Diseases of The Nervous System:

Cerebral Edema: Could happen in two conditions:

1. Vasogenic edema: Occurs when the normal integrity of the BBB is disrupted, allowing fluid to escape to the brain parenchyma. Edema may be localized, near an abscess or a neoplasm or generalized.
2. Cytotoxic edema: Refers to an increase in intracellular fluid secondary to cellular injury (e.g. patients with generalized hypoxic ischæmic insult).

Edematous brain is softer, often appearing to fill the cranial vault. The gyri are flattened, intervening sulci are narrowed and the ventricular cavities compressed. As the brain expands, herniation may occur.

Herniation:

Under the effect of increased intracranial pressure, herniation of brain parenchyma happens in three sites:

1. Transtentorial (uncinate) herniation: The medial aspect of the temporal lobe herniates through the free margins of the tentorium cerebelli, resulting in compression of the third cranial nerve and the posterior cerebral artery resulting in ischæmic injury.
2. Subfalcine (Cingulate gyrus) herniation: The cingulate gyrus is displaced under the falx cerebri, always associated with compression of branches of the anterior cerebral artery.
3. Tonsillar herniation: The cerebellar tonsils herniated through the foramen magnum. This is a life threatening condition because of brain stem compression, associated with hæmorrhagic lesions in the midbrain and pons termed secondary brain stem or Duret's hæmorrhages.

Hydrocephalus:

Refers to accumulation of excessive amount of CSF in the ventricular system as a result of decreased resorption , obstruction , and rarely due to increased production of CSF (e.g. tumours of the choroids plexus), causing elevation of the intracranial pressure (ICP): Three classes of hydrocephaly:

1. Non-communicating hydrocephalus: When obstruction occurs within the ventricular system.
2. Communicating hydrocephalus: when obstruction occurs outside the ventricular system.
3. Hydrocephalus ex vacuo: Dilatation of the ventricular system secondary to loss of brain parenchyma.

Vascular Diseases:

Three categories of vascular insults:

1. Global hypoxic-ischæmic encephalopathy: Decreased perfusion of the brain by low blood pressure flowing leads to hypoxic-ischæmic injury. Neurons are more vulnerable to hypoxic injury than glial cells, as well; neurons of the hippocampus and Perkinje cells of the cerebellum are more vulnerable than other neurons. In the first 24-48 hours, the brain appears softened and edematous with irregular mottled discoloration and hæmorrhage in the grey matter. Laminar cortical necrosis, is a pattern seen due to irregular linear zones of softening and discoloration in the cortical mantle. The demarcation between the grey and the white matter is usually blurred. Microscopic changes appear after 12-24 hours including neuronal shrinkage or swelling, cytoplasmic eosinophilia, and nuclear pyknosis. The parenchyma is

vacuolated with perivascular and pericellular edema. There is little host inflammatory reactions.

2. Infarcts: caused by local circulatory disturbances. It is the most common cause of cerebrovascular disease accounting for 80% of all cerebrovascular accidents, most commonly seen in the seventh decade and in males. Atherosclerosis of cerebral arteries is the most common cause with its predisposing factors (e.g. hypertension, DM, smoking) affecting the larger vessels such as the internal carotid artery. Other causes include; emboli originating from the heart and the bifurcation of the carotid arteries, vasculitis and trauma. In the first 8-12 hours, the affected area appears normal grossly and microscopically. The first changes are ischæmic neuronal changes and neutrophilic inflammatory infiltrate. By 36-48 hours the necrotic area becomes swollen and softer. Areas of hæmorrhage may be seen. Later (1 month) macrophages appear resulting in liquefaction of the infarct with cavitation. By 6 months, most infarcts are completely cavitated.
3. Intracranial hæmorrhages:
   A. Primary brain parenchymal hemorrhage: Causes: 1. hypertension. 2. Systemic coagulation disorders. 3. Open heart surgery. 4. Neoplasms. 5. Amyloid angiopathy. 6. Vasculitis. 7. Saccular aneurysms. 8. Vascular malformations. Hemorrhage occurs most commonly in the area of the basal ganglia, thalamus, cerebral white matter pons and cerebellum.
   B. Saccular aneurysms and subarachnoid hemorrhage: Saccular or berry aneurysm is the most common cause of spontaneous subarachnoid hemorrhage, occurring in 1% of the general population. Its incidence is higher in certain conditions including polycystic disease of the kidney, fibromuscular dysplasia, coarctation of the aorta and arteriovenous malformation. Most saccular aneurysms (80%) arise at arterial bifurcations of the internal carotid artery (branches of the middle cerebral artery, and junction between the anterior cerebral and the anterior communicating arteries). 15-20% occur within the vertebrobasilar circulation. They are thought to arise from congenital defects in the media of arteries at branching points.
   C. Vascular malformations: Including: 1. Arteriovenous malformations in cerebral hemispheres. 2. Capillary telangiectasias in the pons and cerebral white matter. 3. Venous angiomas in the meninges and the spinal cord. 4. Cavernous angiomas.

