Neuropathology
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CME Financial Disclosure Statement
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Lecture Content

- What is normal?
- What is abnormal?
- Specific neuropathologic examples relevant to board exams

The Organization of Nervous System

- Central Nervous System (CNS)
  - Brain
  - Spinal Cord
- Peripheral Nervous System (PNS)
  - Nerves and nerve roots
  - Ganglia
Basic Neuroanatomy

Basic motor pathway
- motor cortex
- corticospinal tract
- lateral c.a. tract
- pyramids
- anterior c.a. tract

Basic sensory pathway (touch)
- cerebral peduncle
- optic tract
- lateral geniculate
- thalamus
- primary somatosensory cortex

Basic motor pathway

Basic sensory pathway (touch)

Courtesy: WUSM tutorial
Principal Cell Types of the Nervous System

- CNS:
  - Neuron
  - Astrocyte
  - Oligodendrocyte
  - Microglia
  - Ependymal

- PNS:
  - Neuron
  - Schwann cell

Basic Patterns of Reaction

- "Red neurons"—acute hypoxia
- "Gliosis"—astrocytic activation, indicative of non-specific injury
- "Microglial nodules"—indicative of infections (viral)
- "Rosenthal fibers"—indicative of non-specific injury, also seen in "Alexander’s disease" (GFAP mutations)
- "Neuronophagy" of anterior horn cells—polio
Cerebral Infarction

- Arterial
  - Regional distribution (MCA/ICA/brainstem etc)
  - General pathology (gross/microscopic)
  - Specific examples (lacunar, Binswanger’s)

- Venous
  - Usually secondary to infection
  - Specific examples (sagittal sinus, vein of Galen)

Regional Distribution

Most common sites:
- Internal carotid (with PCA)= 30%
- A-Comm= 30%
- MCA= 30%

Basic circulation of brain
**General Infarct Pathology (Gross)**

- Early hypoxic changes "laminar necrosis"
- "wedge shaped" infarct
- Lacunar infarcts associated with hypertension
- "Laminar" necrosis in hippocampus
- Old cystic changes following infarct

**General Infarct Pathology (Micro)**

- <4h: subtle changes
- 4-12 h: red neurons
- 24-72 hours: enter inflammatory cells

Courtesy: UCSF Neuropathology
General Infarct Pathology (Micro)

1-2 weeks: proliferation of inflammatory cells

3-4 weeks: reactive astrocytes

>3 months: cavity

Hemorrhage

- Epidural and subdural
- Subarachnoid
  - Vascular malformations
  - Berry aneurysms
  - Inflammatory/infective mycotic
- Intraparenchymal
  - Hypertensive
  - Amyloid
Epidural Vs. Subdural

- **Epidural**
  - Usually secondary to trauma (skull fracture)
  - Arterial, MM artery
- **Subdural hemorrhage**
  - Movement of brain inside skull, elderly
  - Rupture of bridging veins

General Hemorrhage Pathology (Gross)

- Epidural hemorrhage
- Subdural hemorrhage
- Subarachnoid hemorrhage
General Hemorrhage Pathology (Gross)

- “Lobar” hemorrhage - CAA
- Duret hemorrhages
- Vascular malformation

Trauma

- Intracranial hemorrhage (epidural, subdural, subarachnoid, parenchymal)
- Diffuse brain injury

- Contrecoup injuries
- Axonal accumulations

Gliding contusion, diffuse axonal injury
Herniation

- Tonsillar herniation
- Cingulate herniation
- Uncal herniation

Infections

- Bacterial
  - Meningitis (bacterial, fungal)
  - Abscess
- Protozoal/helminthic
  - Amoebic meningoencephalitis
  - Toxoplasmosis
  - Cysticercosis
- Viral
  - ADEM/AHL
  - PML
  - HIV
  - CMV
  - Rabies, polio

Inflammatory cells in meninges
Generic Pathologic Changes—Infection

Temporal lobe hemorrhages (herpes)

