2 Vascular Lesions

I. Anoxia
   A. Anoxia observed in a wide variety of clinical conditions and forms
      • Anoxic anoxia—insufficient oxygen reaches blood (e.g., drowning)
      • Anemic anoxia—insufficient oxygen content in blood (e.g., carbon monoxide poisoning)
      • Histotoxic anoxia—poisons interfere with oxygen utilization (e.g., cyanide, sulfide)
      • Stagnant anoxia—most common, decreased cerebral perfusion (e.g., cardiac arrest); factors that determine amount of brain damage after cardiac arrest include duration of ischemia, degree of ischemia, temperature during the event and blood glucose levels
   B. Precise mechanisms not completely elucidated; however, a number of consequences occur which have a negative effect on the CNS
      • Edema
      • Lactic acid accumulation, decreased pH
      • Increase in free fatty acids
      • Increase in extracellular potassium and ammonia
      • Abnormalities in calcium flux
      • Reperfusion problems
   C. Morphology of ischemia highly variable and unpredictable.
      • Numerous regional and cellular vulnerabilities exist; the entire brain not uniformly involved (selective vulnerability)
      • Neurons most sensitive to anoxia
         ◦ Hippocampal, Sommer sector (CA1) most sensitive
         ◦ Cerebral cortex, layers III, V, and VI (which contain larger-size neurons)
         ◦ Cerebellar Purkinje cells (if patient survives for a period of time, may see Bergmann gliosis)
         ◦ Caudate and putamen
         • Accentuated in the boundary zones between vascular distributions
   D. Gross pathology
      • Swollen, soft
      • Gray matter is dusky
      • Areas of cavitation in a laminar pattern may be observed
         ◦ Pseudolaminar is used to describe involvement of more than one cortical layer
         ◦ Laminar describes involvement of a single cortical layer
   E. Microscopic pathology
      • Dendrite and astrocyte swelling (i.e., sponginess of the neuropil)
      • Ischemic (homogenized) neurons (i.e., “red and dead”)
      • Endothelial hyperplasia
      • Microglial reaction
      • Dissolution of neurons after several days
II. Infarction

A. General

- Cerebral blood flow 20% of cardiac output, 15% of oxygen consumption of body.
- Main anterior flow (70%) through internal carotid arteries; posterior flow via vertebral arteries—the systems anastomose via the anterior and posterior communicating arteries to form the circle of Willis
- Disruption in flow can result in infarct (stroke)
- Stroke is a clinical term referring to “abrupt onset of focal or global neurological symptoms caused by ischemia or hemorrhage”—symptoms >24 h; if symptoms resolve in less than 24 h = transient ischemic attack (TIA)
- Risk of stroke increased with increasing age, male > female, smoking, hypertension, atrial fibrillation, carotid artery stenosis, hyperlipidemia, diabetes, heart surgery, antiphospholipid antibodies, high-estrogen oral contraceptives
- Venous thrombosis associated with pregnancy and oral contraceptive use
  - Most common sites of venous thrombosis in superior sagittal sinus, lateral sinuses, and straight sinus
  - Septic thrombosis most common in cavernous sinus, often due to contiguous spread from soft tissue/sinus infection

B. Determining the age of an infarct either grossly or microscopically can only be done within a wide range. The times given are guidelines rather than absolutes.

C. Gross pathology

- Unequivocal alterations require up to 24 h; early changes include edema, congestion, softening
- 48 h: “cracking”—separation of the necrotic tissue from intact tissue
- 72 h: infarcted area usually clearly delineated; cortex friable and soft
- A 1-cm cavity takes 2–3 months to form
- Once cavitation begins, it is difficult to determine the age of the infarct.

D. Microscopic pathology

- Earliest changes: (1) astrocytic swelling, (2) interstitial edema, (3) pyknosis, (4) hypereosinophilia of neurons, (5) microvacuolization of neurons (swollen mitochondria)
- 24 h: macrophage infiltration begins, axonal swelling, may see neutrophilic infiltration (ceases by d 5)
- 3–4 d: prominent macrophage infiltration
- 7–10 d: astrocytic proliferation and hypertrophy evident
- 30 d: intense gliosis
- May have a hemorrhagic component (18–48%); most hemorrhagic infarcts are embolic artery events; hemorrhage in infarcts due to reperfusion of necrotic vessels or occlusion of venous drainage
- May encounter degeneration of tracts distal to infarct