CNS Trauma:

Epidural Hæmatoma: caused by rupture of the middle meningeal artery between the dura mater and portion of the temporal bone, usually associated with a fracture of the skull. It compresses the subjacent dura and flatted the underlying brain resulting in uncal, gyral and cerebellar tonsillar herniation and death.

Subdural Hæmatoma: Caused by disruption of the bridging veins crossing the surface of the brain to the dural sinuses. Acute subdural hæmatomas are usually associated with a clear history of trauma, may be unilateral or bilateral particulary in infants. They contain clotted blood on the frontoparietal region. The underlying gyral convexities are usually preserved. Chronic subdural hæmatomas are less commonly associated with trauma, but with brain atrophy.

Concussion: A transient loss of consciousness and widespread paralysis, some times seizures followed by recover by hours or days. There is no anatomical changes seen. It is proposed that it is due to a transient injury to the reticular activating system.

Diffuse Axonal Injury: Is the most common cause of post-traumatic dementia, resulting from a sudden angular deceleration or acceleration.

Contusion: Are hæmorrhages in the superficial brain parenchyma caused by blunt trauma.

Congenital Malformations:

1. Anencephaly: Is the most common congenital brain malformation, the cranial vault is hypoplastic or absent, the orbit is shallow, the neurohypophysis is absent and the anterior pituitary is small, the lungs and the adrenal glands are hypoplastic.
2. Encephaloceles and meningoceles: Protrusion of various amounts of brain parenchyma through a defect in the cranial bones.
3. Spinal neural tube defects (spina bifida): May occur at any level, most commonly in the lumbosacral region with four patterns; 1. Myelocele. 2. Spinal meningocele. 3. Meningomyelocele. 4, Spina bifida occulta.

Infections of The Nervous System:

1. Leptomeningitis: *Acute (purulent) leptomeningitis:* H. influenzæ and S. pneumoniæ account for most cases in children. Neisseria meningitides is the most common cause of epidemic meningitis. In adults and the elderly, S. pneumoniæ is common. Grossly the meninges appear intensely congested covered by a creamy exudates from the subarachnoid space.

The normally clear CSF is cloudy and sometimes frankly purulent. In acute meningitis, an exudate is evident within the leptomeninges over the surface of the brain . The meningeal vessels are engorged and stand out prominently. The location of the exudate varies; in *H. influenzae* meningitis, for example, it is usually basal, whereas in pneumococcal meningitis, it is often densest over the cerebral convexities near the sagittal sinus. When the meningitis is fulminant, , producing ventriculitis. On microscopic examination, neutrophils fill the entire subarachnoid space in severely affected areas and are found predominantly around the leptomeningeal blood vessels in less severe cases. In fulminant meningitis, the inflammatory cells infiltrate the walls of the leptomeningeal veins with potential extension of the inflammatory infiltrate into the substance of the brain (focal cerebritis). Phlebitis may also lead to venous occlusion and hemorrhagic infarction of the underlying brain.

Leptomeningeal fibrosis and consequent hydrocephalus may follow pyogenic meningitis .

Acute lymphocytic (viral) meningitis: Also called aseptic meningitis and is self limited. Common viruses include; mumps virus, echovirus, coxsackie virus and EBV.

There are no distinctive macroscopic characteristics except for brain swelling. On microscopic examination, there is either no abnormality or a mild to moderate infiltration of the leptomeninges with lymphocytes.

