

Neurodegenerative diseases:
a lesion-based approach:
combined grey + white

Major lesion groupings

Grey matter

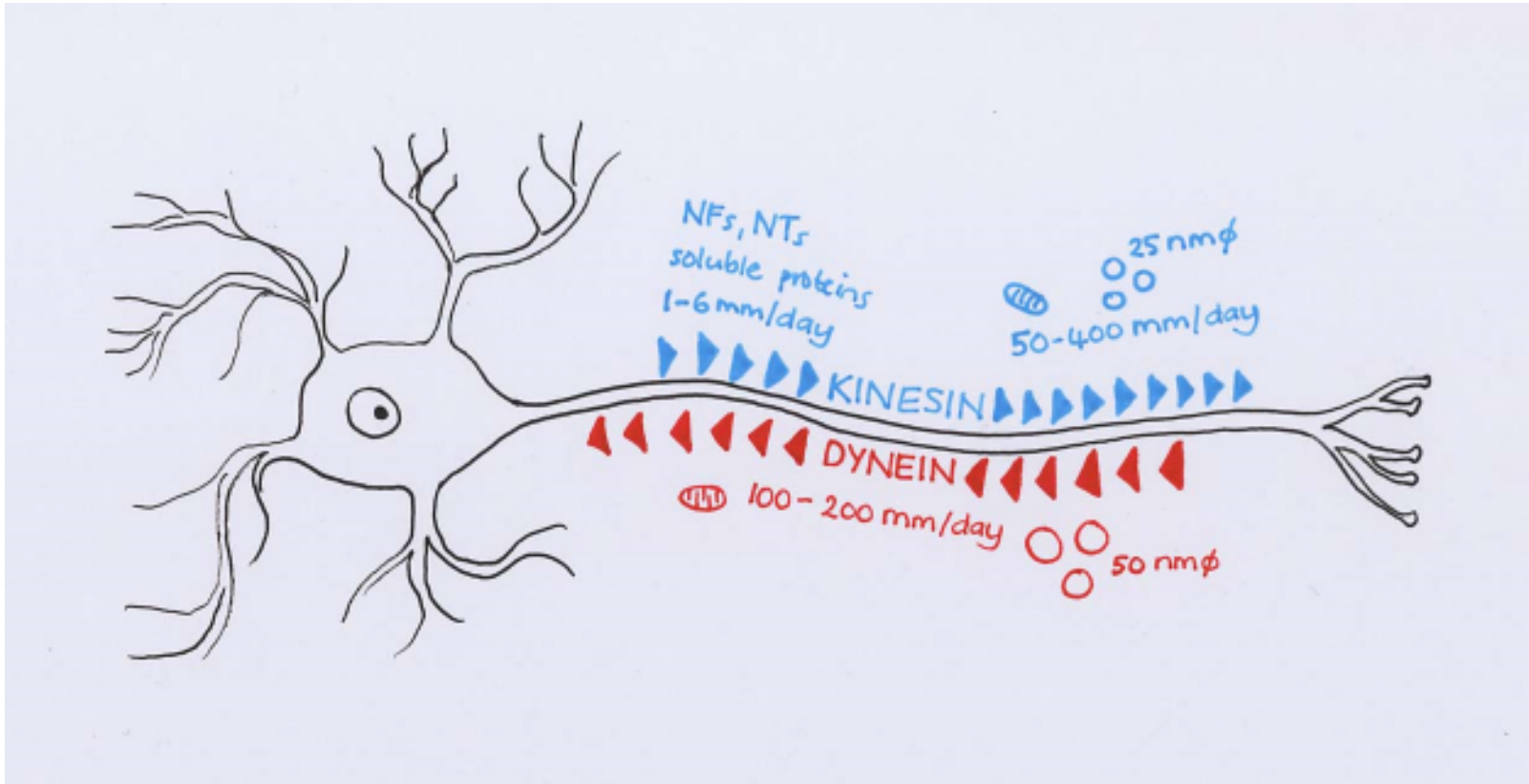
- Neuronal necrosis
 - cerebrocortical, hippocampal, cerebellar
- Neuronal degeneration, spheroid formation
 - Cerebellum, [motor, sensory – with GM / WM], 'multisystem'
- Multi/focal neuroparenchymal necrosis / rarefaction / oedema
- Vacuolation

Grey matter and white matter

- Neuroparenchymal necrosis / rarefaction / oedema
- **Neuronal degeneration + axonal degeneration : long fibre tract
Wallerian degeneration, spheroid formation**
 - **motor neurone + tract, sensory neurone + tract, combination**
- Vacuolation

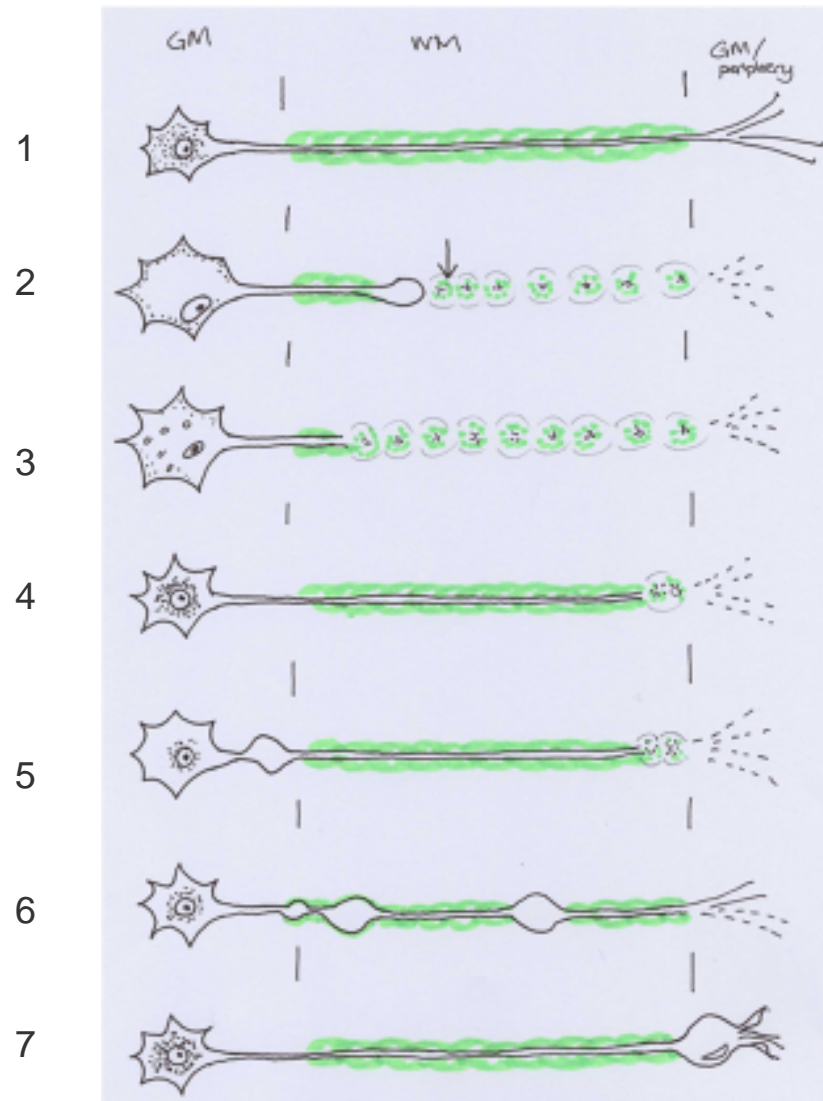
White matter

- Multi/focal neuroparenchymal necrosis / myelinolysis –demyelination / oedema
- Secondary demyelination / Wallerian degeneration
 - Long fibre tract and other patterns of Wallerian degeneration, spheroid formation – with GM+WM
- Hypomyelination
- Dysmyelination (lesions of myelin sheath / oligodendroglia)
- Vacuolation



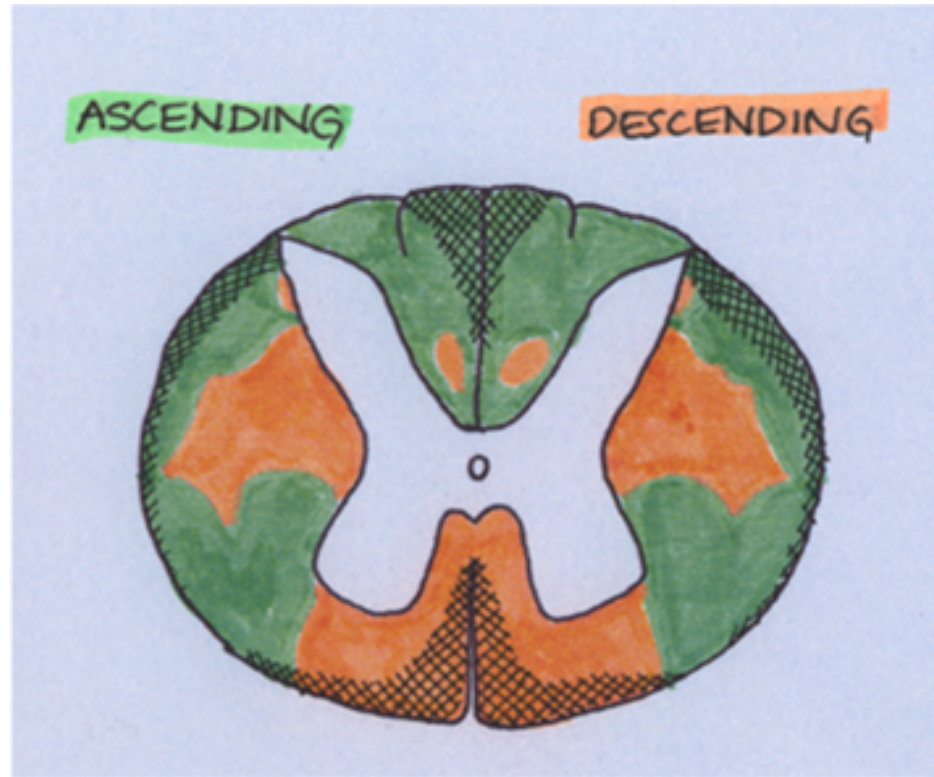
Primary sensory neurone : 70 μm diameter soma can maintain axonal projections > 2m

Categories of axonal degeneration



1. Intact neurone, axon, myelin sheath and dendrites
2. Focal axonal injury : Wallerian degeneration in axon distal to injury, often spheroid formation in region of injury and usually central chromatolysis
3. Extensive axonopathy with WD, may be tendency to involve distal portions first. Often central chromatolysis and variable vacuolation progressing to complete chromatolysis and neuronal loss.
4. Distal axonopathy (dying back phenomenon)
5. Axonopathy with proximal spheroid formation, usually also degeneration of neurone and distal axon
6. Axonopathy with variably located axonal swellings
7. Neuroaxonal dystrophy with swelling of preterminal \pm terminal processes, therefore usually in grey matter

Degeneration of neurones with long projections [long fibre tract]



