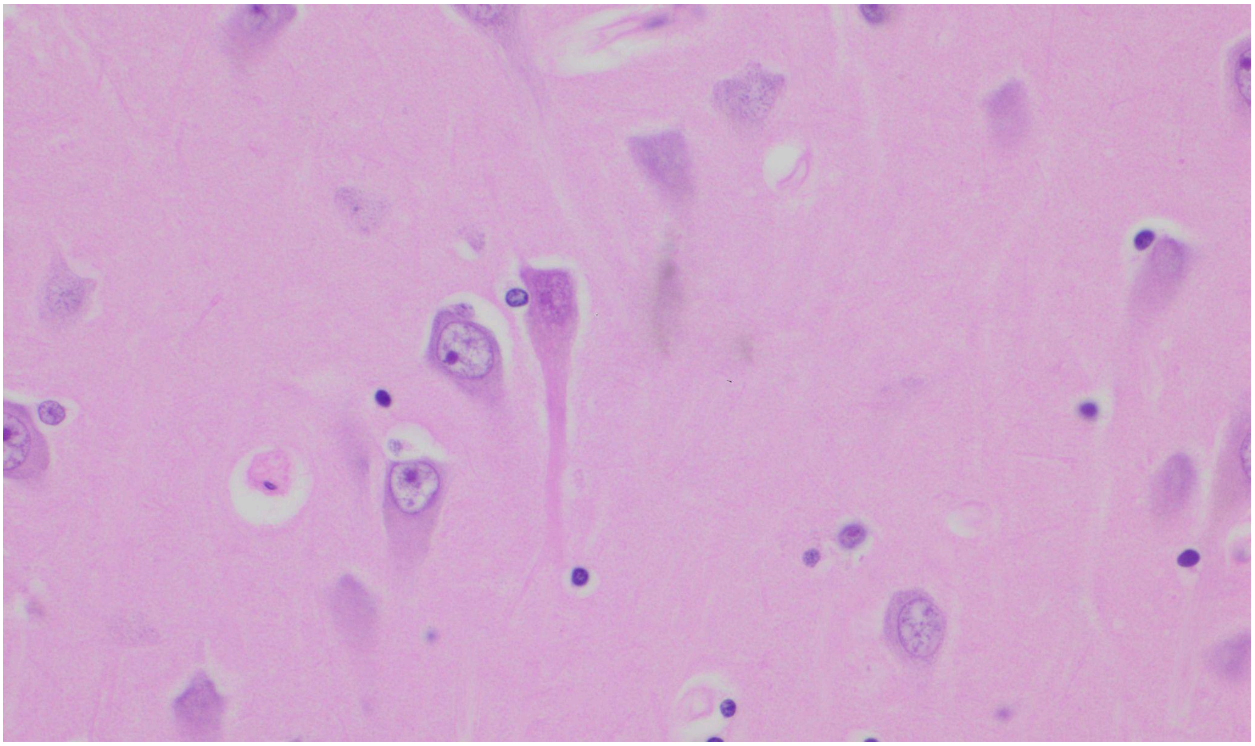

Global CNS Ischemia (Hypoxic-Ischemic Encephalopathy)

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Background

The term hypoxic-ischemic encephalopathy (HIE) encompasses the effects of hypoxia and ischemia on the brain.

- Hypoxia is a lack of oxygen but not necessarily a lack of perfusion. The brain can adapt to pure hypoxia when it happens chronically over time (such as with a progressive lung disease). Carbon monoxide poisoning is an example of an acute, pure hypoxia.
- Ischemia is hypoxia due to decreased perfusion. It includes a tissue's response to decreased oxygenation such as the production of damaging metabolites (//lactic acid). It also includes decreased nutrient delivery (e.g. hypoglycemia) and waste removal (e.g. buildup of cytotoxic glutamate released from damaged neurons).

Hypoxic-ischemic encephalopathy is often a global phenomenon, experienced across the brain as a consequence of low perfusion states such as cardiac arrest, hypotension, or increased intracranial pressure. Depending on the degree of insult and the exact mechanism, the findings can be focal or global - often seeing changes in the most sensitive areas (such as watershed areas) first.

