Pathogenesis & risk factors of

Cerebrovascular Accidents

Including: **Lecture Slides + Our Notes**

The colors indicate: **important points – Team note**

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Introduction

→ *Review the following terms:*

- *Hypoxia:*
  reduction of oxygen supply to a tissue below physiological levels despite adequate perfusion of the tissue by blood

- *Ischemia:*
  insufficient supply of blood to an organ, usually due to a blocked artery.

- *Infarction:*
  a localized area of ischemic necrosis produced by occlusion of the arterial supply or the venous drainage of the part.

Introduction

- The brain may be deprived of oxygen by any of several mechanisms:
  - **functional hypoxia (not only in brain)**, in:
    - a low partial pressure of oxygen (high altitude leads to ↓ PO_2)
    - impaired oxygen-carrying capacity (d/t low hemoglobin or anemia)
    - inhibition of oxygen use by tissue (by chemicals e.g. nitric oxide)

  →*list one example on each mechanism!*

  - **ischemia**, either *transient (temporary)* or *permanent, in*:
    - a reduction in perfusion pressure, as in hypotension
    - vascular obstruction
    - both

Perfusion: the passage of a fluid through a specific organ or an area of the body

Introduction

- 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

•**Prevalent:** سائد
•**Morbidity:** نسبة انتشار المرض
•**Mortality**: معدل الوفيات

The Stroke

- Definition:
  - It is the clinical term for a disease with acute onset of a neurologic deficit (depending on the site) as the result of vascular lesions, either hemorrhage or loss of blood supply.
- **General Symptoms:**

✓ Headache.

✓ Dizziness.

Thrombotic and Embolic stroke

Embolic Stroke:

- Overall, embolic infarctions are more common
- Sources of emboli include:
  - Cardiac mural thrombi (frequent);
    - myocardial infarct
    - valvular disease (rheumatic disease: vegetation happens to the valve, sends emboli to either lung or brain)
    - atrial fibrillation (**stagnation**: formation of an emboli)
  - ***Arteries***; (often atheromatous plaques within the carotid arteries)
  - ***Paradoxical emboli ,*** particularly in children with cardiac anomalies
  - Emboli associated with cardiac surgery
  - Emboli of other material (tumor, fat, or air) (broken leg → fat emboli in blood)
- The territory of distribution of the middle cerebral arteries most frequently affected by embolic infarction → *WHY?*

Most emboli lodge in the **middle cerebral artery** distribution (because 80% of the blood is carried by the large neck arteries flow through the middle cerebral arteries – it is more straight than the others).

Thrombotic and Embolic stroke

Thrombotic Stroke:

- The majority of thrombotic occlusions causing cerebral infarctions are due to ***atherosclerosis***
- The **most common sites** of **primary** thrombosis:
  - The carotid bifurcation
  - The origin of the middle cerebral artery
  - Either end of the basilar artery
- Atherosclerotic stenosis can develop on top a superimposed (on top of) thrombosis, accompanied by **anterograde** **(immediately after trauma)** extension, fragmentation, and distal embolization.

Clinical presentation
Investigations:

- Depends on which part of the brain is injured, and how severely it is injured
- Sometimes people with stroke have a **headache** (most common complaint), but stroke can also be completely painless
- It is very important to recognize the warning signs of stroke and to get immediate medical attention if they occur
  (**signs:** ask them to whistle, smile, speak, limbs weakness ..etc)
- If the brain damage sustained has been slight, there is usually complete recovery, but most survivors of stroke require extensive rehabilitation

Clinical presentation
Symptoms

- Sudden
- 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
- There can be ***speech problems*** and ***weak face muscles***, causing drooling
- ***Numbness or tingling*** is very 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

Drooling: Slaiva runs from mouth.
Tingling: prickling, stinging sensation (as from cold or a sharp slap)

Global (whole brain) Cerebral Ischemia

- Widespread ischemic/hypoxic injury occurs when there is a **generalized reduction of cerebral perfusion**, usually below systolic pressures of less than 50mmHg
  (occurs in severe hypotension: shock)

- **Causes include:**
  - **cardiac arrest** (patients will be having it)
  - severe hypotension or 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

Insult: body injury or trauma

- **In severe global cerebral ischemia**, widespread neuronal death, irrespective of regional vulnerability, occurs.

- **Persistent Vegetative State: (not brain death but brain is impaired)**
  - ❖ Individuals who survive in this state often remain severely impaired neurologically and deeply comatose (deep coma)

- **Respirator Brain (brain death)**
  - ❖ 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 (kills itself)

