

Global cerebral hypoxia/ischemia

Mechanisms · selective vulnerability · morphology · clinicopathologic patterns

Pathology teaching lecture

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Learning objectives

1. Distinguish reduced perfusion from reduced oxygen-carrying capacity

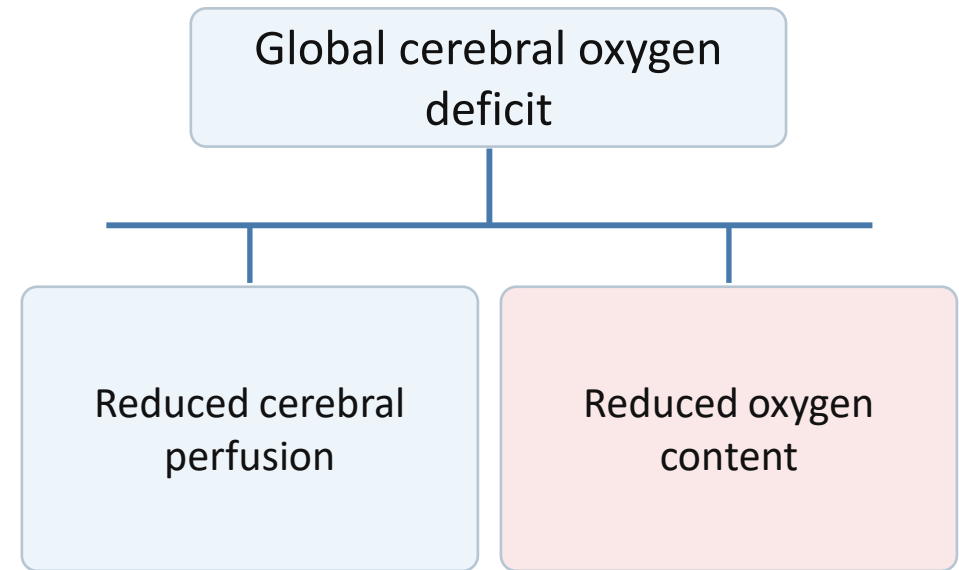
2. Predict selective vulnerability versus diffuse neuronal damage

3. Recognize border-zone injury after systemic hypotension

4. Interpret gross and microscopic changes over time

Global injury is a brain-wide oxygen supply problem

- The initiating disturbance is systemic rather than a single focal arterial occlusion.
- Cerebral perfusion may fall globally, or blood may deliver inadequate oxygen.
- The eventual injury can be diffuse or regionally selective.



Two routes to insufficient cerebral oxygen

- Perfusion failure: Generalized reduction in blood delivered to the brain.
- Oxygen-content failure: Blood flow may occur despite impaired oxygen-carrying capacity.
- Either route can cause neuronal injury if the deficit is sufficiently severe or prolonged.

Perfusion deficit

Cardiac arrest · shock ·
severe hypotension

Oxygen-content deficit

Carbon monoxide
poisoning is the
textbook example.

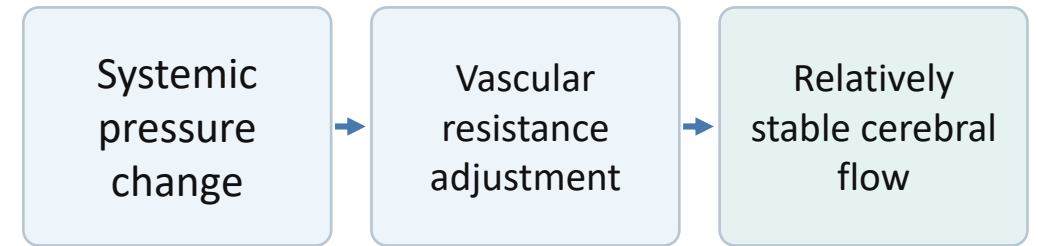
Why the brain has little tolerance for interruption

- The brain accounts for approximately 1–2% of body weight.
- It receives approximately 15% of resting cardiac output.
- It accounts for about 20% of oxygen consumption and depends on aerobic metabolism.

Textbook estimate	Brain
Body weight	1–2%
Resting cardiac output	≈15%
Oxygen consumption	≈20%

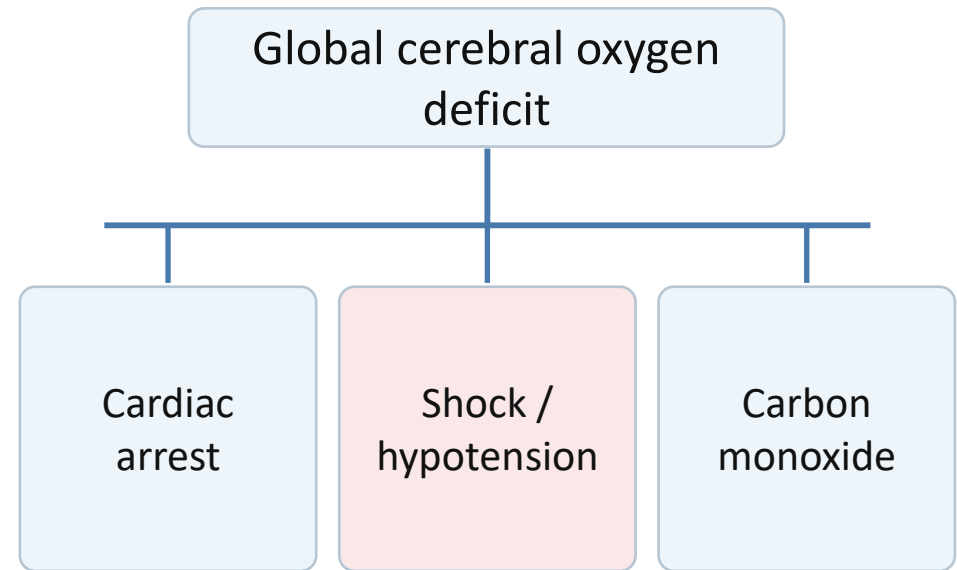
Autoregulation normally stabilizes blood flow

- Cerebral vessels adjust resistance over a wide range of blood pressure and intracranial pressure.
- This autoregulation ordinarily keeps cerebral blood flow relatively constant.
- Profound systemic perfusion failure can exceed the capacity of this protection.



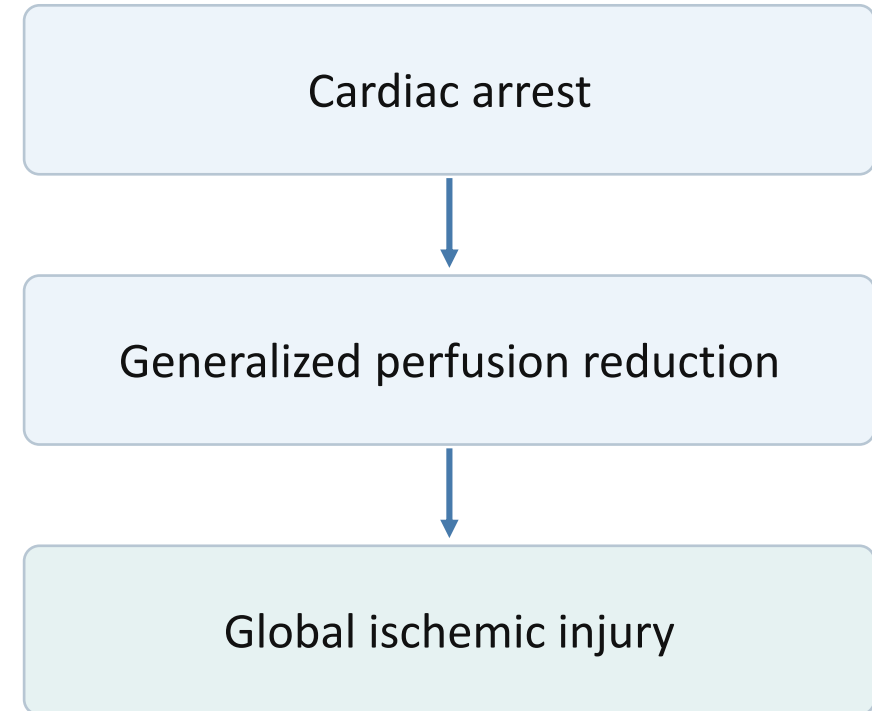
Recognize the principal systemic insults

- Cardiac arrest abruptly impairs cerebral circulation.
- Shock produces generalized failure of tissue perfusion.
- Severe hypotension markedly lowers cerebral perfusion pressure.
- Carbon monoxide poisoning decreases the oxygen-carrying capacity of blood.



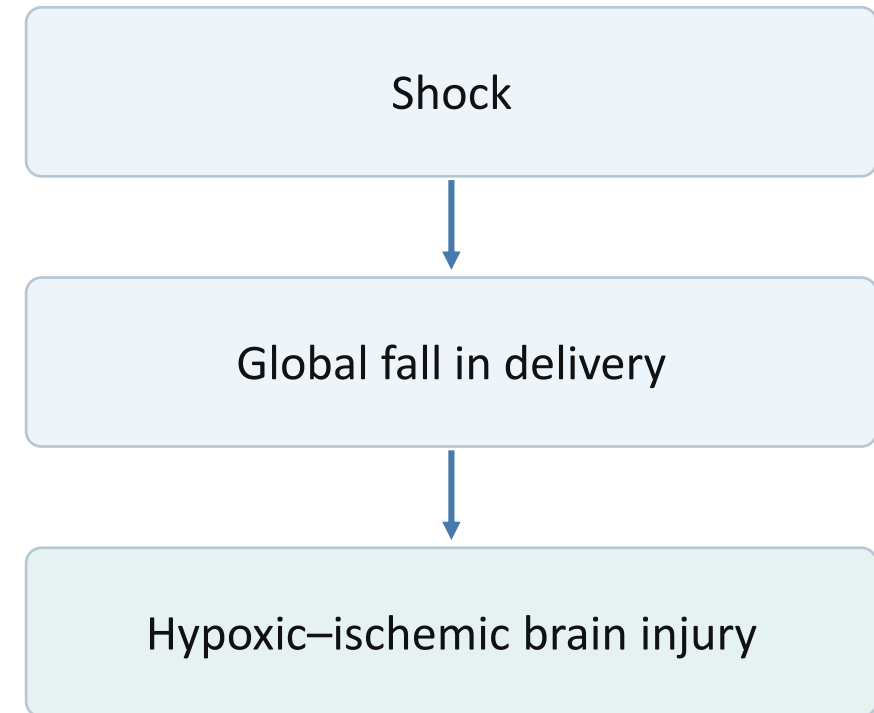
Cardiac arrest: Interruption of perfusion

- Cerebral perfusion may be globally and abruptly compromised.
- The extent of irreversible injury depends on severity and duration.
- A post-resuscitation brain may show selective neuronal or watershed injury.



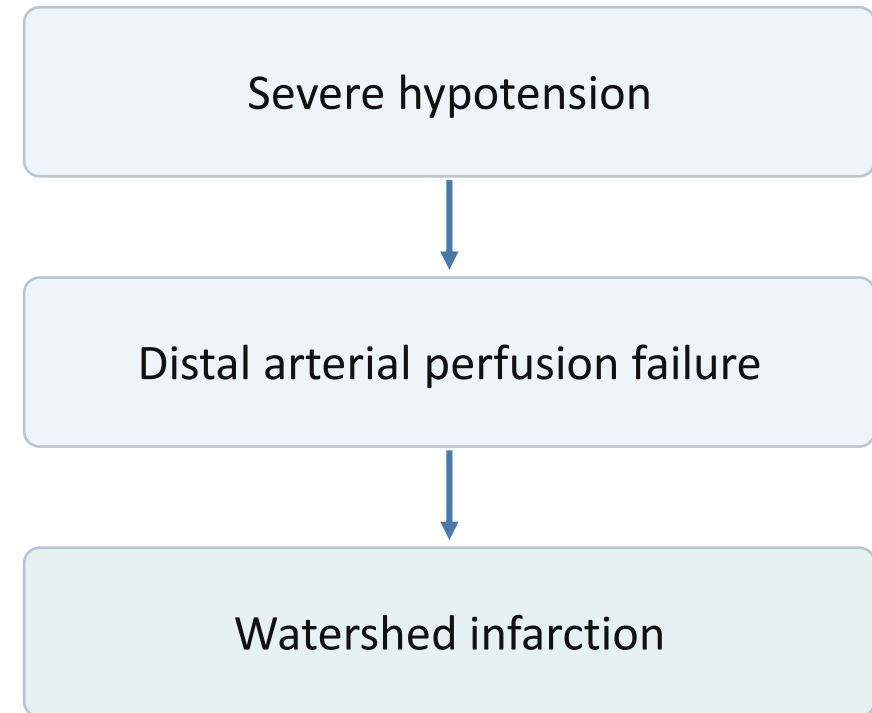
Shock: Systemic circulatory failure

- The pathology-relevant feature of shock is inadequate global cerebral perfusion.
- Regional outcomes depend on the amount and persistence of the flow deficit.
- Shock and focal large-vessel occlusion should not be conflated.



