General Pathology (DENF 2702)

Topic: Neuropathology

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Basic Points

Cells of the CNS:
- **Neurons**: main signal transporter, with axons
- **Astrocytes**: the major supporting cells in the brain
- **Oligodendrocytes**: cytoplasmic processes wrap around axons
  -- To form myelin
- **Ependymal cells**: line cerebral ventricles
  -- Like cuboidal cells
- **Microglia**: as antigen-presenting cells when activated
  -- Arise from monocytes
- **Neuropil**: delicate fibrillar network of all the processes of brain cells

Notes:
- Brain consumes 20% of oxygen used by the body
Fluid Disorders
Cerebral Edema

- Fluid accumulation in parenchyma
  - There is minimal lymphatic drainage in the brain
- Surface of brain becomes flattened (from pressing on skull)
- **Vasogenic edema**
  - Extracellular fluid
  - ↑ permeability
    (Inflammation)
- **Cytotoxic edema**
  - Intracellular fluid
  - Cell injury
  - Trauma, hypoxia
Uncinate (Transtentorial) Hernia and Subfalcine Hernia

- **Uncinate hernia**
  - Uncal gyrus
  - Temporal lobe (medial aspect)
  - Optic nerve involved

- **Subfalcine hernia**
  - Cingulate gyrus
  - Weakness
  - Abnormal leg sensations
Tonsillar Hernia

- Life threatening
- Presses on brain stem
  - Pushes it through the foramen magnum
  - Respiratory center is in medulla oblongata
- Duret hemorrhages
  - Bleeds from trauma
Cerebrospinal Fluid (CSF)

- Formed by choroid plexus cells
- Formed in lateral and fourth ventricles
- Circulates through ventricles
- Absorbed by arachnoid granulations

If flow is blocked: enlarged ventricles
Hydrocephalus
Accumulation of CSF in Ventricles

- Usually from decreased resorption
- Rarely: from ↑ CSF production
  -- e.g. tumors of choroid plexus
- Increased intracranial pressure
- Expand skull in childhood
  -- Sutures aren’t fused
- Compresses brain cells against skull in adults
  -- Sutures are fused
- Loss of brain cells
- Mental retardation
- Hydrocephalus ex vacuo
  -- Loss of brain cells first
  -- Then enlarged ventricles
  - No increased pressures
  - Normal CSF flow
Kleeblattschädel
Clover Leaf Skull; Hydrocephaly
Cerebrovascular Disease
# Cerebrovascular Disease

Cerebrovascular Accident (CVA); Stroke; Apoplexy

- **Global hypoxic-ischemic encephalopathy**
  - Generalized hypoxia
- **Ischemia**
- **Infarction**
- **Hematoma**
  - Intracranial hemorrhage
Global Hypoxia-Ischemic Encephalopathy

- Less than 50 mm Hg:
  - Compensatory mechanisms work poorly
- Generalized hypoxia
  - Usually from cardiac arrest
  - No visible change for 24-48 hours,
  - Then: soft, edematous brain
- Neurons are more susceptible than glial cells
- Increased glutamate in brain
  - Excess neuron activity
  - Damage (excitotoxicity)
- Severity depends on:
  - Patient age
  - Duration of hypoxia
  - Ambient temperature
  (↓ temp. >> ↓ damage)
Brain Infarction

- Localized loss of blood flow
- Usually in a branch of middle cerebral artery
- Accounts for 80% of CVAs
- Most common cause:
  -- Atherosclerosis of brain vessels
- Other causes:
  – Thrombosis
  – Embolism
  – Vasculitis
  --Trauma
- Predisposing factors:
  – Hypertension
  – Smoking
  – Diabetes mellitus
  – Poor heart health
Brain Infarction

- Transient ischemic attack (TIA)
  - In 24 preceding hours
- Sudden onset
- Contralateral hemiparesis
- Contralateral spasticity
  - *Apoplexy* = old name
- Loss of consciousness
- Aphasia (loss of speech)
- Speaking in tongues
- Monocular blindness
- May be quickly fatal
- May be “silent”
Infarction
Necrotic tissue has liquefied, leaving permanent, fluid-filled space

