

Stiftung Tierärztliche Hochschule Hannover  
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## Introduction to Neuropathology – Part IV



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## Epilepsy

**Prevalence in dogs:**

- most common form in general: symptomatic (65%)
- most common form in dogs under 5 years of age: idiopathic
- prevalence of epileptic seizures in dogs: 0.5-5.7 %
- dog breeds with an increased risk for epilepsy have high breed-specific prevalence rates (9% - 18%)
- breed examples: Lagotto Romagnolo dog, Belgian shepherds, Border Collies, Australian Shepherds, Shetland Sheepdogs, Beagle, Keeshound, Golden and Labrador Retriever

## General aspects

**Idiopathic CNS disorders:**  
**Former definition:**  
- cause obscure or unknown!

**New definition:**  
- diseases with abnormal functional neurological signs (e.g. seizures) but without morphologically detectable changes of the nervous tissue

Examples: - epilepsy  
- myasthenia  
- narcolepsy  
- „movement disorders“

## Epilepsy

**Pathology:**

- primary changes (idiopathic forms):  
morphological alterations in canine hippocampal tissue (alterations in neurogenesis)  
neuronal cell loss  
microglia activation  
blood-brain-barrier alterations
- secondary changes (all forms):  
neuronal necroses  
astrogliosis in cerebrum, amygdala and hippocampus

## Epilepsy

**Classification:**

- idiopathic (genetic) epilepsy: various gene mutations
- symptomatic (structural/metabolic) epilepsy: associated with brain insults such as trauma, infections or tumours
- cryptogenic (suspected, but not detectable cause)

**Genetic defects in idiopathic forms:**

- functional dysregulations (e.g. disturbances of ion channels) or
- microglial imbalance of matrix metalloproteinases (MMP) and their inhibitors (TIMPs) associated with an up-regulation of TIMP-2

## General aspects

**Incidence of Primary Tumours of the Nervous System of Domestic Animals**

**Incidence:** low (1.9% of all tumours in dogs)  
- 60-80% in dogs  
- 10-20% in cats  
- 10-20% in others

**Age distribution:** > 70 % in dogs > 6 years (Ø 9.4 y.)  
dogs < 6 years rare (25% in man!)

**Species distribution:**

- Meningeoma: cat
- Peripheral nerve sheath tumours: bovine
- Gliomas: dog

**Breed distribution:**  
Dog: > 50 % brachycephalic (Boxer, English Bulldog)

<b>General aspects</b>	
<b>Neuro-oncology</b>	<p><b>Tumour rate:</b> CNS and PNS: 3:1</p> <p><b>Histogenetic origin of CNS tumours:</b></p> <ul style="list-style-type: none"> <li>➤ primary (approx. 50% of all NS tumours are primary)           <ul style="list-style-type: none"> <li>Metastasis: - no spontaneous metastasis outside the CNS</li> <li>- but: metastatic dissemination within the CSF pathways</li> </ul> </li> <li>➤ secondary           <ul style="list-style-type: none"> <li>infiltrating from adjacent tissues</li> <li>hematogenous</li> </ul> </li> </ul>

<b>Diagnosis of CNS Tumours</b>	
<b>Neuro-oncology</b>	<p><b>Clinical diagnosis:</b></p> <ul style="list-style-type: none"> <li>➤ General check-up</li> <li>➤ Neurological check-up</li> <li>➤ CSF: pleocytosis possible</li> <li>➤ Neuro-imaging methods (X-ray, CT, MRI)</li> <li>➤ CT- or MRI-guided, stereotactic biopsy           <ul style="list-style-type: none"> <li>core tissue → Cytology (smear)</li> <li>→ Paraffin histology</li> </ul> </li> <li>➤ Surgical biopsy</li> </ul> <p><b>Postsurgical/postmortem:</b></p> <ul style="list-style-type: none"> <li>➤ Cytology (smear technique)</li> <li>➤ Histology</li> <li>➤ electron microscopy</li> <li>➤ Immunohistology (Tumour marker, Proliferation marker)</li> <li>➤ Molecular genetic analysis (e.g. FISH)</li> </ul>

<b>Clinical Effects of CNS Tumours</b>	
<b>Neuro-oncology</b>	<p><b>General tumour-related mechanical changes:</b></p> <ul style="list-style-type: none"> <li>➤ Bone defects</li> <li>➤ Compression of the parenchyma</li> <li>➤ Destruction and shifts of the parenchyma</li> <li>➤ Peritumourous oedema (CSF-reflux, endothelial damage, sodium-potassium imbalance)</li> <li>➤ Haemorrhages</li> <li>➤ Necrosis</li> <li>➤ Inflammation</li> <li>➤ Secondary obstructive hydrocephalus</li> <li>➤ CSF: Production disturbance, reduction of liquor space</li> </ul>

