Pathogenesis and Risk Factors of Cerebrovascular Accidents

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In this lecture:

Stroke

Ischemia (focal and global)

Border zone infarct

Intracerebral hemorrhage

Subarachnoid hemorrhage

Hypertensive cerebrovascular diseases

Vasulitis

Arteriovenous malformations

Red: Doctors' and important notes.
Green: Team notes.

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.

Infarction: death of tissue due to inadequate blood supply.

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

1. **functional hypoxia**, in:
   - Low partial pressure of oxygen, e.g. sickle cell disease, especially in environments of poor oxygen concentration like places of high altitude.
   - impaired oxygen-carrying capacity (of the hemoglobin), e.g. in carbon monoxide poisoning
   - Inhibition of oxygen use by tissue, e.g. Cyanide poisoning and other toxins of biological weapons.
2. **ischemia**:

   Types: either *transient* or *permanent*:

   Mechanisms leading to ischemia:
   - a reduction in perfusion pressure, as in hypotension , cardiac arrest, or shock
   - vascular obstruction
   - both

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

Is when blood flow to a part of the brain stops for a brief period of time.

- 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.

Morbidity: The rate of incidence of a disease

Mortality: Death rate

Stroke:

Definition:

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.

The vascular lesions can be cause by:

1. Thrombotic occlusion
2. Embolic occlusion

Both cause ischemia and if continued, infarction of the area supplied by the vessel will occur.

3. Vascular rupture → causes direct tissue damage from the blood that comes out and secondary ischemia from the cessation of blood flow to the intended area.

Types of stroke: 1 . embolic.
2. Thrombotic.

1. ***Embolic stroke:***

Embolic infarctions are more common.

Sources of emboli of stroke:

1. Cardiac mural thrombi (frequent);
   - myocardial infarct
   - valvular disease
   - atrial fibrillation

Mural: occurring in the wall of a body cavity

Generally, The second most common sites of formation of arterial thrombi, after the coronaries, are the cerebral arteries.

2. Arteries; (often atheromatous plaques within the carotid arteries)

Super-imposed (placed on) thrombi caused by atherosclerosis -----> disassociation and fragmentation of thrombus ------> emboli -------> stroke

3. Paradoxical emboli, particularly in children with cardiac anomalies.

This type of emboli is often unexpected or even disregarded and is associated with ASD (Atrial Septal Defect) or VSD (Ventricular Septal Defect). In this case, e.g. DVT (deep venous thrombosis) that originates from the deep veins of the leg, at the knee or above it, forms an embolus and reaches the right ventricle, but instead of going to the lung it reaches the left ventricle through these septal defects and goes to the systemic circulation that may affect the brain at the end.

5. Emboli of other material (tumor, fat -in bone fractures-, or air)

The territory of distribution of the middle cerebral arteries most frequently affected by embolic infarction → *WHY?*

Because it is a direct continuation of the internal carotid artery.

2. *Thrombotic stroke:*

The majority of thrombotic occlusions causing cerebral infarctions are due to *atherosclerosis (a form of endothelial injury)*

The most common sites of primary thrombosis:

1. The carotid bifurcation
2. The origin of the middle cerebral artery
3. Either end of the basilar artery

Thrombosis commonly forms at areas of:

1) Areas or high blood turbulence.
2) Areas of bifurcation.
3) Areas of endothelial injury.

Clinical presentation:

- **Depends on**: 1. which part of the brain is injured
  2. How severely it is injured
- **Symptoms vary between** :

1. General, vague symptoms: headache or vomiting.
2. Specific symptoms (as a result of focal damage to a certain part of a brain) → affect certain areas of the body.
3. Strokes can be completely painless.

- It is very important to recognize the warning signs of stroke and to get immediate medical attention if they occur

When a patient that has multiple risk factors of atherosclerosis (old age, hypertension, diabetes, etc..) presents with non specific symptoms like vomiting, always consider a cerebrovascular accident and perform a neurological examination.

- If the brain damage sustained has been slight, there is usually complete recovery, but most survivors of stroke require extensive rehabilitation

Symptoms:

- Sudden (because it is an acute disease)
- 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 (brainstem) 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

Common microscopic characteristics of stroke:

- Neuronal damage or death.
- If the ischemic damage continues,

  lesions of liquefactive necrosis occur.

Liquefactive necrosis happens when inflammatory cells and the enzymes of leukocytes digest ("liquefy") the tissue. It happens in some focal and bacterial infections, but for unknown reasons, also happens in hypoxic death of the cells of the CNS.

- After time, Gliosis is responsible for repair and scar formation.

Gliosis is done by astrocytes where they undergo hypertrophy and hyperplasia.
Fibrosis may also occur but around blood vessels only.