Brain Hematoma
Acute Intracerebral Hemorrhage

- Vessel ruptures
  50% = chronic hypertension
- Saccular (berry) aneurysm
  -- In subarachnoid space
  – 1% of population has berry aneurysms
- Arteriovenous (AV) malformation
- Patients on anticoagulants
- Hypercoagulation states
  -- Thrombus in vessel >>
  -- Dead vessel ruptures
- Trauma
  -- Subdural hematoma
- Sudden onset
- Severe headache
- Vomiting
- Loss of consciousness
- Usually fatal
Saccular (Berry) Aneurysm

Circle of Willis

Arteriovenous Malformation
With Massive Hemorrhage
Fusiform Atherosclerosis Aneurysm

Brain Trauma

- Epidural hematoma
  - Subdural hematoma
    - Meningeal artery
      - Skull fracture
  - Subdural hematoma
    - Bridging veins
      - e.g. whiplash
- Concussion
- Diffuse axonal injury
- Contusion
Concussion & Contusion

- **Concussion**
  -- Transient loss of consciousness
  -- Seizures
  -- Complete recovery, usually
  -- No memory of the episode
  -- Problem: maybe axonal injury

- **Contusion**
  -- Superficial hemorrhage (bruise)
  -- Brain contacts skull
Diffuse Axonal Injury

- Sudden acceleration or deceleration
- Ruptures brain cells
- Axonal swelling
- Vegetative state
- Dementia
Infections
Meningitis (Leptomeningitis)

- Inflammation of leptomeninges and subarachnoid space
- Creamy purulent exudate on cerebrum
- Severe congestion and brain swelling
- Neutrophils in CSF (acute forms)
- May be from toxic chemicals
- Signs/Symptoms:
  - Fever
    -- Headache
    -- Stiff neck
    -- Altered mental status
- **Acute (purulent) leptomeningitis**
  -- Bacteria
  -- High mortality
- **Acute lymphocytic meningitis**
  -- Virus
- **Chronic meningitis**
Encephalitis

- Generalized infection of brain parenchyma
  - Usually virus
    - HSV I (most common)
    - Rabies
    - CMV
    - HIV
    - Papovavirus
  - Syphilis
  - Tuberculosis
  - Toxoplasmosis
  - Spongiform encephalitis
    - Creutzfeldt-Jakob disease
    - Prions
Herpes Encephalitis
Necrosis of Temporal Lobe


Necrosis & Hemorrhage

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Creutzfeldt-Jakob Disease
Spongiform Encephalitis

- Prion infection
  -- devoid of RNA or DNA
  -- Modification of CNS structural protein
    (PrP\textsuperscript{sc}) \space (sc = scrapie in animals)
- Results from accumulation of abnormally folded prion protein
- Transmissible within same species
  -- Corneal transplant; pituitary extracts
  -- Nonsterile CNS probes
- May be hereditary (auto. dominant)
  -- Most common type = familial
- Resist antivirals (no nucleic acids)
- Rapidly progressive dementia
- Fatal in 1 year
- Gait abnormalities, jerking movements
  -- Startle myoclonus
- Seventh decade of life

Mad cow disease = bovine spongiform encephalopathy

Vacuoles in brain tissue = “spongy” change
Prion Disease
Pathogenesis (Three Patterns)

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Cerebral Abscess

- Usually from bacteremia
  - Staph.
  - Strept.
  - Dental infection!
- Fever
- Headache
  - $\uparrow$ intracranial pressure
- Neurologic deficits
Brain Tumors
Brain Neoplasms

- Seldom metastasize to other parts of body
- Gliomas
  - Astrocytoma
  - Oligodendroglioma
- Ganglion cell tumor
  - Gangliocytoma
  - Ganglioglioma
- Headache
- Nausea
- Seizures
- Neural deficits
- Cognitive problems
- Personality changes
**Astrocytoma**
A Form of Glioma

