7. Neuropathology II

CEREBROVASCULAR DISEASES
Most prevalent neurologic disorders in terms of both morbidity and mortality

Classification
- Hypoxic/ischemic insult due to impaired perfusion
- Hemorrhagic insult due to non-traumatic vessel rupture

Remember!
Hypoxia: reduction in available oxygen, due to
- upper airway obstruction (eg., sudden swelling of laryngeal mucosa)
- inadequate oxygenation of blood in lung diseases
- inadequate O\textsubscript{2} transport in blood because of decreased number of RBCs (anemia)
- inadequate perfusion of blood in the tissues in heart failure

Ischemia: inadequate blood supply to an organ or part of it due to impeded arterial flow or reduced venous drainage

DIFFUSE HYPOXIC INSULT (HYPOXIC ENCEPHALOPATHY)
Pathogenesis
- Transient generalized reduction of cerebral perfusion, ie., in cardiac arrest, severe hypotension of any cause, etc.
  - If the drop of perfusion lasts <3 minutes: reversible hypoxic damage ⇒ transient posthypoxic confusional state ⇒ complete recovery
  - If it lasts >3 minutes (severe global hypoxia) ⇒ irreversible hypoxic damage

Morphology
- Gross: diffuse brain edema with poor demarcation between GM and WM
- LM: red neuron change: in pyramidal neurons and Purkinje cells + laminar necrosis + border zone infarcts

Clinical consequences
- Widespread neuronal damage ⇒ death
- Patients who survive often remain deeply comatose: persistent vegetative state
- Survivors may meet the criteria for "brain death": diffuse cortical injury: isoelectric EEG + brainstem damage: absent reflexes and respiratory drive plus absent cerebral perfusion ⇒ potential donors for organ transplantation

FOCAL ISCHEMIC INSULT
Pathogenesis
- Thrombosis on atheromatous plaques of an artery of the circle of Willis; most frequent site: the middle cerebral artery ⇒ large anemic infarct
- Embolism of the intracerebral arteries from cardiac mural thrombi or thromboemboli from atheromatous plaques within the carotid arteries ⇒ infarct(s) in the territory of the middle cerebral artery
- Narrowing or complete occlusion of small arteries and arterioles in hypertension ⇒ multiple small infarcts in the basal ganglia and deep WM (hypertensive cerebrovascular disease)

CEREBRAL INFARCTION
Morphology
- By 48 hs: the ischemic area becomes pale, soft and swollen, the corticomedullary junction becomes indistinct; LM: red neurons
- From day 2: the ischemic area undergoes colliquative necrosis: grossly wedge-shaped, white-yellow; LM: phagocytosis of myelin breakdown products by foamy macrophages ⇒ astrocytes replace ma-s
- From week 3: gliascar

Clinicopathologic correlations
- Slowly evolving symptoms, taking several hours (clinical designation: stroke)
- Thrombosis of middle cerebral artery (MCA supplies the motor cortex, the sensory cortex, the internal capsule [corticospinal and spinothalamic tract] and nearly all the basal ganglia) ⇒ contralateral hemiparesis and hemisensory loss of the face, upper and lower extremities ⇒ prolonged bed rest
- Thrombosis of internal carotid artery: a) widespread atherosclerosis in the circle of Willis prevents adequate collateral flow ⇒ cerebral infarct; b) minimal atherosclerosis ⇒ excellent collateral circulation ⇒ no consequence
- Thrombosis of basilar artery: lethal before the development of infarction

HYPERTENSIVE CEREBROVASCULAR DISEASE
- Hyaline arteriosclerosis leads to lacunar infarcts and lacunar state: multiple, cavitary lesions of 0.3 to 1.5 cm in diameter, occurring in the basal ganglia, internal capsule, deep WM, and pons

