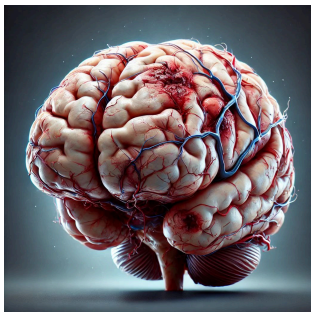
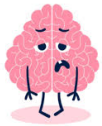


CNS—pathology~1
Written by: Dr.Ali Abujammil.



Definition of CNS Pathology: It is a branch of pathology that focuses on studying diseases affecting the central nervous system, which includes the brain and spinal cord. This field examines pathological changes caused by infections, tumors, degenerative disorders, injuries, and vascular diseases.

Cerebrovascular Diseases (CVA) = Stroke: is a major cause of death and the most common cause of neurological morbidity.

Mechanisms of stroke include:

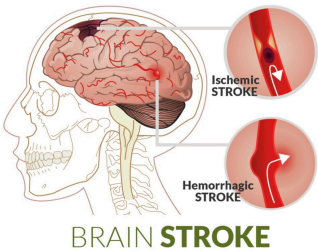
1. Thrombi – Blood clots formed within blood vessels.

2. Emboli – Clots or debris traveling through the bloodstream, blocking vessels in the brain.

3. Vascular Rupture – Rupture of blood vessels leading to bleeding in the brain.

Stroke clinical term that applies to all three mechanisms when symptoms are acute and is the rapid onset of symptoms and signs of focal CNS dysfunction lasting for 24 hours or leading to death; Symptoms develop quickly (within seconds or minutes) but persist for at least 24 hours; If symptoms last less than 24 hours: It is called a Transient Ischemic Attack (TIA).

Types of Stroke; There are two main types of stroke:



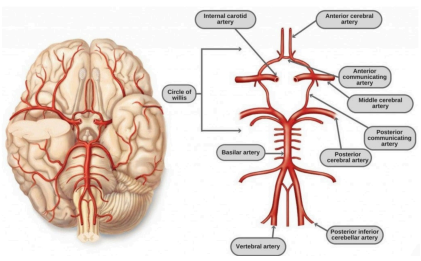
1. Ischemic Stroke: Caused by vascular obstruction by a thrombus or embolus.

2. Hemorrhagic Stroke: Caused by vessel rupture due to vascular diseases like hypertension or vasculitis.

Ischemic strokes account for 85% of strokes; It is very important to distinguish between the two types because ischemic stroke is treated with anticoagulants, whereas using anticoagulants in hemorrhagic stroke can be fatal.

The image is a simplified illustration of the brain's blood supply. a diagram depicts the major arteries supplying blood to the brain, including the internal carotid artery, vertebral artery, and basilar artery, as well as the anterior, middle, and posterior cerebral arteries, and the Circle of Willis, which interconnects these arteries.

Brain blood supply



Ischemic Stroke-Thrombotic Occlusions

Ischemic stroke occurs when blood flow to the brain is blocked due to the formation of a blood clot in the cerebral blood vessels. This is typically caused by atherosclerosis, where fats and cholesterol accumulate on the walls of blood vessels, narrowing the arteries and leading to thrombosis; Common sites for thrombotic occlusions:

1. Carotid Bifurcation: Where the carotid artery branches into smaller arteries.

2. Origin of the Middle Cerebral Artery: Where the middle cerebral artery begins to supply oxygenated blood to the brain.

3. Ends of the Basilar Artery: Where the basilar artery branches to distribute blood to the brain.

Thrombotic occlusions in these areas disrupt blood flow to critical regions of the brain, leading to ischemic stroke. Treatment in this case often involves the use of anticoagulants, along with medical procedures to remove or prevent further clot formation.

Ischemic Stroke-Embolic Infarcts

Embolic infarcts are more common than thrombotic infarcts. In this case, stroke occurs when a blood clot or embolus moves through the bloodstream and blocks a brain vessel, Sources of emboli:

1. Cardiac Mural Thrombi: These arise due to myocardial dysfunction, valvular disease, or atrial fibrillation, where blood clots form in the heart and then travel to the brain.