The mechanism of HIE progresses as follows

- The brain has substantial energy requirements. Reduced cerebral perfusion, hypoxia, hypoglycemia and anemia can produce an energy crisis where insufficient energy (primarily glucose) is available to the brain to maintain normal function.
- Energy depletion leads to depolarization of the neuronal membrane and leads to the release of glutamate into the synaptic cleft. Large quantities of glutamate have a toxic effect (i.e. excitotoxic) on local neurons. Over-activation of ion channels leads to rapid cytotoxic (intracellular) edema, as well as calcium ions which lead to apoptosis via production of nitric oxide (NO) radicals and activating catabolic enzymes. Lactic acidosis secondary to hypoxia also causes damage by diffusion across cellular membranes and worsening edema, damaging neurons as well as astrocytes and microglia.
- These processes can occur rapidly following initial hypoxia, with **permanent neuronal damage in vulnerable cortical areas starting at 4-5 minutes of hypoxia**, and **many of these injury pathways will continue to act even if oxygen/glucose sources are restored.**
- Following the cytotoxic edema in the initial phase, vascular injury signaling (also partially mediated through NO release) leads to vasogenic edema, worsening overall cerebral edema and increased intracranial pressure. Increased intracranial pressure can then compress the cerebral vascular supply, worsening perfusion and ischemia and eventually leading to coma, persistent vegetative state and brain-death.

The processes described above are energy-dependent, and as such, are **more prominent in injuries with reperfusion.** Free radicals, lactic acid, cerebral edema, and inflammation cannot develop in unperfused, completely ischemic tissue. They develop following reperfusion (or in the ischemic penumbra surrounding an infarct where there is sublethal ischemia).

Global hypoxemia, such as from cardiac arrest, hypotension, increased intracranial pressure, etc. is covered here as hypoxic-ischemic encephalopathy. In contrast, ischemia that is localized to a vascular territory is covered under stroke. One specific end point of these processes is covered under brain death.

Quick Tips at Time of Autopsy

Clinical History

- Common causes of HIE include cardiac arrest, prolonged hypotension (i.e. shock), prolonged hypoglycemia, cardiac arrest with successful CPR, and prolonged generalized seizures (>1-2 hours).
- Gradual hypoxemia, such as in patients with respiratory disease, typically does not result in cerebral ischemia due to compensatory mechanisms.

- A cornerstone of treatment in cases of hypoxic-ischemic encephalopathy is global body cooling which has been shown to decrease the extent of brain damage if started within a few hours of the insult. Cooling also slows and/or decreases the gross and histological manifestations of HIE such that someone with a severe insult may not manifest the characteristic changes on examination even after the appropriate amount of time has passed.
    - Methylene blue is also used in the treatment of HIE and can give the brain (and other organs) a diffuse blue-green tinge.