Chronic Meningitis: Most often caused by bacteria and fungi including M. tuberculosis, Cryptococcus neoformans. The meninges and the dura mater are thickened containing a dense exudates with adhesions resulting in obstructive hydrocephaly.

2. Brain abscesses: The infecting organism may reach the brain by: 1. hematogenous spread. 2. Contiguous spread from adjacent infections (sinusitis or chronic suppurative otitis

media). 3. Direct implantation during trauma. Brain abscesses are more common in the cerebral hemispheres and often solitary.
On macroscopic examination, abscesses are discrete lesions with central liquefactive necrosis, a surrounding fibrous capsule, and edema . The most common brain regions that are affected, in descending order of frequency, are the frontal lobe, the parietal lobe, and the cerebellum. On microscopic examination, there is exuberant granulation tissue with neovascularization around the necrosis that is responsible for the marked vasogenic edema. The collagen of the capsule is produced by fibroblasts derived from the walls of blood vessels. Outside the fibrous capsule is a zone of reactive gliosis with numerous gemistocytic astrocytes

3.Viral encephalitis: Viral encephalitis is a parenchymal infection of the brain almost invariably associated with meningeal inflammation (meningoencephalitis) and sometimes with involvement of the spinal cord (encephalomyelitis). The most characteristic histologic features of viral encephalitis are perivascular and parenchymal mononuclear cell infiltrates (lymphocytes, plasma cells, and macrophages), glial cell reactions (including the formation of microglial nodules), and neuronophagia. Direct indications of viral infection are the presence of viral inclusion bodies and, most important, the identification of viral pathogens by ultrastructural, immunocytochemical, and molecular methods

Herpes Simplex Virus Type 1 (HSV-1)
HSV-1 produces an encephalitis that occurs in any age group but is most common in children and young adults. Only about 10% of the patients have a history of prior herpes. The most commonly observed clinical presenting symptoms in herpes encephalitis are alterations in mood, memory, and behavior. PCR-based methods for virus detection in CSF samples have increased the ease of diagnosis of disease. This encephalitis starts in, and most severely involves, the inferior and medial regions of the temporal lobes and the orbital gyri of the frontal lobes . The infection is necrotizing and often hemorrhagic in the most severely affected regions. Perivascular inflammatory infiltrates are usually present, and Cowdry type A intranuclear viral inclusion bodies may be found in both neurons and glia.

Herpes Simplex Virus Type 2 (HSV-2)
HSV-2 also infects the nervous system and usually manifests in adults as a meningitis. A generalized and usually severe encephalitis develops in as many as 50% of neonates born by vaginal delivery to women with active primary HSV genital infections. The dependence on route of delivery indicates that the infection is acquired during passage through the birth canal rather than transplacentally . In AIDS patients, HSV-2 may cause an acute, hemorrhagic, necrotizing encephalitis.

Varicella-Zoster Virus (Herpes Zoster)
Primary varicella infection presents as one of the childhood exanthems (chickenpox), ordinarily without any evidence of neurologic involvement. Reactivation in adults (commonly called "shingles") usually manifests as a painful, vesicular skin eruption in a single or limited dermatomal distribution.
Herpes zoster reactivation is usually a self-limited process, but there may be a persistent postherpetic neuralgia syndrome in up to 10% of patients. Overt CNS involvement with herpes zoster is much rarer but can be more severe. In immunosuppressed patients, herpes zoster may

cause an acute encephalitis with numerous sharply circumscribed lesions characterized by demyelination followed by necrosis. Inclusion bodies can be found in glia and neurons..

Cytomegalovirus
This infection of the nervous system occurs in fetuses and immunosuppressed individuals. The outcome of infection in utero is periventricular necrosis that produces severe brain destruction followed later by microcephaly with periventricular calcification. Cytomegalovirus (CMV) is the most common opportunistic viral pathogen in patients with AIDS, affecting the CNS in 15% to 20% of cases.
Morphology :Although any type of cell within the CNS (neurons, glia, ependyma, endothelium) can be infected by CMV, there is a tendency for the virus to localize in the paraventricular subependymal regions of the brain. This results in a severe hemorrhagic necrotizing ventriculoencephalitis and a choroid plexitis. Prominent cytomegalic cells with intranuclear and intracytoplasmic inclusions can be readily identified by conventional light microscopy, immunocytochemistry, and in situ hybridization.

