OUTLINE

• Cellular components of the CNS
• Pathology of Neurons
• Pathology of Glia
• Microscopic appearance of common CNS disease processes
• Introduction to CNS development
Cellular components of the CNS

• Meninges
• Neurons
• Glia
  - Astrocytes
  - Oligodendroglia
  - Ependymal Cells
• Choroid Plexus
• Microglia
An Axial Section Of Human Cortex

Figure 5. Horizontal section of the brain showing the line of Gennari in the striate cortex. From Polyak (1957).
Neurons

- About $10^{11}$ neurons in the CNS
- Great variation in size and shape
- All have dendrites, soma and axon
- Generally have abundant cytoplasm and prominent nucleolus ("fried egg")
- Nissl substance composed of RER
- Can be organized in groups (nuclei, ganglia) or in layers
- Selective vulnerability of some types

Dendritic Tree

Neurons Drawn by Franz Nissl
1860-1919
Neurons

- Cerebellar granule neurons
- Cerebellar Purkinje Neurons
- Cerebral Cortical Neuron
Glia

- Astrocytes
- Oligodendroglia
- Ependymal Cells (Microglia)

Act as neuronal support system, react to injury, regulate metabolism
Glia - Oligodendrocytes

- Common in white matter
- Cytoplasmic processes of oligodendrocytes wrap around and insulate axons.
- Small, round, lymphocyte-like nuclei with dense chromatin
- Can have clear “halos” around cells
Glia - Astrocytes

- Branched cells found in both white and grey matter
- Astrocytic processes abut neurons, vessels, the pia and ependyma (glia limitans)
- Act as metabolic buffers, detoxifiers, suppliers of nutrients, and physical barriers

- Astrocytic nuclei are round to oval and slightly larger than those of oligodendrocytes
- Major cell in CNS repair

Neuropil = “nerve felt”
Ependyma

- Cuboidal to columnar cells lining the ventricular system
- Cilia/microvilli on apical surface
- Provide barrier between brain and CSF

- Thought to be involved in transport between the brain and CSF
Microglia

- Mesoderm-derived cells that act as a fixed macrophage/monocyte system in the brain
- Proliferate and migrate in response to infection/injury
- Phagocytic
- Act as CNS antigen-presenting cells
Microglia

Neuronophagia

Resting
Activated
Phagocytic
Choroid Plexus

- Specialized cells derived from the ependyma that secrete CSF
- Papillary fronds of cuboidal epithelium covering vascular cores
- Tight junctions maintain blood-CSF barrier
- About 20ml of CSF produced per hour
- Normal CSF volume is ~140ml
- ~25ml in ventricles, the rest in the subarachnoid space
Meninges

- Fibrous dura closely attached to inner skull periostium
- The leptomeninges (arachnoid and pia mater) are made up of meningothelial cells and connective tissue
- The thin, translucent arachnoid membrane drapes over the brain
- The delicate pia mater remains closely attached to the entire cortical surface, and invests arteries as they penetrate the brain
- CSF circulates in the “subarachnoid” space between the arachnoid and pia
CSF flows out of the sub-arachnoid space into the dural sinuses through the arachnoid granulations protruding into the sinuses.

Arachnoid Granulation

Arachnoid cap cells attached to the sinus endothelium

Pia

Artery

Arachnoid

Subarachnoid Space

Cortical Surface
The Black Stain “la reazione nera” formulated by Golgi in 1873

Fixation of CNS tissue in potassium bichromate with application of silver nitrate

Camillo Golgi (1843-1923), Pavia, Italy
Ramon y Cajal improved on Golgi’s silver stain, and developed a gold chloride-mercury stain for astrocytes.

Golgi and Ramon y Cajal shared the 1906 Nobel Prize for Medicine in recognition of their work on the structure of the nervous system.

Santiago Ramon y Cajal (1852-1934), Barcelona and Madrid, Spain
Special Stains In Neuropathology Today

Synaptophysin (Neuronal)

GFAP (Glial)
Commonly Used Special Stains

**Immunohistochemical Stains**
- Glia - GFAP (Glial Fibrillary Acidic Protein)
- Neurons - Synaptophysin, NeuN
- Proliferation – Ki67 (MIB-1)
- Microglia/Macrophages – CD68 (KP1), HAM56
- Lymphoid Cells – CLA, CD3 (T Cells), CD20 (B Cells)
- Infectious Agents – Toxoplasma, Adenovirus, JC Virus
- Inclusion Bodies – Ubiquitin, α-synuclein, Tau