Clinical features
- May be silent
- May cause vascular dementia
- Hypertensive individuals with lacunar state usually suffer from coexisting severe atherosclerosis in the circle of Willis, and can have coexisting glascars due to previous large infarcts. These individuals develop multi-infarct dementia
- Chronic WM injury due to hypertension-induced arteriolar occlusion ⇒ focal myelin loss ⇒ psychomotor slowness (subcortical vascular dementia;Binswanger's disease)

HEMORRHAGIC INSULT
Due to spontaneous vessel rupture. Site:
- In the basal ganglia (ganglionic hemorrhage): cause: hypertensive crisis
- In the lobes (lobar hemorrhage): various causes

HYPERTENSIVE CEREBRAL HEMORRHAGE
Pathogenesis
- In hypertensive adults over 50 years of age
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- Sudden increase in blood pressure (hypertensive crisis) \(\Rightarrow\) rupture of aneurysmally dilated small arteries affected by hyaline arteriolosclerosis

**Localization, complications**
- 75% - putamen of the lentiform nucleus and thalamus; 15% - pons; 10% - cerebellum
- Extension into the ventricular system \(\Rightarrow\) hemocephalus
- Brain swelling + herniation

**Clinicopathologic correlations**
- Sudden onset, hemiparesis, hemisensory loss, raising intracranial pressure, loss of consciousness
- Death within hours from hemocephalus or herniation in 40% of cases
- In survivors, complications of prolonged bed rest occur during the first four weeks. Events in patients who survive the first 4 weeks: the hematoma is resorbed over a period of months, and is replaced by glial scar with central cavity; the wall is rich in hemosiderin-laden macrophages \(\Rightarrow\) the neurologic deficits slowly improve

**LOBAR HEMORRHAGES**
- Multiple; occur in the lobes of cerebral hemispheres
- No association with hypertension
- Causes: thrombocytopenia in blastic crisis of leukemia, cerebral vasculitis, cerebral amyloid angiopathy (amyloidogenic peptides deposit in the meningeal and cortical vessels, weakening of the vessel wall)

**NON-TRAUMATIC SUBARACHNOID HEMORRHAGE**
Rupture of berry aneurysm or arteriovenous malformation

**BERRY ANEURYSM**

Pathogenesis
- Congenital, insidiously growing saccular aneurysm
- Usual site: at proximal branching points on the anterior portion of the circle of Willis

LM
- At the neck of the aneurysm, the muscular wall and intimal elastic lamina are absent, the wall of the sac is made up of thickened hyalinized intima

Clinical course
- Spontaneous growth for 25-40 years; greater than 10 mm: high risk of rupture \(\Rightarrow\) subarachnoid hemorrhage
- Involved individuals: between 30-50 ys
- Rupture occurs often with acute increases in intracranial pressure: hypertensive crisis, straining at stool, etc.
- Excruciating headache and rapid loss of consciousness
- Lethal because of massive bleeding + brain edema \(\Rightarrow\) herniation
- Complications in survivors: early: vasospasm in distal arteries \(\Rightarrow\) infarction; late: hydrocephalus

**ARTERIOVENOUS MALFORMATION**
- Involves vessels in the subarachnoid space extending into the brain parenchyma or may occur exclusively within the brain
- Gross: tangled network of wormlike vascular channels
- Manifest in adolescents and young adults as a seizure disorder, an intracerebral hemorrhage, or a subarachnoid hemorrhage

**TUMORS OF THE BRAIN**

Classification
- Gliomas
- Medulloblastomas
- Metastases

**GLIOMAS**
- Derive from glial cells: astrocytomas, glioblastomas, oligodendrogliomas, ependymomas
- LM: grading of nuclear atypia (Gr I to IV)
- Immunohistochemical feature: glial fibrillary acid protein (GFAP)-positivity

**ASTROCYTOMAS IN CHILDREN**
- Grow slowly; most often located in the cerebellum
- Gross: cystic and well circumscribed
- LM: composed of very well differentiated astrocytes (pilocytic astrocytoma Gr I)
- Most tumors can be resected completely \(\Rightarrow\) good prognosis