<b>Clinical Findings</b>	
<b>Neuro-oncology</b>	<p><b>Signs in animals with intracranial space occupying lesions:</b></p> <p><b>Clinical outcome:</b> Gradually variable clinical symptoms depending on localization, size, peritumourous lesions:</p> <ul style="list-style-type: none"> <li>➤ epileptic seizures,</li> <li>➤ disturbances of consciousness</li> <li>➤ behavioural changes</li> </ul> <ol style="list-style-type: none"> <li>1. Cranial nerve syndrome (total or partial)</li> <li>2. Cerebellar-vestibular syndrome</li> <li>3. Pituitary-hypothalamic syndrome</li> <li>4. Cerebral syndrome</li> </ol>

<b>Clinical Effects of CNS Tumours</b>	
<b>Neuro-oncology</b>	<p><b>Tumour-related non-mechanical changes:</b></p> <ul style="list-style-type: none"> <li>➤ False neurotransmitters</li> <li>➤ Improper neurotransmitters</li> <li>➤ False concentrations of neurotransmitters</li> <li>➤ Immunological reactions</li> </ul>

<b>Effects of CNS Tumours</b>	
<b>Neuro-oncology</b>	<p><b>Effects of intracranial space occupying lesions</b></p> <p><b>Problem:</b> Restricted space of the cranial cavity</p> <p><b>Exceptions:</b> Young animals: open fontanelles Senile animals: hydrocephalus internus ex vacuo (senile brain atrophy)</p> <p><b>Topography:</b> Rostro- (supra)-tentorial Caudo- (infra)-tentorial</p>

**Neuro-oncology**

### Effects of CNS Tumours

**Rostro- (supra)-tentorial space-occupying growth:**

- Broadening of the gyri
- Narrowing of the sulci
- Compression of a lateral ventricle
- Subfalxial herniation ("falx deviation", midline shift)
- Axial dislocation towards the tentorium:
  - "Uncus hernia" or „Dexlers´ pressure bulge“
- Necrosis of the contralateral crus cerebri by the tentorium
- Haemorrhages in the mesencephalon and pons

**Neuro-oncology**

### Descriptive Neuro-Oncology

**Diagnostic pattern**

**1. Macroscopic and subgross appearance**

**1.1. Localization and distribution**

- Intracranial, intraspinal
- Extraaxial, intraaxial, intraventricular
- Rostro-(supra)-tentorial, caudo-(infra)-tentorial
- Rostrosellar, intrasellar, perisellar, caudosellar
- Epidural, dural, leptomeningeal, parenchymatous
- Extradural, intradural, extramedullar, intramedullar
- Exact topography (brain and spinal cord atlas)
- Solitary or multiple

**Neuro-oncology**

### Effects of CNS Tumours

**Caudo- (infra)-tentorial space-occupying growth:**

- Indentation on the cerebellar surface by the tentorium
- Pressure conus of the cerebellar tonsil ("Vermis herniation"), possibly with necrosis and presence of necrotic neurons in the liquor
- Compression of the medulla

**Consecutive lesions:**

- obstructive hydrocephalus
- Brain oedema
- Juxtaneoplastic infarcts

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### Descriptive Neuro-Oncology

**1.2. Size (mm, cm)**

**1.3. Demarcation and growth**

- Circumscribed, diffuse
- Infiltrative, expansive
- Capsule/pseudocapsule
- Mesenchymal infiltration

**1.4. Shape**

- Nodular, multinodular
- Verrucous
- Papillary
- Plexiform (web-like)

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### Descriptive Neuro-Oncology

**Guide-lines for the Examination of CNS Tumours:**  
Not every tumour can be clearly classified!

**Necessity of a complete description:**

- From larger to smaller
- "Keep the reader in mind"
- No beautification/fantasies
- Use of the correct terminology
- Objective size and shape specification
- "There is not only one way to describe a lesion"

**Neuro-oncology**

### Descriptive Neuro-Oncology

**1.5. Consistency**

- soft
- gelatinous
- brain-like
- firm/fibrous

**1.6. Colour**

- red areas (Hemorrhage)
- brain-like
- whitish
- tan

**1.7. Necrosis**

**Neuro-oncology**

**Descriptive Neuro-Oncology**

**2. Histological appearance**

**2.1. Alignment of the tumor cells**

- Nests, strands, bands, tubuli, ducts, acini
- (Pseudo) papillae
- Bundles, rays, streaks
- solid sheets
- (Pseudo) rosettes
- Curls, whirls ("storiform")
- (Pseudo) palisades
- (Pseudo) onion bulb structure