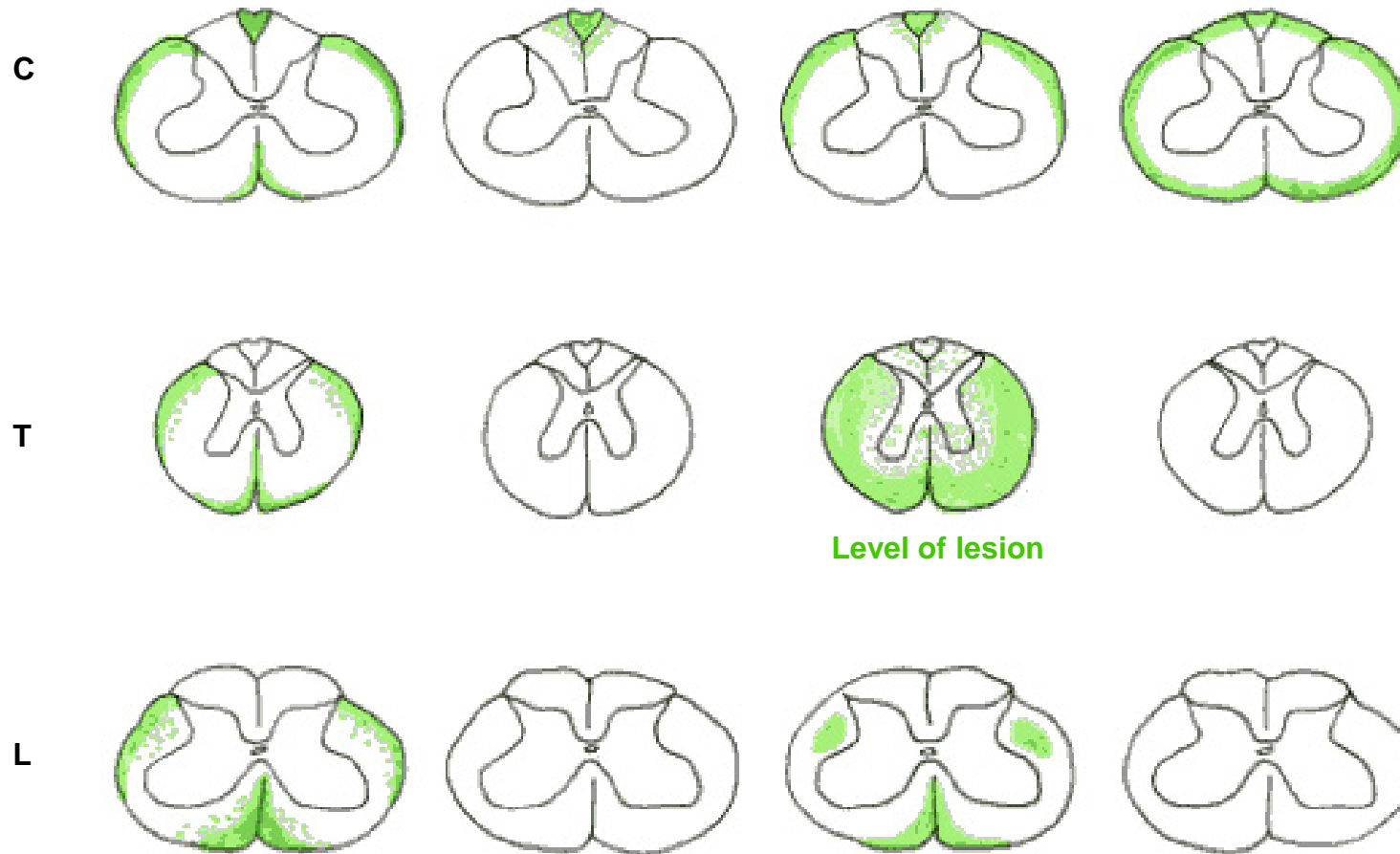
Approximate distribution of some tracts involved in 'long fibre tract distribution' (hatched areas)

Dorsal funiculus : gracile tract

Lateral funiculus : dorsal spinocerebellar tract

Ventral funiculus : tectospinal, vestibulospinal etc

Basic patterns of white matter degeneration in spinal cord



- Neurones with long projections (long fibre tract; LFT) eg upper motor neurones (UMN – eg vestibular complex and red nucleus); lower motor neurones (LMN eg ventral horn); thoracic nucleus (Clarkes column) : histological lesions may involve
 - Mainly neuronal cell bodies
 - Both neuronal cell bodies and axons
 - Mainly axonal lesions
- Dorsal funiculus : central projections of sensory neurones
- Focal injury
- Subpial circumferential (see white matter necrosis / myelinolysis)



Spinal cord : : sampling for histology :: preliminary screen

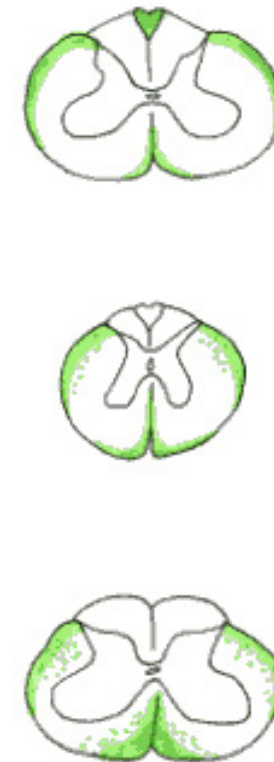
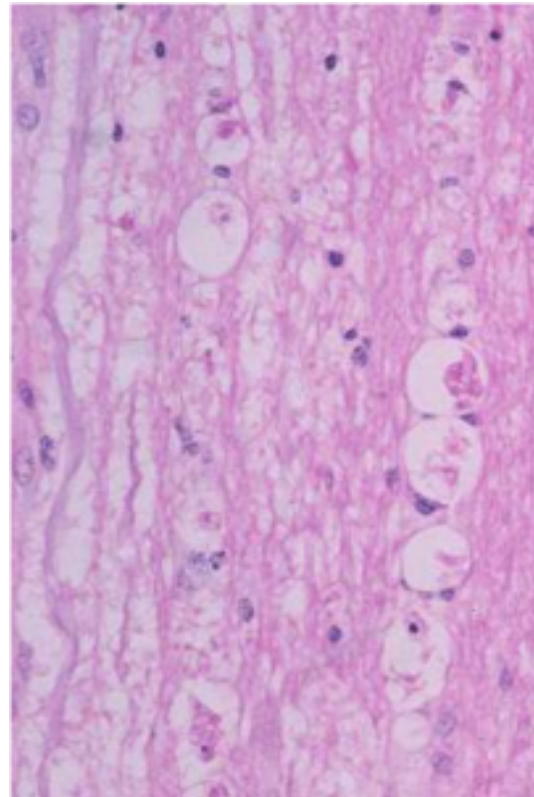
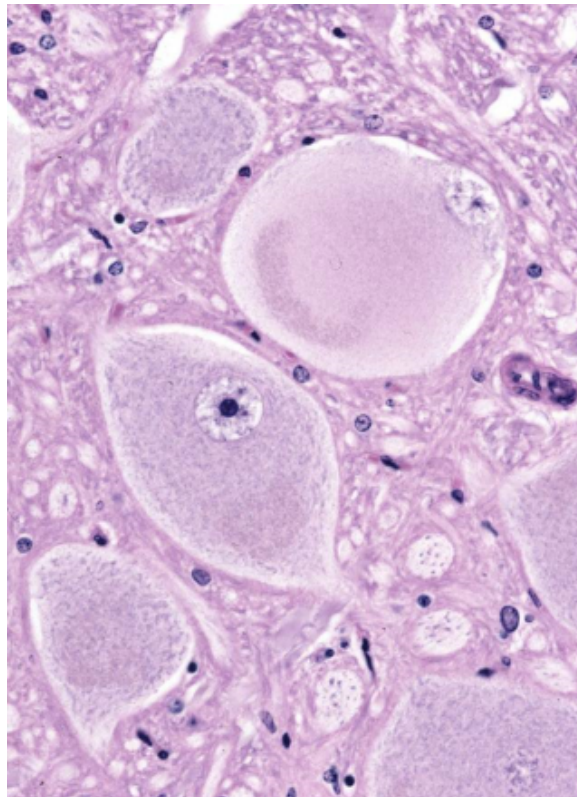
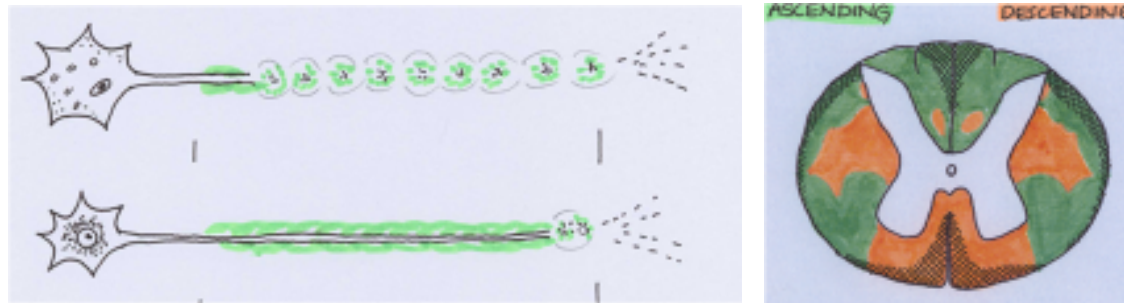


- Transverse sections
 - C1 (from medulla)
 - C3
 - C7
 - T7
 - lumbosacral
- Cord easily 're-assembled' for further investigation of selected levels / longitudinal sections



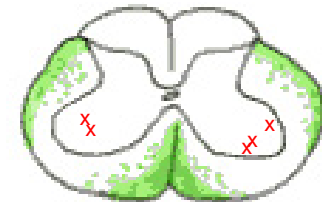
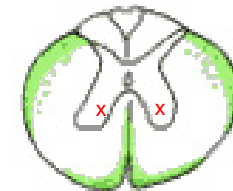
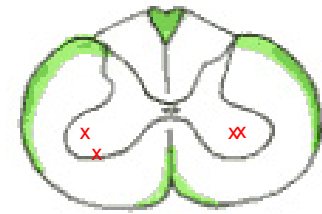
Patterns of axonal degeneration

1. Extensive axonopathy with WD involving much of axon, may be tendency to involve distal portions first. Often central chromatolysis and variable vacuolation progressing to complete chromatolysis and neuronal loss.
2. Distal axonopathy (dying back phenomenon)



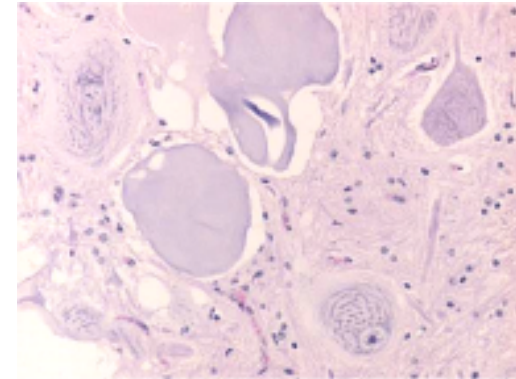
Neurones with long projections (long fibre tract; LFT) nerve cell body and axonal lesions:

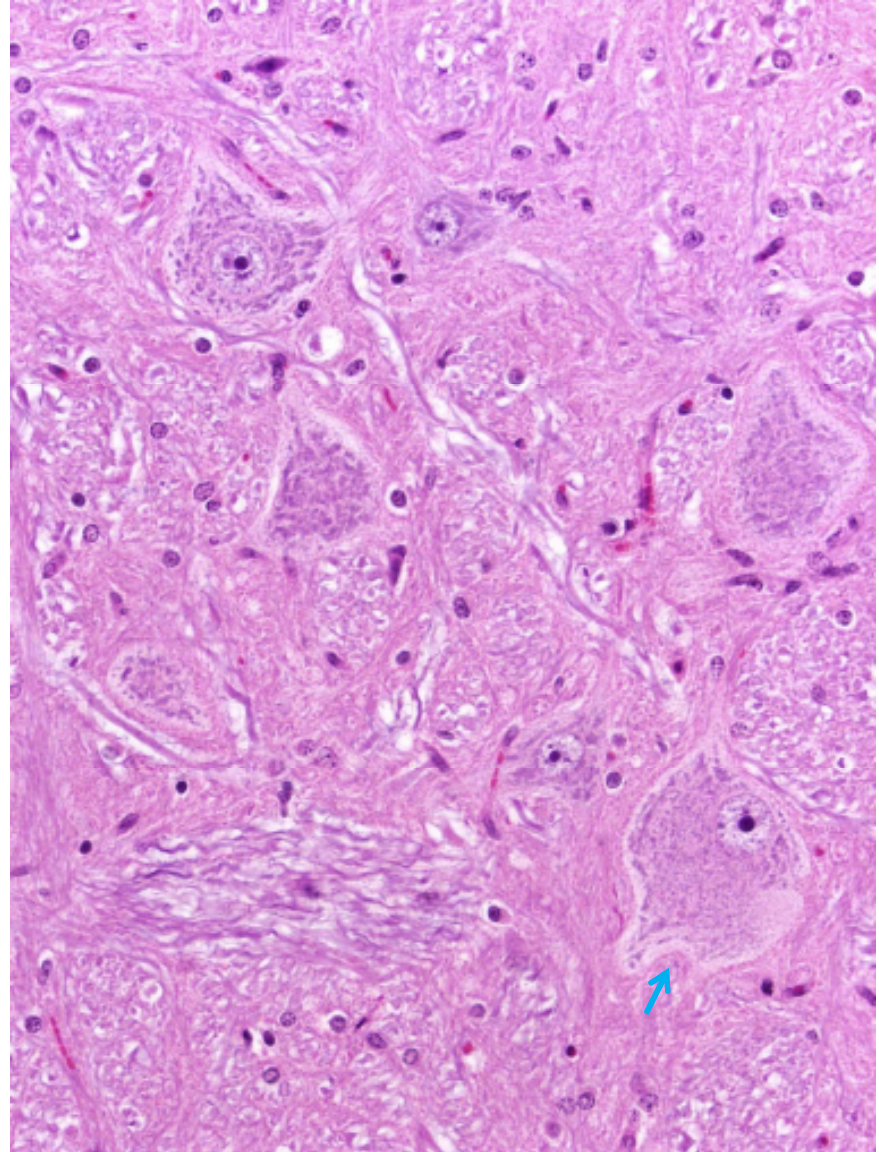
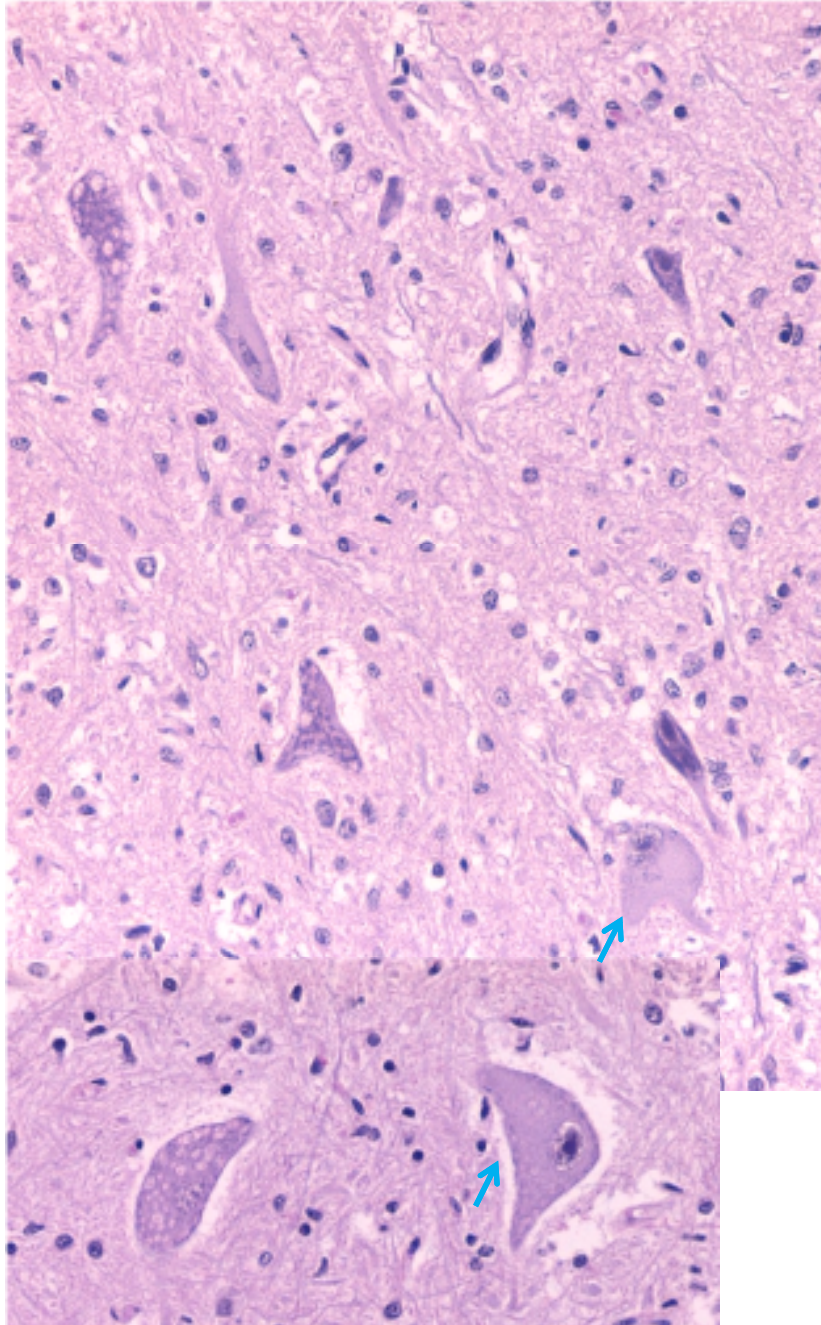
- Congenital and delayed (enzootic ataxia) swayback (*in utero* copper deficiency), sheep and goats
 - **UMN, LMN chromatolysis, WD LFT, cerebellar dysgenesis especially goat kids, porencephaly in severe congenital form**
- Chronic copper deficiency deer
 - **Marked white matter vacuolation in LFT or more widespread pattern; WD often not prominent, neuronal chromatolysis 'UMN'**
- Equine motor neurone disease
 - **Many breeds involved**
 - **Possible association with antioxidant (Vitamin E) deficiency**
- *Aspergillus clavatus* mycotoxicosis
 - **Extensive degeneration of UMN and LMN, LFT WD**
- Breed related motor neurone/axon degenerations
 - **separate list**
- Epidemic motor neurone degeneration in 1-2 m.o. goat kids
 - **?food-borne**
- *Chrysocoma tenuifolia* intoxication lambs
 - **Chromatolysis and vacuolation all spinal neurones esp VH, s/cord vacuolation esp SCT and periphery**
- Bovine brainstem neuronal chromatolysis and hippocampal sclerosis
 - **See multisystem disorders**
- Canine axonopathies
 - **Labrador Retriever : agenesis corpus callosum and other developmental anomalies, WM spheroids particularly in dorsal funiculus, chromatolysis and spheroids in olivary nucleus**
- Unilateral hindleg spasticity outbreak in suckling piglets
 - **Chromatolysis red nuclei, cerebellar nuclei, lumbar ventral horn, WD not recorded (Newsholme, 1980)**



Breed-related motor neurone diseases :

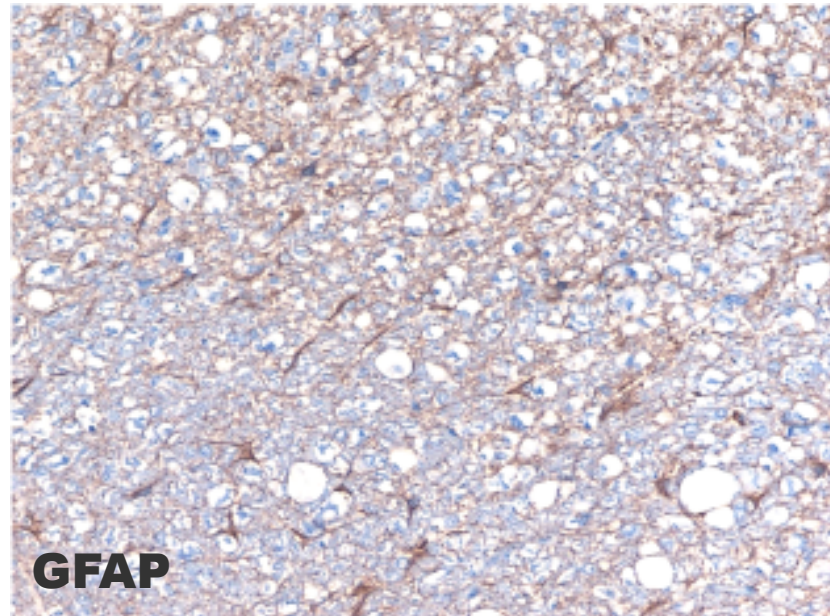
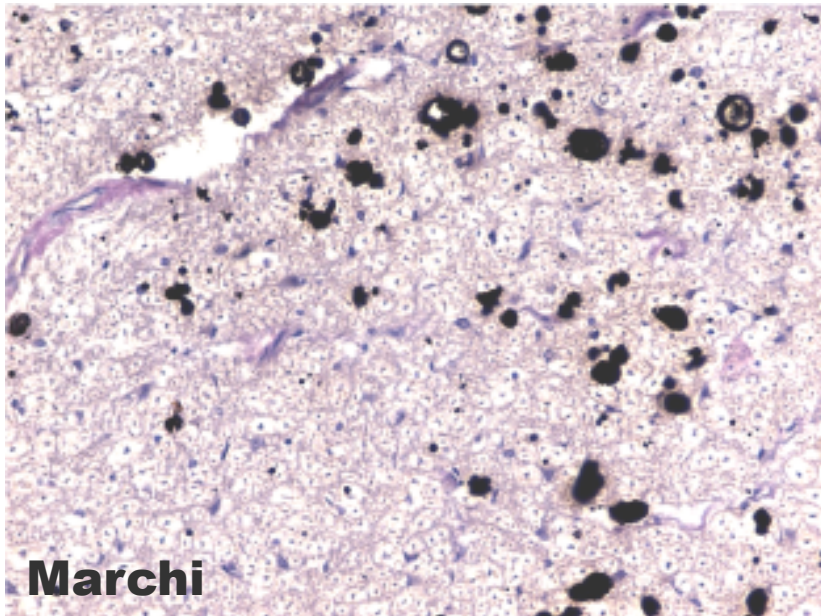
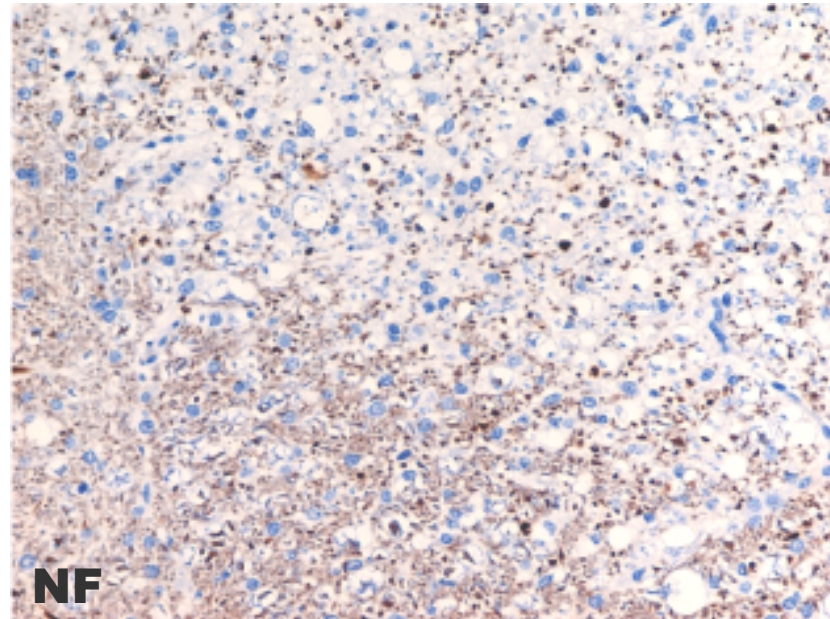
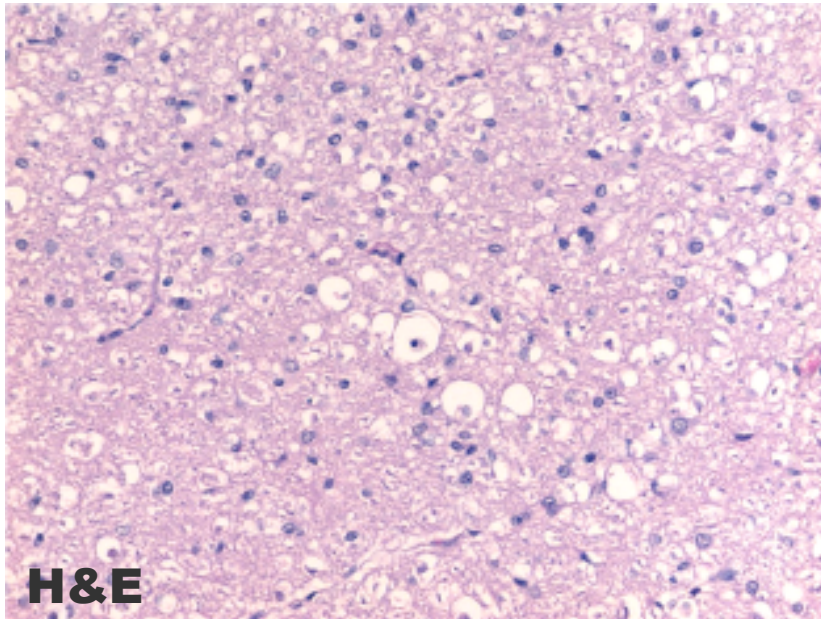
- Bovine
 - Horned Hereford Shaker motor neuronopathy (UMN, LMN, autonomic; marked anomaly Nissl distribution, grey matter spheroids, WD LFT)
 - Spinal ataxia in Afrikaner cattle – ‘Nissl disarray’ prominent
 - Brown Swiss – LMN, UMN, LFT- WD + spheroids
 - Red Danish – IBID
 - Holstein Friesian – LMN (no UMN), LFT WD
 - Progressive spinal myelinopathy in Murray Grey cattle : Myelin loss in LFT pattern (little WD recorded); chromatolysis nucleus thoracicus and ‘UMN’
- Porcine
 - Yorkshire UMN, LMN (NF accum), LFT
 - Hampshire IBID
- Ovine
 - Romney – LMN, spheroids GM, peripheral neuropathy
 - Charollais – mild UMN, LMN, LFT WD; also cerebellar cortical degeneration
- Caprine
 - Progressive neuronal vacuolar degeneration of Angora goats
 - prominent IC vacuoles large neurones midbrain, caudal brainstem, also LFT WD
- Canine
 - Brittany Spaniel (AD) chromatolysis and loss SMN mainly intumescences, hypoglossal, trigeminal motor nuclei
 - Swedish Lapland – SMN lateral aspects intumescences, spinal ganglia, cerebellar purkinje neurones
 - English pointer - lipid inclusions SMN, hypoglossal, spinal accessory nuclei
 - Spinal muscular atrophy German Shephard dogs – ventral horn degeneration asymmetric, only cervical intumescence
 - Stockards paralysis of dogs – Great Dane, Bloodhound and St. Bernard dogs
 - Doberman, Saluki, Griffon Briquet Veendeen breeds