**ASTROCYTOMAS IN ADULTS**
- Arise in the cerebral hemispheres; peak age: 35-40 ys
- Types: well-differentiated astrocytoma, anaplastic astrocytoma
- Molecular genetics: inactivation of the p53 gene; overexpression of the PDGF-A and its receptor; intrinsic tendency to transform into anaplastic astrocytoma \(\Rightarrow\) and then glioblastoma involving the inactivation of several tumor suppr. genes, such as RB and p16/CDKN2A
- Gross: poorly defined, gray-white, infiltrative tumors
- LM: well-differentiated astrocytomas (Gr II): mild nuclear pleomorphism; anaplastic astrocytoma (Gr III): increase in cellularity and nuclear pleomorphism; mitoses
- Outcome of grade II tumors: mean survival with surgery and chemoth: 6-8 ys

**GLIOBLASTOMA (GR IV)**
- Most common glioma, peak: 45- to 60-y-old age group
- Arises de novo or develops from a well-differentiated astrocytoma or oligodendroglioma
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- Highly invasive

**Gross changes**
- Heterogeneous cut surface: areas of necrosis, hemorrhage, cystic change; may extend on the other side of the brain: butterfly pattern of spread through the corpus callosum

**LM**
- Hypercellularity, frank anaplasia, numerous mitoses, necrotic foci surrounded by palisading tumor cells
- Vascular proliferation frequently forming glomeruloid structures

**Prognosis**
- Extremely bad, mean survival: 1 y

**OLIGODENDROGLIOMA (GR II)**
- Uncommon cerebral tumor of adults (40-60 yrs)
- Arises in the cerebral hemispheres; relatively well-circumscribed, calcification is common
- LM: composed of neoplastic oligodendrocytes, the nuclei are surrounded by a clear halo of cytoplasm; low mitotic rate.
- Prognosis: better than for astrocytomas if dedifferentiation does not occur

**EPENDYMOMA (GR II)**
- Uncommon tumor, more often in children than in adults
- In the brain, the tumor usually localizes in and around the fourth ventricle ⇒ sec. hydrocephalus, lethal
- In the spinal cord, the tumor originates from the cauda equina ⇒ the prognosis depends on the resectability; recurrence is likely

**MEDULLOBLASTOMA (GR IV)**
- Childhood tumor (peak: at 7 y of age); derives from primitive neuroectodermal cells
- Usually in the vermis of cerebellum, LM: densely packed small „blue“ cells (darkly staining nuclei, scanty cytoplasm); frequent mitosis and necrosis
- Metastases via the CSF to the spinal cord
- Prognosis depends on the resectability
- Responds to postoperative chemother and radiotherapy
- 5-y survival is 70%

**METASTASES**
- Metastatic carcinomas account for approx. 50% of intracranial tumors
- 5 most common primary tumors: lung carcinoma, breast cc, kidney cc, GI tract cc, melanoma

**Clinical symptoms of brain tumors**
Space-occupying lesion + peritumoral brain edema, may cause
- compression and/or destruction depending on the location: loss of motor functions (paralysis), loss of sensation, stimulation certain part of the brain (epileptic fits)
- obstruction of CSF flow ⇒ hydrocephalus
- sudden hemorrhage ⇒ acute rise in intracranial pressure

Brain tumors do not metastasize; exception: medulloblastoma

**TUMORS OF THE DURA, INTRACRANIAL NERVES, AND NEURAL CREST-DERIVED CELLS**

**MENINGIOMA**
- Solitary tu
- Peak age: 50-70 yrs, more common in women
- Attached to the dura, most often in the parasagittal region along the falx cerebri ⇒ compression of the brain from outside
- LM: meningothelial cells form whorls, often with central calcification (psammoma bodies)
- Complete removal ⇒ excellent prognosis

