

The Central Nervous System: Tumors

The peripheral nervous system

Markéta Hermanová

Tumor of the CNS

- Gliomas
- Chorioid plexus tumors (papillomas and carcinomas)
- Neuronal and mixed (glio)neuronal tumors
- Embryonal tumors (poorly differentiated)
- Pineal tumors
- Meningeal tumors
- Other primary tumors of CNS
- Secondary (metastatic tumors – lung, breast,...)

CNS tumors

■ Clinicopathological features:

■ CNS tumors do not metastasise to other organs

- (only infiltration of adjacent tissues and spreading through
- CSF pathways)

■ Local effects

- Signs related to the site of the tumor
- e.g. epilepsy with a temporal lobe tumor, paraplegias in spinal cord tumor

■ Mass effects

- Signs and symptoms of space occupying lesions
- Vasogenic oedema around CNS tumor
- Herniation
- Hydrocephalus in posterior fossa tumor

Gliomas

■ Astrocytomas (AC)

- Diffuse astrocytomas (grade II) – LG AC (static, with slow progression)

Variants: gemistocytic

- Anaplastic astrocytomas (III)
- Glioblastoma multiforme (grade IV)
- Pilocytic astrocytoma (I)
- Pleomorphic xanthoastrocytoma (II)
- Anaplastic pleomorphic xanthoastrocytoma (III)

■ Oligodendrogliomas

- Oligodendroglioma (II)
- Anaplastic oligodendroglioma (III)

■ Mixed gliomas (provisional entities according WHO 2016)

- Mixed oligoastrocytoma (II)
- Anaplastic mixed oligoastrocytoma (III)

■ Ependymal tumors

- Ependymoma (II)
- Anaplastic ependymoma (III)
- Myxopapillary ependymoma (I)
- Subependymoma (I)

High grade (HG) astrocytomas (AC)

■ Anaplastic astrocytoma (III)

- Increased cellularity
- Increased degree of anaplasia, nuclear pleomorphism, increased proliferative activity

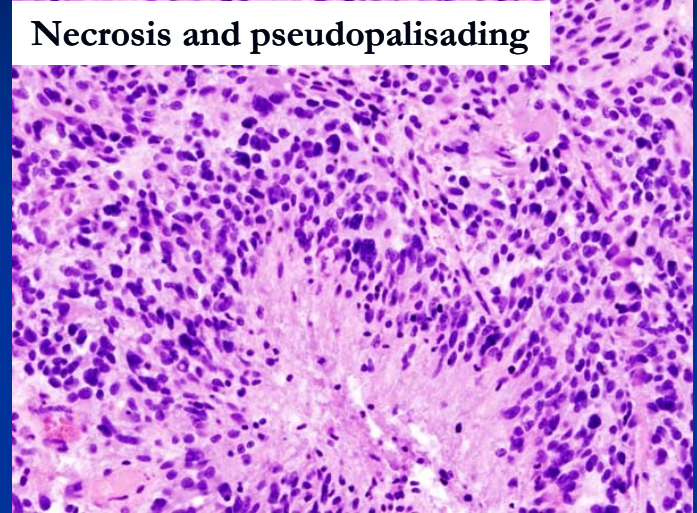
■ Glioblastoma (IV)

- Necrosis and pseudopalisading
- Vascular endothelial proliferation
- Primary (in older) and secondary (in younger with history of LG AC)
- Very poor prognosis

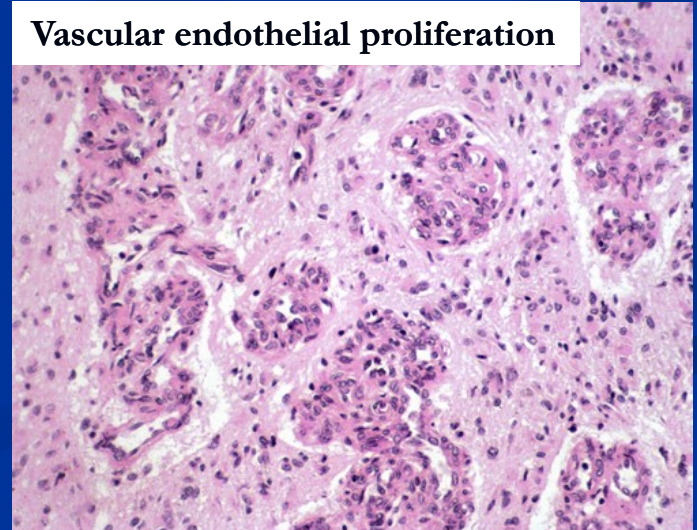
Glioblastoma



Necrosis and pseudopalisading



Vascular endothelial proliferation



WHO 2016: integrated diagnosis

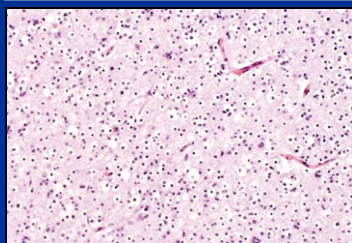
- Histopathological diagnosis/typing
- Histopathological grading/WHO grade
- **Molecular information**

Phenotype of gliomas

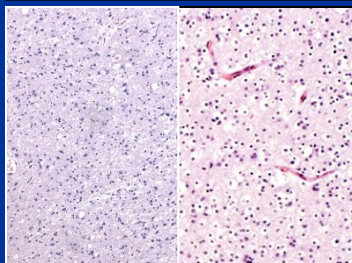
Astrocytic



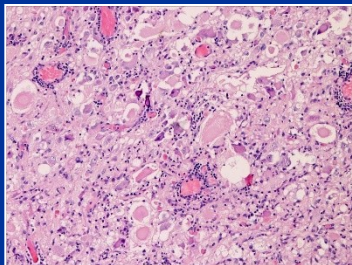
Oligodendrocytic



Oligoastrocytic

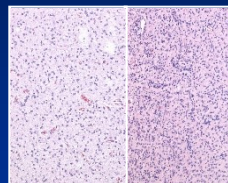


Glioneuronal

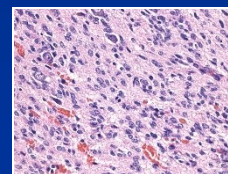


Grading of gliomas

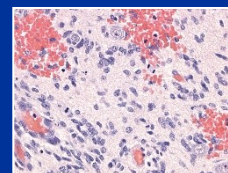
Cellularity



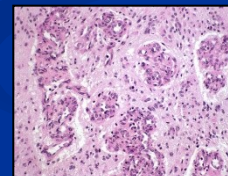
Cytonuclear atypia



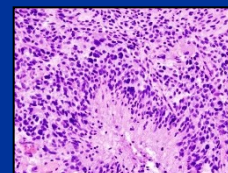
Mitoses



Microvascular proliferates

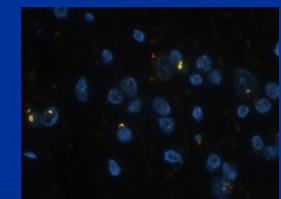
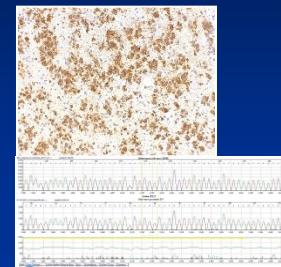


