CNS & peripheral nerve sheath tumors
CNS tumors, in general

• More than half of the cases are: 1ry...the remaining are metastases

• In pediatrics: 20% of all tumors in the body

• In pediatrics: Posterior fossa more

• In adults: Supratentorially more

• Even low-grade tumors may be clinically significant due to their location and mass effect on critical areas

• Even the highly malignant ones rarely spread outside the CNS
CNS tumors, general classification

Parenchymal tumors
- Gliomas
  - Astrocytomas
  - Oligodendrogliomas
  - Ependymomas
- Neuronal tumors
- Embryonal (Primitive) neoplasms
- Medulloblastoma

Meningeal tumors

Metastatic tumors

Others
- Lymphoma
- Germ cell tumors
Grade I

- Parenchymal tumors
- Gliomas
- Neurons

Grade II

- More mitosis
- Grade III = Anaplastic astrocytoma

Grade IV = Glioblastoma (GBM: Glioblastoma multiforme)

- Higher grade... worse prognosis
- Non-infiltrative (Present as discrete mass)
- Remember 2 names:
  - Pilocytic astrocytoma... children/the most common 1st intracranial tumor in them
  - SEGA (Subependymal giant cell astrocytoma)... **Tuberous sclerosis**

- 80% of adult gliomas
- 4th-6th decade
- Cerebral hemispheres more

- Median survival: 15 months... even after resection, radio- & chemotherapy
- Can arise de novo or as anaplastic change from a lower grade

- Histological criteria: Tumor coagulative necrosis or Microvascular proliferation

Astrocytomas

Oligodendroglioma

Can cross corpus callosum ("butterfly glioma")

Diffuse (infiltrative) astrocytomas

*80% of adult gliomas
*4th-6th decade
*Cerebral hemispheres more

Pilocytic astrocytoma... children/the most common 1st intracranial tumor in them
... posterior fossa (e.g., cerebellum) more
... can affect the optic pathway or difficult areas like hypothalamus
... usually with a cystic component
*5-15% of gliomas

*Always infiltrative

*Grade II (average survival: 10-20 years) or III (= anaplastic oligodendroglioma, average survival: 5-10 years)

...the differentiation between them depends on mitoses and/or necrosis/microvascular proliferation

*4th & 5th decades

*Mainly cerebral hemispheres

*Calcification is common...microscopic or even macroscopic
Some genetic alterations

Isocitrate dehydrogenase (IDH) genes:
- IDH1 or IDH2 mutations
- Grade II astrocytomas and oligodendrogliomas

Mutations in the promoter for telomerase:
- GBM and other astrocytic tumors
- Uncommon to occur with IDH mutations
- Common to occur with ATRX loss-of-function mutations

Co-deletion of 1p and 19q chromosomal segments (1p/19q deletion):
- 80% of oligodendroglioma cases
- Differentiates oligodendroglioma from astrocytoma

Some changes that occur elsewhere:
- EGFR overexpression
- p53 & RB mutations

Regarding pilocytic astrocytoma:
* The serine-threonine kinase BRAF, which result in activation of the MAPK signaling pathway is commonly involved
* Not associated with IDH mutations
A new entity categorized as grade IV glioma

• Called: **Diffuse midline glioma (H3 K27M–mutant)**

• Site: brainstem (most commonly the pons), thalamus or spinal cord

• Infiltrative and aggressive...regardless of the histological features

• Acquired point mutations in histone H3 (H3 K27M mutation)

• Mainly children and young adults
- Grade II or III (anaplastic)
- Near 4<sup>th</sup> ventricle in 1<sup>st</sup> 2 decades of life
- Spinal cord in adults and neurofibromatosis type 2 patients
  - Complete resection is possible
- Spinal & supratentorial are better than post. fossa ones
- Perivascular pseudorosettes & true rosettes are common
Central neurocytoma

- Far less frequent than gliomas
- Commonly present with seizures
- Low grade

Dysembryoplastic neuroepithelial tumor (DNET) ... children and young adults

Ganglioglioma
A small round blue cell tumor
- Mainly in children
- The most common malignant brain tumor in children
- Cerebellum (midline in children & lateral in adults)
- Highly malignant
  ...killer if not treated
  ...but very radiosensitive
  & 5-year survival rate may reach 75% if surgery + chemo. + radio.
- Homer Wright rosettes are common

Different categories based on genetics and associated tumor behavior:
1- Wnt pathway activation (commonly: beta-catenin gain-of-function mutation)...good
2- Hedgehog pathway activation (commonly as PTCH1 loss-of-function mutation)...intermediate behavior
  ...bad if with TP53 mutation
3- MYC overexpression...worst prognosis