2. Arterial Atheroma in Carotid Arteries or Aortic Arch: Atherosclerotic plaques in major arteries can form emboli that travel to the brain.

3. Venous Thrombi Crossing to Arterial Circulation Through Cardiac Defects = Paradoxical Embolism: This occurs when venous clots, such as those from Deep Vein Thrombosis (DVT) or Fat Emboli, move through cardiac defects (holes in the atria) and enter the arterial system, reaching the brain.

Most common site of embolic occlusion: Middle Cerebral Artery It is a direct extension of the internal carotid artery, making it the most common site of embolic blockage and Vessels at Branch Points or Stenotic Areas Caused by Atherosclerosis.

Embolic occlusions tend to cause more widespread strokes than thrombotic ones. Quick diagnosis and identifying the source of the embolism are crucial for proper treatment to prevent further brain damage.

Hemorrhagic stroke occurs when there is bleeding in the brain due to the rupture of blood vessels. This bleeding can lead to tissue damage in the surrounding brain areas, as the leaking blood compresses and destroys neural tissues, Hemorrhagic stroke can result from the

rupture of blood vessels due to several factors, including vascular disorders or increased pressure within the blood vessels; The bleeding within the brain can lead to what are called hemorrhagic infarcts, which are areas of the brain damaged by the pressure from the leaked blood. This results in interrupted blood flow to the surrounding brain tissue, causing the destruction of brain cells in that region.

Managing hemorrhagic stroke requires understanding the main causes that lead to vessel rupture. These causes will be discussed in more detail in the next lecture, but it is important to know that rapid intervention is crucial to minimizing the damage caused by the hemorrhage.

The risk factors for stroke are essentially the same as those for atherosclerosis, which involves the buildup of fats and cholesterol in the walls of blood vessels. These factors increase the risk of stroke by affecting the brain's blood vessels and the major arteries that supply it with blood; Key Risk Factors for Stroke: Hypertension-It is the most common risk factor for stroke, as high blood pressure puts constant pressure on blood vessels, leading to damage and increasing the likelihood of clot formation and Smoking and High Cholesterol and Diabetes-It leads to thickening of blood vessel walls and negatively affects blood flow and Genetics-family history of stroke can increase susceptibility and Physical Inactivity and Poor Diet-Diets high in saturated fats and sodium can increase stroke risk. Also Atrial Fibrillation-This heart condition increases the risk of clots forming in the heart and traveling to the brain.

The main symptoms of a stroke can be remembered using the word FAST:

1. Face: face may drop on one side, and the person may not be able to smile, or their mouth or eye may droop. This happens due to muscle weakness on one side of the face caused by the stroke.

2. Arms: person with a suspected stroke may not be able to lift both arms and keep them raised due to weakness or numbness in one arm. This can be tested by asking the person to raise both arms together.

3. Speech: Their speech may be slurred or unclear, or the person may be unable to speak at all despite appearing to be awake. This occurs because the stroke affects the areas of the brain responsible for speech.

4. Time: If any of these signs or symptoms are observed, it is time to call emergency services immediately. Time is critical in stroke treatment, and the quicker intervention happens, the better the chances of minimizing damage and aiding recovery.

Sometimes, a stroke is preceded by Transient Ischemic Attacks (TIA), which are important to recognize clinically because they are a warning sign that a full-blown stroke is imminent; TIA means that the blood supply to the brain is temporarily interrupted, causing a "mini-stroke," often lasting between 30 minutes and several hours. Blood flow is temporarily restored, but the symptoms may resemble those of a full stroke; Importance of Recognizing TIA: are

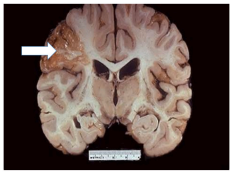
warning signs that the person is at risk of having a full stroke in the near future, Although symptoms usually disappear within a short period, TIAs should be taken seriously and treated promptly to prevent a complete stroke.

A non-hemorrhagic ischemic stroke leads to permanent brain damage due to the lack of blood supply. This results in a series of macroscopic (visible to the naked eye) and microscopic (seen under a microscope) changes that progress over time, ultimately leading to a fluid-filled cavity in the affected brain region.