Necroses

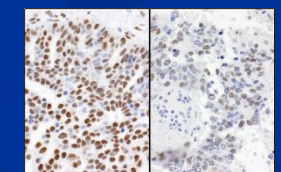


Genotype of gliomas

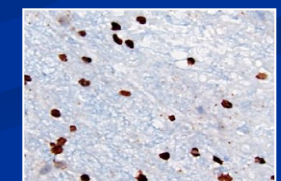
Mutations IDH1, IDH2



Codeletion 1p/19q



Mutation ATRX



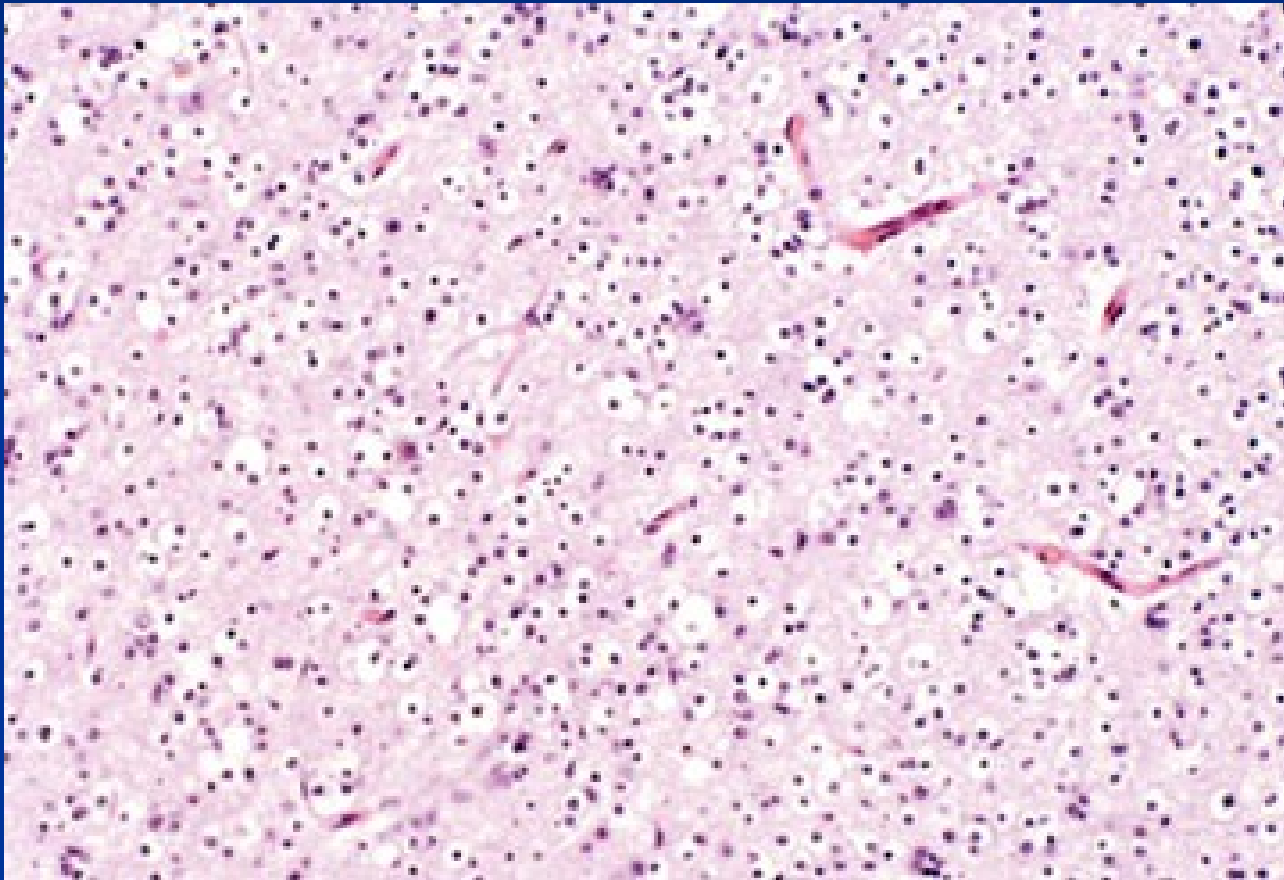
Mutation H3K27M

Oligodendroglioma (II)

- White matter of cerebral hemispheres (most frequently frontal lobes)
- Well circumscribed, gelatinous, gray masses, with cysts, hemorrhage, calcification
- Sheets of regular cells, clear halo of cytoplasm
- Delicate network of anastomosing capillaries
- Perineuronal satellitosis
- LOH for 1p and 9q/IDH mutated
- Better prognosis than AC

+ **anaplastic oligodendroglioma (III)**: hypercellularity, nuclear anaplasia, mitotic activity, necrosis

Oligodendroglioma



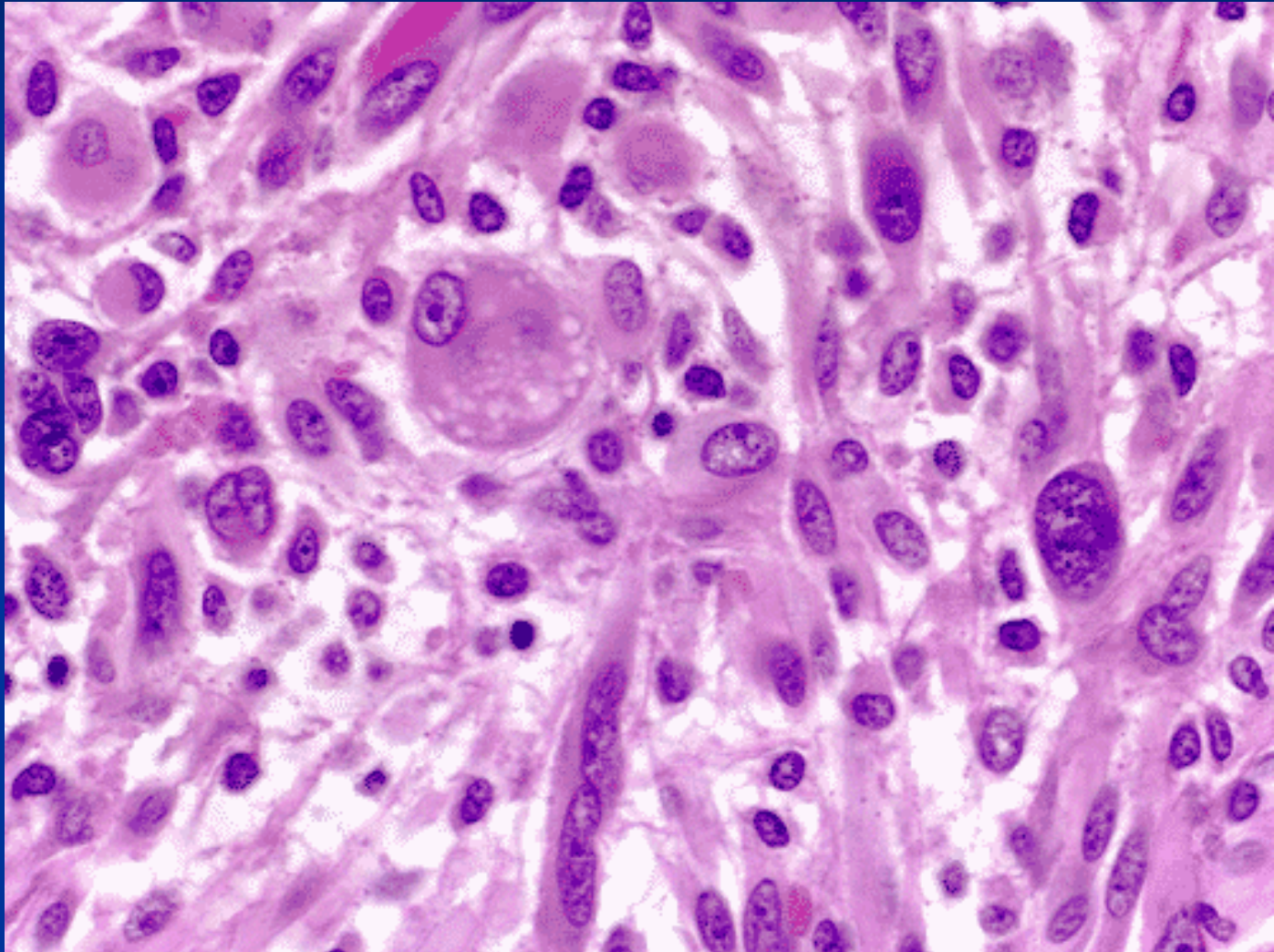
■ **Pilocytic astrocytoma (I)**

- Often cystic, also solid
- Usually circumscribed, arising from optic nerve to conus medullaris
- Bipolar cells („hair cells“) + Rosenthal fibers and eosinophilic granular bodies
- Often biphasic (fibrillary areas + loose microcystic pattern)
- Usually first two decades

■ **Pleomorphic xanthoastrocytoma (II); anaplastic (III)**

- Temporal lobe of children and young adults
- Neoplastic occasionally bizarre astrocytes, also lipidized
- Necrosis and mitotic activity indicate higher grade

Pleomorphic xantoastrocytoma



■ Ependymoma (II)

- Next to ependyma-lined ventricular system, 4th ventricle
- First 2 decades affected
- Solid or papillary masses; complete extirpation due to localization impossible
- Small „blue“ cells, granular chromatin, dense fibrillary background, perivascular pseudorosettes and rosettes

■ Anaplastic ependymoma (III)

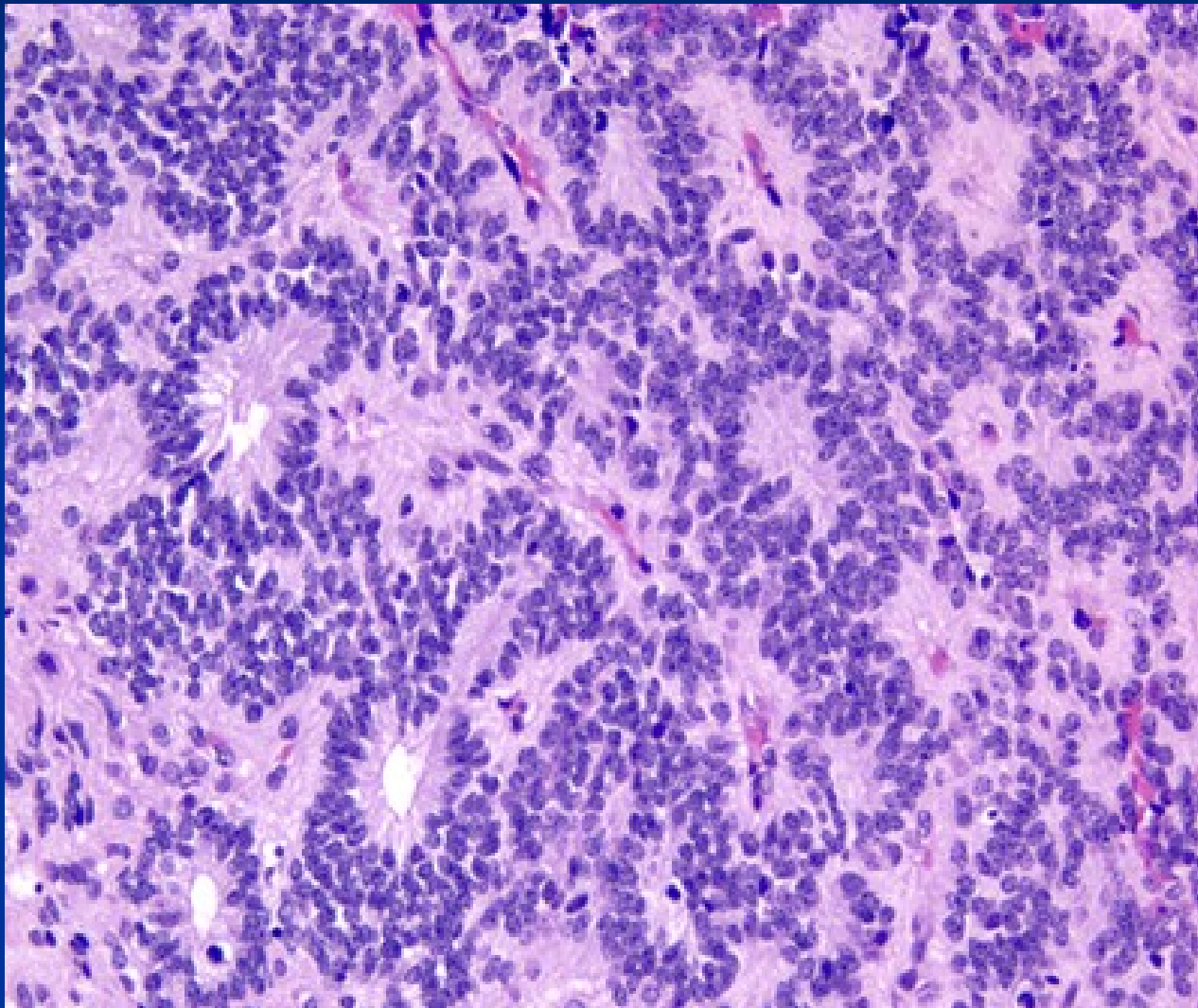
■ Subependymoma (I)