Demyelinating Diseases

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an autoimmune demyelinating disorder characterized by distinct episodes of neurologic deficits, separated in time, attributable to white matter lesions that are separated in space

Pathogenesis. The lesions of MS are caused by a cellular immune response that is inappropriately directed against the components of the myelin sheath. The likelihood of developing this autoimmune process is influenced by genetic and environmental factors . The risk of developing MS is 15-fold higher when the disease is present in a first-degree relative and even an order of magnitude greater for monozygotic twins .

Pathological features :

lesions appear as multiple, well-circumscribed, somewhat depressed, gray-tan, irregularly shaped plaques, both on external examination and on section

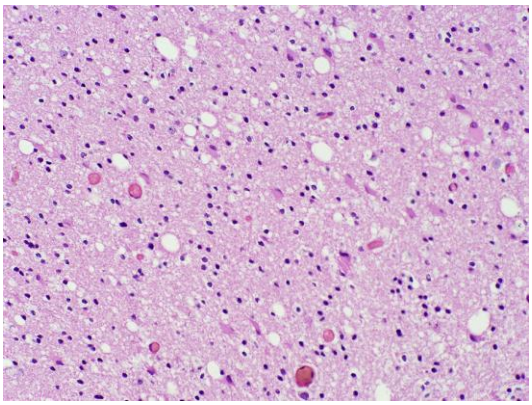
In an active plaque, there is evidence of ongoing myelin breakdown with abundant macrophages containing lipid-rich, Inflammatory cells, including both lymphocytes and monocytes, are present, mostly as perivascular cuffs, especially at the outer edge of the lesion

inactive plaque,in the the center no myelin is found, and there is a reduction in the number of oligodendrocyte nuclei; instead, astrocytic proliferation and gliosis are prominent. Axons in old gliotic plaques show severe depletion of myelin and are also greatly diminished in number

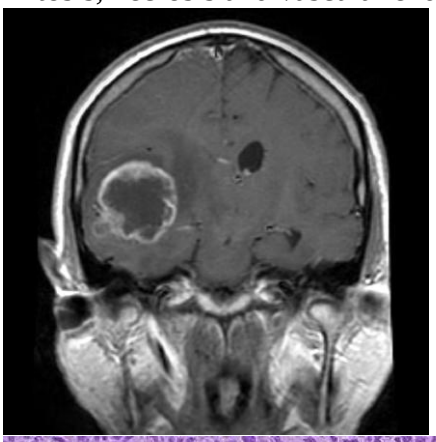
Neoplasms of The CNS:
Astrocytomas: Are characterized by an infiltrative growth pattern, frequently encountered in adults most often in the cerebral hemispheres. It includes many grades; well differentiated (grade II), intermediate grade (anaplastic astrocytopmas, grade III) and high grade (glioblastoma multiforme, grade IV).

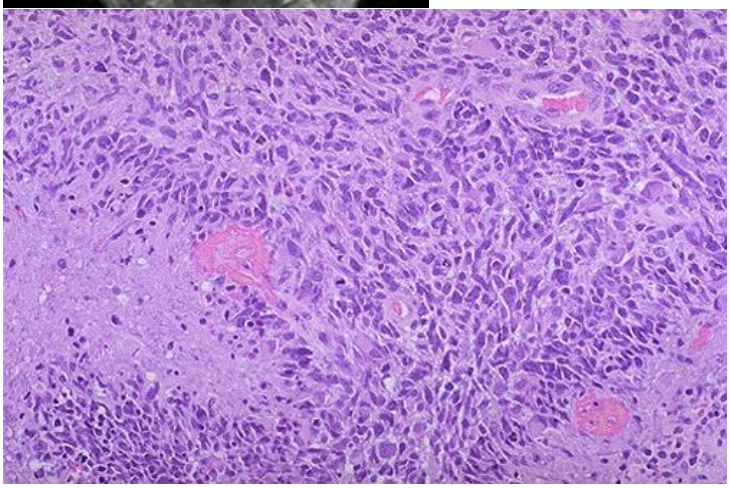
Microscopic description of diffuse infiltrating astrocytoma (grade II)