**2.2. Stroma** (fibrous versus vascular)

- Desmoplasia
- Vascular proliferation:
  - Capillaries, glomeruloid formations

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**Descriptive Neuro-Oncology**

**4. Histological findings indicative for malignancy or regressive changes**

- Invasion into the capsule
- Invasion into the vessels
- Haemorrhages
- Necrosis
- Degeneration (mucoid, hyaline, fatty...)
- Cyst formation
- Calcifications

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**Descriptive Neuro-Oncology**

**Special types of true rosettes:**

- Homer Wright rosette: Cells arranged around central, fibrillar area (PNET)
- Flexner-Wintersteiner rosette: Cells arranged around central tubulus (retinoblastoma)

**Pseudorosette:**  
nucleus-free, fibrillar zone around central vessel (e. g. ependymoma)

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**Clinical Effects of CNS Tumours**

**Histological classification of tumors of the nervous system of domestic animals (WHO, 1999)**

- Typing: Morphological and cytological compilation
- Grading: Differentiation\*
- Staging: TNM

\*importance for **prognosis**  
In man:  
Grade I: ≥ 5 y.; II: 3-5y.; III: 1-3y.; IV: 6-12 mo.

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**Descriptive Neuro-Oncology**

**3. Tumour cells:**

**3.1. Cytological**

- Shape: spindle-shaped, round, epithelial ...
- Size
- Cell borders: distinct, indistinct, interdigitating
- Cytoplasm: amount, quality, character, colour
- Nucleus:
  - a) Shape (round, ovoid, stretched, indented)
  - b) Position (central, excentric)
  - c) Chromatin colouring and distribution
  - d) Nucleolus (polynucleolosis; anisonucleolosis)
  - e) Mitosis (frequency, regularity)
  - f) Apoptosis (frequency)

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**General aspects**

**Classification of Tumours of the Nervous System**

**Veterinary medicine:** WHO Classification (1999)

**Criteria:**

- Histology and cytology
- Growth characteristics
- Degree of differentiation

**Human medicine:** WHO Classification (2016)

**Criteria:**

- Histology and cytology
- Growth characteristics
- Degree of differentiation
- Genetics (molecular profile!)

Due to the striking similarity of histological types and clinical behaviour canine CNS tumours are now classified according to the human WHO classification!

**Neuro-oncology**

**Classification of NS Tumours (human WHO)**

1. Tumours of neuroepithelial tissue

**1.1. Astrocytic tumours**

- pilocytic astrocytoma
- gemistocytic astrocytoma
- subependymal giant cell astrocytoma
- diffuse astrocytoma
- anaplastic astrocytoma
- glioblastoma
- gliomatosis cerebri

**1.2. Oligodendroglial tumours**

- oligodendroglioma
- anaplastic (malignant) oligodendroglioma

**1.3. Mixed glioma (oligoastrocytoma)**

**Neuro-oncology**

**Classification of NS Tumours (human WHO)**

3. Tumours of the meninges

**2.1. Meningiomas**

- transitional (mixed) type
- fibrous type
- angiomatous type
- psammomatous type
- meningothelial type
- microcystic type
- chordoid type
- atypical type
- papillary type
- malignant type

**2.2. Granular cell tumours**

**2.3. Mesenchymal tumours**

- leiomyosarcoma
- hemangiosarcoma

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**Classification of NS Tumours (human WHO)**

1. Tumours of neuroepithelial tissue (contd.)

**1.4. Ependymal tumours**

- ependymoma
  - cellular
  - papillary
  - clear cell

**1.5 Choroid plexus tumours**

- papilloma
- carcinoma

**1.6. Neuronal and mixed neuronal-glia tumours**

- gangliocytoma
- ganglioglioma
- neurocytoma
- paraganglioma

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**Classification of NS Tumours (human WHO)**

4. Lymphomas and hematopoietic tumours

- B and T cell lymphoma
- histiocytic sarcoma

5. Germ cell tumours

- germinoma
- teratoma

6. Miscellaneous tumours

- ectopic nephroblastoma (Thoracolumbar spinal cord tumour in young dogs)

7. Metastatic tumours

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**Classification of NS Tumours (human WHO)**

