Objectives

- Understand the various responses to cell injury in the CNS
- Explain the pathophysiology and consequences of raised intracranial pressure
- Recognise the spectrum of cerebrovascular disease, its causes and outcomes
- Identify the types of intracranial haemorrhage
- Describe the clinicopathologic features of the more common CNS infections
- Have an understanding of the clinicopathologic features of demyelinating and neurodegenerative diseases
- Have an awareness of some of the more common toxic and acquired metabolic diseases
- Have an awareness of the main types of CNS tumours and tumour syndromes
- Have an overview of the main types of CNS malformations

Outline

I. Cellular Injury in the Central Nervous System
- **a. Reaction of different cell types to injury**

II. Raised Intracranial Pressure and Herniation
- **a. Cerebral oedema:** *Vasogenic oedema, Cytotoxic oedema*
- **b. Hydrocephalus:** *Non-communication, Communicating, Hydrocephalus ex vacuo*
- **c. Herniation:** *Subfalcine, Transtentorial, Tonsillar*

III. Cerebrovascular Disease
- **a. Hypoxia and ischaemia:** *Focal vs Global*
- **b. Haemorrhage:** *Intraparenchymal, Subarachnoid*

IV. Intracranial Haemorrhage and Other Trauma-related Injuries
- **a. Intracranial haemorrhage:** *Epidural, subdural, subarachnoid, intracerebral*
- **b. Trauma-related injuries:** *Skull fracture, Parenchymal injuries, Spinal cord injury*

V. CNS Infections
- **a. Mechanisms of spread**
- **b. Patterns of CNS involvement:** *Meningitis / meningoencephalitis, Abscesses*

VI. Demyelinating and Neurodegenerative Diseases
- **a. Demyelinating diseases:** *Multiple sclerosis*
- **b. Neurodegenerative diseases:** *Prior diseases, Alzheimer disease, Parkinson disease*

VII. Toxic and Acquired Metabolic Diseases
- **a. Vitamin deficiencies:** *Thiamine, Vitamin B12*
- **b. Toxic disorders:** *Alcohol*

VIII. CNS Tumours and Tumour Syndromes
- **a. General features and classification**
- **b. Tumour types:** *Gliomas, Embryonal tumours, Midline tumours, Meningeal tumours, Others*
- **c. Familial tumour syndromes:** *NF1, NF2, Tuberous sclerosis, von Hippel Lindau disease*

IX. CNS Malformations

a. **Neural tube defects:** *Anencephaly, Myelomeningocele, Encephalocele, Spina bifida*
b. **Forebrain abnormalities:** *Microencephaly, Agenesis of the corpus callosum etc.*
c. **Posterior fossa anomalies:** *Arnold-Chiari malformation, Dandy-Walker malformation*
d. **Syringomyelia and hydromyelia**

References

Kumar V, Abbas A, Aster J. *Robbins & Cotran Pathologic Basis of Disease*. 10th ed.

WHO Classification of Tumours Editorial Board. *Central nervous system tumours*. Lyon (France): International Agency for Research on Cancer; 2021. (WHO classification of tumours series, 5th ed.; vol. 6).

***Note**: Pathweb Study Notes are based on the key topics covered in the lectures in the Yong Loo Lin School of Medicine, as well as additional topics covered in major texts. For more comprehensive discussion on specific pathology topics, readers are advised to refer to the recommended texts in your respective courses.*

I. CELLULAR INJURY IN THE CENTRAL NERVOUS SYSTEM

Different cellular components of the CNS are affected by distinct neurologic disorders and also respond to injury in a distinct manner:

Cell type	Reaction to injury
Neurons	Neuronal injury may be acute or develop over years. Neurons have high metabolic activity and also a long lifespan (postmitotic cells incapable of proliferation) → unusually susceptible to ischemia and accumulation of misfolded proteins, resulting in apoptosis/necrosis • **Red neurons**: Neuronal injury following acute insults (e.g. ischemia, hypoglycemia). Earliest morphologic marker of neuronal cell death (shrunken cell border with intense cytoplasmic eosinophilia, nuclear pyknosis and loss of Nissl substance) • **Neuronal degeneration**: Neuronal death following progressive (subacute/chronic) injury (e.g. Alzheimer disease), most likely via apoptosis. Hard to appreciate early, best indicated by presence of reactive glial changes • **Axonal reaction**: Enlargement and rounding of the cell body during axon regeneration due to increase in protein synthesis • **Neuronal inclusions**: Intracytoplasmic accumulations of lipofuscin, proteins, carbohydrates in aging, neurodegenerative diseases and sometimes lipids and other substances in inborn errors of metabolism. Viral infections (e.g. CMV, rabies) can also form viral inclusions • **Wallerian degeneration**: Degeneration of axons after disruption of nerve fibers
Astrocytes	• **Gliosis**: Hypertrophy and hyperplasia of astrocytes. Most important histologic marker of CNS injury by any cause • **Cellular swelling**: Acute astrocytic injury e.g. in hypoxia • **Rosenthal fibers**: Thick elongated eosinophilic cytoplasmic inclusions within astrocytic processes (containing heat shock proteins and ubiquitin), typically associated with gliosis • **Corpora amylacea (polyglucosan bodies)**: Round basophilic concentrically lamellated structures in areas with astrocytic end processes, especially with advancing age
Microglia	Can **proliferate**, develop **elongated nuclei**, form **microglial nodules** (aggregates around small foci of tissue necrosis) or display **neuronophagia** (aggregate around cell body of dying neurons)
Other glial cells	• Oligodendrocytes can be injured/undergo apoptosis in demyelinating disorders, or display inclusions (e.g. viral inclusions in progressive multifocal leukoencephalopathy, α-synuclein inclusions in multisystem atrophy) • Ependydmal cells do not show specific reaction patterns to CNS injury

II. RAISED INTRACRANIAL PRESSURE AND HERNIATION

As the brain is encased within the rigid skull and dural reflections with limited capacity to expand, increase in intracranial pressure (increase in mean CSF pressure) can occur in 3 common clinical settings: **cerebral oedema**, **hydrocephalus** and **space occupying lesions** (e.g. tumours, haemorrhage, abscess). Consequences range from subtle neurologic deficits to brain **herniation** and death, depending on the extent and rapidity of pressure increase and nature of the underlying lesion

Cerebral oedema

Due to increased fluid leakage from blood vessels (**vasogenic oedema**), and/or injury to cells in the CNS (**cytotoxic oedema**). Conditions causing generalised oedema usually have elements of both. Grossly,

cerebral oedema is manifest as flattening of the gyri, narrowing of sulci and ventricular compression, and may eventually lead to herniation

1. Vasogenic oedema:

Increase in **extracellular** fluid, caused by disruption of the blood-brain barrier and increased vascular permeability, allowing fluid shift from the intravascular to extravascular compartment. Resorption is hampered by lack of lymphatics. Can be localized (e.g. adjacent to inflammation/tumours) or generalised (e.g. after a global ischemic injury)

