Neuropathology p.1

Cellular Pathology of the Central Nervous System

Reactions of Neurons to Injury

Acute neuronal injury ("red neurons") refers to a spectrum of changes that accompany acute CNS hypoxia/ischemia or other acute insults and reflect cell death, either necrosis or apoptosis

Subacute and chronic neuronal injury ("degeneration") refers to neuronal death occurring as a result of a progressive disease process of some duration.

Axonal reaction refers to the reaction within the cell body that attends regeneration of the axon; it is best seen in anterior horn cells of the spinal cord when motor axons are cut or seriously damaged.

Some degenerative diseases of the CNS are associated with neuronal intracytoplasmic inclusions, such as neurofibrillary tangles of Alzheimer disease and Lewy bodies of Parkinson disease;

Reactions of Astrocytes to Injury

Reactions of ependymal cells to Injury

Ciliated columnar epithelial cells lining the ventricles, do not have specific patterns of reaction.

When there is inflammation or marked dilation of the ventricular system, disruption of the ependymal lining is paired with proliferation of subependymal astrocytes to produce small irregularities on the ventricular surfaces (ependymal granulations).

Reactions of Microglia to Injury

Microglia are mesoderm-derived cells whose primary function is to serve as a fixed macrophage system in the CNS. They share many surface markers with peripheral monocytes/macrophages.

They respond to injury by

(1) proliferating;

(2) developing elongated nuclei (rod cells), as in neurosyphilis;

(3) forming aggregates about small foci of tissue necrosis (microglial nodules); or

(4) congregating around cell bodies of dying neurons (neuronophagia).

RAISED INTRACRANIAL PRESSURE

- ***Intracranial hypertension***

  - Generalized or localized brain edema
  - Hydrocephalus
  - Localized expanding mass lesions

  - *Consequences*:

    – Stop of intracranial circulation

    – Herniation

HERNIATION

Subfalcine (cingulate)
Cingulate gysrus under Falx cererbri

- compression of bracnes of the antrior cerebral artery

Transtentorial (uncinate, mesial temporial)
Medial part of temoral lobe – against the margins of the tentorium cerebelli

- Compression of third cranial nerve
- Compression of the posterior cerebral artery

Tonsillar
Cerebellal tonsils through the foramen magnum

Brain stem compression
Vital respiratori centers
Duret's hemorrhages

CEREBRAL EDEMA

Vasogenic edema is caused by blood-brain barrier disruption and increased vascular permeability, allowing fluid to shift from the intravascular compartment to the intercellular spaces of the brain.

May be either localized or generalized.

Cytotoxic edema is an increase in intracellular fluid secondary to neuronal, glial, or endothelial cell membrane injury, as might be encountered in someone with a generalized hypoxic/ischemic insult or with metabolic damage.

HYDROCEPHALUS

-the accumulation of excessive CSF within the ventricular system of the brain

- ***noncommunicating*** *hydrocephalus*- obstruction to the flow of CSF
- ***communicating*** *hydrocephalus* - no obstruction
  - *hyporesorptive hydrocephalus* - impaired reabsorption of CSF
  - *hypersecretive hydrocephalus* - papiloma of the chorid plexus

HYDROCEPHALUS

- **NONCOMMUNICATING HYDROCEPHALUS:**
  - OBSTRUCTION - the most common location: the aqueduct of Sylvius
    - » (1) A congenital malformation
    - » (2) A neoplasm
    - » (3) Inflammation
    - » (4) Hemorrhage
- **Hydrocephalus ex vacuo**
- - dilatation of the ventricular system due

<u>to the reduction of the brain parenchyma</u>

- - atrophy (vascular, degenerative diseases)

Cerebrovascular Diseases

From the standpoint of pathophysiology and pathologic anatomy, it is convenient to consider cerebrovascular disease as two processes:

Hypoxia, ischemia, and infarction resulting from impairment of blood supply and oxygenation of CNS tissue

Hemorrhage resulting from rupture of CNS vessels

HYPOXIA, ISCHEMIA, AND INFARCTION

Two principal types of acute ischemic injury are recognized:

- **Global cerebral ischemia** (ischemic/hypoxic encephalopathy) occurs when there is a generalized reduction of cerebral perfusion (cardiac arrest, shock, and severe hypotension)
- **Focal cerebral ischemia** follows reduction or cessation of blood flow to a localized area of the brain due to large-vessel disease or to small-vessel disease.