- benign, slowly growing, intraventricular

■ Myxopapillary ependymoma (I)

- Filum terminale of spinal cord

Ependymoma



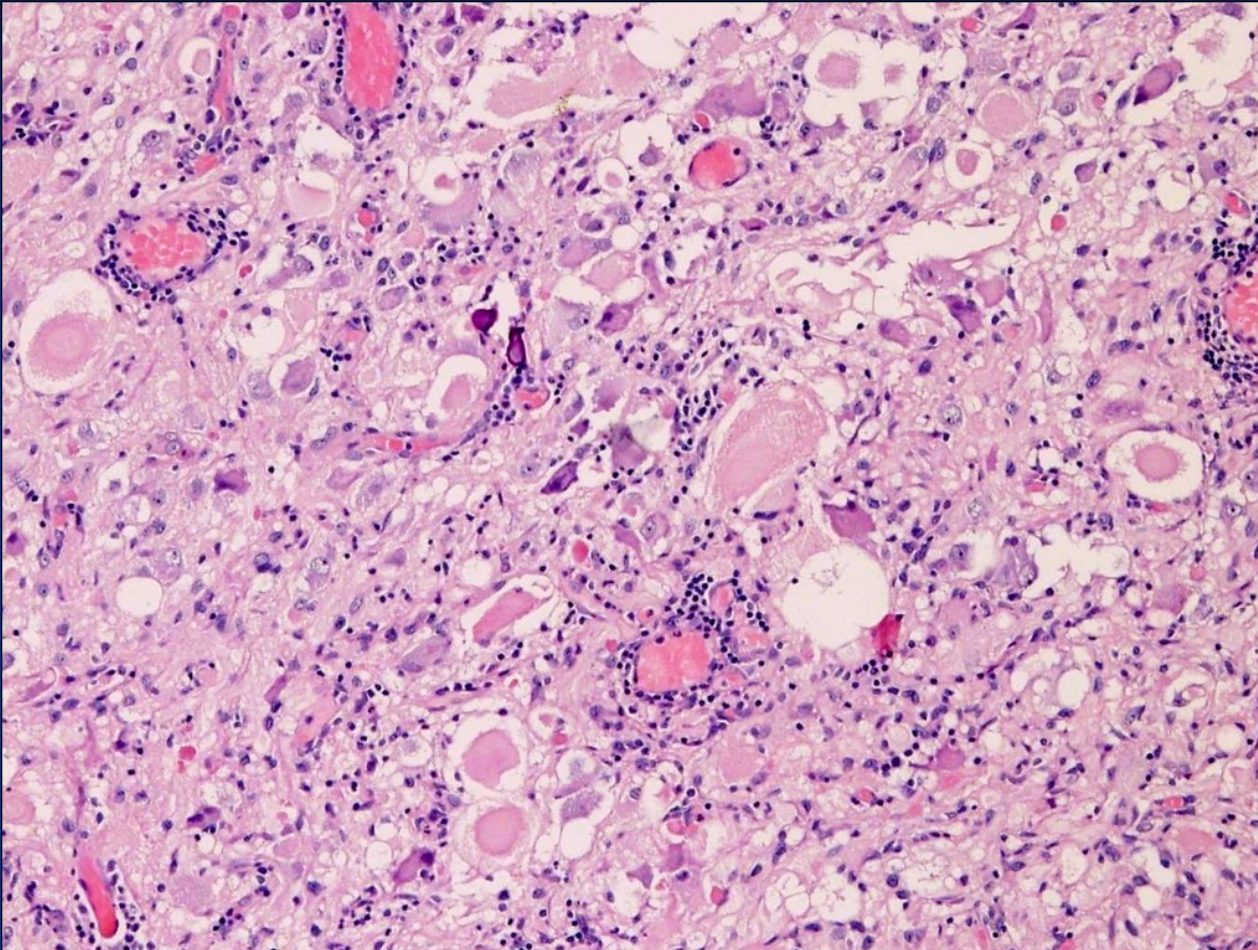
Neuronal and mixed (glio)neuronal tumors

- **Gangliogliomas (I-II)**
- **Dysembryoblastic neuroepithelial tumor (DNET)**
 - In temporal lobe
 - Associated with epilepsy
 - Usually grade I; gangliogliomas may be gr. II/III
- **Dysplastic gangliocytoma of the cerebellum (I)**
- **Central neurocytoma (II)**
 - LG neuronal neoplasms
 - Within ventricular system

Spectrum of long-term epilepsy associated tumors

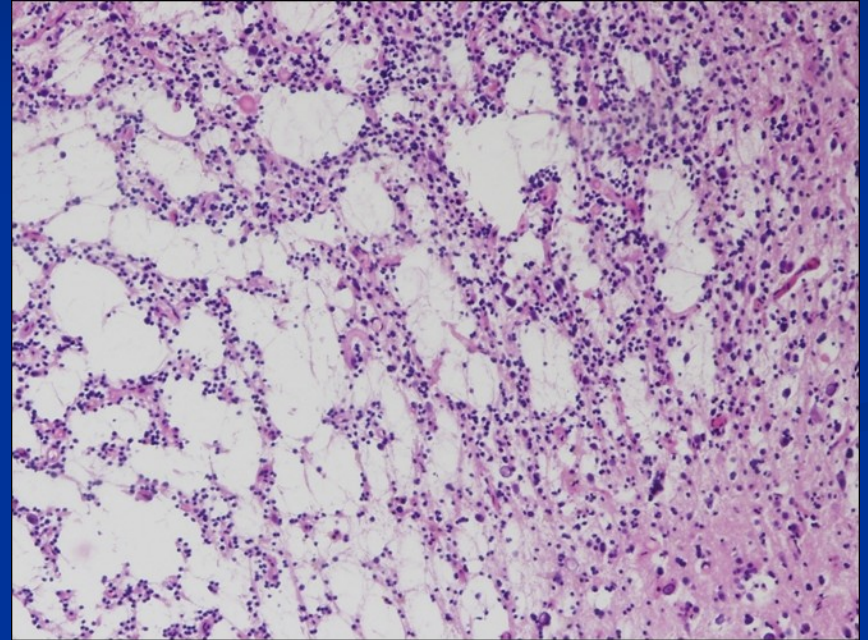
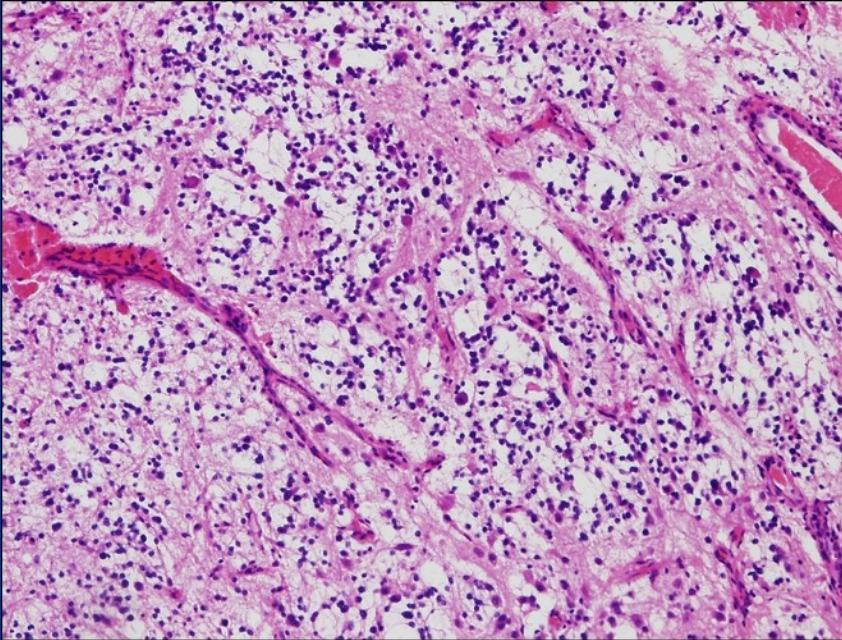
- Usually low grade, well differentiated, with low proliferating activity and low malignant potential, superficially localized (cortical or subcortical; frontal and temporal localization), mixed neuronal-glial tumors, expression of stem cell marker CD34
- Mixed neuronal-glial tumors :
 - Ganglioglioma (GI, rare GII-GIII)
 - Dysembryoplastic neuroepithelial tumor (DNET, GI)
- Others:
 - Pilocytic astrocytoma (GI)
 - Diffuse astrocytoma (GII)
 - Oligodendroglioma (GII)
 - Pleomorphic xanthoastrocytoma (GII)
 - Subependymal giant cell astrocytoma (GI ; associated with tuberous sclerosis)
 - Angiocentric glioma (GI)