**Other Stains**
- Myelin – Luxol Fast Blue
- Alzheimer Dz - Hirano Silver
- Fungi – Methenamine silver (GMS)
Johns Hopkins Department of Pathology

Patient: John Doe       Procedure Date: 1/1/2002

Part 1-3: Temporal Mass (Biopsy):

Frozen Section Diagnosis: Low grade neoplasm

Final Diagnosis: Ganglioglioma, WHO Grade I, See Comment

Comment: The tumor has a solid, non-infiltrating architecture, with no intra-tumoral axons detected using SM31 immunostains. Atypical neuronal and glial cells are present in the lesion, as evidenced by positive synaptophysin and GFAP immunostains. The MIB-1 proliferation index is low (1-2%)
Pathology of Neurons

- Apoptotic neuronal cell death
- Hypoxic/ischemic neuronal necrosis
- Neuronal loss in neurodegenerative disease
- Axonal pathologies
  - Axonal degeneration following neuronal death
  - Neuronal changes following axonal damage
- Neuronal Inclusions
Neuronal Apoptosis

- Plays a major role in pruning neurons during CNS development
- Often caused by withdrawal of trophic factors
- DNA fragmentation (karyorrhexis) and condensation into “apoptotic bodies”
- Commonly seen in brain tumors

Apoptosis in Neuroblastic Tumor

Fragmented Chromatin in Dorsal Root Ganglion Neuron
Heat, Toxic Agents, Hypoglycemia, Hypoxic/Ischemic Damage

- Neurons in Region CA1 (hippocampus), Cortical layers 3 & 5, and Purkinje Cells are especially vulnerable
- See eosinophilic (red) discoloration within approximately 12 Hours
- If ischemia is severe/prolonged glia also die, and the necrotic region is cleared away by macrophages
Axonal Degeneration Following Neuronal Loss

A LFB myelin stain and CD68 macrophage immunostain highlight the axonal degeneration in the crossed and uncrossed corticospinal tracts in Amyotrophic Lateral Sclerosis (ALS)
Neuronal Inclusions in Neurodegenerative Disease

**Cytoplasmic**
- Alzheimer’s – Neurofibrillary Tangles
- Parkinson’s - Lewy body
- Pick’s – Pick body

**Nuclear**
- Huntington’s

- [Image of Lewy Body]
- [Image of Ubiquitin + Inclusion]
- [Image of Huntington’s Dz]
- [Image of Parkinson’s Dz]
Pathology of Glia

Reactive Astrocytosis
A non-specific reaction to infection, seizures, autoimmune disease, infarction, etc

Fibrillary Gliosis
Proliferation of reactive astrocytes

Piloid Gliosis
Seen around spinal cord cavities (syrinx)
And other long-standing reactive gliosis
In cerebellum and hypothalamus. Also
In Alexander’s disease
Glial Nuclear Changes in Progressive Multifocal Leukoencephalopathy

JC Virus Immunostain

Infected Oligodendrocytes
Overview of CNS Pathology

This last section is intended to introduce you to the microscopic appearance of several common CNS diseases. More detailed examples and explanations will be provided in later lectures.

- Ischemic damage/stroke
- Infection – viral, bacterial, fungal
- Neurodegenerative disease
- Demyelinating disease
- Trauma
- Tumors
Infarction

Hours – Days: Neurons become eosinophilic and shrunken. Neutrophils infiltrate the lesion.

Days - Weeks: Neurons gone, macrophages infiltrate lesion. Reactive astrocytosis around edge.

Weeks – Months: Cystic cavity.

Old Cystic Infarction

Macrophages
Bacterial Infection

Meningitis  Abcess
Viral Infection

- Viral agents involving CNS include echo, coxsackie, herpes, mumps, measles adenovirus, polio, VZV, EBV, CMV, rabies, arboviruses, JC, HIV
- Can cause meningitis or encephalitis
- Often see perivascular and intraparenchymal lymphocytes
- Elongated microglial “rod” cells and microglial nodules also commonly present
Demyelinating Disease

- Myelin loss seen as region of pallor on LFB stain
- Demyelinated regions tend to have sharp borders
- Numerous macrophages and reactive astrocytes found in plaque

![Loss of myelin on HE/LFB stain](image)

MACROPHAGES
CNS Tumors

All of the cell types in the brain can give rise to tumors:

- Astrocytoma
- Oligodendroglioma
- Ependymoma
- Choroid Plexus Tumor
- Meningioma
- Neurocytoma
- Gangliocytoma
- Medulloblastoma (Embryonal)

Glial tumors are the most common malignant lesions.
Shifting Gears….
A very brief introduction to CNS development and imaging
It has long been thought that brain tumors resemble (and perhaps arise from) stem/precursor cells.