Global Cerebral Ischemia

Also called Hypotension, Hypoperfusion, and Low-Flow States

The clinical outcome of a severe hypotensive episode that produces varies with the severity of the insult.

Morphology.

Brain is swollen, the gyri are widened, and the sulci are narrowed. The cut surface shows poor demarcation between gray and white matter.

Microscopically are divided into:

Early changes, occurring 12 to 24 hours after the insult

Subacute changes, occurring at 24 hours to 2 weeks

Repair, robust after approximately 2 weeks

Focal Cerebral Ischemia

•- a third major cause of morbidity and mortality

•- atherosclerosis - thrombosis and embolic events

•

•***Pathology***:

- - ”hemorrhagic” or ”bland“ encephalomalacia
- - liquefactive necrosis - resorption by macrophages (gitter cells) - postmalatic pseudocyst filled with fluid

•***Clinical Features***:

•- internal capsule - hemiparesis

•- the middle cerebral artery - the parietal cortex - motor and sensory deficits

•

•***Clinical syndromes:***

- **Transient ischemic attack (TIA) -** less than 24 hours - few minutes’ duration
- **Stroke in evolution** - the propagation of a thrombus
- **Completed stroke -** stable neurological deficit resulting from a cerebral infarct.

Infarcts

Two broad groups based on the presence of hemorrhage.

Hemorrhagic (red) infarction, characterized by multiple, sometimes confluent, petechial hemorrhages, is typically associated with embolic events. The hemorrhage is presumed to be secondary to reperfusion of damaged vessels and tissue, either through collaterals or directly after dissolution of intravascular occlusive material.

In contrast, **nonhemorrhagic (pale, bland, anemic) infarcts** are usually associated with thrombosis.

HYPERTENSIVE CEREBROVASCULAR DISEASE

The most important effects of hypertension on the brain include lacunar infarcts, slit hemorrhages, and hypertensive encephalopathy, as well as massive hypertensive intracerebral hemorrhage.

Lacunar Infarcts

Single or multiple, small, cavitary infarcts known as lacunae.

These are lake-like spaces, less than 15 mm wide, which occur in the lenticular nucleus, thalamus, internal capsule, deep white matter, caudate nucleus, and pons, in descending order of frequency.

On microscopic examination they consist of areas of tissue loss with scattered lipid-laden macrophages and surrounding gliosis.

Depending on their location in the CNS, lacunae can either be clinically silent or cause severe neurologic impairment.

Slit Hemorrhages

Hypertension also gives rise to rupture of the small-caliber penetrating vessels and the development of small hemorrhages. In time these hemorrhages resorb, leaving behind a slitlike cavity (slit hemorrhage) surrounded by brownish discoloration; on microscopic examination, slit hemorrhages show focal tissue destruction, pigment-laden macrophages, and gliosis.

Hypertensive Encephalopathy

Acute hypertensive encephalopathy is a clinicopathologic syndrome arising in an individual with malignant hypertension, and is characterized by diffuse cerebral dysfunction, including headaches, confusion, vomiting, and convulsions, sometimes leading to coma.

Hypertensive Encephalopathy

At postmortem examination such individuals may show an edematous brain with or without transtentorial or tonsillar herniation.

Petechiae and fibrinoid necrosis of arterioles in the gray and white matter may be seen microscopically.

Individuals who, over the course of many months and years, suffer multiple, bilateral, gray matter (cortex, thalamus, basal ganglia) and white matter (centrum semiovale)

infarcts may develop a distinctive clinical syndrome characterized by dementia, gait abnormalities, and pseudobulbar signs, often with superimposed focal neurologic deficits.

INTRACRANIAL HEMORRHAGE

Hemorrhages may occur at any site within the CNS.

Primary hemorrhages within the epidural or subdural space are typically related to trauma and were discussed earlier with traumatic lesions.

Hemorrhages within the brain parenchyma and subarachnoid space, in contrast, are more often a manifestation of underlying cerebrovascular disease, although trauma may also cause hemorrhage in these sites.

