

CNS Pathophysiology

PD, AD, MG, Epilepsy, Stroke + Cases

By James Melvin
MD3, B.Sc. Biochemistry

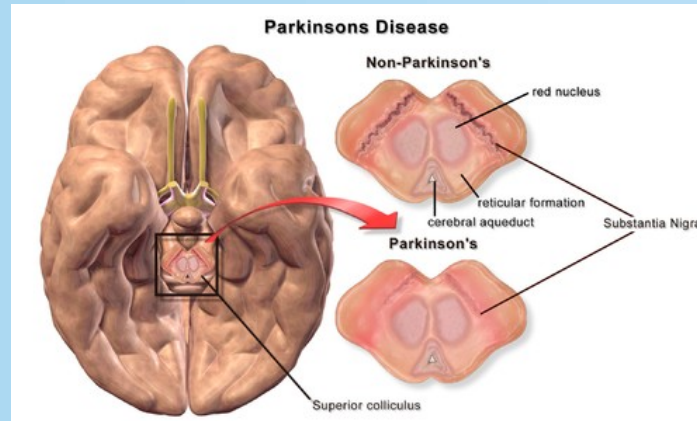
Parkinson's Disease

Pathophysiology:

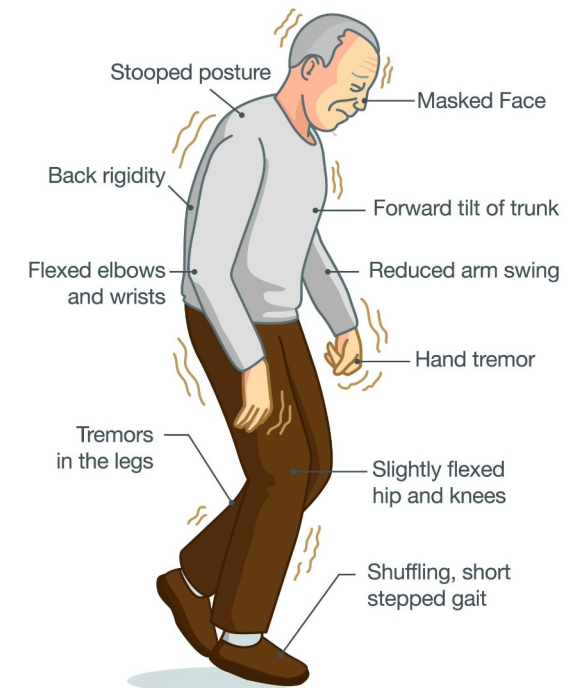
- Progressive loss of dopaminergic neurons in the substantia nigra pars compacta → ↓ dopamine in basal ganglia → impaired motor control
- Lewy bodies (α -synuclein) present in CNS and PNS; astrocyte loss and microglial activation

Etiology:

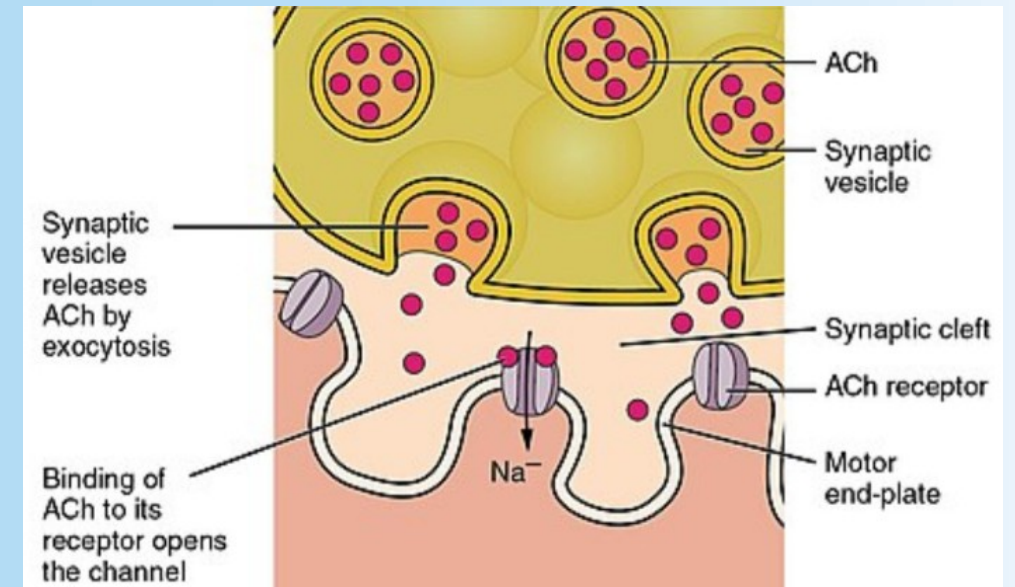
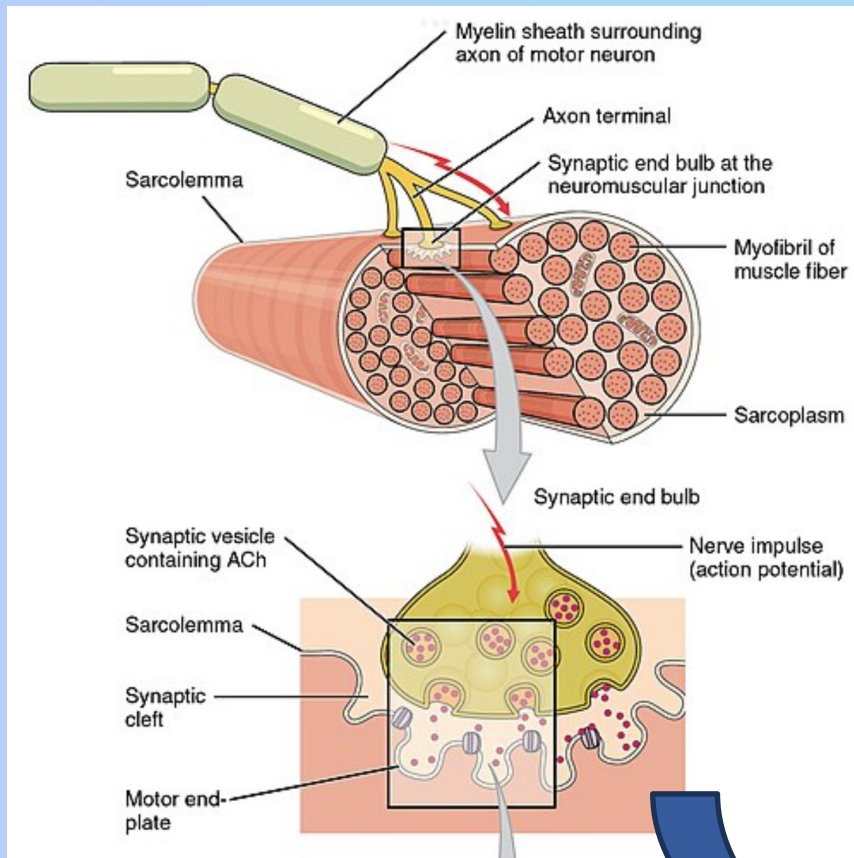
- Mostly idiopathic
- Familial forms: PARK, PINK1, DJ-1 mutations



Parkinson's Disease Symptoms



Neuromuscular junction (NMJ)



Myasthenia Gravis

- Autoimmune neuromuscular junction disorder

Pathophysiology:

- IgG autoantibodies against nicotinic acetylcholine (ACh) receptors or MuSK → impaired neuromuscular transmission → fatigable skeletal muscle weakness
- Type of hypersensitivity: Type II (antibody-mediated)

Key clinical features:

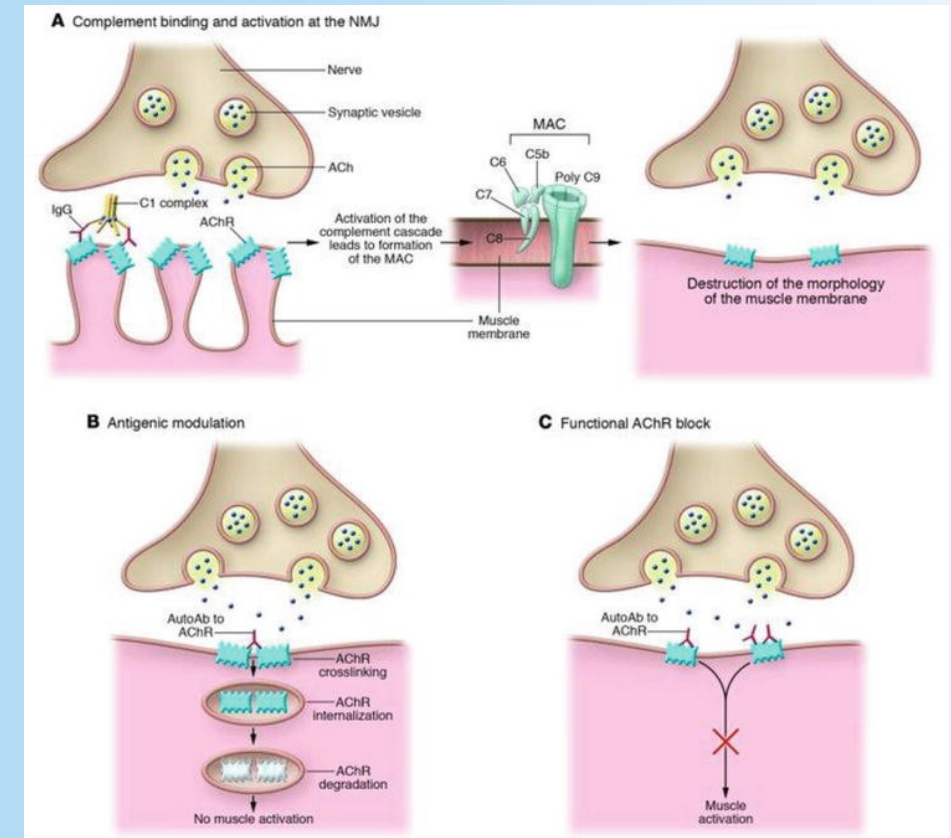
- Fluctuating weakness, worse with use, better with rest
- Ptosis, diplopia (most common initial)
- Bulbar symptoms: dysarthria, dysphagia, fatigable chewing
- Proximal limb weakness; reflexes and sensation normal

Diagnosis:

- Serum anti-AChR or anti-MuSK antibodies

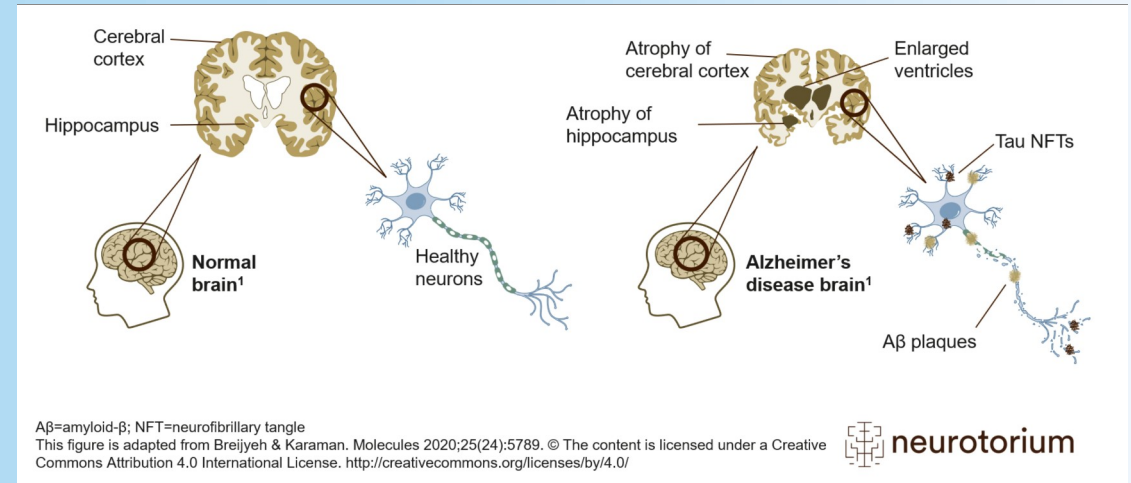
Txt:

- Acetylcholinesterase inhibitors (pyridostigmine, neostigmine) + Mechanical ventilation if respiratory failure



Alzheimer's Disease (AD)