Severe hypotension is especially relevant to border zones

- Reduced perfusion pressure can affect distal vascular territories.
- The anterior–middle cerebral arterial boundary is especially vulnerable.
- Border-zone infarcts are associated with severe hypotensive episodes.



Carbon monoxide causes oxygen-content failure

- Carbon monoxide poisoning as a cause of decreased oxygen-carrying capacity.
- The initiating defect differs from generalized low-flow states.
- Both pathways can culminate in global cerebral hypoxia.

Circulation problem

Insufficient blood
reaches brain tissue.

Oxygen content problem

Circulating blood
carries insufficient
usable oxygen.

Do not equate reduced flow with reduced oxygen content

Feature	Systemic ischemia	Blood oxygen-content failure
Primary disturbance	Generalized cerebral perfusion decreases	Blood transports inadequate oxygen
Robbins examples	Arrest, shock, severe hypotension	Carbon monoxide poisoning
Shared consequence	Reduced tissue oxygen availability	Reduced tissue oxygen availability
Interpretive priority	Ask what happened to circulation	Ask what happened to oxygen transport

Global and focal cerebral ischemia are different patterns

- Global ischemia arises from a generalized perfusion disturbance.
- Focal ischemia follows insufficient flow in a particular vascular territory.
- Watershed injury is a regionally concentrated consequence of systemic hypoperfusion.

Global

Systemic perfusion deficit; Selective, diffuse or watershed injury.

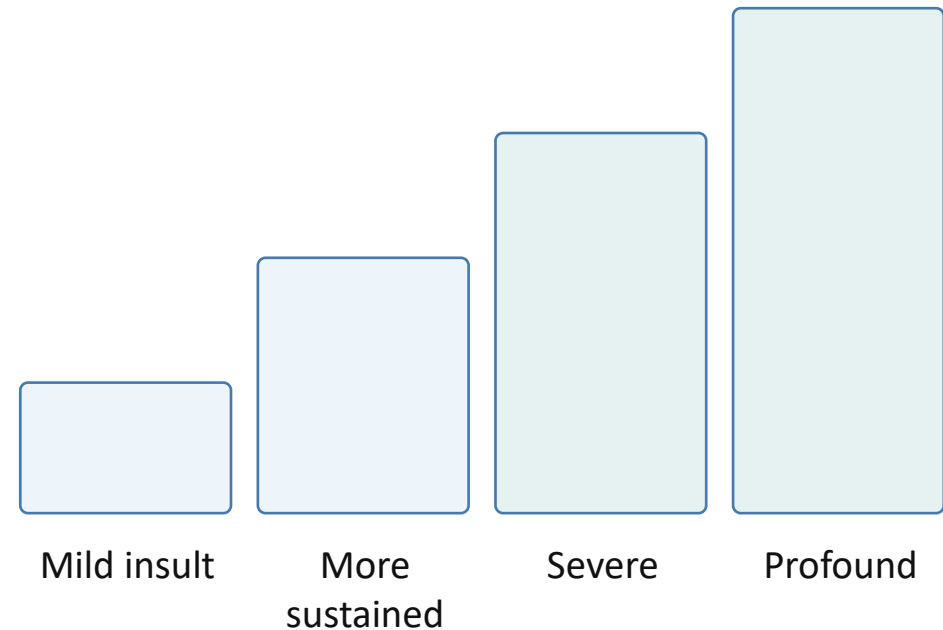
Focal

Localized arterial supply deficit; Territorial injury.

Severity and duration jointly shape outcome

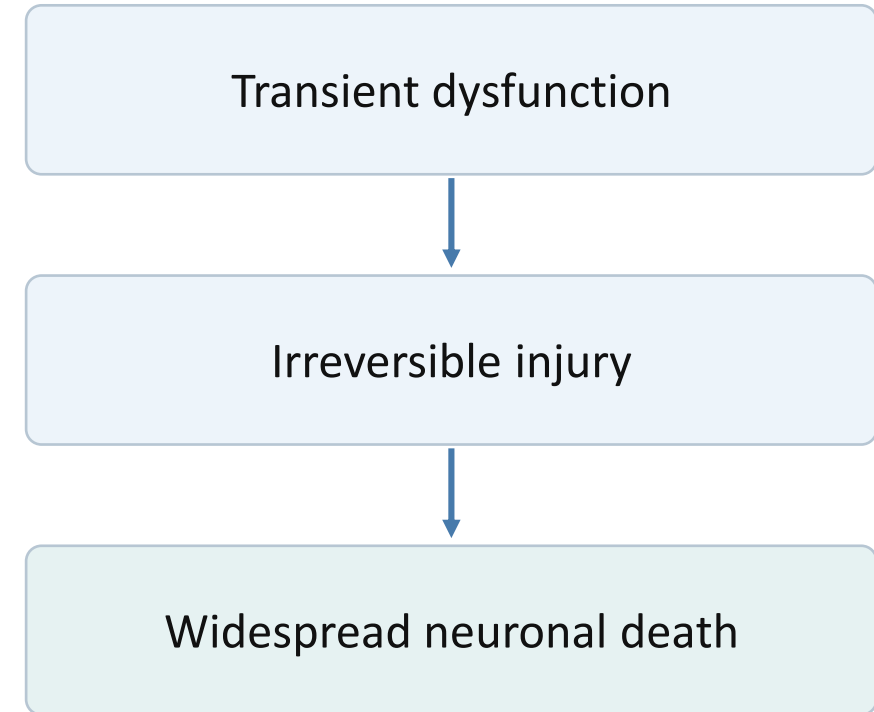
- Clinical severity cannot be interpreted from the trigger alone.
- Shorter or milder insults may be followed by complete recovery.
- Longer or more severe deficits can cause irreversible encephalopathy.

Increasing insult severity or duration →



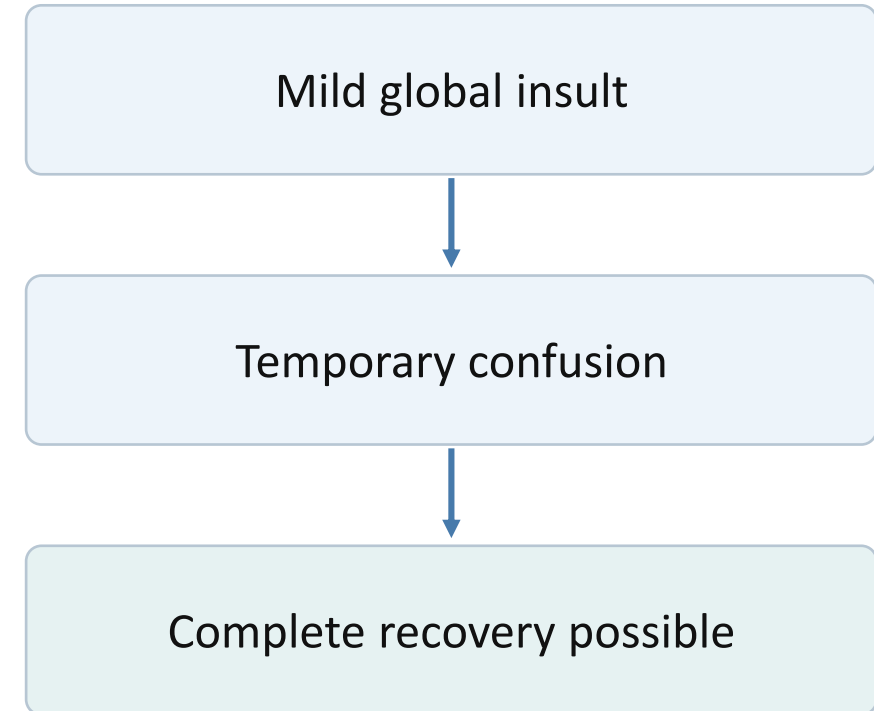
Global hypoxia is a spectrum, not one endpoint

- Mild insults may produce a transient postischemic confusional state.
- Greater injury can produce diffuse hypoxic–ischemic encephalopathy.
- At extreme severity, widely distributed neuronal death occurs.



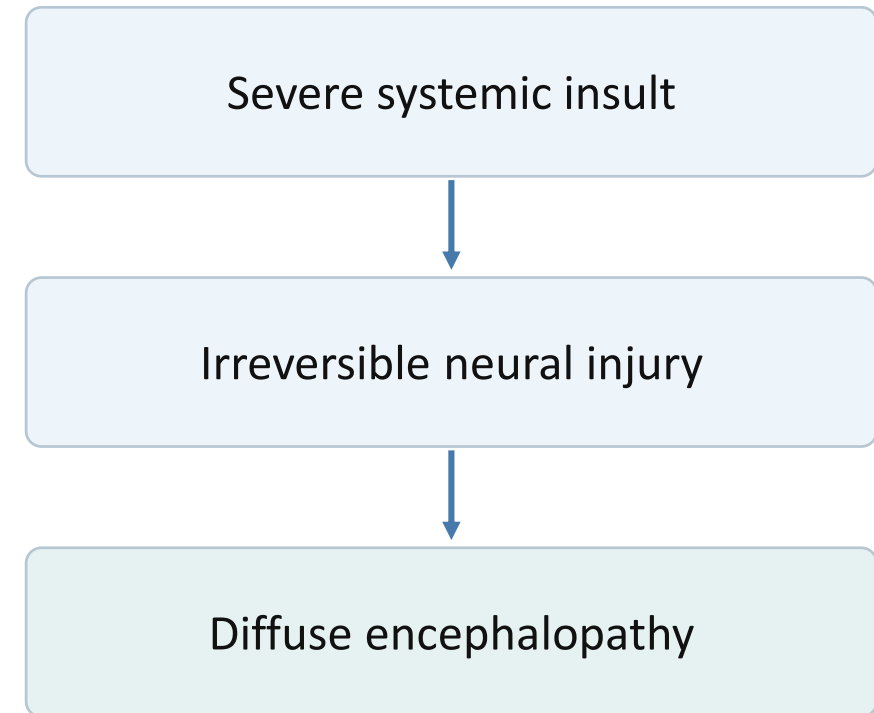
Transient postischemic confusion

- This is a possible outcome of a relatively mild global insult.
- Clinical recovery may be complete.
- The label alone does not establish a fixed structural injury.