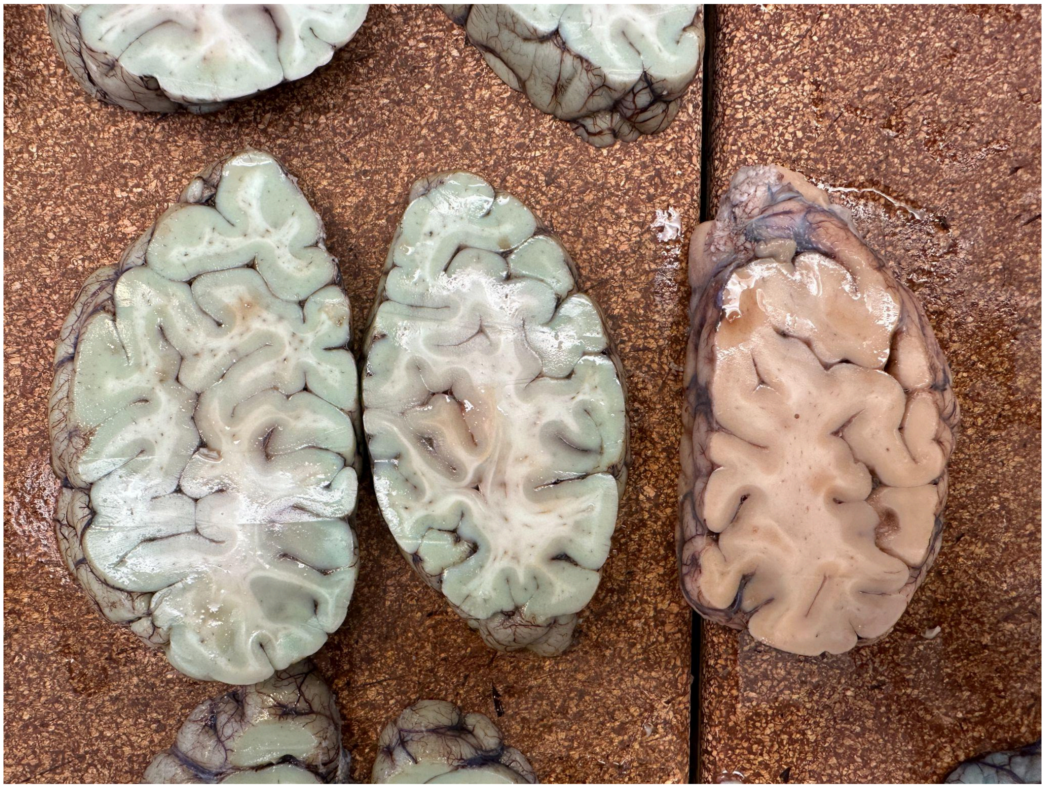

Image: Two sections of the occipital lobe in a patient treated with methylene blue. A third section on the left demonstrates the typical fixed color of a brain not treated with methylene blue. (Image source: Meagan Chambers/University of Washington).

External examination

There are limited findings on external examination of global cerebral ischemia without specific etiologies.

- Severe carbon monoxide poisoning typically presents with cherry-red tissues, particularly mucosal surfaces and pink flushing of the skin. Of note, fatal, acute carbon monoxide poisoning will not have many of the histologic manifestations of HIE as the interval between insult and death is too short to manifest most changes.
- Prolonged history of cerebral ischemia or brain-death can be related to contractures and eventually atrophy of the extremities.

Gross examination

- Gross examination of the brain may reveal signs of increased intracranial pressure and herniation. Global edema would produce effacement of cerebral gyri.