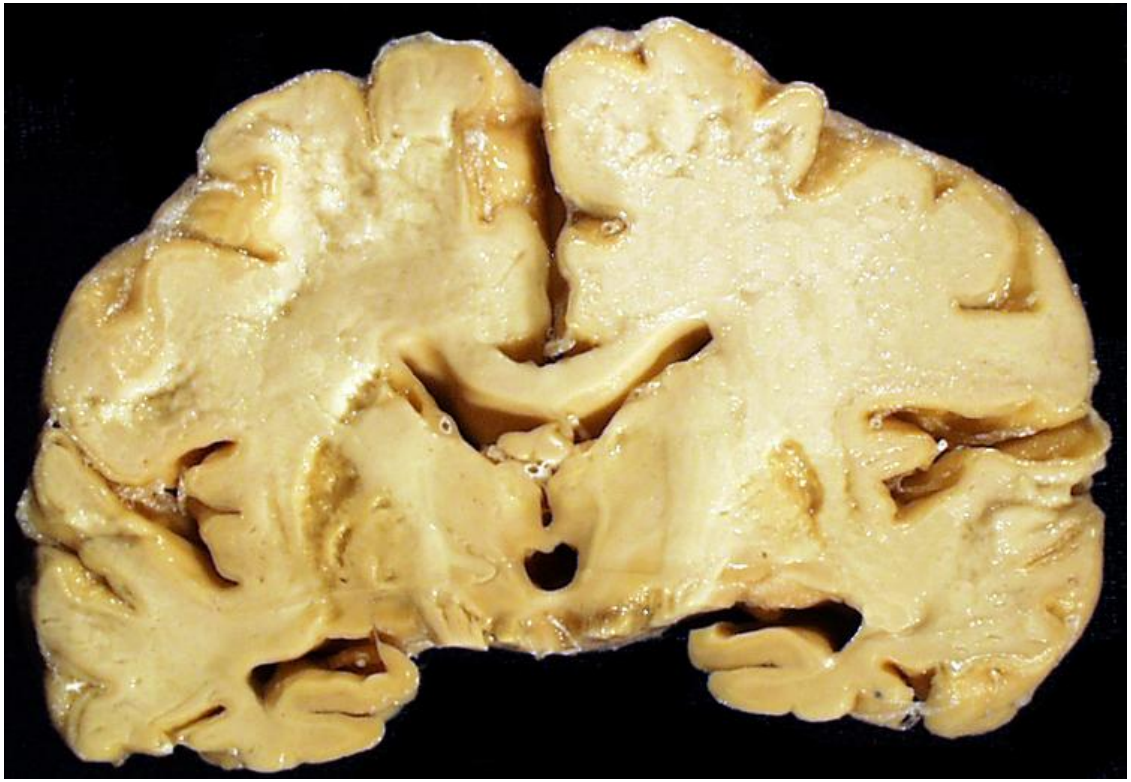
- **Sensitivity to ischemia:**

❖ 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

Nervous cells are the **most sensitive** cells to Hypoxia >>> then **Glial cells**

Gross Pathology



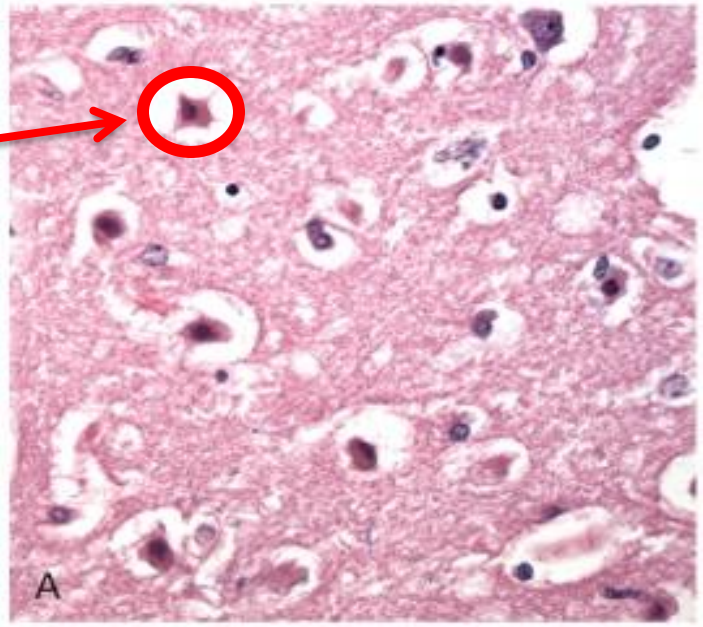
- The brain is swollen (d/t high intra cranial pressure), with wide gyri and narrowed sulci
- The cut surface shows poor demarcation between gray and white matter

