Lectures 5 & 6
Cerebrovascular Accidents

PATHOLOGY TEAM 435

{ ومن لم يذق مرّ التعلُّمِ ساعةً.. تجرع ذلَّ الجهل طوال حياتهِ }

Revised by

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Red: Important. Grey: Extra Notes Doctors Notes will be in text boxes

Objectives:

The student should:

- 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.

Background:

Cerebrovascular disease is one of the leading causes of death and morbidity in Saudi Arabia. It is the most prevalent neurologic disorder in terms of both morbidity and mortality. The term cerebrovascular disease denotes any abnormality of the brain caused by a pathologic process involving blood vessels. The three basic processes are (1) thrombotic occlusion of vessels, (2) embolic occlusion of vessels, and (3) vascular rupture.

Key principles to be discussed:

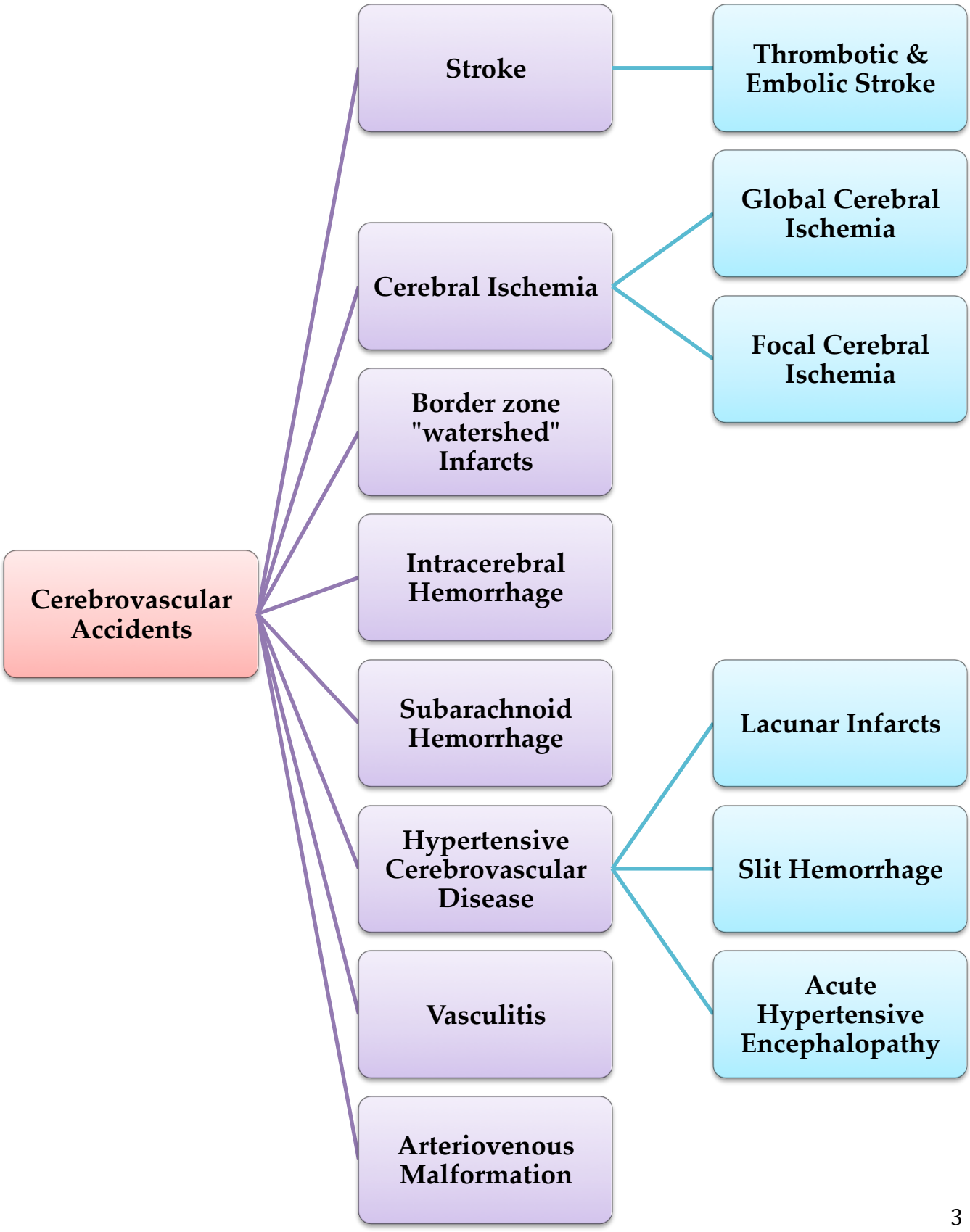
- The concept of “stroke”.
- Thrombotic and embolic stroke: incidence, significance of classification, causes and major clinicopathological features.
- Global Cerebral Ischemia, Border zone ("watershed") infarcts and focal Cerebral Ischemia: definition, causes and main gross and histopathological features.
- Intracerebral and subarachnoid hemorrhage: causes and major clinicopathological features.
- Vascular malformations: definition
- The main possible CNS cerebrovascular complications of hypertension including intracerebral hemorrhage, lacunar infarct, slit hemorrhages and hypertensive encephalopathy: definitions
- Vasculitis: possible causes.