2. Cytotoxic oedema:

Increase in **intracellular** fluid, due to neuronal, glial or endothelial cell injury e.g. in generalized ischemia/hypoxic insults

Hydrocephalus

Accumulation of **excessive cerebrospinal spinal fluid (CSF) within the ventricular system**, usually due to impaired flow and resorption of CSF by the arachnoid granulations rather than overproduction by the choroid plexus. In infancy before closure of the cranial sutures, hydrocephalus results in enlargement of the head; once the sutures fuse, hydrocephalus causes ventricular expansion and increased intracranial pressure

- **Non-communicating (obstructive) hydrocephalus**: Focal obstruction of ventricular system e.g. due to mass in third ventricle or aqueductal stenosis
- **Communicating hydrocephalus**: Enlargement of the entire ventricular system, which remains in continuity with the subarachnoid space e.g. due to arachnoid fibrosis after meningitis
- **Hydrocephalus ex vacuo**: Compensatory increase in ventricular volume secondary to loss of brain parenchyma

Herniation

Displacement of brain tissue past rigid dural folds (falx and tentorium) or through skull openings because of increased intracranial pressure, usually resulting from diffuse cerebral oedema (see above '*Cerebral oedema*') or space-occupying lesions. Cerebral oedema can be worsened by the increased intracranial pressure causing compression of cerebral vasculature, reduced perfusion and ischemic brain injury. Herniations can occur in different locations:

- **Subfalcine (cingulate) herniation**: Displacement of the cingulate gyrus under the falx in unilateral/asymmetric expansion of a cerebral hemisphere
    - Can cause compression of the anterior cerebral artery, causing secondary infarcts
- **Transtentorial (uncal, mesial temporal) herniation**: Displacement of medial aspect of the temporal lobe against the free margin of the tentorium
    - Can cause compression of cranial nerve III, causing pupil dilation and impaired ocular movements on the side of the herniation (ipsilateral)

  - Can cause compression of the posterior cerebral artery, causing secondary infarcts
  - Can cause compression of the contralateral cerebral peduncle, resulting in hemiparesis on the side of the herniation (ipsilateral)
  - Progression can cause secondary (Duret) haemorrhages in the midbrain and pons
- **Tonsillar herniation**: Displacement of cerebellar tonsils through the foramen magnum
  - Can cause life-threatening brainstem compression

III. CEREBROVASCULAR DISEASE

Altered blood flow (hypoxia/ischaemia or haemorrhage) causing brain injury (tissue infarction). Manifest clinically as "**stroke**" – acute onset of neurologic signs and symptoms explained by a vascular mechanism and persist beyond 24 hours, or "**transient ischemic event**" if the signs and symptoms disappear within 24 hours.

There are 2 main processes that may be seen in cerebrovascular disease: **Hypoxia/ischaemia** and **Haemorrhage.**

i. Hypoxia and ischemia: results from impairment of oxygenation and/or blood supply, the latter which may be due to reduction in perfusion pressure (e.g. hypotension) and/or small or large-vessel obstruction. Important because the brain is strictly dependent on aerobic metabolism. Cause can be **global** or **focal**, with clinical manifestations depending on region of brain affected (determined by the presence of collateral circulation, duration of ischemia, magnitude and rapidity of reduction in blood flow)

Focal cerebral ischemia

- Partial or complete arterial obstruction causing reduction or cessation of blood flow to a localized area, which results in infarction in the territory of the compromised vessel. Extent of tissue damage depends on duration of ischemia and adequacy of collateral flow (mainly from circle of Willis, sometimes collateral leptomeningeal vessels at the brain cortex)
- **Causes**: Frequently associated with cardiovascular disease
  - **Embolism:** More common than thrombosis in the brain
    - **Source**: Usually from cardiac mural thrombi (e.g. after myocardial infarction, valvular disease, atrial fibrillation), or thromboemboli from arteries esp. carotid arteries. Less commonly, paradoxical thromboemboli in children with cardiac anomalies, from cardiac surgery or fat, air, tumour emboli
    - **Location**: Emboli usually lodge where vessels branch or areas of stenosis. Usually territory supplied by middle cerebral artery (MCA), a direct extension of the internal carotid artery. Fat emboli e.g. after fracture may occur as a "shower" causing widespread lesions involving the white matter without localizing signs
  - **Thrombotic occlusion of cerebral arteries:**
    - Usually due to acute change of vulnerable atherosclerotic plaques, mostly at the carotid bifurcation, MCA origin or either end of the basilar artery. Thrombi cause

luminal narrowing and may also be complicated by anterograde extension, fragmentation and distal embolism. Associated with hypertension and diabetes
    - Can be due to hypercoagulable states, drug abuse (e.g. cocaine)
- **Inflammation of blood vessels:** Can cause luminal narrowing and occlusion. Can be infectious (e.g. syphilis, tuberculosis, opportunistic infections in immunocompromised) or non-infectious vasculitides (e.g. polyarteritis nodosa, primary angiitis of the CNS)

- **Types of infarcts:** Affects clinical management even if underlying cause is the same
  - **Non-haemorrhagic** (pale/anaemic): Clinically termed 'ischaemic' infarcts although all infarcts result from ischaemia and generally start out as non-haemorrhagic because the brain is an end-organ with limited collateral supply. Early diagnosis and rapid treatment with thrombolytic agents can limit or prevent permanent neurologic deficits

	Time	Gross	Microscopy
Acute infarct	< 6h	Changes not obvious	Changes not obvious
	6-48h	Infarct appears ill-defined, pale, soft and swollen with indistinct gray-white matter junction	- Cytotoxic and vasogenic oedema - Neurons undergo eosinophilic necrosis ('red neurons'), with disintegration and loss of the usual tinctorial characteristic of white and gray matter structures - Some neutrophils also emigrate to the area and then decrease
Subacute (evolving infarct)	2-10 days	Infarct appears gelatinous and friable, with more distinct boundary with the adjacent viable tissue as the peri-lesional oedema resolves	Phagocytic cells (from circulating monocytes and activated microglia) appear
	10 days-3 weeks	Infarct liquefies (liquefactive necrosis), leaving a fluid-filled cavity	- Phagocytic cells are predominant as liquefactive necrosis progresses - Reactive astrocytes and newly formed vessels are seen at the periphery of the lesion
Healed infarct	Months	Cavity after removal of all necrotic tissue	- Astrocytic response recedes, leaving a dense meshwork of glial fibers admixed with new capillaries and some perivascular connective tissue (gliosis) - Foamy macrophages (with products of myelin breakdown) may persist

  - **Haemorrhagic**: Due to ischaemia-reperfusion injury causing secondary haemorrhagic transformation of the infarct. Occurs after the causative ischaemic event has lasted long enough to damage small blood vessels in the infarct, with resulting petechial or confluent haemorrhage. This may follow spontaneous or therapeutic dissolution / fragmentation of the intravascular occlusive material e.g. individuals on anticoagulant therapy, or patients with venous thrombosis. Thrombolytic therapy is contraindicated
    - **Gross and microscopy**: Features and temporal evolution similar to non-haemorrhagic infarcts, with additional blood extravasation and resorption