Microscopically

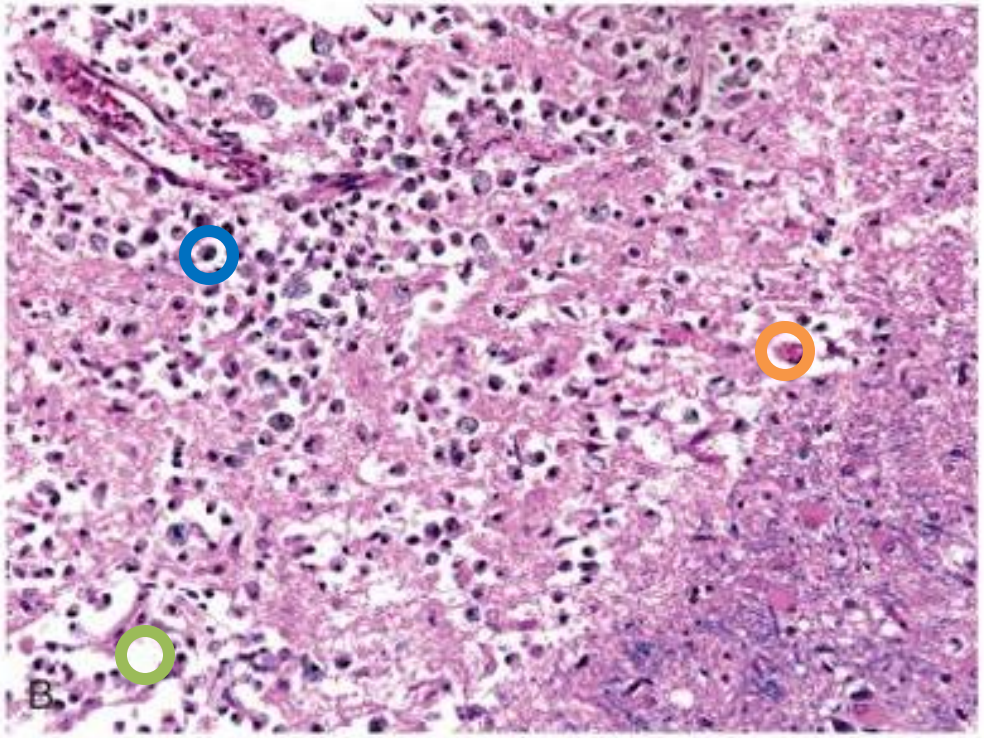
❖ **Early changes:**

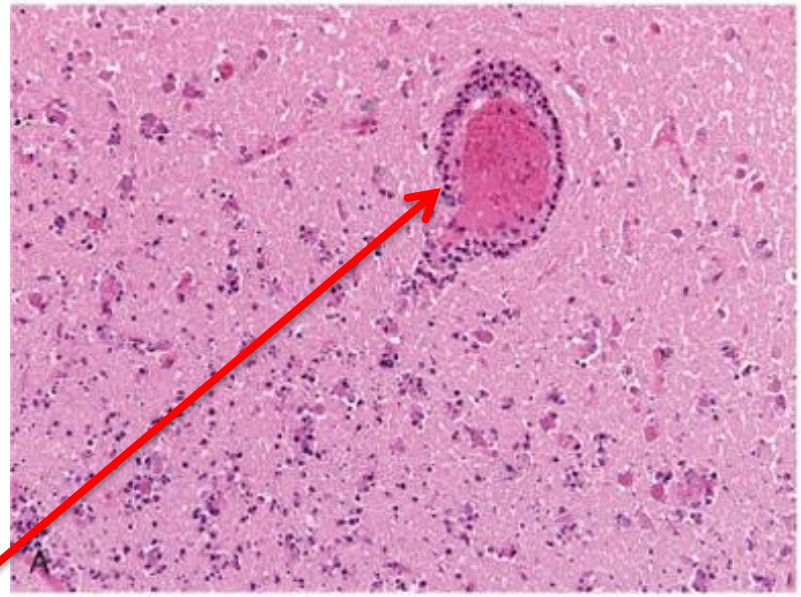
(12 to 24 hours after the insult)

- **red neurons (ischemic neurons)**
  an early sign of ischemia
  contains inside :
  MICRO-VACUOLIZATION
  (cytoplasmic eosinophilia,
  later nuclear **pyknosis** & **karyorrhexis**).



Pyknosis: shrinkage of nucleus' size
Karyorrhexis: rupture or fragmentation of cell nucleus





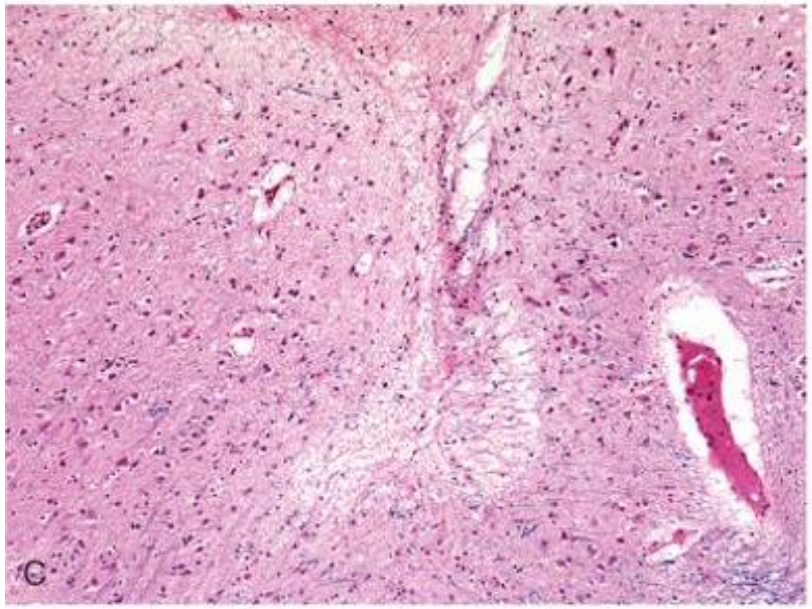
❖ **Subacute changes:** (24 hours to 2 weeks)

- Beginning, **infiltration by neutrophils** where vascular supply remains intact
- **Necrosis** of tissue, influx of **macrophages**, **vascular proliferation** and **reactive gliosis.**

Gliosis: glial cell proloferation in reaction to infarction (not glioma)

❖ **Repair:** (after 2 weeks)

- removal of all necrotic tissue, loss of organized CNS structure and gliosis



Focal Cerebral Ischemia

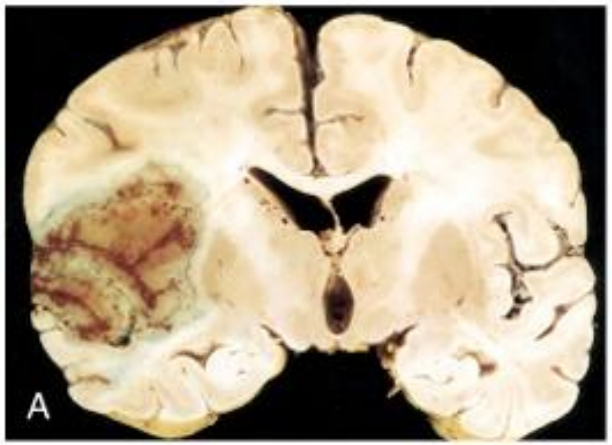
- **Cerebral arterial occlusion** → focal ischemia (caused by thrombus or emboli)
- The size, location, and shape of the infarct and the extent of tissue damage that results are determined by modifying variables, most importantly the adequacy of collateral flow:
  - **The major source of collateral flow** is the circle of Willis
  - **Partial collateralization** is also provided over the surface of the brain through cortical-leptomeningeal anastomoses
  - **Very Little Collateral Flow** at the deep penetrating vessels supplying structures such as:
    - **Thalamus**
    - **Basal ganglia**
    - **Deep white matter**

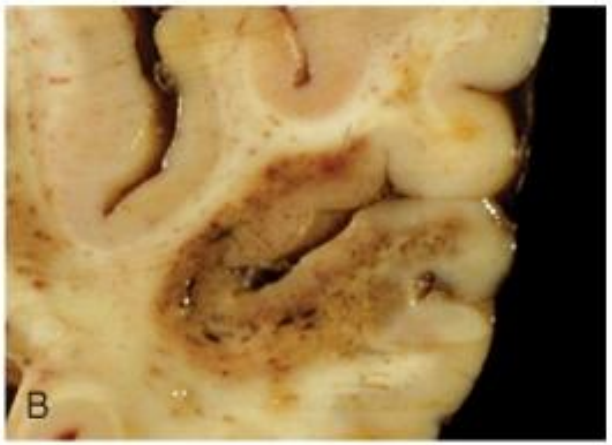
Collatral Flow: a good bypass (compensating roads for occluded arteries).