Key principles to be covered by self-directed learning:

- Hypoxia, Ischemia, and Infarction: revision of definitions.
- Risk factors of cerebrovascular accidents.
- Transient ischemic attacks: definition.

References:

Lecture, Robbins, Kaplan Lecture Notes.


Cerebrovascular Accidents
Stroke
Thrombotic & Embolic Stroke
Cerebral Ischemia
Global Cerebral Ischemia
Focal Cerebral Ischemia
Border zone "watershed" Infarcts
Intracerebral Hemorrhage
Subarachnoid Hemorrhage
Hypertensive Cerebrovascular Disease
Lacunar Infarcts
Slit Hemorrhage
Acute Hypertensive Encephalopathy
Vasculitis
Arteriovenous Malformation

Introduction:

Hypoxia:

Deficiency in the amount of oxygen reaching the tissues.

Ischemia:

An inadequate blood supply to an organ or part of the body.

Ischemia could be reversible while infarction isn't

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 any of several mechanisms:

Functional hypoxia, in:	**Ischemia, (*transient* or *permanent*), *in:***
A low partial pressure of oxygen (e.g., high altitude)	A reduction in perfusion pressure, as in hypotension.
Impaired oxygen-carrying capacity (e.g., severe anemia, carbon monoxide poisoning)	Vascular obstruction.
Inhibition of oxygen use by tissue (e.g., cyanide poisoning)	Both

Difference between ischemia and infarction:

- Ischemia is poor blood supply when demand is more than supply.
- Infarction is dead tissue caused by ischemia.

Example: a young male who is healthy who had a trauma leading to bleeding because of rupture of spleen. He might not get any abnormalities in the brain nor suffering
Same situation an elderly male who has atherosclerotic blood vessels and got the same rupture he may suffer from brain ischemia which might turn into an infarction, Why? Because he has already atherosclerotic blood vessels

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

Cerebrovascular accident=Stroke
Could be due to: -Thrombosis –Hemorrhage

Stroke:

It is the clinical term for a disease with acute onset of a neurologic deficit as the result of vascular lesions, either hemorrhage or loss of blood supply.

Thrombotic and embolic stroke:

Overall, **embolic infarctions** are more common.

Embolic Stroke

Sources of emboli include:

- Cardiac mural thrombi (frequent):
  - Myocardial infarct.
  - Valvular disease.
  - Atrial fibrillation.

Embolic stroke might appear in cardiac surgery because the blood becomes very hyper-coagulable.

Fat emboli may result from bone fractures

- Arteries: often atheromatous plaques within the carotid arteries.
- Paradoxical[1] emboli, particularly in children with cardiac anomalies.

Emboli associated with cardiac surgery or other material (tumor, fat, or air).

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

Why? Because it's an extension of the internal carotid artery and emboli tend to lodge where vessels branch or in areas of stenosis (usually caused by atherosclerosis).

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 occlusions causing cerebral infarctions are due to **atherosclerosis**[2]
- Atherosclerotic stenosis: can develop on top a superimposed thrombosis, accompanied by anterograde extension, fragmentation, and distal embolization.

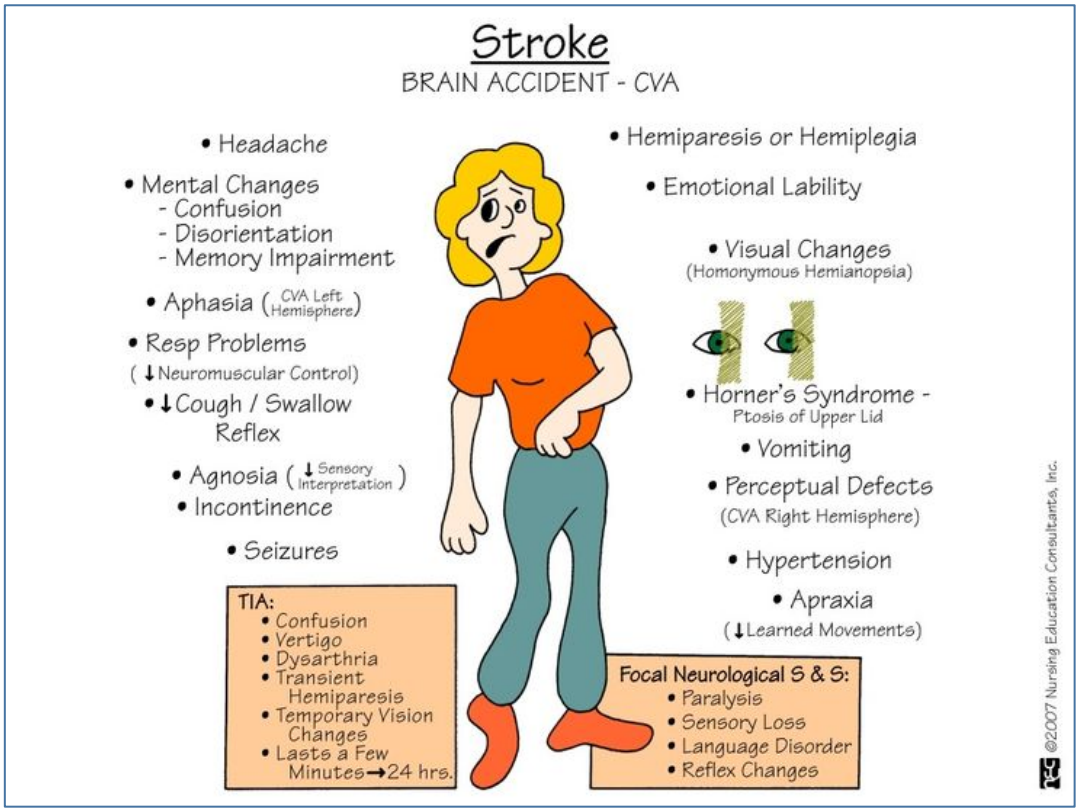
  Thrombotic infarction is characteristically an anemic (white) infarct.