  - **Lacunar**: Small cavitary infarcts < 15mm wide (lacunes). Usually due to arteriolosclerosis of the deep penetrating arteries and arterioles supplying the basal ganglia, brainstem and cerebral hemispheres in patients with hypertension, progressing to thrombosis and complete vessel occlusion. Depending on location, can be clinically silent or cause neurologic impairment
    - **Gross**: Single or multiple small lake-like spaces, often involving putamen, globus pallidus, thalamus, internal capsule, deep white matter, caudate nucleus and pons
    - **Microscopy**: Tissue loss with surrounding gliosis
- **Clinical features:** Neurologic symptoms depend on anatomic distribution of damage rather than the underlying cause, often developing rapidly over minutes and evolving after hours. Symptoms may improve if ischaemic injury reverses and perilesional oedema decreases, although generally symptoms slowly improve over months
- **Vascular dementia:** Individuals who suffer multiple bilateral gray and white matter infarcts over the course of many months and years may develop a distinctive clinical syndrome characterized by dementia, gait abnormalities, pseudobulbar signs and often superimposed focal neurologic deficits. This multifocal vascular disease may be due to cerebral atherosclerosis or vessel thrombosis or embolization from carotid arteries or heart

Global cerebral ischaemia / hypoxia

- Due to generalised decrease in cerebral perfusion (e.g. shock) or decreased oxygen carrying capacity of blood (e.g. carbon monoxide poisoning)
- CNS cells show selective vulnerability to hypoxia/ischaemia – neurons are most sensitive (particularly the pyramidal neurons in the hippocampus, cerebellar Purkinje cells and pyramidal neurons in the cerebral cortex)
- **Border zone ('watershed') infarcts** may be seen after severe hypotensive episodes (e.g. patients resuscitated after cardiac arrest) and occur in border zones between arterial territories of the brain or spinal cord (e.g. between the anterior and middle cerebral artery distribution). This may appear as bilateral cortical wedge-shaped infarcts with secondary haemorrhagic transformation
- **Clinical features**: Clinical outcome depends on severity and length of insult, varying from transient confusion to irreversible damage (diffuse hypoxic/ischaemic encephalopathy) which may result in a persistent vegetative state with widespread neuronal death
- **Gross:** Oedematous swollen brain with widened gyri, narrowed sulci and poor demarcation between gray and white matter
- **Microscopy:** Cellular changes are similar to those seen in focal cerebral ischaemia; difference is in the overall pattern of brain involvement e.g. laminar necrosis may be seen in the cerebral neocortex with preservation of some layers and destruction of others

ii. Haemorrhage: Non-traumatic intraparenchymal or subarachnoid haemorrhage due to rupture of CNS vessels, usually due to hypertension or vascular anomalies (aneurysms, malformations)

Intraparenchymal haemorrhage

- Due to rupture of a small intraparenchymal vessel
- **Causes**: Usually due to **hypertension** (usually causing ganglionic haemorrhage i.e. in the basal ganglia and thalamus) or **cerebral amyloid angiopathy** (usually causing lobar haemorrhage i.e. in the lobes of the cerebral hemisphere). Others include systemic coagulopathy, neoplasms, vasculitis, aneurysms and vascular malformations
    - **Hypertension**: Leads to hyaline arteriolosclerosis in smaller arteries – these vessels with hyaline change are thickened but more fragile, which can rupture especially in the basal ganglia and subcortical white matter. If they undergo occlusion instead of rupture, lacunar infarcts result *(see above 'Focal cerebral ischaemia – Types of infarcts')*
    - **Cerebral amyloid angiopathy (CAA)**: Amyloidogenic peptides (usually Aβ) are deposited in the walls of medium- and small- caliber meningeal, cortical and cerebellar vessels. Amyloid deposition makes vessels more rigid but weaker, leading to haemorrhage. Risk is associated with apolipoprotein E (ApoE) gene polymorphisms as well as *APP* gene mutations
- **Clinical features**: Location and size of haemorrhage determines the clinical manifestations. Can be clinically silent or evolve like an infarct if affecting smaller regions, sometimes with clinical improvement with gradual removal of the haematoma over weeks or months
- **Morphology**: Acute haemorrhages comprise a central core of clotted blood compressing adjacent parenchyma, leading to secondary infarction with oedema and anoxic neuronal and glial changes. Old haemorrhages show parenchyma cavitary destruction with surrounding rim of brownish discolouration

Subarachnoid haemorrhage

- **Causes**: Most frequent atraumatic cause is due to rupture of a **saccular ("berry") aneurysm** in a cerebral artery. Other causes include rupture of a primary intraparenchymal haemorrhage into the ventricular system, vascular malformation, coagulopathies and tumours
    - **Saccular aneurysm**: Most common type of intracranial aneurysm. Other aneurysm types (atherosclerotic, mycotic, traumatic, dissecting) more often cause infarction rather than haemorrhage
        - Thin-walled outpouching few mm to 2-3 cm wide. 90% are found near major arterial branch points in the anterior circulation in the circle of Willis and can be multiple
        - Mostly sporadic but may also have genetic component; other risk factors are cigarette smoking and hypertension. Not present at birth but develops over time due to underlying defect in the media of the vessel wall
        - May have atheromatous plaques, calcification or thrombi in the wall or lumen of the aneurysm. Rupture usually occurs at the apex of the sac with extravasation of blood into the subarachnoid space, brain parenchyma or both
    - **Vascular malformations**: Includes arteriovenous malformations (AVM), cavernous malformations, capillary telangiectasias and venous angiomas – the first 2 are associated with risk of haemorrhage. May also present as seizures. Large AVMs in newborns can lead to congestive heart failure because of shunting effects

- **Clinical features**: Subarachnoid haemorrhage from ruptured saccular aneurysm is most frequent in the fifth decade and slightly more frequent in women. May be associated with acute increase in intracranial pressure e.g. straining at stool. Presents with sudden severe headache with rapid loss of consciousness. 25-50% of patients die with the first rupture, with survivors often showing improvement and recovery of consciousness within minutes. Repeat bleeding is common with worsening prognosis

IV. INTRACRANIAL HAEMORRHAGE AND OTHER TRAUMA-RELATED INJURIES

Intracranial haemorrhage: Can be traumatic (due to disruption of the vessel wall) or atraumatic *(see also above section 'Cerebrovascular disease – Haemorrhage')*

