Outline

I. Cellular Pathology of the CNS
II. Cerebral Edema, Raised ICP, Herniation, and Hydrocephalus
III. Malformation and Developmental Disease
IV. Trauma
V. Cerebrovascular Disease
VI. Infections
VII. Demyelinating Diseases
VIII. Degenerative Diseases
IX. Tumors

Neurology
Dr. G. Missiona

Points To Consider

- Selective vulnerability
- Inability to regenerate neurons
- Localization of specific neurologic function to distinct group of neurons
- Physical restriction of skull and spine
- CSF and Blood brain barriers

Disease	Preferential
Huntington disease	Selective degeneration of neurons in the caudate nuclei
Parkinson Disease	Nigrostriatal system
Amyotrophic lateral sclerosis (ALS)	Upper and lower motor neurons of cerebrum, brainstem, and spinal cord
Poliomyelitis	Anterior horn cells of the spinal cord and the motor nuclei of the brainstem
Herpes simplex	Temporal lobes
Rabies	Medulla

Cellular Pathology of the CNS

Neuron	Astocytes	Oligodendria	Microglia	Ependyma
EXECUTIVE	PROVIDES ADEQUATE ENVIRONMENT			

Pathology of Neurons

- Acute Neuronal Injury (Red Neuron)
  - Hypoxic/ ischemic injury
  - Evident at about 12-24 hrs
  - Increased cytoplasmic eosinophilic nuclei
- Subacute and Chronic Neuronal Injury
  - Degeneration
  - Progressive disease processes that lead to neuronal loss or death
  - Characteristic histologic feature is cell loss
- Axonal Reaction
  - Axonal changes develop in response to a transaction of the axon
  - Reactions that attends to regeneration or axonal sprouting
  - Cellular swelling
  - Nissl bodies are partially dissolved
  - Eccentrically displaced nucleus
- Neuronal Inclusion
  - Manifestation of aging
  - Abnormal accumulated substance- metabolic disorders
  - Infections

Pathology of Astrocytes

- Gliosis
  - Most important indication of CNS injury
  - Astrocytes undergoes both hyperplasia and hypertrophy
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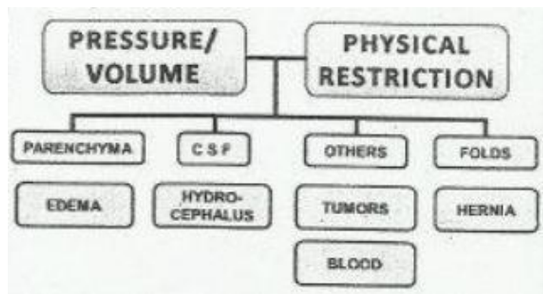
  - Astrocyes replace destroyed tissue by producing more fibrils and ultimately forming a dense fibrillary gliosis or glial scar
  - Gemistocytic astrocytes:
    - Expansion of the cytoplasm into a bright pink, irregular swath around the nucleus
    - Hematoxylin and eosin- stained reactive astrocytes are plump with pink cytoplasm (gemistocytic astrocytes)
  - Bergmann gliosis:
    - Proliferation of astrocytes replacing degenerated purkinje cells
- Cellular swelling
  - Results from an influx of fluid and electrolytes into the cytoplasm
  - Occurs in hypoxia, hypoglycaemia and toxic injuries
- Rosenthal fibers
  - These alterations in astrocytic processes appear as homogenous oval, round, elongated, or carrot-shaped eosinophilic structures
  - They are found in the walls of cystic cavities, fibrillary gliosis, astrocytictumors, and alexander's leukodystrophy
- Corpora amylacea
  - Degenerative products of astrocytic processes
  - Commonly occur beneath the pia matter, around the ventricles and blood vessles
  - They contain polyglucosans, are PAS positive and immunoreact for ubiquitin
  - Corpora amylacea are found in variable amounts in brain after the age of 40 to 45 years, and are particularly abundant in chronic degenerative diseases
  - Round basophilic and argyrophilic structures
- Inclusions
  - Usually seen in neurodegenerative diseases
  - Consist of protein α-synuclein, and oftentimes, Tau proteins

Viven

Cerebral Edema, Raised ICP, Herniation, and Hydrocephalus

Pressure/volume	Physical restriction
Fluid Parenchyma Others	Skull Vertebrae



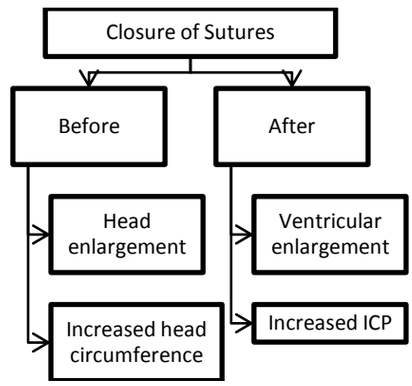
- **Raised Intracranial Pressure (ICP)**
  - Normal: 90-180 mmH_2O
  - When ICP exceeds 200 mmH_2O, clinical symptoms develop: headache, nausea, vomiting, altered mentation, visual impairment, and papilledema
  - When ICP reaches the level of systemic BP, the circulation ceases and death occurs
- **Cerebral Edema**
  - Abnormal accumulation of fluid in the brain parenchyma resulting in an increase in brain volume
  - Usually a complication of an underlying disease
  - Conditions that cause cerebral edema:
    - Expanding mass lesion
    - Ischemic or hemorrhagic stroke
    - Head injury
    - Infections
    - Ischemic-hypoxic injury
    - Metabolic
    - Toxins
    - Hypertensive encephalopathies
  - **Types of cerebral edema:**

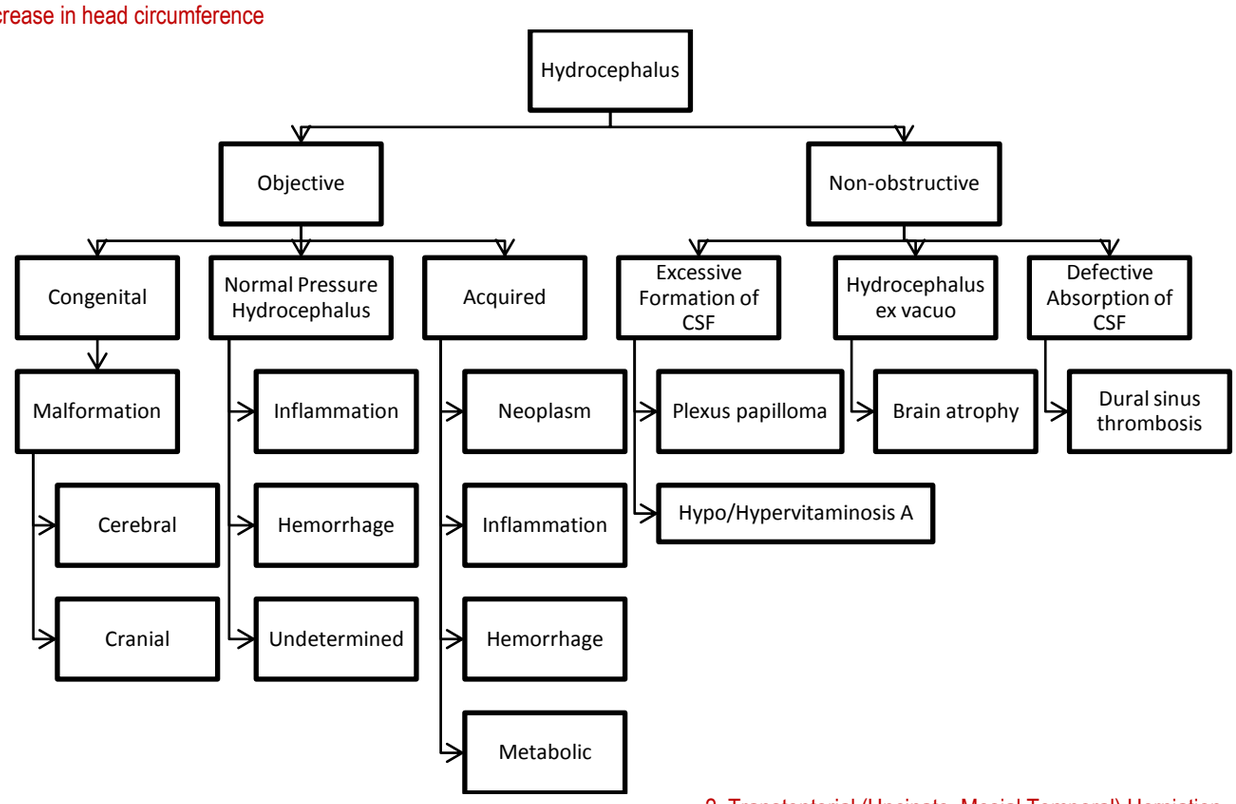
    1. Vasogenic
       - Injury to the vasculatures
       - Mechanisms:
         > Disruption of normal BBB
         > Increase vascular permeability to the mucrovessels
         > Product of vasoactive substanced
       - NET EFFECT: escape of fluid and protein into the inter cellular spaces of the brain
    2. Cytotoxic (cellular)