Types of ischemia that may lead to strokes are:

1. **Global Cerebral Ischemia:**

   Definition:

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

   Causes of low systolic pressure:

   - cardiac arrest
   - severe hypotension
   - shock

Sensitivity to ischemia:

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

- The most susceptible neurons 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

Sommer sector is Regional part of hippocampal formation.

CA1: stands for" cornu Ammonis" and it is one of the histological divisions of the hippocampus:

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:** widespread neuronal death, irrespective of regional vulnerability, occurs. Patients will be either in:

1. **persistent vegetative state:**

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

2. **respirator brain:**

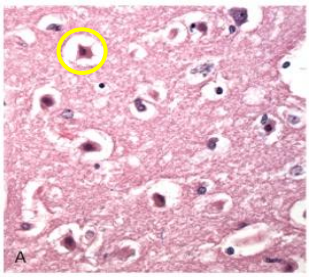
   - Other patients meet the clinical criteria for "brain death," including evidence of diffuse cortical injury (isoelectric, or "flat," electroencephalogram) and brain stem damage, including absent reflexes and respiratory drive
   - When patients with this pervasive form of injury are maintained on mechanical ventilation, the brain gradually undergoes an autolytic process.

Gross pathology:

1. The brain is swollen (duo to edema), with wide gyri and narrowed sulci.
2. The cut surface shows poor demarcation between gray and white matter.

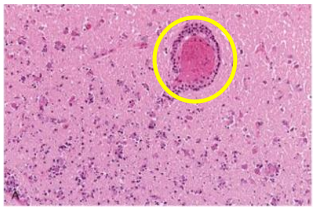
Microscopically:

- **Early changes:**
  - 12 to 24 hours after the insult
  - red neurons, characterized initially by: microvacuolization (A small cavity in the cytoplasm of a cell) →cytoplasmic eosinophilia (An increase in the number of eosinophils), and later nuclear pyknosis (condition where the nucleus shrinks and the DNA in it condenses) and karyorrhexis (where the nucleus in the pyknotic cell fragments).

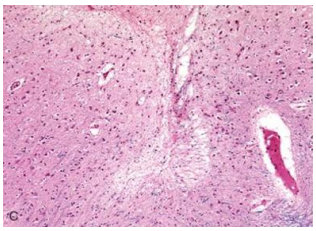


Why there is eosinophilia? In cell death resulting from lack of oxygen, necrotic cells show increased eosinophilia (the pink staining from the eosin dye in "H&E stain"). This is mostly attributable to increased binding of eosin to denatured cytoplasmic proteins.

- **Subacute changes: (inflammatory stage)**
  - 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.



2. Focal Cerebral Ischemia:

- Cerebral arterial occlusion → focal ischemia→ infarction
- The adequacy of collateral flow determines: The size, location, and shape of the infarct and the extent of tissue damage that results.

1. **The major source of collateral flow:** is the circle of Willis (therefore Infarcts rarely happen at this region).
2. **Partial collateralization** is also provided over the surface of the brain through cortical-leptomeningeal anastomoses
3. **Areas that lack or don't have collaterals flow are**:
   - Thalamus
   - Basal ganglia
   - Deep white matter

Leptomeninges: The two innermost layers of tissues that cover the brain and spinal cord, the arachnoid mater and pia mater

Types of infarcts occurring duo to sustained focal ischemia are:

- Nonhemorrhagic. This type can be treated with thrombolytic therapy.
- hemorrhagic

Gross pathology:

Nonhemorrhagic infarct (pale):

Caused by: thrombus (also called in-situ thrombus) or an embolus

1. **The first 6 hours** of irreversible injury: little can be observed
2. **By 48 hours:** 1.the tissue becomes pale, soft, and swollen.

   2.corticomedullary junction becomes indistinct
3. **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
4. **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.

Microscopically:

Non-hemorrhagic:

- **After the first 12 hours:**

- Red neurons and both cytotoxic and vasogenic edema predominate

Just for you to understand: Vasogenic edema (regular edema) occurs when the normal blood-brain barrier is disrupted. With increased vascular permeability, fluid shifts from the vascular compartment into the intercellular spaces of the brain. It is a result of increased permeability due to inflammation or tumors. Cytotoxic edema is an increase of intracellular fluid from neuronal, glial, or endothelial cell membrane injury as in hypoxic/ischemic insult or with exposure to some toxins.

- 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 (fragment).

