

Neuroscience I

Cerebrovascular diseases

Dr. Hani Ahmed Alanqar
Consultant of pathology



CEREBROVASCULAR DISEASE

- Cerebrovascular disease—injury to the brain as a consequence of altered blood flow—can be grouped into ischemic and hemorrhagic etiologies, with tissue infarction the ultimate consequence of both.
- “Stroke” is the clinical designation applied to these conditions and is defined as neurologic signs and symptoms that can be explained by a vascular mechanism, have an acute onset, and persist beyond 24 hours. (If symptoms disappear within 24 hours, the event is termed “transient ischemic event.”).
- Cerebrovascular disease is the third leading cause of death (after heart disease and cancer).



Stroke stems from two major mechanisms:

- **Ischemia and/or hypoxia** resulting from impairment of blood supply and oxygenation of CNS tissue. This can be either a global or focal process, with the clinical manifestations determined by the region of brain affected. In the brain, embolism is a more common cause of vascular occlusion than thrombosis.
- **Hemorrhage** resulting from rupture of CNS vessels. Common etiologies include hypertension and vascular anomalies



Hypoxia and Ischemia

Although the brain accounts for only 1% to 2% of body weight, it receives approximately 15% of the resting cardiac output and accounts for 20% of the body's oxygen consumption. Cerebral blood flow remains relatively constant over a wide range of blood pressure and intracranial pressure because of autoregulation of vascular resistance. The brain is strictly dependent on aerobic metabolism to meet its constant energy demands, and it may be deprived of oxygen by either hypoxemia (low blood oxygen content) or ischemia (inadequate blood flow). Inadequate blood flow may result from a reduction in perfusion pressure (as in hypotension), small- or large-vessel obstruction, or both.



When blood flow to a portion of the brain is reduced, the survival of the tissue at risk depends on the presence of collateral circulation, the duration of ischemia, and the magnitude and rapidity of the reduction of flow. These factors determine, in turn, the precise anatomic site and size of the lesion and, consequently, the clinical deficit.



Focal Cerebral Ischemia

Focal cerebral ischemia follows reduction or cessation of blood flow to a localized area of the brain due to partial or complete arterial obstruction. When the ischemia is sustained, infarction follows in the territory of the compromised vessel. The size, location, and shape of the infarct and the extent of tissue damage that results are influenced by the duration of the ischemia and the adequacy of collateral flow



Occlusive vascular disease of severity sufficient to lead to cerebral infarction may be due to embolization from a distant source, in situ thrombosis, or various vasculitides;

- Embolism to the brain occurs from a variety of sources. Cardiac mural thrombi are among the most common culprits; myocardial infarct, valvular disease, and atrial fibrillation are important predisposing factors. Next in frequency are thromboemboli originating from arteries, most often atheromatous plaques within the carotids. Other sources of emboli include paradoxical thromboemboli, particularly in children with cardiac anomalies; thromboemboli associated with cardiac surgery; and emboli of other types (tumor, fat, or air).



- Thrombotic occlusion of the cerebral arteries is most commonly caused by acute change of vulnerable atherosclerotic plaques, as in coronary artery disease
- Inflammatory processes that involve blood vessels may also lead to luminal narrowing, occlusion, and, hence, cerebral infarcts. Although infectious vasculitis of small and large vessels occurs with syphilis and tuberculosis
- Other conditions that may cause thrombosis (and intracranial hemorrhage) include hypercoagulable states, dissecting aneurysm of extracranial arteries in the neck that supply the brain, and drug abuse (amphetamines, heroin, cocaine).



Brain infarcts are subdivided into two broad groups based on the presence of secondary hemorrhage. Because the brain has end-organ circulation with limited collateral supply, occlusive brain infarcts generally start as nonhemorrhagic (pale/anemic; clinically, these nonhemorrhagic infarcts are called ischemic, a confusing term as every infarct, not just this type, is caused by tissue ischemia. Secondary hemorrhage can occur from ischemia-reperfusion injury following spontaneous or therapeutic dissolution or fragmentation of the intravascular occlusive material.