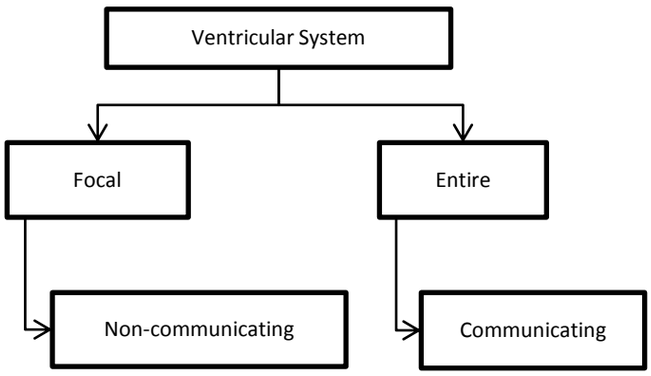
- Increase in intracellular fluid secondary to neuronal, glial, or endothelial cell membrane injury
- Encounter in generalized hypoxic/ischemic insult or in some intoxication

3. Interstitial (hydrocephalic)
   - Occurs especially around the lateral ventricles with increase intraventricular pressure
   - CSF cross the ependymal lining to the periventricular white matter

- **Hydrocephalus**
  - Denotes an excessive accumulation of the CSF that considerably enlarges the ventricles
  - Caused by impaired flow and resorption of CSF and rarely overproduction of CSF
  - When hydrocephalus develops before closure of the cranial sutures, there is an enlargement of the head, manifested by an increase in head circumference
  - If developed after fusion of sutures, it is associated with expansion of ventricles and increased in ICP







  - ***Hydrocephalus ex vacuo***
    - Refers to dilatation of the ventricular system with compensatory increase in CSF volume secondary to a loss of brain parenchyma

- **Herniation**
  - Because the cranial vault is subdivided by rigid dural folds, a focal expansion of the brain causes it to be displaced in relation to these partitions
  - **Types of Herniation:**

1. Subfalcine or Cingulate Herniation
   - Occurs when there is unilateral/asymmetric expansion of a cerebral hemisohere displaces the cingulated gyrus under the falxcerebri
   - Associated with compression of the branches of the anterior cerebral artery

2. Transtentorial (Uncinate, Mesial Temporal) Herniation
   - Occurs when the medial aspect of the temporal lobe is compressed against the free margin the the tentorium cerebella
   - The 3rd cranial nerve compression, resulting in papillary dilatation and impairment of acular movements on the side of the lesion
   - The posterior cerebral artery may also be compressed resulting in ischemic injury to the territory supplied by the vessel, including the visual cortex
   - Progression usually accompanies hemorrhagic lesions in the mid brain and pons termed as Duret or secondary brainstem hemorrhage
3. Tonsillar Herniation
   - Displacement of the cerebellar tonsils through the foramen magnum
   - Life-threatening pattern because it causes brain steam compression and comprises vital respiratory and cardiac centers in the medulla oblongata

Malformation & Developmental Disease

- Pathogenesis and etiology of CNS malformations are largely unknown
  - Genetic and environmental
  - Many toxic compounds and infectious agents
- Account for 75% of fetal deaths and 40% of deaths during the first year of life
- Anomalies reflect interruptions in the completion of critical developmental processes

- Congenital malformations are defined more by the time of the insult than by the nature of the injury itself.

Major Etiology of CNS Malformation

- Chromosomal aterations
- Genetic mutation
- Maternal diseases
  - Infection – Viral, CMV, Varicella
  - Ionizing radiation
  - Metabolic disease – DM, PKU
- Alcohol consumption
- Illicit substance abuse - Cocaine
- Teratogenic
  - Anticonvulsant
  - Warfarin
  - Retinoid
- Industrial chemical – methylmercury

Approximate Timing of Major Developmental Events

Major Events	Gestational Age
Development of neural plate	18 days
Development of neural tube	23 d
Closure of neural tube	23-26 d
Development of primary vesicle and cleavage of prosencephalon appears	4-8 weeks
Cerebellar primordium	4 w
Cerebellar development completed	24 w
Beginning of migration of neuroblast	4 w
Completion of migration	20 w
Corpus callosum develops	12 w
Opening of foramen Magendie	12 w
Opening of foramina Luschka	16 w
Sylvian fissure appears	14 w
Rolandic and calcarine fissure appears	24-26 w
Secondary and tertiary sulci appear	7-9 mos

CLASSIFICATION

- Neural tube defects (NTD)
- Forebrain anomalies
- Posterior fossa anomalies
- Syringomyelia and Hydromyelia

Neural tube defects (NTD)

- **Most common malformation of the CNS**
- Caused by a **failure of closure or by reopening of the neural tube**
- Combination of brain and spinal cord defects with their meninges

ANENCEPHALY

- Fa**ilure of closure of the anterior neuropore**
- **Failure of development of the brain and the calvarium**
- Incidence: 2-3 in 1000 livebirths
- **Brain is absent or rudimentary**; instead a friable red mass of tissue contains thin-walled vascular channels and neural elements (**area cerebrovasculosa**)

MENINGOENCEPHALOCOELE/MYELOMENINGOCOELE/ MENINGOCOELE

- Protrusion of the meninges and the portion of the brain/spinal cord through a congenital defect in the skull or vertebrae
- *Myelomeningocoele*occur **most commonly in the lumbrosacral region**
- *Meningocoele*are usually in the occiput

SPINA BIFIDA and SPINA BIFIDA OCCULTA

- **Failure of closure of the posterior neuropore**
- Less severe form, such as *Spina bifida occulta,* are the result of failure of secondary neuralation and failure of tail bud formation
- Fatty tissue may be present under the skin or in the extra- or intradural spaces
- Early Dx is possible using UTZ and screening of maternal blood samples for elevation of α-fetoprotein
- Risk factors include maternal folate deficiency
  - Folate deficiency may affect cell division during critical periods that coincide with the closure of the neural tube

Disorder of Forebrain Development

- Prosencephalon cleaves into two telecephalic vesicles – develop into 2 cerebral hemisphere and 2 lateral ventricles
- Failure of this cleavage results in *Holoprosencephaly*