[1] Means not following the normal root of embolism movement

[2] Disease of elastic arteries and large and medium-sized muscular arteries; a form of arteriosclerosis caused by buildup of cholesterol plaques

Clinical presentation 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 and to get immediate medical attention if they occur.
- If the brain damage sustained has been slight, there is usually complete recovery, but most survivors of stroke require extensive rehabilitation.
- **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.



If the injury was on the left part of the face then the right arm and right leg will get affected and vice versa.

We ask the patient to blow (whistle) if we were suspecting a stroke because this kind of movement is very sensitive to the muscle of the face and its function he won't be able to do it.

Global Cerebral Ischemia: (diffuse ischemic encephalopathy)

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

That's why a person might tolerate hypertension more than hypotension because the brain cannot function without Oxygen and Glucose

Causes include:

- Cardiac arrest
- Severe hypotension or shock

Septic, Hypovolemic or Toxic shock

The clinical outcome varies with the severity of the insult:

- If mild → may be only a transient postischemic confusional state, with eventual complete recovery
- In 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, resulting in the so-called "respirator brain'.

Neocortex = cerebral cortex

Sensitivity to ischemia:

- Neurons are much more sensitive to hypoxia than are glial cells.
- **The cells 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.

Note that when there is Global ischemia all of the cells will suffer

Pathology:

Gross

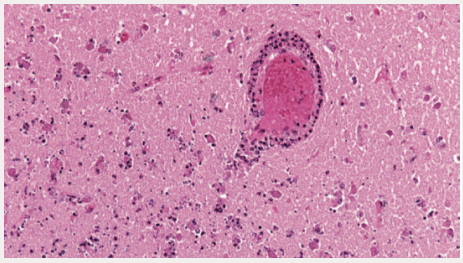
- The brain is swollen, with wide gyri and narrowed sulci. "Opposite to Alzheimer"
- The cut surface shows poor demarcation between gray and white matter.

Swollen brain (edema) might lead to herniation of the base of the brain

Microscopic

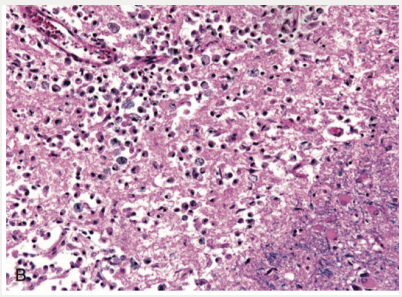
Early changes

- 12 to 24 hours after the insult.
- Karyorrhexis
- Red neurons, characterized initially by microvacuolization → cytoplasmic eosinophilia, and later nuclear pyknosis.



Subacute changes

- 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.



Repair

- After 2 weeks.
- Removal of all necrotic tissue, loss of organized CNS structure and gliosis.

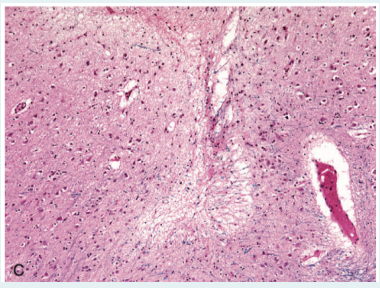


Figure 22–6 Cerebral infarction. **A,** Infiltration of a cerebral infarction by neutrophils begins at the edges of the lesion where the vascular supply is intact. **B,** By day 10, an area of infarction shows the presence of macrophages and surrounding reactive gliosis. **C,** Old intracortical infarcts are seen as areas of tissue loss with a modest amount of residual gliosis.

Collateral flow: when an artery supplies an area and another artery supplies adjacent area meet together.