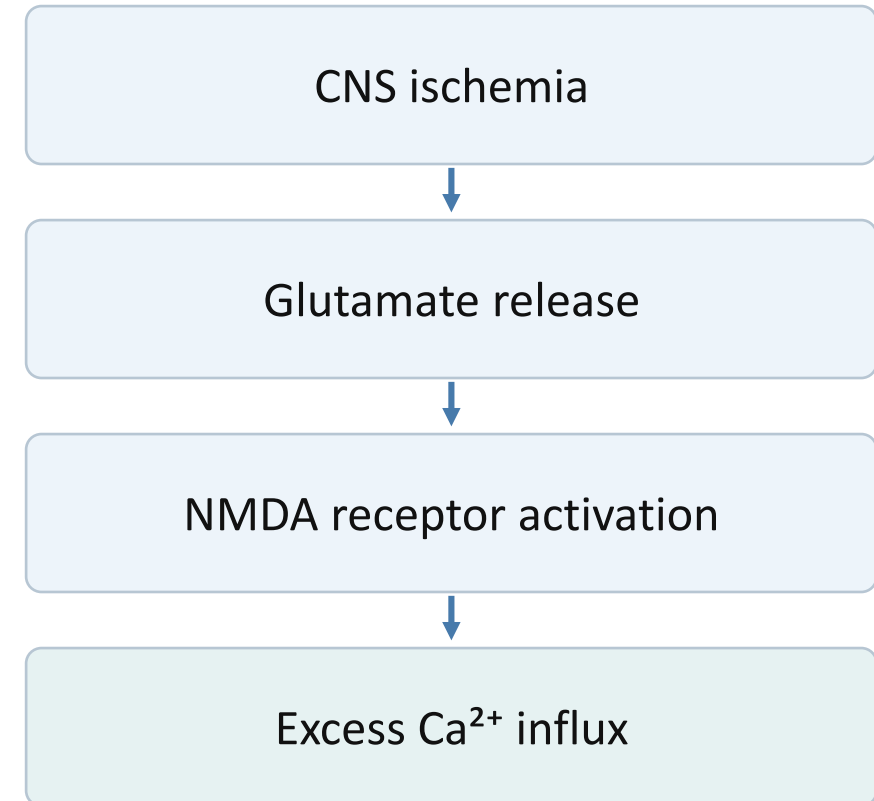
Diffuse hypoxic–ischemic encephalopathy

- Severe global deprivation may produce irreversible CNS damage.
- The injury can include neurons and, with sufficient severity, glial cells.
- Microscopic evolution follows an ischemic tissue-response sequence.



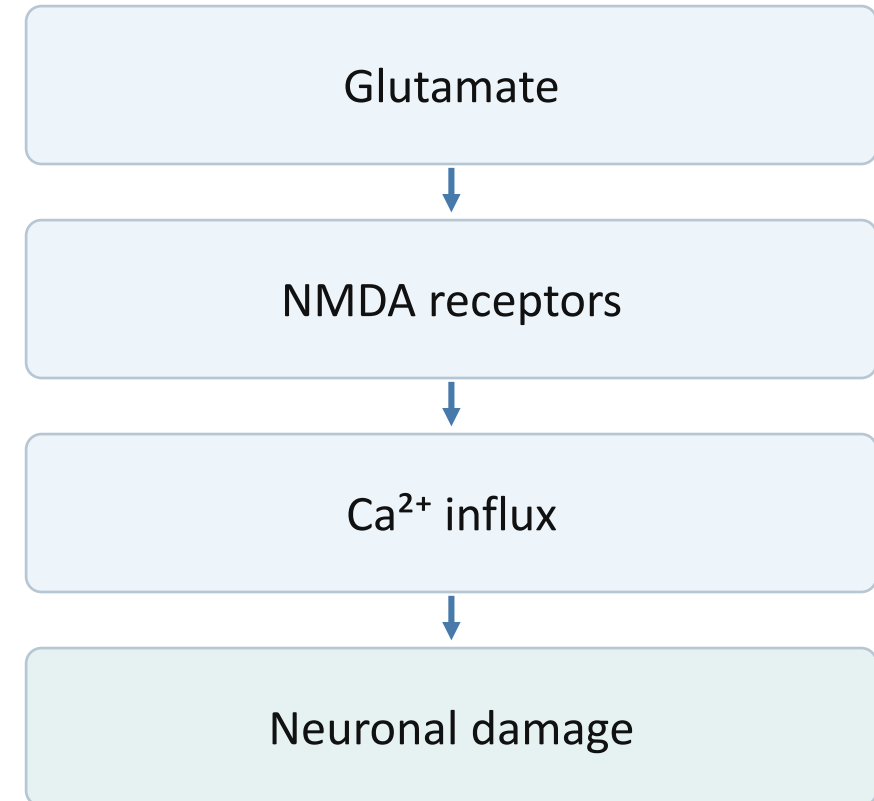
Excitotoxicity amplifies ischemic neuronal injury

- The adjacent Robbins section describes inappropriate release of excitatory neurotransmitters during CNS ischemia.
- Glutamate can activate NMDA-type receptors.
- Excessive calcium entry contributes to neuronal damage.



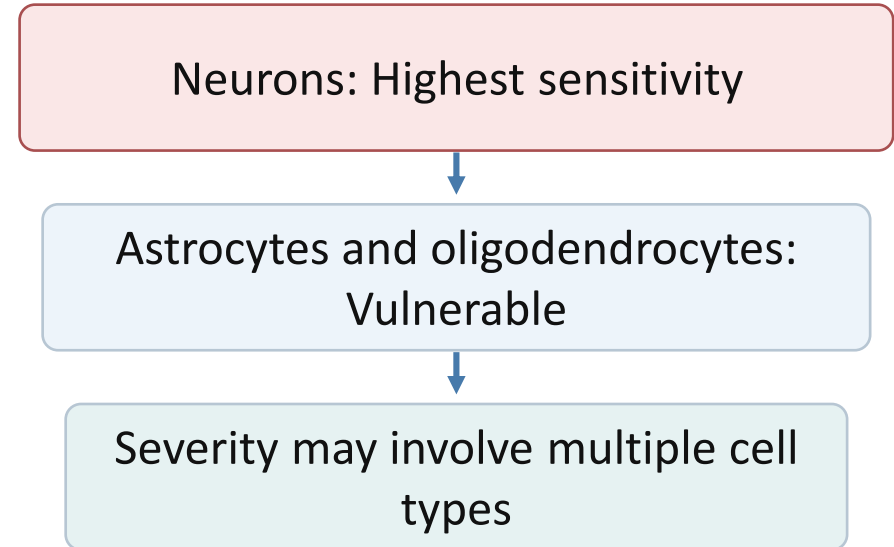
Glutamate–NMDA–calcium injury sequence

- Neurotransmitter excess is harmful when receptor activation becomes inappropriate.
- NMDA-type glutamate receptors permit calcium entry.
- Excess calcium influx participates in neuronal injury.



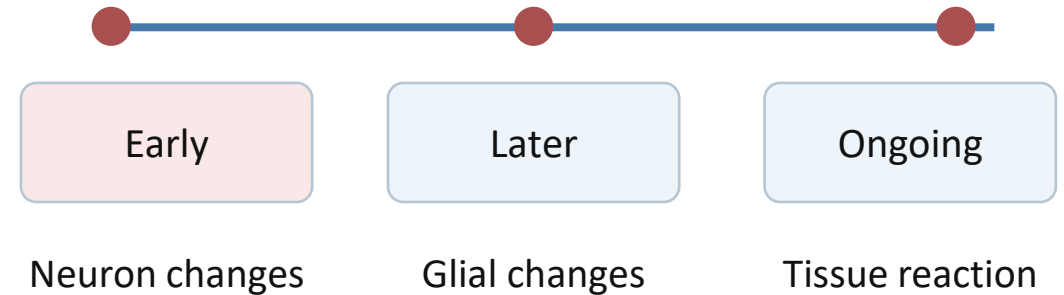
CNS cell types differ in ischemic sensitivity

- Neurons are the most sensitive cellular population.
- Astrocytes are also vulnerable.
- Oligodendrocytes are also vulnerable, but their acute morphologic injury appears later.



Neuronal injury often precedes visible glial injury

- The first described irreversible histologic changes occur in neurons.
- Early neuronal alterations are detectable after roughly 6–12 hours.
- Comparable acute changes become apparent somewhat later in glial cells.



Three neuronal populations are especially susceptible

- Hippocampal pyramidal neurons, particularly region CA1.
- Cerebellar Purkinje cells.
- Cerebral cortical pyramidal neurons, especially layers III and V.

Hippocampal CA1 pyramidal cells



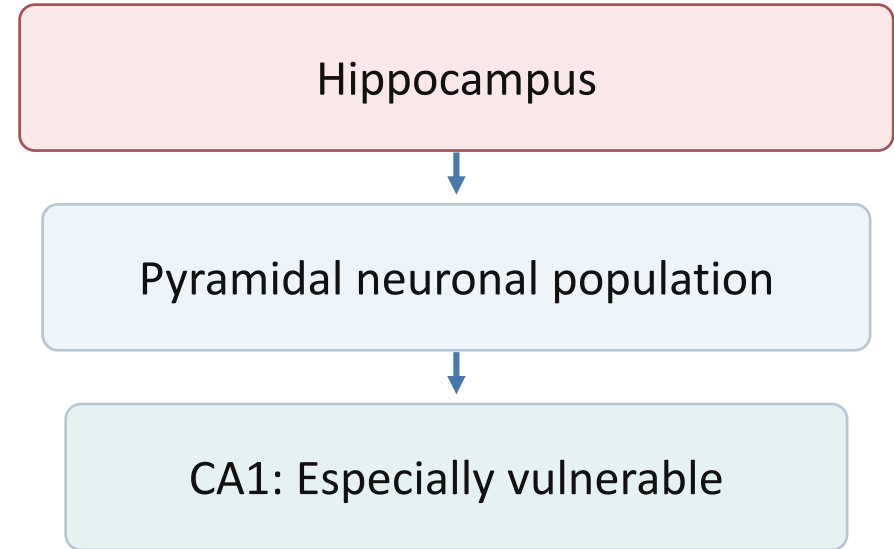
Cerebellar Purkinje cells



Neocortical pyramidal cells (III / V)

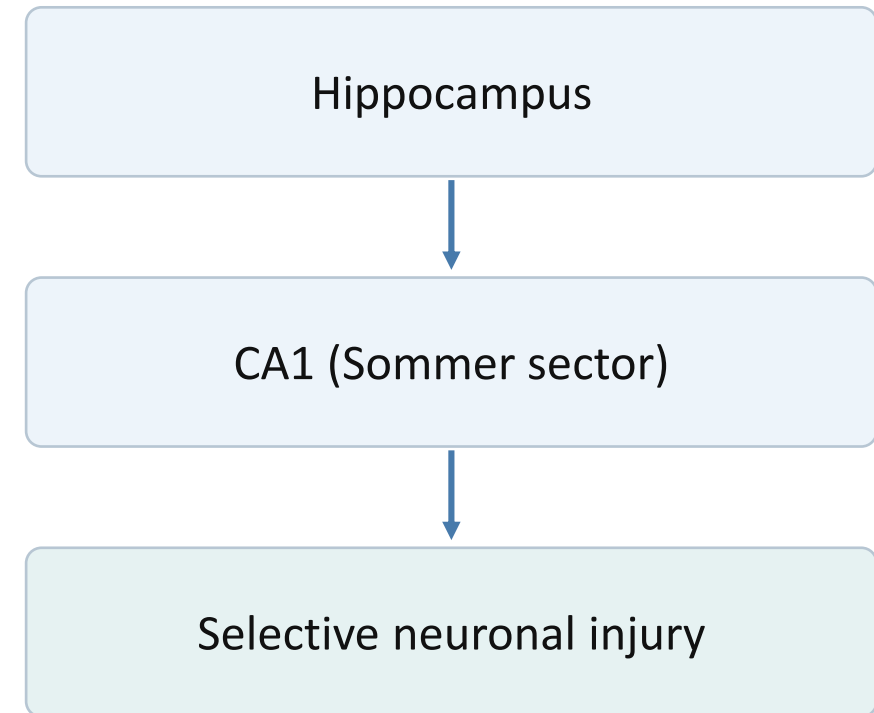
Hippocampal CA1 is a classic vulnerable region

- The hippocampus contains particularly sensitive pyramidal neurons.
- Region CA1 is emphasized over other hippocampal subdivisions in the text.
- Selective injury can occur even without uniform global neuronal loss.