HOLOSENCEPHALY

- **Malformation resulting to a cerebrum that is undivided into hemispheres and has a single ventricular cavity**
- Incidence: 1 in 30,000 livebirths
- Most cases are sporadic, but familial forms also occur
- Risk factors: certain maternal and environmental factors (e.g. maternal diabetes mellitus, fetal alcohol syndrome, congenital infections), trisomy 13, and mutations in the *ZIC2* gene in 13q. Other causes of holosencephaly have been mapped to several additional genetic loci
- Morphology (3 types:
  - **Alobarholosencephaly**
    - *Brain has no hemispheric development*
    - A rudimentary forebrain overlies a common ventricular cavity. The straight gyri, olfactory structures, and commissural structures (e.g. corpus callosum) are absent
    - There are also severe facial abnormalities (e.g. cyclopia)
  - **Semilobarholosencephaly**
    - *Some development of an interhemispheric fissure;* straight gyri, olfactory structures, and corpus callosum usually are still absent
  - **Lobar holosencephaly**
    - *Interhemispheric fissure is present*, and individual lobes are indistinguishable; however, there is some continuity of the cerebral cortex in the midline and aplasia or dysplasia of the corpus callosum
- Most infants are stillborn or die in early infancy
- Those who survive a few years suffer profound psychomotor retardation, intractable seizures, apneic episodes, temperature irregularities, and diabetes insipidus
- Antenatal Dx is possible using UTZ

LISSENCEPHALY (Agyria)

- **Decrease in the number of gyri to total absence**, leaving a smooth-surfaced brain
- Occurs sporadically or is inherited as an autosomal dominant, autosomal recessive, or X-linked trait
- Mutations in four different genes have been identified:
  - *LIS1* – chr. 17
  - *XLIS* – X22.3-23 associated with male occurrence
  - *RELN* associated with recessive inheritance and cerebellar hypoplasia
  - *ARX* – chr. X
- Accompanied by cortical dysplasia
- Secondary to disorders of neuronal migration and organization
- Common clinical manifestation: Seizures, often intractable, mental retardation and motor deficits of variable severity

POLYMICROGYRIA

- Characterized by **small, unusually numerous, and irregularly formed cerebral convolutions**
- The gray matter is composed of four layers (or fewer) with entrapment of apparent meningeal tissue at points of fusion that would otherwise be the cortical surface
- Can be induced by localized tissue injury toward the end of neuronal migration although genetically determined forms, which are typically bilateral and symmetric, are also recognized

NEURONAL HETEROTROPIA

- Group of migrational disorders that are commonly associated with epilepsy
- They consist of **collections of neurons in inappropriate locations along the migrational pathways**
- **Most commonly located along the ventricular surface**
- Caused by mutations in the gene encoding filamin A, an actin-binding protein responsible for assembly of complex meshworks of filaments
- Consist of discrete nodules of neurons sitting in the subcortical white matter or complete ribbons that parody the overlying cortex

AGENESIS OF CORPUS CALLOSUM

- There is an **absence of white matter bundles** that carry cortical projections from one hemisphere to the other
- Radiologic imaging studies show misshapen lateral ventricles (**"bat-wing" deformity**); on coronal whole-mount sections of the brain, bundles of anteroposteriorly oriented white matter can be demonstrated
- Agenesis of the corpus callosum can be associated with mental retardation or may occur in clinically normal individuals
- It can be present in isolation or can be associated with a wide range of other malformation
- Unlike patients with surgical callosal section, who show clinical evidence of hemispheric disconnection, individuals with this malformation can have minimal deficit

Posterior Fossa Anomalies

DANDY-WALKER MALFORMATION

- Characterized by an **enlarged posterior fossa**
- The cerebral vermis is absent or present only in rudimentary form
- In its place is a large midline cysts that is lined by ependyma
- This cyst represents the expanded, roofless fourth ventricle in the absence of a normally formed vermis
- Dysplasias of brainstem nuclei are commonly found in association with *Dandy-Walker malformation*

ARNOLD-CHIARI MALFORMATION

- Consists of a **small posterior fossa**, a misshapen midline cerebellum with downward extension of vermis through the foramen magnum and almost invariably, hydrocephalus and a lumbar myelomeningocoele
- Other associated changes may include caudal displacement of the medulla, malformation of the tectum, aqueductal stenosis, cerebral heterotropias, and hydromyelia
- In the *Chiari malformation*, low-lying cerebellar tonsils extend down into the vertebral canal
- In contrast to the significant clinical consequences of the preceding two malformations, this may be a silent abnormality or may cause symptoms referable to obstruction of CSF flow and medullary compression; if present, these symptoms can usually be corrected by neurosurgical intervention.

Syringomyelia and Hydromyelia

- Characterized by a discrimination multisegmental or confluent expansion of the ependyma-lined central canal of the cord (***hydromyelia***) or by the formation of a fluid-filled cleftlike cavity in the inner portion of the cord (***syringomyelia***, syrinx) that may extend into the brainstem (syringobulbia)
- *Syringomyelia*may be associated with the *Chiari I malformation;* it may also occur in association with intraspinaltumors or following traumatic injury
- In general, the histiologic appearance is similar in all these conditions, with destruction of the adjacent gray and white matter, surrounded by a dense feltwork of reactive gliosis
- S/Sx of a syrinx are the **isolated loss of pain and temperature sensation in the upper extremities** because of the predilection for early involvement of the crossing anterior spinal commissural fibers of the spinal cord.

TRAUMATIC BRAIN INJURY

- Factors:
  - The anatomic location of the lesion
  - Limited capacity of the brain for functional repair
  - Shape of the object
  - Force of impact
  - Whether the head is in motion
- The physical forces associated with traumatic brain injury (TBI)
  - Skull fracture
  - Parenchymal injury
  - Vascular injury
- Severe brain damage can occur in the absence of external signs of head injury
- Severe lacerations and skull fractures do not necessarily indicate damage to the underlying brain
- A blow in the head may be **penetrating** or **blunt**; it may cause either an **open** or **closed** injury

Skull Fracture

- The kinetic energy that causes a fracture is dissipated at the fused structure; fracture that cross sutures are termed **diastatic**
- A fracture in which bone is displaced into the cranial cavity by a distance greater than the thickness of the bone is called a **displaced skull fracture**
- When a individual falls while **awake,** the site of impact is often the **occipital bone**
- In contrast, a fall that follows **loss of consciousness**, commonly result in **frontal impact**

Parenchymal Injury

CONCUSSION

- Clinical syndrome of alteration of consciousness 2ndary to head injury typically brought about by a **change in the momentum of the head** (movement of the head arrested by a rigid surface)
- Attributed to a transient biochemical dysfunction of the neurons that causes no structural alteration
- The characteristic neurologic picture includes instantaneous onset of transient neurologic dysfunction, including loss of consciousness, temporary respiratory arrest, and loss of reflexes

DIRECT PARENCHYMAL INJURY

- ***Contusion* and *Laceration***
  - either through transmission of kinetic energy to the brain and bruising or by penetration of an object and tearing tissue
  - lead to rapid tissue displacement, disruption of vascular channels and subsequent hemorrhage, tissue injury, and edema
  - the **crests of gyri are most susceptible**, whereas the cerebral cortex along the sulci is less venerable
  - the most common location correspond to the most frequent sites of direct impact and to regions of the brain that overlie a rough and irregular inner skull surface such as the frontal lobes along the orbital gyri, and temporal lobe
- a patient who may suffer a blow to the head may develop a cerebral injury at the point of contact (**coup injury**) or damage to the brain surface diametrically opposite to it (**contrecoup injury**)
- in general, if the head is immobile at the time of trauma, only a coup injury is found
- when the head is mobile, there may be a coup lesions beneath the site of impact and also a contrecoup lesion
- ***Coup lesions*** are caused by the force of the direct impact between the brain and skull **at the site of impact**
- ***Contrecoup lesions*** develop when the brain strikes the **opposite inner surface** of the skull after sudden deceleration