Ganglioglioma



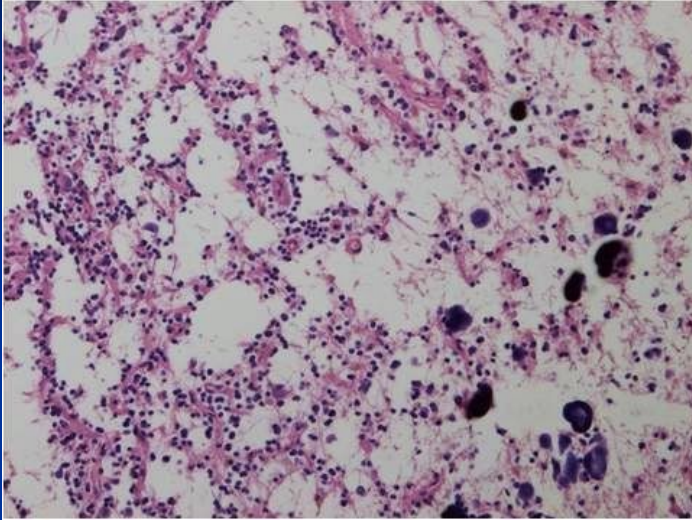
- well differentiated, slowly growing neuroepithelial tumor
- neoplastic ganglion cells + neoplastic glial cells
- WHO GI; higher grades very rare; >70 % in temporal lobe

DNET

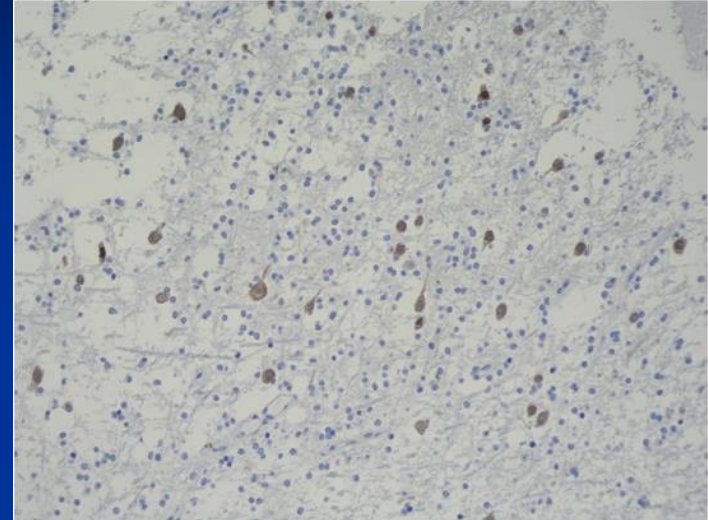


- WHO GI, benign, usually supratentorial glial-neuronal neoplasms
- in children and young adults
- cortical location
- complex columnar and multinodular architecture, „specific glioneuronal elements“
(bundles of axons lined by oligodendroglia-like cells+floating neurons)