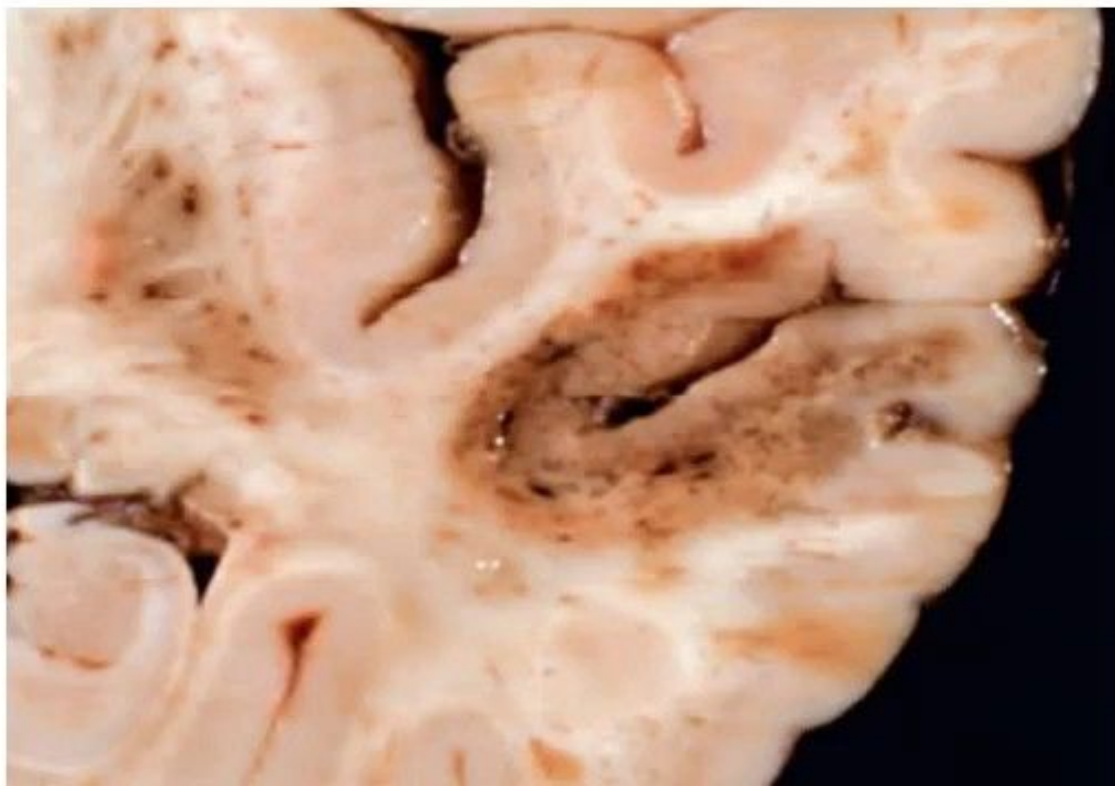
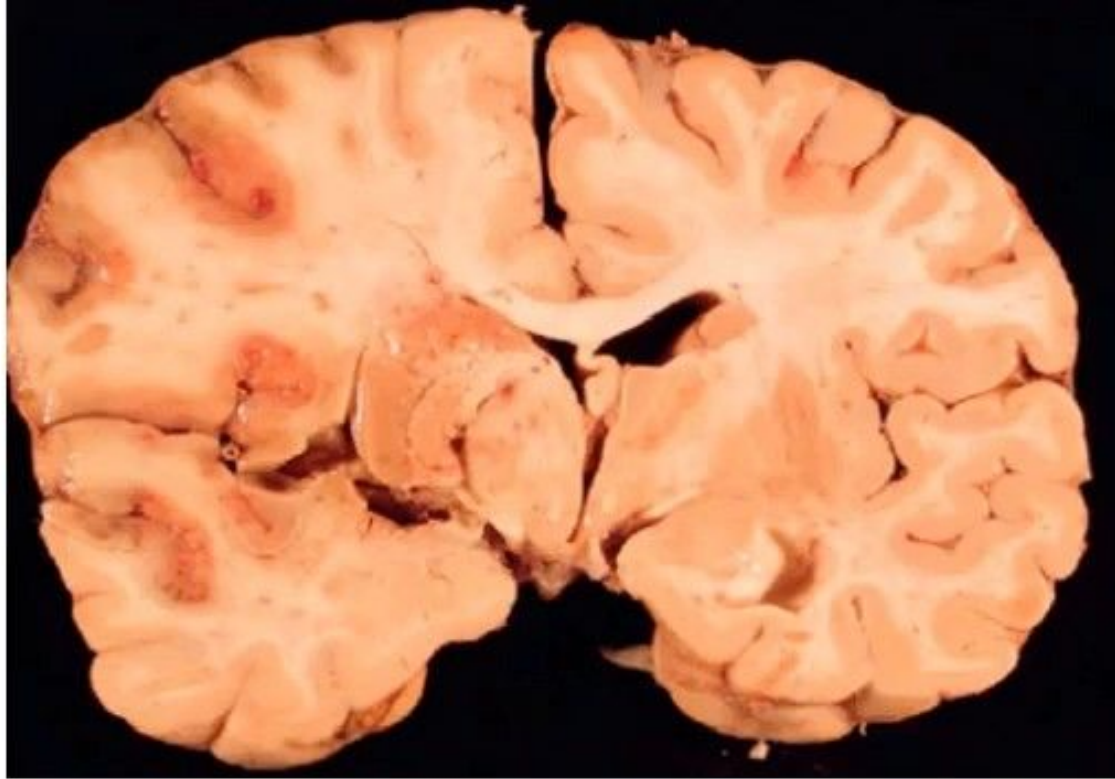
This process (termed secondary hemorrhagic transformation and leading to a hemorrhagic infarct) develops if the causative ischemic event lasts long enough to damage small blood vessels in the affected area; the resulting reperfusion hemorrhages are largely petechial in nature, but may be multiple or even confluent . The clinical management of patients with nonhemorrhagic and hemorrhagic infarcts differs greatly, although the underlying causes are the same (for instance, thrombolytic therapy is contraindicated in a patient with brain hemorrhage of any etiology).