E. Lacunar infarct

- The infarcts range in size from 3–4 mm up to 1.5 cm
- Most common sites: putamen, caudate, thalamus, pons, internal capsule, and convolutional white matter
- Causes: (1) lipohyalinosis, (2) occlusion of small penetrating vessels, (3) dissection, (4) emboli
- Small perivascular cavities common in basal ganglia and deep white matter; état lacunaire (gray matter) and état cribré (deep white matter)

F. Respirator brain

- Also known as (AKA) diffuse anoxic encephalopathy
- Permanent global ischemia due to nonperfusion of entire brain
- Brain perfusion depends on mean arterial blood pressure exceeding the intracranial pressure (cerebral perfusion pressure = mean arterial blood pressure − intracranial pressure)
- The most extreme form of stagnant anoxia
- Grossly—dusky brown discoloration of cortex, blurring of gray–white junction, general friability of tissue (brain often does not fix well in formalin)
- Microscopically—ischemic neurons everywhere ± infarcts
G. Carbon monoxide (CO) poisoning
- A form of anemic anoxia due to displacement of oxygen from its binding site on hemoglobin
- CO binds irreversibly to hemoglobin, reducing its oxygen-carrying capacity
- CO directly binds to iron-rich areas of brain (globus pallidus and pars reticulata of substantia nigra)
- Pathologically marked by necrosis of globus pallidus and substantia nigra.
- May see demyelination and cerebral white matter destruction (Grenker’s myelinopathy)
- Etiology
  - CO directly binds to iron-rich areas of brain
  - Many theories
    - Congenital defects of part or all of the media at the arterial bifurcation, does not explain why most arise in adulthood
    - Remnants of embryonic vessels
    - Focal destruction of the internal elastic membrane due to hemodynamic alterations, about 3–9% of patients with arteriovenous malformation (AVM) have aneurysms
    - Abnormalities in specific collagen subsets
  - Associated conditions:
    - Polycystic kidney disease, Potter type 3
    - Ehlers–Danlos syndrome (types IV and VI)
    - Coarctation of the aorta
    - Marfan’s syndrome
    - Pseudoxanthoma elasticum
- Pathology
  - Media usually defective
  - Intimal hyperplasia and sometimes a gap in the internal elastic membrane seen
  - Aneurysm wall usually contains fibrous tissue
  - Atherosclerotic changes occasionally seen
  - Phagocytosis and hemosiderin deposition may be present

H. Air embolism
- May be related to decompression sickness “the bends”—nitrogen gas in blood, can cause spinal cord microinfarcts
- May also occur related to cardiac bypass surgery

I. Hypoglycemic brain damage
- Causes selective neuronal necrosis-like ischemia
- Different mechanism of injury than ischemia
  - Decreased lactate and pyruvate
  - Tissue alkalosis
- Neuronal necrosis in cerebral cortex superficial layers, hippocampus (CA1 and dentate) and caudate; no Purkinje cell necrosis

III. Aneurysms
A. Saccular aneurysms
- AKA: “berry,” congenital or medical defect
- Usually present at arterial bifurcation; most asymptomatic
  - 85% in anterior circle of Willis
  - 25% multiple
  - 20% bilateral
- Most common sites
  - Middle cerebral artery trifurcation
  - Anterior communicating artery junction
  - Internal carotid artery—posterior communicating artery junction
- Risk of rupture, greatest in aneurysms > 1 cm in size
- “Giant aneurysm” defined as > 2.5 cm, usually causes compressive or embolic symptoms
- Etiology
  - Many theories
  - Congenital defects of part or all of the media at the arterial bifurcation, does not explain why most arise in adulthood
  - Remnants of embryonic vessels
  - Focal destruction of the internal elastic membrane due to hemodynamic alterations, about 3–9% of patients with arteriovenous malformation (AVM) have aneurysms
  - Abnormalities in specific collagen subsets
  - Associated conditions:
    - Polycystic kidney disease, Potter type 3
    - Ehlers–Danlos syndrome (types IV and VI)
    - Coarctation of the aorta
    - Marfan’s syndrome
    - Pseudoxanthoma elasticum
- Pathology
  - Media usually defective
  - Intimal hyperplasia and sometimes a gap in the internal elastic membrane seen
  - Aneurysm wall usually contains fibrous tissue
  - Atherosclerotic changes occasionally seen
  - Phagocytosis and hemosiderin deposition may be present

B. Infectious (septic) aneurysms
- Most related to bacterial endocarditis
  - Arterial wall weakened by pyogenic bacteria which usually reach the wall by an infected embolus
  - May be multiple
  - Located on distal branches of the middle cerebral artery
Organisms usually of low virulence, particularly *Streptococcus viridans* and *Staphylococcus aureus*