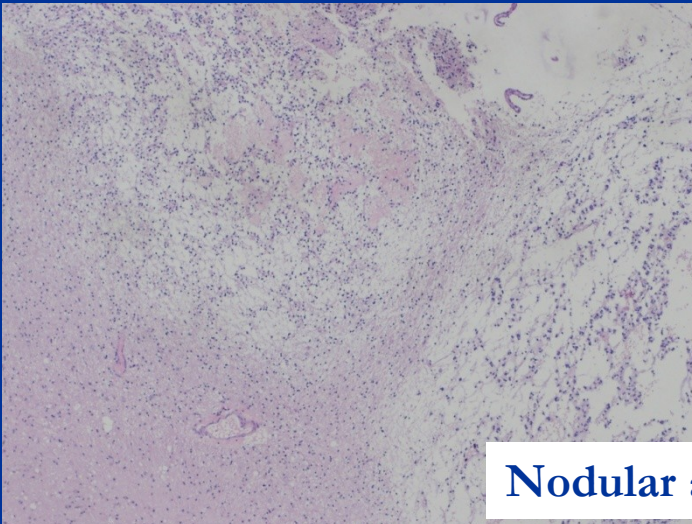
DNET



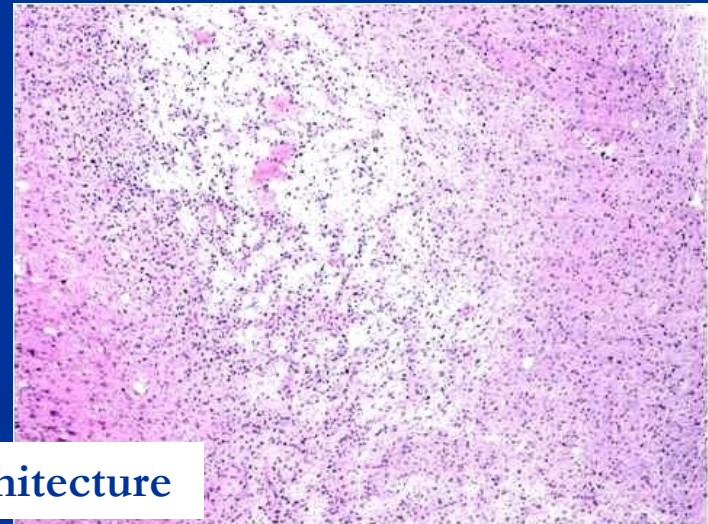
Calcification in DNET



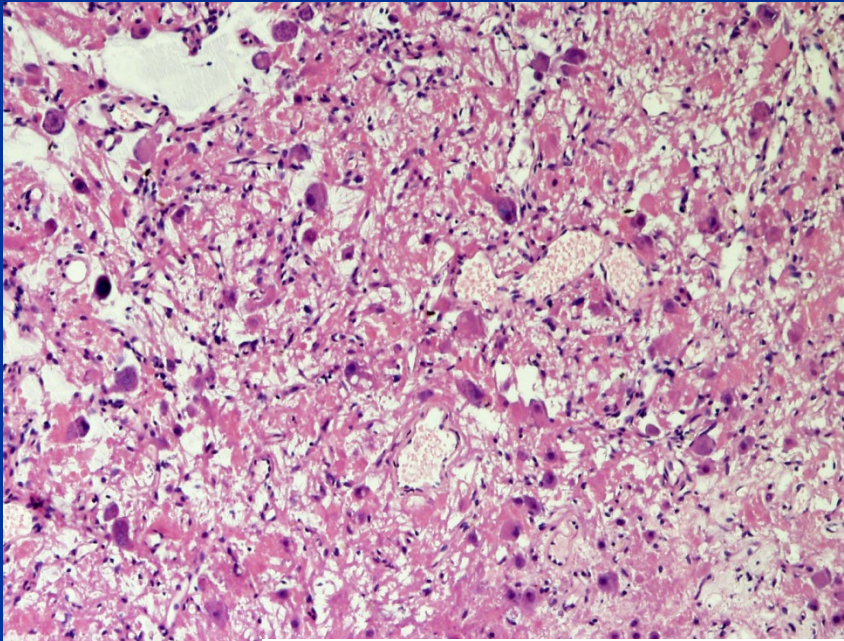
NeuN immunohistochemistry



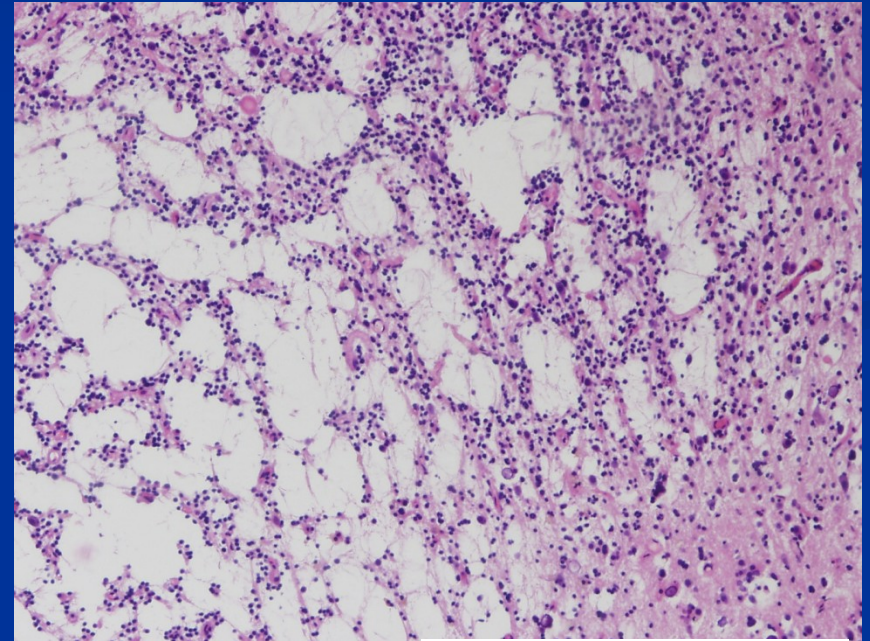
Nodular architecture



Composite glioneuronal tumour: DNET and ganglioglioma component

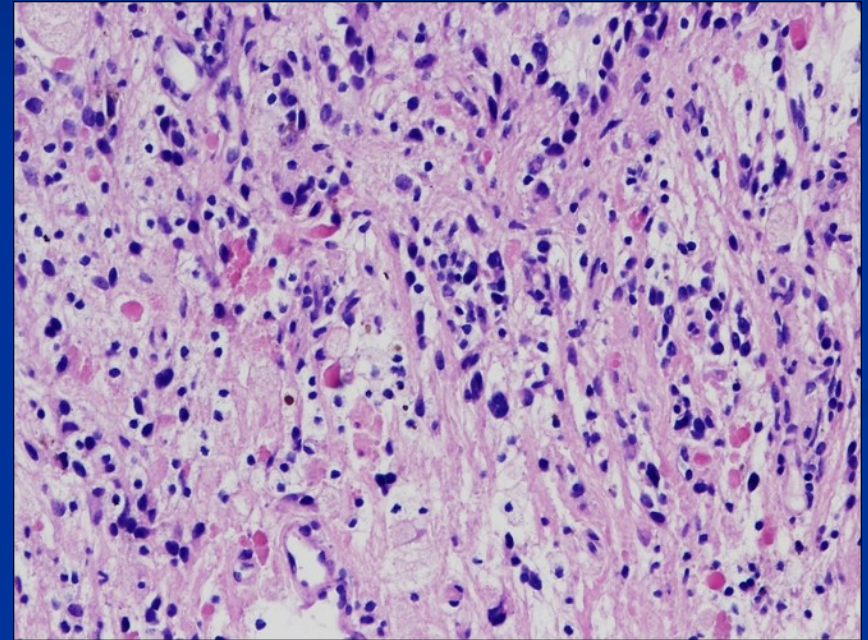
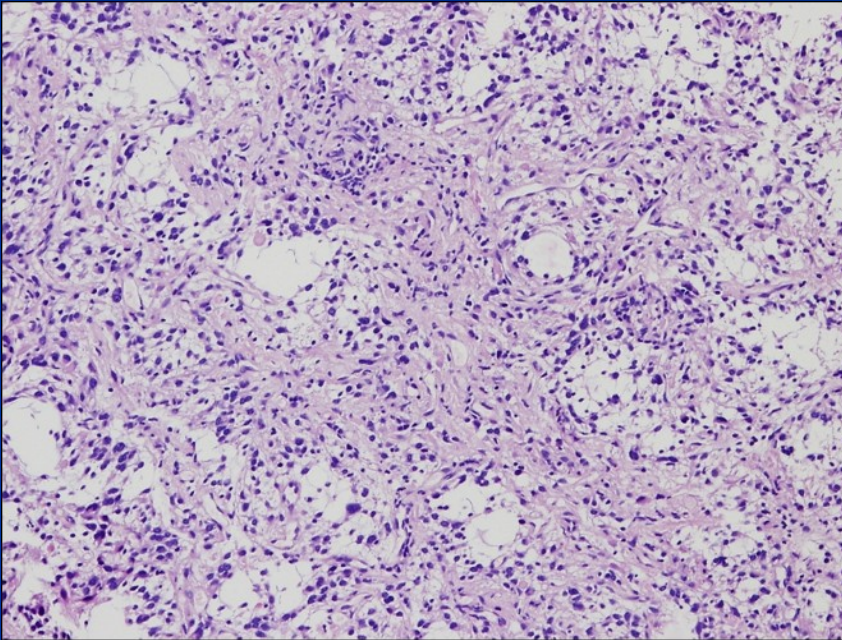


Ganglioglioma component



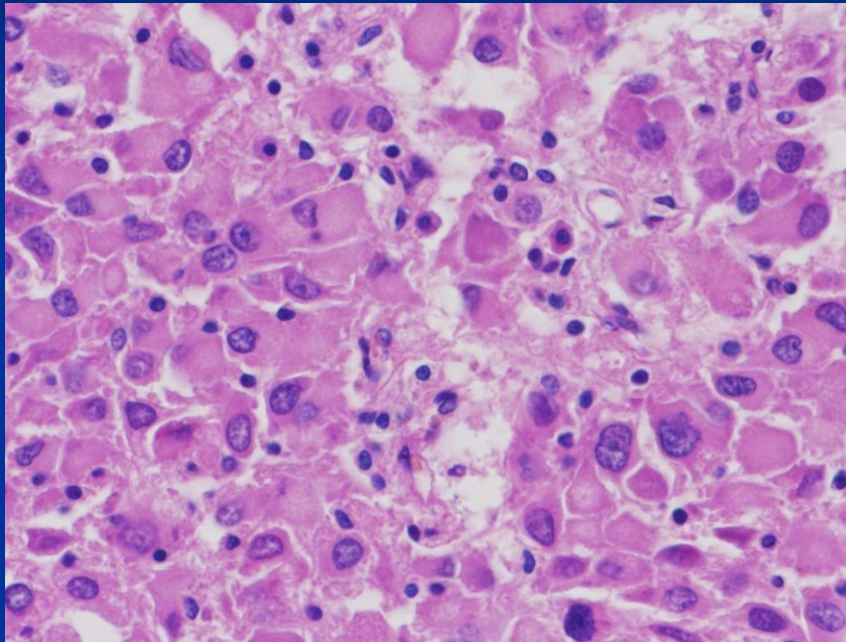
DNET component

Pilocytic astrocytoma

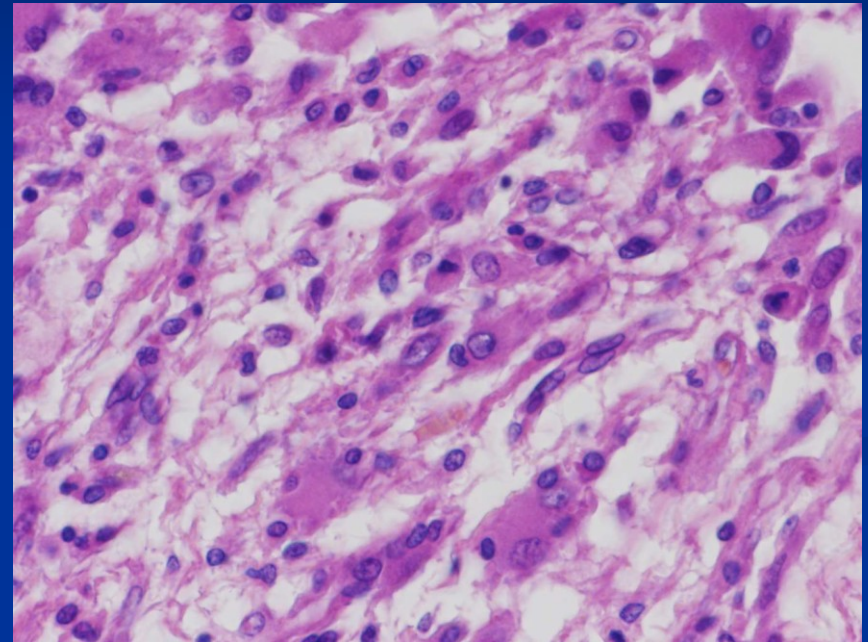


- WHO GI, relatively circumscribed, slowly growing, often cystic
- histologically biphasic pattern (compacted bipolar cells and loose-textured multipolar cells + Rosenthal fibers and eosinophilic granular bodies)

Subependymal giant cell xanthoastrocytoma

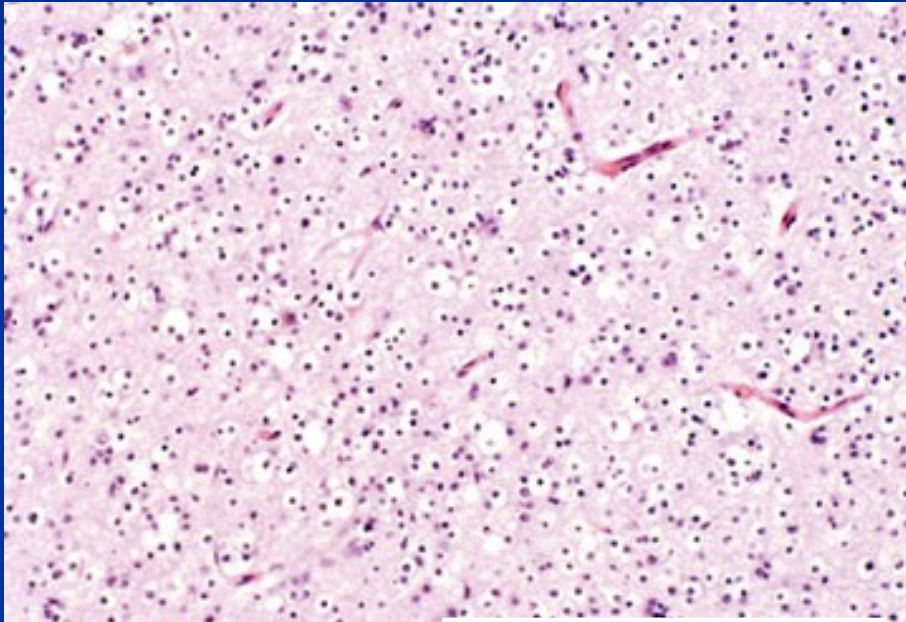


Pleomorphic eosinophilic tumour cells



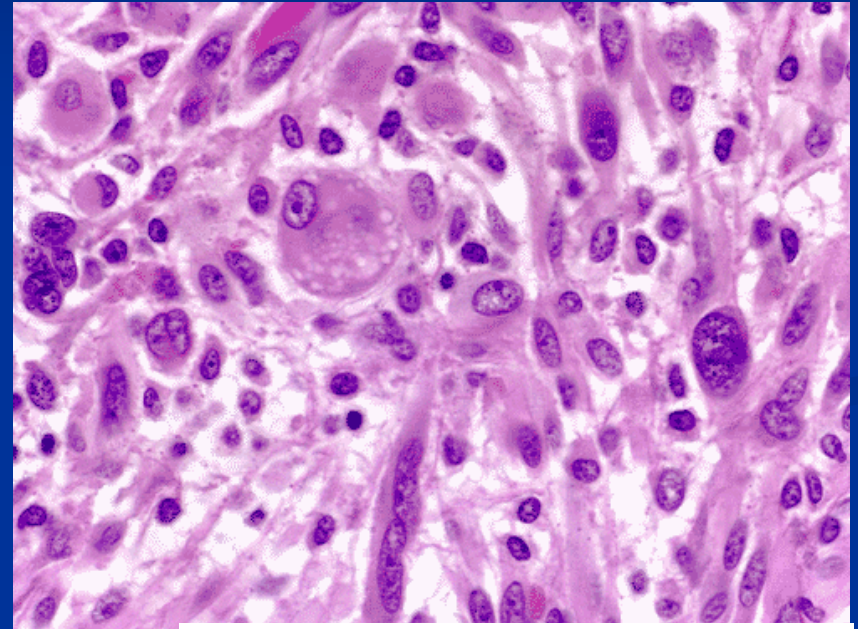
Elongated tumour cells forming streams

- WHO GI; tuberous sclerosis complex
- benign, slowly growing, arising in the wall of the lateral ventricles, composed of the large ganglioid astrocytes