Focal Cerebral Ischemia:

- Cerebral arterial occlusion → focal ischemia
- 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
  - In contrast, there is little if any collateral flow for the deep penetrating vessels supplying structures such as:
    - Thalamus
    - Basal ganglia
    - Deep white matter

Nothing will be seen when taking a biopsy from an ischemic area of the brain within the first 6 hours of the incident

Gross pathology:

Nonhemorrhagic infarct: (Irreversible injury)

First 6 hours	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, eventually leaving a fluid-filled cavity lined by dark gray tissue, which gradually expands as dead tissue is removed

Activated astrocytes are called gemistocytes

Microscopically the tissue reaction follows a characteristic sequence:

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
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
Then?	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
After several months	The striking astrocytic nuclear and cytoplasmic enlargement recedes

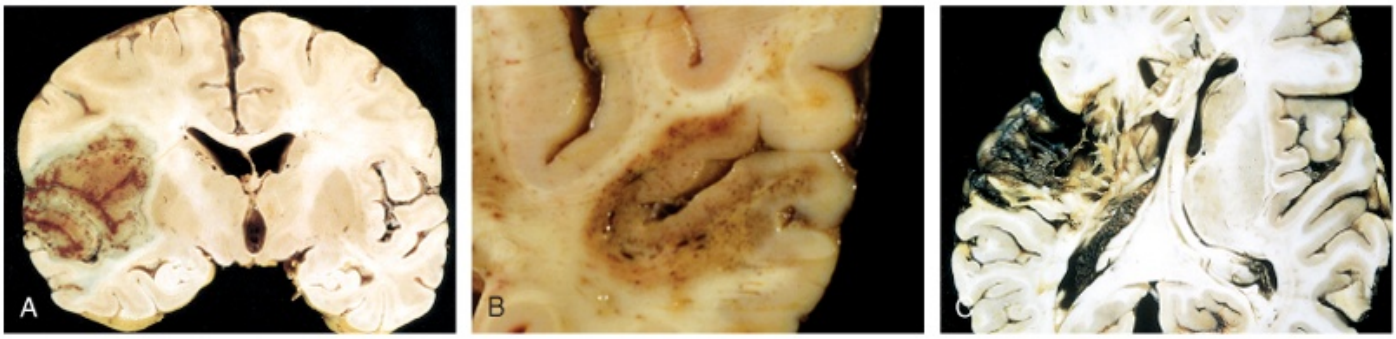
The healing process:

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 (تم عزله) from the meninges and subarachnoid space by a gliotic layer of tissue, derived from the molecular layer of cortex
Pia and arachnoid are not affected and do not contribute to the healing process	

Microscopic appearance (hemorrhagic infarct):

- Parallel ischemic infarction.
- Blood extravasation and resorption.
- If the person is receiving anticoagulant treatment, may be associated with extensive intracerebral hematomas.

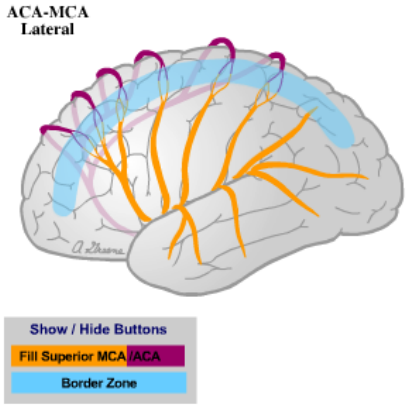
The brain usually does not get scarred because the scar might trigger the risk of epilepsy

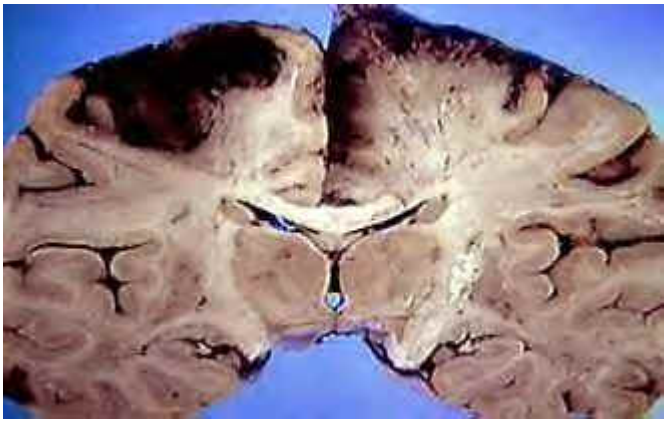


- **Section of the brain showing a large, discolored, focally hemorrhagic region in the left middle cerebral artery distribution (hemorrhagic, or red, infarction).**
- **An infarct with punctate hemorrhages, consistent with ischemia-reperfusion injury, is present in the temporal lobe.**
- **Old cystic infarct shows destruction of cortex and surrounding gliosis.**

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**
- 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
- Border zone infarcts are usually seen after hypotensive episodes





Wedge-shaped areas of infarction: very typical, the lesion occurs where we have two arteries. Also defined as the border zone between two areas of irrigation from two different arteries, which occurs at the most distal fields of arterial perfusion.