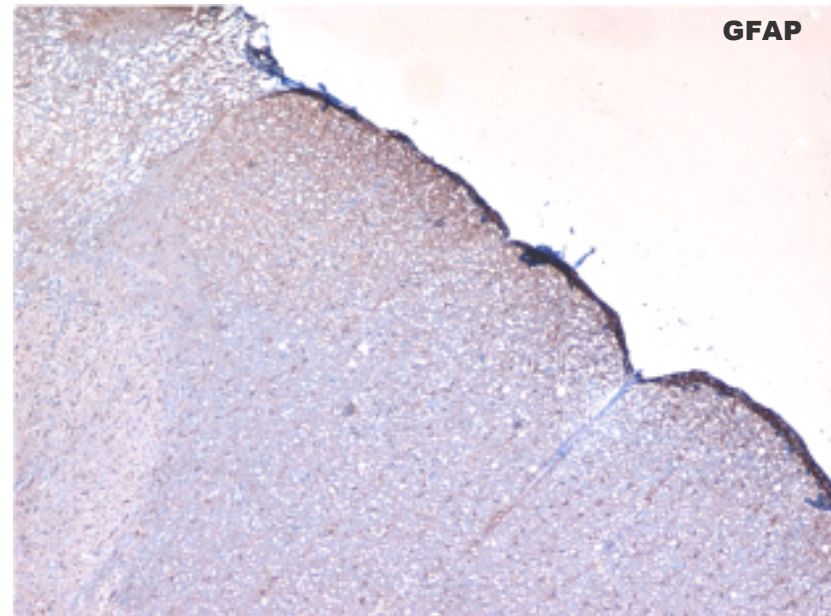
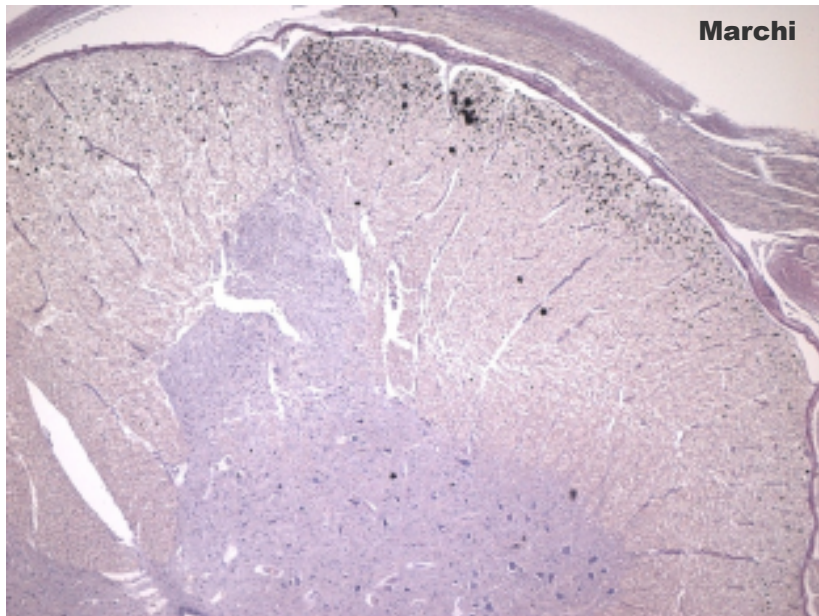
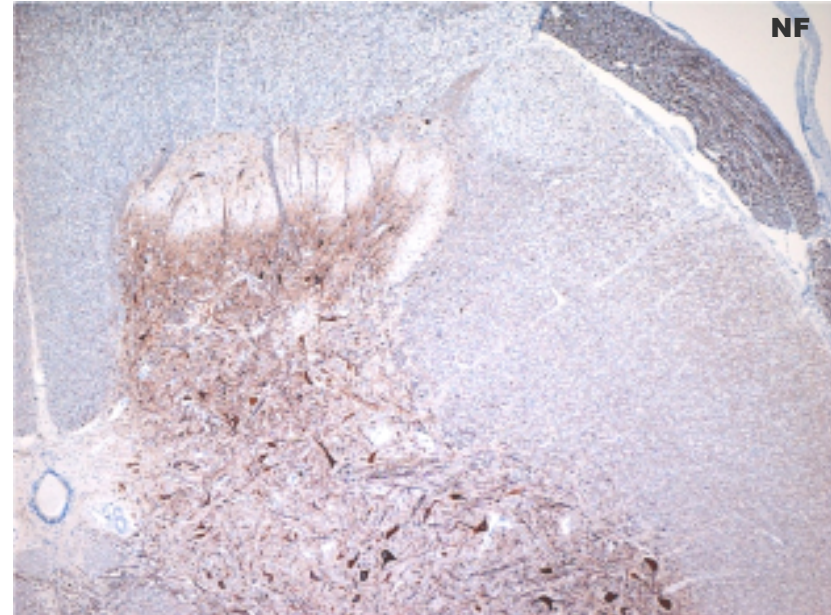
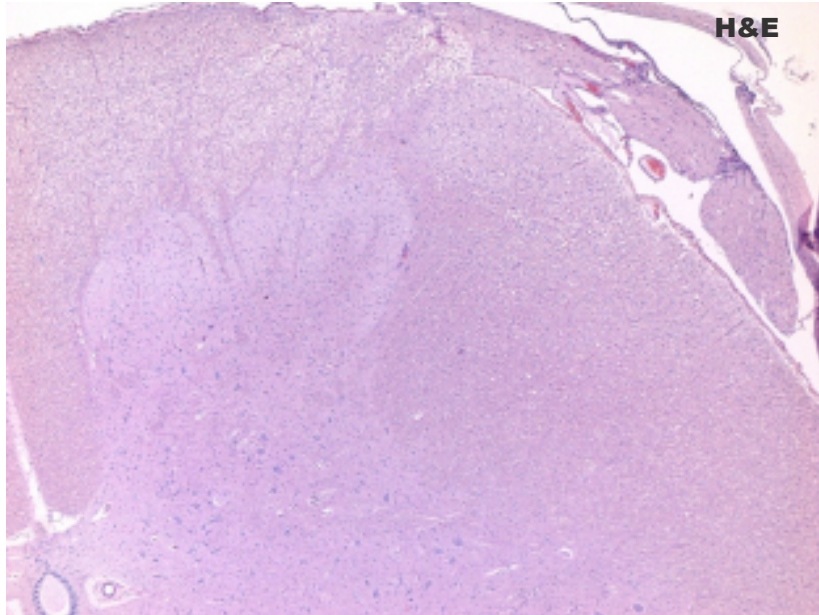


Early chromatolysis, Left : vestibular complex, swayback; Right: red nucleus, Charollais lamb ataxia