Oligodendroglioma

- WHO GII, a diffusely infiltrating
- WD glioma
- cerebral hemispheres
- deletions 1p and 19q



Pleomorphic xanthoastrocytoma

- WHO GII
- superficial localisations in cerebral hemispheres + involvement of meninges
- pleomorphic lipidized cells

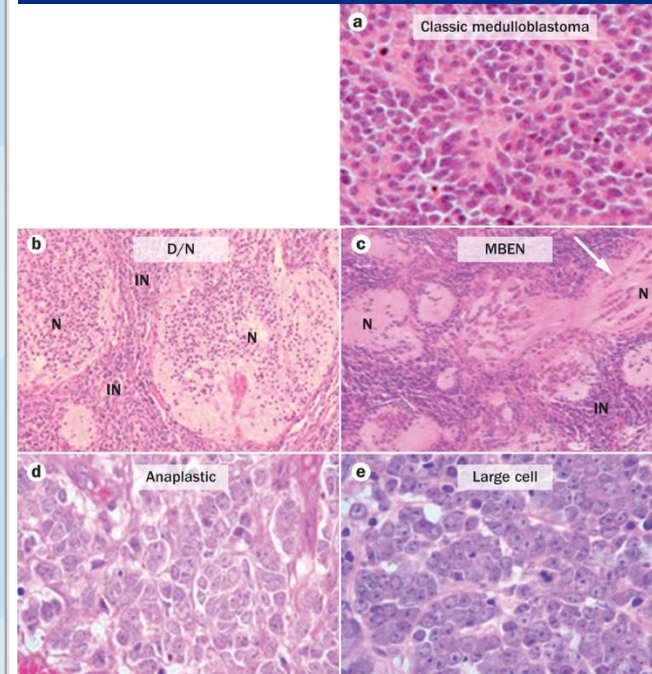
Medulloblastoma (gr. IV)

- 20 % of brain tumors in children
- In the midline of cerebellum; 4th ventricle, hydrocephalus
- Well circumscribed, grey
- hypercellular, „small blue cells“, neuroblastic rosettes (Homer Wright rosettes)
- High proliferation, mitoses
- Expression of neuronal markers (synaptophysin, NF; GFAP+ cells, vimentin)
- Dissemination through the CSF
- 4 histological subtypes; 4 molecular subtypes
- Prognosis in untreated dismal; with total excision and irradiation: 5-year survival rate as high as 75 %

Integrated diagnosis of medulloblastomas:

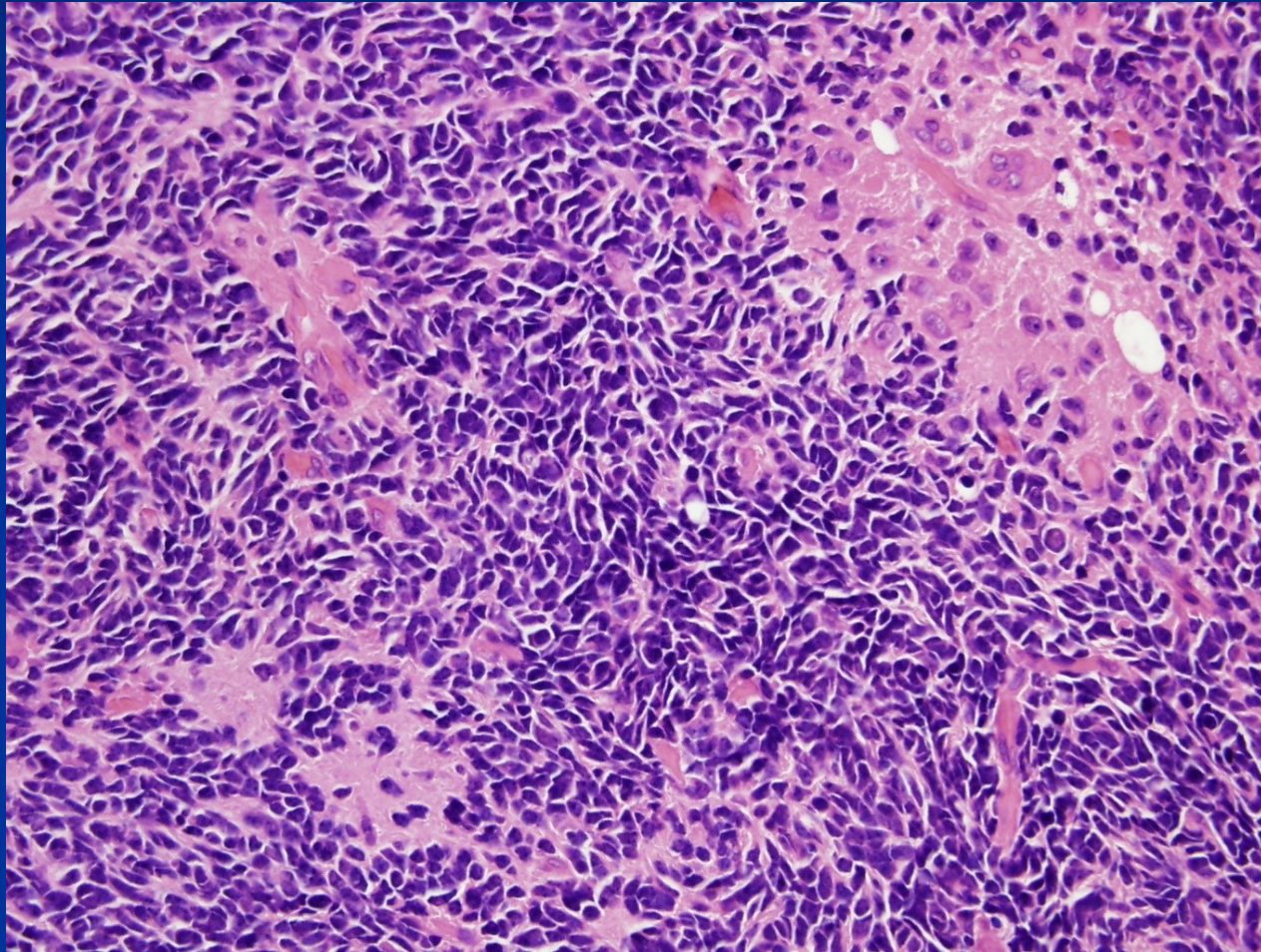
- histopathological diagnosis/typing
- genetic profiling – 4 molecular subtypes

Genetic profile	Histology	Prognosis
Medulloblastoma, WNT-activated	Classic	Low-risk tumour; classic morphology found in almost all WNT-activated tumours
	Large cell / anaplastic (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, TP53-mutant	Classic	Uncommon high-risk tumour
	Large cell / anaplastic Desmoplastic / nodular (very rare)	High-risk tumour; prevalent in children aged 7–17 years Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, TP53-wildtype	Classic	Standard-risk tumour
	Large cell / anaplastic	Tumour of uncertain clinicopathological significance
	Desmoplastic / nodular	Low-risk tumour in infants; prevalent in infants and adults
Medulloblastoma, non-WNT/non-SHH, group 3	Extensive nodularity	Low-risk tumour of infancy
	Classic	Standard-risk tumour
	Large cell / anaplastic	High-risk tumour
Medulloblastoma, non-WNT/non-SHH, group 4	Classic	Standard-risk tumour; classic morphology found in almost all group 4 tumours
	Large cell / anaplastic (rare)	Tumour of uncertain clinicopathological significance



Histological subtypes of medulloblastomas

Medulloblastoma



Other embryonal tumors/ WHO gr. IV

- **Atypical teratoid/rhabdoid tumors**
(posterior fossa, supratentorially; under 5, dismal prognosis)
- **Embryonal tumor with multilayered rosettes, C19MC altered**
- **Medulloepithelioma**
- **CNS neuroblastoma/ganglioneuroblastoma**
- **CNS embryonal tumor**

Other tumors of CNS

- **Primary CNS lymphomas (DLBCL)**
- **Germ cell tumors**
 - Midline structures, pineal region, suprasellar region
 - Teratomas; germinomas (similar to seminomas),...
- **Pineal parenchymal tumors**
 - Pinealoblastomas (high grade tumors)
 - Pineocytomas (well differentiated)
 - Gliomas in pineal region