1. Tumours of neuroepithelial tissue (contd.)

**1.7. Embryonal tumours**

- medulloblastoma
- PNET [Neuroblastoma]

2. Tumours of cranial and paraspinal nerves

**2.1. Schwannoma**

**2.2. Neurofibroma**

**2.3 Perineurinoma**

**2.4. Malignant PNST**

**Neuro-oncology**

**Immunohistochemistry of CNS Tumours**

**Immunohistochemical phenotyping**

→ confirmation of the histological diagnosis

Examples for IHC on formalin-fixed paraffin-embedded CNS tumours:

**Gliomas:**

Astrocytomas: GFAP, Vimentin

Oligodendrogliomas: Olig2, GFAP

**Ependymomas:** GFAP, Vimentin, CK

**Choroid plexus tumours:** CK, GFAP

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### Immunohistochemistry of CNS Tumours

Examples for IHC on formalin-fixed paraffin-embedded CNS tumours:

**Neuronal tumours:**  
 Ganglioglioma: Synaptophysin, NeuN, NF  
 Gangliocytoma: Synaptophysin, NeuN, NF

**Embryonal tumours:**  
 Medulloblastoma: Syn, NeuN, GFAP, NF, NSE  
 PNET: Syn, NeuN, GFAP

**Meningiomas:** CK, Vimentin

**Neuro-oncology**

### Tumours of neuroepithelial tissue

**Well circumscribed astrocytomas**  
**Pilocytic astrocytoma**  
**Grading: WHO grade I**

- > extremely rare in dogs
- > mainly located in thalamus
- > well circumscribed neoplasms
- > gray-white
- > characteristic: multiple cysts
- > low cellularity
- > bipolar fibrillary tumour cells
- > sometimes Rosenthal fibres
- > rarely mitoses
- > GFAP +

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### Tumours of neuroepithelial tissue

**Astrocytoma**

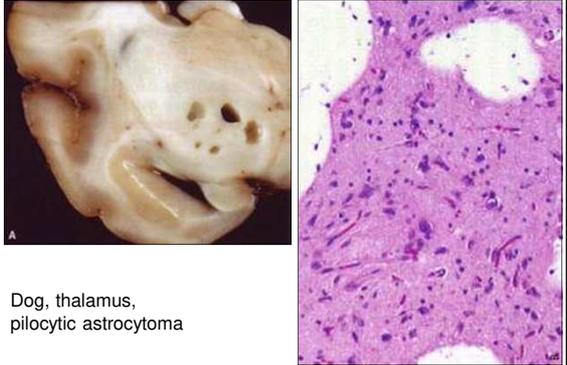
- > incidence (dogs): 15% of all primary NS tumours
- > increasing occurrence with age
- > disposition of some brachycephalic breeds (e.g. Boxer)
- > rarely observed in cats, cattle, horses and pigs

**Pathology:**  
 Well circumscribed subtypes:  
 - pilocytic  
 - gemistocytic  
 - subependymal giant cell type

Diffusely infiltrating  
 - diffuse  
 - anaplastic  
 - glioblastoma  
 - gliomatosis cerebri

**Neuro-oncology**

### Tumours of neuroepithelial tissue



Dog, thalamus, pilocytic astrocytoma

Vandevelde et al., 2012

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### Tumours of neuroepithelial tissue

**Astrocytoma**  
**Pathology:**

- > generally located supratentorially
- > white matter of cerebral hemispheres
- > less common: thalamus, midbrain, brainstem, spinal cord
- > firmer than normal brain tissue
- > white colour
- > margins indistinct
- > no invasion of ventricles

IHC: GFAP

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### Tumours of neuroepithelial tissue

**Well circumscribed astrocytomas**  
**Subependymal giant cell astrocytoma (SEGA)**  
**Grading: WHO grade I**

- > rare in dogs and cats
- > restricted to subependyma around the lateral ventricles
- > in dogs also adjacent to IV. ventricle
- > expansile growth into ventricular lumen → hydrocephalus
- > gemistocytic, spindle and ganglioid-like tumour cells
- > fibrous stroma
- > mitoses absent
- > GFAP +

Tumours of neuroepithelial tissue	
Neuro-oncology	<p><b>Well circumscribed astrocytomas</b>  <b>Gemistocytic astrocytoma</b>  <b>Grading: WHO grade II</b></p> <ul style="list-style-type: none"> <li>➤ uncommon in dogs</li> <li>➤ cerebellum, rarely spinal cord</li> <li>➤ well defined border lines</li> <li>➤ white to tan colour</li> <li>➤ roughened cut surface</li> <li>➤ gemistocytic astrocytic tumour cells: polygonal-angular shape, swollen, eosinophilic cytoplasm, eccentric nucleus</li> <li>➤ mitotic activity minimal</li> <li>➤ GFAP +</li> </ul>