- Chronic, progressive neurodegenerative disorder
- → most common cause of dementia (~60-70%)
- Insidious onset, slow progression
- Earliest and most prominent symptom:
- Short-term (episodic) memory loss
- Progresses from mild cognitive impairment (MCI) → dementia



AD Pathophysiology & Etiology

Core pathology: protein misfolding disorder

β -amyloid plaques (extracellular)

- **Neurofibrillary tangles (intracellular hyperphosphorylated tau)**

Amyloid hypothesis:

Abnormal processing of amyloid precursor protein (APP) → β -amyloid accumulation

Tau pathology:

Microtubule dysfunction → neuronal death

Neuroanatomy:

Cortical and hippocampal atrophy

- Enlarged sulci, widened ventricles
- Loss of neurons and synapses

Etiology

Mostly sporadic

- Early-onset familial AD (<65): mutations in APP, presenilin 1 & 2
- Genetic risk: APOE ϵ 4

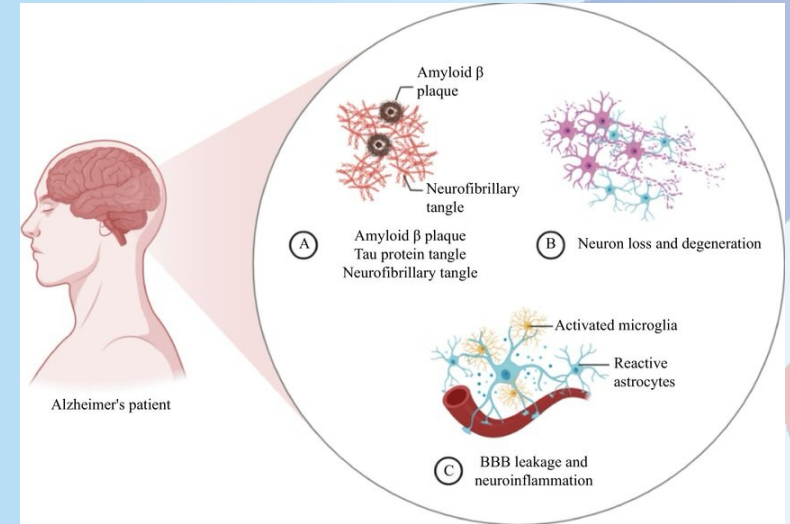
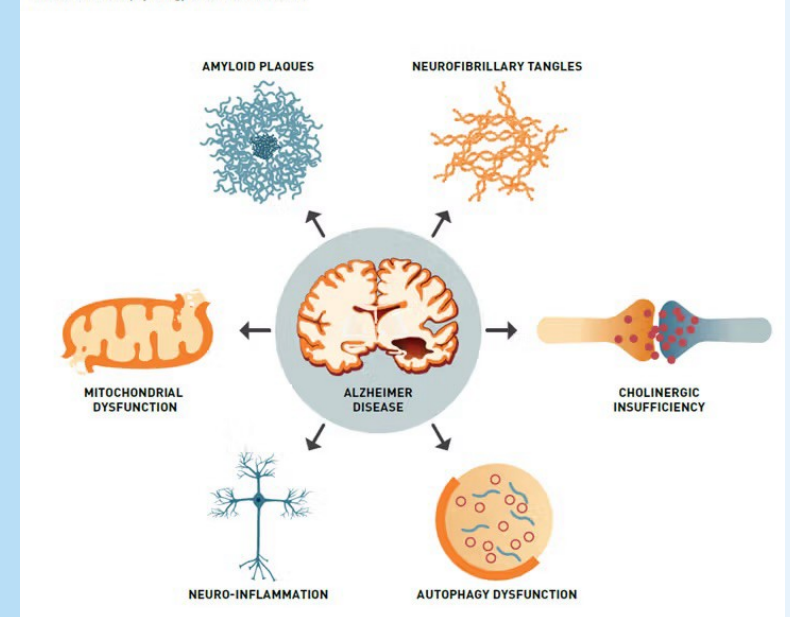


FIGURE 1. Pathophysiology of Alzheimer Disease^a



Epilepsy

Epilepsy: a group of neurological disorders characterized by a persistent predisposition to seizures

Diagnostic criteria (any one):

