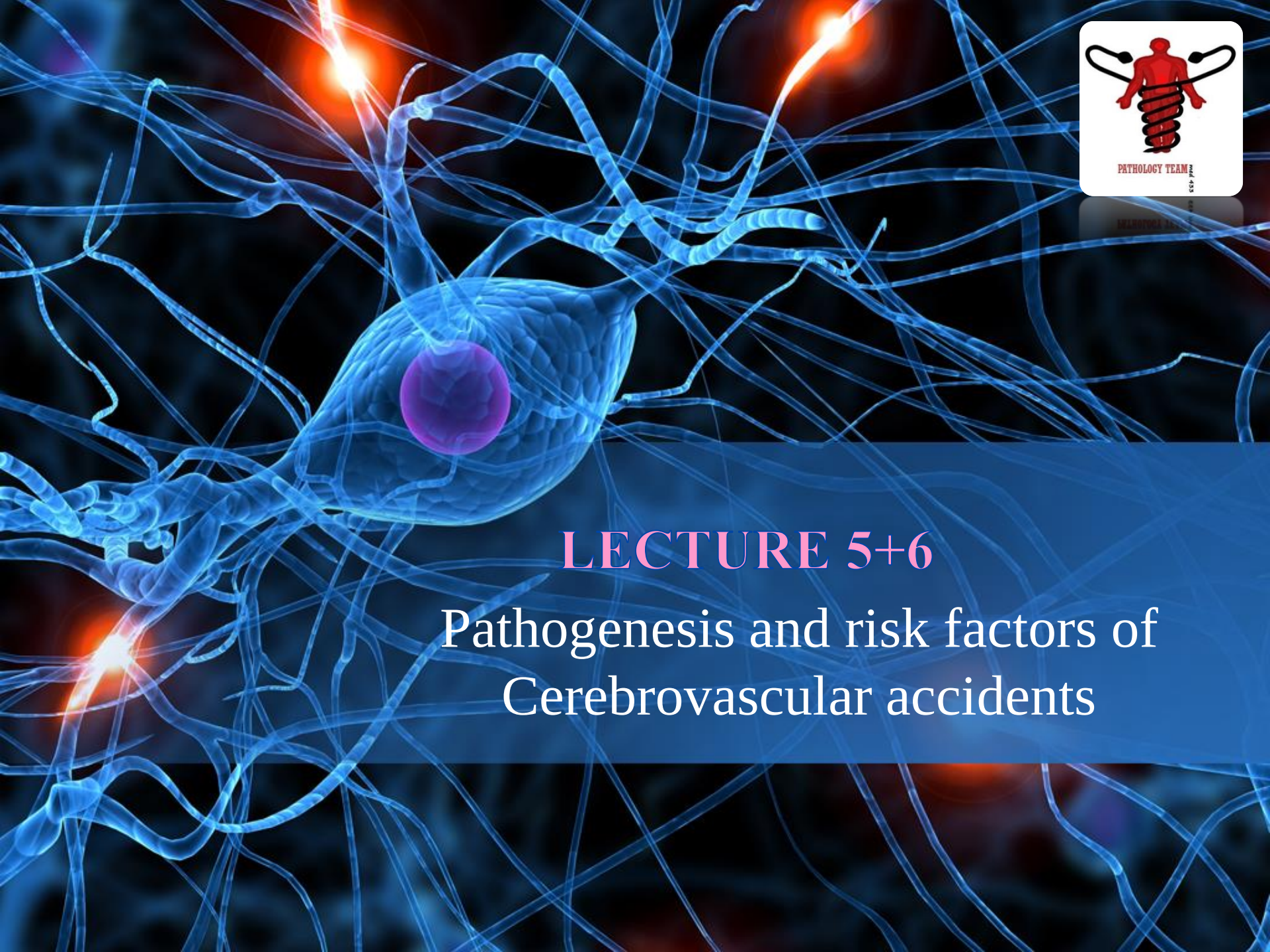



# LECTURE 5+6

## Pathogenesis and risk factors of 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.


hemorrage stroke: http://youtu.be/bp1HRfpOUo0
Ischemic stroke: http://youtu.be/7FR1TsKLoDI