- Most common brain tumor
  - Astrocytes
- Usually in adults
- Usually fatal
  - May behave benignly
- Headache, seizures
- **Fibrillar astrocytoma**
  - Diffuse infiltration
- **Pilocytic astrocytoma**
  - In children
  - Less aggressive
  - Rosenthal fibers
  - Hyaline granular bodies
- **Ependymoma**
  - Ventricular walls
  - May cause hydrocephaly

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Oligodendroglioma

- Usually in adults
- In cerebral hemispheres
- Calcification is common
- Prognosis varies
  -- Grade of tumor
- Often fatal
Ganglion Cell Tumor
Gangliocytoma; Ganglioglioma

- Benign neoplasm of ganglion and glial cells
- Occasionally is aggressive
- Most common tumor of neurons
- Children & teens
- Seizures, headache
Degenerative Disorders
Alzheimer Disease

- Most common cause of dementia
- Mutation on chromosome 21
  - Amyloid precursor protein (APP)
  - Amyloid plaques: breakdown of APP
  - Also: bad tau protein
  - Lewy bodies
    (Parkinsonism also)
- Three other mutations
- After 50 years of age
  - ↑ incidence with ↑ age
- 10% are familial
- Almost all Down syndrome patients > 40 yrs.

Senile Plaque:
Red = β-Amyloid
Brown = Tau Protein
Alzheimer Disease
Plaques (Left) & Tangles (Right)

Alzheimer Disease

- Brain is very atrophic
- Neurofibrillar tangles
  -- **Tau protein** is major component
- **Senile plaques**
  -- Amyloid cores
- Progressive over 5-16 years
- Cognitive impairment
- Disorientation
- Loss of short term memory
- Loss of language
- Personality change
- Movement disorders
  -- Like **Parkinson disease**
- Death
  -- Lung infection
Alzheimer Disease
Cerebral Atrophy

Normal Alzheimer
Parkinson Disease
Idiopathic Parkinsonism; Paralysis Agitans

- Disturbance of motor function
- Parkinsonism is not one disease
  -- Manifestation of defective dopaminergic pathways connecting substantia nigra to basal ganglia
- Parkinson disease is most common form of parkinsonism
- Dopamine-secreting neurons of substantia nigra
  -- Degenerate
  -- Lose color
Parkinson Disease
Idiopathic Parkinsonism; Paralysis Agitans

- Usually idiopathic
- Sometimes: familial susceptibility
  - Mutated gene coding for α-synuclein
    (used in neuronal synapses)
- Typical age: 6th decade
- "Pill-rolling" tremors
- Rigidity
- Expressionless face
- Gait disturbances
- Postural instability
- Slow muscle movements
- Insidious onset
  - Progression over 10 years
- Eventual dementia
Parkinson Disease
Idiopathic Parkinsonism; Paralysis Agitans

- Lewy bodies in brain
  -- Cytoplasmic eosinophilic inclusions
  -- Abundant α-synuclein
  – Also seen in Alzheimer disease

- Death
  -- Infections
  -- Trauma, falling down
Huntington Disease
Huntington’s Chorea; St. Vitus Dance

- Hereditary (AD) degeneration of extrapyramidal motor system
  -- Caudate nucleus
- Mutation of huntingtin gene on chromosome 4
  -- Leads to abnormal huntingtin protein
- Excessive CAG (cytosine-adenine-guanine) triplet sequences
  -- ↑ triplets >> worse disease
- Adult onset (4th, 5th decades)
- Usually after children are born, i.e. like “carrier” state
- Progressive over 15-20 years
Huntington Disease
Atrophy of Caudate

Huntington Disease
Huntington’s Chorea; St. Vitus Dance

- Involuntary, writhing movements
  - Chorea
  - Choreiform movements
  - St. Vitus’ dance
- Seizures
- Rigidity in some
  - Rigid-akinetic variant
- Psychiatric disturbances
  - Depression
  - Cognitive impairment
- Death: infections, suicide
Multiple Sclerosis