A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis. (1926)

Harvey Cushing
Cerebellar Anlage

VZ

Mesencephalon (midbrain)
Diencephalon
Fourth ventricle
Telencephalon
Eye

6 wk

Cerebellar Anlage
Figure 8. Patterns of neuronal proliferation in specific brain regions of mice. Illustration of overall mouse brain development showing critical windows of peak neuroepithelial cell proliferation (neurogenesis) within specific brain regions and nuclei throughout gestation. Figure reproduced from Rodier (1977) and reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.
Conventions & Terminology

Body Planes

- Horizontal plane
- Sagittal plane
- Coronal plane
Conventions & Terminology
Right-Left Confusion

As If From Front
Diagram

As If From Back
Pathology Specimen

As If From Front
MRI-CT-Radiograph
Conventions & Terminology

More Right-Left Confusion

Visual Field Pathways As If From Top Of Head

MRI As If From Bottom Of Feet
Brief Review of Neuroradiology
IMAGING:

MRI Brain with intraparenchymal hemorrhage from mycotic aneurysm

Elucidates...

1) pathoanatomy,
2) pathology,
3) pathophysiology
4) clinical risk
### Non contrast or plain imaging appearances

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<th>Scan</th>
<th>Uses</th>
<th>CSF</th>
<th>Lesion</th>
<th>Blood</th>
<th>Bone</th>
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<td>Rapid screen</td>
<td>Dark</td>
<td>Dark</td>
<td>White</td>
<td>White</td>
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<tr>
<td>T1 MRI</td>
<td>Anatomy</td>
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<td>Varies</td>
<td>Dark</td>
</tr>
</tbody>
</table>
CT is useful for...

- **Quick look**
  - Major mass effect with midline shift
  - (Obstructive) hydrocephalus

- **Blood**
  - E.g., Subarachnoid, Intraparenchymal

- **Bone**
  - Skull fractures
  - Bone erosion from infection

- **Bullets**
  - Bullets and other metal

- **Imaging vessels acutely**
  - CT Angiography (e.g. for acute stroke)

- **Imaging when the patient cannot get an MRI**
  - Pacemaker or other paramagnetic retained foreign body
  - Severe claustrophobia
  - None available
CT, Noncontrast (soft tissue window)

**CT:** skull is white

**Soft Tissue Window:** skull detail not visible, CSF black, gray vs. white matter discrimination fuzzy

**Noncontrast:** vessels are inapparent
CT, Noncontrast (bone window)

**CT**: skull is white

**Bone Window**: skull detail visible, soft tissues indiscernable (CSF, gray & white matter, vessels)
CT Subarachnoid Hemorrhage

Dilated temporal horn lateral ventricle

Bright BLOOD in the peri-mesencephalic SA spaces

Normal CT
Normal MRI T1 contrast @ lvl. of ear

Normal CT Bone Windows @ lvl. of ear

Note that MRI is useless for imaging bone rel. to CT
MRI is useful for...

- Anatomic detail
- Subtle or small pathology
  - including lesions without large mass effect (esp. white matter disease)
- Posterior fossa lesions
- Acute stroke (Diffusion Weighted Imaging [DWI])
- Imaging Vessels (MR angiogram or venogram [MRA/V])
MRI, T1, noncontrast

MRI: skull is black (scalp fat & bone marrow white)

TI: CSF black, & differentiation of gray vs. white matter good

Noncontrast: vessels inapparent
MRI, T1, Contrast

**MRI**: skull is black (scalp fat & bone marrow white)

**TI**: CSF black, & differentiation of gray vs. white matter good; gray matter darker than white matter

**Contrast**: vessels white
T1 Noncontrast

T1 Contrast

Note subtle appearance of contrast in blood vessels
MRI, T2, noncontrast

**MRI**: skull is black (scalp fat & bone marrow white)

**T2**: CSF white, & differentiation of gray vs. white matter fair; white matter darker than gray matter

*Non Contrast*: vessels inapparent (small black flow voids)
**MRI FLAIR** (fluid attenuated inversion recovery)

**MRI:** skull is black (scalp fat & bone marrow white)

**FLAIR:** CSF black, & differentiation of gray vs. white matter poor; white matter darker than gray matter

Essentially a T2 image with the CSF ‘averaged’ out
As a result, FLAIR images end up being more sensitive, but less specific.

Note that pathology ‘stands out’ when CSF is ‘averaged out’ of the image.