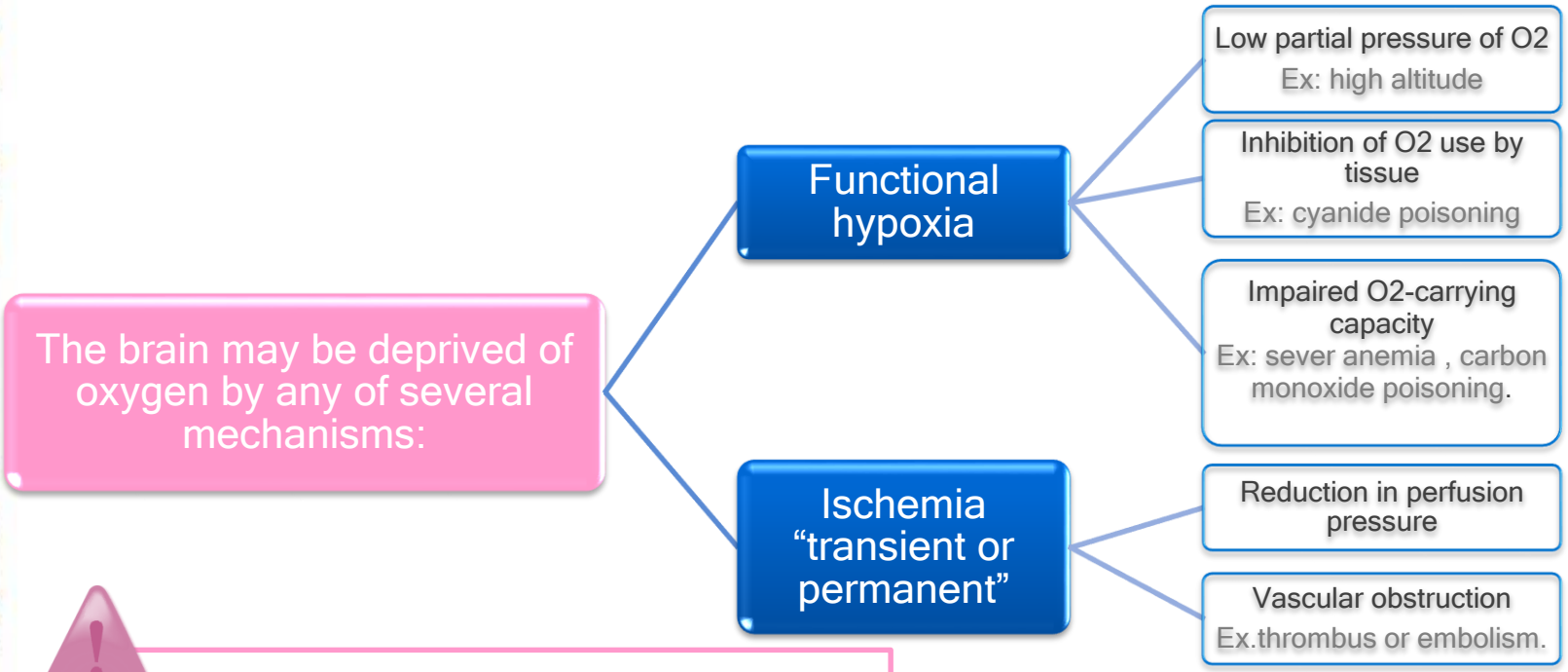
# Introduction

**Terminology you need to remember:-**

**Hypoxia:** is a condition in which the body or a region of the body is deprived of adequate O2 supply.

**Ischemia:** is a restriction in blood supply to tissues, causing a shortage of O2 and Glucose needed for cellular metabolism.