Intracerebral (intracranial) hemorrhage: (intraparenchymal)

Causes severe headache, frequent nausea/vomiting, steady progression of symptoms over 15–20 minutes, and coma.
Hemorrhages within the brain (intracerebral) can occur secondary to:

- Hypertension (most frequently)
- Other forms of vascular wall injury (e.g. vasculitis)
- Arteriovenous malformation
- An intraparenchymal tumor
- Hemorrhages associated with the dura (in either subdural or epidural spaces) make up a pattern associated with trauma (discussed in another lecture)

Hypertension: up to 200-240-250.
A lot of people die because of hypertension hemorrhage
Tumors: Glioblastoma

In cases of hemorrhagic infarct, patients should NOT take anti-coagulant.

They start in the epidural or dura but they sometimes extend to intracerebral hemorrhage.

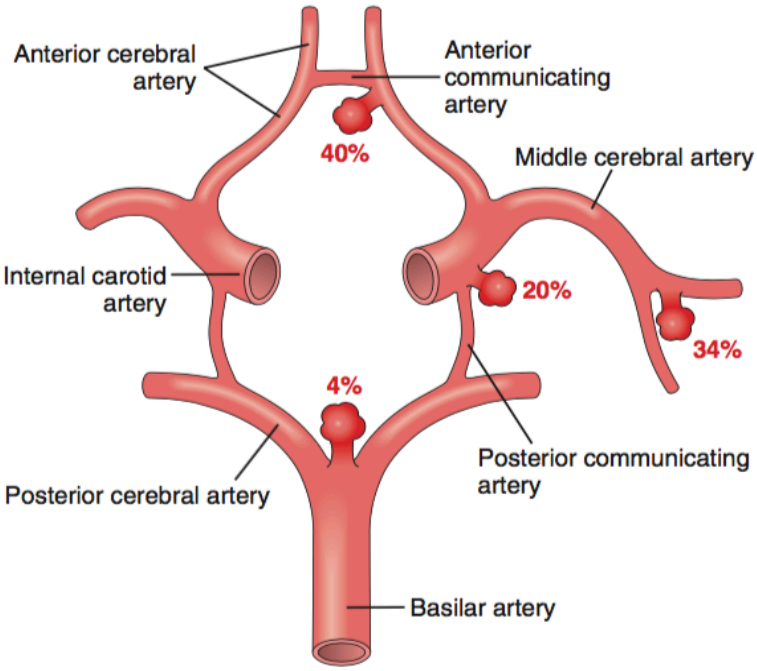
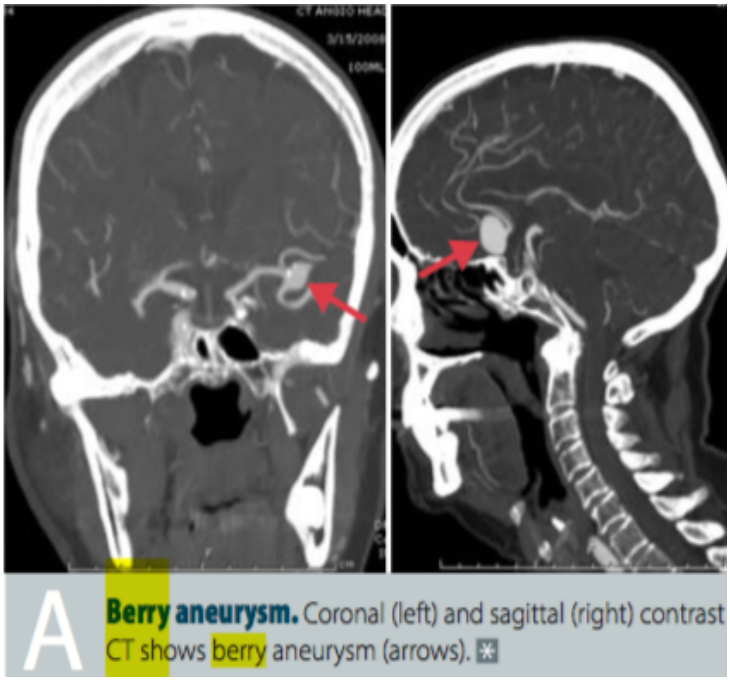


Figure 22–9 Common sites of saccular aneurysms.



Berry Aneurysms:
Weakness in the wall of the artery most important "frequent" site between: Anterior communicating artery and anterior cerebral artery.
Some of them are Congenital but they don't show until adulthood and other get it with age.
If they bleed for one time the chance will be higher every year, increasing risk 50% for another time.
Causes of rupture: Hypertension.
If a FEMALE patient comes in with murmur in her ear it means that the blood is flowing in the aneurysm and going out of it (usually in the middle cerebral artery) intracerebral arteriography should be done for her.

Subarachnoid Hemorrhage:

Causes of subarachnoid hemorrhage:

- Rupture of a saccular (berry) aneurysm[1] (The most frequent cause).
- 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.

- **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.
- 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 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.
- 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.

- In the early period after a subarachnoid hemorrhage, there is a risk of additional ischemic injury from vasospasm involving other vessels.

- **Healing phase of subarachnoid hemorrhage:**
  - Meningeal fibrosis.
  - Scarring occurs.

  They lead to obstruction of CSF flow as well as interruption of the normal pathways of CSF resorption

The patient may develop hydrocephalus due to adhesion in the arachnoid.