MORPHOLOGY

Both the gross and microscopic appearance of a nonhemorrhagic infarct changes over time. Grossly, there is little change in appearance during the first 6 hours of irreversible injury. By 48 hours, however, the tissue becomes pale, soft, and swollen, and the gray-white matter junction becomes indistinct. From 2 to 10 days, the brain becomes gelatinous and friable, and the previously ill-defined boundary between normal and infarcted tissue becomes more distinct as edema resolves in the viable adjacent tissue. From 10 days to 3 weeks, the tissue liquefies, eventually leaving a fluid-filled cavity that continues to expand until all of the dead tissue has been removed. Microscopically, the tissue reaction evolves along the following sequence:





- **Acute infarct** . After the first 6 to 12 hours, neurons in the affected area show eosinophilic neuronal necrosis (increased eosinophilia of the cytoplasm followed by nuclear pyknosis and karyorrhexis; “dead red neurons”); both cytotoxic and vasogenic edema are present. Endothelial and glial cells, mainly astrocytes, swell, and myelinated fibers begin to disintegrate. Up to 48 hours, neutrophilic emigration progressively increases and then falls off (but is never as prominent as in myocardial infarction).



- **Subacute (evolving) infarct** . Phagocytic cells, derived from circulating monocytes and activated microglia, are evident at 48 to 72 hours and become the predominant cell type in the ensuing 2 to 3 weeks. The macrophages become stuffed with the products of myelin breakdown or blood and may persist in the lesion for months to years. Reactive astrocytes and newly formed vessels can be seen at the periphery of the lesion as early as 1 week after the insult. As the process of liquefaction and phagocytosis proceeds, astrocytes at the edges of the lesion progressively enlarge, divide, and develop a prominent network of cytoplasmic extensions.



- **Healed infarct** . After several months, the astrocytic response recedes, leaving behind a dense meshwork of glial fibers admixed with new capillaries and some perivascular connective tissue. In the cerebral cortex, the cavity is separated from the meninges and subarachnoid space by a gliotic layer of tissue, which is derived from the molecular layer of the cortex. The pia and arachnoid are not affected.





Lacunar Infarcts

Hypertension affects the deep penetrating arteries and arterioles that supply the basal ganglia and hemispheric white matter as well as the brainstem; these cerebral vessels develop arteriolosclerosis, also known as small vessel disease because it affects arteries 40 to 900 μm in diameter, described in more detail later. If this disease process progresses to thrombosis and complete vessel occlusion, the end-result is development of small cavitory infarcts known as lacunes or lacunar infarcts . These lakelike spaces, defined as less than 15 mm wide, can be single or multiple.