DIRECT AXONAL INJURY

- Microscopic findings include axonal swelling indicative of diffuse axonal injury and local hemorrhagic areas
- In a few cases, the axonal injuries are grossly identified as minute haemorrhages in the dorsal aspect of the corpus callosum and fornices and the lateral aspect of the rostral brainstem
- They appear as eosinophilic and argyrophilic balls (**blobs**) of axoplasm extruded from the sheared ends of axons
- In chronic stages, microglial clusters indicate the sites of axonal injuries

Traumatic Vascular Injury

- Results from direct trauma and disruption of the vessel wall leading to **hemorrhage**
- Occur in any of several compartments:
  - Epidural
  - Subdural
  - Subarachnoid
  - Intraparenchymal

EPIDURAL HEMATOMA

- Vessels that courses within the epidural, **middle meningeal artery**, are vulnerable to injury and skull fracture
- Once a vessel has been torn, the accumulation of blood under arterial pressure can cause separation of the dura from the inner surface of the skull
- Being an arterial bleed, it has rapidly progressing course
- Brain edema, ↑ICP, and cerebral herniations rapidly develop
- If the blood is not evacuated, mortality is 10%

SUBDURAL HEMATOMA

- The space beneath the inner surface of the dura mater and the outer arachnoid layer
- **Bridging veins** travel the surface of the convexities of the cerebral hemispheres through the subarachnoid space
- The most commonly accepted mechanism of damage postulates that the brain, floating freely in its bath of CSF, can move within the skull, but the venous sinuses are fixed
- The displacement of the brain that occurs in trauma can tear the veins at the point where they penetrate the dura
- In elderly px with brain atrophy, the bridging veins are stretched out and the brain has additional space for movement, hence the increase rate of subdural hematoma, even in minor trauma
- Infants are also prone to subdural hematomas because their bridging veins are thin-walled
- Acute subdural hematoma appears as a collection of freshly clotted blood along the contour of the brain surface without extension into the depth of the sulci
- The underlying brain is flattened and the subarachnoid space is often clear
- Typically, venous bleeding is self-limited; breakdown and organization of the hematoma take place in time

Cardiovascular Disease

- 3rd leading cause of death
  - Most prevalent neurologic disorder in terms of both morbidity and mortality
- The term denotes any abnormality in the brain caused by a pathologic process of blood vessels
- It results from an alteration of cerebral blood flow in an arterial territory.
- **Stroke**
  - Presents with a sudden onset and rapid progression of focal neurologic symptoms and signs.
  - A clinical designation that applies to all these conditions, particularly when symptoms begin acutely.
- **3 major categories of CVD:**
  - Thrombosis
  - Embolism
  - Hemorrhage
- **Pathophysiologic standpoint:**
  - Hypoxia, ischemia and infarction resulting in impairment of blood supply and oxygenation of CNS tissue
  - Hemorrhage resulting from rupture of CNS vessel

Hypoxia, Ischemia and Infarction

- The brain is highly aerobic tissue requiring constant supply of blood glucose.
- Receives 15% of the resulting cardiac output
- Reduction of cerebral blood flow -> ischemia (neurologic deficits)-> infarction/ ischemic infarction
- **Mechanism of oxygen deprivation:**
  - **Functional hypoxia**: impaired oxygen carrying capacity of blood or inhibition of oxygen used by the tissue.
  - **Ischemia** (transient or permanent): interruption of the normal circulatory flow.
- **Two principal types of acute ischemic injury:**
  - **Global cerebral ischemia**
    - Occurs when there is generalized reduction of cerebral perfusion, such as in cardiac arrest, shock and severe hypotension.
  - **Focal cerebral ischemia**
    - Reduction or cessation of blood flow to a localized area of the brain due to large vessel disease or small vessel disease

Global Cerebral Ischemia

- Clinical outcome of severe hypotensive episode
- Transient episodes can result in reversible or irreversible CNS damage.
- Neurons are the most sensitive to ischemia
  - **Selective vulnerability**- "susceptibility of neurons in different regions of the CNS varies"
  - **Areas most susceptible to global ischemia**
    - Pyramidal cells of the Sommer sector (CA1) of the Hippocampus
    - Purkinje cells of the Cerebellum
    - Pyramidal Neurons in the Neocortex
- **Morphology**:
  - **Early changes** (12-24 hours)
    - Acute neuronal cell changes (red neurons)
    - PMN infiltration
  - **Subacute changes** (24 hrs-2 weeks)
    - Necrosis of tissues, influx of macrophages, vascular proliferation and reactive gliosis
  - **Repair** (> 2 weeks)
    - Eventual removal of all necrotic tissue, loss of normally organized CNS structure and gliosis
    - In the cerebral cortex, the neuronal loss and gliosis produce an uneven destruction of the neurocortex with preservation of some layers and involvement of others- **pseudolaminar necrosis**
- **Border Zone (Watershed) Infarcts**
  - Occur in the regions of the brain and spinal cord that lie at the most distal fields of arterial irrigation, i.e., *between the terminal branches of adjacent major arteries*
  - At greater risk is the border zone between the **Anterior and the Middle Cerebral arteries**

Infarction from Obstruction of Local Blood Supply (Focal Ischemia)

- Cerebral blood flow occlusion
- *The size, location, and shape of the infarct and the extent of tissue damage are determined by several factors, the most important being* ***adequacy of collateral flow***
- Circle of Willis
  - The major source of collateral flow
  - Reinforcement over the surface of the brain
  - *In contrast there is little collateral flow for the deep penetrating vessels,* ***thalamus, basal ganglia and deep white matter***
- Thrombosis vs Embolization

	THROMBOSIS	EMBOLIZATION
SOURCE	- Atherosclerosis	- Cardiac mural thrombi - Atherosclerosis of major arteries (carotid artery)
SITE	- Carotid bifurcation - MCA - Basilar artery	- MCA
PATHOLOGY	- Evolution of arterial stenosis - Fragmentation and distal embolization	- Lodgement where blood vessels branch or in areas of pre-existing luminal stenosis
PREDISPOSING CONDITIONS	- DM - HPN	- MI - Valvulardse - Atrial fibrillation

- **Assessment of arterial infarcts**

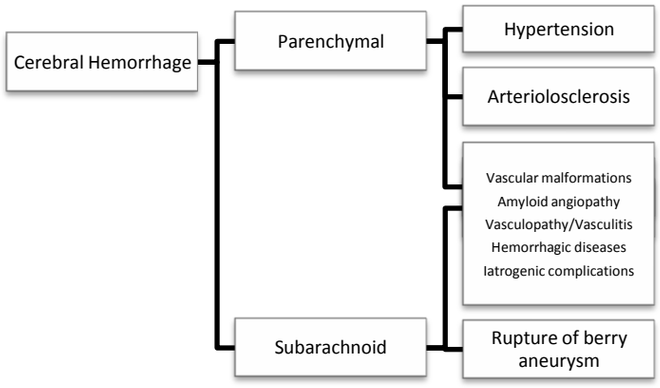
Type	Pale Hemorrhagic
Arterial Territory	Carotid Vertebrobasilar
Size	Large- macrovessels Lacune - microvessels
Age	Acute- ischemic necrosis Subacute-liquefaction Chronic- cavitation

- **Morphology:**
  - **Hemorrhagic (red) infarction**
    - Multiple, sometimes confluent petechial hemorrhages
    - Associated with embolic events
    - Hemorrhage is presumed to be secondary to reperfusion of damage vessels and tissue
  - **Nonhemorrhagic (pale, bland, anemic) infarct**
    - Usually associated with thrombosis

Approximate Timetable of Histologic Events of Ischemic Necrosis	
EVENT	**TIME**
Tissue Necrosis	
Neuron/Glial Cells	1 hour
Myelin/Axon	3 – 4 days
Edema	
Cytotoxic	3 hours
Vasogenic	72 hours
Inflammation	26 – 72 hours
Macrophage Invasion	48 – 72 hours
Capillary Proliferation	48 hours
Marginal Astrocytosis	48 hours – days

  - **Inflammatory reaction (~ first 24 hours)**
    - Tissue invasion of neutrophils
    - This inflammatory reaction, mediated by cytokines, produce toxic substances and microcirculatory obstruction
  - **Macrophage activation (~ 3rd day)**
    - Predominant WBC are macrophages
    - Phagocytosis and removal of tissue debris
    - Gradually, the infracted tissue is transformed into a cystic cavity, the lumen of which is traversed by a fine fibrous meshwork derived from surviving capillaries
  - **Marginal astrocytic proliferation**
    - At the margin of the ischemic tissue, the astrocytes proliferate into large **gemistocytic astrocyte,** forming a transition zone between the infarct and the healthy tissue.
- **Clinical Features:**
  - The area of the brain affected determines whether the patient remains asymptomatic or develops a hemiplagia, sensory deficits, blindness, aphasia or some other deficits.