Location	Aetiology	Features
Epidural haematoma	**Trauma** (esp. temporal skull fractures in adults), causing injury to dural arteries esp. middle meningeal artery	- Extravasation of blood from the torn vessel under arterial pressure causes the dura to separate from the periosteum; blood accumulates in this space - Patients may have a short lucid period (if blood accumulates slowly enough) before onset of rapidly evolving neurologic symptoms due to brain compression - Neurosurgical emergency – fatal brain herniation may result
Subdural haematoma	**Trauma**, causing injury to bridging veins between the brain (suspended in CSF) and dural venous sinuses (fixed relative to the dura) often at the point where they penetrate the dura	- Extravasated blood dissects between the dura and inner more cellular meningeal layer adherent to the arachnoid membrane) - Increased incidence with aging (due to brain atrophy) as well as in infants (thin-walled bridging veins) – may follow minor trauma in these age groups - Slowly evolving neurologic symptoms, often delayed from time of injury but usually manifest within 48h if symptomatic – if acute, high mortality rate; if chronic, good prognosis as venous bleeding is often self-limited (although can re-bleed, possibly from granulation tissue as the hematoma organizes in the first few months) - **Gross**: Collection of clotted blood along brain surface without extension into sulci or subarachnoid space, and flattening the underlying brain. Once organized, becomes firmly attached to the inner surface of the dura and free of the underlying arachnoid
Subarachnoid haemorrhage	**Trauma**	- Usually associated with underlying parenchymal injury
	Vascular abnormality (e.g. berry aneurysm, arteriovenous malformation)	- Sudden onset of severe headache with rapid neurologic deterioration
Intracerebral haemorrhage	**Trauma** (contusions)	- Usually crests of gyri (see below – *Trauma-related injuries*)
	Ischemia	- Haemorrhagic conversion of ischemic infarct - Usually following the cortical ribbon
	Hypertension	- "Ganglionic" haemorrhagic usually in the deep white matter, thalamus, basal ganglia or brainstem - May extend into ventricular system
	Cerebral amyloid angiopathy (CAA)	- "Lobar" haemorrhage involving subcortical white matter - May extend into subarachnoid space
	Tumours (primary or metastatic)	- Certain high grade gliomas or vascular metastases (e.g. melanoma, choriocarcinoma, renal cell carcinoma)

Trauma-related injuries: Skull fractures, parenchymal injury and/or vascular injury (intracranial haemorrhage – see above) can result, depending on the force of impact, object causing injury and whether the head is in motion at the time of injury. Long term sequelae include **post-traumatic hydrocephalus** (due to obstruction of CSF resorption from subarachnoid haemorrhage), **chronic traumatic encephalopathy** (dementia puglistica after repeated head trauma), **post-traumatic epilepsy** etc.

Skull fractures: Location of fracture depends on the thickness of various cranial bones and type of injury and point of impact e.g. pattern of falls (occipital when individual is awake vs either occipital or frontal if person falls because of loss of consciousness), base of skull fracture from impact to occiput

Parenchymal injuries:

- **Concussion**: Clinical syndrome of altered consciousness secondary to head injury, usually due to change in momentum of the head likely due to dysregulation of the reticular activating system in the brainstem. Neurologic recovery is usually complete although amnesia for the event often persists, and post-concussive neuropsychiatric syndromes may result with repetitive injuries
- **Contusions** (bruise) **and lacerations** (tearing of tissue): Direct parenchymal injuries caused by transmission of kinetic energy to the brain, often affecting the crests of gyri where the direct force is greatest. Locations are usually the sites of direct impact and areas that overlie a rough irregular inner skull surface e.g. frontal lobes along the orbital ridges
- **Diffuse axonal injury**: Damaged deep white matter regions, cerebral peduncles, superior colliculi and deep reticular formation in the brainstem likely due to direct axonal injury by mechanical forces causing alterations in axoplasmic flow, which may result in coma even without cerebral contusions e.g. after marked changes in angular acceleration in absence of physical skull impact

Spinal cord injury: Usually associated with transient / permanent displacement of the vertebral column encasing the spinal cord. Neurologic manifestations depends on the level of cord injury due to interruption from the brain and localized damage at the level of impact

V. CNS INFECTIONS

Infections cause damage to nervous system directly or indirectly through microbial toxins, inflammatory response or immune-mediated mechanisms

Mechanisms of spread

1. **Haematogenous**: Most common, usually via arterial circulation but sometimes retrograde venous spread from anastomoses with facial veins
2. **Direct implantation**: Usually due to trauma, rarely due to congenital malformations
3. **Local extension**: From infected adjacent structures e.g. sinuses, teeth
4. **Via the peripheral nervous system**: Viruses e.g. herpes zoster, rabies

Patterns of CNS involvement

Meningitis / Meningoencephalitis

- **Meningitis** = inflammatory process of the leptomeninges and CSF within the subarachnoid space
  Meningoencephalitis = inflammation of meninges and brain parenchyma
- **Causes**: Usually due to infections; less commonly nonbacterial irritants (chemical meningitis) or autoimmune disease

Clinical type	Organisms	Clinical features and morphology
Acute pyogenic meningitis	Bacterial - **Neonates**: *E.coli, group B streptococci* - **Infants**: *Haemophilus influenzae* - **Adolescents/young adults**: *Neisseria meningitidis* - **Elderly**: *Streptococci pneumoniae, Listeria monocytogenes*	- **Symptoms & signs**: Meningeal irritation and neurologic impairment: Headache, neck stiffness, photophobia, irritability, impaired consciousness - **CSF spinal tap**: ↑pressure, cloudy/purulent, neutrophils+++, ↑↑protein, ↓ glucose - **Clinical course**: Can be fatal if untreated - **Treatment**: Antibiotics - **Complications**: Ventriculitis, cerebritis, secondary vasculitis and venous thrombosis leading to cerebral infarction, leptomeningeal fibrosis causing hydrocephalus, arachnoid fibrosis, cranial nerve damage and mental retardation in children - **Gross**: Leptomeningeal exudate with prominent meningeal vessels. Depending on organism, can be over cerebral convexities or base of brain - **Microscopy**: Neutrophils in subarachnoid space
Aseptic meningitis	Aetiologic agent identified only in a minority - Usually viral e.g. enterovirus - Rarely bacterial, rickettsial, autoimmune	- **Symptoms & signs**: Meningeal irritation but with absence of organisms by bacterial culture - **CSF**: lymphocytes++, ↑protein, glucose normal - **Clinical course**: Less fulminant than pyogenic meningitis
Chronic bacterial meningoencephalitis	*Mycobacterium tuberculosis*	- May be part of active systemic disease or appear following seeding of silent lesions e.g. lung - Can involve brain or meninges; most commonly causes a diffuse meningoencephalitis - **Symptoms & signs**: Headache, malaise, mental confusion and vomiting - **CSF**: Mononuclear cells +/- neutrophils, ↑↑↑protein, N/↓ glucose - **Complications**: Arachnoid fibrosis causing hydrocephalus, obliterative endarteritis causing brain infarction - **Gross**: Gelatinous / fibrinous exudate characteristically at base of brain +/- discrete white areas of inflammation over the leptomeninges. Discrete intraparenchymal masses (tuberculomas) may also form and present as space-occupying lesions - **Micro**: Mixed inflammatory infiltrate +/- necrotizing