Brain abscess—gross

Microglial nodules—viral infections

CNS target of particular viruses

<table>
<thead>
<tr>
<th>CNS Target</th>
<th>Virus Description</th>
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<tbody>
<tr>
<td>Meninges</td>
<td>Mumps virus</td>
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<tr>
<td></td>
<td>Enteroviruses</td>
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<td></td>
<td>Coxsackieviruses</td>
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<td></td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>Motor neurons</td>
<td>Polioviruses</td>
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<tr>
<td></td>
<td>Enteroviruses</td>
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<tr>
<td>Neurons and glia</td>
<td>Herpes simplex virus (primarily temporal lobe)</td>
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<td></td>
<td>Rabies virus</td>
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<tr>
<td></td>
<td>Measles virus</td>
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<tr>
<td>Neurons, glia and endothelium</td>
<td>Cytomegalovirus (in immunocompromised subjects)</td>
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<tr>
<td>Oligodendroglia</td>
<td>Papovavirus (usually in immunocompromised subjects)</td>
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<tr>
<td>Microglia</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>Dorsal root ganglia</td>
<td>Herpes zoster–varicella</td>
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<tr>
<td>Fetal nervous system</td>
<td>Rubella</td>
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<tr>
<td></td>
<td>Cytomegalovirus</td>
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**Viral Infections**

- Progressive multifocal leukoencephalopathy
- HIV encephalitis
- Intranuclear inclusions with CMV virus
- Rabies virus neuropathology
- Myelin stain showing “punched out” demyelinated areas
- Intranuclear inclusions with JC virus
- Intranuclear inclusions with CMV virus
- “Neuronophagy” of anterior horn cells
- Intranuclear inclusions “Negri bodies”

**Non-Viral Infections**

- Radiologic features of toxoplasmosis
- Aspergillosis (note 90° branching)
- Neuropathology of toxoplasmosis (bradyzoites)
- Cryptococcosis
Demyelination/Dysmyelination

Gross—foci of periventricular demyelination in multiple sclerosis

Histology:
1. Accumulation of inflammatory cells (macrophages)
2. Loss of myelin with relative preservation of axons (d/d with infarction)
### Demyelination/Dysmyelination

<table>
<thead>
<tr>
<th>Patchy loss of myelin (myelin stain)</th>
<th>Preservation of axons—silver stain</th>
</tr>
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### Demyelination/Dysmyelination

<table>
<thead>
<tr>
<th>“Gaucher cells”—Gaucher’s disease</th>
<th>Accumulation of “Rosenthal fibers”—Alexander’s disease</th>
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</table>
Classification of Tumors of the Nervous System

- Histology
- Location
  - Intra vs. extra-parenchymal
  - Supra vs. infra-tentorial
- Patient age
  - Adult vs. pediatric

Pediatric Vs. Adult Brain Tumors

- Pediatric: about 70% posterior fossa:
  - Pilocytic astrocytoma
  - Medulloblastoma
  - Ependymoma

- Adult: about 70% supratentorial:
  - Metastatic carcinoma
  - Glioblastoma
  - Meningioma
Grading of CNS Tumors

- Grade I: discrete, well circumscribed, potentially amenable to complete surgical excision
- Grad II: low grade malignancy. Invades surrounding brain. Not amenable to complete surgical excision
- Grade III-IV: high grade malignancy. Invades surrounding brain and histologically anaplastic

Features Suggesting a Low Grade Tumor

- Long history of seizures
- Cyst with an enhancing mural nodule
Meningioma

- Meningothelia
- "whorls"
- Intranuclear inclusions

Pilocytic Astrocytoma

- Grade I
- Circumscribed, non-infiltrating
- Cyst with enhancing mural nodule
- Common location:
  - Cerebellum
  - Third ventricle
  - Optic nerve/tract

DDx of cyst with mural nodule:
- Pilocytic (child)
- Hemangiopericytoma (adult)
- Glioma
Pilocytic Astrocytoma

- Histology: bipolar astrocytes with delicate “hairlike” processes
- Loose microcystic spongy areas alternating with compact fiber-producing spindle cell areas
- Rosenthal fibers: eosinophilic intracytoplasmic inclusions

Fibrillary Astrocytoma—Grading

- Prognostically important histologic features:
  - Nuclear pleomorphism
  - Mitotic activity
  - Endothelial proliferation
  - Necrosis
- 1 feature—grade II
- 2 features—grade III
- 3 features—grade IV
Low Grade Fibrillary Astrocytoma

