I. **Astrocytomas:**

A. Diffusely infiltrating (astrocytoma, anaplastic astrocytoma, GBM)

B. Localised (pilocytic astrocytoma, pleomorphic xanthoastrocytoma, SGCA)

*Grading:

**Diffuse:**

1. Astrocytoma WHO grade II (Hypercellularity, pleomorphism, minimal nuclear atypia, no mitosis, no endothelial proliferation, no necrosis)
   A. Fibrillary: grossly the tumour is infiltrative, poorly demarcated and firm. This is the most common form. The tumour cells have elongated fibrillary processes that stain positive for GFAP and Vimentin.

B. Gemistocytic: > 60% gemistocytes (round or slightly angulated cells with abundant eosinophilic cytoplasm and eccentric nuclei. The presence of gemistocytes is a sign of poor prognosis in low grade astrocytomas

C. Protoplasmic: rare <1%, gelatinous due to microcystic degeneration. Plumb swollen astrocytes with short processes dispersed uniformly within eosinophilic matrix. **Cells stain –ve for GFAP**

2. Anaplastic astrocytoma: (hypercellularity, increased mitosis >5/10HPF, no necrosis, no endothelial proliferation). May arise denovo or progress from low grade astrocytomas.

3. GBM (AA+ necrosis or and endothelial proliferation)
   A. Primary: arising de novo, most commonly in elderly. (Amplification of EGFR gene on 7p)
   B. Secondary: progresses from low grade astrocytoma, more common in younger patients (loss of heterozygosity at 17p or mutations of P53).

Other systems include Ringert’s, Kernohan’s and St Ann Mary classifications

**Localised:**

1. Pilocytic astrocytoma:
   - Biphasic tumour consisting of area of bipolar, highly fibrillated (piloid or hairy) cells accompanied with Rosenthal fibres (bundles of fibrillary processes) and eosinophilic granules and loose less cellular microcystic area. The fibres stain positive for GFAP, and Vimentin.
   - Glumeruloid microvascular proliferation is common and does not imply malignant transformation
   - Affects children and young adults. Commonly affects midline neureaxis (cerebellum, spinal cord, hypothalamic –Chiasmatic region and brain stem). Well circumscribed tumours which tend to displace rather than invade. CSF metastases have been reported. More commonly in hypothalamic –chiasmatic lesions up to 12% in Mamelac report

2. Subependymal giant cell astrocytoma:
• Subependymal enhancing nodules most commonly in the region of foramen of Munro occur mostly in the setting of tuberous sclerosis (pathognomonic for TS).
• Three types of cells (small spindle shaped, large ganglion-like cells and intermediate gemistocytic like cells). The majority of cells stain positive for GFAP, S-100. The presence of mitosis, necrosis and nuclear pleomorphism does not indicate malignancy.
• Molecular genetics (loss of heterozygosity of TSC2 gene (16p) in some cases (different from diffuse astrocytomas)

3. Pleomorphic xanthoastrocytoma:
• Spindle cells intermixed with multinucleated giant cells. The cells show pleomorphism, intracellular inclusions and lipidisation. Variable collagen extracellular matrix.
• Superficial tumours of children and young adults, mostly affect the temporal lobe and present with seizures
• Biologic behaviour remains uncertain. Although initially described as low grade tumours, some tumours exhibit anaplastic progression and aggressive biological behaviour (WHO grade II-III).

II. Oligodendroglial tumours:
1. Oligodendrogliomas (50-70%) have deletions of 1p or 1p and 19q and this may indicate a more benign clinical behaviour and better response to chemotherapy). Deletion of 19q can be found in other astrocytomas while 1p is rare in other astrocytomas
• Diffuse or pseudo lobulated, the lobules are circumscribed by delicate branching vessels “chicken wire” pattern. The cells are uniform with round nucleus and perinuclear halo (fried eggs: the result of autolysis because of delay in fixation (. No necrosis or endothelial proliferation. Intercellular microcyst formation due to mucin accumulation is common.
• Ki67 labelling index for OD is 2%. Ki 67> 5 is associated with shorter survival
• 4-15% of gliomas, mostly fronto-temporal region. Calcification is common.
• No specific immunohistochemical markers. Some neoplastic oligodendroglial cells stain positive for GFAP, therefore, it is very important to differentiate these tumours from mixed oligoastrocytomas. (Common progenitor cell for astro and oligo. cells? Or transient expression of GFAP in immature oligodendrocytes.
• Higher tendency for haemorrhage than other gliomas
2. Anaplastic oligodendroglioma: prominent nuclear atypia, hypercellularity, high mitotic index, necrosis and endothelial proliferation.
III. Ependymal tumours:

1. Ependymoma
   • 6% brain gliomas. More common in children and young adults. Occur in the periventricular regions, 4th ventricle being the most common site. Account for 60% of spinal intramedullary cord tumours in adults. Well demarcated with plane of cleavage
   • Uniform cells with round nuclei. Rosettes (polarisation around extracellular matrix) and pseudorosettes (polarisation of cells around the blood vessels). GFAP +ve
   • Calcification in 25-50%. Cystic degeneration is common.
   • WHO classification
     A. Cellular:
     B. Papillary: differentiated from choroid plexus tumours by immunohistochemistry (stain positive for GFAP and negative for cytokeratin)
     C. Clear cell: differentiated from oligodendroglioma by the presence of rosettes and intercellular cilia and microvilli on electron microscope

2. Anaplastic ependymoma (nuclear atypia, mitosis, necrosis and endothelial proliferation)
   • Poor correlation between anaplastic features and biological behaviour

3. Myxopapillary ependymoma (elongated cells around blood vessels surrounded by mucinous stroma. Cell stain positive for GFAP)
   • Occurs in cauda equina of adults. Well circumscribed sausage like tumour, which enhances with gadolinium. It has a high tendency of local recurrence and drop metastasis. Every effort should be made to resect the lesion intact.

4. Subependymoma (WHO I)
   • Well circumscribed generally asymptomatic nodules located in the wall of fourth or lateral ventricles. Variable enhancement
   • Ependymal and astrocytic differentiation. Pseudorosettes and clusters of cells with fibrillar processes.
IV. Mixed gliomas:

- At present there is no accepted definition of mixed gliomas. Some workers defined mixed gliomas as gliomas in which the minor cell component exceeds 30%.
- Mixed oligoastrocytoma: contains neoplastic astrocytes and neoplastic oligodendrocytes and should be distinguished from oligodendrogliomas that contain reactive astrocytes (GFAP can be positive in both reactive and neoplastic astrocytes and in some anaplastic oligodendrocytes).
- Cytogenetics: 1p or 1p,19q deletions in the oligo component and loss of heterozygosity of 17p and mutation of P53 in the astrocytic component.
- Malignant oligoastrocytoma (high mitosis, necrosis and endothelial proliferation). The astrocytic component is more susceptible to anaplastic changes.

V. Choroid plexus tumours:

1. Choroid plexus papilloma:
   - Papillary pattern with fibrovascular stroma surrounded by pseudostratified columnar epithelium.
   - Stain +ve for cytokeratin, transthyretin and GFAP.

2. Choroid plexus carcinoma:
   - Hypercellular, nuclear atypia, mitosis and necrosis. Poorly differentiated cells with loss of the papillary pattern. Stains +ve for transthyretin and cytokeratin. CSF dissemination is not rare.

VI. Neuronal and mixed neuroglial tumours:

1. Gangliocytoma: composed of mature neurons, these neurons show nuclear pleomorphism and can be multinucleated. Slow growing tumours commonly arise in the temporal lobe, not associated with chronic seizure disorder.
2. Dysplastic gangliocytoma of cerebellum: hypertrophy of normal neurons resembling Purkinje cells. MRI-peculiar thickening of cerebellar folia.
3. Central neurocytoma: Intraventricular tumour arising in the region of foramen of Munro. Affects young adults. Histologically composed of homogenous small cells. The cells are arranged in cellular areas alternating with areas of dense fibrillary matrix. There is poor correlation between the presence of nuclear atypia, mitosis and necrosis and the prognosis. Cells stain +ve for synaptophysin, which indicates the neuronal origin of these tumours.
4. Ganglioglioma (WHO I-II):
   - Variable admixture of neoplastic neurons that stain +ve for synaptophysin and chromogranin A, tubulin III and neoplastic glial cells (stain for GFAP).
• 1% of brain tumours in adults, 5% of paediatric CNS tumours. Temporal lobe is the most common location and epilepsy is the most common presentation, usually minimal enhancement.
• The astrocytic component has the potential for anaplastic progression although this is rare.