Intracranial Hemorrhage



Intracerebral (Intraparenchymal)

- Hypertension is the most common underlying cause.
- Most commonly affected area is the **basal ganglia**
- Hypertension causes weaker vessels due to
  - Accelerated atherosclerosis
  - Hyaline arteriolosclerosis
  - Proliferative changes
  - Frank necrosis
- In some cases, chronic hypertension causes minute aneurysms – **Charcot Bouchard microaneurysms**

Subarachnoid Hemorrhage and Ruptured Berry (Saccular) Aneurysms

- Most frequent cause of clinically significant subarachnoid hemorrhage
- About 90% occurs in the anterior circulation and are found near major arterial branch
- Etiology is unknown genetic factor maybe important in their pathogenesis
- Smoking and hypertension are also predisposing factors
- They are not present at birth but develop over time owing to underlying defect in the media of the vessels
- **Morphology:**
  - A thin wall outpouching at an arterial branch point along the circle of Willis or a major vessel beyond
  - Measures a few millimeters to a 2-3 cm in diameters and have a bright red, shiny surface and thin, translucent wall
  - Muscular wall and elastic lamina stop at the neck and are absent in the aneurysm sac itself
  - The sac is made up of **thickened hyalinized intima**
  - The adventitia covering the sac is continuous with that of the parent artery
- Rupture of aneurismal sac is most frequent in the 5th decade and is slightly more frequent in females
- Probability of rupture increases with size
- Aneurysms >10 mm in diameter have a roughly 50% risk of bleeding per year
- Blood under arterial pressure is forced into the subarachnoid space and patients are stricken with a sudden, excruciating headache- "the worst headache I've ever had" and rapidly lose consciousness
- 25-50% die with the first rupture
- **Rebleeding** is common, and with each episode of bleeding, prognosis get worst
- **Vascular malformations**
  - **Four principal groups:**
    - Arteriovenous (AV) malformation – most common type
      - **Middle cerebral artery**- most common site
      - Resemble tangled network of wormlike vascular channels
      - Composed of greatly enlarged blood vessels separated by gliotic tissues often with evidence of prior hemorrhage
    - Cavernous angiomas
    - Capillary telangiectasia
    - Venous angiomas
  - Presents as seizure, intracerebralhemorrhage, or subarachnoid haemorrhage

Hypertensive CVD

- **Most important effects of hypertension:**
  - Intracerebralhemorrhage
  - Lacunar infarcts and slit hemorrhages
  - Hypertensive Encephalopathy
- **Atherosclerosis and DM** are frequently associated diseases
- **Lacunar infarcts**
  - HPN affects the deep penetrating arteries/arterioles that supply the **basal ganglia** and hemispheric white matter as well as the midbrain
  - The cerebral vessels develop arteriolar sclerosis and may become occluded
  - Leads to the development of single or multiple, small, cavitary infarcts- lacunes or lacunar state
  - **Lake-like spaces**, <15 mm wide, which occur in the lenticular nucleus, thalamus, internal capsule, deep white matter, caudate nucleus and pons, (in descending order of frequency)
  - Consist of cavities of tissue loss with scattered fat-laden macrophages and surrounding gliosis
- **Slit hemorrhages**
  - HPN can rupture the small-caliber penetrating vessels and cause the development of small hemorrhages
  - In time, these hemorrhages resorb, leaving behind a slit-like cavity (slit hemorrhage) surrounded by brownish discoloration
- **Hypertensive Encephalopathy**
  - A clinicopathologic syndrome arising in a hypertensive patient characterized by diffuse cerebral dysfunction, including headaches, confusion, vomiting and convulsions, sometimes leading to coma.
  - Accompanied by cerebral edema with or without herniation

- Rapid therapeutic intervention as the syndrome does not remit spontaneously
- Petechiae and fibrinoid necrosis of arterioles in the gray and white matter may be seen

CNS Infections

- **Overview**
  - Meningitis
  - Brain abcess
  - Encephalitis
- **Routes of infection**
  - Hematogenous
  - Direct implantation
  - Local extension
  - Spread along the PNS
- Some microorganisms are detedted in histologic sections stained with hematoxylin-eosin (HE), but most are visualized using special stains
- Other microorganisms are identified only in tissue cultures or by techniques based on PCR or using immunologic stains

Meningitis

- Inflammation of the leptomeninges and subarachnoid space
- Remains localized and does not involve the cerebral parenchyma
- Types and causes:
  - Acute purulent (pyogenic) meningitis
    - Usually bacterial in origin
  - Acute lymphocytic (aseptic) meningitis
    - Viral in origin, commonly echovirus, coxsackie, mumps, or HIV
  - Chronic meningitis (bacterial or fungal)
    - Causes include TB, Cryptococcus, or dimorphic fungi
  - Chemical meningitis
    - Causes include an irritating parameningeal process such as a tumor or abcess, or a foreign substance such as air, or medications
- Complications
  - Bacterial meningitis: scarring with resultant hydrocephalus, mental retardation, seizures, or focal cranial nerve deficits
  - Viral meningitis: usually resolves with no complications, unless accompanied by encephalitis
- In children, *H. influenza* was at one time the most common cause of bacterial meningitis
- Causative organisms of meningitis by age group:
  - Neonates – E. coli, group B strep, Listeria monocytogenes
  - Children, young adults – Streptococcus pneumonia, H. influenza
  - Epidemics in young adults in crowded living vonditions (college dorms, military barracks) – N. meningitides
- **Gross morphology**
  - **Acute bacterial meningitis**
    - **S. pneumonia –** purulent exudates on the cerebral convexities
    - **H. influenza** – classically associated with basal exudates
    - **N. meningitides –** infection is often associated with a cutaneous petechial rash and haemorrhage into the adrenal glands **(Waterhouse-Freidrichsen Syndrome)**
  - **Tuberculous meningitis** – classically associated with a thick basilar exudates
  - **Cryptococcal meningitis –** gelatinous slick material in leptomeninges; usually no associated exudates
  - **Acute lymphocytic meningitis –** parenchyma may be edematous; leptomeninges are usually clear
- **Microscopic morphology**
  - **Bacterial –** neutrophilic infiltrates
  - **Mycobacterial –** granulomas and giant cells
  - **Cryptococcal meningitis**
    - Numerous budding yeasts with little inflammation
    - Mucicarmine stain is used to identify organisms in tissue sections and India Ink in CSF smears
  - **Viral –** lymphocytic infiltrates, many organisms have associated parenchymal inflammation (encephalitis)
- **Signs of meningitis:**
  - **Brudzinski sign –** passive flexion of the neck results in reflex flexion of one or both knees
  - **Kernig sign –** neck pain with knee extension while the hip is flexed.
- **Laboratory analysis of CSF for infectious meningitis**

Type	CSF Pressure	WBC Count	Protein	Glucose
Bacterial	200 - 500	100 – 10000	50 – 5000	Absent, or greatly decreased
Tuberculosis	200 – 500	10 – 500	50 – 500	< 40
Viral	200 – 500	10 – 500	45 – 200	Normal
Normal CSF	50 - 200	0 - 10	< 45	50 - 80

Brain Abscess

- **Causes**
  - **Hematogenous dissemination**
    - Bacterial endocarditis
    - Organisms: Staphylococcus, streptococcus
    - Locations: Frontal lobe, more commonly than parietal lobe
  - **Local extension**
    - From sinusitis, otitis media
  - **Implantation**
- **Clinical Presentation**
  - Signs and symptoms due to local destructive effects: hemiparesis, aphasia, personality changes, seizures, ataxia, and visual disturbances
  - Signs and symptoms due to mass effect causing increased ICP: headache, nausea and vomiting, papilledema, and CN palsies
- **Diagnosis**
  - A CT scan or MRI will reveal ring enhancing mass, which is characteristic of an abscess
  - Brain biopsy will rule out a neoplasm.