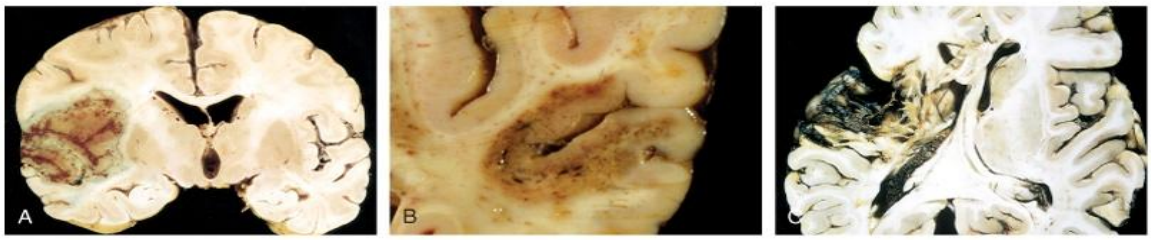
- **Until 48 hours:** there is some neutrophilic emigration followed by mononuclear phagocytic cells (macrophages) in the following 2-3 weeks.

- **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.

- **After several months:**
  - The striking astrocytic nuclear and cytoplasmic enlargement recedes (stops).
  - In the wall of the cavity, astrocyte processes form a dense feltwork (fibrous network) of glial fibers admixed with new capillaries and a few perivascular connective tissue fibers.
  - In the cerebral cortex the cavity is encircled 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.

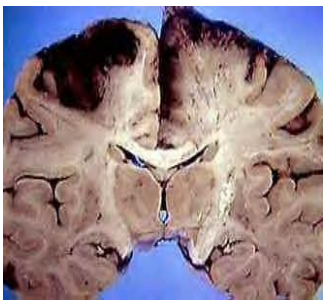
- Hemorrhagic:

- Parallel (similar) ischemic infarction, with the addition of blood extravasation (blood going out to the surrounding areas) and resorption (the process of reabsorption).
- Hemorrhagic infarcts might be seen in a patient suffering from extensive intracerebral hematomas (solid swelling of clotted blood within the tissues) and he is on anticoagulant treatment.

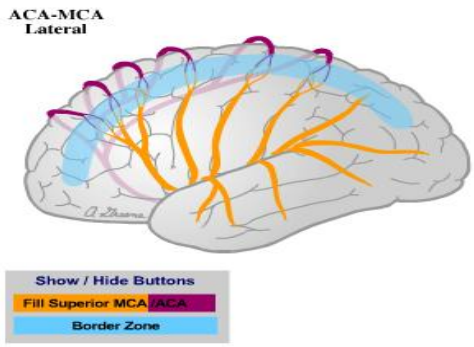


Cerebral infarction. A, Section of the brain showing a large, discolored, focally hemorrhagic region in the left middle cerebral artery distribution (hemorrhagic, or red, infarction). B, An infarct with punctate hemorrhages (dot hemorrhages), consistent with ischemia-reperfusion injury, is present in the temporal lobe. C, Old cystic (not an actual cyst, only in a cyst form) 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 (between the two hemispheres) fissure
- It is seen after hypotensive episodes



Intracerebral hemorrhage:

- Hemorrhages within the brain (intracerebral) can occur secondary to:
  1. Hypertension.
  2. Other forms of vascular wall injury (e.g. vasculitis like poly arthritis nodosa, aneyrsms, and aneurysms like berry (saccular) aneurysms).
  3. Arteriovenous malformation.
  4. An intraparenchymal tumor e.g: GBM. Where the vessels that undergo endothelial cell proliferation become weak may rupture and cause hemorrhage.
- Hemorrhages associated with the dura (in either subdural or epidural spaces) make up a pattern associated with trauma (discussed in another lecture)

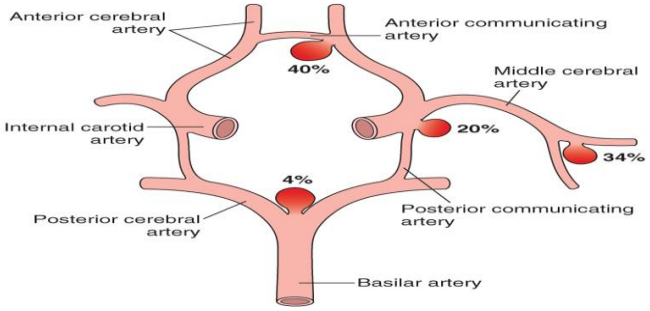


Illustration showing common sites of berry (saccular) aneurysms. Note that about 90% of saccular aneurysms occur in the anterior circulation near major arterial branch points.

If a patient presents with a history of a murmur in the ear and now she has a headache. You have to think of aneurism which has ruptured or beginning to rupture.

The rupture occur when an increase in blood pressure happens such as while exercising

Subarachnoid Hemorrhage:

Causes:

- Rupture of a saccular (berry) aneurysm (The most frequent cause of clinically significant) the patient is usually of young age and complains of a headache.
- 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

Depending on the size of the aneurysm, treatment may be different. If it is large, patient might have to undergo surgery. If it is small then a clinician may favor only constant follow up to ensure stability.

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 complication diseases, like hydrocephalus and adhesions causing obstruction of the CSF pathway.