- WHO grade II
- Peak incidence 4th decade
- Life expectancy <10 years

Grade II Astrocytoma

- Neoplastic astrocytes diffusely infiltrating white or grey matter
- Increased cellularity, nuclear enlargement and hyperchromasia

Neoplastic Astrocytes  Neuron
Anaplastic Astrocytoma

- WHO Grade III
- Peak incidence 5th decade
- Life expectancy 2–3 years
- High cellularity
- Greater nuclear atypia
- Mitotic activity

Glioblastoma Multiforme

- Peak incidence 5th–6th decades
- Life expectancy <1 year
- Anaplastic astrocytoma with endothelial proliferation or necrosis
- Highly variable histologic appearance
- Multiple molecular pathways
Glioblastoma Multiforme
Ring Enhancing Lesion

The neuroimaging appearance of a hypodense center with an enhancing rim corresponds pathologically to central necrosis surrounded by proliferating tumor with endothelial proliferation.

Glioblastoma Multiforme
Endothelial Proliferation

- Abnormal vessels with endothelial cell hyperplasia lack a blood-brain barrier and are the histologic correlate of contrast enhancement in diffuse gliomas.
**Glioblastoma Multiforme**

**Pseudopalisading Necrosis**

- The presence of necrosis adjacent to densely cellular and actively proliferating tumor is characteristic of glioblastoma.

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**Pseudopalisading Necrosis Vs. Radiation Necrosis**

- **Pseudopalisading**
  - Note “geographic” necrosis
  - Lack of atypical cytology

- **Radiation-induced**
Glioblastoma Multiforme
Molecular Biology

- Secondary glioblastoma—arise from progression of low astrocytoma
  - TP53 mutation
  - Rare EGFR amplification

- Primary glioblastoma—no clinical or pathologic evidence for pre-existing low grade astrocytoma
  - EGFR amplification
  - LOH chr 10
  - Rare mutations of TP53

Other brain tumors

- Oligodendroglioma
- Medulloblastoma (“rosettes”)
- Ganglioglioma
- Craniopharyngioma—“picket fence” and “wet keratin”
- Rosenthal fibers
Neurofibroma Vs. Schwannoma

- Neurofibroma: Tau positive inclusions composed predominantly of PiD
- Schwannoma: Absence of tau positive inclusions

Neuropathological Examination of Frontotemporal Dementia Patients

- Tau positive inclusions - composed predominantly of:
  - Pick bodies 3R-tau
  - NFTs 3R/4R-tau
  - Neuronal/glia inclusions 4R-tau
  - Ubiquitinated TDP-43+ inclusions
  - Neurofilament inclusions
  - Absence of inclusions
  - Other

- Absence of tau positive inclusions

- LBD/FTLD: AD

- Other: AGD

General Principles of Neurodegenerative Diseases

- Selective vulnerability
- Reactive gliosis
- Protein aggregation that leads to specific intracellular inclusion bodies or extracellular deposits
- Familial forms, some with known genetic mutations

Alzheimer’s Disease

- Tangle - tau
- Plaque - amyloid
Pathological Hallmarks of AD

- Senile plaque
- Neurofibrillary tangle

Genes Associated with Alzheimer’s Disease

- Amyloid Precursor Protein (APP)
- Presenilin 1
- Presenilin 2
- Apolipoprotein E
Parkinson’s Disease

- Normal Pigmented Neuron
- Lewy Body of Parkinson Disease

Neuropathology in Other Neurodegenerative Diseases

- Tau positive inclusions in hippocampal dentate neurons
- Picks disease—frontotemporal dementias
- Huntington’s disease (caudate atrophy)
- Amyotrophic lateral sclerosis (CS tract degeneration)
Skeletal Muscle Diseases

- Normal muscle biopsy
  - Uniform, polygonal fibers, no central nuclei (~95%), delicate endomysial tissue, no adipocytes.
  - Roughly equal number of type 1 and type 2 muscles