Mycotic aneurysms typically refer to fungal aneurysms; Aspergillus the most common organism responsible

C. Fusiform aneurysms
- Related to dolichoectasia (elongation, widening, and tortuosity of a cerebral artery)
- Supraclinoid segment of internal carotid artery and basilar artery most common sites
- Fusiform aneurysm refers to dilated segment of artery
- Seen commonly with advanced atherosclerosis

IV. Vascular Malformations
A. General information
- True malformations result from the embryonic vascular network
- Some increase in size by incorporating adjacent vessels—“recruitment”
- Clinical symptoms include seizures, “steal” phenomenon, hemorrhage
- In children, excessive shunting may lead to cardiac decompensation (especially vein of Galen malformations).
- True incidence of hemorrhage unknown, estimates = 5–10% overall
- A subset of malformations is of mixed type.

B. Arteriovenous malformation (AVM)
- Admixture of arteries, veins, and intermediate size vessels
- Vessels are separated by gliotic neural parenchyma
- Foci of mineralization and hemosiderin deposition common
- Typically superficial, wedge-shaped with the apex directed toward the ventricle
- Commonly found in surgical series; the most common vascular malformation associated with hemorrhage; peak presentation 2nd–4th decades

C. Venous malformation (angioma)
- Veins of varying sizes
- Vessels separated by mostly “normal” parenchyma
- Less compact than AVM or cavernous malformation
- May have a large central draining vein
- Varix is a single dilated/large vein

D. Cavernous malformation (angioma)
- Large, sinusoidal-type vessels in apposition to each other
- Little or no intervening parenchyma
- Compact malformations
- Mineralization and ossification common; occasionally massive
- May bleed

E. Capillary telangiectasia
- Capillary sized vessels
- Separated by normal neural parenchyma
- Common in the striate pons
- Often an “incidental” finding at autopsy

V. Hemorrhage
A. Common causes
- Spontaneous intracerebral hemorrhage, often ganglionic (caudate, putamen) related to hypertension—most common cause of nontraumatic hemorrhage
- Ruptured saccular aneurysm
- Vascular malformation, particularly AVM and cavernous angioma
- Coagulopathy associated, may have both platelet and prothrombin time abnormalities
- Congophilic (amyloid) angiopathy
  - Lobar hemorrhage
  - Elderly
  - Amyloid deposition in vessel walls both in meninges and cortex
  - Most commonly β-amyloid type (chromosome 21)
  - Associated with Down’s syndrome and Alzheimer’s disease
  - Highlighted on Congo red (apple green birefringence with polarized light), thioflavin S or T, and crystal violet stains
- Neoplasms
- Blood dyscrasias (i.e., sickle cell anemia)
- Vasculitis
B. Pathology
- Soft, gelatinous clot
- Small vessels with thrombosis may project into the hemorrhage
- Petechial hemorrhage may be seen around the large hemorrhage
- Ischemic necrosis seen in associated brain tissue
- Clot edge often has hemosiderin-laden macrophages
- Astrocytic proliferation often prominent at the edge
- Amyloid may be seen in adjacent vessels if congophilic angiopathy is the cause
- Venous hemorrhage—usually the infarcts are larger and not confined to any arterial distribution, often over the convexity

VI. Vasculitis
A. Common causes
- Polyarteritis nodosa (PAN) and its variants
  - Systemic disease
  - Male : female 2 : 1
  - Any age, peak 40–50 yr
  - Necrotizing vasculitis with fibrinoid necrosis of medium-sized vessels
  - May represent immune-complex-mediated vasculitis (subset of patients are hepatitis B or C positive)
- Hypersensitivity angiitis
- Wegener’s granulomatosis
  - Systemic disease often with respiratory tract component
  - Most patients 40–60 yr
  - ANCA (anti-neutrophil cytoplasmic antibodies)—directed against proteinase 3
- Lymphomatoid granulomatosis
- Giant cell arteritis
  - The most common of the granulomatous vasculitides
  - Older patients >50 yr
  - Primary target is extracranial arteries of head, but may involve cerebral vessels
  - Headache, blindness, increased erythrocyte sedimentation rate (ESR)
- Takayasu’s arteritis
  - Aortic arch and branches and descending aorta
  - Younger patients (15–40 yr), Oriental females at higher risk
  - Lymphoplasmacytic inflammation of the media with fibrosis, granulomas/giant cells
- Thromboangiitis obliterans
- Vasculitis associated with connective tissue disease, (i.e., systemic lupus erythematosus [SLE], Sjögren’s syndrome, Behçet’s syndrome
- Churg-Strauss—necrotizing vasculitis with eosinophilia
- Primary angiitis of central nervous system
  - Headaches, multifocal deficits, diffuse encephalopathy
  - Adults (ages 30–50 yr)
  - ESR normal or mildly elevated
  - Biopsy of nondominant temporal tip, including leptomeninges (highest yield), cortex, and white matter recommended
  - Arteries involved more than veins
  - May be granulomatous or nongranulomatous
  - May be complicated by infarct or hemorrhage
- Other causes
  - A variety of other conditions can result in a “vasculitic” pattern of injury pathologically
  - Drugs (e.g., cocaine, amphetamines)
  - Infection (e.g., Treponema, Borrelia, Herpes, HIV, Aspergillus, Mucor)
  - Lymphoproliferative disorders
  - Other (demyelinating disease, atherosclerosis, amyloid, etc.)