Can spread via CSF along the neuraxis
Primary Central Nervous System Lymphoma

*Diffuse large B cell lymphoma is the most common
*2% of extranodal lymphomas and 1% of intracranial tumors
*The most common CNS neoplasm in immunosuppressed individuals
  ...in these patients: nearly always EBV-positive
*Poor response to chemotherapy as compared with peripheral lymphomas
*Commonly as multiple nodules but rare outside spread

*Along the midline, mostly pineal and suprasellar regions
*1st 2 decades of life
*The most common is germinoma (its counterpart in the testis is seminoma)
*Arise from arachnoid meningothelial cells
*Mainly in adults
*Women more
*Radiation, head trauma, hormonal effects (especially progesterone) are all associated
*Often attached to the dura
*Mostly benign and easily resected but can be infiltrative with more chance of recurrence and may be of grade I, II (atypical) or III (anaplastic)
*Most common mutation: NF2
*If multiple meningiomas + 8th nerve schwannoma (= acoustic neuroma) or gliomas: consider neurofibromatosis 2
*Several histological patterns (meningothelial (whorls, left image)-fibroblastic-psammomatous (right image)-others)
*Grade II has more mitoses/necrosis/cellularity/other features than grade I
*Grade III resembles high-grade sarcoma or carcinoma with much more mitoses than grade II
*Brain tissue invasion makes the grade at least II
*Bone invasion doesn’t affect the grade

The most common primary intracranial tumor in adults is meningioma...the 2nd is GBM
*The most common sites of origin are:
- Lung
- Breast
- Skin (melanoma)
- Kidney
- Gastrointestinal tract
Now let’s talk briefly about
peripheral nerve sheath tumors

• Mainly as soft tissue tumors or at the cerebellopontine angle or at spinal nerve roots or in internal organs

• The malignant among them is called: malignant peripheral nerve sheath tumor (MPNST)...aggressive

• Schwannomas (= neurilemmoma):
  ...benign and encapsulated...they bulge out easily for the surgeon
  ...the vestibular portion of the eighth nerve is the most common (= acoustic neuroma)...may be associated with hearing loss
  ...Antony A (hypercellular with Verocay bodies) and Antony B (hypocellular) areas are seen microscopically
Peripheral nerve sheath tumors, cont’d

• Neurofibromas:
  ... not encapsulated
  ... 3 types:
  1-Localized cutaneous neurofibromas
    ...solitary sporadic or multiple in NF1
    ...well-circumscribed and superficial
  2-Plexiform neurofibromas
    ...only seen in NF1
    ...risk (although small) for transformation into MPNST
    ...involve multiple fascicles of the affected nerve
  3-Diffuse neurofibromas
    ...often associated with NF1...can be large and disfiguring
    ...infiltrative in the dermis and subcutis
Familial tumor syndromes of the CNS & PNS

• Tuberous sclerosis

...Autosomal dominant...TSC1 (hamartin) or TSC2 (tuberin) mutations (these genes are inhibitors of mTOR oncogenic pathway)

...Hamartomas:
  - Cortical tubers...seizures that are difficult to control
  - Subependymal hamartomas (including a large form called SEGA which is almost exclusively seen here)...obstructive hydrocephalus due to the proximity to foramen of Monro

...Renal angiomyolipomas, retinal glial hamartomas, pulmonary lymphangioleiomyomatosis, and cardiac rhabdomyomas

...Cutaneous lesions include angiofibromas, leathery thickenings in localized patches (shagreen patches), hypopigmented areas (ash leaf patches), and subungual fibromas
Familial tumor syndromes of the CNS & PNS

• von Hippel–Lindau Disease

...Autosomal dominant

...Hemangioblastomas within the cerebellar hemispheres, retina, and, less commonly, the brain stem, spinal cord, and nerve roots

The most common cerebellar tumor in adults

...Other things discussed in the past
Familial tumor syndromes of the CNS & PNS

• Neurofibromatosis type 1 (NF1)

  ...Autosomal dominant

  ...Neurofibromin mutation on chromosome 17 (tumor suppressor...negative regulator of RAS)

  ...-Neurofibromas
    -Malignant peripheral nerve sheath tumor
    -Optic gliomas and other gliomas
    -Pigmented nodules of the iris (Lisch nodules)
    -Pigmented skin lesions (café-au-lait spots)
    -Others
Familial tumor syndromes of the CNS & PNS

• **Neurofibromatosis type 2 (NF2)**

• Autosomal dominant (Merlin loss-of-function mutation on chromosome 22, a tumor suppressor)

• Multiple schwannomas, meningiomas, and ependymomas

• The presence of bilateral vestibular schwannomas is a hallmark of NF2

• Despite the name, neurofibromas are not found in NF2 patients
Thank You