		granulomas. Arteries in subarachnoid space may show obliterative endarteritis
	Treponema pallidum	- **Meningovascular neurosyphilis**: Chronic meningitis involving the base of the brain +/- cerebral convexities and spine +/- obliterative endarteritis - **Paretic neurosyphilis**: *T.pallidum* involves the brain parenchyma and causes progressive cognitive impairment a/w mood alterations (general paresis of the insane) - **Tabes dorsalis**: Damage to sensory axons in dorsal roots of spinal cord - **Risk factors**: HIV (impaired cell-mediated immunity)
	Borrelia sp. (Neuroborreliosis)	Variable neurologic symptoms, including aseptic meningitis, neuropathies, encephalopathy
Viral meningoencephalo-myelitis		- Brain parenchymal infection + meningeal inflammation +/- spinal cord involvement - Some viruses show neural tropism of specific cell types or particular areas of the brain - Several viruses also show latency - **Complications**: Immune-mediated disease e.g, demyelination, congenital malformations in fetus, post-encephalitic progressive degenerative diseases
	Herpes simplex virus type 1	- Usually children, young adults - **Symptoms & signs**: mood, memory and behaviour alterations - **Pattern of involvement**: Inferior and medial regions of temporal lobes, orbital gyri of frontal lobes - **Micro**: Necrotizing haemorrhagic infection, perivascular inflammation, Cowdry type A intranuclear inclusions in both neurons and glia
	Herpes simplex virus type 2	- Adults: usually meningitis (in HIV patients, acute haemorrhagic necrotizing encephalitis) - Neonates: severe encephalitis
	Varicella-Zoster virus	- After the primary cutaneous infection (chickenpox), virus enters a latent phase within sensory neurons of the dorsal root or trigeminal ganglia, which can reactivate as shingles +/- postherpetic neuralgia
	Cytomegalovirus	- Fetuses: Periventricular necrosis followed by calcification and microcephaly - Immunosuppressed individuals: Opportunistic infection causing subacute encephalitis, subependymal region causing severe haemorrhagic necrotizing ventriculoencephalitis, choroid plexitis - **Micro**: Intranuclear and intracytoplasmic inclusions
	Poliomyelitis	- Eradicated by vaccination in most of the world - Usually causes subclinical or mild gastroenteritis; may secondarily invade the nervous system in some - **Symptoms & signs**: Initially meningeal irritation; may then advance to involve spinal cord causing flaccid paralysis with hyporeflexia and muscle wasting - **Pattern of involvement**: Anterior horn motor neurons of the spinal cord

		- **Micro**: Mononuclear perivascular cuffs, neuronophagia +/- cavitation
	Rabies	- Severe encephalitis transmitted by bite of rabid animal, usually dog. Virus ascends peripheral nerves from the wound site to enter the CNS - **Symptoms & signs**: Incubation period depends on distance of wound from brain. Starts with headache, fever, malaise + local paresthesia around the wound, then CNS excitability (painful touch), mouth foaming and hydrophobia due to pharyngeal muscle contracture. Subsequently, flaccid paralysis and death from respiratory failure - **Gross**: Severe oedema and vascular congestion - **Micro**: Widespread neuronal degeneration and inflammation most severe in brainstem. Negri bodies are pathognomonic – cytoplasmic round-oval eosinophilic inclusions in pyramidal neurons of the hippocampus and cerebellar Purkinje cells
	Human immunodeficiency virus	- **Direct infection**: Aseptic meningitis occurs within 1-2 wks of seroconversion in ~10% of patients; encephalitis can be seen in the chronic phase - **Symptoms & signs**: HIV-associated neurocognitive disorders (HAND), cognitive changes closely related to inflammatory activation of microglia and perivascular macrophages, some infected by HIV - **Micro**: Microglial nodules often with macrophage-derived multinucleated giant cells +/- necrosis and reactive gliosis in encephalitis - **Secondary effects** e.g. opportunistic infections (toxoplasmosis etc.) and primary CNS lymphoma - After effective treatment, some AIDS patients suffer from immune reconstitution inflammatory syndrome (IRIS) which can cause a paradoxical exacerbation of symptoms in the CNS of patients with opportunistic infections
	JC polyomavirus (progressive multifocal leukoencephalopathy)	- Encephalitis with predominant demyelination as the virus preferentially infects oligodendrocytes - Due to reactivation in immunocompromised patients e.g. AIDS as primary infection is asymptomatic - **Symptoms & signs**: Focal progressive neurologic deficits - **Imaging and gross**: Extensive multifocal cerebral or cerebellar white matter lesions - **Micro**: Area of demyelination, often subcortical, comprising sheets of lipid-laden macrophages and reduced axons. Lesion edge shows enlarged oligodendrocyte nuclei with amphophilic viral inclusions. Reactive astrocytes with interspersed bizarre giant astrocytes
Fungal meningoencephalitis		- Usually in immunocompromised patients, after widespread haematogenous fungal dissemination; rarely direct extension e.g. mucormycosis in diabetes

	Cryptococcus neoformans	- **Chronic meningitis**: Cryptococcal meningitis is common opportunistic infection in AIDS - **CSF**: few cells but ↑↑↑ protein
	Mucor sp. *Aspergillus fumigatus*	- **Vasculitis**: usually with mucormycosis and aspergillosis, which directly invade blood vessels and cause thrombosis, causing haemorrhagic infarction
	Candida albicans *Cryptococcus neoformans*	- **Parenchymal invasion**: often coexists with meningitis; usually granulomas or abscesses

Acute focal suppurative infections (abscess)

- Usually caused by pyogenic bacteria or fungi

Location	Clinical features
Brain abscess	- Discrete focus of necrosis with inflammation, usually caused by bacteria e.g. Streptococci, staphylcocci - **Routes of infection**: Direct implantation, local extension e.g. from mastoiditis, or haematogenous spread e.g. primary site from heart, lungs etc. or secondary to bacteraemia from dental procedures - **Risk factors**: Acute bacterial endocarditis (can result in multiple abscesses), congenital heart disease with right to left shunting, chronic pulmonary sepsis e.g. bronchiectasis, immunosuppression - **Clinical features**: Focal neurologic deficits - **Complications**: Increased intracranial pressure with herniation, abscess rupture with ventriculitis or meningitis, venous sinus thrombosis - **Treatment**: Antibiotics, surgery - **Microscopy**: Discrete lesion with central liquefactive necrosis, surrounding oedematous granulation tissue that may mature into a fibroblastic capsule with reactive gliosis
	- **Cerebral toxoplasmosis**: Opportunistic infection by *Toxoplasmosis gondii* commonly found in HIV-associated immunosuppression, forming multiple ring-enhancing brain abscesses on imaging in the cerebral cortex and deep gray nuclei - Primary material infection in pregnant women can cause the fetus to develop multifocal necrotizing lesions that calcify
Subdural empyema	- Usually spread of bacterial and rarely fungal infections from skull bones / sinuses - **Clinical features**: Localising symptoms, fever, headache, neck stiffness - **Complications**: Mass effect, thrombophlebitis of bridging veins causing thrombosis and brain infarction
Extradural abscess	- Usually a/w osteomyelitis, arising from adjacent focus of infection e.g. sinusitis - Surgical emergency if in the spinal cord with risk of spinal cord compression