Tumours of neuroepithelial tissue	
Neuro-oncology	<p><b>Diffusely infiltrating astrocytomas</b>  <b>Glioblastoma (Glioblastoma multiforme, GBM)</b>  <b>Grading: WHO grade IV</b>          („The terminator“)</p> <ul style="list-style-type: none"> <li>➤ common in dogs</li> <li>➤ frontal and temporal cerebral lobes</li> <li>➤ well defined boundaries</li> <li>➤ hemorrhages, necroses</li> <li>➤ hypercellularity</li> <li>➤ cell and nuclear pleomorphism</li> <li>➤ prominent nuclear atypia</li> <li>➤ mitotic activity high; atypical bizarre mitotic figures</li> <li>➤ microvascular (glomeruloid) proliferation (due to paracrine secretion of VEGF and PDGF)</li> <li>➤ glial cell pseudopalisading around necroses</li> </ul>

Tumours of neuroepithelial tissue	
Neuro-oncology	<p><b>Diffusely infiltrating astrocytomas</b>  <b>Diffuse astrocytoma</b>  <b>Grading: WHO grade II</b></p> <ul style="list-style-type: none"> <li>➤ common in dogs</li> <li>➤ supratentorially</li> <li>➤ frontal and temporal cerebral lobes</li> <li>➤ occasionally brainstem, spinal cord</li> <li>➤ undefined border lines</li> <li>➤ firm</li> <li>➤ white colour</li> <li>➤ uniform fibrillary astrocytes: elongate, hyperchromatic nucleus, scant cytoplasm</li> <li>➤ mitotic activity low</li> <li>➤ GFAP +</li> </ul>

Tumours of neuroepithelial tissue	
Neuro-oncology	<p><b>Diffusely infiltrating astrocytomas</b>  <b>Glioblastoma (Glioblastoma multiforme, GBM)</b>  <b>Grading: WHO grade IV</b>          GFAP + and EGFR +</p> <ul style="list-style-type: none"> <li>➤ tumour cell migration through normal brain parenchyma             <ul style="list-style-type: none"> <li>→ impossibility to cure by surgery</li> <li>→ secondary structures of Scherer:                 <ol style="list-style-type: none"> <li>a) perivascular spread</li> <li>b) perineuronal satellitosis</li> <li>c) subpial spread</li> <li>d) intrafascicular spread in white matter tracks</li> </ol> </li> </ul> </li> </ul>

Tumours of neuroepithelial tissue	
Neuro-oncology	<p><b>Diffusely infiltrating astrocytomas</b>  <b>Anaplastic astrocytoma</b>  <b>Grading: WHO grade III</b></p> <ul style="list-style-type: none"> <li>➤ frontal and temporal cerebral lobes</li> <li>➤ occasionally brainstem, spinal cord</li> <li>➤ undefined border lines</li> <li>➤ firm</li> <li>➤ white colour</li> <li>➤ increased cellularity and cell density</li> <li>➤ minimal fibrillary cytoplasm</li> <li>➤ nuclear atypia</li> <li>➤ mitotic activity moderate</li> <li>➤ GFAP + and Vim +</li> </ul>

Tumours of neuroepithelial tissue	
Neuro-oncology	<p><b>Diffusely infiltrating astrocytomas</b>  <b>Gliomatosis cerebri</b>          (in dogs: formerly mistakenly termed microgliomatosis)</p> <ul style="list-style-type: none"> <li>➤ disseminated involvement of the brain</li> <li>➤ cerebral hemispheres, cerebellum, brainstem</li> <li>➤ tumour cells:             <ul style="list-style-type: none"> <li>- elongate, hyperchromatic nucleus</li> <li>- without detectable cytoplasm</li> </ul> </li> <li>➤ variable cell density</li> <li>➤ secondary structures of Scherer common!</li> <li>➤ GFAP +</li> </ul>

### Tumours of neuroepithelial tissue

#### Oligodendroglioma

Grading: WHO grade II or III (anaplastic)

- in dogs: common primary NS tumour (20%)
- incidence increases with age
- infrequently in cattle, cats, horses
- disposition of some brachycephalic breeds (e.g. Boxer Bulldogs, Boston Terrier)
- predilection sites: frontal, parietal, temporal lobes
- gray and white matter around lateral ventricles with preference for intraventricular growth
- infrequently brainstem, spinal cord