Enchephalitis

- **Inflammation of the cerebral parenchyma, which is often viral in origin, including arboviruses, HSV, CMV, and HIV**
- **HSV-1 encephalitis**
  - **Epidem:** children and young adults; most common cause of sporadic encephalitis in adults in the US
  - **Symptoms:** alteration in mood, memory, and behaviour related to temporal lobe involvement
- **HSV-2 encephalitis**
  - May cause meningitis in adults or a more generalized encephalitis; most common cause of encephalitis in neonates
- **HIV encephalitis –** occurs in HIV-infected individuals, usually in the later stages of HIV infection
- **CMV encephalitis –** occurs in the fetus and in immunosuppressed patients
- **Rabies encephalitis**
  - **Epidem:** most commonly follows a bite from an infected animal
  - **Symptoms:** parasthesias at the site of the bite; hypersalivation and hydrophobia, CNS hyperexcitability→ RESPIRATORY FAILURE
- **Microscopic morphology:** (3 non-specific features)
  - **Microglial nodules**
  - **Lymphocytic cuffling of vessels**
  - **Neuronophagia –** engulfment/destruction of neurons by inflammatory cells
- **Specific Microscopic Features For Certain Pathogens**
  - **HSV:** intranuclear inclusions; usually involves inferior and medial temporal lobes and orbital gyri
  - **HIV:** multinucleated giant cells
  - **CMV:** intranuclear ("owl's eye") inclusions; may also have intracytoplasmic inclusions. CMV may involve ependyma and subependymal white matter, causing hemorhhagic necrotizing ventriculo-encephalitis and choroid plexitis
  - **Rabies:** round to oval eosinophilic inclusions (i.e. Negri bodies) in pyramidal neurons of the hippocampus and Purkinje cells of the cerebellum. "Bullet-shaped" virion seen on electron microscopy

Demyelinating Diseases

- Myelin Loss: loss of the transmission of electrical impulses along the axons

- Preferential damage to the oligodendroglia or the myelin sheath itself.
- Limited capacity of the CNS to regenerate normal myelin and the degree of secondary damage to axons as the disease run its course

Multiple Sclerosis

- The most common demyelinating disorder
- Affecting chiefly individuals between 20 and 40 years of age; it rarely occurs earlier or later in life
- **Autoimmune Disorder**
  - There is presence of CD4+ TH1+ T cells in lesions, which are reactive against myelin basic protein
  - Environmental and hereditary factors→play a role
- **Pathologic Hallmark:**multiple focal areas of demyelination called PLAQUES(typically occur within the white matter)
  - Histologically, 3 basic processes characterize plaque formation: **I**nflammation, **M**yelin Breakdown, and **A**stryocytic Fibrillary Gliosis **(MIA)**
  - Inflammation occurs with vasogenic edema and perivascular infiltrations with lymphocytes chiefly T cells
  - Myelin breaks down into neutral lipid globules, are phagocystosed by macrophages and gradually removed to the perivascular and subarachnoid spaces
  - Astrocytes proliferation, becoming plump with homogenouseosinophilic cytoplasm and numerous fibrillary processes
  - The astrocytes produce more fibers and, ultimately, forming a denseand firm fibrillary gliosis (glial scar) filling the demyelinated plaque (astrocytic fibrillary gliosis)
  - 3 Types of Plaque:
    - **Inactive (burnt-out) chronic plaque:** consists of a dense astrofibrosis with a reduced number of astrocytic nuclei, sparse or absent oligodendrocytes and variably damaged nerve fibers
    - **Active chronic plaque:** shows marginal perivascular lymphocyte cuffings, ongoing myelin destruction macrophages and a variable number of oligodendrocytes
    - **Shadow or remyelinating plaque:** shows reduced myeline density, thin and faintly showing myelin sheaths and moderate to large number of oligodendrocytes
  - Among the diagnostic tests, MRI is particularly valuable in supporting the diagnosis
    - It shows the typical periventricular plaques and also plaques as small as 3 to 4 mm
    - Identifies acute plaques
    - Helpful in monitoring therapeutic efficacy
  - CSF abnormalities are not specific
    - An increase gamma-globulin function and the presence of oligoclonalIgG bands futher support the diagnosis
  - Clinical course evolves as relapsing-remitting or progressive
    - The attack is defined by the anatomic and functional relationships between the myelin sheath and its axons
    - Resolution of inflammation, removal of myelin debris, and reestablishment of conduction of the neural impulses – remission with full or partial recovery of neurologic deficits
    - Relapses is accounted by formation of new plaques
    - Progression is further destruction of nerve fiber and formation of multiple plaques
- **Variants of Multiple Sclerosis**
  - **Neuromyelitisoptica or Devic's disease –** characterized by an acute inflammatory demyelination to the optic nerves and spinal cord, often the cervical segments
  - **Charcot classic type MS** shows the typical clinical features and course of MS
  - **Marburg type MS** has an acute onset and rapid progression. Death usually occurs within 1 to 6 months of onset
  - **Balo's concentric sclerosis** is characterized by concentric zones of demyelination alternating with zones of intact myelin, believed to represent remyelination
  - **Schilder's Disease** refers to extensive demyelinations in the cerebral hemispheres, with sudanophilic breakdown products

Central Pontine Myelinolysis

- A rare demyelinating disorder that affectsthe pons
- Occurs in ALCOHOLICS
- Discrete areas of selective demyelination occur in the pons, although the lesions often are too small to have clinical manifestations and are discovered only at autopsy
- In a few patients, quadriparesis, pseudobulbar palsy or severe depression of consciousness (pseudocoma) may occur
- Central pontinemyelinolysis is thought to arise from overly rapid correctin of HYPONATREMIA in alcoholics, malnourished persons, or individuals with marked electrolyte instability including persons with renal failure and liver transplant recipients.