Macroscopic Appearance (Gross Changes):

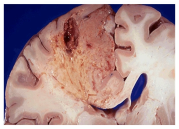
1. Within the First 48 Hours: The affected area appears pale (Pale), soft (Soft), and swollen (Swollen) due to cerebral edema caused by fluid accumulation in damaged cells, The boundary between the infarcted and healthy tissue is unclear because of widespread swelling, The brain tissue loses its normal firmness due to cellular breakdown.

Infarct



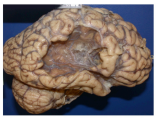
2. From Day 2 to Day 10: The infarct becomes gelatinous (Gelatinous) and friable (Friable), meaning it is weak and easily broken, Cellular disintegration continues, and inflammatory cells migrate into the area to begin clearing dead tissue, The normal brain structure in the affected area starts to disintegrate.

infarct: note the cavity and liquefaction.
Ischemic damage to the brain causes liquefactive necrosis.



3. From Day 10 to Week 3: Liquefactive necrosis occurs, where dead brain tissue turns into a fluid-filled cavity, The infarcted tissue is completely broken down and absorbed, leaving behind an empty space surrounded by reactive glial tissue.

Old infarct: the infarct is resolved leading a cavity.

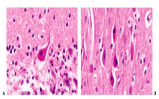


4. After Several Weeks to Months (Old Infarct): The necrotic tissue is completely removed, leaving behind a permanent cavity.The damaged area is replaced by reactive gliosis, a process where supporting glial cells proliferate to form a scar-like structure, Since neurons in the brain do not regenerate, the lost tissue is not replaced by new neurons, leading to permanent loss of function in the affected region.

Why does liquefactive necrosis occur in the brain? Unlike other tissues that respond to ischemic injury with fibrous scarring, the brain contains high lipid content and lysosomal enzymes, which cause complete tissue breakdown instead of forming a solid scar. This results in the formation of a fluid-filled cavity instead of a fibrotic scar.

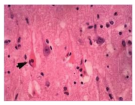
Microscopic Appearance (Histological Changes):

Red neurones

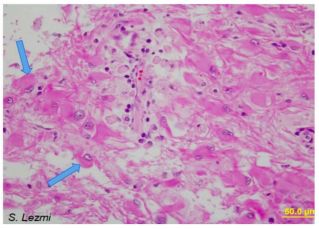


1.Early Changes (First 24 Hours)-Acute neuronal damage: Red neurons appear due to protein coagulation inside the dying neurons and Cytoplasmic eosinophilia-The cytoplasm turns deep pink under the microscope due to loss of normal cellular components and Pyknosis and karyorrhexis-The nuclei shrink and eventually fragment, marking irreversible cell death and Inflammatory Response-Neutrophils (first responders) infiltrate the infarcted area within the first 24 hours, breaking down damaged tissue and triggering the immune response.

Red neurones



gemistocytes



2. Subacute Changes (24 Hours to 2 Weeks)-Continued necrosis: More neuronal cell death and tissue breakdown occur and Macrophages (scavenger cells) appear to clear the dead tissue and Reactive Gliosis-Gemistocytic astrocytes (enlarged, reactive glial cells) proliferate to form a supportive framework in the infarcted area.

3. Repair Phase (After 2 Weeks)-Removal of necrotic debris: Macrophages completely clear the dead cells, leaving behind an empty cavity and Gliosis-Astrocytes proliferate to form a scar-like barrier, replacing the lost neurons with a dense glial network, These astrocytes undergo hypertrophy (increase in size) and hyperplasia (increase in number) to stabilize the damaged area, Enlarged nuclei, prominent nucleoli, and increased cytoplasmic volume are seen in reactive astrocytes and Astrocytes develop branched, ramified processes, characteristic of gemistocytic astrocytes.

Loss of Organized CNS Structure: Since neurons cannot regenerate, the infarcted brain area loses its original organization, resulting in permanent functional impairment.

Clinical Significance: Understanding these changes highlights the importance of early treatment in ischemic stroke: If treated within the first few hours (using clot-busting drugs like tPA), tissue damage can be minimized before necrosis becomes permanent, and Once liquefactive necrosis and cavitation occur, the damage is irreversible, leading to permanent neurological deficits and Recognizing transient ischemic attacks (TIA) or early stroke symptoms can prevent permanent brain damage through immediate intervention.