Neuro-oncology

### Tumours of neuroepithelial tissue

#### Mixed glioma (oligoastrocytoma)

Grading: WHO grade II

- Dog: ca. 5% of all gliomas
- diffusely infiltrating neoplasm
- two distinct tumour cell populations:
  - well differentiated astrocytoma
  - oligodendroglioma
  - diffuse or biphasic (collision) pattern
- Differentiation of normal or reactive proliferated astrocytes is difficult (< 30 % of the astrocytes)
- minimal cell pleomorphism
- mitoses rare

Neuro-oncology

### Tumours of neuroepithelial tissue

#### Oligodendroglioma

Grading: WHO grade II or III (anaplastic)

- anaplastic type:
  - local invasion meninges
  - metastasis through ventricular system
- intratumoral hemorrhages common
- well circumscribed, sharply demarcated
- gelatinous or translucent
- soft
- gray to white
- intratumoral cystic myxoid areas
- white-yellow areas of necrosis (grade III)

Neuro-oncology

### Tumours of neuroepithelial tissue

#### Ependymoma

- Dog [2% of all primary tumours] (cat, horse, cattle)
- origin: ependymal lining cell
- supra- or subtentorial localization
- expansile growth within lateral, III. or IV. ventricle
  - non-communicating hydrocephalus
- large, well demarcated
- soft
- tan
- intraventricular
- sometimes fine granular texture of cut surface (papillary)
- occasionally hemorrhages, white-yellow areas of necrosis, fluid-filled cysts

Neuro-oncology

### Tumours of neuroepithelial tissue

#### Oligodendroglioma

Grading: WHO grade II or III (anaplastic)

- monomorphic, densely packed cells
- round basophilic nucleus
- vacuolated or eosinophilic cytoplasm, well defined borders
- delayed formalin fixation → honeycomb-appearance
- thin-walled branching capillaries („chicken-wire“)
- grade III:
  - microvascular (glomeruloid) proliferation
  - necroses, hemorrhages, thrombi
  - normal and abnormal mitoses
  - nuclear atypia,
  - secondary structures of Scherer
- GFAP → reactive astrocytes along the borderline
  - minigemistocytes (round tumour cells without cell processes)
- PDGFR- $\alpha$  +; Olig2 + (also astrocytomas)

Neuro-oncology

### Tumours of neuroepithelial tissue

#### Ependymoma

- monomorphic cells
- round to oval nuclei with finely stippled chromatin and a prominent nucleolus
- supra- or subtentorial localization
- perivascular pseudorosettes (GFAP +) with a characteristic nuclear-free perivascular zone
- occasionally ependymal rosettes
- subtypes in dogs:
  - papillary (finger-like processes)
  - cellular (round-elongate cells, nucleus-free perivascular spaces)
  - clear cell (oligodendroglial-like cells)

Neuro-oncology

Tumours of neuroepithelial tissue	
Neuro-oncology	<p><b>Choroid plexus tumours (CPT)</b> (papilloma and carcinoma)</p> <ul style="list-style-type: none"> <li>➤ Dog [7% of all primary tumours] (horse, cattle)</li> <li>➤ middle-aged dogs (~ 6 years)</li> <li>➤ disposition: Golden Retriever</li> <li>➤ origin: epithelium of choroid plexus</li> <li>➤ intraventricular localization (→ hydrocephalus, -myelia)</li> <li>➤ IV. ventricle &gt; III. ventricle &gt; lateral ventricles</li> <li>➤ intraventricular and subarachnoid metastases</li> </ul>

Tumours of neuroepithelial tissue	
Neuro-oncology	<p><b>Embryonal tumours</b> Primitive neuroectodermal tumours (PNET) (syn. neuroblastoma)</p> <ul style="list-style-type: none"> <li>➤ extremely rare neoplasms</li> <li>➤ young animals (dog, cattle, horse)</li> <li>➤ origin: poorly differentiated neuroepithelial cell</li> <li>➤ location supratentorially</li> <li>➤ similar to medulloblastomas, but less differentiated</li> <li>➤ large, fleshy, soft, well demarcated, whitish</li> <li>➤ necroses, hemorrhages</li> <li>➤ uniform cells with elongate to ovoid, basophilic, hyperchromatic nuclei and minimal cytoplasm</li> <li>➤ occasionally neuroblastic Homer-Wright-rosette</li> <li>➤ frequent mitoses</li> <li>➤ variable immunoreactivity for neuronal marker</li> </ul>