Intracerebral hemorrhage ”strokes” or ”apoplexy,”

TYPICAL = hypertension

→ **Hypertensive intracerebral hemorrhage**

ATYPICAL = vascular anomaly (AV malformation), trauma, anticoagul. therapy

Preferential sites:

- **basal ganglia – thalamus 65%**
- pons 15%
- the cerebellum 8%

Death by:

- transtentorial herniation
- rupture into a lateral ventricle - intraventricular hemorrhage

Epidural Hematoma

- Trauma

- *Rupture of a middle meningeal* artery, in association with a skull fracture

Subdural Hematoma

- *disruption of bridging veins* (from the surface of the brain to the dural sinuses)
- rapid changes in head velocity (e.g., whiplash injury; blows to the head)
- most often over the cerebral convexities

- *Acute subdural hematomas*
- *Chronic subdural hematomas*

Subarachnoid Hemorrhage and Ruptured Saccular Aneurysms

- = nontraumatic intracranial hemorrhage = *spontaneous subarachnoid hemorrhage*

- *- rupture of a saccular,* or berry, **aneurysms**

Saccular Aneurysms

The etiology of saccular aneurysms is unknown. Although they are sometimes referred to as congenital, theaneurysms are not present at birth but develop over time because of an underlying defect in the media of the vessel.

Saccular Aneurysms

Most frequent in the fifth decade and is slightly more frequent in females.

Rupture may occur at any time, but in about one third of cases it is associated with acute increases in intracranial pressure (straining at stool or sexual orgasm).

Blood under arterial pressure is forced into the subarachnoid space and affected individuals are stricken with a sudden, excruciating headache (“the worst headache I've ever had”), rapidly losing consciousness.

Between 25% and 50% of patients die with the first rupture, but patients who survive often improve and recover consciousness in minutes.

Vascular Malformations

Vascular malformations of the brain are classified into four principal groups: arteriovenous malformations,
cavernous malformations,
capillary telangiectasias,
venous angiomas.

INFECTIOUS DISEASES

3 main types of CNS infections:

1. **Meningitis**
2. **Cerebral abscess**
3. **Viral encephalitis**

Meningitis

1. Leptomeningitis

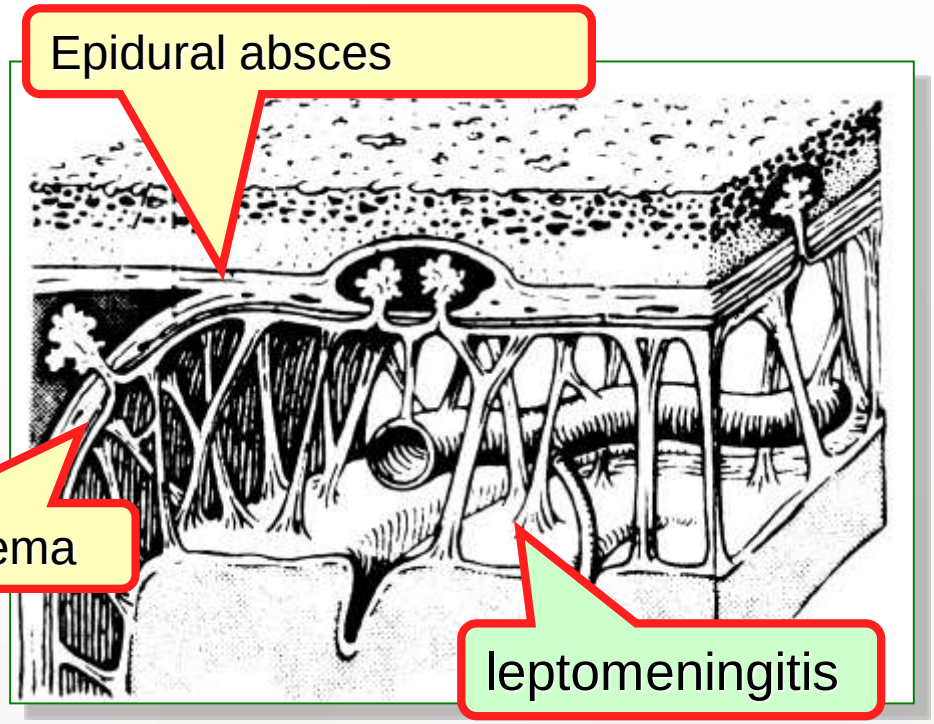
- interfacing surfaces of the pia and arachnoid
- the CSF - an excellent culture medium for most microorganisms

2. Pachymeningitis

- inflammation of the dura
- the consequence of contiguous infection:
  - chronic sinusitis
  - mastoiditis

..