Neurodegenerative Diseases

- Characterized as **progressive degeneration of neurons i**n a specific reproducible and defined area of the brain
- Exhibit **selective neuronal loss** with no inciting event
- Some diseases result in progressive **dementia** and others result in impairment of motor function or other abnormalities
- Development of protein aggregates that are resistant to normal cellular degradation.
  - These are usually seen as inclusions histologically and often a HALLMARK OF DIAGNOSIS
- Both hereditary and sporadic forms exist
- NEURODEGENERATIVE DISEASE PRIMARILY CAUSING DEMENTIA
  - **A**lzheimer Disease
  - **F**rontotemporal Dementia
  - **V**ascular Dementia

Alzheimer Disease

- Most common cause of dementia in the elderly(causes 70% of cases of dementia)
- Usually occurs in patients older than 65 years of age
- Pathogenesis:
  - Aβ is a critical molecule in the pathogenesis of dementia
  - Aβ aggregations, forms β pleated sheets and is relatively resistant to degradation, elicits a response to astrocytes and neuroglia and can be directly neurotoxic
- Risk factors
  - Increasing age
  - Genetics: genes involved include the gene for the amyloid precursor protein (APP) on chromosome 21, the gene for presenilin-1 on chromosome 14, and the gene for presenilin-2 on chromosome 1. Presenilins are a component of γ-secretase
  - Increase presenilins leads to increase production of Aβ
  - A4 allele of apoE on chromosome 19
- MORPHOLOGY
  - GROSS: cerebral atrophy with hydrocephalus ex vacuo
  - MICROSCOPIC:
    - Neurofibrillary tangles and senile (neuritic) plaques, particularly in the Hippocampus, cerebral neocortex and in some subcortical neurons
    - Amyloid angiopathy and "granulovacuolar degeneration" in hippocampal neurons
- Neuritic/Senile Plaques: swollen neuronal processes rich in hyperphosphorylated tau protein, usually surrounding a β-amyloid core
- Neurofibrillary tangles: intracellular aggregates of hyperphosphorylated tau protein (paired helical filaments)
- Symptoms: gradual decline in cognitive function leading to severe cognitive dysfunction
- Diagnosis:
  - The diagnosis of Alzheimer disease is made by the clinical diagnosis of dementia without another
  - Imaging techniques has limited usefulness
  - Definitive diagnosis requires the demonstration of significant neocortical accumulations of plaques and tangles

Frontotemporal Dementia

- **Degeneration and atrophy of temporal and frontal lobes**

- Present clinically with progressive deterioration of language and changes in personality
- **Pick Disease (Lobar atrophy)**
  - Rare
  - Early onset of behavioral changes and language disturbance
  - **Gross Morphology**
    - ASYMMETRIC atrophy of frontal and temporal lobes
  - **Microscopic Morphology**
    - Particularly common in the dentate gyrus of the hippocampus and deeper cortical neurons and Pick bodies
    - Pick bodies are round eosinophilicintracytoplasmic inclusions containing accumulation of abnormal 3-repeat tau protein

Vascular Dementia

- Clinical presentation: Step-wise decline in cognitive function
- Pathogenesis: small microinfarcts and/or strategic infarcts (i.e. infarcts affecting the hippocampus and other areas specifically involved with memory function)

Other Neurodegenerative Diseases

- Other neurodegenerative diseases affect other areas of the brain, including the basal ganglia and brainstem, causing movement disorders
- The features of some of these other neurodegenerative disorders, including Huntington chorea, idiopathic Parkinson disease, progressive supranuclear palsy and amyotrophic lateral sclerosis.

- **Huntington Chorea**
  - Characterized by choreic movement, psychiatric features and dementia and degeneration of striatal neurons
  - There is an increase in the number of CAG repeats in the huntingtin gene
  - Transcription of the expanded CAG repeats results in the accumulation of excess numbers of polyglutamine residues in the hungtingtin protein
  - The chemical pathology is characterized by a deficiency of inhibitory neurotransmitter GABA and of the enzyme glutamine decarboxylase
  - MORPHOLOGY:
    - Gross: bilateral atrophy of the nuclei and putamen
    - Microscopic: loss of medium spiny GABA-ergic neurons in the caudate and putamen; associated with gliosis

- **IDIOPATHIC PARKINSON DISEASE**
  - Degenerative disease with impairment of motor function; 20% of patients have dementia
  - Represents a spontaneous systems degeneration (i.e. it is not caused by an exogenous insult)
  - Similar clinical abnormalities ("parkinsonism") may be caused by certain exogenous insults (secondary forms)
  - PATHOGENESIS: reduced level of dopamine because of loss of dopamine-containing neurons, particularly in the substantianigra
  - Mutations of α-synuclein and parkin (substrate of α-synuclein)
  - MORPHOLOGY:
    - GROSS: pallor of substantianigra and locus ceruleus
    - MICROSCOPIC: Lewy bodies, which are round well demarcated intracytoplasmiceosinophilic inclusions that stain with antibodies to ubiquitin and α-synuclein
  - Clinical Findings:
    - Cogwheel rigidity (ratchet-like movements), bradykinesia, flat affect, "masked facies", and pill-rolling tremor plus a shuffling gait

- **Secondary Parkinsonism**
  - Parkinsonian symptoms caused by an exogenous insult
  - Causes
    - Medications (e.g. anti-psychotic agents)
    - Toxins (e.g. carbon monoxide)
    - Encephalitis (e.g. West-Nile virus)
    - Hypoxic-ischemic injury

- **Progressive Supranuclear Palsy**
  - Occurs in the fifth to seventh decades, male predominace (male:female ratio of 2:1)
  - Associated with the accumulation of tau-rich globose neurofibrillary tangles and tau-rich aggregates in glial cells

  - Microscopic:
    - Neuronal loss in the globuspallidus, subthalamic nucleus and dentate nucleus of cerebellum
  - Clinical:
    - Shows some of the features of Parkinson disease
    - Patients have truncal rigidity, disequilibrium, pseudobulbar palsy, abnormal speech and ocular disturbances

Tumors

Introduction

Tumors of the CNS:

1. Gliomas
2. Neuronal Tumors
3. Poorly Differentiated Neoplasm
4. Meningiomas
5. Metastases

Differences Across Ages

	Adult	Pedia
Location	Supratentorial	Infratentorial
Tumors	Metastases • Carcinoma or Melanoma	Primary • Gliomas

Preferential Sites

- Astrocytoma → ADULT: CEREBRUM; PEDIA: CEREBELLUM, PONS
- Oligodendroglioma→ CEREBRUM
- EPENDYOMA → 4th VENTRICLE

Benign VS Malignant

- Main determinant: ability of tumor to cause ill effects
- Histologically bland, non-invasive tumor can be lethal based on the ability to expand within a confined space and eventually cause **herniation**

Gliomas

- Derived from GLIAL CELLS
  - Astrocytomas
  - Oligodendrogliomas
  - Ependymoma

Astrocytomas

Several types:

a. Fibrillary Astrocytoma
b. Pilocytic Astrocytoma
c. Pleomorphic xanthoastrocytoma

FibrillaryAstrocytomas

- 80% of adult primary brain tumors
- All are infiltrative lesions!
  - Well differentiated astrocytoma (WHO grade II)
  - Anaplastic astrocytoma (WHO grade III)
  - GlioblastomaMultiforme (GBM) (WHO grade IV)
- **WHO GRADING**

I	Tumors with low proliferative potential and the possibility of cure following surgical resection alone
II	Infiltrative in nature and, despite low level proliferative activity, often recur
III	Histological evidence of malignancy, including nuclear atypia and brisk mitotic activity
IV	Cytologically malignant, mitotically active, necrosis-prone neoplasms often associated with rapid disease evolution and a fatal outcome

- **Morphology**
  - All are infiltrative lesions!
  - Expands and distorts the invaded brain

- Tumors are either soft or firm with or without cystic degeneration
- NOTE: regional variation is characteristic of GBM
- Microscopically, features are based upon nuclear pleomorphism, mitotic figures, necrosis, and/or microvascular proliferation

	WD FIBRILLARY ASTROCYTOMA	ANAPLASTIC ASTROCYTOMA	GBM
CELLULARITY	Mild - moderate	Dense	Dense
PLEOMORPHISM	Variable	Marked	Marked
MITOSIS	Absent	Prominent	Prominent
CAPILLARY PROLIFERATION	Absent	Prominent	Prominent
NECROSIS	Absent	Absent	Absent

- A special type of astrocytoma composed predominantly of neoplastic astrocytes showing brightly eosinophilic cytoplasm with numerous stout processes – GEMISTOCYTIC ASTROCYTOMA (WHO grade III)
- Important points regarding astrocytomas
  - Well-differentiated astrocytomas
    - Virtually impossible to completely excise
    - Patients can live 5-10 years after diagnosis of the tumor
  - GBM
    - Can arise from preexisting lower grade astrocytomas
    - Highly aggressive, median survival is approximately 12 months