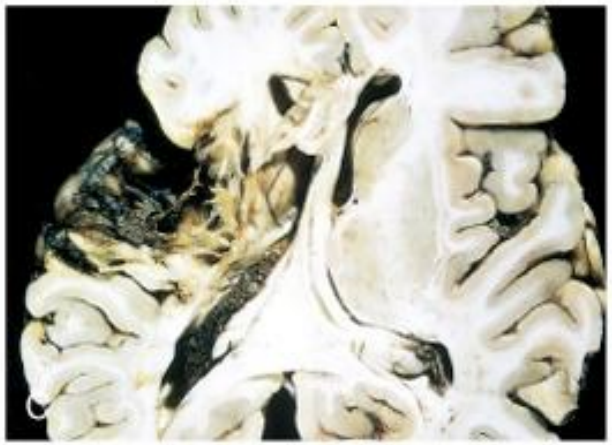
Gross Pathology

Nonhemorrhagic infarct:

- The first 6 hours of irreversible injury, little can be observed
- By 48 hours the tissue becomes **pale**, **soft**, and **swollen**, and the **corticomedullary junction becomes indistinct.**
- From 2 to 10 days the brain becomes **gelatinous and friable,** and the previously ill-defined boundary between normal and abnormal tissue becomes more distinct as **edema resolves** in the adjacent tissue that has survived
- From 10 days to 3 weeks, the tissue **liquefies** (liquifactive necrosis of the brain)**,** eventually leaving a fluid-filled cavity lined by dark gray tissue, which gradually expands as dead tissue is removed







Microscopically

- **After the first 12 hours:**

  - **Red neurons** and both cytotoxic and vasogenic **edema** predominate

  - There is loss of the usual characteristics of white and gray matter structures

  - **Endothelial and glial cells**, mainly **astrocytes**, swell, and **myelinated fibers** begin to disintegrate - **Rosenthal**

- **Until 48 hours,** there is some **neutrophilic** emigration followed by **mononuclear phagocytic cells** in the ensuing **2 to 3 weeks.**
  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.**

Vasogenic Edema: large fluid volume in circulatory system
Disintegrate: become reduced or fragmented
Emigration: change in position
Ensuing: following action or result

After several months

- the striking astrocytic nuclear and cytoplasmic enlargement recedes (moves back).
- ***In the wall of the cavity,*** **astrocyte processes** form a dense **feltwork** of glial fibers **are mixed with** new capillaries and a few perivascular connective tissue fibers
- ***In the cerebral cortex*** the cavity is delimited (demarcated) 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 (if they heal they would cause scarring which is not good – epilepsy !)

Feltwork: fibrous network

- **Deep structures** of brain are more affected than the **superficial structures** because **they have less collateralization**.
- The microscopic picture and evolution of **hemorrhagic infarction** parallel ischemic infarction, with the addition of blood extravasation and resorption **(ischemic infarction = hemorrhagic infarction – with minor additions)**
- **In persons receiving anticoagulant treatment,** hemorrhagic infarcts may be **associated with** extensive intracerebral hematomas

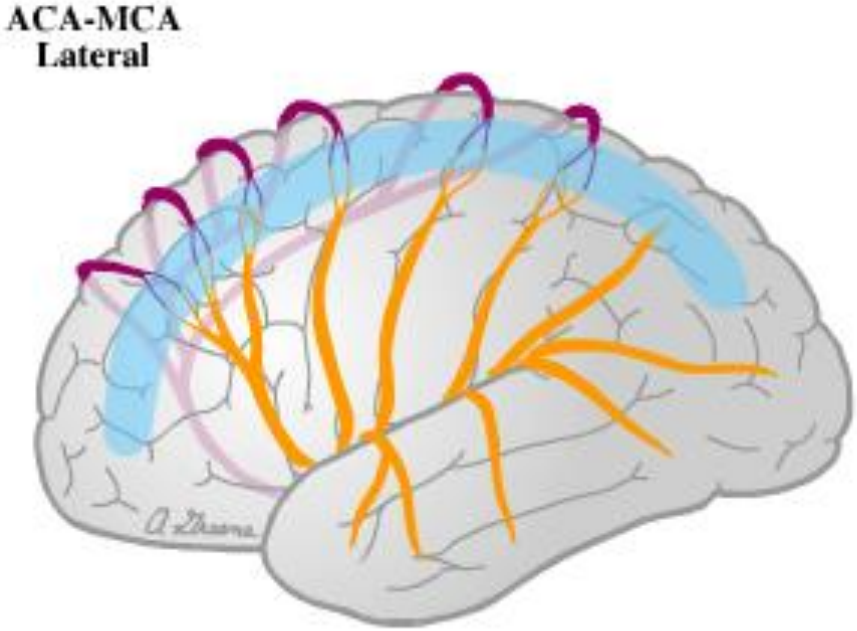
Border zone ("watershed") infarcts

- 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.**
- **Most Region Affected:**
  In the cerebral hemispheres, the border zone between the anterior and the middle cerebral artery distributions
- **Damage produces :**
  a band of necrosis over the cerebral convexity
  a few cms lateral to the ***inter-hemispheric fissure***
- **Usually Seen After:**
  hypotensive episodes

Border zone ("watershed") infarcts

It's a pattern of infarction, occur in the stenosis areas.

Anterior and middle cerebral arteries are more common to be affected.