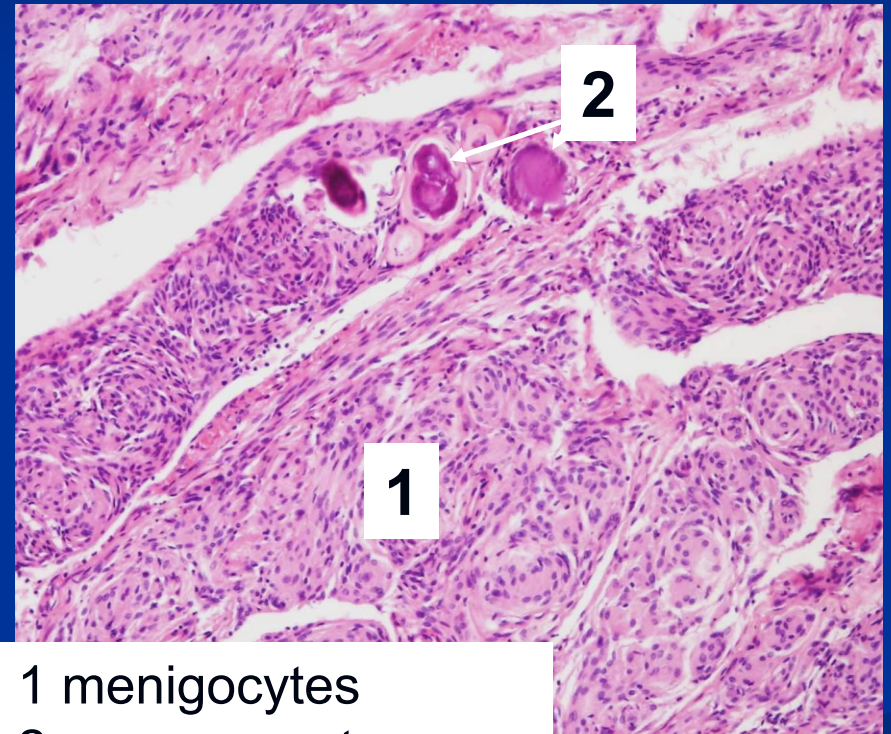
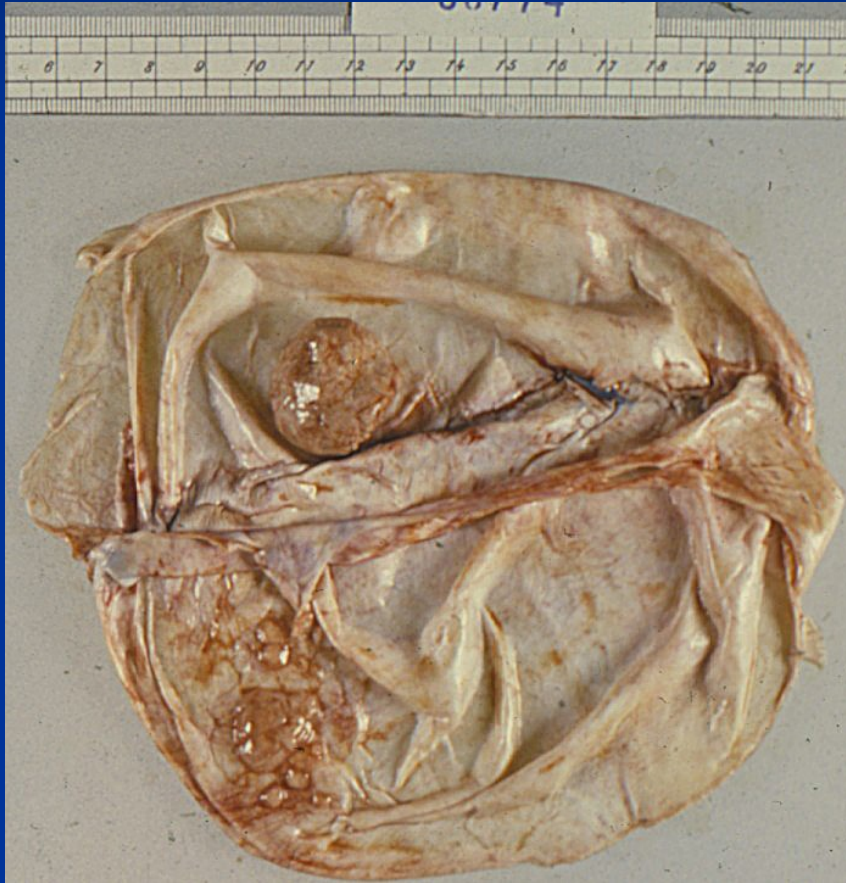
Tumors of the meninges

- **Meningioma** (meningothelial)
 - nonmeningothelial
- **Meningeal hemangiopericytoma (so-called)**
- **Solitary fibrous tumors**

Meningioma (gr. I-III)

- Usually well defined rounded masses, adjacent to dura; encapsulated, extension into bone (reactive hyperostotic changes); less common „en plaque“ growth
- **Grade I meningiomas:**
 - meningotheelial
 - fibroblastic
 - transitional
 - psammomatous
 - microcystic, secretory, angiomatous,....
- **Grade II meningiomas:**
 - atypical, clear cell, chordoid
- **Grade III meningiomas:**
 - anaplastic (malignant), rhabdoid, papillary

Meningioma



1 meningiocytes
2 psammomata

■ **Craniopharyngeoma:**

- Arise from squamous cell rests (derived from Rathke pouch) in sellar region
- Benign (gr. I), partly cystic epithelial tumor

■ **Hemangioblastoma:**

- Sporadic or ass. with VHL sy (in younger)
- Cerebellum (medulla, spinal cord,....., supratentorial, retinal in VHL)
- Well circumscribed, cystic, with mural nodule(s)
- Capillary-size and larger thin-walled vessels with intervening neoplastic „stromal cells“ (large polygonal, vacuolated, lipid-rich, PAS+)

Familial tumor syndromes with involvement of tumor suppressor gene (AD)

- **Cowden syndrome**
 - *PTEN* mutation
 - Dysplastic gangliocytoma of the cerebellum
- **Li Fraumeni syndrome**
 - Inactivation of p53
 - Medulloblastoma
- **Turcot syndrome**
 - Mutations in *APC* or mismatch repair gene
 - Medulloblastoma or glioblastoma
- **Gorlin syndrome**
 - *PTCH* mutations, upregulation of SHH
 - medulloblastoma

■ Neurofibromatosis type I

- AD; neurofibromas (plexiform and solitary)+gliomas of optic nerve+pigmented nodules of iris-cutaneous hyperpigmented macules (*café au lait spots*)
- Malignant transformation of neurofibromas
- *NF1* gene (17q11.2); neurofibromin

■ Neurofibromatosis type II

- AD; 8th nerve schwannomas and multiple meningiomas + gliomas, ependymomas of spinal cord + non-neoplastic lesions of Schwann cells, meningeal cells, hamartia
- *NF2* gene (22q12); merlin

■ Tuberous sclerosis complex

- AD; hamartomas and benign tumors of the brain and other tissues: cortical tubers (epileptogenic), subependymal nodules, subependymal giant cell astrocytomas,..., + renal angiomyolipomas, retinal glial hamartomas, pulmonary lymphangiomyomatosis, cardiac rhabdomyoma + cysts – cutaneous lesions (angiofibromas, subungual fibromas, hypopigmented lesions)
- tuberin or hamartin genes mutated

■ Von Hippel Lindau Disease

- AD; hemangioblastomas + cysts (pancreas, liver, kidney) + renal carcinomas, pheochromocytomas
- tumor suppressor gene – pVHL – 3p25-p26

Peripheral nerve sheath tumors

■ Schwannoma

- benign, from neural crest-derived Schwann cell, component of NF2
- well circumscribed, encapsulated, attached to nerve; 2 patterns: Antoni A and Antoni B
- often vestibular branch of 8th nerve; sensory nerves preferentially involved (trigeminal, dorsal roots,..); extradurally – large nerve trunks

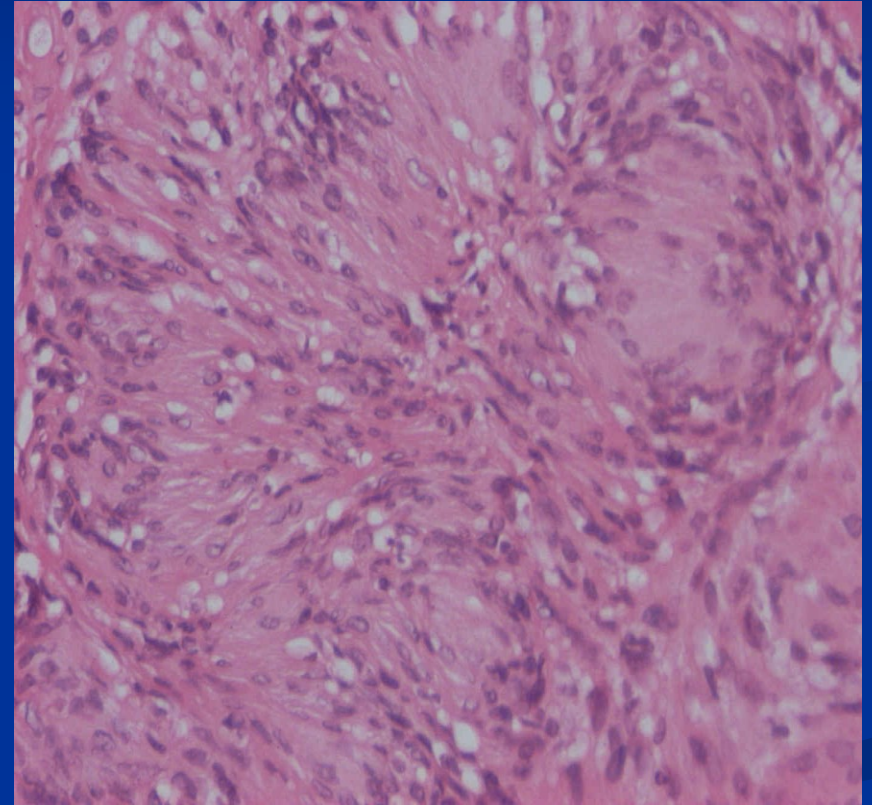
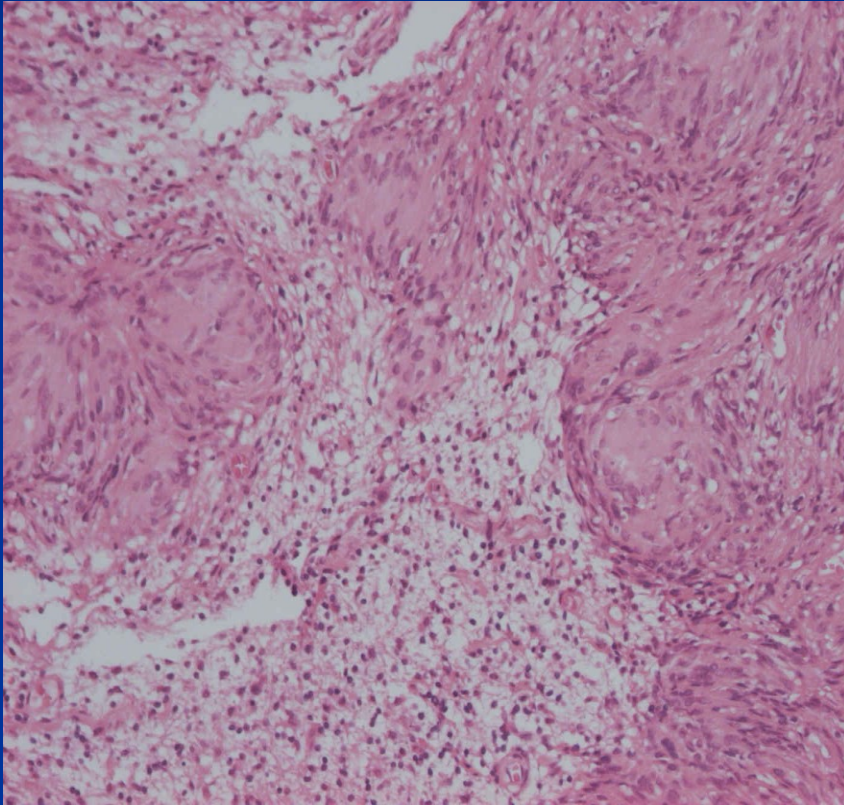
■ Malignant peripheral nerve sheath tumor