Summary of Morphological Changes in Non-Hemorrhagic Infarcts:

Phase	Macroscopic Changes	Microscopic Changes
Within 48 Hours	Pale, soft, swollen area	Red neurons, edema, neutrophil infiltration
2-10 Days	Gelatinous, friable tissue	Necrosis, macrophages, gemistocytic astrocytes
10 Days - 3 Weeks	Liquefactive necrosis, fluid-filled cavity	Extensive gliosis, macrophages remove debris
After 3 Weeks	Permanent cavity formation	Glial scarring (Gliosis), loss of CNS

Summary regarding Stroke:
- **Stroke = CVA, is a clinical term describing acute neurological symptoms caused by vascular disease.**
- **Stroke can be ischemic or hemorrhagic. Ischemic is commoner**
- **Ischemic stroke can be embolic or thrombotic. Embolic is commoner.**
- **Most common site of embolic occlusion is the middle cerebral artery.**
- **Ischemic strokes might be preceded by TIA= vascular occlusion causing symptoms lasting from minutes to several hours.**
- **TIAs predict a full stroke and should be treated promptly.**
- **Ischemic infarcts in the brain cause liquefactive necrosis.**
- **In the acute stage we see red neurones and neutrophilic infiltrate**
- **In subacute stage we see macrophages ,gemistocytes and gliosis.**
- **In the late stages, gemistocytes disappear leaving a cavity behind.**

Intracranial pressure (ICP) is the pressure inside the skull, exerted by the brain tissue, cerebrospinal fluid (CSF), and blood circulating within the cranial cavity.

Normal ICP Ranges: 7–15 mmHg in a supine (lying down) adult at rest while >20 mmHg is considered abnormally high and can cause neurological complications and >40 mmHg is life-threatening and requires immediate intervention.

ICP plays a critical role in maintaining brain homeostasis. The brain is a highly sensitive organ that requires constant blood flow and oxygen delivery. If ICP increases beyond normal limits, it can compress brain structures, reducing cerebral perfusion pressure (CPP), which can lead to ischemia, neuronal death, and brain herniation.

The skull (cranium) is a rigid, non-expandable structure in adults. Because it cannot stretch or grow, any increase in its contents leads to increased intracranial pressure (ICP).

The total intracranial volume is made up of three primary components: Brain Tissue (80%) Includes neurons, glial cells, and interstitial fluid (which makes up ~75% of brain weight) and Blood (10%) The cerebral circulation, which delivers oxygen and nutrients to brain tissue and Cerebrospinal Fluid (CSF) (10%) clear fluid that cushions and protects the brain, maintaining stable intracranial pressure.

Because the skull is a closed space, the brain has limited ways to compensate for volume increases: Displacement of CSF into the spinal subarachnoid space or Reduction of blood volume by compressing veins and reducing venous outflow or Compression of brain tissue (a dangerous mechanism that leads to herniation), Once these compensatory mechanisms fail, ICP rises, leading to brain damage and death.

The Monro-Kellie Doctrine states that: Total cranial pressure= VBrain, Volume of brain tissue + VCSF, Volume of cerebrospinal fluid+ VBlood , Volume of cerebral blood+ VLesion , Any additional volume (tumor, hematoma, edema, abscess, etc.).

Clinical Relevance:If one component increases, the others must decrease to maintain normal ICP. If this balance is lost, intracranial hypertension develops, leading to brain dysfunction and herniation, Examples of Space-Occupying Lesions That Disrupt This Balance: Brain tumors (benign or malignant growths) and Hematomas (epidural, subdural, or intracerebral bleeding) and Brain abscesses (pus-filled infections inside the brain) and Severe cerebral edema (swelling due to stroke, trauma, or infection).

Causes of Increased Intracranial Pressure (ICP):

1. Mass Effect (Space-Occupying Lesions): Any growth or abnormal accumulation inside the skull that increases pressure. Examples include: Brain tumors (gliomas, meningiomas, metastases), Hematomas (blood accumulation from hemorrhage), Abscesses (infectious collections).