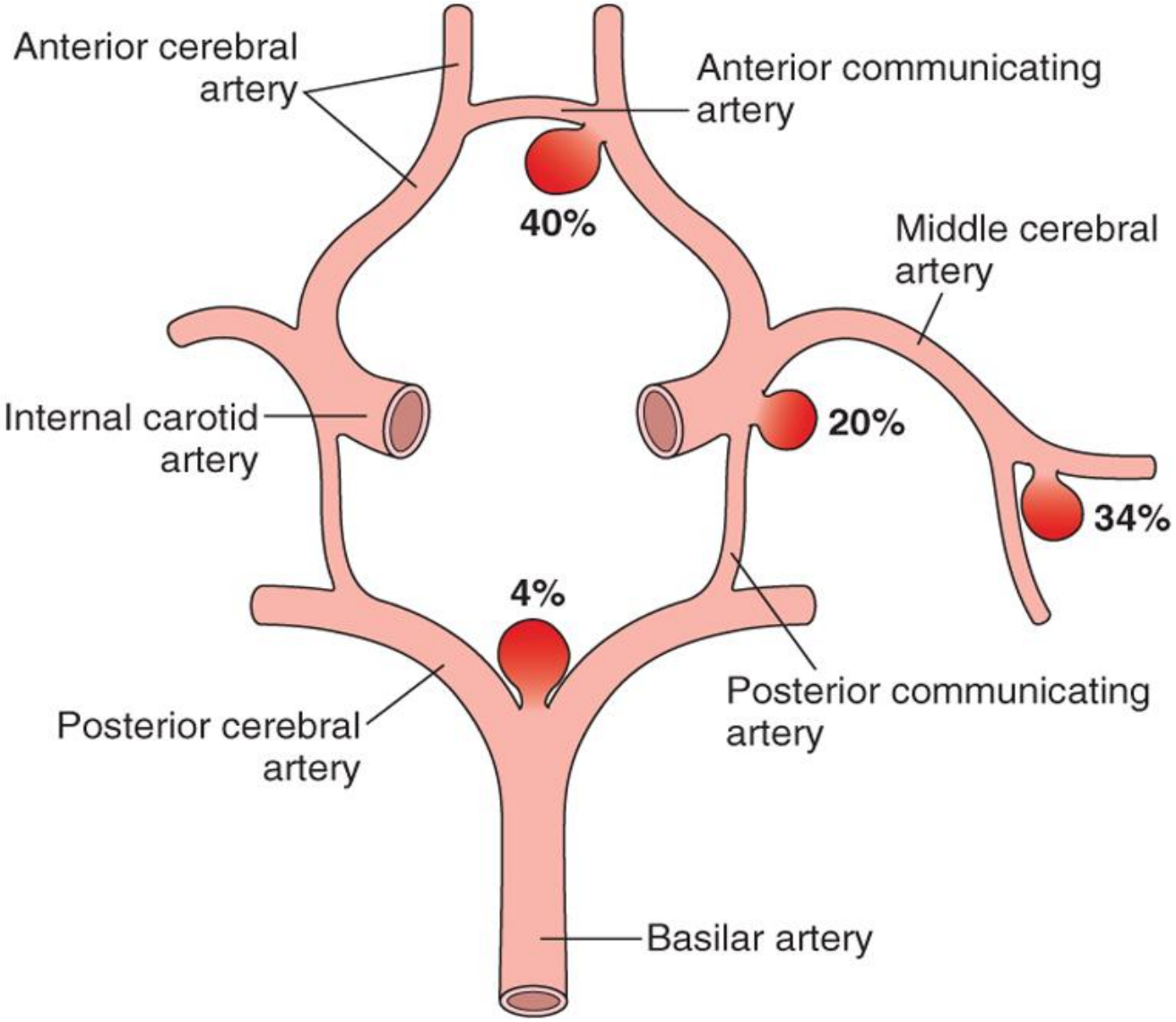
Intracerebral hemorrhage

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

- Hypertension
- Other forms of vascular wall injury (e.g. vasculitis)
- Arterio-venous malformation
- An intra-parenchymal tumor

Commonest site: anterior part of circle of willis

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



Aneurysms: A localized, pathological, blood-filled dilatation of a blood vessel caused by a disease or weakening of the vessel's wall.

Subarachnoid Hemorrhage

- **Causes of subarachnoid hemorrhage:**
  - rupture of a saccular (berry) aneurysm (The most frequent cause of clinically significant) **occur in Basilar Artery**
  - vascular malformation
  - trauma (in which case it is usually associated with other signs of the injury)
  - rupture of an intra-cerebral hemorrhage into the ventricular system
  - hematologic disturbances
  - Tumors

- Rupture can occur at any time, but in about one-third of cases it is associated with **acute increases in intracranial pressure**, such as with straining at stool or sexual orgasm **(doing physical activities that cause high ICP suddenly)**