- ≥ 2 unprovoked seizures >24 hours apart
- 1 unprovoked seizure + high recurrence risk
- Diagnosis of an epilepsy syndrome

Seizure definition:

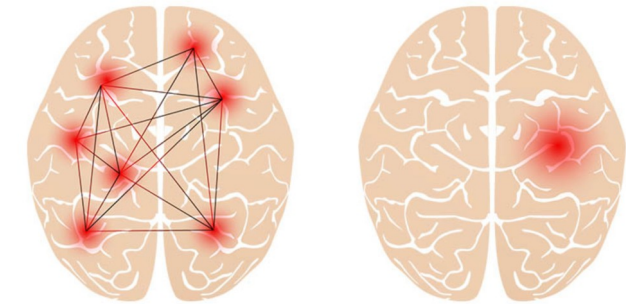
A sudden, transient change in behavior caused by hypersynchronous electrical activity in cortical neuronal networks

Seizure threshold:

Amount of stimulus required to provoke a seizure is lowered in epilepsy

- Acute symptomatic seizures (not epilepsy):
- Stroke, hemorrhage, TBI
- CNS infection, abscess
- Metabolic disturbances (hypoglycemia, hyponatremia, hypocalcemia, hypomagnesemia)
- Drugs and intoxication (cocaine, amphetamines, overdose)
- Eclampsia
-

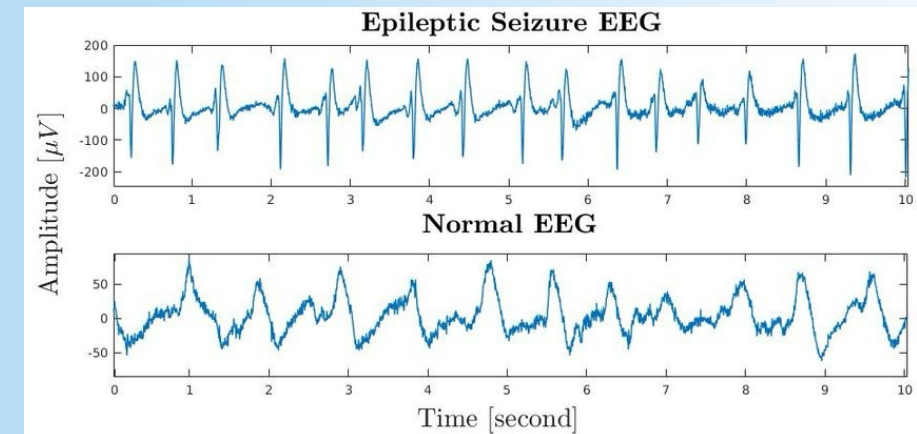
More than 30 types have been reported



Generalized Seizure

Focal Seizure

Generalized seizures affect both sides of the brain whereas focal seizures happen in one area of the brain.



Pathophysiology of Epilepsy

Core mechanism:

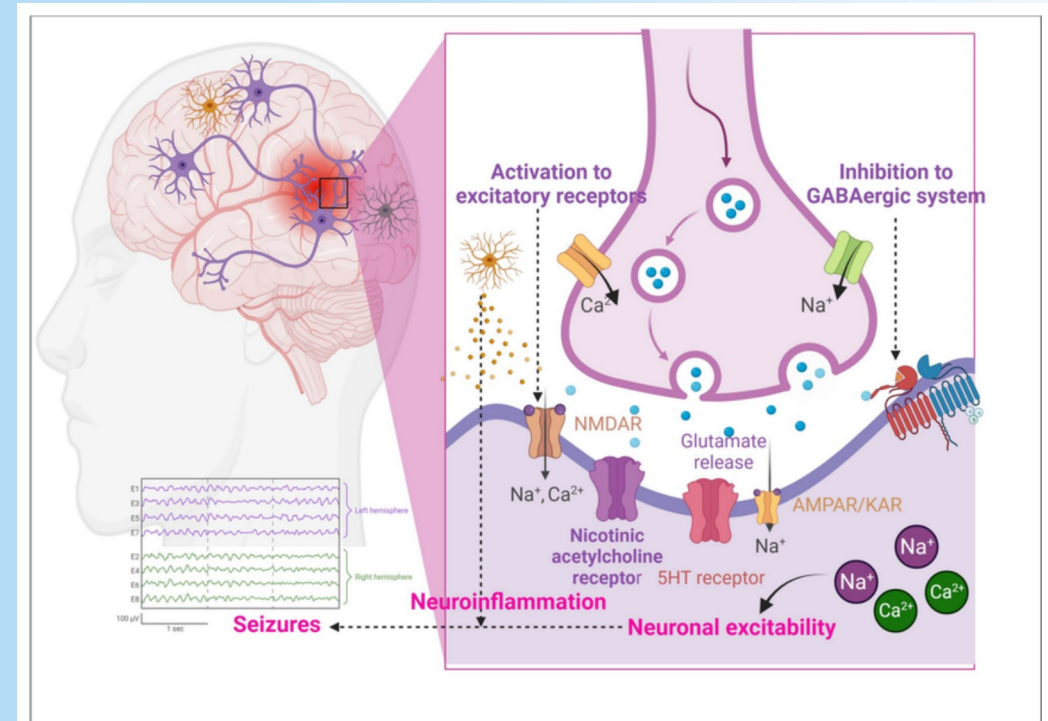
- Neuronal hyperexcitability + hypersynchronization
- Paroxysmal Depolarizing Shift (PDS): Sudden, prolonged depolarization of neurons
- Leads to repetitive firing and seizure propagation
- Appears as spike activity on EEG

Epileptogenesis:

- Process by which normal brain tissue becomes epileptic
- Loss or dysfunction of GABAergic inhibition
- Increased glutamatergic excitation
- Abnormal ion channel function (Na^+ , Ca^{2+} , K^+)
- Reduced inhibitory neuromodulators (e.g. adenosine)

Network-level changes:

- Imbalance between excitation and inhibition
- Abnormal cortical-thalamic circuits
- Enables focal seizures $\pm$ secondary generalization or primary generalized seizures



Pathophysiology of epilepsy: Activation of excitatory receptors or gamma-aminobutyric acid (GABA) neurotransmitter or inhibition of inhibitory receptors or excitatory glutamate promotes activation of N-methyl-D-aspartate (NMDA) receptors, nicotinic acetylcholine receptor with subsequent dysregulation of voltage-gated Na^+ and Ca^{2+} and K^+ channels incite neuronal hyper-excitability and reduce seizure threshold leading to seizure development. "created with BioRender.com"

Stroke Definition

“Cerebral infarction results from ischemia due to reduced or absent blood flow, leading to irreversible neuronal injury and necrosis.” (Robbins & Cotran, 10th ed., Chapter: Diseases of Blood Vessels)

- Deficit persists >24 hours or results in death
- Transient ischemic attack (TIA):
- Temporary neurologic dysfunction
- No permanent infarction (classically <24 h)

Major types

- Ischemic stroke (≈85%)

Hemorrhagic stroke (2 types)

- Intracerebral hemorrhage (ICH) (≈10-15%)
- Subarachnoid hemorrhage (SAH) (≈5%)

Ischemic Stroke

Causes:

1. Thrombosis

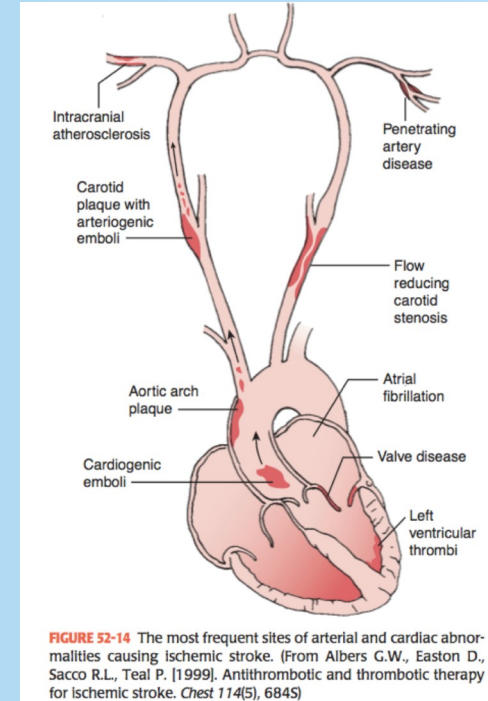
In situ vessel occlusion

- Large vessel disease: atherosclerosis (carotids, Circle of Willis)
- Small vessel disease: lipohyalinosis (lacunar strokes)
-