**Infarction:** is tissue death caused by a local lack of O2, due to an obstruction of the tissue's blood supply.




Cerebrovascular diseases are the most widespread neurologic disorder in terms of both morbidity and mortality.

# Stroke

Stroke: is the clinical term (not pathological) for a disease with acute onset of a neurologic deficit as the result of vascular lesions, either hemorrhage or ischemia.

– **NOTE:**

- if stroke occurs , It needs immediate medical attention
- 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 differentiate the cause of stroke in knowing the treatment . Like if you give anti-coagulants medicine to someone suffer from cerebrovascular accident due to hemorrhage this will increase the bleeding and the patient will die .

## Clinical presentations of Strokes

- 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.
- It is very important to recognize the warning signs of stroke.
- If the brain damage sustained has been slight, there is usually complete recovery, but most survivors of stroke require extensive rehabilitation

## Symptoms of Strokes

- 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.
- Speech problems and weak face muscles, ***causing drooling*** سيلان اللعاب
- Numbness or tingling is common.
- A stroke **involving the base of the brain** can affect balance, vision, swallowing, breathing and even unconsciousness.
- 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.

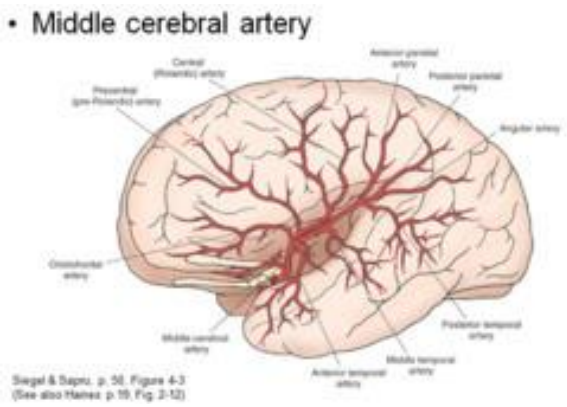
# Thrombotic and Embolic stroke

## Embolic Stroke.

- Sources of Emboli:
  - **Cardiac mural thrombi** (frequent): myocardial infarct, valvular disease, atrial fibrillation.
  - **Arteries** (often atheromatous plaques **within the carotid arteries).**
  - **Paradoxical emboli**, particularly in children with cardiac anomalies.
  - **associated with cardiac surgery.**
  - **Emboli of other material** (tumor, fat: through femur fracture or liposuction , or air: by impropriate injection.

- **The territory of distribution of the middle cerebral arteries most frequently affected by embolic infarction, Why?**
- Because, 80% of the blood carried by the large neck arteries flow through the middle cerebral arteries**. (pic)**

***In general, Embolic Infarctions are more common.***




## Thrombotic Stroke.

- The most common sites of primary thrombosis:
  - **The carotid bifurcation.**
  - **The origin of the middle cerebral artery.**
  - **At either end of the basilar artery.**

The majority of thrombotic stroke are due to ***Atherosclerosis***
***(remember HTN leads to atherosclerosis)***

# 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* . It can be caused by cardiac arrest and severe hypotension or shock.

**The clinical outcome varies with the severity of the insult:**

**Mild Global Cerebral Ischemia**: only a transient postischemic confusional state, with eventual complete recovery

**Severe Global Cerebral Ischemia:** **widespread neuronal death occurs irrespective of regional vulnerability.**

**Persistent vegetative state:**

Individuals who survive in this state often remain severely impaired neurologically and deeply comatose.

**Respirator brain:**

Other patients meet the clinical criteria for brain death, including evidence of diffuse cortical injury (isoelectric, or "flat," electroencephalogram) and brain stem damage, including absent reflexes and respiratory drive

When patients with this pervasive form of injury are maintained on mechanical ventilation, the brain gradually undergoes an **autolytic process***

*in (scoliosis ) operation for a child to correct vertebra column, surgeons decrease pressure to 50 mmHg of the patient to prevent bleeding but it can choose Global cerebral ischemia

*Apoptosis is programmed cell death involves a series of biochemical events.