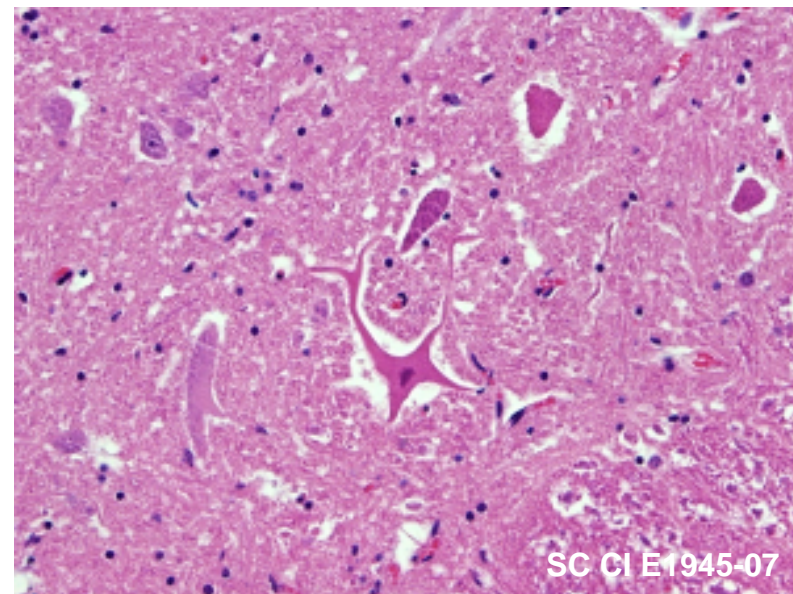
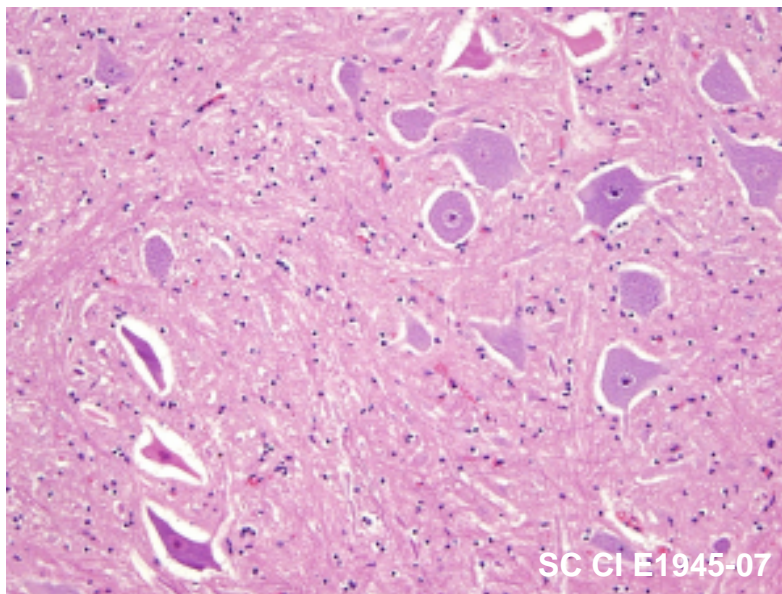
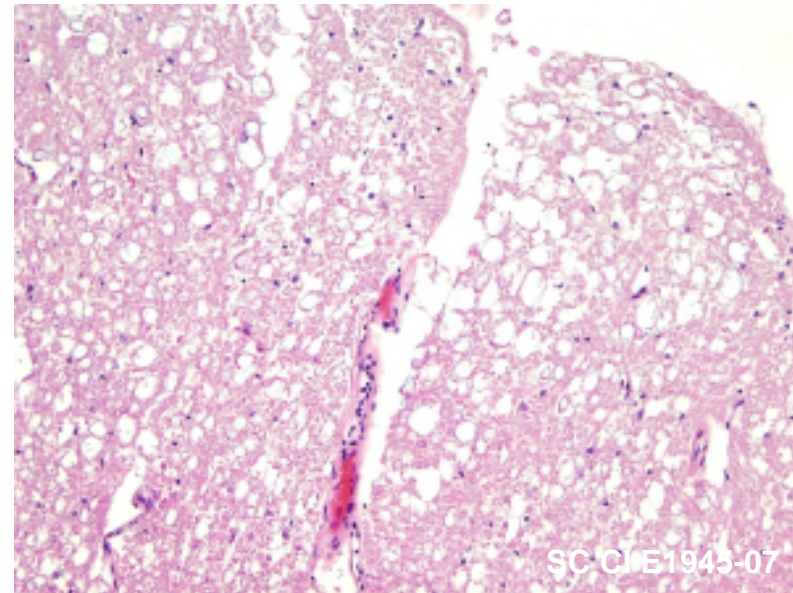
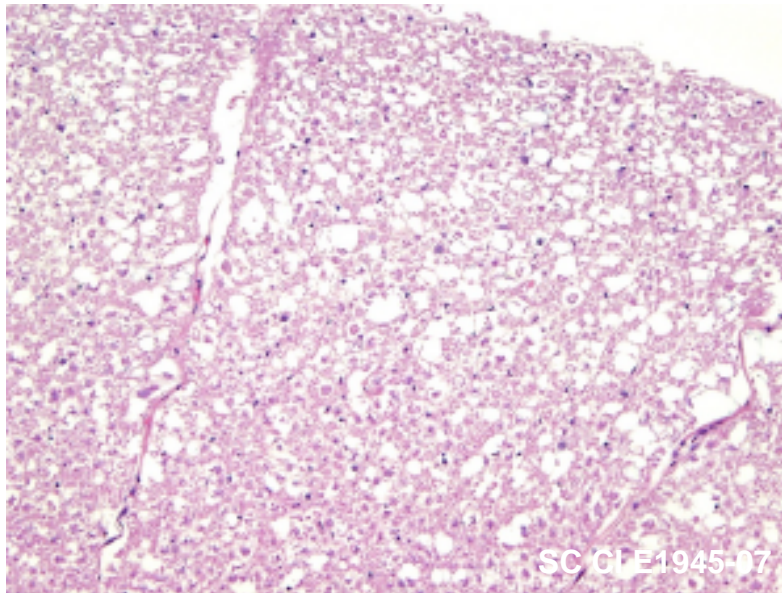
Cervical spinal cord, delayed swayback, ovine



Cervical spinal cord, delayed swayback, ovine

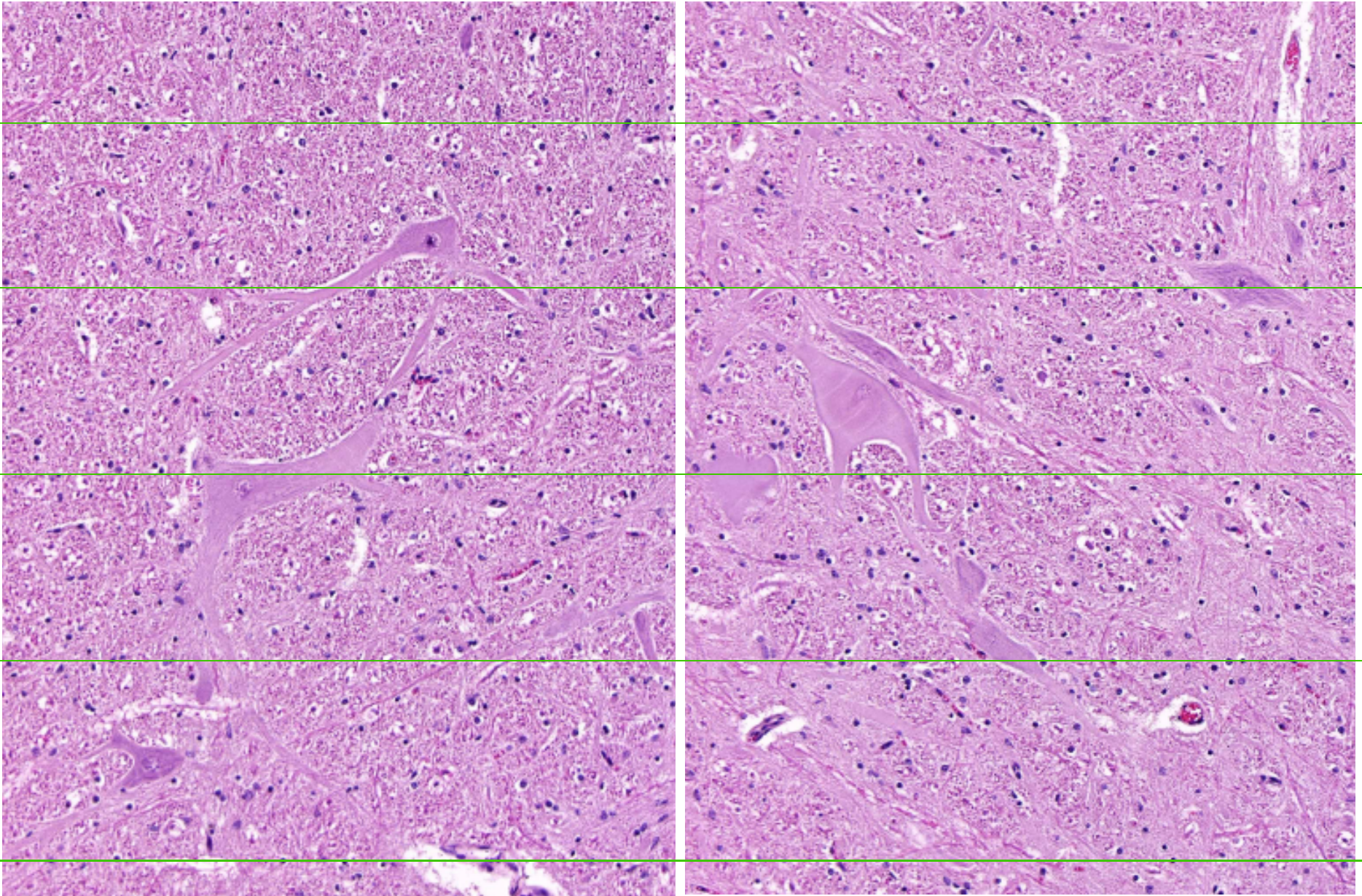


Caution

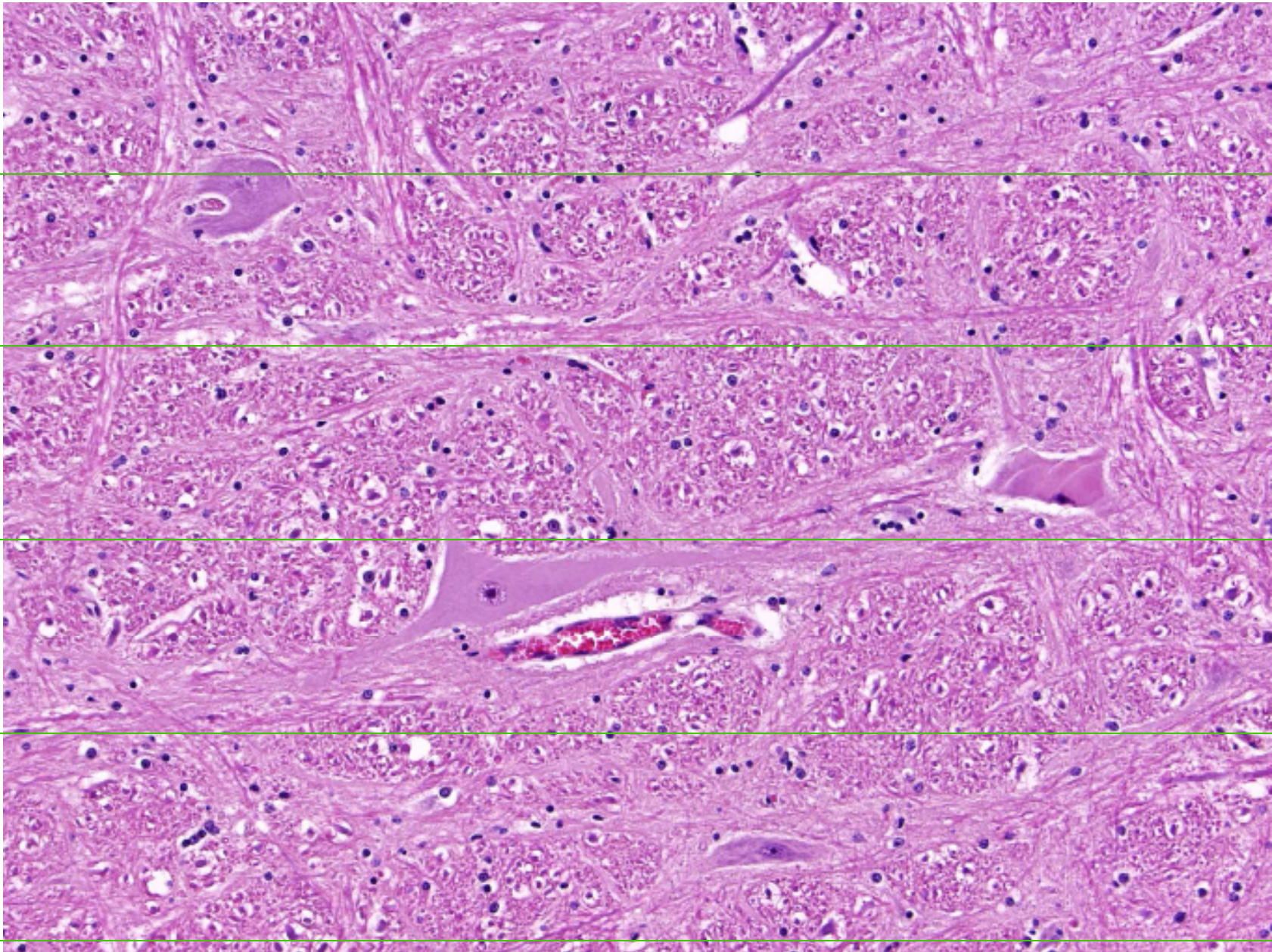


Variations on a theme :

- Main lesion [in CNS] involves neuronal cell body
 - [lower] motor neurone disease [wallerian degeneration in peripheral nerve]
 - aspergillus clavatus mycotoxicosis
- Mainly axonal lesions
 - a long list!



