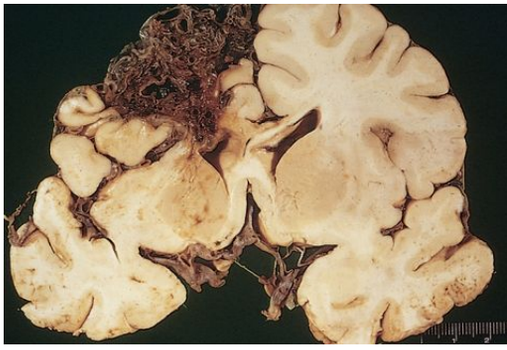
- An inflammatory disorder involving multiple **small to medium-sized** parenchymal and subarachnoid vessels.
- Affected individuals manifest a diffuse encephalopathic clinical picture, often with **cognitive dysfunction.**
- Improvement occurs with **steroid** and **immunosuppressive** treatment.

Females slides only:

Vascular malformation

- Classified into four principal types based on the nature of the abnormal vessels:
  - Cavernous malformations
  - Capillary telangiectasias
  - Venous angiomas.
  - **Arteriovenous malformations** (AVM):
    - The most common, affect males as twice as females.
    - Most commonly manifest between the ages of (10-30 years) with seizures, an intracerebral hemorrhage, or a subarachnoid hemorrhage.
    - The risk of **bleeding** makes AVM the most dangerous type.
    - **Multiple AVMs** can be seen in the setting of **hereditary hemorrhagic telangiectasia** (autosomal dominant condition), often associated with mutations affecting **TGFβ** pathway.

Arteriovenous malformation



So what can cause or contribute to a stroke?

- Hypertension
- Atherosclerosis
- Thrombophilia (e.g. Sickle cell anemia)
- Embolic diseases
- Systemic hypoperfusion/Global hypoxia (e.g. shock)
- Vascular malformations
- Vasculitis
- Tumors
- Venous thrombosis
- Amyloid angiopathy (leptomeningeal and cortical vessels)

DID YOU KNOW!

- Brain tissue ceases to function if deprived of oxygen for **more than 60 to 90 seconds** and after approximately three hours, will suffer irreversible injury possibly leading to death of the tissue.

Homework

What are the risk factors of stroke ?

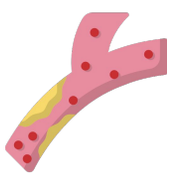
Old age

Smoking

Adult male

Obesity

Hypertension



High Cholesterol

Define Transient ischemic attack ?

- **Regional Ischemia that results in neurological deficits with symptoms lasting less than 24 hours. Is like a stroke, producing similar symptoms, but usually lasting only a few minutes and causing no permanent damage.**

Summary

Cerebrovascular diseases have three main pathogenic mechanisms:
1- Thrombotic occlusion **2-** Embolic occlusion **3-** Vascular rupture

STROKE: 

A disease with acute onset of a neurologic deficit occurring as the result of vascular lesions, either hemorrhage or loss of blood supply.

Thrombotic stroke:

- Thrombotic occlusions are due to **atherosclerosis**
- The 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**.

VS

Embolic stroke:

- More common than thrombosis.
- Sources of emboli include:
  a) Cardiac mural thrombi.
  b) carotid arteries.
  c) Paradoxical emboli.
  d) Emboli after cardiac surgery.
  e) Emboli of other material (tumor,fat or air).
- Most affected site: **middle cerebral arteries**

Global Cerebral Ischemia:

Etiology: severe hypotension, shock and cardiac arrest.
Clinical outcome:
If mild → transient confusional state, with complete recovery
If severe → diffuse necrosis, survival leads to vegetative state or respirator brain .