B. Pathology
- Segmental inflammation and necrosis of
vascular walls are the common features of the above-listed vasculitides.

- Vasculitis associated with SLE and lymphomatoid granulomatosis are the only two which typically involve brain parenchyma.
- PAN, Wegener’s granulomatosis, and giant cell arteritis involve vessels in the subarachnoid space, peripheral nervous system, or the extracranial vessels.
- Neurologic dysfunction in all entities is related to ischemia.

VII. Miscellaneous

A. Binswanger’s disease

- Rare condition generally presenting between ages 50–60 yr; evolves over 3–5 yr
- Also called subcortical arteriosclerotic encephalopathy
- Moderate intermittent hypertension and progressive, often profound dementia are features.
- Widespread vascular alterations and white matter changes are seen and readily demonstrated with neuroimaging.
- Ventricular dilatation, often secondary to hydrocephalus ex vacuo
- Focal and diffuse myelin loss with associated reactive astrogliosis in the deep hemispheric white matter
- Subcortical arcuate fibers are spared.
- Changes most severe in the temporal and occipital lobes.
- Demyelination is thought to be secondary to reduced perfusion due to arteriosclerosis of small penetrating vessels.

B. CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)

- Mutation of notch 3 gene on chromosome 19q12
- Strokes and vascular dementia
- Systemic disorder
- Thickened vessel walls (media and adventitia) with basophilic, PAS-positive granules within smooth muscle cells
- Variable degrees of perivascular atrophy

C. Atherosclerosis/hypertensive angiopathy

- Risk factors: dyslipidemia, hypertension, smoking, diabetes
- Initial atherosclerotic lesion is fatty streak marked by foam cells filled with low-density lipoprotein (LDL) cholesterol.
- Fatty streaks may develop into fibrous plaques (especially develop at outer aspects of arterial bifurcation where laminar flow is disturbed)—connective tissue, smooth muscle cells, foam cells, lymphocytes, necrotic cell debris, and extracellular lipids/cholesterol
- Turbulence caused by plaque may cause further disease progression.
- Complicated plaque results from disruption of endothelium resulting in thrombus formation (risk for occlusion and emboli).
- Hypertensive angiopathy shifts the autoregulation (maintains cerebral blood flow at a constant level between mean arterial pressures of 50–150 mm Hg) curve to the right, raising the lower limit of regulation at which adequate cerebral flow can be maintained.
- Malignant hypertension–acute hypertension
  - Diffuse cerebral dysfunction, headache, nausea, vomiting, altered consciousness
  - May be the result of pheochromocytoma (release of catecholamine), disseminated vasculitis, eclampsia, rebound drug effect
  - Brain edema, focal ischemia, and intracerebral hemorrhage
- Chronic hypertension
  - Further worsens atherosclerotic changes in large arteries
  - Causes small vessel disease with disruption of blood-brain barrier resulting in basal lamina thickening and reduplication, smooth-muscle degeneration, fibroid change (necrosis), and increased collagen deposition (lipohyalinosis—collagenous fibrosis)
  - May form Charcot-Bouchard microaneurysms (miliary aneurysms)—dilatations/outpouchings of vessel wall caused by fibrinoid change

D. Moyamoya syndrome

- Defined angiographically by spontaneous
occlusion of the circle of Willis and the presence of abnormal collateralization

- Two peaks of incidence—1st and 4th decades
- Most patients young, <20 yr, females > males

- Hemiparesis and hemorrhage
- Intimal fibroplasia usually without atherosclerotic changes, no inflammation
Neuropathology Review
Prayson, R.A.
2001, VII, 230 p., Hardcover
ISBN: 978-1-58829-024-3
A product of Humana Press