Pathologic Changes in Muscle Fibers

- Variations in size and shape—angulated, hypercontracted
- Atrophy and hypertrophy
- Predominance or deficiency of a fiber-type
- Structural anomalies—nuclear, split fibers (hypertrophy), necrotizing change (myopathic process), basophilic fibers (regenerating), “target fibers” (neurogenic), inclusions, vacuoles, “ragged red” (mitochondrial), interstitial changes
Muscle Diseases (Neurogenic)

- Clustering of fiber-type (“grouping”) - Target fibers

Muscle Diseases (Myogenic)

- Inflammatory myopathies
  - Dermatomyositis
  - Polymyositis
  - Inclusion body myositis

- Genetic myopathies
  - Muscular dystrophy—Duchenne
  - Congenital myopathies—nemaline myopathy, central-core disease
  - Metabolic—mitochondrial, lipid, steroid, drugs
Dermatomyositis

1. Painful, proximal muscle weakness
2. Cutaneous signs: erythema, 15% associated with visceral cancers
3. High CK levels
4. “Marginal atrophy”- atrophy of perifascicular fibers
5. Ischemic “punched out” vacuoles and microinfarcts
6. SEPTAL inflammatory infiltrates, mixture of both B, T (CD4>CD8) and macrophages
7. No significant inflammation in non-necrotic fibers

Polymyositis

1. Symmetric, subacute/chronic presentation
2. No skin changes
3. High CK levels, EMG consistent with myositis
4. Endomysial inflammation surrounding fibers that may look only slightly abnormal (non-necrotic)
5. Predominantly T cells (CD8+) and large number of macrophages
6. No perifascicular atrophy, no other ischemic changes
Dermato Vs. Polymyositis

- Perifascicular atrophy, inflammation confined to septa vs endomysial, both B and T vs. T only, CD4>CD8 T cells, no lymphocytic infiltration in non-necrotic fibers

Inclusion Body Myositis

- Most common myopathy >50 yrs, M>F
- Insidious, painless, distal>proximal, CK normal or slightly elevated
- Pathology—“rimmed vacuoles”, mild inflammation, mild neurogenic-type atrophy
Genetic—Muscular Dystrophy

- Variability (hypertrophic+atrophic), rounded atrophic fibers, endomysial fibrosis, loss of dystrophin in Duchenne and Becker

Miscellaneous Myopathies

- Glycogen storage diseases
- "Ragged red" fibers—mitochondrial myopathies
- Drug reactions (eosinophilia)
- Nemaline rod myopathies
Neuropathy

Patient Complained: Neuropathy

History and examination compatible with neuropathy?

Yes

Mononeuropathy

EMG

Polyneuropathy

Evaluation of other disease or treatment and discharge from care

No

Mononeuropathy multiple

EMG

Demyelinating, with focal conduction block

Axonal

Subsystem course (months)

Chronic course (years)

Uniform slowing, conduction block

Axonal

Demyelinating

Test for paraneoplastic, if negative

For other studies (QGB)

Test for paraneoplastic, if negative

Focal slowing, conduction block

Normal Nerve

Ep

Pn

In the lesion surgical or decompression? Is entrapment or compression present? Is a contributing systemic disease present?

Bilateral neuropathy

Diagnosis needed for surgery (nerve repair, transplantation, or release procedure)

Possible nerve biopsy

Treatment appropriate for specific diagnosis

If test is negative, consider corticosteroid treatment.

Review family history; obtain family members

Possible: radiation-related and/or other treatment

If yes or paresthonesia; supportive care including sleep therapy assistance

Donate crying, if appropriate
Axonal Vs. Demyelinating

Axonal: degenerating and regenerating clusters, focal accumulations in teased preps, demyelination is present but is global, ie secondary to axonal damage. Examples: diabetes, neuroaxonal dystrophy, toxins

Demyelinating: Remember “onion bulbs” due to repeated bouts of degeneration and regeneration of myelin. Examples: CIDP, GB syndrome

“Vasculitis”

For pathologic diagnosis

- Inflammatory cells (lymphocytes and macrophages) surrounding and infiltrating vessel wall
- “Fibrinoid necrosis” of vessel wall
- Clinical context—very important!
Questions and Answers