- ***Subdural empyema***
- ***Epidural abscess***



Bacterial Meningitis

AGENTS:

- suppurative microorganisms :

♦ ***Escherichia coli:***

- the newborn

→ cross-placental transfer of maternal IgG imparts protection to the newborn against many bacteria x E. coli require IgM for neutralization

♦ ***Haemophilus influenzae***:

- the incidence between 3 months and 3 years

♦ ***Streptococcus pneumoniae***:

predominates as a cause of meningitis later in life

basilar skull fracture

♦ ***Neisseria meningitidis***

- airborne transmission in crowded environments (military barracks)

1. Nasopharynx
2. Initial phase bacteriaemia - fever, malaise, petechial rash.
3. Intravascular coagulopathy (DIC) with lethal adrenal hemorrhages = ***Waterhouse – Friderichsen syndrome***
4. Untreated meningococcal bacteriaemia - an acute fulminant meningitis.

Pathology:

Exsudate of leukocytes and fibrin of the arachnoid

→ a creamy appearance

Meningococcus, H.influ. - base

Pneumococcus - convexity

Bacterial Meningitis

Clinical Features:

- headache, vomiting, fever

- convulsions children

- classic signs: so called **meningeal signs**:
    - cervical rigidity
    - head retraction
    - pain in the knee when the hip is flexed (Kernig sign)
    - spontaneous flexion of the knees and hips when the neck is flexed (Brudzinski sign)

- stupor, coma, eventually death.

Cerebral Abscess

- Hematogenous

- Complication of meningitis

Viral Encephalomyelitis

- Heterogeneous
- **Propensity for localization** in specific areas of the nervous system:

•***Poliomyelitis*** - the motor neurons of the spinal cord
specific binding sites on the membranes of motor neurons

•***Rabies*** - the brainstem

•***Herpes simplex*** - the temporal lobes - latently in the Gasserian ganglion
proximity of this ganglion to the temporal lobe

POLIOMYELITIS (acuta anterior)

- infection with one of three strains of poliovirus (enteroviruses)

Epidemiology:

- occurred in epidemic form since antiquity
- The medical triumph - in the 1950s of effective vaccines
- Infected persons - virus in their stools
- Spreads by fecal-oral route
- Contaminated hands, food
- Most rapidly among children

Clinical Features:

1. nonspecific symptoms, such as fever, malaise, and headache,
2. in several days - signs of meningitis
3. paralysis

In severe cases - ***paralysis of the respiratory muscles***

(mortality varies from 5% to 25%)

Milder cases - asymmetric and patchy ***paralysis***

Rabies

- RNA virus of the rhabdovirus group
- Reservoir: dogs, fogs, wolves, skunks
- Through contaminated saliva introduced by a bite

Pathogenesis

1. virus enters a peripheral nerve
2. centripetal axoplasmic flow - the spinal cord and brain
3. latent interval 10 days to 3 months
4. centrifugal intra-axonal transmission - contaminates visceral organs

the salivary glands the saliva becomes infectious.

Rabies

Pathology:

- Brainstem + *cerebellum and hypothalamus*
- Lymphocytes aggregate about small arteries and veins in the brainstem
- Neurons show chromatolysis and neuronophagia
- Glial nodules
- **Negri bodies** in the hippocampus, brainstem, and Purkinje cells of the cerebellum

Rabies

Clinical Features:

Destruction of neurons in the brainstem:

1. Initiates painful spasms of the throat, difficulty in swallowing, and tendency to aspirate fluids - ”hydrophobia”

2. General encephalopathy: irritability, agitation, seizures, and delirium.

3. Progress to death in an interval of 1 to several weeks

- Specific treatment of rabies is not available

- Postexposure prophylaxis is accomplished by a series of vaccine injections

Arthropod-borne viral encephalitis (ARBO-viruses)

- Transmitted by blood-sucking vectors
    - Mosquitoes
    - Ticks

- Encephalitides named principally for the geographic regions where they were first noted

Herpes Viruses encephalitis

- Herpes simplex (types 1 and 2)
- Varicella-zoster virus
- Cytomegalovirus
- Epstein – Barr virus

HERPES SIMPLEX VIRUS TYPE 1

- a major viral infection of the human nervous system.

Pathogenesis:

1. ”Cold sore” - the vesicular lesion on the lip
2. Gasserian ganglion
3. Latent proliferation - stress - centrifugally to the lip.
4. Predisposition

→ intra-axonal spread from the gasserian ganglion to the overlying brain through meningeal nerve fibers

→CNS fulminant infection

Predominantly **temporal lobes**.

Pathology:

- ***hemorrhagic, and necrotic***
- ***eosinophilic intranuclear inclusions***

CYTOMEGALOVIRUS

- in utero

- periventricular areas

- necrosis and calcification

proximity of these lesions to the third ventricle and the aqueduct
→ hydrocephalus