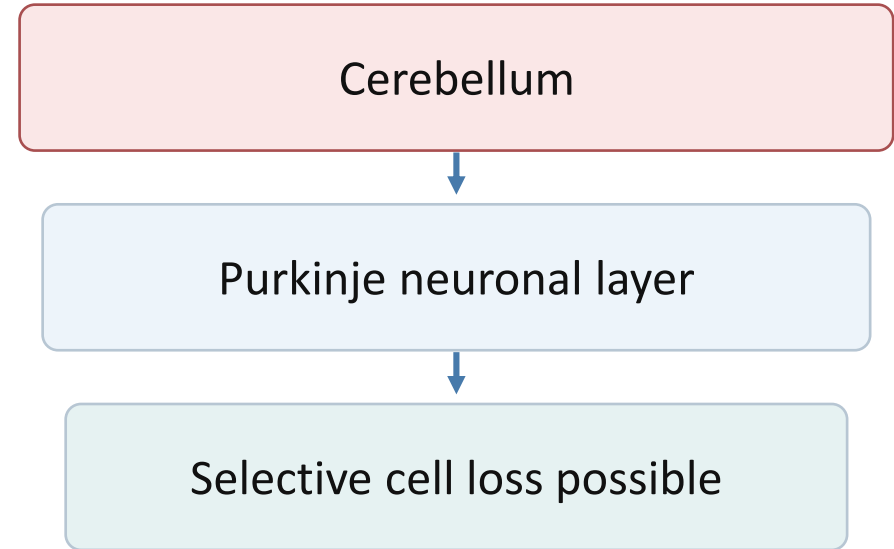
CA1 is also called the Sommer sector

- “Sommer sector” is the alternate name used for hippocampal area CA1.
- The nomenclature identifies a selective neuronal vulnerability site.
- It is an anatomic localization, not a separate etiologic diagnosis.



Purkinje neurons are vulnerable in global injury

- The cerebellum is among the regions displaying selective neuronal sensitivity.
- Purkinje cells are the named vulnerable cerebellar population.
- Their sensitivity does not imply all cerebellar cell types are affected equally.



Cortical pyramidal neurons: Layers III and V

- The neocortex has a layered organization.
- Pyramidal neurons in layers III and V are particularly susceptible.
- Uneven layer involvement contributes to cortical laminar necrosis.

Layer I	
Layer II	
Layer III	Particularly vulnerable
Layer IV	
Layer V	Particularly vulnerable
Layer VI	

Simplified neocortical layer map

Neuronal vulnerability is anatomically selective

Site	Vulnerable cells / region	Teaching interpretation
Hippocampus	Pyramidal neurons, CA1	Sommer sector
Cerebellum	Purkinje neurons	Selective cell vulnerability
Neocortex	Pyramidal neurons, layers III and V	Basis for laminar injury
Severe generalized insult	Widely distributed neurons	Selectivity may be eclipsed

The molecular reason for selectivity is unresolved

- Selective regional vulnerability as an established observation.
- It explicitly states that its molecular mechanisms are not understood.
- Do not present a single proposed molecular explanation as proven by the source.

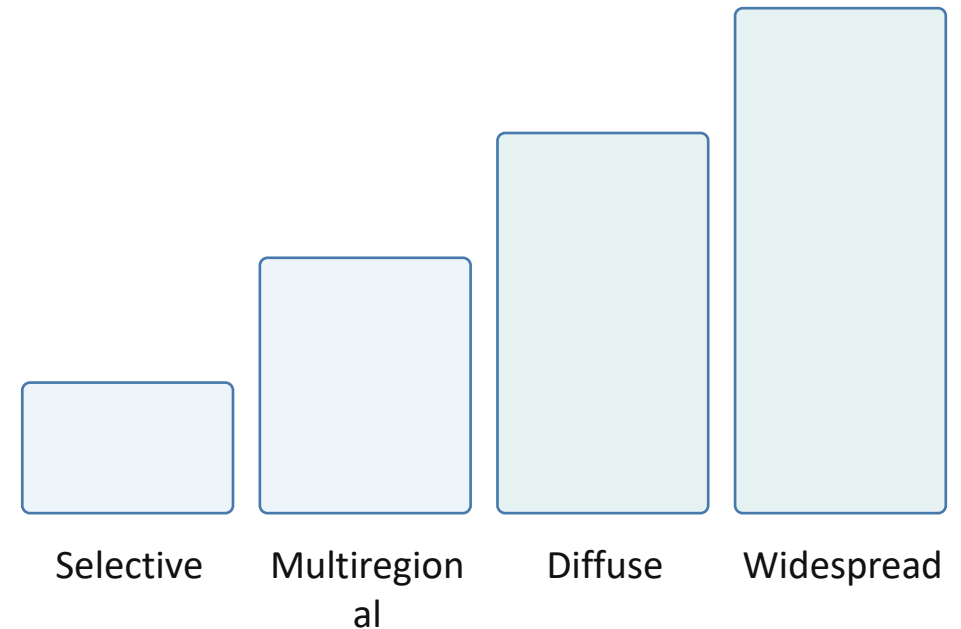
Observed: Regional selective sensitivity

Not established here: A definitive molecular mechanism

With profound injury, selectivity is overwhelmed

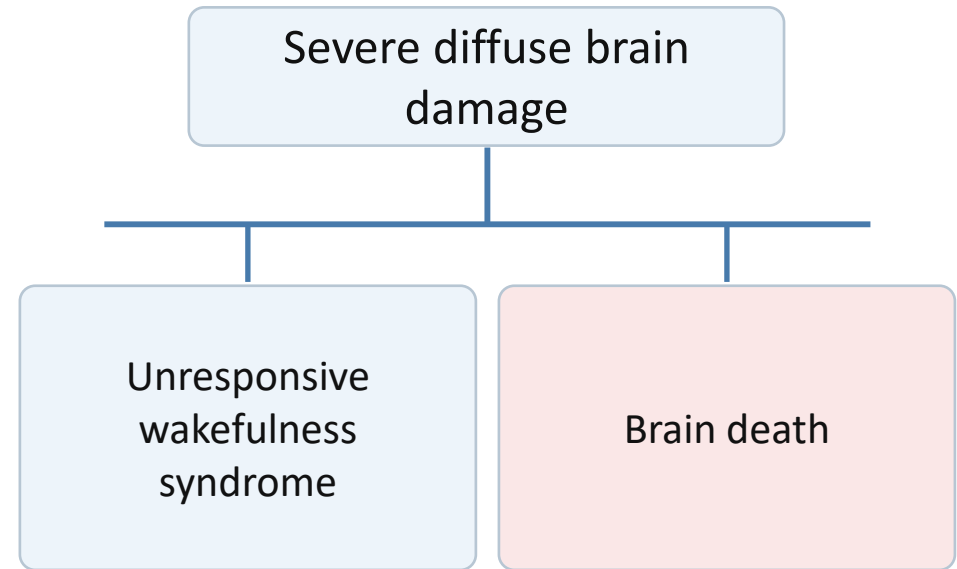
- Severe global hypoxia/ischemia can cause widespread neuronal death.
- The injury may extend well beyond the usually sensitive neuronal groups.
- The clinical consequences then reflect diffuse brain dysfunction.

Increasing insult severity or duration →



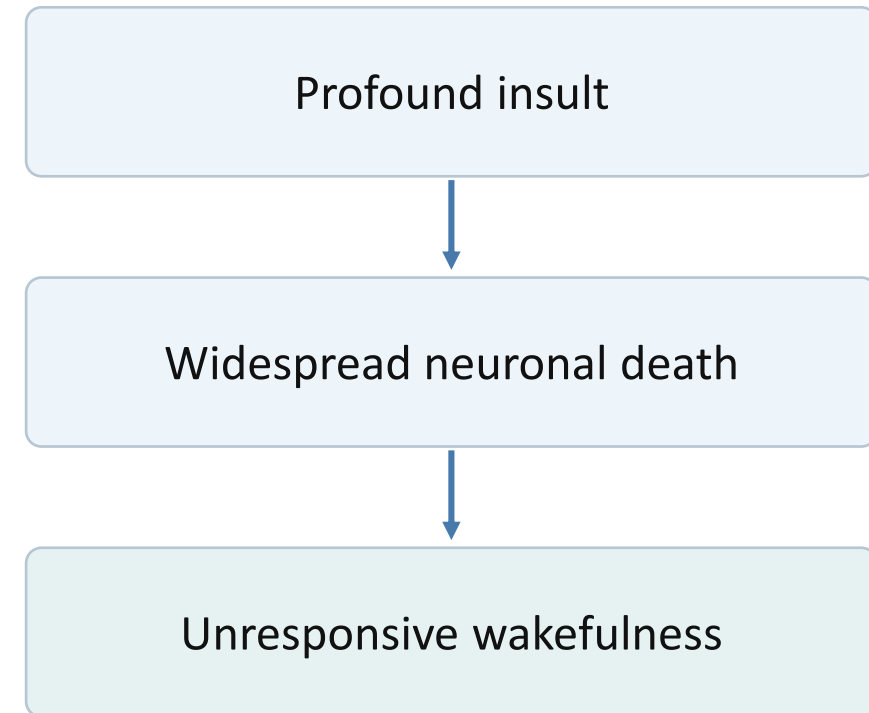
Widespread neuronal death and severe outcomes

- Survivors of profound global injury may develop unresponsive wakefulness syndrome.
- Others meet clinical criteria for brain death.
- Clinical syndromes must not be inferred from a single histologic feature alone.



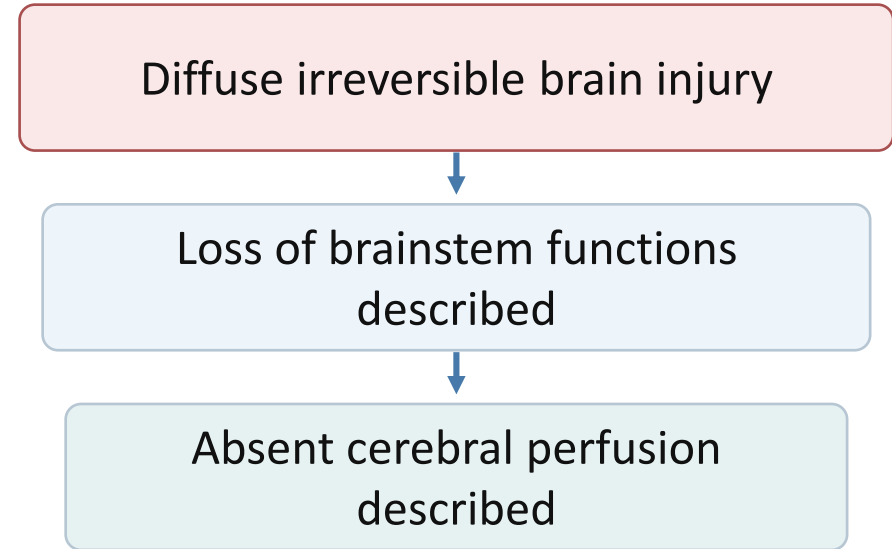
Unresponsive wakefulness syndrome

- “unresponsive wakefulness syndrome.”
- The historical label is “persistent vegetative state.”
- It is discussed as a possible consequence among survivors of severe diffuse injury.



