NEUROPATHOLOGY

Intracranial hypertension

Intracranial hypertension

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

Consequences:

- Stop of intracranial circulation
- Herniation

Brain herniation

1. ***Transtentorial (uncinate, mesial temporal) herniation***
the medial aspect of the temporal lobe -against the margin of the tentorium cerebelli

→ compression:
the third cranial nerve
posterior cerebral artery

2. ***Subfalcine (cingulate gyrus) herniation***
the cingulate gyrus under the falx cerebri

→ compression of branches of the anterior cerebral artery

3. ***Tonsillar (occipital) herniation***

-cerebellar tonsils through the foramen magnum,
- brain stem compression - vital respiratory centers *Duret's hemorrhages*

Cerebral Edema

1. ***Vasogenic edema***

- disrupted integrity of the normal blood-brain barrier
- fluid escapes into the interstitial space of the brain

Localized: abnormally permeable vessels adjacent to abscesses and neoplasms
generalized: heat shock, endotoxin…

2. ***Cytotoxic edema*** = increase in intracellular fluid

cellular injury

Morphology:

- the gyri - flattened
- the intervening sulci narrowed
- the ventricular cavities compressed

As the brain expands → herniation

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

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 to the reduction of the brain parenchyma
- atrophy (vascular, degenerative diseases)

Ischemia and Infarction

- inadequate perfusion of the brain

GLOBAL ISCHEMIA

- generalized low blood flow resulting from extracerebral events (shock or cardiac arrest)

- Selective neuronal sensitivity:

- Purkinje cells of the cerebellum
- the pyramidal neurons of Sommer sector in the hippocampus

WATERSHED INFARCTS
LAMINAR NECROSIS

Regional ischemia and cerebral infarction

- 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.

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*

subdural hygroma

SUBARACHNOID HEMORRHAGE

= nontraumatic intracranial hemorrhage = *spontaneous subarachnoid hemorrhage*

*- rupture of a saccular (*berry) **aneurysms**

- **1%** of the general population
- atherosclerosis
- infectious (”mycotic”) aneurysms

INFECTIOUS DISEASES

- virtually all types of microorganisms

- localize in preferred intracranial and intraspinal sites

  - *poliovirus* - the motor neurons of the spinal cord
  - *herpes simplex virus* - the temporal lobes
  - *progressive multifocal leukoencephalopathy* (JC virus) – the parasagittal white matter
  - *bacteria* generally localize in the leptomeninges

Routes of ENTRY:

- Hematogenic
- Rhinogenic
- Otogenic
- Through nerve fibers
- Directly - trauma

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.

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

COMMON PATHOLOGY

1. **Perivascular lymphocytic cuffs**

2. Neuronophagy

3. Glial nodule

4. I N C L U S I O N S

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

Pathology:

Binding sites on **motor neurons** - the favorable intracellular conditions for viral replication

- chromatolysis
→ Loss of motor neurons

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

DEMYELINATING DISEASES

= disorders in which myelin is lost selectively, whereas other neural structures are preserved

CLASSIFICATION:

1. **LEUKODYSTROPHIES**

   = inherited with enzyme defect of the formation and preservation of myelin

2. **ACQUIRED DEMYELINATING DISEASES**

   = destruction of normally developed myelin

   - **Multiple sclerosis**
   - Postinfectious and Postvaccinal Encephalomyelitis
   - Central pontine myelinolysis

LEUKODYSTROPHIES

- heterogeneous group of inherited diseases
= enzyme defect - disturbances in the formation and preservation of myelin.

CLIN - **psychomotor retardation, progressive dementia, and paralysis**

Metachromatic Leukodystrophy (MLD)

- the most common type leukodystrophy
- AR accumulation of a *cerebroside* (*galactosyl sulfatide*) in the white matter of the brain and peripheral nerves.
- lethal within several years.

-deficiency of ***arylsulfatase A***, a lysosomal enzyme involved in the degradation of myelin.

Krabbe disease
Adrenoleukodystrophy (ALD)
Alexander Disease

Multiple Sclerosis (MS)

- Chronic demyelinating disease
- **Characterized by the presence of numerous patches of demyelination throughout the white matter**

- Prevalence approaching 1 in 1000.

***Epidemiology*:**

- mean age of onset: 30 years
- temperate climates, rare in the tropics
- increasing frequency with distance from the equator
- emigrating before age 15 years from areas with low prevalence of MS to endemic areas acquire an increased risk of developing the disease
- environmental factor acting early in life.

Pathogenesis:
remains obscure.

♦ GENETIC FACTORS:
- A genetic predisposition: familial aggregation, increased risk in second- and third-degree relatives of patients with MS.
- Associated with a number of major histocompatibility complex (MHC) alleles - **HLA-DR2**.