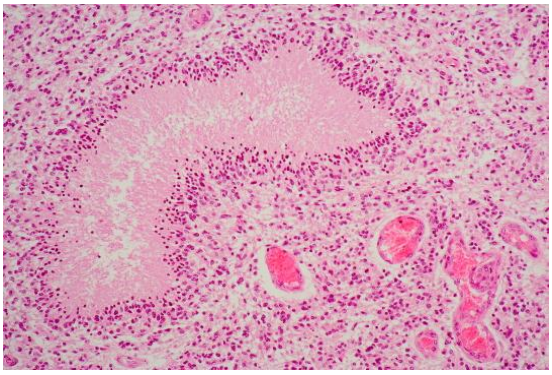
- Appears as hypercellular area as compared to the normal white matter ,background is fibrillary .May have microcysts, calcification .No mitotic figures (a single mitosis in a large biopsy is accepted), no vascular proliferation and no necrosis



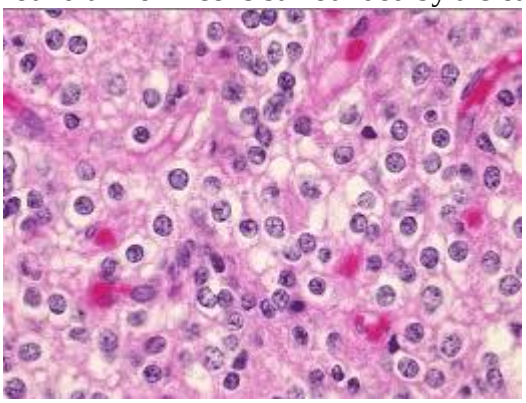
high grade (glioblastoma multiforme, grade IV) : Microscopically, it is composed of growth of astrocytes infiltrating native brain tissue, with increasing degrees of cellularity, pleomorphism, mitosis, necrosis and vascular endothelial proliferation.



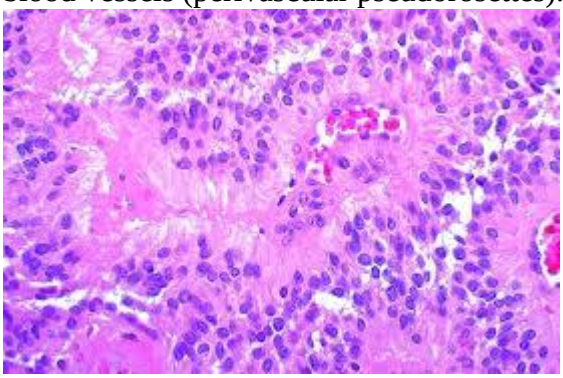




Oligodendrogliomas: Are most common during adulthood in the cerebral hemispheres. Grossly it is soft and gelatinous with frequent calcifications. Microscopically, it is composed of infiltrating round uniform cells surrounded by a clear perinuclear halo.