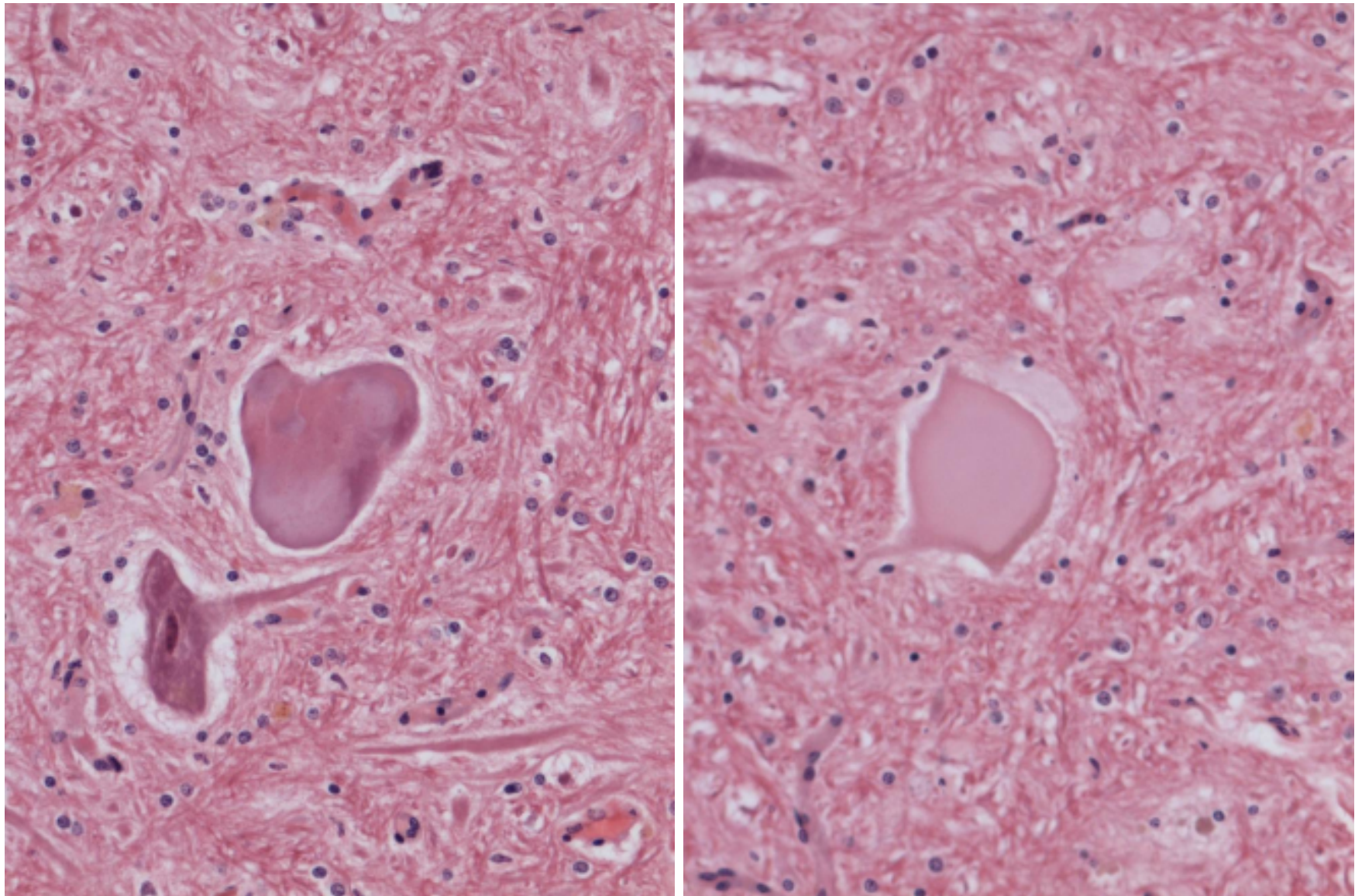
Med RF, varying stages of chromatolysis



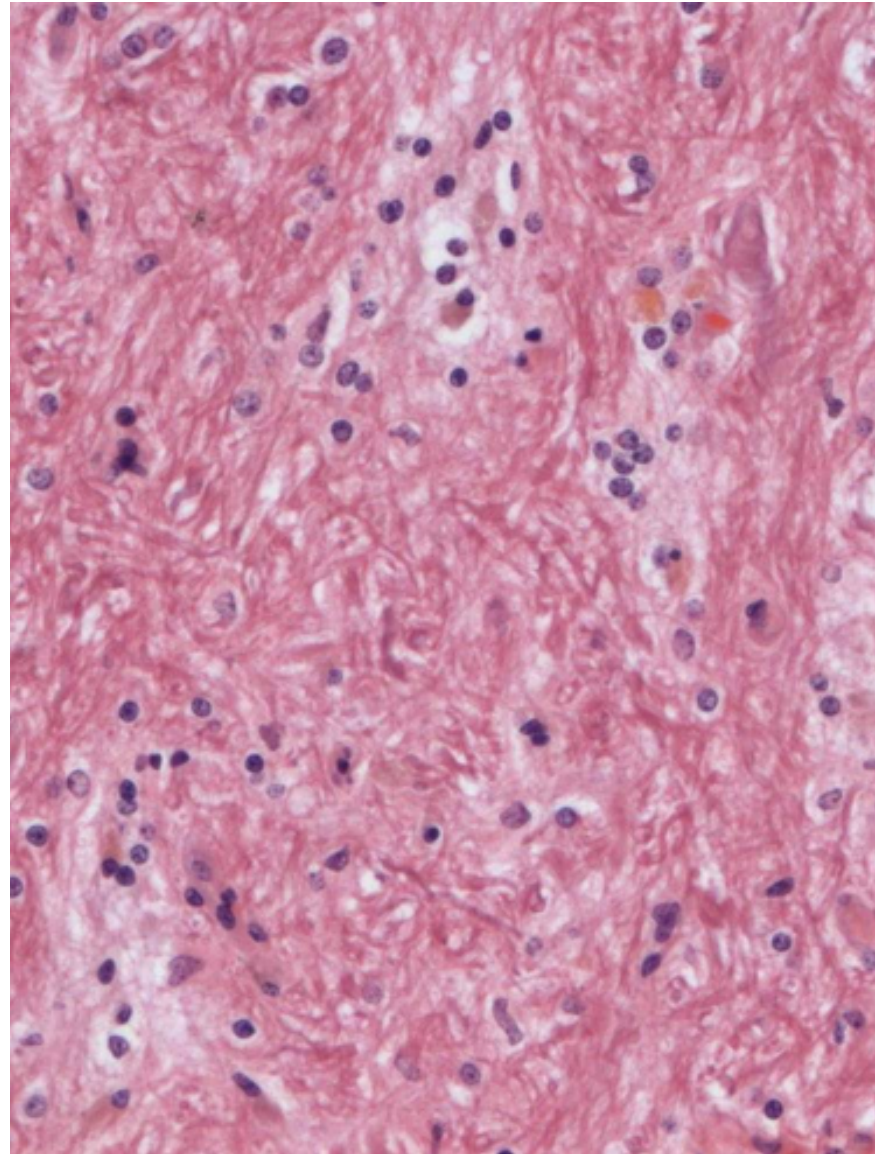
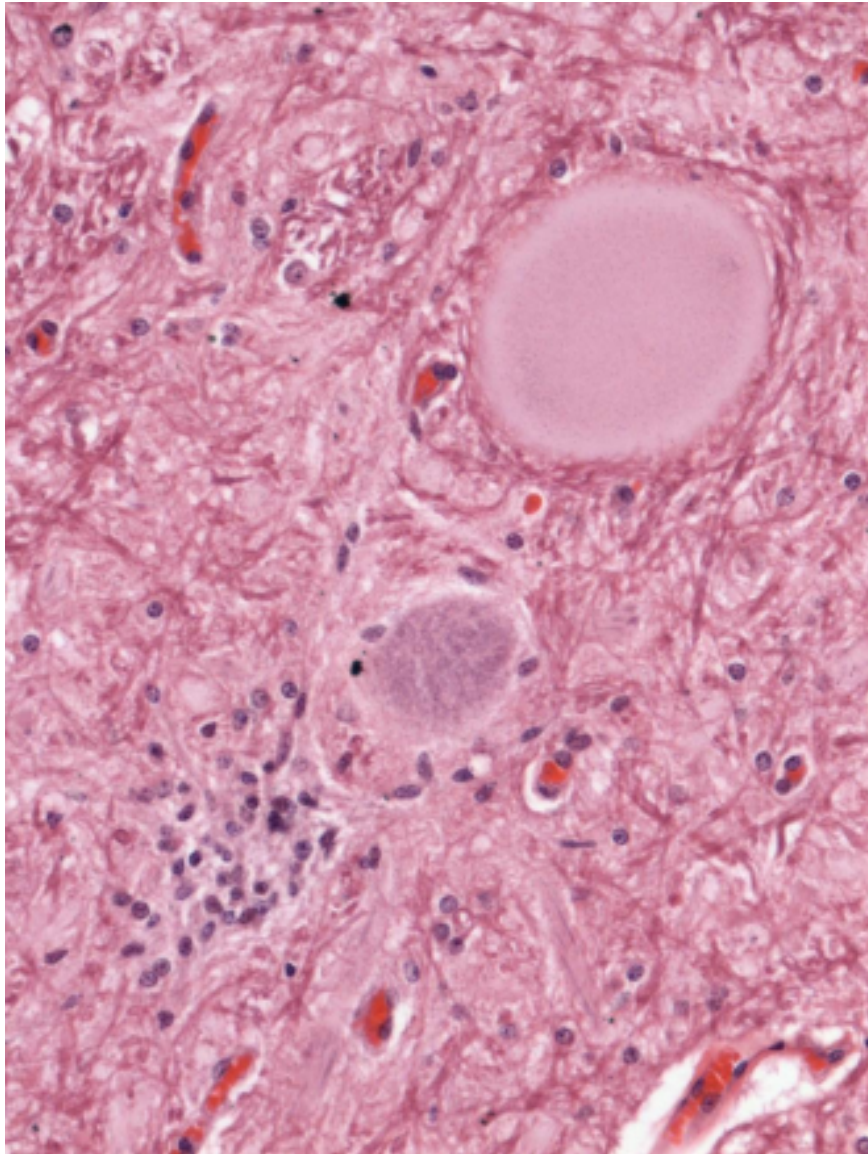
Med RF, chromatolysis