- highly malignant, medium and large nerves affected; in NF1

■ Neurofibroma:

- **Cutaneous:** localized, in dermis or subcutaneously
- **Plexiform:** infiltrating lesion growing within and expanding a peripheral nerve; NF1; potential for malignant transformation; significant neurologic deficits

Schwannoma



Diseases of peripheral nerves

- Inflammatory neuropathies
- Infectious polyneuropathies
- Hereditary neuropathies
- Acquired metabolic and toxic neuropathies
- Traumatic neuropathies

Inflammatory neuropathies

- **Immune mediated neuropathies: Guillain-Barré syndrome – GBS** (acute inflammatory demyelinating polyradiculoneuropathy)
 - Weakness in distal limbs, ascending paralysis, hospital intensive care before recovering normal function (up to 20 % long term disability); in some patients followed by a subacute or chronic course
 - Inflammation and demyelination of spinal nerve roots and peripheral nerves (radiculoneuropathy)
 - Infections or prior vaccination ass. with GBS
 - T-cell mediated immune response

Infectious polyneuropathies

■ Leprosy (Hansen disease)

- **Lepromatous leprosy:** Mycobacterium leprae invading Schwann cells
- Segmental demyelination, remyelination, loss of axons; endoneurial fibrosis and multilayered thickening of perineurial sheaths
- Symmetric polyneuropathy; pain fibers (loss of sensation)
- **Tuberculoid leprosy:** cell-mediated immune response to M. leprae – granulomatous inflammation in dermis, cutaneous nerves affected

■ Diphtheria (diphtheria exotoxin; selective demyelination of axons)

- **Varicella zoster virus** (varicella zoster virus; following chickenpox virus persists in neurons and sensory ganglia with potential reactivation)

Hereditary neuropathies

- Hereditary motor and sensory neuropathies (HSMN I-III,....)
- Hereditary sensory and autonomic neuropathies (HSANs)
- Familial amyloid polyneuropathies
- Peripheral neuropathy accompanying inherited metabolic disorders

HSMN

- **HSMN - Charcot-Marie-Tooth** (peripheral myelin protein 22, myelin, connexin,...)
 - Demyelinating neuropathy; usually AD
 - Repetitive de- and remyelinations (onion bulbs – Schwann cell hyperplasia)
 - Slowly progressive, progressive muscular atrophy (legs) , uscle weakness, pes cavus
- **HSMN II** (kinesin family member KIF1B)
 - Axonal form – loss of myelinated axons
- **HSMN III – Dejerine-Sottas neuropathy**
 - AR, genetically heterogeneous (the same genes as in HSMN I)
 - Enlarged peripheral nerves, trunk and limb muscles affected

Acquired metabolic and toxic neuropathies

- **Peripheral neuropathy in adult onset diabetes mellitus** (polyol pathway and nonenzymatic glycation of proteins involved)
 - Distal symmetric sensory or sensorimotor neuropathy
 - Autonomic neuropathy
 - Focal or multifocal asymmetric neuropathy
 - Loss of small myelinated fibers, also unmyelinated fibers
 - Thickening of endoneurial arterioles
- **Metabolic and nutritional neuropathies**
 - Uremic neuropathy
 - Chronic liver disease, respiratory insuf., thyroid dysfunction
 - Thiamine deficiency (neuropathic beriberi)
 - Avitaminosis B₁₂, B₆, and E
- **Neuropathies associated with malignancy**
 - Brachial plexopathy (apex of a lung), obturator palsy (pelvic tumors), cranial nerve palsies (intracranial tumors,....)
 - Paraneoplastic effect (small cell ca of lungs, plasmocytoma)
- **Toxic neuropathies**
 - Heavy metals, lead, arsenic

Tumors of autonomic nervous system

- **Extraadrenal paragangliomas** (carotid body paragangliomas, vagal and other paragangliomas)
 - non-chromaffin paragangliomas, usually related to parasympathetic nervous system
 - Alveolar pattern, cell nests; chief cells and sustentacular cells
 - Also malignant forms
- **Extraadrenal paragangliomas** of sympathoadrenal neuroendocrine system (anywhere from the pelvic floor to the neck)
- **Pheochromocytomas** (adrenal paraganglioma) (production of catecholamins, hypertension, usually benign)
- **Gangliocytic paraganglioma** (benign, in duodenum)

Tumors of autonomic nervous system

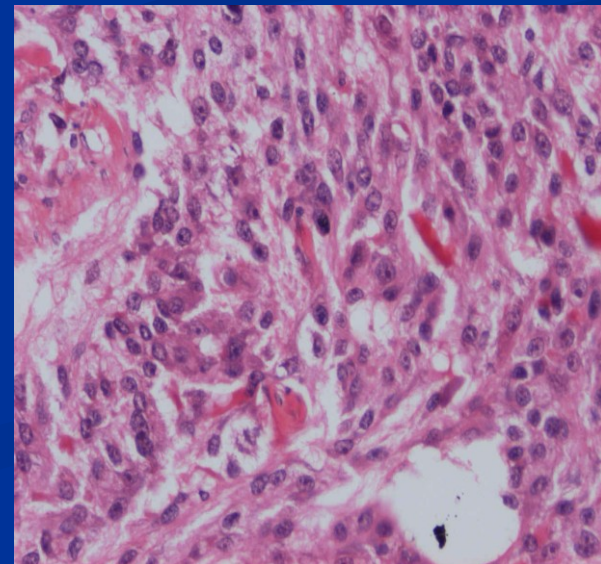
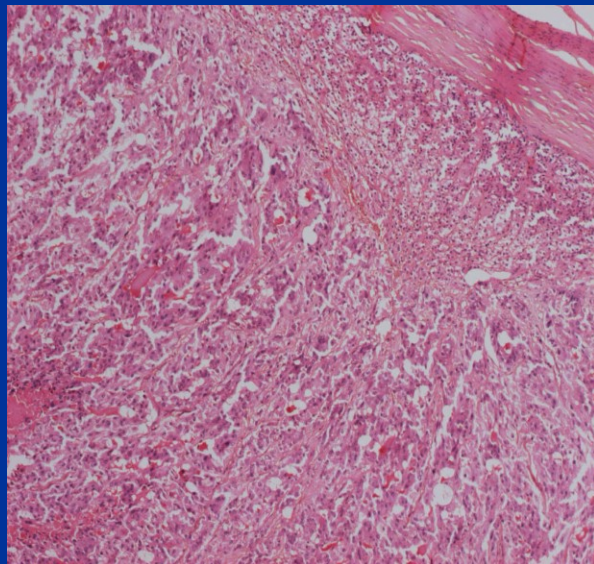
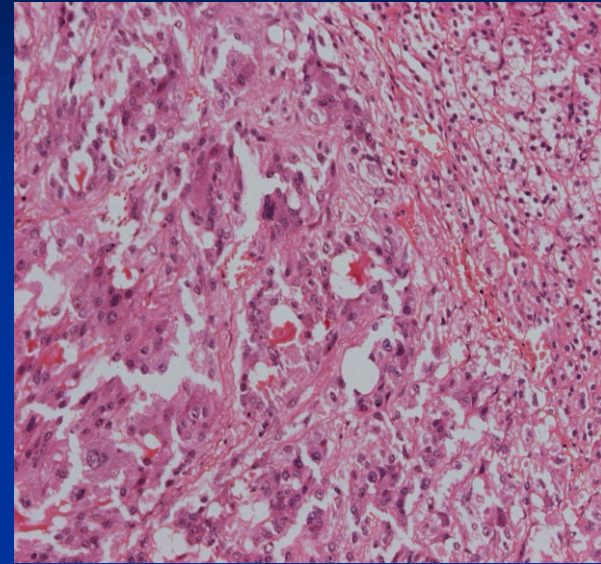
■ Neuroblastoma and ganglioneuroblastoma

- In children under 4 ys (85 %)
- In adrenal gland or intra-abdominal sympathetic chain (70 %) and in thorax (at least 20 %)
- „Small blue cell“ tumor, bulky, multinodular, hemorrhages and necrosis often, calcification, also pseudocystic, lobular or nesting pattern, fibrillary material between cells (neuritic cell processes) – neurofibrillary matrix, rosettes, chromatin: „salt-and-pepper“ appearance
- Ganglioneuroblastoma – some cytodifferentiation or maturation with recognizable ganglion cells

■ Ganglioneuroma

- In posterior mediastinum or retroperitoneum; some arising in adrenal gland
- Patient over 10 ys
- Well, circumscribed, with no necrosis or hemorrhages, on cut surface whorled or trabecular pattern
- Spindle cell matrix and mature ganglion cells

Pheochromocytoma



Neuroblastoma