Autolysis is a lysosome allows the digestive enzymes out of its membranes

## Sensitivity to Ischemia

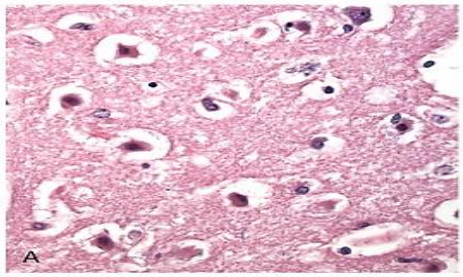
- Neurons are **much more** sensitive to hypoxia than are glial cells.
- The most susceptible to ischemia of short duration are:
  - Pyramidal cells of the Sommer sector (CA1) of the hippocampus.
  - Purkinje cells of the cerebellum.
  - Pyramidal neurons in the neocortex .

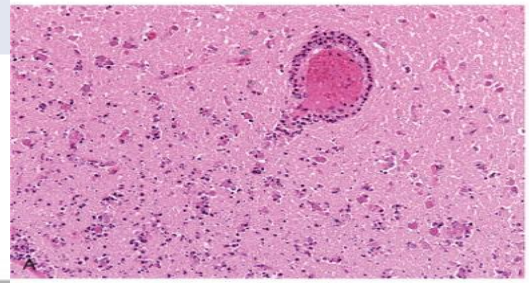
## Gross pathology

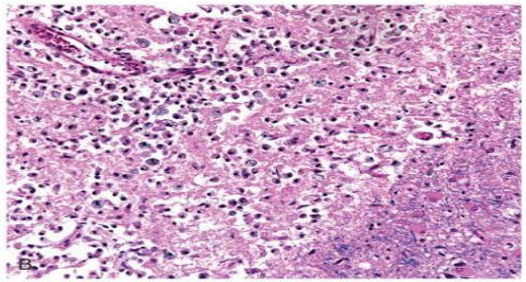
- The brain is swollen, with **wide gyri** and **narrowed sulci**.
- The cut surface shows poor demarcation between gray and white matter.

### Microscopically, infarction shows:

| Early changes | Subacute changes | Repair |
|---|---|---|
| 12 to 24 hours | 24 hours to 2 weeks | 2 weeks |
| **red neurons**, characterized initially by microvacuolization →cytoplasmic **eosinophilia,** and later nuclear pyknosis and karyorrhexis. | **-Necrosis of tissue**<br>- influx of macrophages<br>-vascular proliferation<br>- **reactive gliosis** | **- removal of all necrotic tissue**<br>- loss of organized CNS structure and gliosis.<br>- Pseudolaminar necrosis (preservation some layers and devastation دمار other lavers ) |







# 2-Focal Cerebral Ischemia

- The most important factor affects size, location and shape of infarcts is **collateral flow** which is the **circulation** in an area of tissue or an organ that blood can reach by more than one pathway "anastomosis"

- Sources of collateral flow:
  - The major source of collateral flow is the circle of Willis
  - cortical-leptomeningeal anastomoses
  - Some areas lack collateral flow (deep structures) such as:
    - **Thalamus**
    - **Basal ganglia**
    - **Deep white matter**

***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

# Gross pathology

Non hemorrhagic infarct:

First 6 hours: No changes

By 48 hours: pale, soft, and swollen-corticomedullary junction indistinct(not clear).