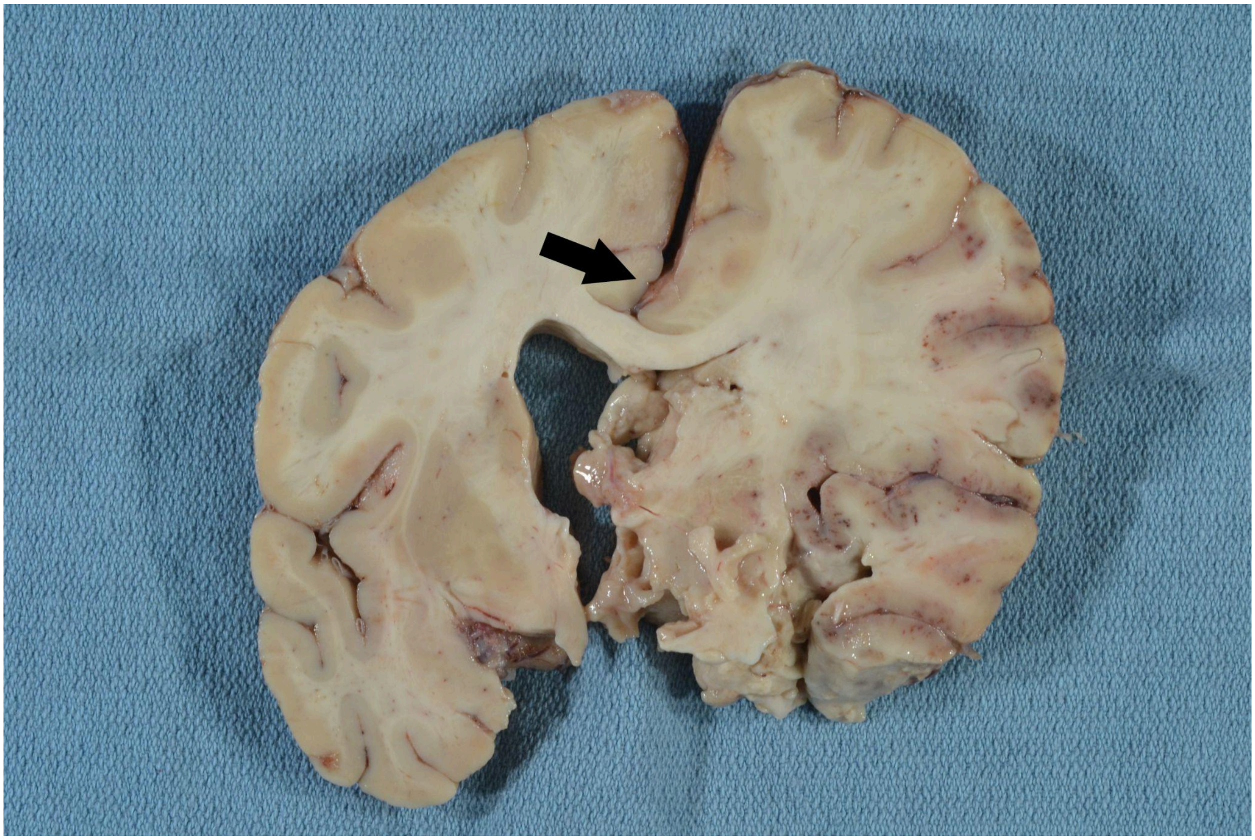

Image: Right to left subfalcine herniation (arrow) viewed on cross section of the brain. This was in the setting of a right middle cerebral artery stroke and therefore the additional gross findings of softening and petechiae are not represented on the left. (Image credit: Meagan Chambers/University of Washington).

- In cases with HIE related to brief ischemic insults, selective neuronal injury and necrosis in the most vulnerable layers of the cortex (layers 3, 5, and 6) with preservation of adjacent glial cells is pseudolaminar necrosis. It can be visible grossly in the subacute to chronic phase as a thin whiter linear lesion within the gray matter or as thinning of the cortex.

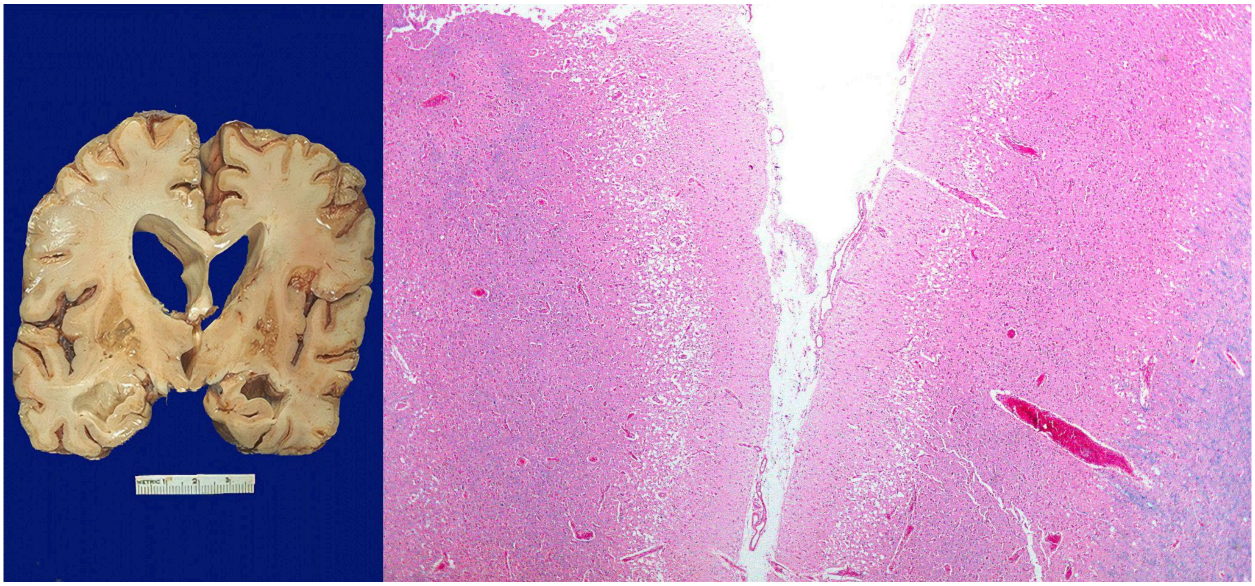

Image: (Left) Gross evaluation of a brain with pseudolaminar necrosis may show diffuse thinning of the cortical ribbon. (Right) Histologically, laminar necrosis shows loss of neurons in selective layers of the cortex. (Image credits: (Left) University of Utah's Internet Pathology Laboratory, (Right) Wikipedia.)