2. Generalized Brain Swelling (Cerebral Edema): Ischemia (stroke, hypoxia) → causes cytotoxic edema (cell swelling) or Hypertension → causes vasogenic edema (fluid leakage into brain tissue) or Head trauma → leads to swelling and increased ICP.

3. Increased Venous Pressure: Heart failure → leads to cerebral venous congestion, increasing ICP while Jugular vein obstruction → prevents normal blood drainage from the brain.

4. CSF Flow Obstruction or Overproduction: Hydrocephalus-Excess CSF accumulation due to impaired drainage or excessive production and Meningitis-causes inflammation and blockage of CSF pathways.

5. Idiopathic Intracranial Hypertension (Pseudotumor Cerebri): Seen mostly in young obese females, Increased ICP with no obvious cause (no tumor, no hemorrhage), Leads to headaches, visual disturbances, and papilledema (optic disc swelling).

Clinical Features of Increased Intracranial Pressure (ICP)

Early Symptoms (Mild to Moderate Increase in ICP):

1. Headache Worsens in the morning (due to increased pressure when lying down), Exacerbated by coughing, sneezing, or straining.

2. Nausea and vomiting, Due to compression of the brainstem's vomiting center.

3. Visual disturbances, Blurred vision, double vision (diplopia), or papilledema.

Cushing's Reflex (Cushing's Triad) – A Sign of Severe ICP Increase; A late and life-threatening sign of increased ICP, consisting of:

1. Hypertension (high blood pressure) – as the body tries to push blood into a compressed brain.

2. Bradycardia (slow heart rate) – caused by brainstem compression.

3. Irregular breathing (respiratory dysfunction) – due to brainstem failure.

Advanced Symptoms (Severe ICP Increase): Altered consciousness → confusion, lethargy, then coma and Seizures → due to cortical irritation and Herniation syndromes (when brain tissue is pushed through rigid structures).

Complications of Increased ICP:

1. Brain Herniation – The Most Dangerous Consequence of High ICP: If pressure becomes too high, brain tissue is forced through anatomical openings inside the skull, leading to severe neurological damage or death; Types of Herniation: Subfalcine herniation → Cingulate gyrus pushed under the falx cerebri and Uncal herniation → Medial temporal lobe herniates through the tentorium cerebelli, compressing the midbrain and Tonsillar herniation → Cerebellar tonsils are forced into the foramen magnum, compressing the brainstem (fatal).

2. Seizures: Increased ICP can irritate neurons, leading to epileptic activity.

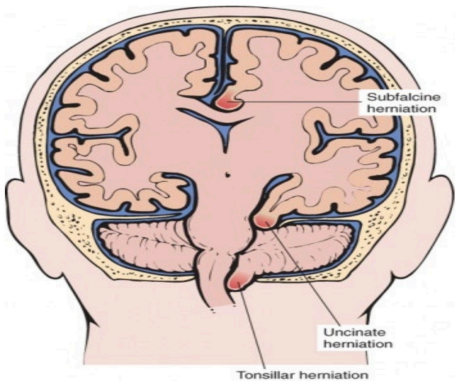
3. Hydrocephalus: If ICP increases due to CSF obstruction, it can lead to ventricular enlargement and brain atrophy.

Brain edema refers to the accumulation of excess fluid within the brain parenchyma, leading to brain swelling and increased intracranial pressure (ICP), There are two major types of brain edema, and they often coexist: Vasogenic Edema Caused by increased permeability of the blood-brain barrier (BBB) Results in fluid leakage from blood vessels into the extracellular space More common in the white matter, Associated with conditions such as brain tumors, infections, hypoxia, and meningitis, the second type is Cytotoxic Edema Occurs due to failure of sodium-potassium pumps in the cell membrane, leading to fluid accumulation inside neurons and glial cells More common in the gray matter, Associated with ischemic stroke, toxins, and hypoxia.

Brain edema causes swelling, reducing the distinction between gyri and sulci, as the sulci become filled with fluid and narrow, while the gyri appear swollen, If severe and untreated, it can lead to brain herniation, one of the most life-threatening complications.