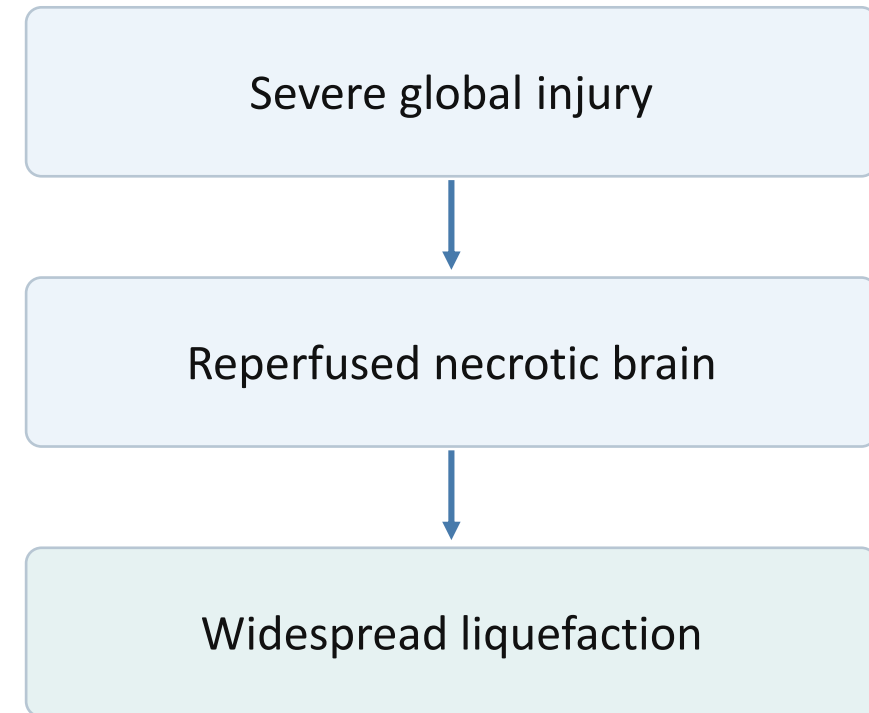
Brain death: Source description, not a checklist

- Robbins mentions irreversible diffuse cortical injury, brainstem damage and absent perfusion.
- The cited manifestations include absent brainstem reflexes and respiratory drive.
- An isoelectric EEG is mentioned, but the excerpt does not establish a complete clinical protocol.



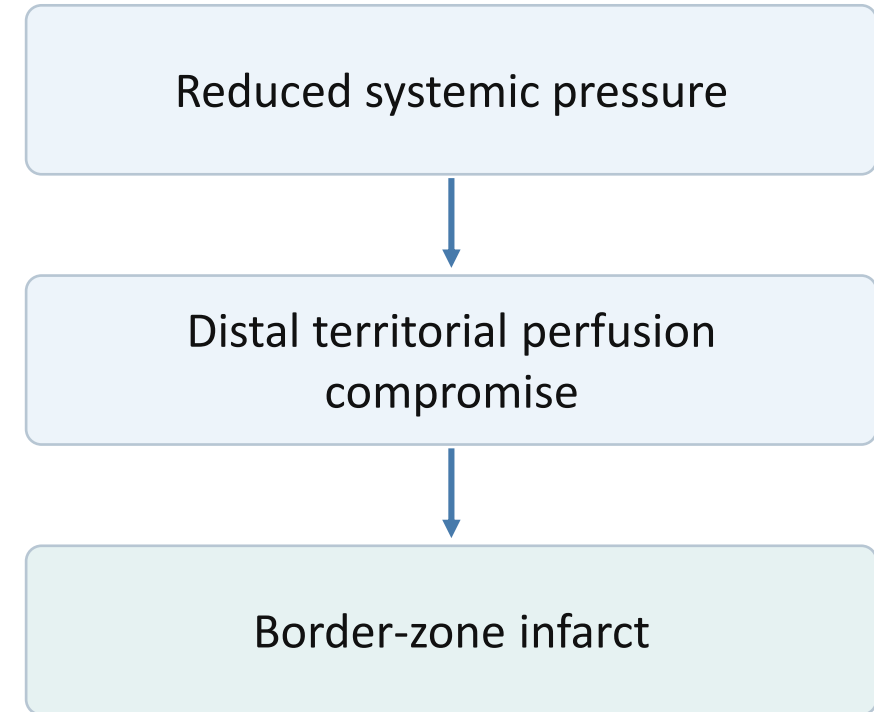
Severe reperfused brain may undergo liquefaction

- With catastrophic injury, extensive tissue liquefaction may develop over time.
- This in ventilated individuals after severe brain injury.
- The ventilator is not the cause of the neuropathologic damage.



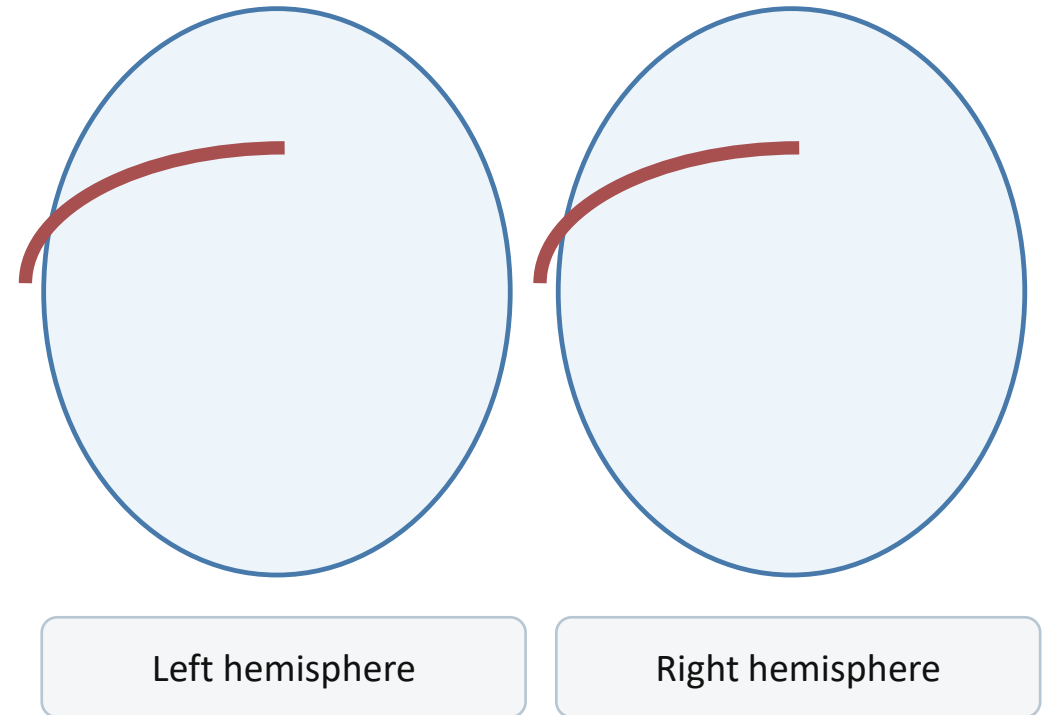
Watershed infarcts are a global low-flow pattern

- Border zones lie at the most distal reaches of arterial supplies.
- They are susceptible when systemic perfusion falls severely.
- The lesion may occur at the interface of two arterial territories.



The border-zone concept is an arterial geography concept

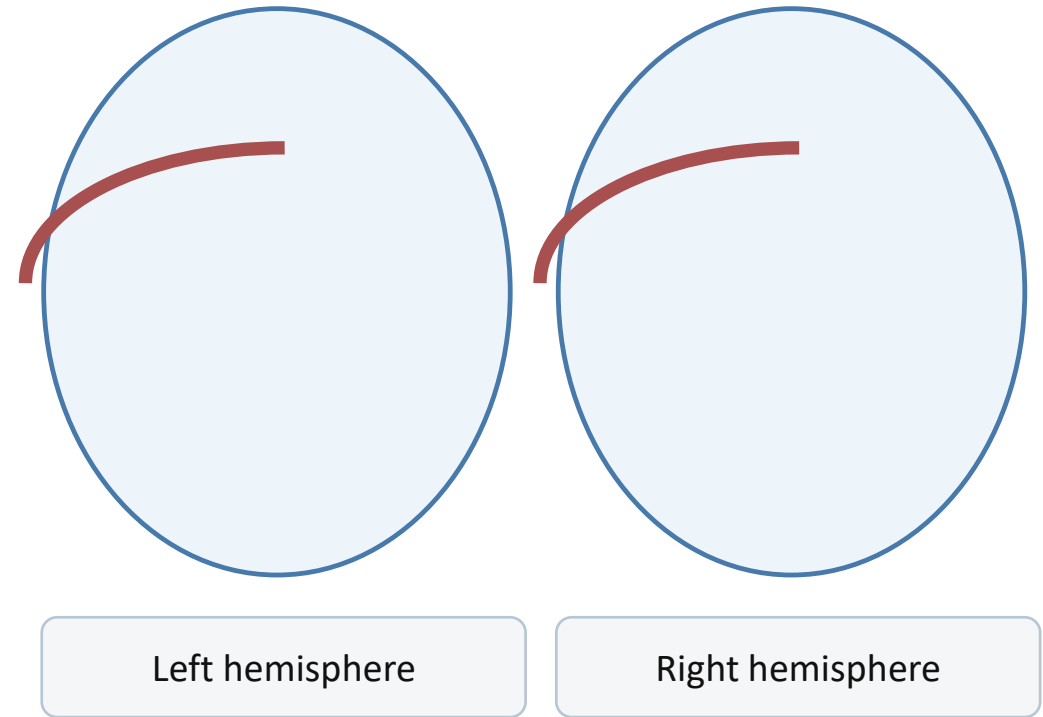
- Adjacent large arterial territories meet at perfusion boundaries.
- Tissue at the distal ends of supplies may receive inadequate flow during severe hypotension.
- The pattern is therefore regional despite a systemic initiating event.



Red arcs: Schematic ACA–MCA border zones

ACA–MCA border: The classic hemispheric watershed

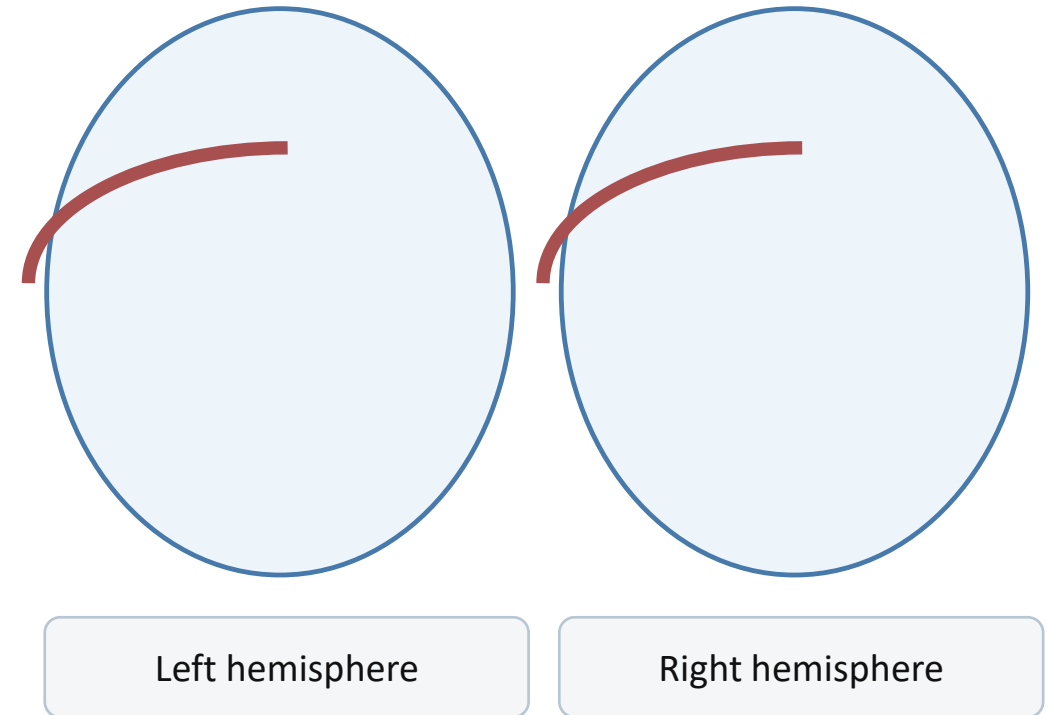
- The anterior–middle cerebral artery border as especially at risk.
- It is located a few centimeters lateral to the interhemispheric fissure.
- This location is more specific than saying only “cortex.”