The most susceptible cells to ischemia of short duration are:

1. **Pyramidal cells of the hippocampus.**
2. **Purkinje cells of the cerebellum.**
3. **Pyramidal neurons in the neocortex.**

Microscopically:

Early changes

12 to 24 hours
1. Pyknotic nuclei (Red neurons)
2. Eosinophilic cytoplasm

Subacute changes

24 hours to 2 weeks
1. infiltration by neutrophils.
2. necrosis,macrophages, vascular proliferation
3. reactive gliosis.

Repair

After 2 weeks
1. Glial scar

Summary

Focal Cerebral Ischemia:

1. Non Hemorrhagic infarcts
2. Hemorrhagic infarcts

Border zone ("watershed") infarcts:

- infarction that occur in those regions of the brain and spinal cord that lie at the most distal fields of arterial perfusion especially the **border zone area** lying between regions fed by **the anterior and middle cerebral artery.**
- Caused by: hypotensive episodes

Intracerebral (Intracranial) hemorrhage:

Secondary to:

01 Hypertension

02 Arteriovenous malformation

03 Intraparenchymal tumor

04 Cerebral amyloid angiopathy

Subarachnoid Hemorrhage:

symptoms: sudden excruciating headache (worst headache of my life!)

Causes: 1-Rupture of a berry aneurysm (↑ intracranial pressure) 2-Vascular malformation 3-Hematologic disturbances 4-Rupture of an intracerebral hemorrhage into the ventricular system 5-Trauma 6-Tumors

location: Mostly in the anterior circulation near major arterial branch points (Recurrent bleeding is common in survivors)

Hypertensive Cerebrovascular Disease:

effects of hypertension on the brain include:

1- Massive hypertensive intracerebral hemorrhage **2-** Lacunar infarcts **3-** Slit hemorrhage **4-** Acute hypertensive encephalopathy

Vasculitis: Primary angiitis:

An inflammatory disorder that involves parenchymal and subarachnoid vessels. Patients manifest a diffuse encephalopathic with cognitive dysfunction.

Vascular Malformations:

Classified into four principal types:

1- AVMs **2-** Cavernous Malformations **3-** Capillary Telangiectasis **4-** Venous Angiomas

Quiz

Q1: Which of the following is not a common site of primary thrombosis in the brain:

A) The carotid bifurcation
B) The anterior cerebral artery
C) The origin of the middle cerebral artery.
D) At either end of the basilar artery

Q2: Which one of the following is the pathogenesis of "watershed" strokes?

A) Thromboembolism
B) Sagittal sinus thrombosis
C) Spontaneous cerebral hemorrhage
D) Prolonged hypotension

Q3: A 82-year-old male had a cerebrovascular accident causing left hemiplegia, the neurologist told the patient's son that it's a cerebrovascular hemorrhage. What is the most susceptible area for bleeding in this lesion?

A) Basal ganglia and internal capsule
B) Midbrain
C) Frontal lobe
D) Occipital lobe

Q4: Regarding subacute changes of GCI, which of the following is not present in histopathological slide examination:

A) Neutrophils infiltration
B) Reactive Gliosis
C) Red neurons
D) Necrosis

Q5: Charcot-Bouchard Aneurysms are associated with:

A) Chronic hypertension
B) Slit hemorrhage
C) Vasculitis.
D) Lacunar Infarcts

Q6: Which of the following triggers a Subarachnoid Hemorrhage with the highest clinical significance:

A) Hematologic disturbance
B) Tumors
C) Hypertension
D) Rupture of a saccular aneurysm

Q7: An autopsy was applied on a body suffering of malignant hypertension what do you expect to see as a microscopic findings:

A) Hyaline arteriolar sclerosis in arterioles
B) Liquefactive necrosis
C) Gliosis
D) New vascularization

Q8: An inflammatory disorder that involves multiple small to medium-sized parenchymal and subarachnoid vessels, is:

A) Hypertension
B) Secondary Angiitis
C) Slit hemorrhage
D) Primary Angiitis

1-B 2-D 3-A 4-C 5-A 6-D 7-A 8-D

Team Leaders

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Thank you