Tumours of neuroepithelial tissue	
Neuro-oncology	<p><b>Choroid plexus tumours (CPT)</b> (papilloma and carcinoma)</p> <ul style="list-style-type: none"> <li>➤ expansile growth within ventricles</li> <li>➤ well demarcated</li> <li>➤ granular, rough texture (cauliflower-like)</li> <li>➤ gray to red</li> <li>➤ carcinoma: necroses, hemorrhages, infiltrative growth</li> <li>➤ Grade I (dog): papilliform organoid growth, single layer</li> <li>➤ Grade II (man, not dog): atypical CPT</li> <li>➤ Grade III (dog): increased cell density, nuclear atypia, frequent mitoses, focal loss of papillary formation</li> <li>➤ CK +, E-cadherin +; variably GFAP +</li> </ul>

Tumours of neuroepithelial tissue	
Neuro-oncology	<p><b>Embryonal tumours</b> Primitive neuroectodermal tumours (PNET) (syn. neuroblastoma)</p> <ul style="list-style-type: none"> <li>➤ classification depending on the location and histology: <ul style="list-style-type: none"> <li>- olfactory neuroblastoma (esthesioneuroblastoma)</li> <li>- cerebral neuroblastoma</li> </ul> </li> </ul>

Tumours of neuroepithelial tissue	
Neuro-oncology	<p><b>Embryonal tumours</b> Medulloblastoma</p> <ul style="list-style-type: none"> <li>➤ rare malignant neoplasms of the <b>cerebellum</b></li> <li>➤ young animals</li> <li>➤ dog, cat, cattle, pig</li> <li>➤ large, fleshy, soft, gray well circumscribed mass</li> <li>➤ often located midline (vermis)</li> <li>➤ densely cellular</li> <li>➤ sheets of cells with ovoid, elongate to round, basophilic, hyperchromatic nuclei and minimal cytoplasm („small blue tumours“)</li> <li>➤ occasionally neuroblastic Homer-Wright-rosette</li> <li>➤ frequent mitoses</li> <li>➤ invasion: meninges, IV. ventricle, cerebellar hemispheres</li> <li>➤ NSE +; Syn +, chromogranin A and B</li> </ul>

Tumours of the meninges	
Neuro-oncology	<p><b>Meningioma</b></p> <ul style="list-style-type: none"> <li>➤ origin: meningotheial cell (arachnoidal cap cell) or other cells of the arachnoid granulations (multipotent mesodermal cell or dural fibroblast)</li> <li>➤ most common intracranial and intraspinal neoplasm in dogs (40%) and cats</li> <li>➤ sporadically in horses, cattle, sheep</li> <li>➤ increasing incidence with age (dog, cat)</li> <li>➤ breed disposition: Golden retriever, Boxer</li> <li>➤ most common location: over cerebral convexity</li> <li>➤ in cats often multiple masses of variable size</li> </ul>

## Tumours of the meninges

Neuro-oncology

### Meningioma

- **dog:** well demarcated, lobulated, firm, often granular, white to tan-coloured mass with broad-based attachment
- **cat:** nodular, well demarcated, hard, solid, yellow-gray
- intra-axial expansion
- topography: 82% intracranial
  - 15 % intraspinal
  - 3 % retrobulbar
- classification:
  - Grade I (with diverse histological subtypes)
  - Grade II (atypical)
  - Grade III (malignant)
- Vim +, occasionally CK +
- TEM: interdigitating cytoplasmic membranes

## Tumours of the meninges

Neuro-oncology

### Granular cell tumour

- topography in dogs: - cerebral hemispheres
  - in neurohypophysis combined with meningioma
  - lumbar spinal nerves
- histogenetic origin: uncertain
- broad-based mass lesion
- firm, well demarcated, non-encapsulated
- solid sheets of large, polygonal granule cells with eccentric nucleus, granular, eosinophilic cytoplasm (PAS-positive, diastase-resistant)
- S100 +, ubiquitin +,  $\alpha$ -1-antitrypsin +
- EM: granules = autophagic lysosomes

## Tumours of the meninges

Neuro-oncology

### Meningioma

- Grade I subtypes (dog):
  - transitional: mixture of meningotheial and fibrous cells
  - meningotheial: solid sheets of polygonal cells
    - occasionally "whorl" formation
  - psammomatous: background: transitional meningioma
    - numerous psammoma bodies
  - fibrous: interwoven spindle-shaped tumour cell strands
  - angiomatous: background: transitional or meningotheial meningioma with numerous large/small blood vessels
  - microcystic: widespread intracellular and interstitial vacuolation