Red arcs: Schematic ACA–MCA border zones

Watershed injury may involve both hemispheres

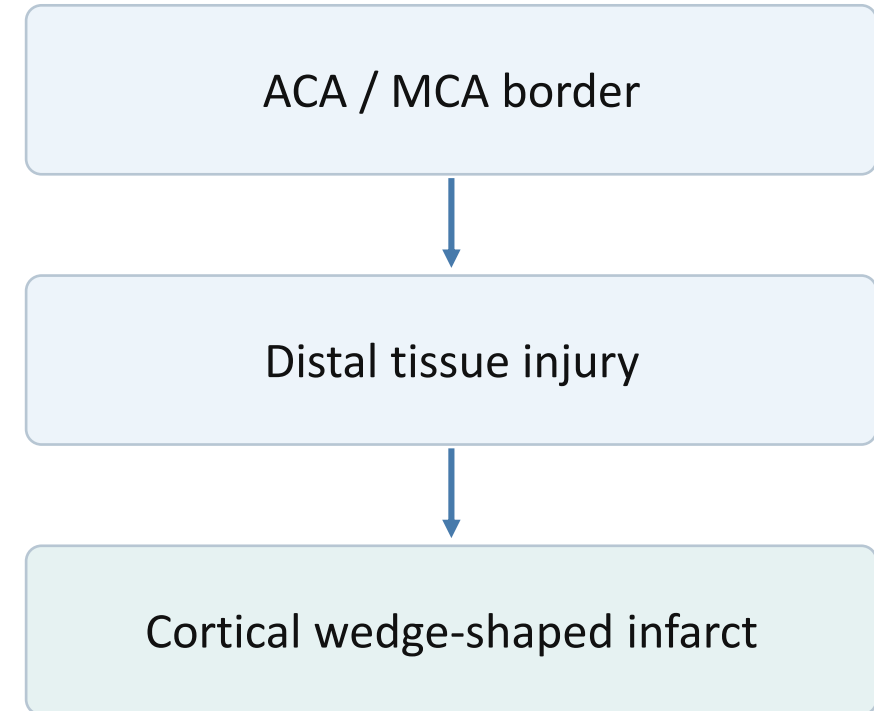
- The hemispheric border-zone infarct is often bilateral.
- Bilateral distribution supports a generalized hemodynamic mechanism in the appropriate setting.
- Symmetry is suggestive; Not every watershed lesion must be bilateral.



Red arcs: Schematic ACA–MCA border zones

Cortical watershed infarction may be wedge-shaped

- The typical cortical lesion is described as wedge-shaped.
- Its territory corresponds to the border between arterial distributions.
- Gross pattern is linked to vascular topology, not a discrete named tissue disease.



Secondary hemorrhagic transformation can occur

- Watershed infarcts usually show secondary hemorrhagic transformation.
- This is hemorrhage into already ischemically injured tissue.
- It differs conceptually from a primary intracerebral hemorrhage.

Ischemic lesion

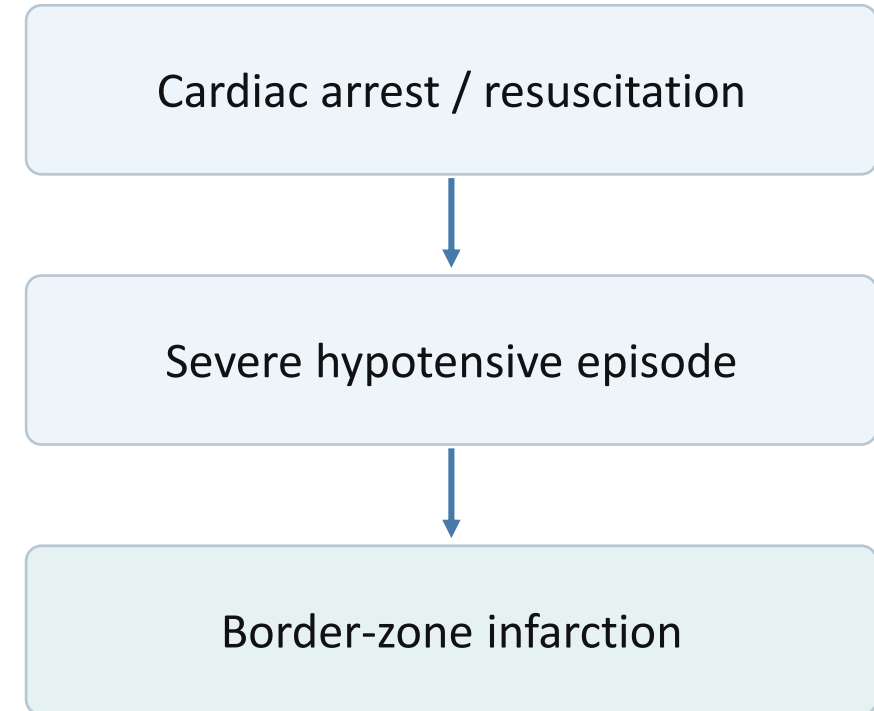
Initial tissue injury
follows inadequate
perfusion.

Transformation

Secondary blood
extravasation
complicates the
infarct.

Watershed infarcts after resuscitated arrest

- Robbins particularly associates watershed infarcts with resuscitated cardiac arrest.
- The lesion reflects vulnerability of distal arterial territories after severe systemic hypotension.
- The history helps explain a possibly bilateral regional distribution.

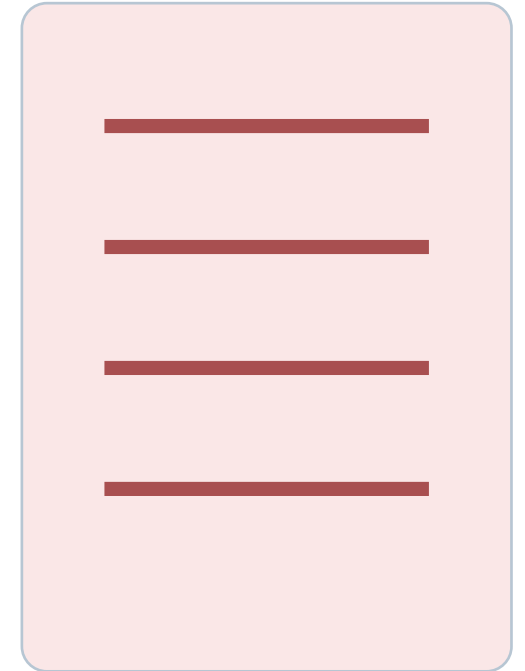


Global ischemia produces diffuse brain swelling

- The brain becomes edematous and swollen.
- Gyri widen as tissue volume increases.
- Sulci become narrowed by the expansion of adjacent gyri.



Usual sulcal relief



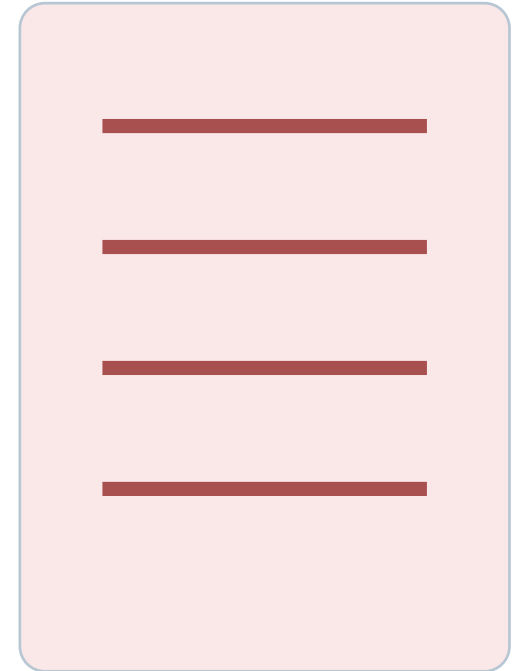
Widened gyri; Narrow sulci

Edema changes the surface anatomy

- Surface gyri appear broad and flattened relative to normal relief.
- Sulcal spaces become less conspicuous.
- These findings describe global swelling rather than a focal territorial map.



Distinct relief



Blunted relief

Gray–white differentiation becomes poorly defined

- On cut surface, the normal distinction between gray and white matter is obscured.
- This is a macroscopic consequence of severe diffuse ischemic injury.
- A grossly swollen brain and loss of gray–white demarcation should be interpreted together.

Usual cut surface

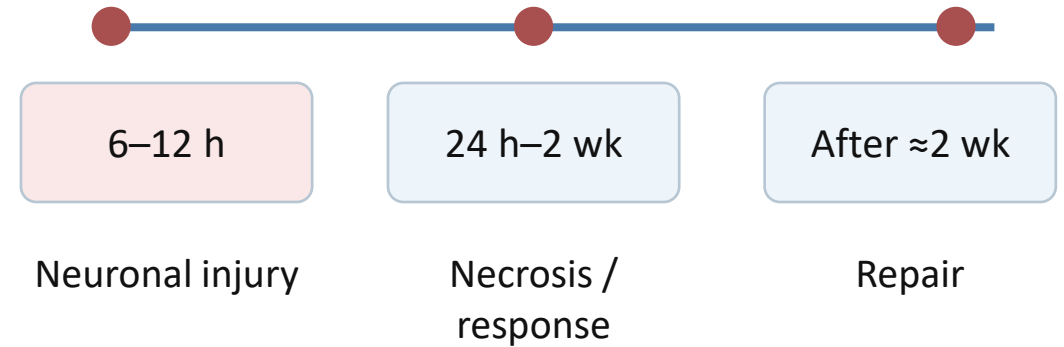
Gray and white matter show visible distinction.

Global ischemia

Edema with poor gray–white demarcation.

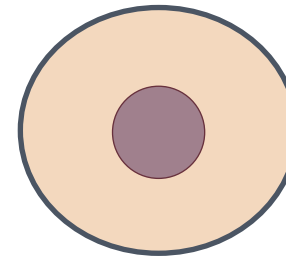
Microscopy follows an injury-to-repair sequence

- Early stage: Acute neuronal changes.
- Subacute stage: Necrosis with cellular clearance and reactive responses.
- Late stage: Tissue loss, cystic change and gliosis.

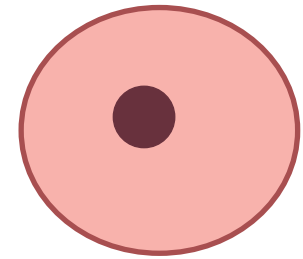


Acute changes: Dead red neurons

- The earliest characteristic alterations appear approximately 6–12 hours after irreversible injury.
- Affected neurons become eosinophilic and shrunken.
- This is a microscopic marker of ischemic neuronal necrosis.



Comparative normal
neuron

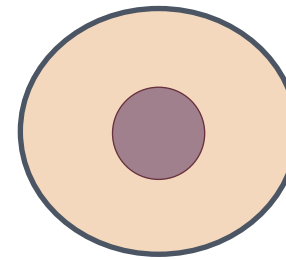


Injured: Shrunken,
eosinophilic

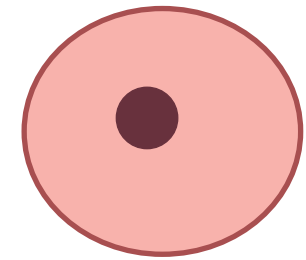
Morphologic teaching schematic — not histology

What gives the “red neuron” its appearance?

- The cytoplasm becomes more eosinophilic on H&E-stained tissue.
- Neurons shrink and nuclear pyknosis or karyorrhexis can follow.
- These descriptions come from the adjoining infarct morphology section.



