Degenerative & toxic metabolic diseases
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Toxic metabolic and degenerative diseases

Toxic –metabolic
- All age classes
- Sporadic/outbreaks
- (Per)acute clinical course
- Massive destruction of tissue/sometimes discrete
- Bilateral - symmetrical
- Specific areas
- Massive invasion with macrophages

Degenerative
- Juvenile animals
- Family history/hereditary
- Slowly progressive
- Discrete lesions, rarely malacia
- Bilateral-Symmetrical
- Specific areas
- Gliosis
Major patterns

Gray matter
• Malacia
• Spongy state
• Axonal swellings
• Neuronal loss
• Neuronal storage

White matter
• Malacia
• Spongy state
• Axonal swellings
• Pallor/loss of myelin
• Axonal degeneration
Malacia

- Grey or white matter or both
- Often grossly visible
- Complete destruction of selected areas
- Invasion with macrophages
- Vascular proliferation
- In some conditions also hemorrhage
Toxic metabolic malacias examples

**Grey matter**

- Cerebro-cortical necrosis in ruminants
- Thiamin deficiency in carnivores
- Hippocampal necrosis in cats
- Nigropallidal encephalomalacia in horses

**White matter**

- Equine Leukoencephalomalacia
Hippocampal necrosis in cats
Thiamin deficiency in ruminants
Thiamin deficiency in cats
Selective symmetrical encephalomalacias

Symmetrical areas of tissue destruction

Mitochondrial encephalopathies?

In Alaskan Husky:
Genome-Wide Association Analysis Identifies a Mutation in the **Thiamine Transporter 2 (SLC19A3) Gene** Associated with Alaskan Husky Encephalopathy.

*Karen M. Vernau et al. Plos One 2013*

- Australian cattle dog
- English Springer spaniel
- Jack Russel Terrier
- **Alaskan Husky**
- **Yorkshire terrier**
Alaskan husky encephalopathy: Detection of bilaterally symmetrical areas of malacia in MRI
Malacia in white matter

• Toxic metabolic causes
  – Equine Leukoencephalomalacia
  – Clostridium perfringens

• Degenerative
  – Leukodystrophies
Leukodystrophy

• Lysis of myelin+axons, often bizarre distribution

• Hereditary forms:
  – Cavitating leukodystrophy, Dalmatians
  – Leukomyeloencephalopathy in Rottweiler/Leonberger dogs
  – Fibrinoid leucodystrophy, Labrador ret.
  – Necrotizing myelopathy Afghan, Kooiker dog
  – Globoid cell leucodystrophy (storage disease)
Afghan Dog Myelopathy
Leukomyeloencephalopathy in Leonberger & Rottweiler
Spongy state

• Autolysis
• Old age
• Toxic metabolic diseases
  – Liver failure
  – Poisons
• Degenerative diseases
  – Spongiform encephalopathies
  – Spongy degenerations
Metabolic encephalopathy

• Mostly liver failure (hepatoencephalopathy)
• Vacuolation of white matter/grey matter areas
  – In ruminants extensive mostly white matter
  – In carnivores discrete esp. cerebellar and brainstem nuclei
• Alzheimer type II astrocytes in grey matter
Alzheimer type II cells
Spongy degenerations

- Massive vacuolation of the tissue
- Grey or white matter or both
- Often congenital tremor
- Defect in electrolyte/water metabolism
- Visible in MRI
- Cause:
  - Genetic defects: organic acidurias: West highland, Staffordshire terriers
Spongy degeneration: bilaterally symmetrical vacuolation of the tissue
Spongiform encephalopathies/Prion diseases
Examples: Scrapie in sheep, BSE in cattle
Motor neuron diseases

**Spinal Muscular Atrophy in:**
- Brittany Spaniels
- Lapland dogs
- Rottweilers
- ......

Neurons degenerate in spinal cord and brainstem
Spinal Muscular Atrophy

Neurogenic Atrophy
Purkinje cell degenerations

- very large spectrum
- dog, cat
ca. 40 breeds affected
Purkinje cell degeneration