5. Desmoplastic infantile Ganglioglioma (DIG): WHO I
• Large superficial tumour of infants which has large cystic part and enhancing solid component usually adjacent to leptomeninges
• Histologically there are three types of cells, small astrocytic, large ganglion like cells and spindle cells in fibrous desmoplastic stroma. It is believed that the presence of mitosis and necrosis does not correlate with prognosis.

6. Dysembryoplastic neuroepithelial tumour (DENT):
• Multinuclear intracortical non-enhancing tumours of children and young adults. Most commonly located in temporal lobe and present with partial complex seizures. Good prognosis with resection. No place for adjuvant chemo and radiotherapy
• Histologically composed of oligodendrocyte like cells and astrocytes and neurons. The neurons of the cortex appear to float in mucoid matrix within the proliferating oligodendrocytes. MIB< 1%.

VII. Pineal parenchymal tumours: < 1% of intracranial tumours and 15-30% of pineal region tumours
1. Pineocytoma (30%, WHO II): moderately cellular, uniform cells arranged around a nuclear centre formed by argyrophilic processes (pineocytomatous rosettes). No necrosis, low mitotic rate. Occurs in adults and tend to displace rather than invade brain structures
2. Pineoblastoma (60%, WHO IV): highly cellular composed of small round or oval cells with hyperchromatic nuclei, high mitotic index, and necrosis These tumours commonly express photosensory retinal S-Ag (This reflects the biochemical relationship between the pineal gland and retina). Homer Wright and Flexner Wintersteiner rosettes are occasionally seen. Highly malignant tumour. More common in children. Tends to invade the brain and cause CSF metastases.
3. Pineal parenchymal tumour with intermediate differentiation (10%, WHO III): Moderate cellularity, areas that resemble pineoblastoma, pineocytomatous rosettes are rare. Like pineoblastoma it shows photosensory differentiation. Prognosis is variable
VIII. Embryonal tumours: Tumours of immature cells capable of divergent differentiation. Features common to all of them are (hypercellularity, small cells with hyperchromatic nuclei, mitosis, necrosis and rosettes)

1. Medulloblastoma:
   - 25% of brain tumours in children, mostly arises in the vermis rarely in cerebellar hemisphere
   - Highly cellular, small poorly differentiated cells with hyperchromatic nuclei. Necrosis focal or confluent, Homer Wright (neuroblastic rosettes in 40%). As in most embryonal **tumours the cells are capable of divergent neuroglial differentiation** (some cells stain +ve for GFAP, others for Synaptophysin and other neuronal proteins). Less frequent variants may show striated muscle differentiation (medulomyoblastoma) or into melanin like cells (melanotic neuroectodermal tumour)
   - 1/3 of tumours show isochromosome 17q or loss of heterozygosity on 17p
   - The most common histological variant is desmoplastic (20% of adult and 10% of children tumours).

2. Neuroblastoma: supratentorial tumour of early childhood (hypercellular, small hyperchromatic cells, mitosis, necrosis and Homer Wright rosettes (neuroblastic) (polarisation of the cells around anuclear zone formed by cellular processes that stain with silver stains). Ganglion cell differentiation is seen in 50% of cases.

3. Ependymoblastoma: aggressive large supratentorial tumours of early childhood. (Common features + ependymoblastic rosettes “pseudo stratified with juxtraluminal mitosis”). Should be differentiated from anaplastic ependymoma (type of rosettes). Poor prognosis

4. Retinoblastoma:
   - Inactivation of both alleles of Rb tumour suppressor gene on chromosome 13
   - Most common intraocular tumour in children
   - Common features + Homer Wright rosettes and Flexner Wintersteiner rosettes (photosensory rosettes)
   - Photosensory and neuronal differentiation