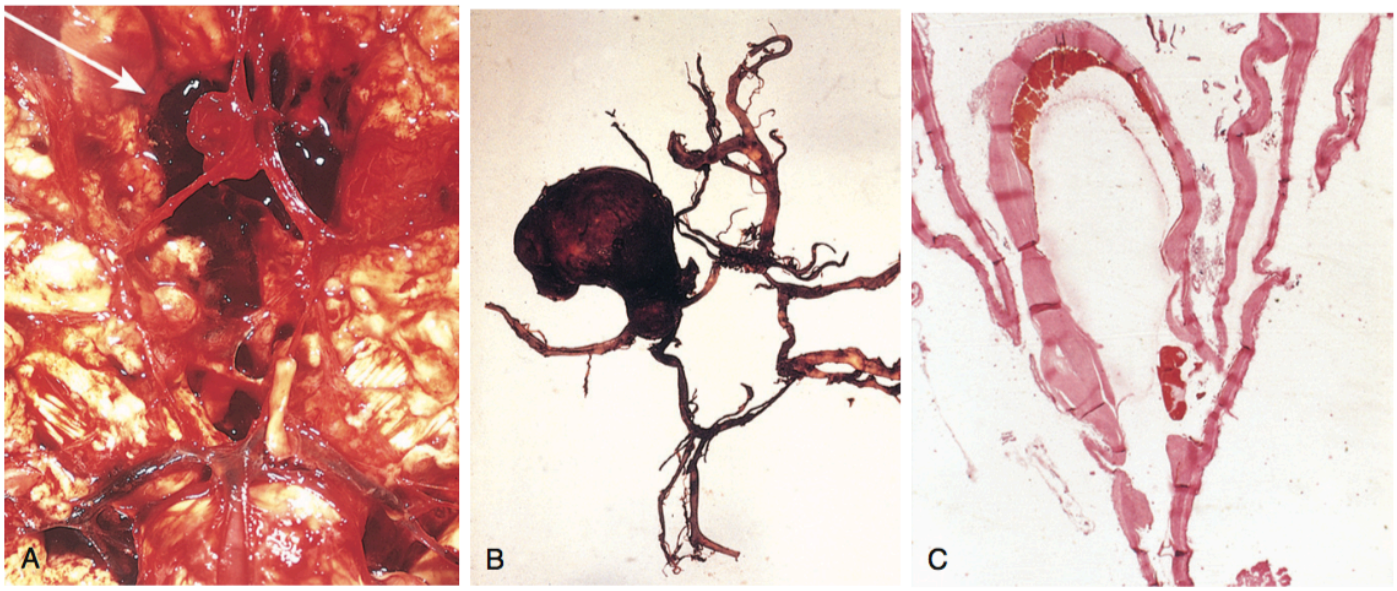


Figure 22–10 Saccular aneurysms. **A,** View of the base of the brain, dissected to show the circle of Willis with an aneurysm of the anterior cerebral artery *(arrow)*. **B,** Circle of Willis dissected to show large aneurysm. **C,** Section through a saccular aneurysm showing the hyalinized fibrous vessel wall. Hematoxylin-eosin stain.

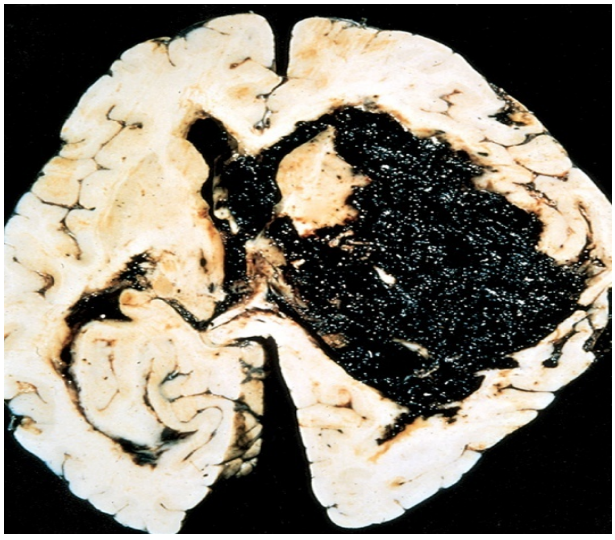
Hypertensive Cerebrovascular Disease:

- **The most important effects of hypertension on the brain include:**
  - Massive hypertensive intracerebral hemorrhage
  - Lacunar infarcts
  - Slit hemorrhages
  - Hypertensive encephalopathy

Hypertension is a Silent killer!
Hypertensive encephalopathy: Generalized edema, herniation of brain
Lacunar infarct: small empty space, slit hemorrhage.
A frequently asked question: what are the autopsy findings of a 63-year-old male who died of hypertensive crisis

- Hypertension affects the deep penetrating arteries and arterioles that supply the basal ganglia, hemispheric white matter and the brain stem
- Hypertension causes several changes, including hyaline arteriolar sclerosis in arterioles → weaker than normal vessels and are more vulnerable to rupture
- In some instances, chronic hypertension is associated with the development of minute aneurysms in vessels that are less than 300 μm in diameter → ***Charcot-Bouchard microaneurysms***, which can rupture.