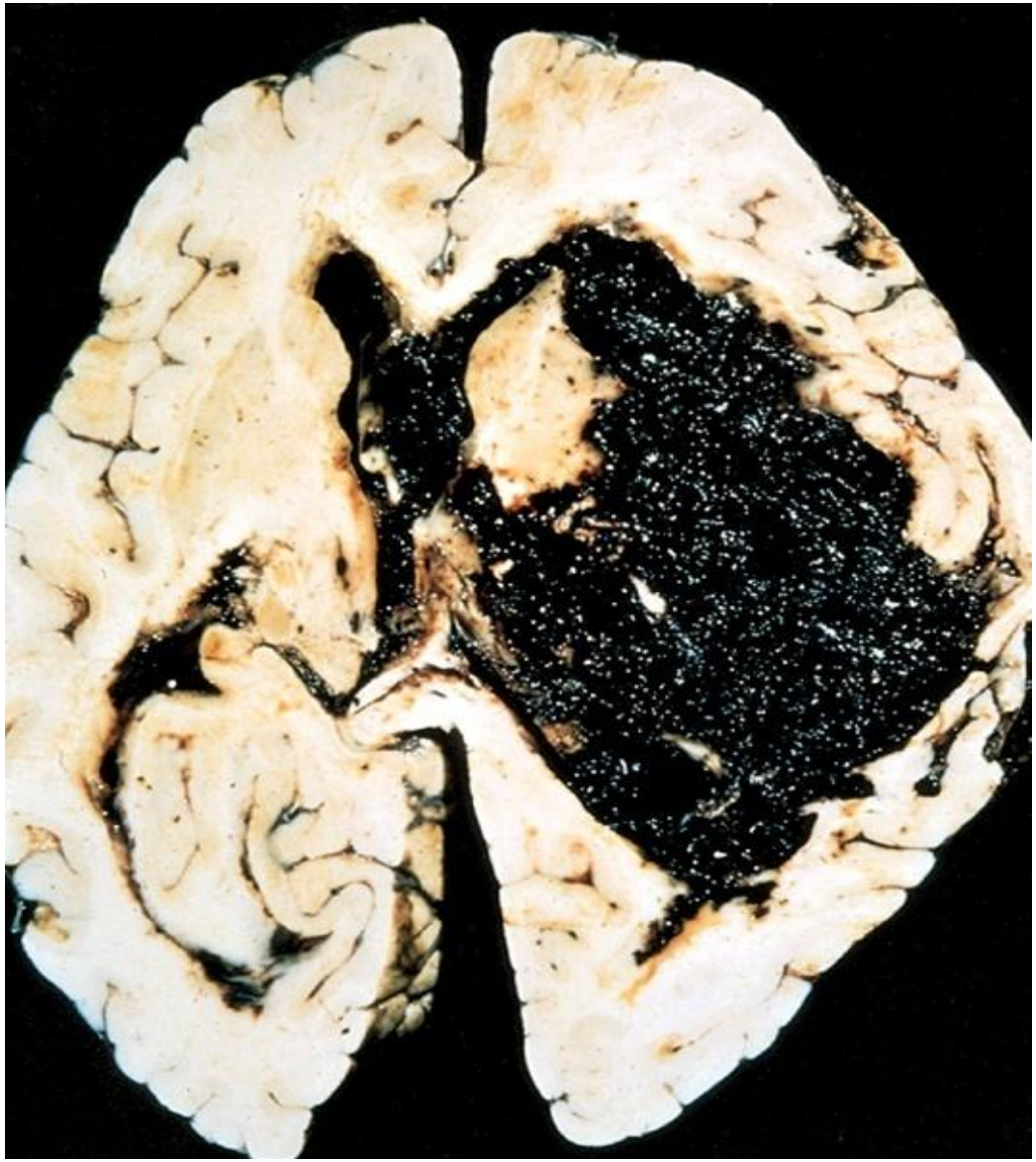
- Blood under arterial pressure is forced into the subarachnoid space, and individuals are stricken with **sudden, severe headache**
  (classically described as "the worst headache I've ever had")
  and rapidly lose consciousness

- 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 exist in 20% to 30% of cases. Although they are sometimes referred to as *congenital,* they are not present at birth but develop over time because of underlying defects in the vessel media **(multiple aneurysms are usually congenital)**
- The probability of aneurysm rupture increases with the size of the lesion, such that aneurysms greater than 10 mm have a roughly 50% risk of bleeding per year **(the bigger the aneurysm the bigger the size of the lesion)**
- **In the early period after a 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 resorption

Hypertensive Cerebrovascular Disease

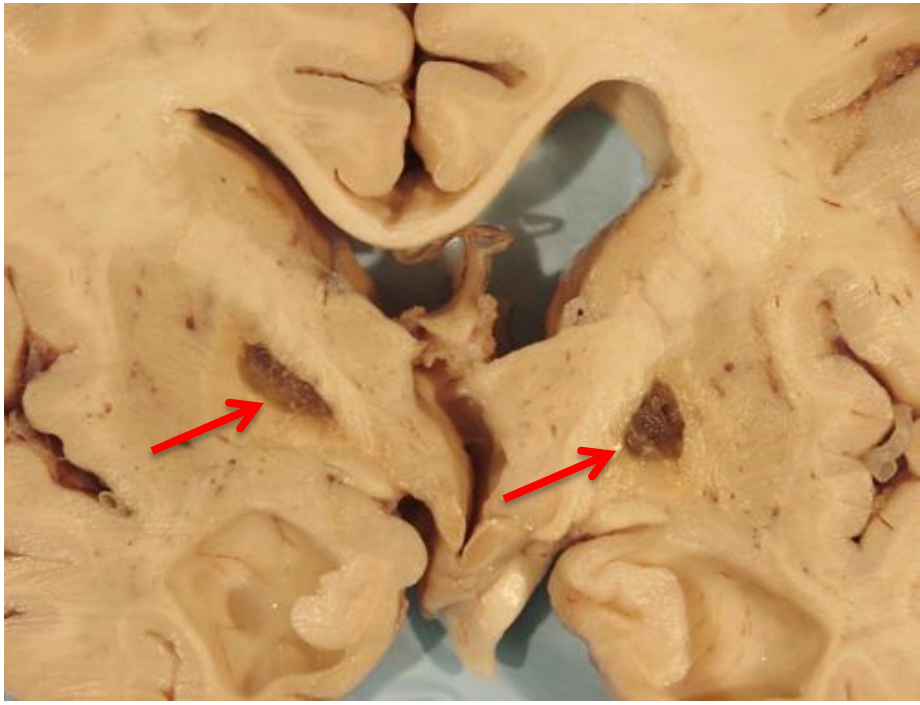
- The most important **Effects Of Hypertension** on the brain include:
  - Massive hypertensive intra-cerebral hemorrhage (discussed earlier, most important)
  - Lacunar infarcts
  - Slit hemorrhages
  - Hypertensive encephalopathy (high Intracranial pressure from CSF)
- Hypertension **affects** the deep penetrating arteries and arterioles that supply the basal ganglia and hemispheric white matter (white matter of cerebral hemispheres) and the brain stem
- Hypertension **causes** several changes, including **hyaline arteriolar sclerosis** in arterioles → weaker than are normal vessels and are more vulnerable to rupture.
- **In some instances**, **chronic hypertension** is associated with the development of minute (small) aneurysms in vessels that are less than 300 μm in diameter → ***Charcot-Bouchard micro-aneurysms,*** which can rupture