On microscopic examination, there is tissue loss surrounded by gliosis. Depending on their location in the CNS, lacunar infarcts can be clinically silent or cause severe neurologic impairment. Affected vessels may also be associated with widening of the perivascular spaces without tissue infarction.



Clinical Features Deficits produced by infarction are determined by the anatomic distribution of the damage, rather than the underlying cause. Neurologic symptoms referable to the area of injury often develop rapidly, over minutes, and may continue to evolve over hours. There can be improvement in severity of symptoms that is associated with reversal of injury in the ischemic penumbra and resolution of associated local edema. In general, there is often slow improvement during a period of months. Because strokes are frequently associated with cardiovascular disease, many of the genetic and lifestyle risk factors are shared. Early diagnosis is of critical importance, as rapid treatment of nonhemorrhagic strokes with thrombolytic agents can often limit or entirely prevent the development of permanent neurologic deficits.



Global Cerebral Hypoxia/Ischemia

Global cerebral hypoxia or ischemia occurs when there is a generalized reduction of cerebral perfusion (as in cardiac arrest, shock, and severe hypotension) or decreased oxygen carrying capacity of the blood (e.g., in carbon monoxide poisoning). The clinical outcome varies with the severity and length of the insult. In mild cases, there may only be a transient post ischemic confusional state, followed by complete recovery. Nevertheless, irreversible CNS damage may occur in individuals who experience global hypoxic and/or ischemic insults (diffuse hypoxic/ischemic encephalopathy). Among CNS cells, there is a hierarchy of sensitivity to hypoxia/ ischemia: neurons are the most sensitive, although glial cells (oligodendrocytes and astrocytes) are also vulnerable.



The most sensitive neurons in the brain are pyramidal neurons in the hippocampus (especially area CA1, also referred to as Sommer sector), cerebellar Purkinje cells, and pyramidal neurons in the cerebral cortex (especially layers III and V); the molecular mechanisms underlying this selective vulnerability are not understood. With severe global cerebral hypoxia/ ischemia, widespread neuronal death occurs, irrespective of regional vulnerability; patients who survive this injury often remain in a persistent vegetative state. Other patients meet the current clinical criteria for “brain death,” including evidence of irreversible diffuse cortical injury (isoelectric, or “flat,” electroencephalogram), brainstem damage (such as absent reflexes and respiratory drive), and absent cerebral perfusion. When individuals with this pervasive form of injury are maintained on mechanical ventilation, the brain gradually undergoes widespread liquefaction, producing so-called “respirator brain.”



Border zone (“watershed”) infarcts occur in the regions of the brain or spinal cord that lie at the most distal reaches of the arterial blood supply (i.e., the border zones between arterial territories). In the cerebral hemispheres, the border zone between the anterior and the middle cerebral artery distributions is at greatest risk. Damage to this region, located a few centimeters lateral to the interhemispheric fissure, results in a cortical wedge-shaped infarct that usually shows secondary hemorrhagic transformation and is often bilateral. Border zone infarcts usually develop after severe hypotensive episodes and are most commonly seen in patients resuscitated after cardiac arrest.



MORPHOLOGY In the setting of global ischemia, the brain becomes edematous and swollen, producing widening of the gyri and narrowing of the sulci. The cut surface shows poor demarcation between gray and white matter. The microscopic features of irreversible ischemic injury evolve over time and mimic the changes seen in infarcts; the distinction between global and focal ischemic injury is based not on the nature of cellular pathology but on the overall pattern of brain involvement.



Early changes, occurring 6 to 12 hours after the insult, are seen in neurons (dead red neurons described earlier); similar acute changes occur somewhat later in astrocytes and oligodendroglia. Subacute changes, occurring at 24 hours to 2 weeks, include tissue necrosis, influx of macrophages, vascular proliferation, and reactive gliosis. Repair, robust after approximately 2 weeks, is characterized by removal of necrotic tissue, loss of normal CNS architecture, and gliosis. In the cerebral neocortex, the neuronal loss and gliosis are uneven, with preservation of some layers and destruction of others, producing a pattern of injury termed laminar necrosis.