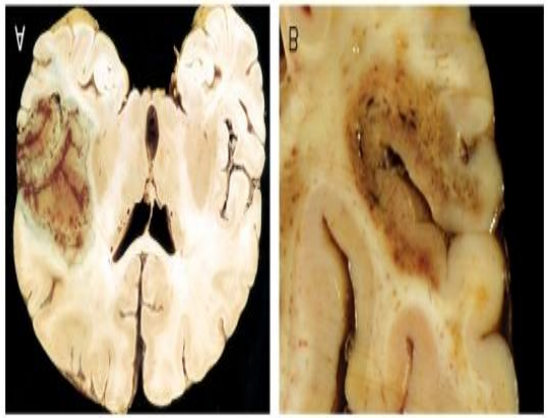
From 2 to 10 days: gelatinous and friable. boundaries distinct (become clear) - edema subsides.

From 10 days to 3 weeks: liquefaction (Fluid filled cavity).

**-Notice :**

**- hemorrhagic infarct is same in gross pathology as non hemorrhagic with the addition of blood extravasation and resorption.**

**- In persons receiving anticoagulant treatment, hemorrhagic infarcts may be associated with extensive intracerebral hematomas which is dangerous (because its mass effects and herniation to skull foramens)**



# Histopathology(Microscopic changes)

| After the first 12 hours | Until 48 hours |
|---|---|
| - Red neurons and cerebral edema .<br>- Endothelial and glial cells, mainly astrocytes, swell<br>- myelinated fibers begin to degenerate.<br>-Loss of usual characteraristics of white and grey matter | - neutrophilic emigration.<br>- mononuclear phagocytic cells. |

| in the next 2 to 3 weeks | After several months |
|---|---|
| Macrophages containing myelin breakdown or blood may persist in the lesion for months to years.<br>products | Astrocytic nuclear and cytoplasmic enlargement decrease. In the wall of the cavity, astrocyte processes form a dense feltwork (network) of glial fibers admixed with new capillaries and a few perivascular connective tissue fibers. In the cerebral cortex the cavity is limited from the meninges and subarachnoid space by a gliotic layer of tissue, derived from the molecular layer of cortex.<br>The Pia and Arachnoid **are not** affected and do not contribute to the healing process. |

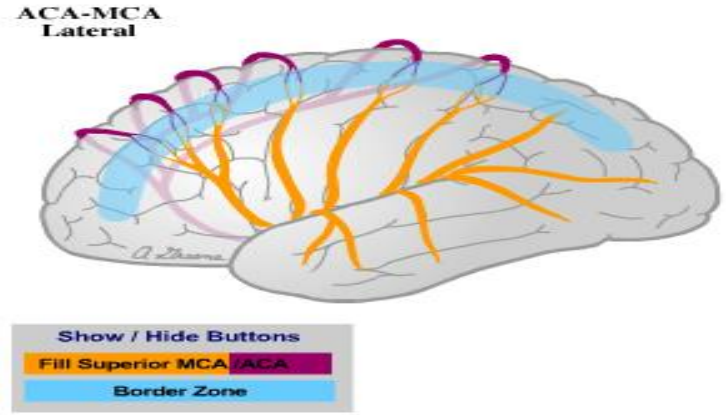
## Border zone infarcts ("watershed“ (خط فاصل :

Definition : Wedge -shaped areas of infarction that occur in the **most distal fields of arterial perfusion**

most common location : In the cerebral hemispheres, the greatest risk is the border zone between the anterior and the middle cerebral artery distributions **(pic)**
(يوجد بين المنطقة التي تتغذى بالشريان الدماغي الأمامي و المنطقة التي تتغذى بالشريان الدماغي الوسطي حدود أو منطقة يصلها تغذية أقل من كليهما وهي الأكثر عرضه لهذا النوع من الموت)

Morphology : a band of **necrosis** over the cerebral convexity a few centimeters lateral to the interhemispheric fissure

Border zone infarcts are usually seen after **hypotensive** episodes
(Because already there is no enough blood flow in this region)



# 1- Intracerebral hemorrhage:

## Definition :

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

1- Hypertension (Because it increases the impact of blood flow on blood vessels leading to aneurysm which may rupture and lead to hemorrhage).