- Purkinje cells die and are lost
- Cerebellar cortex shrinks

normal
degenerated
Normal

Purkinje cell loss > Cortex shrinks

Normal

Atrophy
Lysosomal storage diseases

- Genetic defects of lysosomal enzymes
- Enzyme substrate is no longer degraded
- And accumulates in the lysosome
# Examples of Lysosomal storage diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Breed</th>
<th>Age at onset of symptoms</th>
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</thead>
<tbody>
<tr>
<td>GM1 Gangliosidosis</td>
<td>Beagle, Siamese, domestic cat</td>
<td>3 to 6 months</td>
</tr>
<tr>
<td>GM2 Gangliosidosis</td>
<td>German Pointer (male), Japanese and Springer Spanie; domestic cat</td>
<td>6 - 12 months</td>
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<tr>
<td>Sphingomyelinosis</td>
<td>Poodle; Siamese, Domestic cat</td>
<td>4 - 6 months</td>
</tr>
<tr>
<td>Glucocerebrosidiosis</td>
<td>Silky Terrier</td>
<td>6 - 8 months</td>
</tr>
<tr>
<td>Globoid-Cell-Leukodystrophy (Krabbe)</td>
<td>Westhighland White and Cairn Terrier, Beagle, Poodle; Domestic Cat</td>
<td>6 - 12 months</td>
</tr>
<tr>
<td><strong>Ceroid Lipofuscinosis</strong></td>
<td>Chihuahua, Saluki, English Setter, Dachshound, Am. Staffordshire Terrier</td>
<td>6 months to 2 years (sometimes later)</td>
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<tr>
<td>Fukosidosis</td>
<td>Springer spaniel</td>
<td>2 - 3 years</td>
</tr>
<tr>
<td>Glycoproteinosis</td>
<td>Beagle, Basset, Poodle</td>
<td>2 - 12 months</td>
</tr>
<tr>
<td>Mannosidosis</td>
<td>Persian Cat, Domestic cat</td>
<td>1 - 3 months</td>
</tr>
</tbody>
</table>
Ceroid lipofuscinosis: atrophy of cortex
Widening of meningeal space

Lysosomes filled with Storage material
Axonal Transport

- Everything is produced in the cell body
- Transportation along the axon often over long distances

A lot can go wrong
Axonal diseases

2 major types:

• Wallerian like degeneration

• Axonopathies with axonal swelling
Wallerian degeneration

Lesion of the axon

Lysis of the axon distal to the lesion

Many axonal degenerations look like Wallerian degeneration; the primary lesion is not known
Distal axonopathies

**concept of dying back axonopathy**

A metabolic problem in the neuron

Its most distal part (end of axon) is the first to suffer

Degeneration then progresses towards the neuronal cell body

Many axonal degenerations are probably dying back axonopathies
Wallerian-like degenerations
Myelinstain
Axonal diseases

- Ataxia in smooth haired Fox/JR Terriers
- Labrador retriever axonopathy
- Degenerative myelopathy in Welsh Corgi-Pembroke
- Distal axononopathy in Birman cats
- Degenerative myelopathy in large breed dogs
- ..................
Degenerative Myelopathy in large breed dogs

• Large breed dogs, >7 years
• Slow onset and progression of paresis and ataxia in hind limbs
• Diffuse/dissiminated loss of axons in spinal cord
• Cause/pathogenesis?
  – Hereditary factors/ SOD 1 mutations?
German shepherd dog; degenerative myelopathy: diffuse loss of axons (red areas)
Axonal dystrophy

- Starts at axon endings
- Primary lesions in gray matter
- Marked axonal swelling
- In Rottweilers, Papillon, Chihuahua, cats, horses
Equine axonal dystrophy

- Equine degenerative myelo-encephalopathy (EDME)
- Originally thought to be deficiency (Vit E)
- Probably combination of hereditary + environmental factors
- Dystrophic axons in grey matter nuclei brainstem and cord
- Secondary degeneration white matter cord
Abnormal Myelin Development