- Areas most sensitive to hypoxic injury are neurons of **CA1 of the hippocampus**, **cerebral watersheds (see picture below)** and the **purkinje cells of the cerebellum**. Routine sampling of these areas is recommended in all autopsy cases undergoing examination of the brain even without gross findings.

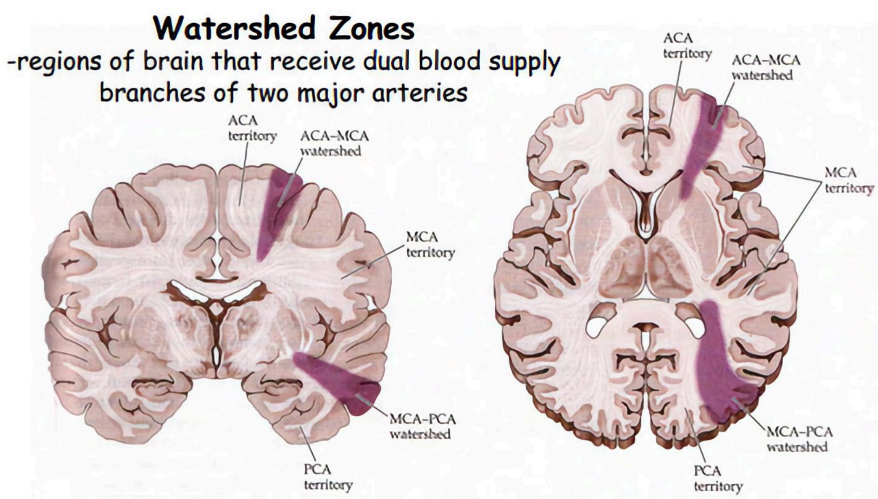

Image: Cortical watershed areas (purple) including the frontal watershed which can be sampled at the level of the anterior commissure. (Image credit: UCSF.)

- After these areas, the rest of the cerebral cortex and striatum are most vulnerable, followed by the thalamus, followed by the brainstem and spinal cord.
- Prolonged ventilator use (with or without brain death) can result in ongoing low-level hypoxic-ischemia. The findings are characteristic and are described in the Brain Death article.

Quick Tips at Time of Histology Evaluation

- Microscopic changes of cerebral ischemia will appear following transient or persistent metabolic disruption, with changes becoming easily detectable at 6-12 hours. These changes overlap with those seen in an infarct, but should be present more diffusely, rather than in a single well-demarcated vascular territory.
- One of the earliest changes can be diffuse edema, which can develop in less than an hour. However, this is non-specific and can be seen with a wide variety of pathologies.
- The earliest, more specific, sign of hypoxic-ischemic damage is the “red dead” neuron - neurons with shrunken nuclei, loss of nucleoli, and hypereosinophilic cytoplasm. Of note, hypereosinophilic cytoplasm can be an artifact of staining and in these cases the loss of nuclear detail can help make the distinction between hypoxic-ischemic change and artifact.
    - As above, red-dead neurons can appear in sensitive areas first including CA1 pyramidal neurons, watershed cortex, and pyramidal neurons of the cerebellum. (Patchy *loss* of purkinje neurons can also be seen in chronic cases of ischemia).
    - After these areas, red dead neurons can be seen in the rest of the cerebral cortex and striatum, followed by the thalamus, followed by the brainstem and spinal cord.