Lacunar Infarcts: a type of stroke that results from occlusion of one of the penetrating arteries that provides blood to the brain's deep structures



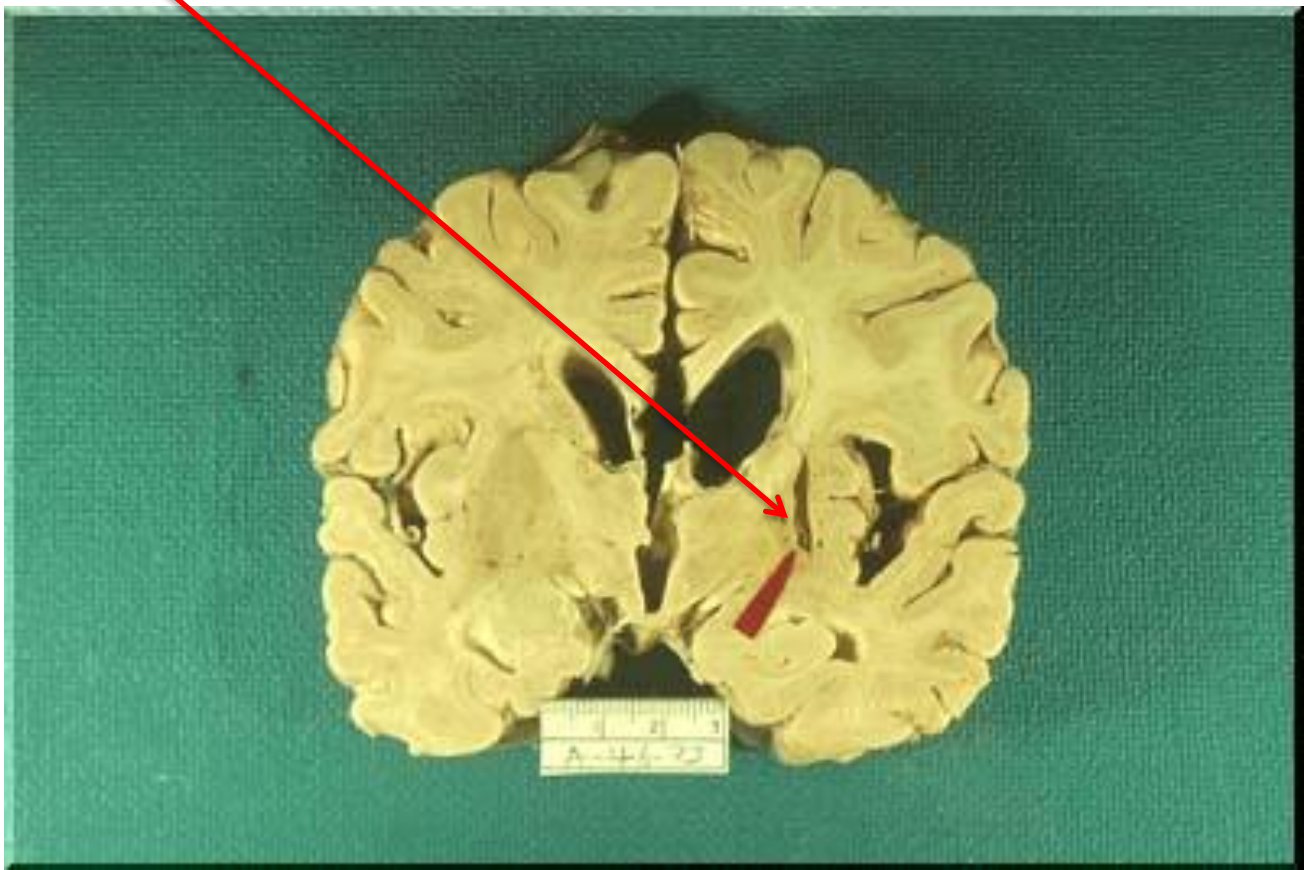
Lacunar infarcts:

- small cavitary infarcts
- **most commonly in** deep gray matter (basal ganglia and thalamus), internal capsule, deep white matter, and pons
- **consist of**
  -cavities of tissue loss
  -scattered lipid-laden macrophages
  -surrounding gliosis
- depending on their location in the CNS, lacunes can either be clinically silent or cause significant neurologic impairment



Slit hemorrhage:

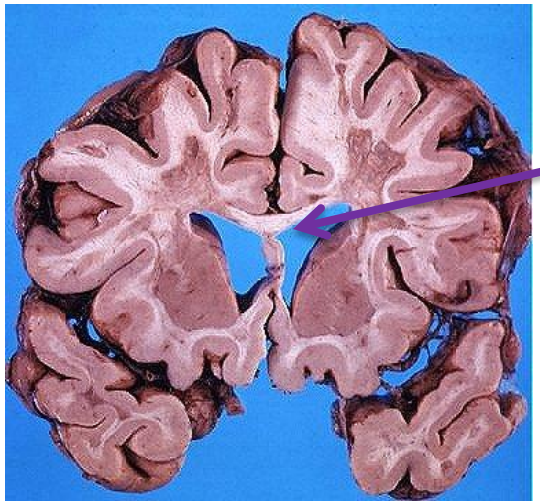
- rupture of the small-caliber penetrating vessels
  → the development of small hemorrhages
- in time, these hemorrhages reabsorps, leaving behind **a slit-like cavity** surrounded by brownish discoloration



Acute hypertensive encephalopathy:

A clinicopathologic syndrome:

- Diffuse cerebral dysfunction, including headaches, confusion, vomiting, and convulsions, sometimes leading to coma
- Does not usually remit (goes away) 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 .