## Lymphomas and hematopoietic tumours

Neuro-oncology

### Primary T and B cell lymphomas

- single mass lesions in the CNS (absence of extraneural involvement)
- rare occurrence (dog: 3%), cat, cattle, pig
- rostro-tentorial, deep-seated sites (intra-axial) close to the ventricles, midbrain, spinal cord
- grayish, soft, poorly defined margins, yellow-white necroses
- dense sheets of lymphoblastoid cells
- at periphery: perivascular infiltration with concentric bands of reticulin within angiocentric infiltrates
- high mitotic rate
- high degree of individual cell necrosis
- CD3 +/CD79a +

## Tumours of the meninges

Neuro-oncology

### Meningioma

- Grade II subtypes (dog):
  - chordoid: cords or columns of eosinophilic vacuolated cells in a mucoid basophilic matrix
  - atypical: nuclear atypia, necrosis, increased cellular density, > 4 mitotic figures/10 hpf
- Grade III subtypes (dog):
  - malignant: > 20 mitotic figures/10 hpf
    - anaplastic cytological appearance
  - papillary: rare in dogs

## Lymphomas and hematopoietic tumours

Neuro-oncology

### Intravascular lymphoma

- (syn. angiocentric, endotheliotropic, intravascular lymphoma)
- B cell lymphoma
  - sometimes exclusively in CNS, normally in various organs
  - dog, cat, sheep
  - secondary thrombosis → infarctions

### Metastatic lymphoma

- restricted to dura and meninges
- secondary invasion of the parenchyma

## Lymphomas and hematopoietic tumours

Neuro-oncology

### Primary CNS histiocytic sarcoma

- older dogs
- disposition: Bernese Mountain dog, Rottweiler, Dobermann, Pembroke Welsh Corgi, Retriever
- single, large, broad-based, meningeal masses
- intracranially, occasionally in the spinal cord
- secondary invasion of parenchyma
- eccentric oval to reniform pleomorphic nuclei
- eosinophilic sharply demarcated cytoplasm with phagocytized nuclear debris
- bi- and multinucleated cells frequent
- numerous normal and abnormal mitotic figures
- CD1c +, CD11b +, CD11c + (frozen native tissue)
- CD18 + (FFPE tissue)

## Germ cell tumours

Neuro-oncology

### Teratoma

- wide variety of species including birds
- disorganized mixture of variably differentiated tissues from ecto-, endo- and mesodermal cell lines
- composed of brain, choroid plexus, glandular tissue, cartilage, osteoid tissue, fat, hair follicles, skeletal and smooth muscle, bone with hematopoietic tissue

## Germ cell tumours

Neuro-oncology

### Germinoma

- dog
- lateral suprasellar region or thalamus
- origin: extraneuroaxial gonadal germ cells
- closely attached to the meninges
- irregular rough border
- infiltrative growth
- sheets or lobules of large cells
- large nuclei, large eosinophilic cytoplasm
- numerous infiltrating T lymphocytes

## Embryonal tumours of non-neuroepithelial origin

Neuro-oncology

### Thoraco-lumbar spinal cord tumour of young dogs (ectopic nephroblastoma)

- mainly large-breed dogs (German Shepherd dog, Golden Retriever, Boxer)
- age: 5- 48 months (Ø 14 months)
- Topography: T9 – L3
- incidence: < 1% of all primary CNS tumours
- undetermined origin: intradural extramedullary or intramedullary
- pinkish-gray, bulging mass (up to 2 cm Ø)
- mixture of epithelial and solid mesenchymal tissue
- forming tubular and acinar structures with glomeruloid structures
- mitotic figures numerous
- CK +; WT-1 + (Wilms nephroblastoma tumor gene product)

## Germ cell tumours

Neuro-oncology

### Mixed germ cell tumour

- dog
- midline supra- and perisellar
- grey-white;
- compression of pituitary gland and hypothalamus
- composed of:
  - germinative cells
  - hepatoid cells
  - epithelial cells (intestinal/respiratory differentiation)
  - lymphocytic infiltrates
- α-fetoprotein +

## Metastatic tumours

Neuro-oncology

- incidence: in dogs similar to primary CNS tumours
- predominantly hematogenous metastases from primary extraneural neoplasms
- local extension (bone or nasal tumours, pituitary tumours)
- frequency:
  - hemangiosarcoma (29%)
  - carcinomas (12%) [mammary, lung, kidney]
  - metastatic malignant lymphomas (12%)
  - nasal tumours
  - disseminated histiocytic sarcomas
  - malignant melanomas