Comparative normal
neuron

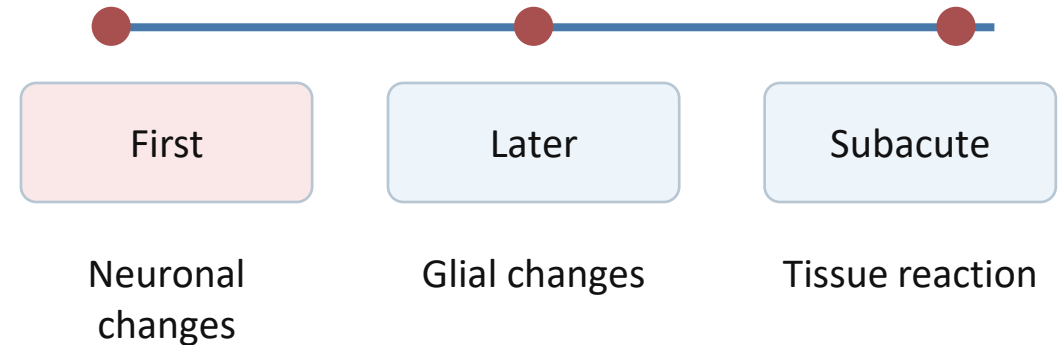


Injured: Shrunken,
eosinophilic

Morphologic teaching schematic — not histology

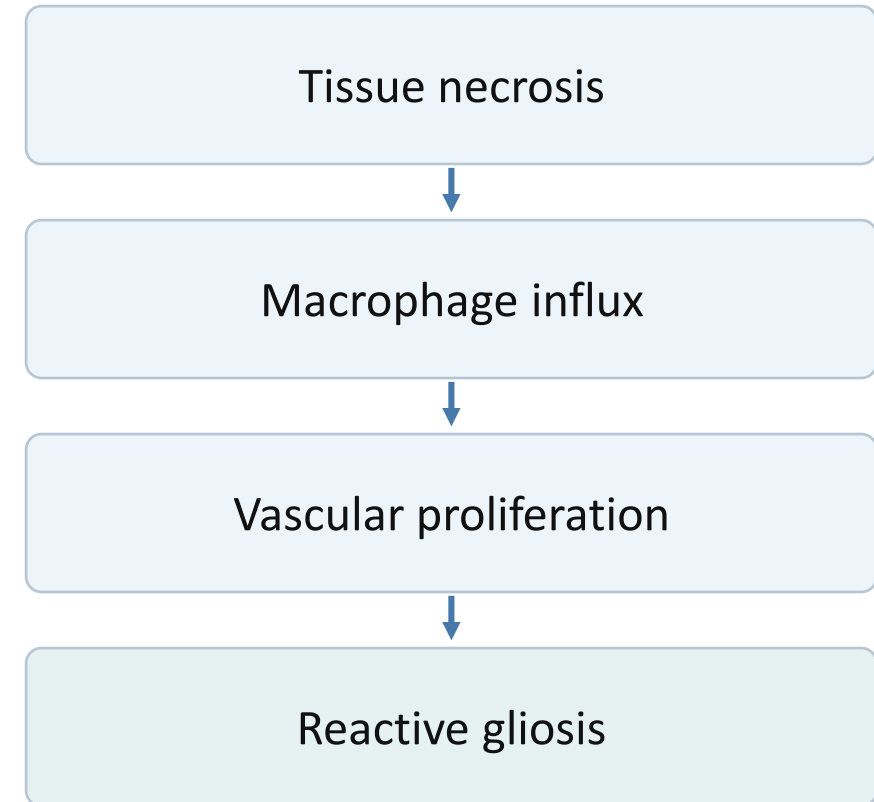
Acute glial injury is delayed relative to neurons

- Astrocytes and oligodendroglia are susceptible to ischemic damage.
- Similar acute morphologic changes become apparent somewhat later than neuronal changes.
- This relative timing reflects cellular susceptibility, not absolute protection.



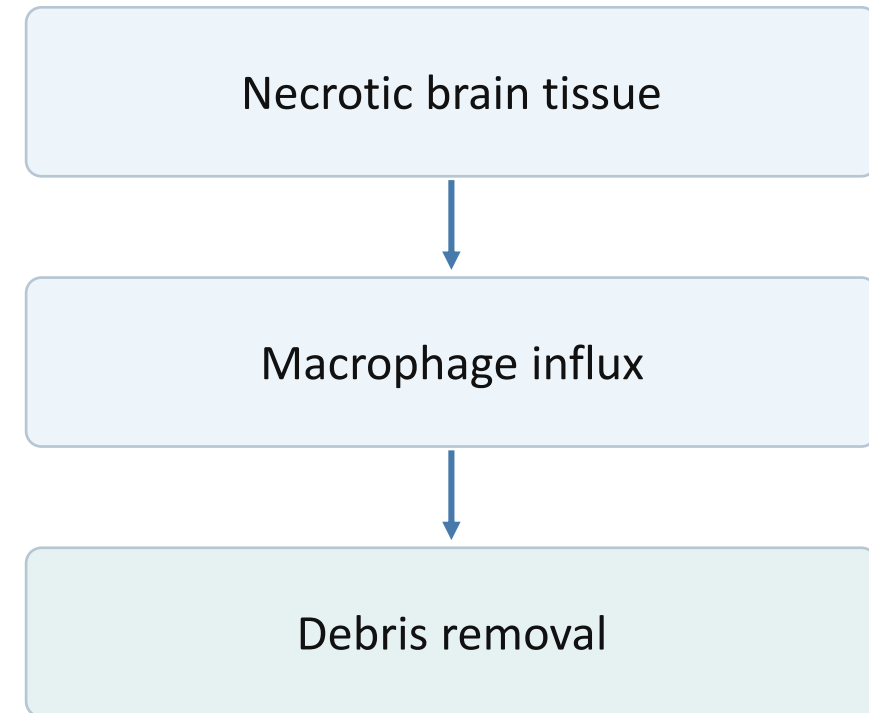
Subacute injury spans about 24 hours to 2 weeks

- Irreversibly damaged tissue undergoes necrosis.
- Macrophages are recruited to the injured area.
- Vascular proliferation and reactive gliosis develop.



Macrophages indicate clearance of injured tissue

- The subacute response includes an influx of macrophages.
- These phagocytes participate in the removal of necrotic debris.
- Their presence belongs to a temporal sequence rather than identifying the initial cause.



Vascular proliferation and gliosis are reactive

- New vessels emerge during evolution of the injury.
- Astrocytic gliosis accompanies the necrotic tissue response.
- These findings reflect organization and repair rather than restoration of normal neuronal architecture.

Vascular response

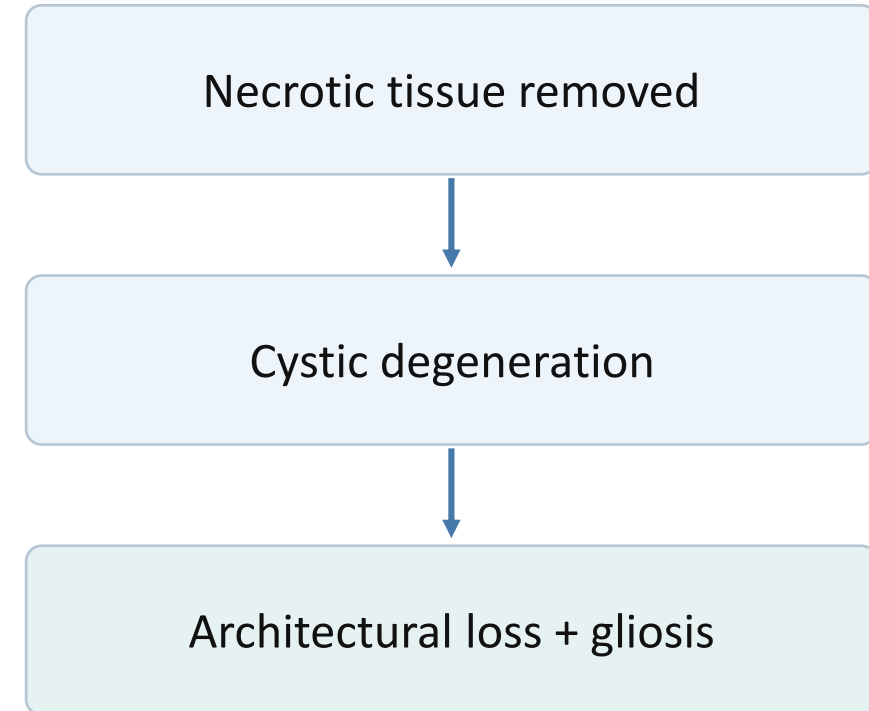
Proliferation of small vessels in evolving injury.

Glial response

Reactive gliosis around damaged parenchyma.

After approximately 2 weeks, repair dominates

- Necrotic brain tissue is progressively removed.
- Cystic degeneration can appear at sites of parenchymal loss.
- Loss of normal CNS architecture and gliosis characterize the repair phase.



Cystic change signifies loss—not regeneration

- Cystic degeneration follows removal of necrotic parenchyma.
- Gliosis occurs at the margins of damaged tissue.
- A cavity does not represent replacement of lost neurons with normal cortex.

Lost tissue

Necrotic neural
parenchyma is
removed.

Residual response

Cavitation and
reactive gliosis
remain.

Cortical laminar necrosis is layer-selective loss

- In neocortex, neuronal destruction can be uneven across different layers.
- Some cortical layers are comparatively preserved; Others are lost.
- The resulting pattern is termed laminar necrosis.

Layer I	Relative preservation may occur
Layer II	Relative preservation may occur
Layer III	Selective neuronal loss
Layer IV	Relative preservation may occur
Layer V	Selective neuronal loss
Layer VI	Relative preservation may occur

Schematic injury pattern; Actual morphology varies

Layer III and V vulnerability helps explain laminar injury

- Pyramidal neurons in layers III and V are selectively sensitive.
- Severe ischemia may produce uneven neuronal loss and gliosis across cortex.
- The pattern is structural; Exact layer preservation varies between lesions.

Layer I	
Layer II	
Layer III	Particularly vulnerable
Layer IV	
Layer V	Particularly vulnerable
Layer VI	

Simplified neocortical layer map

Microscopic evolution: Compare the stages

Phase	Approximate window	Principal microscopic findings
Acute	6–12 hours onward	Eosinophilic shrunken neurons; Glia later
Subacute	24 hours–2 weeks	Necrosis; Macrophages; Vessels; Gliosis
Repair	After approximately 2 weeks	Debris removal; Cystic change; Gliosis
Cortical pattern	Dependent on region and severity	Uneven layer loss: Laminar necrosis

Three distributions should not be conflated

Pattern	Distribution	Textbook basis
Selective neuronal injury	CA1; Purkinje; Cortical III/V	Intrinsic regional vulnerability
Diffuse hypoxic–ischemic injury	Widespread neuronal injury	Severe/profound generalized insult
Watershed infarction	Distal territorial border zones	Severe hypotension
Cortical laminar necrosis	Uneven cortical layer destruction	Layer-selective neuronal loss

Case 1 — brief global oxygen deprivation

After a brief systemic hypoxic–ischemic event, an individual experiences transient confusion and subsequently returns to the previous neurologic state.

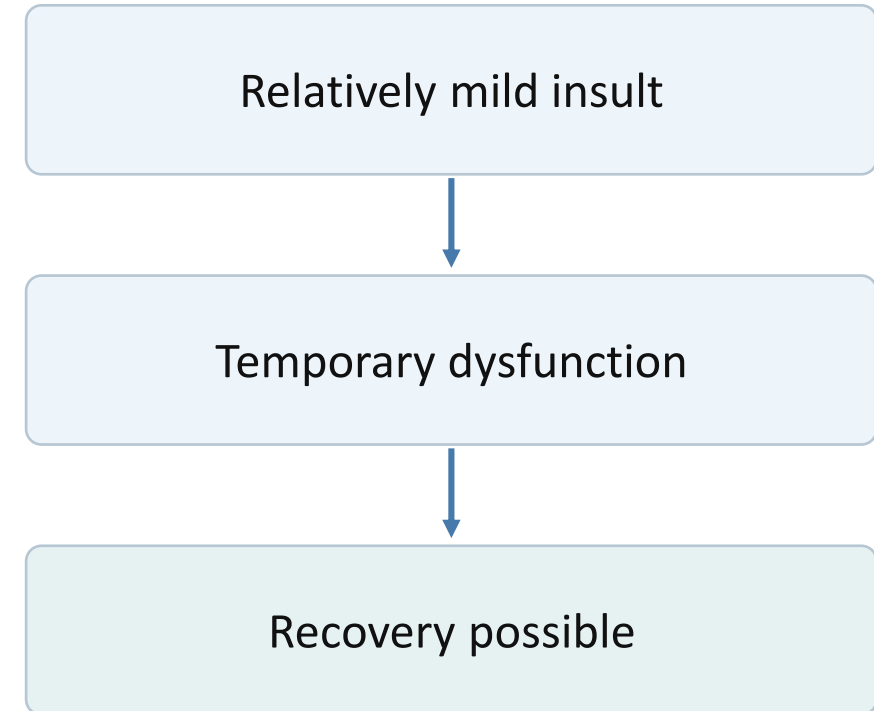
Interpretation task

Which clinical outcome best fits this course?