Brain herniation occurs when increased intracranial pressure (ICP) causes displacement of brain tissue across rigid structures such as the falx cerebri or tentorium cerebelli; There are three major types, each with serious complications:

1. Subfalcine (Cingulate) Herniation: Occurs when the cingulate gyrus is pushed beneath the free edge of the falx cerebri, May compress the anterior cerebral artery (ACA), causing ischemia and infarction in its territory.



2. Transtentorial (Uncal) Herniation: Occurs when the medial temporal lobe (uncus) is pushed downward against the tentorium cerebelli, shifting brain tissue from the supratentorial to the infratentorial compartment; Major complications:

- Compression of the oculomotor nerve (CN III): Ipsilateral pupil dilation (mydriasis) and loss of pupillary reflex also Impaired eye movement on the same side as the lesion.

- Compression of the posterior cerebral artery (PCA): Causes ischemic injury in PCA-supplied areas, including the visual cortex, leading to cortical blindness.

- Duret Hemorrhages: Downward displacement of the brainstem stretches and tears small perforating arteries, causing fatal hemorrhages in the midbrain and pons.

3. Tonsillar Herniation: Occurs when the cerebellar tonsils are forced through the foramen magnum Compresses the brainstem, especially the medulla oblongata, affecting the respiratory and cardiovascular centers, This is life-threatening and requires immediate medical intervention.

Duret hemorrhages are small, fatal hemorrhages in the midbrain and pons, caused by brainstem compression due to transtentorial herniation; Causes of Duret Hemorrhages: Transtentorial herniation and Severe ICP elevation, leading to rupture of small perforating

brainstem arteries and Fatal in most cases, as it damages brainstem centers controlling respiration and heart function.

If not treated promptly, brain edema and herniation lead to: Brain ischemia and infarction due to vessel compression and Permanent neurological deficits, such as blindness or paralysis and Death, due to respiratory or cardiac failure when the brainstem is compressed.

Summary

• The skull protects the brain but leaves little space to accommodate for any increase of the cranial contents.

• increased cranial contents cause increased intracranial pressure. This can be due to increased brain tissue (tumours), fluid (edema due to hypoxia or inflammation or other causes), CSF (hydrocephalus) or blood (haemorrhage)

• increased ICP manifests as headache and vomiting, Cushing triad (hypertension, bradycardia, irregular slow breathing)) and can progress to coma.

• increased ICP can be complicated by herniation; which is a displacement of brain tissue from a compartment to another.

• Subfalcian herniation displaces the cingulate gyrus under edge of falx, it causes compression of anterior cerebral artery

• Transtentorial herniation displaces the medial aspect of temporal lobe against the free margin of the tentorium. This compresses the third cranial nerve, posterior cerebral artery and can cause Duret haemorrhage in the midbrain which is usually fatal.

• Tonsillar herniation displaces the cerebellar tonsils through foramen magnum causing brain stem compression, which is usually fatal.

Question:A 54 year old man complained of severe headache and vomiting. imaging studies showed a large subdural hematoma. Two days later he had dilated pupil of the right eye with and his visual acuity decreased.Which of the following is incorrect about his condition?

• A. Can be complicated by haemorrhage in the pons.

• B. His eye symptoms could be related to ischemic injury to the visualcortex

• C.The medial aspect of his temporal lobe is compressed against the free margin of the tentorium

• D. The dilated pupil indicated damage of the left third cranial nerve

• E. He might develop fatal brain stem complications.

Answer: The scenario describes increased ICP due to hematoma. The complications he had

indicate herniation, and the symptoms are those of transtentorial herniation, the answer is D: the lesion is related to the ipsilateral nerve (at the same side of the lesion).. so his right third cranial nerve is compressed.

• A is correct, it describes Duret hemorrage . Also E is correct , again it describes Duret haemorrhage.

- **C :correct, it simply describes his main complication: transtentorial herniation note that the decreased visual acuity is due to effect on the visual cortex (ischemic damage due to compression on the posterior cerebral artery) , however, the dilated pupil and impaired ocular movement are effects of compression on the third cranial nerve**

Deep understanding of disease mechanisms is the key to effective treatment; don't just focus on diagnosing symptoms, but dive into the underlying causes and biological roots of each condition to provide precise and comprehensive care.