Pilocytic Astrocytoma
- Most common in children
- Location: Most common sites include the cerebellum, third ventricle, and optic nerves
- Morphology
  - Often cystic or solid
  - Well circumscribed or infiltrating
  - Biphasic pattern
    - Bipolar cells with long, thin "hairline" processes
    - Loose-textured multipolar cells
  - Rosenthal fibers, eosinophilic granular bodies and microcysts are often present
  - Very low grade neoplasms (WHO grade I)
  - Excellent prognosis
  - Surgical excision alone resulting in long term cure

Pleomorphic Xanthoastrocytoma
- Occurs most often relatively superficially in the temporal lobe of children and young adults
- Tumors consists of neoplastic, often bizarre, astrocytes, which are sometimes lipidized
- Degree of nuclear atypia can be extreme and may suggest a high grade astrocytoma, but no necrosis and mitotic figures
- Low grade tumor (WHO grade II) with survival rate of 80%

Oligodendroglioma
- Epidemiology: adults, fourth to fifth decades; represent 5-15% of gliomas
- Less aggressive than astrocytomas when comparing similar grades
- More responsive to chemotherapy
- Morphology
  - GROSS: more well circumscribed than astrocytomas; most cases have calcification
  - MICROSCOPIC: round nuclei with perinuclear halos (i.e. "fried egg appearance"); clustering of neoplastic cells around neurons and blood vessels (satellitosis); and branching capillaries ("chicken-wire vasculature")

Ependymoma
- Location: in proximity to ventricular cavities or within spinal cord
- Complications: noncommunicating hydrocephalus in the case of ventricular lesions
- MICROSCOPIC: ovoid nuclei with cytoplasmic processes forming pseudorosettes (radiate around vessel) or true rosettes (radiate around a central lumen)

Poorly-differentiated Neoplasm

Medulloblastoma
- Poorly differentiated neuroectodermal neoplasm arising in the cerebellum
- Histologically similar tumors may arise in other (extracerebellar) sites; these are sometimes designated simply as "primitive neuroectodermal tumors".
- **Epidemiology**: most occur in childhood
- **Location**: Vermis in younger children; cerebellar hemispheres in older children and adults
- **Complications**: noncommunicating hydrocephalus, gait abnormalities, dissemination through CSF via "drop mestastases"
- **MICROSCOPIC:**
  - "Small round cell tumor"
  - Homer-Wright rosettes (circle of neoplastic cells around a central fibrillar core)

Meningioma
- Epidemiology: usually adults; female predominance (meningiomas have progesterone receptors)
- Locations: cranial vault, spinal cord
- Morphology
  - GROSS: firm dural-based tumor, usually well demarcated from adjacent brain parenchyma. May invade the skull and overlying soft tissues. Brain invasion is uncommon and when present, usually indicates an aggressive variant.
  - MICROSCOPIC: wide range of histologic patterns. Common growth patterns include whorls of meningothelial cells associated with psamomma bodies.

CNS NEOPLASMS			
NEOPLASM	**AGE**	**LOCATION**	**HISTOLOGIC FEATURES**
ASTROCYTOMA	ANY, 80% of primary brain tumors	Cerebral hemispheres	Grading is based upon pleomorphism, mitotic figures, and microvascular proliferation
PLIOCYTIC ASTROCYTOMA	Any; more common in childred	Any; common in cerebellum, 3rd ventricle	Hair-like cell processes; Rosenthal fibers
OLIGODENDROGLIOMA	4th – 5th decade	Cerebral hemispheres	Round cells with perinuclear halos, satellitosis
EPENDYMOMA	Any	Periventricular; spinal cord	Psudorosettes and rosettes
MEDULLOBLASTOMA	Peak at 7 y.o.	Cerebellar vermis in children, cerebellar hemispheres in adults	Small round cell tumor; Homer-Wright rosettes
MENINGIOMA	adults	Cranial vault, spinal cord	Whorls, psammoma bodies

Clinical Presentation of Tumors of the CNS

- **Mechanisms for clinical presentation of tumors:**
  - Expansion and compression of the brain by a tumor mass or associated edema
  - Infiltration of cerebral parenchyma

- **General symptoms (resulting from a mass effect)**
  - Headache: most common general symptom. When caused by brain tumors, the headaches are usually worse in the morning or in situations that increase intracranial pressure
  - Changes in personality
  - Projectile vomiting: common in children, rare in adults
  - Seizures

- Focal symptoms, which result from localized disruption of cerebral parenchyma and depend upon location of tumor
  - Frontal: personality changes; impaired concentration and memory
  - Parietal: spatial disorientation; aphasia
  - Temporal: personality changes; complex partial seizures

- Diagnosis
  - MRI is more sensitive at evaluating the posterior fossa and in detecting infiltration of the cerebral parenchyma
  - Biopsy

Peripheral Nervous System

- Neuropathies are conditions involving primary injury to the axon, nerve cell body or myelin sheath
- If the disease primarily affect the Schwann cells – SEGMENTAL DEMYELINATION
- If the disease primarily affect the Axons – AXONAL DEGENERATION
- Types
  - Axonal neuropathy
  - Demyelinating neuropathy
  - Immune neuropathy
  - Metabolic and Toxic neuropathy
  - Infectious neuropathy

Axonal Neuropathy

- Primary injury of the axonal processes, associated with the formation of fragmented axonal processes and myelin debris ("myelin ovoids")
- The most common type of neuropathy
- WALLERIAN DEGENERATION
  - Represents degeneration of the distal axonal process following transaction
  - Seen in segmental ischemic nerve injury associated with vasculitis

Demyelinating Neuropathy

- Primary damage is to Schwann cells, typically in a multifocal segmental distribution along the length of the axon
- It is characterized by selective myelin injury and relative preservation of the axon
- Chronic cases are associated with concentric layers of Schwann cell cytoplasm and collagen (so-called "onion bulbs") around residual axons

Immune Neuropathy

- Although there are several immune neuropathies, one of the most important is Guillain-Barré syndrome
- Clinical presentation:
  - Usually begins with weakness in the distal extremities and progresses to involve the proximal muscle groups – ascending paralysis
  - Respiratory muscles may be involved
- Predisposing factor:
  - Two thirds of cases follow an influenza like illness
  - Others: Campylobacter jejuni, CMV, and Epstein-Barr Virus (EBV) infections
- MICROSCOPIC: inflammation and demyelination of nerves

Metabolic and Toxic Neuropathies

- Diabetes mellitus (various types of neuropathy): distal symmetric sensor or sensorimotor, autonomic and focal or multifocal asymmetric
- Other causes: vitamin deficiencies, malignancy, heavy metals

Infectious Neuropathy

- Causes include leprosy, diphtheria and varicella-zoster virus

MANY THANKS TO THE SOPHOMORES! YOU ROCK!

The Wisdom of Winnie-the-Pooh about Fear

-retold by Holly ☺

Piglet was a small creature and thus was subject to a lot of nervousness and fear.

One day, as he was walking home from Rabbit's house with Pooh, it was unfortunate that a thunderstorm came rolling into the sky out of nowhere. Lightning struck the trees that were swaying madly in the wind and the mighty oaks were even uprooted and crashed burning into the ground.

It was too much for the little Piglet to take. With knees trembling, he stopped running and shouted:

"I can't take it, Pooh. I can't take it any longer! What if a tree falls, and we were underneath it?!"

Winnie-the-Pooh stopped too and thought about what Piglet said. Indeed, it was frightening to imagine those heavy branches rushing at you from above.

But then he said,

"Yes, well, what if it doesn't?"

He took Piglet by the hand and they both hurried away. Surely enough, no harm came their way and hey both made it safely home.

So if we think we can't pass this exam, let's just ask, "what if we do?" ☺

(ay, goodluck!)