Equine motor neurone disease

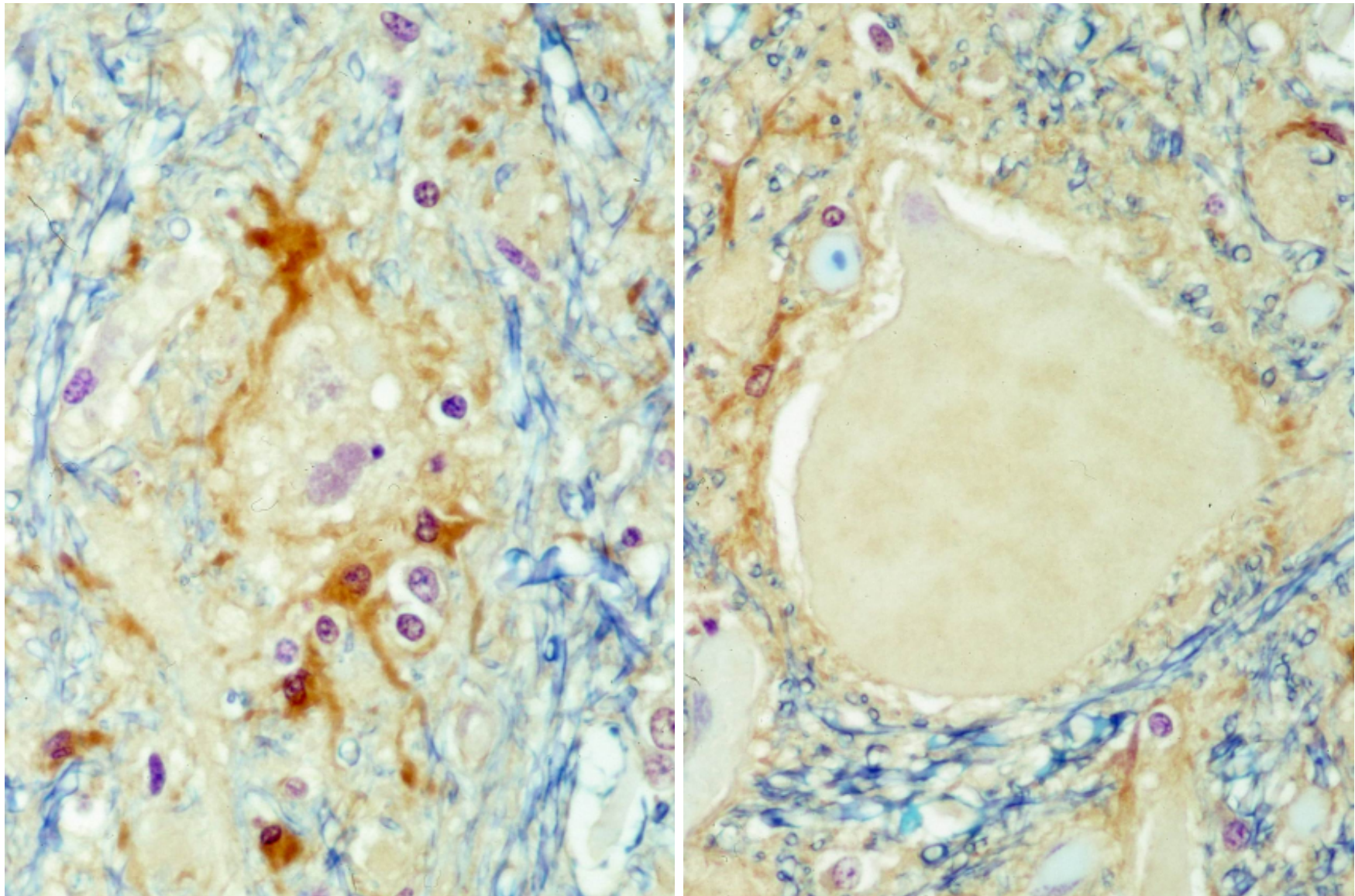
- Wide age range : 1 – 25 years+
- Wide range of breeds and crossbreeds
- Chromatolysis and loss with gliosis particularly in ventral horns, also hypoglossal, facial, nucleus ambiguus and trigeminal nuclei
- Lipofuscin deposits in some degenerating ncbs, also microglia and (EM) endothelial
- Axonal degeneration mainly in ventral radices and also in connecting fascicles in ventral funiculi
- ? Acquired ? Vitamin E deficiency



Equine motor neurone disease : courtesy Prof. Brian Summers



Equine motor neurone disease : courtesy Prof. Brian Summers

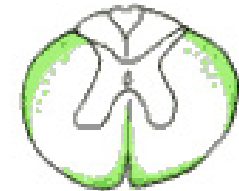
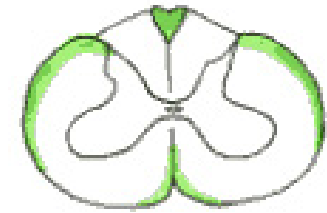


Equine motor neurone disease : GFAP : courtesy Prof. Brian Summers

Axonopathy LFT / diffuse, minimal / undetectable nerve cell body lesions

1 : Toxicities

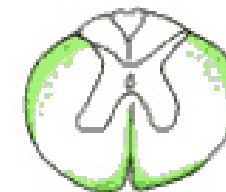
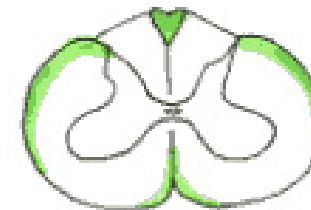
- Chronic organophosphate toxicity
 - WD, spheroids LFT mainly spinal cord
- 3-nitro-4-hydroxyphenylarsonic acid ('3-nitro'), pigs
 - WD LFT beginning in dorsal funiculus
- Humpy back in sheep
 - Extensive WD throughout all funiculi, ascending into caudal cerebellar peduncles? Solanum esuriale toxicity
- Sorghum; sudan grass, Johnson grass
 - Cattle, horses: WD in spinal white matter especially thoracic segments, lateral and ventral funiculi
- Chronic phalaris intoxication
 - Neuronal pigmentation with indole melanins, axonal degeneration, astrogliosis
- Cycad spp (Zamia)
 - WD spinal cord (gracile, DSCT, descending ventrolateral) and ascending tracts medulla, distal axonopathy pattern
- Derengue - ? Melochia pyramidata toxicity
 - Peripheral neuropathy, in severe cases also WD cerebellar peduncle, SCT and ventral funiculi
- Acrylamide intoxication Charolais X cattle
 - Clinically consistent with distal axonopathy
- nitro-containing Astragalus spp – spinal WD cattle
 - Also peripheral neuropathy



Axonopathy LFT / diffuse, minimal / undetectable nerve cell body lesions

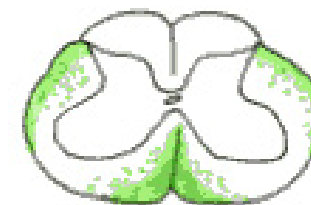
2 : Metabolic, unknown

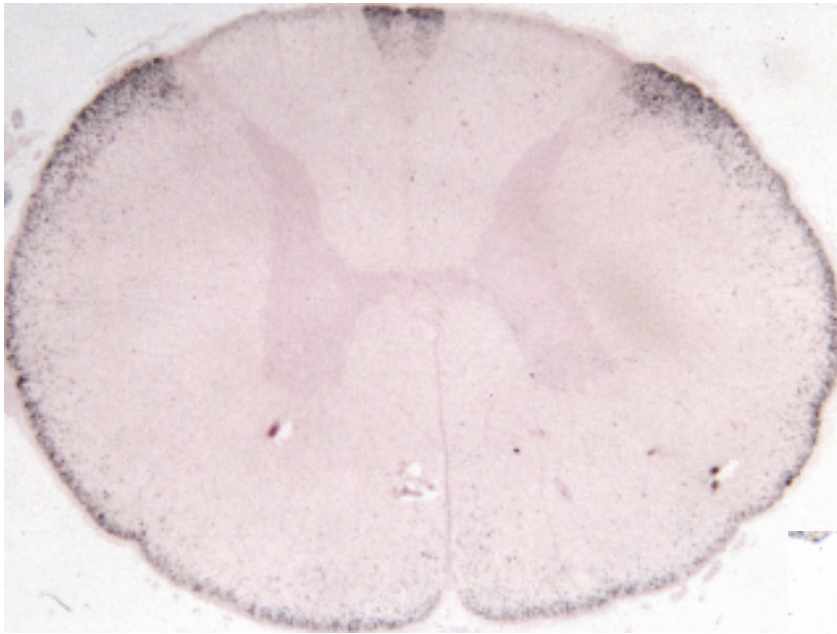
- Equine degenerative myeloencephalopathy (EDM)
 - WD often mainly subpial in L and V funiculi, NAD in nucleus thoracicus;
 - Hypothesis: vitamin E deficiency that has a familial, predisposing component
 - Familial in Appaloosa, Standardbred and Paso Fino breeds, suspected inherited in Norwegian Fjord, Arabian, Quarter horse, Welsh pony and Haflinger breeds
 - Also recognised in Burchell's zebra and Przewalski's horse
 - ? Inherited NAD of Morgan horses and Burchell's zebras may be an expression of EDM
- Degenerative radiculomyelopathy German Shepherd dog and other dogs : variable descriptions
 - Random / asymmetric Wallerian degeneration, myelin vacuolation, spheroid formation most marked in thoracic spinal cord
 - Axonal degeneration symmetrically LFT
 - More than one aetiology? Not considered to be vitamin E-dependent
- Post viral neuronal degeneration – scattered WD may involve all (PTV)
- Leukoencephalopathy on cats fed γ -irradiated dry diet: WD and vacuolation all funiculi spinal cord > brain (widespread)
- Copper deficiency, pigs
 - mainly LFT WD
- Hound ataxia (Beagle, Harrier and Foxhounds)
 - WD all funiculi but mildest dorsal, ? Methionine deficiency associated with predominantly tripe diet