♦ IMMUNE FACTORS:
- Experimental allergic encephalitis (EAE)

♦ INFECTIOUS AGENTS:
- vaccinia, mumps, rubella, herpes simplex, and measles
- no direct evidence
- recently: *JC virus* (replicates in oligodendrocytes)

Pathology

- The hallmark of MS: the **plaques** in the brain + spinal cord (white matter)
- Preference for: the optic nerves and chiasm, paraventricular white x **ANYWHERE**
- The distribution is random

Clinical Features:

- **onset** - third or fourth decades
- **abrupt and brief episodes** of clinical progression + periods of relative stability
- **exacerbation** = expression of the formation of additional plaques of demyelination

- ***optic nerves*** → blurred vision or the loss of vision in one eye
- ***brainstem*** → the most troubling early symptoms double vision and vertigo.
- **spinal cord** → weakness legs and sensoric symptoms

- death of respiratory paralysis or urinary tract infections
- survive 20 to 30 years after the onset

Postinfectious and Postvaccinal Encephalomyelitis

- foci of perivascular demyelination
    - viral exanthems (e.g., measles, varicella: rubella)
    - between 3 and 21 days after the rash.
    - immunization against smallpox

- Headache, vomiting, fever
- Meningeal signs
- In severe cases → paraplegia, incontinence, and stupor

Central Pontine Myelinolysis

- Rare
- Pons of:
    - malnourished persons
    - alcoholics

DEGENERATIVE DISEASES

of CNS

DEGENERATIVE DISEASES of CNS

- Heterogeneous group of disorders characterized by spontaneous, progressive degeneration of neurons in a specific region or system in the brain, spinal cord, or both.

- Degenerative diseases may be sporadic or familial.

- **Cortex - Alzheimer´s disease, Pick´s disease**
- **Expy (BG) - Parkinsonism, Huntington´s disease**
- **Motor neurons - ALS**

Alzheimer's Disease

- the most common cause of dementia in the elderly
- (the remaining cases of dementia = cerebrovascular disease)

- occur after the age of 50
- a progressive increase in incidence with increasing age

- most cases are sporadic
- 10% of patients - a family history of dementia

Genetic factors:

= genetic abnormalities on chromosomes 21, 19, 14, and 1

1. **Amyloid precursor protein - APP**
   - the breakdown product (**Aβ-amyloid**) = component of both:
     - •the neurofibrillary tangles
     - •senile plaques
     - •within the walls of cerebral blood vessels
   - β-amyloid - toxic to neurons in cell cultures

2. **tau- protein**

3. Expression of specific alleles of **apoprotein E (apoE)**
   - ε4 allele of apoE = increased frequency in patients with late-onset AD
   - apoE = involved in the transport or processing of the β-amyloid precursor protein.

Clinical features

- progressive impairment of memory and other cognitive functions
- subtle at first (depression)
- cognitive impairment over the course of 5 to 15 years
- complete disorientation and loss of language and other higher cortical functions
- Death - intercurrent bronchopneumonia

Alzheimer's Disease

MORPHOLOGY

Gross:

- brain atrophy - frontal, temporal, or parietal lobes

- cerebral ventricles are symmetrically dilated (hydrocephalus ex vacuo)

Microscopic

• **neurofibrillary tangles** = coarse, filamentous aggregates within the neurons
- neocortex, hippocampus, basal forebrain and brain stem

• **senile plaques** = as aggregates of coarse neurites in the neuropil of the cerebral cortex
- a central amyloid core (β-amyloid)

• **amyloid angiopathy** = β-amyloid deposits in vessels

PICK'S DISEASE

- Rare presenile dementia - usually presents in 6th-7th decades
- Familial and sporadic occurrence
- Course - 2-10 years

Pathology:

- Circumscribed frontal and temporal lobe atrophy
- **lobar atrophy** or sclerosis,
- Severe neuronal loss and gliosis in atrophic areas
- Argyrophilic cytoplasmic inclusions - Pick bodies
- Typically without senile plaques or neurofibrillary tangles

Parkinsonism

Parkinsonism is not a single disease:
= a clinical manifestation of a **disturbance in the dopaminergic pathways connecting the substantia nigra to the basal ganglia**

- disturbance in motor functions characterized by

- rigidity,
- expressionless facies
- stooped posture
- gait disturbances
- slowing of voluntary movements
- ”pill-rolling” tremor

Parkinsonism

- trauma
- certain toxic agents
- vascular diseases
- encephalitis
- Parkinson’s disease

Parkinson's disease = idiopathic parkinsonism (paralysis agitans)

= degenerative disorder involving the dopamine-secreting neurons of the substantia nigra, as well as the locus ceruleus.

- manifests by the sixth decade
- usually sporadic

Parkinson's disease

MORPHOLOGY.

Gross:

- externally normal or mildly atrophic

- the substantia nigra and locus ceruleus are depigmented

Parkinson's disease

Microscopically

the neuropil in **substantia nigra** and **locus coeruleus**:

- gliosis
- **Lewy bodies** = concentrically laminated intracytoplasmic inclusions

Huntington Disease

- hereditary, progressive, fatal disorder involving the ”extrapyramidal” motor system
- characterized by
    1. **involuntary movements (chorea)**
    2. **dementia**
- autosomal dominant trait with complete penetrance

Pathogenesis:

The responsible gene: chromosome 4 (product = huntingtin)
-caused by **trinucleotide repeat expansion** in the Huntington gene:
- in Huntington disease, the number of triplet repeats is increased

- the larger the number, the earlier the onset of disease.
- the molecular pathogenesis of Huntington disease is not fully understood

MORPHOLOGY:

Gross

- brain atrophy (less than 1000 g)
-striking atrophy of the caudate nucleus, putamen, and globus pallidus,

Microscopically

- severe loss of neurons within the caudate and putamen,
- accompanied by fibrillary gliosis

Diseases of Motor Neurons

Amyotrophic lateral sclerosis (ALS)

- degenerative disorder involving the upper and lower motor neurons of the pyramidal system
- resultant progressive muscle weakness, atrophy, and spasticity

Pathogenesis of most cases of ALS - unknown

? mutations in the gene coding for the enzyme superoxide dismutase?