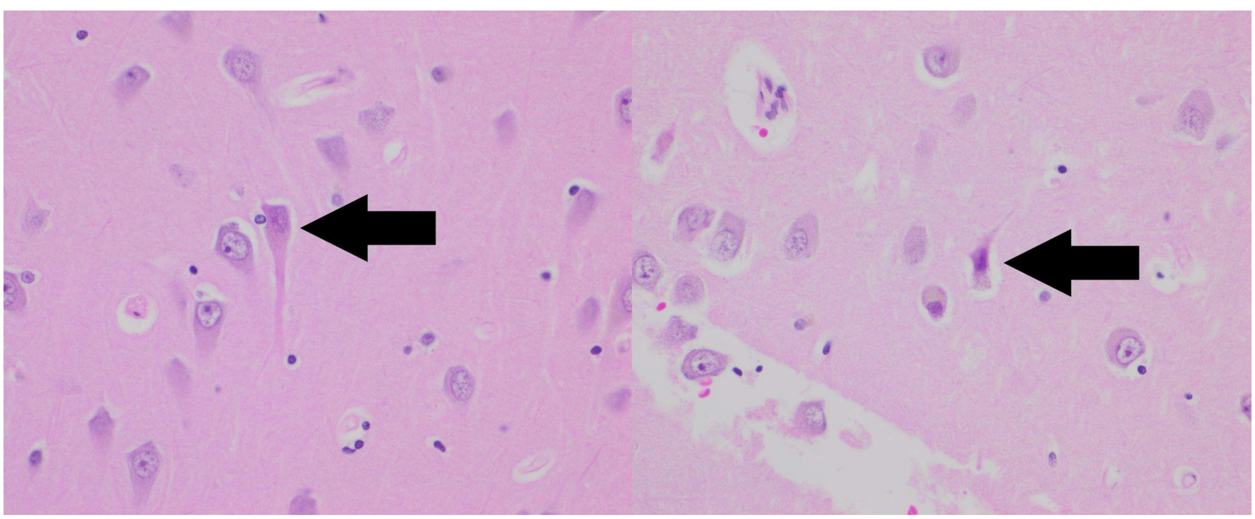

Image: (Left and Right) Red dead neurons with eosinophilic cytoplasm and loss of nuclear details such as the nucleoli (arrows). These can be compared to nearby neurons which do not show these changes. These images demonstrate that mild hypoxemia-ischemia can result in only some neurons being affected.

- Selective neuronal necrosis (pseudolaminar necrosis) can be seen as selective vulnerability of neurons in layers 3, 5, and 6 resulting in laminar changes within the cortex. (See image above in the gross exam section).
- Reactive gliosis is also a non-specific change that can be seen in hypoxemic-ischemic change. Microglial activation can occur within minutes to hours after injury. Astrocytes may begin to show morphological changes (such as abundant pink cytoplasm - “gemistocytic astrocytes”) within days. These can continue to develop over weeks and months.