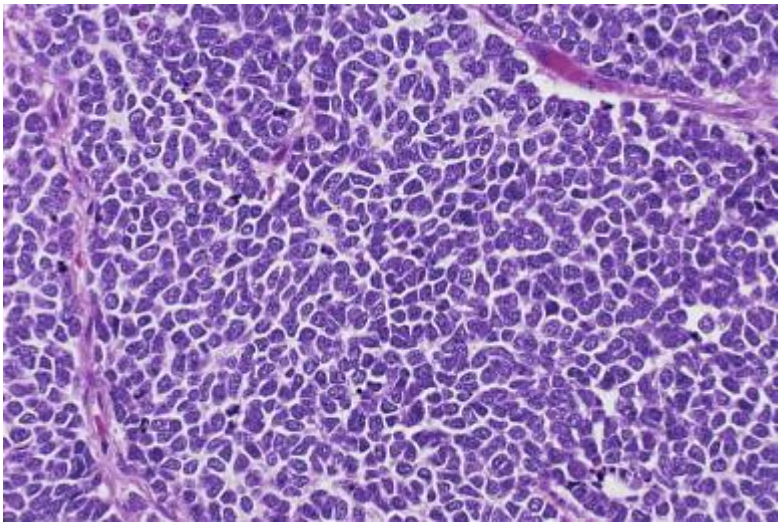


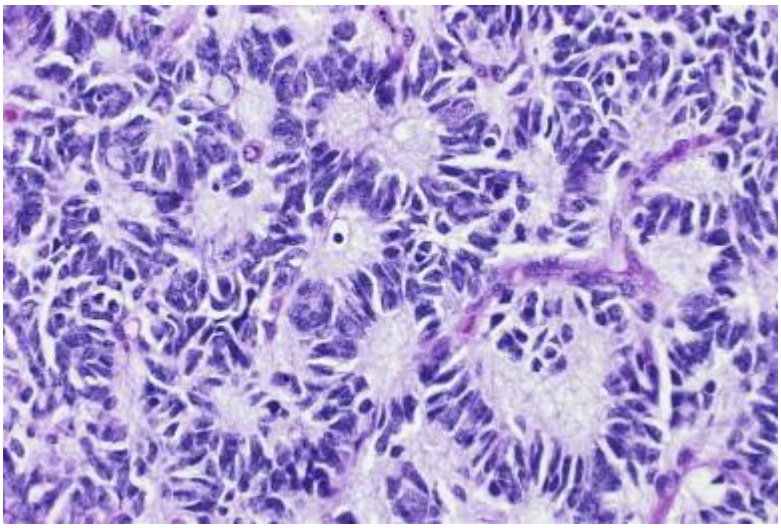
Ependymomas: May occur at any age, arising within one of the ventricular cavities or the central canal of the spinal cord. Microscopically appearing as having elongated cells radiating around blood vessels (perivascular pseudorosettes).



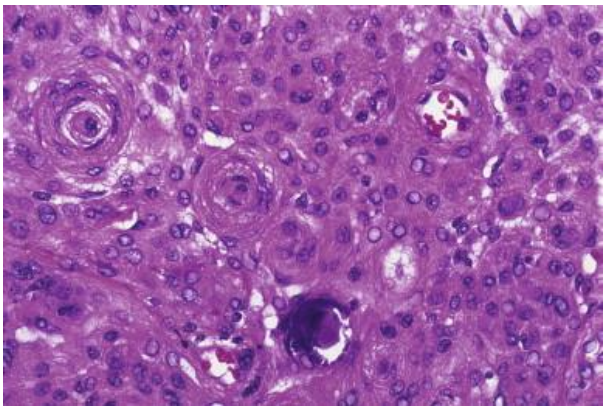
- Medulloblastomas: Are lesions of the cerebellum, occurring within the first two decades of life. It may disseminate through the CSF. Medulloblastoma is grade IV tumor with poor prognosis . Cerebellum and dorsal brain, fourth ventricle

Microscopically, they are composed of small primitive cells with scant cytoplasm , prone to nuclear molding , cells are forming small rosettes called Homer-Wright rosettes.





Meningiomas: Are tumours derived from the meningothelial cells. Most lesions occur outside the brain parenchyma, usually in adults with a slight female predominance especially in spinal tumours. Grossly, they are firm, lobulated masses attached to the dura mater. A variety of microscopic patterns seen, commonly with compact cellular whorls.



Secondary tumors

- Secondary involvement of the CNS by direct extension or hematogenous metastasis is a common complication of systemic cancer .
- Most common brain tumors in community hospitals are metastases (50% of intracranial tumors in hospitalized patients)
- Primary is usually known: melanoma or carcinoma (lung, breast, kidney and GU), occasionally germ cell tumor
- Common with choriocarcinoma
- Common presentation is adult with seizures or ataxia
- Dural metastases are often from breast and prostate

- Metastases to vertebral column: often prostate, breast or hematopoietic neoplasm
- Metastases with unknown primary: lung, colon, kidney
- Multiple lesions are suggestive of metastasis vs. primary CNS tumor
- Usually to cerebrum, but no distinct patterns

Meningeal carcinomatosis:

- Represents 4-8% of metastatic brain tumors
- Diffuse spread of tumor in subarachnoid space
- Associated with carcinoma of lung and breast and ALL
- Poor prognosis
- Repeat lumbar punctures and immunocytochemistry may be helpful in differentiating from aseptic meningitis

Gross description

- Sharply demarcated lesion at gray-white matter junction, surrounded by edema

Microscopic

Epithelial cells with discrete cell boundaries, pushing margin except for small cell carcinoma (infiltrative)