2- Other forms of vascular wall injury (e.g. vasculitis)*

3- Arteriovenous malformation (Genetic disorder in which we can not differentiate between artery and vein )

4- tumors : (Because tumors lead to Angiogenesis which may burst causing hemorrhage)

*we must know the cause (infection or autoimmune) to choose the treatment (antibiotics or steroid) even if the vasculitis due to infection we give steroid to reduce the inflammation

# 2- Subarachnoid Hemorrhage :

- Causes :

- Rupture of a saccular (berry) **aneurysm** (the most frequent cause of clinically significant)
- Vascular malformation
- Trauma (in which case it is usually associated with other signs of the injury)
- Rupture of an intracerebral hemorrhage into the ventricular system
- Hematologic disturbances
- Tumors

- Clinical presentation :

Individuals are stricken with sudden, excruciating headache (described as "the worst headache I've ever had") and rapidly lose consciousness due to blood under arterial pressure is forced into the subarachnoid space

- Ability to rapture :

Rupture can occur at any time, but in about one-third of cases it is associated with acute increases in intracranial pressure.

- Recurrent :

bleeding is common in survivors; it is currently not possible to predict which individuals will have recurrences of bleeding.

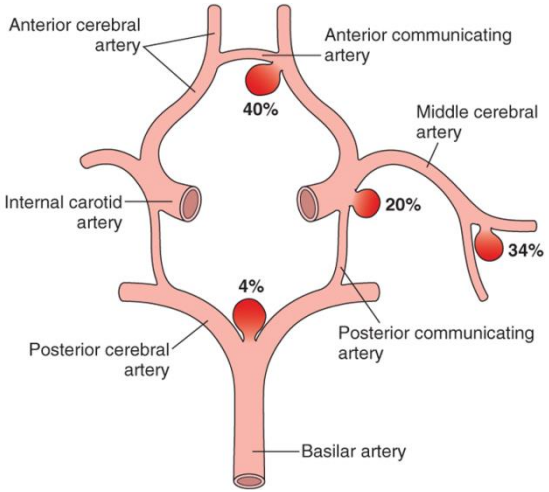
## Aneurysms :

- between 25% and 50% of individuals die with the first rupture, although those who survive typically improve and recover consciousness in minutes.

- Multiple aneurysm sometimes is genetic.

- The probability of aneurysm rupture increases with the size of the lesion.

## Out comes after subarachnoid hemorrhage :




- There is a risk of additional ischemic injury From vasospasm* involving other vessels.

- 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

- The prognosis worsens with each episode of bleeding

* Because the artery will do vasospasm to reduce the hemorrhage so the underling tissue will suffer from loss of oxygen

# Hypertensive Cerebrovascular Disease:

## The effect of hypertension on CNS :

*Hypertension causes **hyaline arteriolar sclerosis** in arterioles → weaker than are normal vessels and are more vulnerable to rupture

*chronic hypertension is associated with the development of minute aneurysms in vessels → *Charcot-Bouchard microaneurysms* → may rapture

## Type of Hypertensive Cerebrovascular Disease

| Lacunar infarcts | Slit hemorrhage | Acute hypertensive encephalopathy* | Massive hypertensive Intracerebral |
|---|---|---|---|
| *small cavitary infarcts.<br>*most commonly in deep gray matter .<br>*consist of cavities of tissue loss with scattered **lipid-laden macrophages** and surrounding **gliosis**<br>* can either be clinically silent or cause significant neurologic impairment | *Rupture of the small-caliber penetrating vessels.<br>*In time, these hemorrhages resorb, leaving behind a slitlike cavity surrounded by brownish discoloration (due to iron from blood) | A clinicopathologic syndrome:<br>Definition : Diffuse cerebral dysfunction.<br>- sometimes leading to coma<br>- May be associated with an edematous brain, with or without transtentorial or tonsillar herniation →Does not usually remit spontaneously<br>*Microscopically :<br>• Petechiae (red or purple spot on the skin)<br>• fibrinoid necrosis | |