Herniation: a protrusion through an abnormal bodily opening.
Fibrinoid Necrosis: a type of necrosis affecting the blood vessels.
Petechiae: A small purplish spot on a body surface, such as the skin or a mucous membrane, caused by a minute hemorrhage and often seen in **typhus** (an infectious disease).

Vasculitis

Infectious arteritis of small and large vessels:

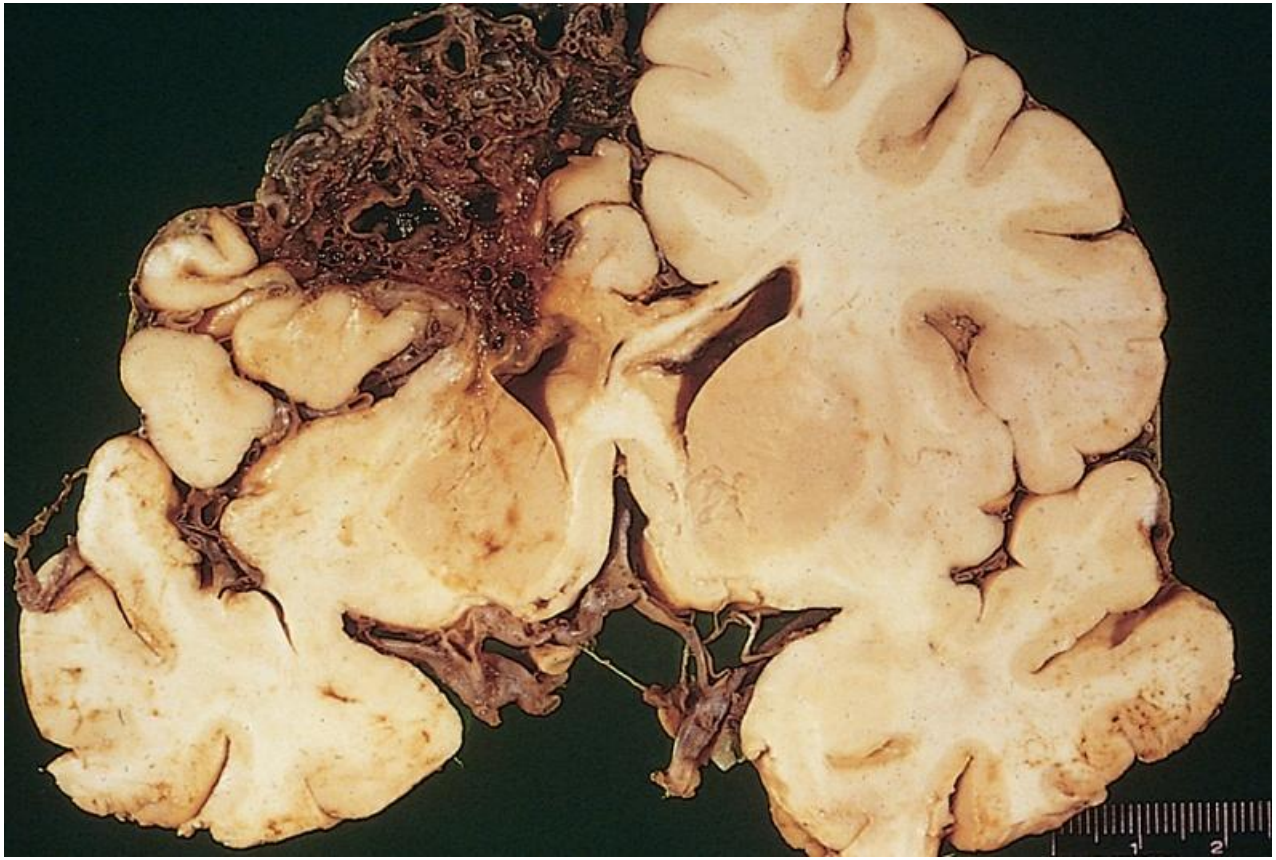
- Previously **in association with** syphilis and tuberculosis
- Now more commonly occurs in the setting of immunosuppression and **opportunistic infection** (such as toxoplasmosis, aspergillosis, and CMV encephalitis) – common when immunosuppressed

- **Systemic forms of vasculitis**, such as **polyarteritis nodosa (PAN)**, may involve cerebral vessels and cause single or multiple infarcts throughout the brain.
- **Primary angiitis of the CNS:**
  - 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

Opportunistic infection: an infection caused by pathogens (bacterial, viral , fungal or protozoan) that usually do not cause disease in a healthy host .. But immunosuppressed.
Angiitis: inflammation of a blood vessel or lymph duct.

Arterio-venous malformation

an abnormal connection between veins and arteries



→ So what can cause or contribute to a stroke?

- Hypertension
- Athersclerosis
- Thrombophilia, e.g. Sickle cell anemia
- Embolic diseases
- Systemic hypoperfusion/ Global hypoxia, e.g. shock
- Vascular malformations
- Vasculitis
- Tumors
- Venous thrombosis
- Amyloid angiopathy (deposition of amyloid in media adventitia of arteries) (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.

→*What are **the risk factors of stroke**?*

- **Hypertention.**
- **Atrial Fibrillation.**
- **Blood Lipids.**
- **Diabetes Mellitus.**
- **Surgery.**
- **Nutrition and metabolic interventions.**

→ *Define: **Transient ischemic attack***

(A mini stroke)

a change in the blood supply to a particular area of the brain, resulting in brief neurologic dysfunction that persists, by definition, for less than 24 hours. If symptoms persist longer, then it is categorized as a stroke.