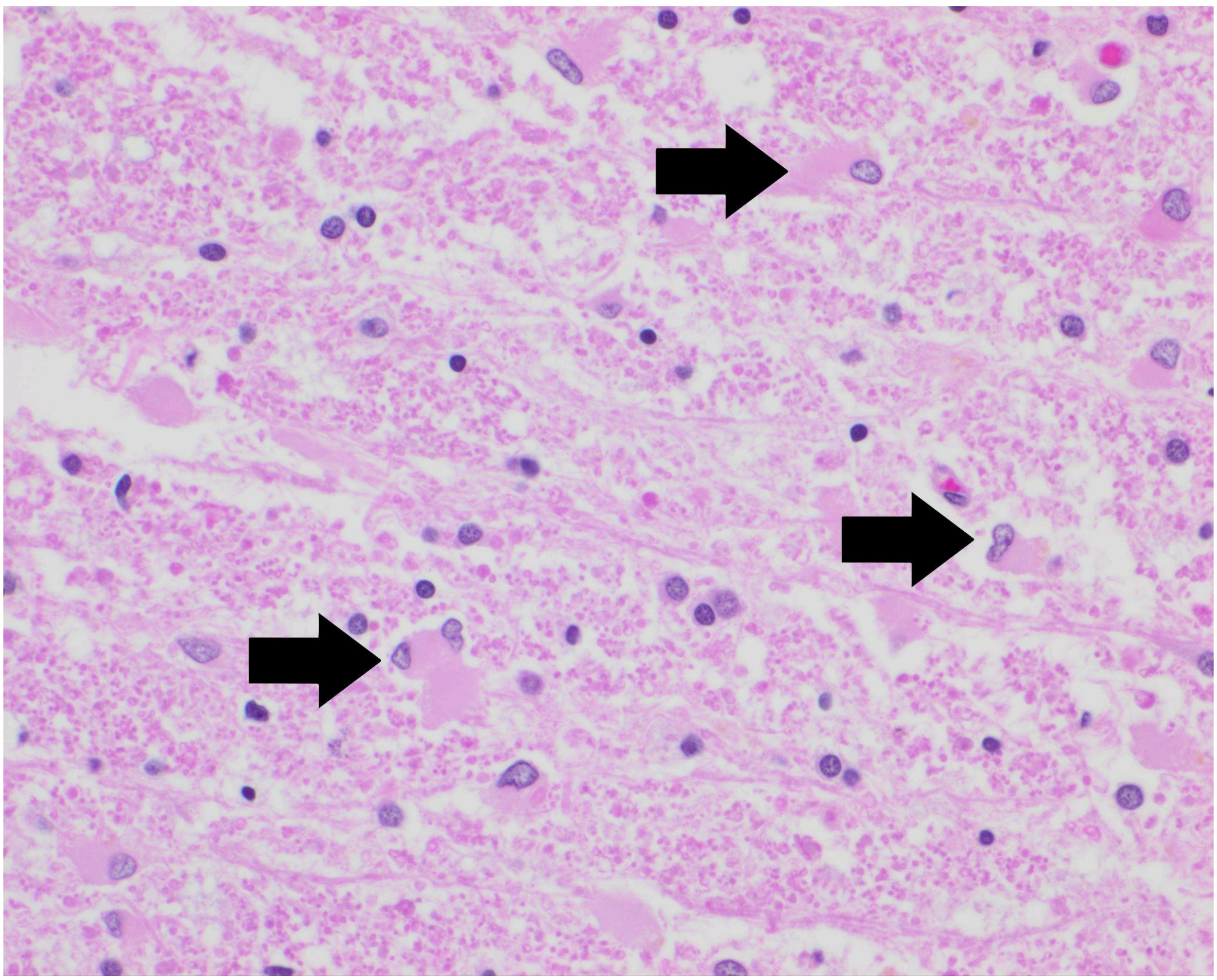

Image: Viable cells with disrupted neuropil in the background and reactive gemistocytic astrocytes (arrows). (Image source: Meagan Chambers/University of Washington).

Clinical Tidbits

- Patient's with a clinical history of prior mild HIE (e.g. related to cardiac arrest with restoration of circulation) may have Korsakoff's amnesia, with loss of episodic memory and preserved semantic memory. This is due to selective injury/necrosis of CA1 neurons in bilateral hippocampi.
- Persistent vegetative state (loss of cognitive/emotional functions with retained autonomic function) is related to diffuse cortical, thalamic or combined neuronal loss with relative preservation of brain stem function.

Quick Tips at Time of Reporting

Examples of report comments in cases with diffuse ischemic changes:

- Comment for pure hypoxic-ischemic changes: "COMMENT: Rare acutely necrotic (hypereosinophilic) neurons are present in watershed cortex. These histopathologic changes are indicative of global cerebral hypoperfusion or hypoxemia near the time of death, and are often seen in the setting of ventilatory support or death resulting from cardiopulmonary disease or impairment. Purkinje neuron loss is patchy and mild, without hypereosinophilia or inflammation, and may be related to prior global hypoperfusion/hypoxic injury."
- Comment for mixed global hypoxic-ischemic changes with additional findings of acute and chronic hypoxic changes consistent with stroke/infarct: "COMMENT: The histologic examination is remarkable for evolving diffuse hypoxic-ischemic (HI) changes throughout the sampled tissues characterized by variable degrees of neuronal hypereosinophilia and pyknosis associated with pericellular clearing and white matter vacuolization consistent with edema. Patchy acute/recent hemorrhage is present in association with more pronounced hypoxemix-ischemic changes within tissues sampled from the border of right intraparenchymal hemorrhage. Early reactive white blood cell margination is present with rare parenchymal examples. A zone of temporally distinct subacute infarct characterized by liquefaction, dense macrophage infiltrates, and reactive neovascularization is identified in the right temporal cortex. Examples of remote hypoxic-ischemic injury are identified in the left frontal watershed (pseudolaminar necrosis with deep cortical layer neuron loss and gliosis) and cerebellum (geographic zones of granular and Purkinje loss with gliosis)."

Recommended References

- Agamanolis D."Hypoxic-Ischemic Encephalopathy." Neuropathology-Web.org. 2023. https://neuropathology-web.org/chapter2/chapter2aHIE.html

- Gray F., Duyckaerts C., & Girolami D. U. Neuropathology of Vascular Disease. In *Escourolle & Poirier's Manual of Basic Neuropathology*, 2019. Oxford University Press, 6th edition.