Hypertensive Cerebrovascular Disease:

- The most important effects of hypertension on the brain include:
  1. Massive hypertensive intracerebral hemorrhage (discussed earlier, most important)
  2. Lacunar (small spaces) infarcts
  3. Slit hemorrhages
  4. Hypertensive encephalopathy

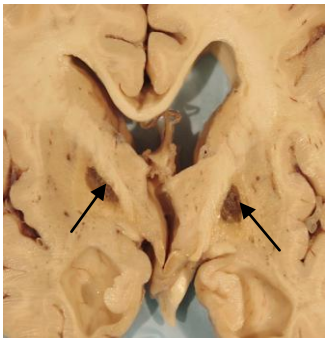
  The latter three happen because of hyalinization of arteries and cause abnormal function of blood vessels.
- Hypertension affects the deep penetrating arteries and arterioles that supply the basal ganglia and hemispheric white matter and the brain stem especially the pons.
- Hypertension causes several 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 aneurysms in vessels that are less than 300 µm in diameter e.g: *Charcot-Bouchard microaneurysms (microaneurysms in the retinal arteries caused by hypertention).These aneurysms can easily rupture*.

Examples on the hypertensive cerebrovascular diseases:

1. 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



2. Slit hemorrhage:

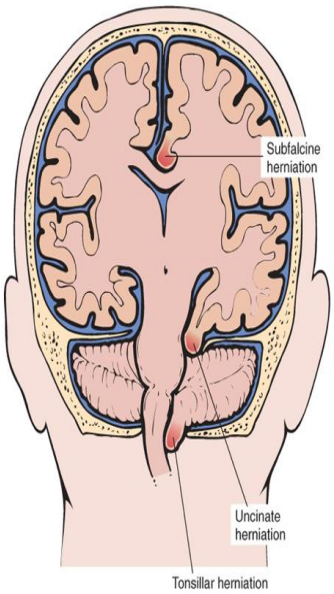
- rupture of the small-caliber penetrating vessels and the development of small hemorrhages
- in time, these hemorrhages resorb, leaving behind a slitlike cavity surrounded by brownish discoloration

3. 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 herniation(transtentorial or tonsillar)

This condition may cause sever pressure on certain parts by bones like the occulomotor nerve and the base of the brain. When the brain stem is pushed at the foramen magnum, this causes intense pressure on it where it can lead to damage to the respiratory and cardiac centers in the brain stem and then cardiorespiratory arrest and death.



Transtentorial (uncinate) herniation occurs when the medial aspect of the temporal lobe is compressed against the free margin of the tentorium.

Tonsillar herniation refers to displacement of the cerebellar tonsils through the foramen magnum.

Microscopically:

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

Fibrinoid necrosis is a special form of necrosis usually seen in immune reactions involving blood vessels. Deposits of these "immune complexes," together with fibrin that has leaked out of vessels, result in a bright pink and amorphous appearance in H&E stains, called "fibrinoid" (fibrin-like).

Petechiae are Minute (1- to 2-mm) hemorrhages that are (the smallest kind seen on skin and mucus membranes) are typically associated with locally increased intravascular pressure and other factors.

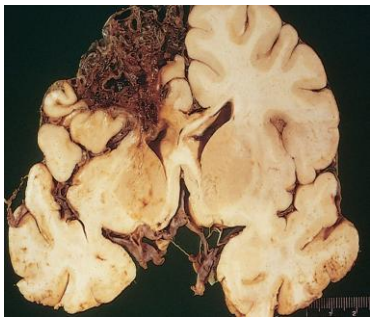
Vasculitis:

Is a variety of inflammatory process that involves blood vessels and may lead to cerebral infarcts. The inflammation can be duo to:

- **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 - Cytomegalovirus- 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 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

Arteriovenous malformation:

It is most dangerous and most important of the four types of vessel malformation that can occur in the vessels of the brain. It is twice common in males than in females. They are present clinically.



For your information:

The four classes of the vessels malformations are:

Arteriovenous malformations

Cavernous angiomas

Capillary telangiectasias

Venous angiomas

Clinical manifestation:

1) Seizure disorder

2) intracerebral hemorrhage or subarachnoid hemorrhage.

So what can cause or contribute to a stroke?

- Hypertension
- Athersclerosis
- Thrombophilia, e.g. Sickle cell anemia
- Hematological diseases like hemophilia.
- Embolic diseases
- Systemic hypoperfusion/ Global hypoxia, e.g. shock
- Vascular malformations
- Vasculitis
- Trauma
- Tumors
- Venous thrombosis in parts of the brain.
- Amyloid angiopathy (in leptomeningeal and cortical vessels)

Amyloid deposition in the vessels greatly increases risk of rupture.

It can be seen when the tissue is stained with Congo Red .

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