VI. DEMYELINATING AND NEURODEGENERATIVE DISEASES

Demyelinating diseases

Acquired conditions characterized by preferential damage to myelin with relative axon sparing. However, the CNS has limited capacity to regenerative normal myelin, hence secondary axonal damage usually eventually occurs. Causes include infections (progressive multifocal leukoencephalopathy – see

above section '*Viral meningoencephalitis - JC polyomavirus*'), immune-mediated (e.g. multiple sclerosis, neuromyelitis optica) or inherited disorders (leukodystrophies)

Multiple sclerosis

- Most common autoimmune demyelinating disorder characterized by relapsing and remitting course of episodes of neurologic deficits separated in time, due to patchy white matter lesions separated in space
- **Pathogenesis**: Autoimmune response is directed against components of the myelin sheath likely initiated by Th1 and Th17 T cells; involves interplay of both genetic and environmental factors
- **Clinical features**: Optic neuritis is frequent initial presentation; multiple episodes of neurologic deficits required for diagnosis. **Treatment**: Immunosuppressive/modulatory agents but not curative
- **Gross**: Well-circumscribed irregular depressed glassy gray-tan plaques in the white matter (commonly adjacent to lateral ventricles, also corpus callosum, optic nerves, brainstem, spinal cord etc.); can extend into gray matter
- **Microscopy**: Active plaque – ongoing myelin breakdown characterized by abundant foamy macrophages and perivascular lymphocytes. Myelin absent but axons preserved. Inactive plaque – no macrophages, little/no myelin, reduced oligodendrocyte nuclei, prominent reactive gliosis and decreased axons

Neurodegenerative diseases

Disorders characterized by progressive loss of particular neural groups, thereby presenting with relatively stereotypic signs and symptoms e.g. neocortical involvement presents as cognitive impairment and dementia. Pathogenesis is usually due to accumulation of protein aggregates due to imbalance between synthesis and clearance. The aggregates are often resistant to degradation and show aberrant localization within neurons, recognized histologically as inclusions

Prion diseases

- Rapidly progressive neurodegenerative disorders caused by aggregation and intercellular spread of a misfolded prior protein (PrP), characterized morphologically by "spongiform" change in the brain
- **Pathogenesis**: Can be sporadic, familial or transmitted
    - **Initiation**: Normal PrP is a cytoplasmic protein or unknown function. PrP may spontaneously undergo a conformational change from its normal α-helix isoform (PrP^{c}) to an abnormal β-pleated sheet isoform (PrP^{sc}), which is resistant to protease digestion. This spontaneous conversion can occur at a higher rate in familial disease associated with germline PrP mutations e.g. familial forms of Creutzfeldt-Jakob disease
    - **Propagation**: PrP^{sc} facilitates the conversion of other PrP^{c} to PrP^{sc} molecules; prion diseases are therefore transmissible
    - **Aggregation**: Accumulation of pathogenic PrP^{sc} aggregates within neural tissue causes disease

- **Creutzfeldt-Jakob Disease (CJD)**: Most common prion disease, usually in elderly. 90% sporadic, 10% familial (due to mutations in *PRNP*, the gene that encodes PrP) and iatrogenic (e.g. corneal transplantation). Onset marked by subtle changes in memory and behaviour followed by rapidly progressive dementia, often associated with startle myoclonus. Disease is fatal
- **Variant CJD**: Affected young adults instead in the UK with slower progression of symptoms. Likely linked to bovine spongiform encephalopathy either via consumption of contaminated foods or blood transfusions, leading to public health measures to contain the spread
- **Microscopy**: Multifocal spongiform transformation of the cerebral cortex and deep gray matter structures manifest as uneven small and apparently empty microscopic vacuoles within neuropil and sometimes perikaryon of neurons, which may expand into cystic spaces (status spongiosus) in advanced cases together with neuronal loss and reactive gliosis. No inflammation. Prion protein plaques are seen – known as Kuru plaques; they are extracellular deposits of aggregated abnormal PrP, usually in cerebellum but also cerebral cortex in vCJD. Immunohistochemistry shows presence of proteinase K-resistant PrP^{sc} in tissue

Alzheimer disease (AD)

- Most common cause of dementia in older adults; incidence increases with age
- **Pathogenesis**: Due to accumulation of two proteins (Aβ and tau) in specific brain regions, as a result of excessive production and defective removal. This is manifest in the brain as the diagnostic **amyloid plaques** and **neurofibrillary tangles**, both of which contribute to neural dysfunction. Aβ generation (from proteolytic cleavage of amyloid precursor protein APP) appears to be the critical initiating event for the development of AD
    - **Genetics**: 5-10% familial. The genetic locus on chromosome 19 that encodes apolipoprotein E (ApoE) also has a strong influence on the risk of developing AD - ε4 allele increases the risk of AD and lowers the age of onset of the disease. Other genetic loci may also contribute
    - **Other host factors**: Aβ deposits elicit an inflammatory response, which likely contributes to damage and alterations in tau phosphorylation
- **Clinical features**: Slow progressive disease eventually leading to patients becoming incontinent, mute and unable to walk; concurrent illness e.g. pneumonia is often the terminal event
- **Gross**: Brain shows cortical atrophy (gyral narrowing and widening of sulci), most pronounced in the frontal, temporal and parietal lobes, which may be accompanied by compensatory ventricular enlargement (hydrocephalus ex vacuo) due to the reduced brain volume. The medial temporal lobe (including the hippocampus) is involved early in the disease course and severely atrophied later
- **Microscopy**:
    - **Neuritic (senile) plaques**: Focal spherical collections of dilated, tortuous, axonal or dendritic processes (dystrophic neurites) often around a central amyloid core which may be surrounded by a clear halo. The dystrophic neurites contain tau aggregates, while the amyloid core predominantly contains Aβ
    - **Diffuse plaques**: Deposition of Aβ peptides in the absence of surrounding neurites (believed to be an early stage of plaque development)

- **Neurofibrillary tangles**: Tau-containing bundles of filaments in the cytoplasm of the neurons that displace or encircle the nucleus. Appear "flame" shaped in pyramidal neurons and rounded "globose" shape in rounder cells
- **Cerebral amyloid angiopathy**: Found in both AD and non-AD patients

Parkinson disease (PD)

- Neurodegenerative disease characterised by a hypokinetic movement disorder (parkinsonism) caused by loss of dopaminergic neurons from the substantia nigra. These symptoms may also be seen in other rare diseases (e.g. progressive supranuclear palsy) and drugs that affect the dopaminergic system
- **Pathogenesis**: Due to protein accumulation and aggregation, mitochondrial abnormalities, and neuronal loss in the substantia nigra and elsewhere in the brain
  - Most are sporadic; environment risk factors include pesticide exposure
  - Genetic causes include *SNCA* mutations (gene encoding α-synuclein, a major component of the Lewy body), mutations causing mitochondrial dysfunction, lysosomal enzyme glucocebrosidase mutations and *LRRK2* mutations
- **Clinical features**: Parkinsonism includes slowing of voluntary movement (bradykinesia), rigidity, 'pill-rolling' tremor, festinating gait, diminished facial expression (masked facies), stooped posture. **Clinical course**: Disease eventually progresses to involve the cerebral cortex, leading to cognitive impairment (Lewy body dementia). **Treatment**: Symptoms due to dopamine deficiency can be relieved by replacement therapy with levodopa (the immediate precursor of dopamine); this becomes less effective as the disease progresses as therapy does not arrest or reverse disease
- **Gross**: Substantia nigra pallor due to the loss of the pigmented catecholaminergic neurons there
- **Microscopy**: Lewy bodies - single or multiple, cytoplasmic, eosinophilic, round to elongated inclusions composed of α-synuclein that often have a dense core surrounded by a pale halo, found in the remaining neurons in the substantia nigra and other brainstem nuclei. Gliosis is seen in areas of neuronal loss