- Most common demyelination disease of CNS
  - 350,000 patients in US
  - More frequent in temperate than in equatorial climates
  - More frequent in whites
- Unknown etiology
  -- Autoimmune T-cell and antibody injury of myelin?
  -- CD4+ and CD8+ cells in lesions are reactive to myelin basic protein
  -- Environmental (infections)
  -- Heredity (HLA-DR2 gene)
  -- If you have MS and an identical twin:
    30% chance your twin will have MS
  -- Animal model: chronic experimental allergic encephalomyelitis
    -- Uses sensitized T cells
Multiple Sclerosis

- Waxing and waning of neurologic problems
- Usually normal lifespan
  - Progressive degeneration for many years
    - Acute MS: death within a few months of onset
- Acute or insidious onset
- Visual disturbances
- Paresthesia; peripheral neuropathy
- Depression; mood lability
- Idiopathic pain
  - Trigeminal neuralgia
- Elevated gamma globulin in CSF
  - Oligoclonal band with electrophoresis
- Myelin basic protein in CSF
Multiple Sclerosis
Plaque Adjacent to Lateral Ventricle

Multiple Sclerosis

- **MS plaques**
  -- Demyelination products
  -- Bare axons in small numbers
- **Shadow plaques**
  -- Attempted remyelination
Guillain-Barré Syndrome
Landry-Guillain Barré Syndrome; Acute Idiopathic Polyneuropathy

- One of most common life-threatening diseases of PNS
- Progressive and segmental demyelination of nerves
  -- Exposed axons
- Unknown etiology
  -- Infection (viral, Mycoplasma)
  -- Allergic reaction
  -- Surgical procedure
    – Immune disorder?
- Rapidly progressive motor weakness
- Death from respiratory muscle failure
- Sensory deficits, but less pronounced
- Macrophages and lymphocytes in peripheral nerves
- Segmental demyelination
Myelin

Peripheral Neuropathy

Axonal Degeneration

Primary Demyelinating Neuropathy

Amyotrophic Lateral Sclerosis (ALS)  
ALS; Lou Gehrig’s Disease

- Motor neuron disease
- Motor neurons of brain and spinal cord after infection
- Genetic susceptibility
- Maybe autoimmunity
- Insidious onset
- Clumsiness
- Weakness
- Speech difficulties
- Small, involuntary muscle contractions
  -- Fasciculations
Amyotrophic Lateral Sclerosis (ALS)
ALS; Lou Gehrig’s Disease

- Relentlessly progressive
- Muscle atrophy, eventually
- Death in 5 years
  -- Respiratory failure
  -- Infections
Recent Cerebral Infarct

Lacunar Infarcts

Cortical Lamellar Necrosis

Prolapse of intervertebral disc

Osteophytes caused by spondylosis

Bone disease (rheumatoid or Paget’s)

Extradural tumour or abscess, or meningeal fibrosis

Intradural tumour (schwannoma, arteriovenous malformation, meningioma)
Spinal Cord Trauma
Vertebral Fracture; Compression; Narrow Canal