**SCHWANNOMA**
- Benign intracranial nerve sheath tumor at the cerebellopontine angle, attached to the vestibular branch of the 8th nerve (called acoustic neurinoma by the clinicians)
- Derives from Schwann cells
- LM: mixture of two growth patterns: cellular areas of elongated cell alternate with looser, myxoid regions

Clinical features
- Symptoms: from compression of the nerve (tinnitus, different and sometimes variably changing and intertwining sounds like ringing, hissing, static, etc.; hearing loss)
- If the tumor is greater than 2.5 cm, facial nerve and acustic nerve are damaged during surgical resection

**NEUROBLASTOMA**
- Highly malignant childhood tumor
- Arise in the adrenal medulla or anywhere along the sympathetic chain

Molecular pathology
- Mutations in the anaplastic lymphoma kinase gene (ALK) and in advanced-stage disease in the NMYC gene

Morphology
- Large retroperitoneal mass
- LM: small, primitive-appearing cells with dark nuclei and scant cytoplasm; sometimes the tumor cells are concentrically arranged about a central space filled with neuropil

Prognostic factors and other features
- Age: children younger than 18 months have a better prognosis
Higher stage or NMYC amplification predict poor outcome
- Secrete catecholamines (similarly to pheochromocytomas), whose metabolites can be used for screening patients

**DEMYELINATING DISEASES**
In the CNS, axons and dendrites are ensheathed in myelin, formed from folds of oligodendrocyte cell membranes. Functions of myelin: to protect and insulate neuronal processes, to allow rapid transmission of electrical impulses along axons.
- DDs can be due to immunological, viral or chemical mechanisms
- The myelin sheath is destroyed, but the axons remain preserved; the debris of myelin breakdown is phagocytosed by ma-s
- Types:
  - multiple sclerosis - common
  - acute encephalomyelitis - rare
  - central pontine myelinolysis - rare

**MULTIPLE SCLEROSIS**
- The prevalence is high in countries with moderate or cool climate (ie., northern Europe), and low in the tropics
- More common in whites than other races
- More common in females (3:1); most cases present between 20-40 ys of age

Pathomechanism
- Autoimmune disease directed against myelin, possibly triggered by a virus infection in a genetically susceptible host

Cellular response
- CD4+ TH1 T cells react against self myelin antigens, and secrete IFN-γ, TNF ⇒ activate ma-s, which damage myelin
- CD4+ TH17 T cells secrete IL17, IL22 that recruit neutrophils at sites of myelin damage ⇒ amplification of the inflammatory damage

Humoral response
- IgG autoantibodies may also play a role in the demyelinating process

**Morphology**

**Gross**
- Gray-tan, irregularly shaped firm plaques in the WM of brain and spinal cord; commonly beside the lateral ventricles
- Optic nerve is frequently involved

**LM**
- Active plaques: apoptosis of oligodendrocytes, loss of myelin, foamy ma-s, perivascular ly-c cuff
- Inactive plaques: almost devoid of myelin, the inflammatory process is replaced by gliosis

**Clinical features**
- Sudden onset of a focal neurological deficit which spontaneously recovers
- Symptoms vary from case to case:
  - limb weakness (most frequent)
  - visual symptoms
  - paresthesia
  - vertigo
  - bladder incontinence

**Clinical course**
- Relapsing and remitting course; recovery of from each episode of demyelination (relapse) is incomplete ⇒ progressive clinical deterioration
- Most patients die from consequences of prolonged bed rest

**ACUTE ENCEPHALOMYELITIS**
- Viral inflammation of the brain and spinal cord associated with oligodendrocyte injury, demyelination, and fatal outcome

**CENTRAL PONTINE MYELINOLYSIS**
- Loss of myelin with preservation of axons and neurons in a symmetric pattern involving the pons
- Occurs in alcoholism, severe electrolyte or osmolar imbalance, rapid correction of hyponatremia
- Rapid development of tetraplegia