VII. TOXIC AND ACQUIRED METABOLIC DISEASES

Vitamin deficiencies

Neural tissue is mainly affected by vitamin B deficiencies due to its high metabolic demand:

- **Thiamine (vitamin B1) deficiency**: Common in chronic alcoholism but also thiamine deficiency from gastric disorders. Manifests as **Wernicke-Korsakoff syndrome** – Wernicke encephalopathy is reversible, characterized by acute psychosis and ophthalmoplegia, while the irreversible Korsakoff syndrome marked by confabulation and short term memory loss ensues if the thiamine deficiency is left untreated. Grossly, foci of haemorrhage and necrosis in the mamillary bodies are seen early on, which may progress to cystic degeneration in later stages

- **Vitamin B12 deficiency**: Manifests as **subacute combine degeneration of the spinal cord** (degeneration of ascending and descending tracts) due to a defect in myelin formation, starting with symmetrical numbness and slight ataxia in lower limbs and progressing to spastic weakness and paraplegia

Toxic disorders

Alcohol

- Acute ethanol intoxication: Effects reversible
- Chronic alcohol abuse: Direct or indirect (due to nutritional deficiency) effects
    - **Wernicke-Korsakoff syndrome** (due to thiamine deficiency)
    - **Cerebellar atrophy** (predominantly superior anterior vermis): ataxia, unsteady gait, nystagmus
    - **Fetal alcohol syndrome**: growth retardation, cerebral malformations

VIII. CNS TUMOURS AND TUMOUR SYNDROMES

- Majority are primary tumours (especially in children). Location depends on age: 70% of childhood tumours arise in the posterior fossa; in adults, most arise in the cerebral hemisphere above the tentorium
- **Clinical presentation and course**: Can present with general symptoms e.g. seizures or raised intracranial pressure e.g. headache, vomiting in addition to focal neurologic deficits. Clinical course depends on focal vs diffuse pattern of tumour growth and tumour location – diffusely infiltrative tumours are harder to resect, but benign focal tumours can also cause significant neurologic deficits if located in a critical brain region e.g. posterior fossa meningiomas can compress the brainstem and cause cardiorespiratory arrest. May spread via cerebrospinal fluid (e.g. ependymomas)
- **Tumour grade**: Based on both histologic and molecular findings. Has some correlation with the expected natural history within each tumour type, generally ranging from grade 1 to 4 (although some tumour types may not have a grade 1 or grade 4 due to historical reasons). Malignant tumours can progress and become more aggressive with time, changing to a higher tumour grade
- **Classification**: Based on integration of histology, immunohistochemistry and molecular changes

Tumour type	Classification notes	Some individual entities and features
Gliomas		
Astrocytoma (astrocytes)	Circumscribed gliomas e.g. pilocytic astrocytoma have better prognosis	**Pilocytic astrocytoma** - Circumscribed cystic glioma with variable proportions of bipolar hair-like (pilocytic) cells, compact and loose or myxoid regions, Rosenthal fibres, and eosinophilic granular bodies. Associated with MAPK pathway gene alterations (usually *BRAF* fusion) - Most common in cerebellum (esp. in children) - Favourable overall survival
	Diffuse gliomas (gliomas with a non-contained growth pattern) can be divided into adult-	**Astrocytoma, *IDH*-mutant** (grades 2, 3 or 4) - Diffusely infiltrating tumour, adult-type - Range from well-differentiated low cellularity slow-growing tumours (grade 2) to highly anaplastic hypercellular rapidly progressive tumours with necrosis and/or microvascular

	type and paediatric due to clinical and biologic differences	proliferation and/or CDKN2A/B homozygous deletion (grade 4 – no longer equivalent to "glioblastoma")
		Glioblastoma, *IDH*-wildtype (grade 4) - Diffusely infiltrating tumour, adult-type, IDH- and H3-wildtype with one or more of the following features: necrosis, microvascular proliferation, *TERT* promoter mutation, *EGFR* gene amplification - Irregular highly cellular pleomorphic tumour often centred in the subcortical white matter and deeper grey matter of the cerebral hemispheres (ring enhancing on imaging), frequently extending across the midline into the contralateral hemisphere ('butterfly glioma') - Poor survival even with chemoradiation (worse than grade 4 IDH-mutant astrocytomas)
Oligodendroglioma (oligodendrocytes)		**Oligodendroglioma, IDH-mutant and 1p/19-codeleted** (grade 2 or 3) - Diffusely infiltrating tumour, adult-type - Grossly appear relatively well-defined +/- local invasion into the overlying leptomeninges, frequent cystic degeneration and intratumoral haemorrhage - Microscopically round cells with distinct cell membranes and clear cytoplasm around central round nucleus ('fried egg' appearance) on formalin-fixed paraffin embedded tissue, frequently with microcalcifications - Overall favorable response to therapy
Ependymoma (ependymal cells lining ventricular system)	Classified by anatomical site and additional genetic/ epigenetic changes	- Entities by site include: **Supratentorial**, **Posterior fossa**, **Spinal**, and each can be further categorized by molecular changes e.g. *YAP1* fusion (grade 2 or 3) - Spinal cord ependymomas more common in adults, esp. in *NF2* - Generally characterized by uniform small round cells in a fibrillary matrix +/- pseudorosettes or ependymal rosettes - Can cause hydrocephalus due to location (periventricular). Supratentorial location generally poorer outcome than infratentorial tumours
Embryonal tumours		
Medulloblastoma	Can be molecularly defined (based on *WNT*, *SHH* and *TP53* status) or histologically defined (classic, large cell /anaplastic, desmoplastic /nodular)	- Usually occurs in childhood (2nd most common CNS tumour in children after high grade glioma) - All are Grade 4 tumours although some molecular groups e.g. *WNT*-activated medulloblastomas show very good response to treatment and almost all can be cured - Usually located in the brainstem; high tendency to spread to subarachnoid space and form "drop metastases" via CSF - Microscopically, hypercellular tumour comprising small primitive cells with high N:C ratio, high mitotic and apoptotic activity +/- Homer Wright rosettes
Other midline tumours		
Pituitary tumours	Arise from hormone-producing cells (pituitary adenoma / carcinoma) or embryonal remnants (craniopharyngioma)	**Pituitary adenoma** - Clonal neoplastic proliferation of anterior pituitary hormone-producing cells - May be incidental, present with hormone excess syndromes e.g. Cushing disease, or mass effects if large (e.g. visual field disturbances due to compression of optic chiasm)