5. Atypical teratoid/rhabdoid tumour:
   - Tumour of children <3 years of age
   - Commonly in the posterior fossa
   - Rhabdoid cells-large cells with eosinophilic cytoplasm and intracytoplasmic inclusions. Although called rhabdoid these cells are immunonegative to desmin and other muscle proteins

6. Medulloepithelioma: rare tumour composed of pseudostratified columnar epithelium (similar to the epithelium lining the neural tube) with high mitosis. Cells can have divergent neuroglial differentiation

7. PNET
IX. Tumours of cranial and spinal nerves:

1. Schwannoma: sporadic or part of neurofibromatosis (more in NF2). Schwann cell is the cell of origin. Biphasic tumour with cellular area formed by spindle bipolar cells with nuclear palisading and Verocay body formation (Antoni A) and loose less cellular areas formed by multipolar or spindle cells separated by myxomatous material. The nerve fibres are displaced around the tumour (basketing). Usually affects the dorsal spinal root. Malignant transformation is very rare< 0.001%. 1% is intraparenchymal. Bilateral acoustic schwannomas is the hallmark of NF2. Stain for S-100. Classified into cellular, plexiform and melanocytic. Cellular schwannoma (Hypercellularity, Antoni A areas and mitosis) must be differentiated from MPNST.

2. Neurofibroma: the cells of origin are Schwann cells, fibroblasts and perineuronal cells. Histologically the tumour is composed of spindle cells arranged in bundles within collagen and mucopolysaccharides matrix that makes the tumour soft and even gelatinous. The nerve fibres are within the lesion. Can be sporadic or part of NF1 less commonly NF2. Plexiform neurofibromas are pathognomonic for NF1 and have high potential of malignant degeneration 5-10%. Stain for S-100,NEA(marker of perineural cells)

3. Malignant peripheral nerve sheath tumours: Most MPNST are sporadic. Malignant changes in Schwannomas are rare <0.001% in sporadic disease and 4% in NF1. Plexiform neurofibroma can undergo malignant changes in 10%. Histologically the tumour is characterised by hypercellularity, pleomorphism, mitosis and necrosis. Cells arranged in fascicles of spindle cells with nuclear atypia, mitosis, necrosis and endothelial proliferation. Heterologous differentiation into muscle, bone, cartilage and epithelium is not uncommon. Immunoreactivity to S-100 is strong. 5 year survival in patients with NF1 is 16-18% , while 5 year survival in patients with sporadic MPNST is around 50%. Classified into epithelioid, MPNST with mesenchymal and epithelial differentiation, melanocytic and psammomatous-melanocytic.

X. Tumours of the meninges:

1. Meningiomas:
   • Derived from arachnoidal cap cells or meningotheial cells, 15% of intracranial tumours, and 25% of spinal tumours. M:F 1:3
   • 8% multiple, more with NF2. 50-70% of sporadic cases show LOH for 22q (22 monosomy)
   • WHO three type’s A. Typical meningioma B. Atypical C. Anaplastic (malignant).
   • Typical meningioma can exhibit epithelial and mesenchymal phenotypes, hence the many described variants( clear cell, secretory, chordoid, papillary, fibroblastic, chondroblastic, angiomatous, myxoid, psammomatous and so on)
• The most common variants are 1. Meningothelial: plump cells arranged in sheaths, lobules and whorls 2. Transitional: more whorls3. Fibroblastic: rich in collagen and reticulin.
• Atypical meningioma: hypercellular, nuclear atypia, high mitosis, necrosis, no brain invasion and no metastasis
• Anaplastic: prominent anaplastic changes (these can be absent), Brain invasion and metastases.

XI. Tumours of unknown histogenesis (hemangioblastoma)

Types of rosettes 1. True rosettes: polarisation of cells around extracellular matrix (ependymoma)
   2. Pseudorosettes: polarisation of cells around blood vessel (ependymoma)
   3. Homer-Wright rosettes “neuroblastic rosettes”: Polarisation of cells around argyrophilic cell processes (medulloblastoma)
   4. Ependymoblastic rosettes: pseudostratified cells around extracellular matrix with juxtraluminal mitosis
   5. Flexner-Wintersteiner rosettes: in retinoblastoma and medulloblastoma