Hyaline arteriolar sclerosis is seen in diabetic and hypertensive patients.
In VERY VERY severe cases "Crisis" of hypertension we see fibroid changes in the artery angry red in trichrome

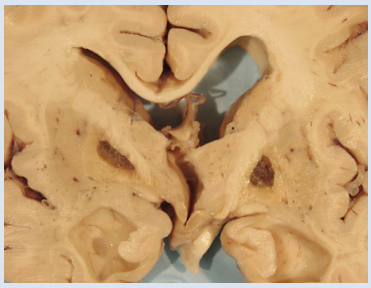


Massive intracerebral hemorrhage with extension to the ventricles due to malignant hypertension

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 with scattered lipid-laden macrophages and surrounding gliosis
- Depending on their location in the CNS, lacunes can either be clinically silent or cause significant neurologic impairment

Remember Swiss cheese



Slit hemorrhage

- Rupture of the small-caliber penetrating vessels and the development of small hemorrhages
- In time, these hemorrhages resorb, leaving behind a slitlike cavity surrounded by brownish discoloration

Rare hemorrhage.
Why is there brownish discoloration?
Due to iron and hemoglobin deposition

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[3] and fibrinoid necrosis of arterioles in the gray and white matter may be seen microscopically

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

May be autoimmune.
When your body doesn't recognize your blood vessels.
Vasculitis → Hemorrhage in the brain.

[3] Small Hemorrahge

- **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

What can cause or contribute to a stroke? (Risk Factors)

- Hypertension
- Vasculitis
- Systemic hypoperfusion/ Global hypoxia, e.g. shock
- Athersclerosis
- Tumors
- Thrombophilia, e.g. Sickle cell anemia
- Embolic diseases
- Amyloid angiopathy (leptomeningeal and cortical vessels)
- Venous thrombosis
- **Vascular Malformations:**
  Vascular malformations of the brain are classified into four principal types based on the nature of the abnormal vessels: arteriovenous malformations (AVMs), cavernous malformations, capillary telangiectasias, and venous angiomas.

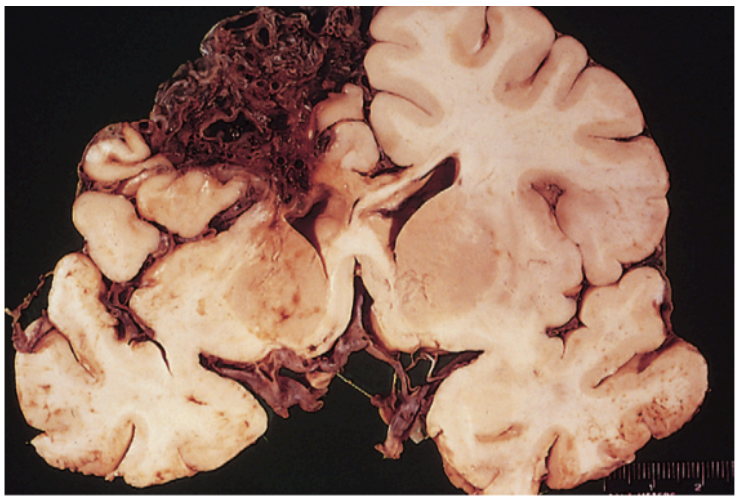


Figure 22–11 Arteriovenous malformation.

Arteriovenous malformation (most common)

Note:

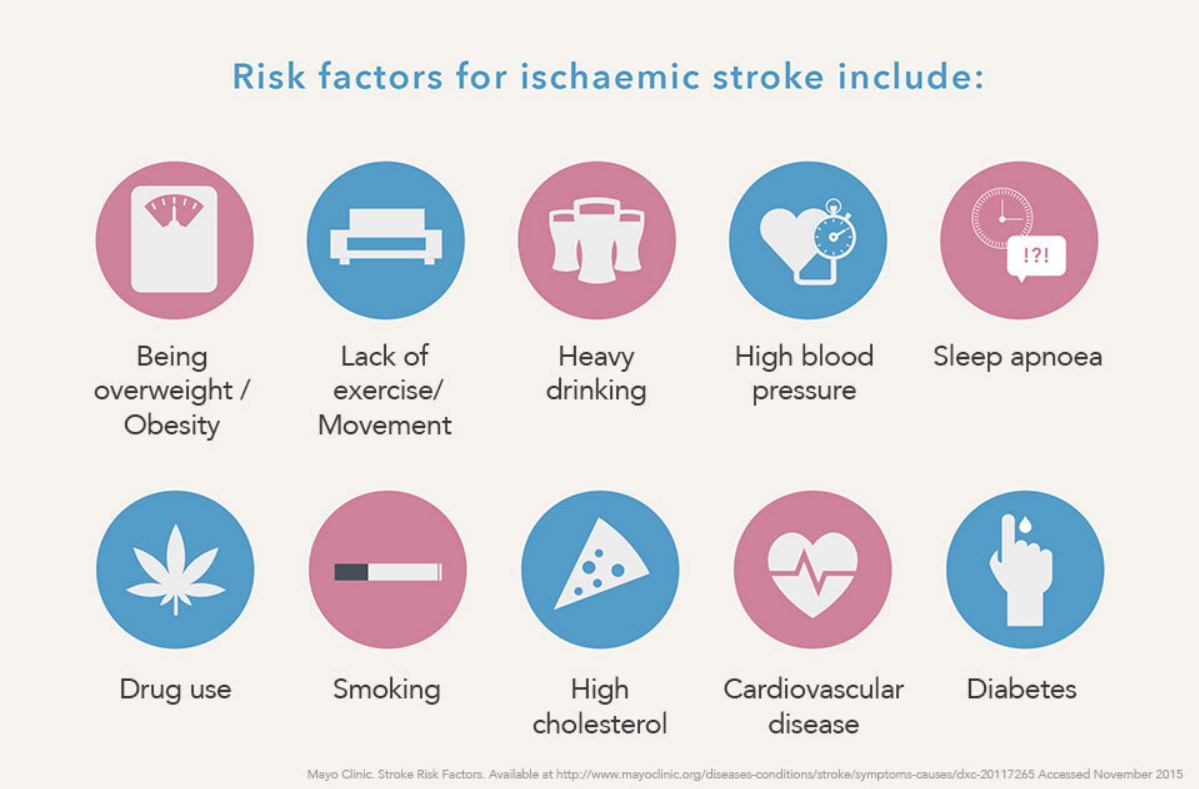
Brain tissue ceases to function if deprived of oxygen for more than 60 to 90 seconds and after approximately three hours, will suffer irreversible injury possibly leading to death of the tissue.

Take home messages:

- Stroke is the clinical term for a disease with acute onset of a neurologic deficit as the result of vascular lesions, either hemorrhage or loss of blood supply.
- Cerebral infarction follows loss of blood supply and can be widespread, focal or affect regions with the least robust vascular supply ("watershed" infarcts).
- Focal cerebral infarcts are most commonly embolic; if there is subsequent fragmentation of an embolism, a non-hemorrhagic infarct can become hemorrhagic.
- Primary intraparenchymal hemorrhages are typically due to either hypertension (most commonly in white matter, deep gray matter, or posterior fossa contents) or cerebral amyloid angiopathy.
- Spontaneous subarachnoid hemorrhage is usually caused by a structural vascular abnormality, such as an aneurysm or arteriovenous malformation.

Homework

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



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

Transient ischemic attack (TIA):

Happens due to small platelet thrombi or atheroemboli and is characteristically reversible, with symptoms lasting less than 24 hours.

TIA is caused by a clot; the only **difference between** a **stroke** and **TIA** is that with **TIA** the blockage is transient (temporary). **TIA** symptoms occur rapidly and last a relatively short time. Most TIAs last less than five minutes; the average is about a minute.

Check Your Understanding

MCQs:

1. **Which one of the following is hypoxia?**
   A. Deficiency in the amount of oxygen reaching the tissues.
   B. An inadequate blood supply to an organ or part of the body.
   C. Obstruction of the blood supply to an organ or region of tissue.

2. **Which of the following is one of the most common sites of primary thrombosis?**
   A. Anterior cerebral artery.
   B. The origin of the middle cerebral artery.
   C. Posterior cerebral artery.

3. **Regarding the pathogenesis of global cerebral ischemia, after 12 hours you can see microscopically all of the following except:**
   A. Red Neurons.
   B. Karyorrhexis.
   C. Neutrophills.

4. **A stroke patient has balance and vision disturbance what is true about his stroke:**
   A. He has severe brain damage.
   B. The stroke involved the base of the brain.
   C. He is probably going to die.

5. **Which one is more sensitive to hypoxia?**
   A. Neurons
   B. Glial cells
   C. Both are the same

1. A 2. B 3. C 4. B 5. A

6. **Which one can NOT cause intracerebral hemorrhage?**
   A. Hypertension.
   B. Vacuities.
   C. Decreased heart rate.

7. **Charcot-Bouchard Aneurysms are associated with:**

   A. Chronic hypertension.
   B. Slit hemorrhage
   C. Vasculitis.
   D. All of the above

8. **An inflammatory disorder that involves multiple small to medium-sized parenchymal and subarachnoid vessels, is:**
   A. Hypertension.
   B. Vacuities.
   C. Secondary Angiitis
   D. Primary Angiitis

9. **Berry Aneurysms are more common in:**
   A. Anterior communicating artery
   B. Internal Jugular vein
   C. External carotid artery

10. **Which of the following defines a TIA?**
   A. Permanent blockage.
   B. Asymptomatic.
   C. Temporary blockage

6. C 7. A. 8. D 9.A 10. C

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قال صلى الله عليه وسلم: {من سلك طريقًا يلتمس فيه علمًا سهَّل الله له بهِ طريقًا إلى الجنة}

دعواتنا لكم بالتوفيق