2. Embolism

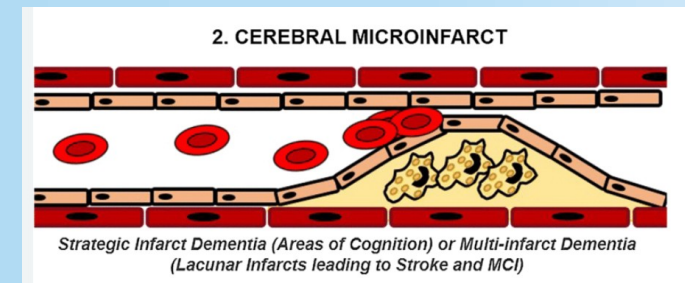
Cardiac (AF, mural thrombus, valve disease)

- Artery-to-artery
- Systemic hypoperfusion
- Cardiac failure, shock, severe hypotension
- Causes bilateral, watershed infarcts
-



Core pathophysiology:

↓ Cerebral blood flow → ↓ oxygen & glucose
ATP depletion → membrane depolarization
Glutamate excitotoxicity (NMDA activation)
↑ Intracellular Ca^{2+} → mitochondrial failure → cell death



Ischemic Brain Injury + Edema

Critical blood flow thresholds:

- ↓ Protein synthesis → neuronal electrical failure
- Infarction at ~10-12 mL/100 g/min
- Ischemic core: irreversible damage
- Penumbra: salvageable tissue (target of reperfusion therapy)

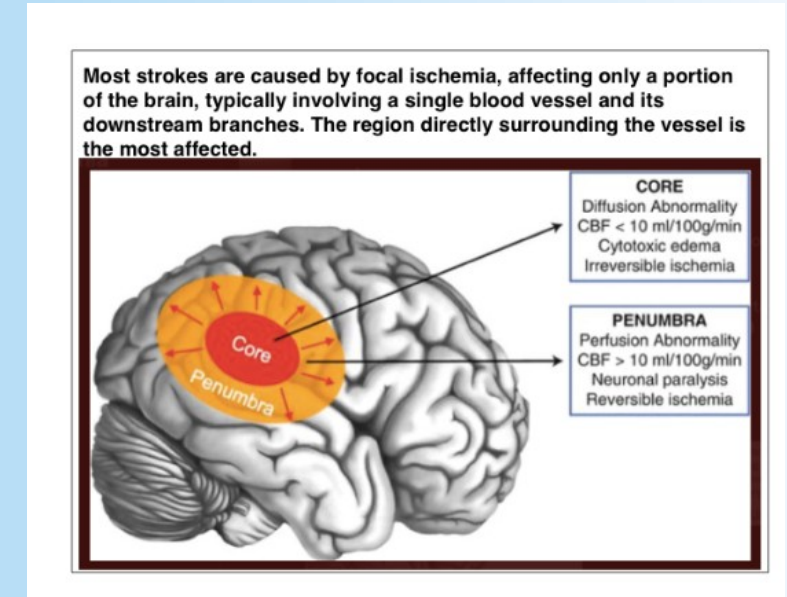
Edema types

1. Cytotoxic edema

- Early
- Cellular swelling from $\text{Na}^+/\text{Ca}^{2+}$ influx

2. Vasogenic edema

- BBB breakdown
- Extracellular fluid accumulation



Hemorrhagic Stroke (ICH & SAH)

Intracerebral Hemorrhage (ICH)

Most common causes: hypertension, trauma

- Others: anticoagulation, cocaine/amphetamines, vascular malformations

Injury from:

1. Mass effect

↑ Intracranial pressure

2. Secondary ischemia

Symptoms depend on bleed location

- Treatment goal: limit bleeding & control ICP
-

Subarachnoid Hemorrhage (SAH)

Usually due to ruptured saccular (berry) aneurysm

- Sudden, severe “thunderclap” headache
- Rapid ↑ ICP → vomiting, neck stiffness, loss of consciousness
- High risk of vasospasm → delayed ischemia
-