Consider severity, duration and the possibility of complete recovery.

Case 1 — interpret the reversible syndrome

- A relatively mild global insult can produce postischemic confusion.
- Complete clinical recovery is compatible with the textbook description.
- Permanent structural infarction should not be assumed from transient confusion alone.



Case 2 — severe hypotension with bilateral lesions

A resuscitated patient has a history of severe systemic hypotension. Neuropathologic examination shows bilateral cortical wedge-shaped infarcts near the anterior–middle cerebral artery boundary.

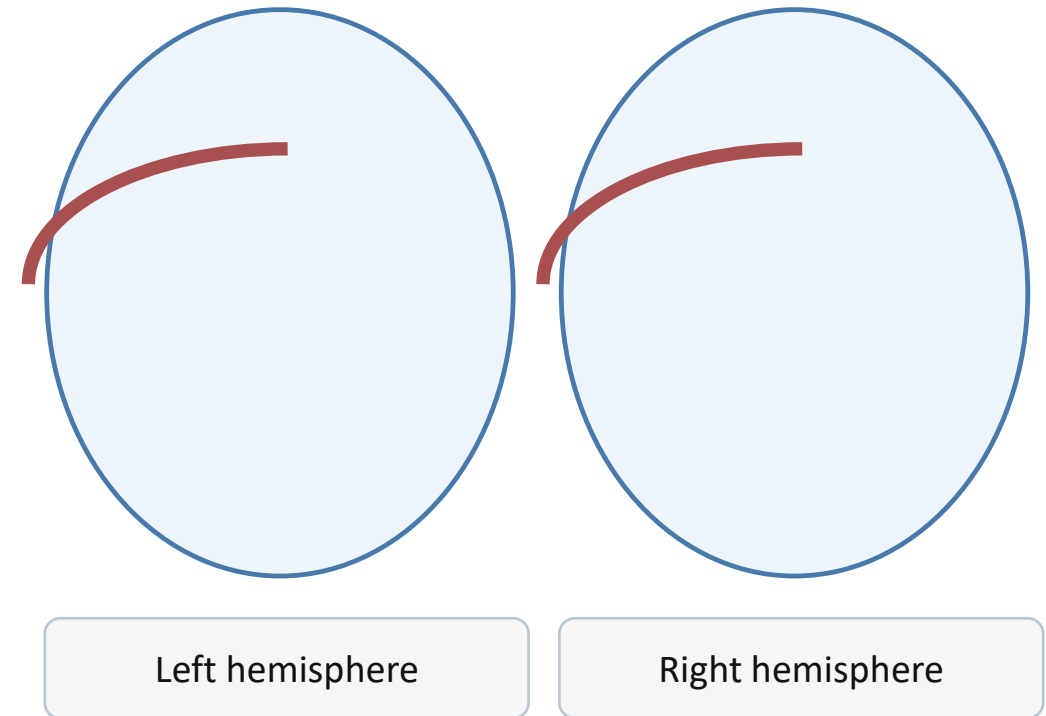
Interpretation task

Name the lesion pattern and explain why it localizes there.

Identify the distal arterial supply territories and systemic trigger.

Case 2 — recognize watershed infarction

- A severe hypotensive event compromises distal perfusion zones.
- ACA–MCA border regions are particularly susceptible.
- Bilateral wedge-shaped cortical lesions are characteristic of this scenario.



Red arcs: Schematic ACA–MCA border zones

Case 3 — profound, prolonged global insult

Following a profound global hypoxic–ischemic insult, a patient survives with severe diffuse neurologic injury. Histology later shows extensive neuronal loss with evolving reactive changes.

Interpretation task

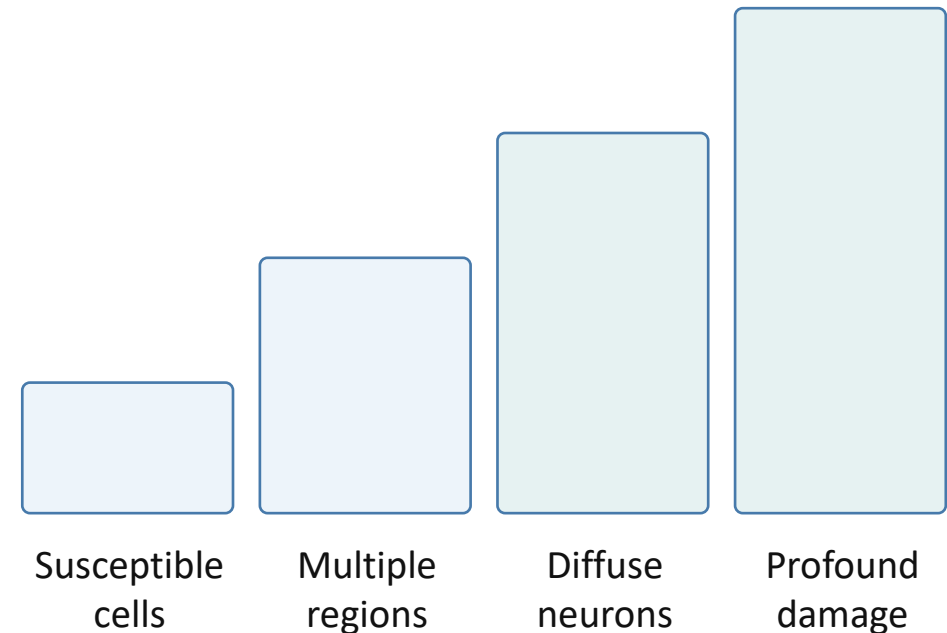
Why might the damage be widespread rather than confined to CA1 or Purkinje cells?

Compare selective vulnerability with the consequences of severe global injury.

Case 3 — severity can overwhelm selectivity

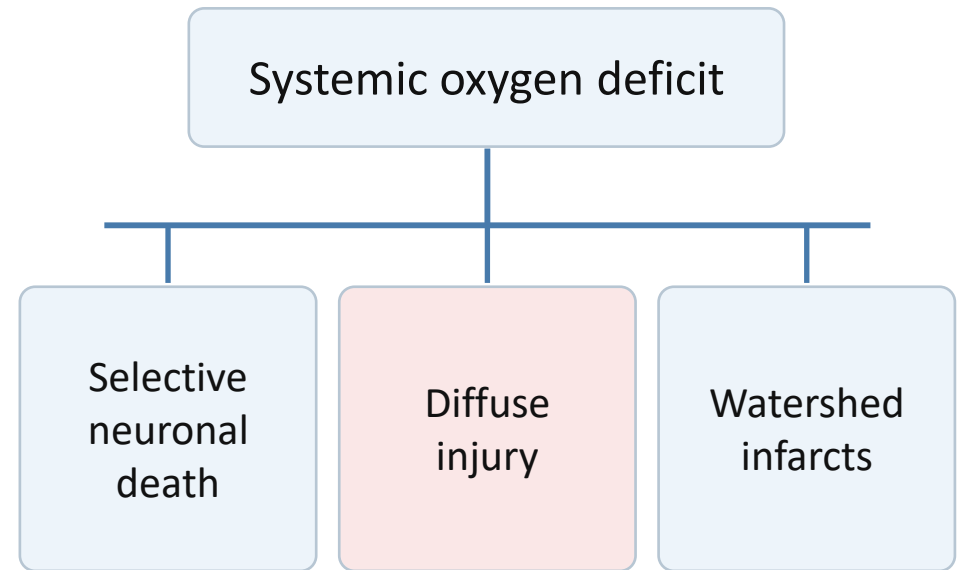
- Selective populations are most sensitive when the insult is less extensive.
- Profound deprivation can kill neurons throughout the brain.
- Widespread injury can lead to devastating clinical syndromes.

Increasing insult severity or duration →



Link the insult to the anatomic outcome

- Cardiac arrest, shock and hypotension reduce generalized cerebral perfusion.
- Carbon monoxide reduces blood oxygen-carrying capacity.
- Severity, duration and vascular geography shape selective, diffuse or watershed injury.



Important interpretation pitfalls

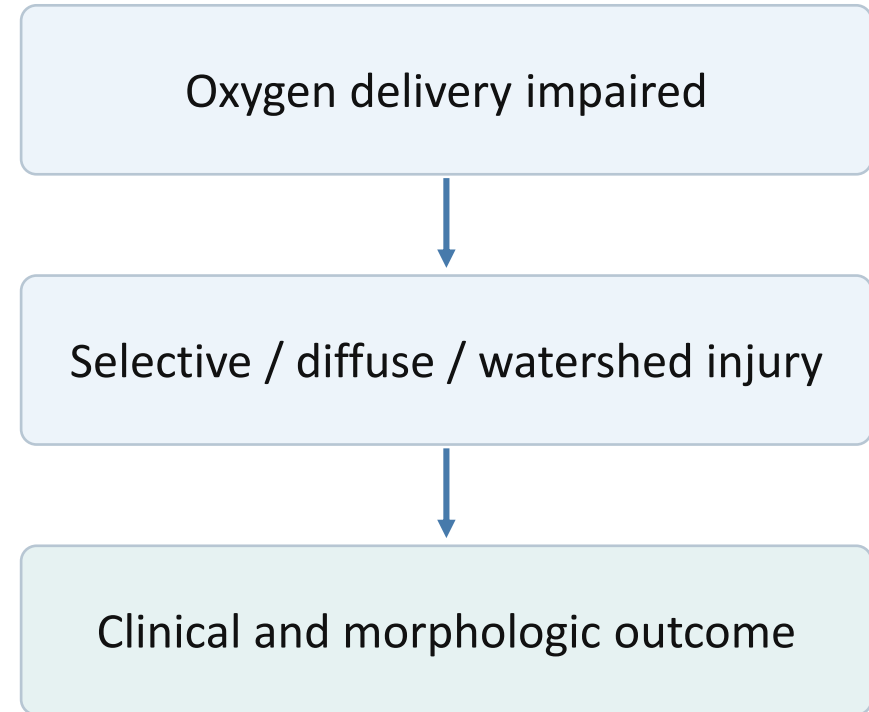
- Do not treat global hypoxia as synonymous with a uniform whole-brain lesion.
- Do not assume glial cells are immune to ischemia.
- Do not confuse secondary hemorrhagic watershed infarction with primary hemorrhage.
- Do not use a textbook vignette as complete clinical brain-death criteria.

Match the pattern to
Severity + duration + anatomic
distribution

Avoid inferring cause from one
feature alone.

A compact synthesis of global cerebral injury

- Mechanisms: Systemic low flow or low oxygen-carrying capacity.
- Selective sites: CA1, Purkinje cells, cortical layers III and V.
- Morphology: Red neurons → subacute necrosis/reactivity → cystic loss/gliosis.
- Outcomes: Recovery, encephalopathy, widespread injury or border-zone infarction.



Knowledge check

1. Which neuronal populations are most vulnerable?

2. Why are ACA–MCA border zones prone to low-flow injury?

3. What neuronal change appears around 6–12 hours?

4. What defines cortical laminar necrosis?

Primary reference and scope

1. Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026)

2. Chapter 28: The Central Nervous System

3. Global Cerebral Hypoxia/Ischemia, printed pages 1138–1139

4. Physiologic and infarct-morphology context from the adjacent Hypoxia and Ischemia / Focal Cerebral Ischemia sections