- To know if the hemorrhage is due to hypertension we examine the retina of eye it will be edematous (papilloma )

# Vasculitis

- Infectious arteritis
e.g (syphilis and tuberculosis).
- In immunocompromised
(toxoplasmosis, aspergillosis*, and CMV encephalitis)

- Systemic arteritis
e.g ( polyarteritis nodosa)

Primary angitis of the CNS

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

* Granuloma microscopically feature

# Homework

## 1-What are the risk factors of strokes?

- Controllable: generally fall into two categories: lifestyle risk factors or medical risk factors.(table)
- Uncontrollable: include being over age 55, being male, being African American, 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.

# Summary from Robbins

## SUMMARY

### Cerebrovascular Diseases

- *Stroke* is the clinical term for acute-onset neurologic deficits resulting from hemorrhagic 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 ("watershed" 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.

# MCQs

**Q1: A kind of stroke of venous origin that enter the systemic arterial circulation through a lateral opening in the heart?**

A – Cardiac mural thrombi
B – Paradoxical emboli
C – emboli associated with cardiac surgery
D – arteries

**Q2: what is the most frequently affected by embolic infarction?**

A – End of basilar artery
B – Middle cerebral artery
C – Carotid bifurcation
D- None

**Q3: what usually seen after hypotensive episode?**

A– Reactive gliosis
B – lequifactive necrosis
C – Watershed
D – pseudolaminar necrosis

**Q4: intraparenchymal tumor may lead to?**

A – Intracerebral hemorrhage
B – Subarachnoid hemorrhage
C – slit hemorrhage
D – lacunar infarcts

**Q5: neurons are much more sensitive to hypoxia than are glial cells?**

A – True
B – False

**Q6: 54 years old female died from a brain disease, after 12 hours biopsy was taken and sent to the lab, they found edema, red neurons and glial cells. What could this disease be?**

A – global Cerebral ischemia
B – border zone infarct
C– focal Cerebral ischemia
D – hemorrhage slit

Ans: 1-B 2- B 3-C 4-A 5-A 6- C

# MCQs

**Q7: 47 years old male came with significant neurologic impairment , CT scan show small cavitary infarct in the brain. What is the most likely diagnosis?**

A – Lacunar infarct
B – acute hypertensive encephalopathy
C– slit hemorrhage
D– massive hypertensive intracerebral

**Q8: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

**Q9: the major source of contralateral flow is :**

A – circle of Willis
B – middle cerebral artery
C –posterior cerebral artery

**Q10: hemorrhagic infarcts in person receiving anticoagulant treatment, may be associated with**

A – extensive intracerebral hematomas
B – subdural hematoma
C – epidural hematoma

**Q11: Border zone infarcts are usually seen after**

A – hypertensive episodes
B – hyperglycemic episodes
C – hypotensive episodes

Ans: 7-A 8-C 9-A 10-A 11-C

# MCQs

**Q12: the most common cause of subarachnoid hematoma**

A – tumors

B –rupture of a saccular aneurysm

C – vascular malformation

**Q13: 35 years old lady came to the ER having a constant murmur sound in her left ear especially when making efforts (without pain) and if she squeeze the left side of her neck, the sound stops completely but start soon as she let go again , that may indicate :**

A – hematoma

B – increased intracranial pressure

C- aneurysm

**Q14: hematoma with infarction may cause :**

A- herniation of the brain

B- abscess

C- none of the above

**Q15: herniation of the brain through the foramen magnum happens due to :**

A- increased intracranial pressure

B-decreased intracranial pressure

C- none of the above

**Q16: granuloma is a prominent microscopic feature of :**

A- fungal vasculitis

B- viral vasculitis

C- bacterial vasculitis

**Q17: chronic hypertension is associated with the development of :**

A- lacunar infarct

B- Charcot-Bouchard microaneurysms

C- arteriolar sclerosis

Ans: 12- B 13- C 14-A 15-A 16- A 17- B

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