Acute Purulent Leptomeningitis

Cerebral Abscess

Herpes Encephalitis
Necrosis of Temporal Lobe

Herpes Simplex I

Spongiform Encephalopathy

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<th>Chromosomal abnormalities</th>
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<td>Down's syndrome (trisomy 21)</td>
<td>Abnormal gyral formation and defective arborization of neuronal processes</td>
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<tr>
<td>Trisomy 13–15 (Patau's syndrome)</td>
<td>Forebrain abnormalities with midline facial clefts</td>
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<tr>
<td>Trisomy 17–18 (Edwards' syndrome)</td>
<td>Gyral maldevelopment</td>
</tr>
<tr>
<td>Single gene abnormalities</td>
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<tr>
<td>Autosomal recessive gene</td>
<td>Meckel syndrome (encephalocele)</td>
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<td>Robert's syndrome (encephalocele)</td>
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<tr>
<td><strong>Multifactorial</strong></td>
<td></td>
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<tr>
<td>Genetic and environmental</td>
<td>Anencephaly, meningocele, encephalocele</td>
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<tr>
<td><strong>Infections</strong></td>
<td></td>
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<tr>
<td>Rubella</td>
<td>Microcephaly, focal necrosis of brain areas</td>
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<tr>
<td>Cytomegalovirus</td>
<td>Necrosis and developmental failure</td>
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<tr>
<td>Toxoplasmosis</td>
<td>Necrosis and developmental failure</td>
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<tr>
<td><strong>Teratogens</strong></td>
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<tr>
<td>Thalidomide</td>
<td>Anencephaly and meningomyelocele</td>
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<tr>
<td>Aminopterin</td>
<td>Anencephaly and encephalocele</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agyria and pachygyria</td>
<td>Brain is smooth or has few gyri due to failure of migration of neuroblasts into developing brain</td>
</tr>
<tr>
<td>Heterotopia</td>
<td>Ectopic foci of grey matter due to premature arrest of migrating neuroblasts in developing brain</td>
</tr>
<tr>
<td>Holoprosencephaly</td>
<td>Single large ventricle with non-division of forebrain</td>
</tr>
<tr>
<td>Porencephaly and schizencephaly</td>
<td>Cystic cavities in the brain with gliosis following infarction caused by intrauterine vascular occlusion</td>
</tr>
<tr>
<td>Ulegyria</td>
<td>Gliotic shrunken gyri caused by hypoxic necrosis</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>Small brain with many causative factors</td>
</tr>
</tbody>
</table>

Meningioma
Compressing Frontal Lobe

Low-Grade Astrocytoma

Glioblastoma
With Necrosis & Hemorrhage

Glioblastoma Multiforme

# Genetic Changes in Brain Tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Genetic Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade astrocytoma</td>
<td>p53 mutation. Loss of alleles from chromosome 17</td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td>p53 mutation. Loss of alleles from chromosomes 17 and 19</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>p53 mutation. Loss of alleles from chromosomes 17, 19 and 10 EGF-R amplification</td>
</tr>
</tbody>
</table>

Oligodenroglioma

Ependymoma

Tubular structure
(like central canal of spinal cord)

Medulloblastoma

Primitive Neuroectodermal Tumor
PNET

Craniopharyngioma

Regeneration of Peripheral Nervous System

# Muscular Dystrophy

<table>
<thead>
<tr>
<th>Type of dystrophy</th>
<th>Inheritance</th>
<th>Muscle involved in initial stages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchenne type</td>
<td>X-linked recessive</td>
<td>Pelvic girdle</td>
</tr>
<tr>
<td>Becker type</td>
<td>X-linked recessive</td>
<td>Pelvic girdle</td>
</tr>
<tr>
<td>Limb girdle</td>
<td>Autosomal recessive</td>
<td>Pelvic girdle</td>
</tr>
<tr>
<td>Facioscapulohumeral</td>
<td>Dominant</td>
<td>Face, shoulder girdle, arm</td>
</tr>
<tr>
<td>Scapulohumeral</td>
<td>Autosomal recessive</td>
<td>Shoulder girdle and arm</td>
</tr>
<tr>
<td>Oculopharyngeal</td>
<td>Dominant</td>
<td>External ocular and pharynx</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>Dominant</td>
<td>Face, respiratory, limbs</td>
</tr>
</tbody>
</table>

Dystrophin = Brown Stain

Mitochondrial Myopathy
Trichrome Stain (Red = “Ragged Red Fibers”)

Mitochondrial Myopathy
Crystalline Inclusions in Mitochondria = “Parking Lot Inclusions”

Spinal Muscular Atrophy
Loss of Innervation = Small Fibers