		- Many are non-invasive (expansile) but some are invasive, or can display aggressive clinical behaviour and rapid growth **Pituitary carcinoma** - Requires craniospinal dissemination and/or metastases **Craniopharyngioma** - Squamous epithelial tumours thought to arise from elements from Rathke pouch / craniopharyngeal duct - Two distinct types: Adamantinomatous and papillary, with distinct clinical, imaging and pathologic features
Germ cell tumours	Various types paralleling gonadal and other extragonadal germ cell tumours	- Includes mature and immature teratomas, germinoma, embryonal carcinoma, yolk sac tumour etc. - Usually in children - 80-90% arise in the midline (pineal region, suprasellar). Often compress the cerebral aqueduct causing hydrocephalus, compress the optic chiasm causing visual disturbances or disrupt the hypothalamic-pituitary axis
Meningeal tumours		
Meningiomas		- Usually slow-growing tumours likely arising from meningothelial cells of the arachnoid mater in intracranial (falx, cerebral convexities), intraspinal or orbital sites , and often attached to the dura (grade 1, 2 or 3) - Often present with neurologic symptoms depending on tumour location and compression/mass effect - Can invade dura, brain and bone - Most common cytogenetic abnormality is loss of chr22 (including the region with the *NF2* gene – can therefore be a/w neurofibromatosis 2) - Grossly, usually solid circumscribed masses with a broad dural attachment, compressing but detachable from adjacent brain - Microscopically, >10 different histologic subtypes (commonest is meningothelial subtype)
Others		
Lymphoma	Lymphoma types similar to that seen in other sites	- Primary CNS lymphomas need to be distinguished from brain metastases from other primary lymphoma sites - Most common CNS lymphoma: **diffuse large B-cell lymphoma (CNS-DLBCL)**; usually elderly patients, worse prognosis than systemic DLBCL - Primary CNS lymphomas are the most common CNS tumour in immunosuppressed patients (often EBV-driven)
Metastases		- 80% are located in the cerebral hemispheres, particularly in arterial border zones and junction of grey-white matter; some also metastasize to meninges as solitary mass or disseminated pattern (meningeal carcinomatosis) - Most are multiple rather than solitary metastases - Commonly from lung carcinoma; also breast carcinoma, melanoma, renal cell carcinoma and colorectal carcinoma - Some may present with **paraneoplastic syndromes** in addition to the symptoms caused directly by the metastasis, likely due to the development of an immune response against tumour antigens that cross-reacts with antigens in the central or peripheral nervous system e.g. limbic encephalitis

Familial tumour syndromes

Tumour syndrome	Gene involved	Features
Neurofibromatosis type 1	*NF1* (neurofibromin)	- Autosomal dominant (AD) - Neurofibromas, optic nerve gliomas, café au lait spots - Non-CNS lesions: Phaeochromocytomas
Neurofibromatosis type 2	*NF2* (merlin)	- Autosomal dominant (AD) - Bilateral vestibular (CN VIII) schwannomas, multiple meningiomas, ependymomas of cervical spinal cord
Tuberous sclerosis complex	*TSC1* (hamartin) *TSC2* (tuberin)	- Autosomal dominant (AD) - CNS hamartomas and benign tumours (cortical tubers and subependymal nodules), often presenting as seizures - Non-CNS lesions: renal angiomyolipomas, pulmonary lymphangioleiomyomatosis, cardiac rhabdomyomas, cysts - Cutaneous lesions: angiofibromas, shagreen patches
Von Hippel Lindau disease	*VHL* (VHL protein)	- Autosomal dominant (AD) - Haemangioblastomas of the CNS, often in cerebellum and retina - Non-CNS lesions: pancreas/liver/kidney cysts, renal cell carcinomas, phaeochromocytomas

IX. CNS MALFORMATIONS

Due to both genetic (single gene or larger scale alterations) and environmental influences (toxic compounds, infectious agents). Generally, the earlier in development it occurs, the more severe the morphologic and functional changes. In general, CNS malformations can be classified into neural tube defects, forebrain, posterior fossa abnormalities and spinal cord abnormalities

Neural tube defects

- Most common malformation; Midline malformations involving neural tissue, meninges and overlying bone or soft tissue
- **Risk factor**: Folate deficiency during first weeks of gestation
- **Pathogenesis**:
  (1) Failure of neural tube closure, with secondary mesenchymal tissue defects
    - **Anencephaly**: Absence of most of the brain and calvarium due to malformation of anterior end of the neural tube; may still have posterior fossa structures
    - **Myelomeningocele**: Extension of CNS tissue through a defect in the vertebral column, most often in lumbosacral region. Causes motor and sensory deficits in lower extremities, bladder and bowel control issues and risk of spinal cord infection

  (2) Primary bony defects caused by abnormal axial mesoderm development, leading to secondary CNS abnormalities
    - **Encephalocele**: Extrusion of malformed brain tissue through midline defect in skull
    - **Spina bifida**: Most common neural tube defect. May be asymptomatic bony defect (spina bifida occulta) or severe malformation associated with overlying meningeal outpouching

Forebrain abnormalities

- May be focal or more extensive, due to abnormalities in generation and migration of neurons
- **Volume of brain**:
    - **Megalencephaly**: abnormally large
    - **Microencephaly**: abnormally small. More common, associated with chromosomal abnormalities, fetal alcohol syndrome, in utero viral infection e.g. Zika virus
- **Abnormalities of the gyri**:
    - **Lissencephaly**: reduced number of gyri (agyria = no gyral pattern)
    - **Polymicrogyria**: numerous small irregularly formed cerebral convolutions with shallow sulci
- **Others**:
    - **Holoproscencephaly**: spectrum of malformations characterized by incomplete separation of cerebral hemispheres across the midline. A/w trisomy 13 and other genetic syndromes
    - **Agenesis of the corpus callosum**: relatively common; may be associated with intellectual disability but also found in normal individuals

Posterior fossa anomalies

- May be accompanied by morphologic changes in other brain regions
- **Chiari type II malformation (Arnold-Chiari malformation)**: small posterior fossa, misshapen midline cerebellum with downward extension of vermis through the foramen magnum, hydrocephalus and lumbar myelomeningocele
- **Chiari type I malformation**: less severe than Chiari type II malformation, in which low-lying cerebellar tonsils extend down the vertebral canal
- **Dandy-Walker malformation**: enlarged posterior fossa, with absent/rudimentary cerebellar vermis

Syringomyelia and hydromyelia

- **Hydromyelia** = expansion of the ependyma-lined central canal of the spinal cord
  Syringomyelia / syrinx = fluid-filled cleft-like cavity in the inner portion of the cord (syringobulbia if it extends into the brainstem)
- Syringomyelia may be associated with Chiari malformation, intraspinal tumours or following trauma. Disrupts the crossing anterior spinal commissure fibers of the spinal cord, causing isolated loss of pain and temperature sensation in the upper extremities