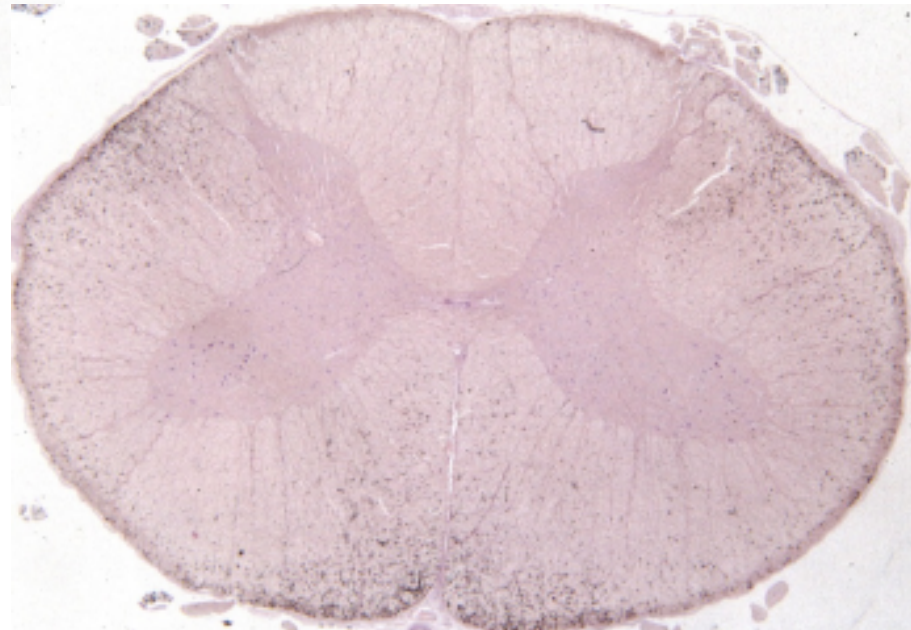
Intrinsic

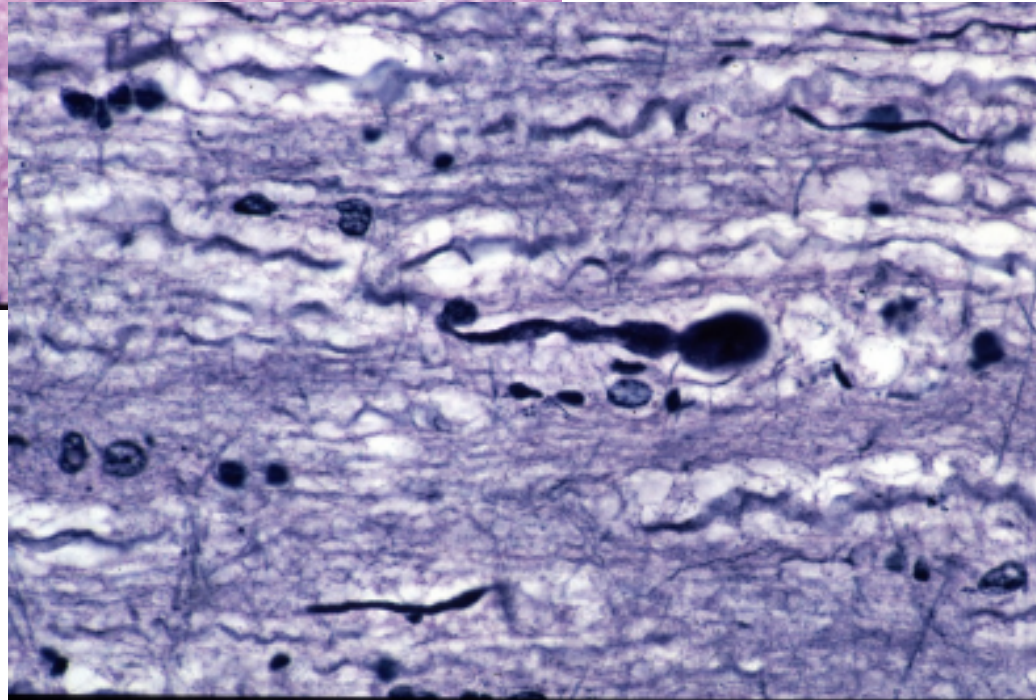
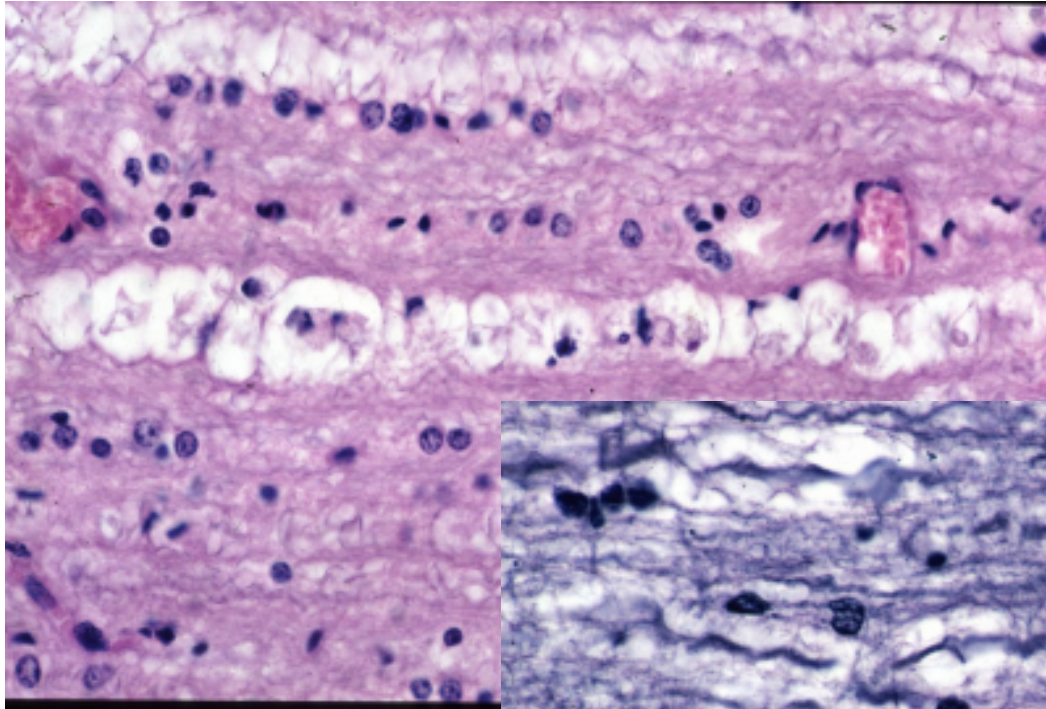
- Congenital axonopathy of Holstein calves
 - mainly LFT WD in cord, lesser involvement brainstem
- Myelopathy in Holstein x Gir calves Brazil
 - Spinal cord chronic WD LFT-like pattern
- Progressive ataxia associated with degenerative thoracic myelopathy in Merino sheep
 - WD, ventromed and dorsolateral tracts
- Bovine progressive degenerative myeloencephalopathy (weaver syndrome) of Brown Swiss cattle;
 - LFT-diffuse WD and spheroids esp thoracic, also PKC degeneration
- Breed-related myelopathies in dogs with LFT distribution
 - Smooth Fox terriers, Jack Russell terriers (also spheroids in dorsal nucleus of trapezoid body), Ibizan hound (also prominent spheroids in trapezoid body), Labrador Retriever (also agenesis corpus callosum and other developmental anomalies, WM spheroids particularly in dorsal funiculus, chromatolysis and spheroids in olivary nucleus)





**Porcine delayed organophosphate toxicity
(isophenphos)**

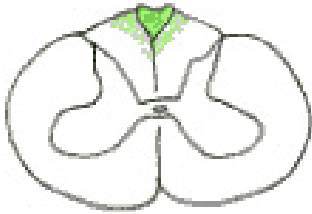




**Porcine delayed
organophosphate
toxicity
(isophenphos)**

Basic patterns of white matter tract degeneration in spinal cord

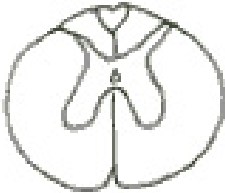
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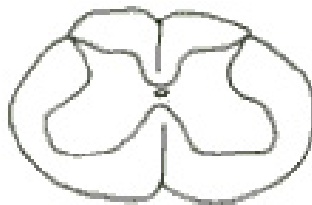
Dorsal funiculus : ascending central sensory projection

- Post viral axonal degeneration secondary to viral cytolysis of DRG neurones ? (PTV)
- Pantothenic acid deficiency
- Pyridoxine toxicity (megadoses in dogs; also sensory neuropathy)
- Thallium toxicity
- Chronic methyl mercury toxicity (horse, rabbit, rat)
- Peripheral neuropathy and glomerulopathy in Gelbvieh cattle
- Breed related sensory neuropathies:
 - Sensory neuropathy longhaired Dachshund dogs

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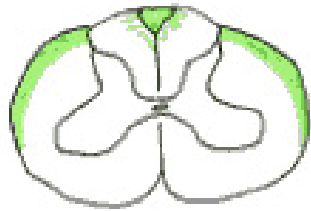
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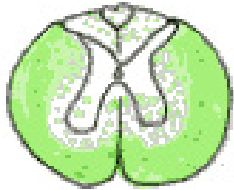


'Goose-stepping' gait, porcine pantothenic acid deficiency

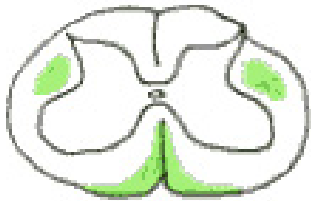
Basic patterns of white matter tract degeneration in spinal cord



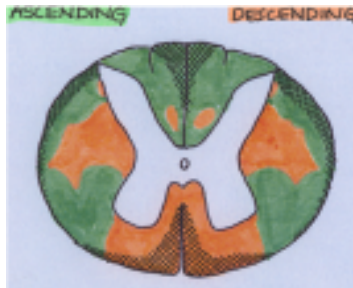
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T /
lesion

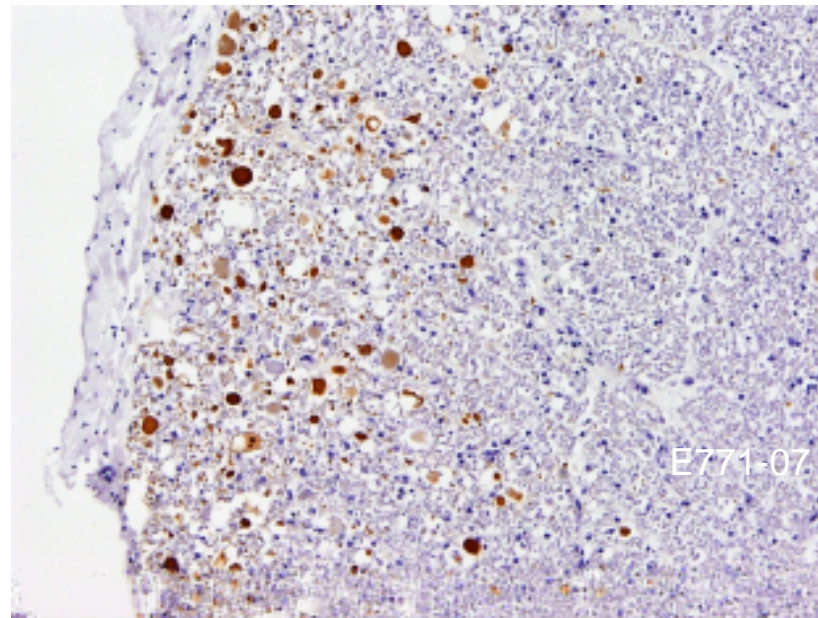


L



Focal compressive:

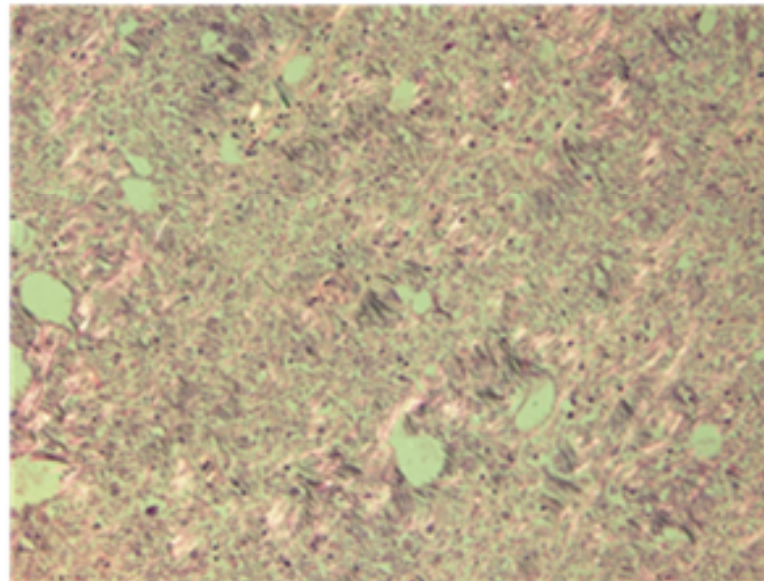
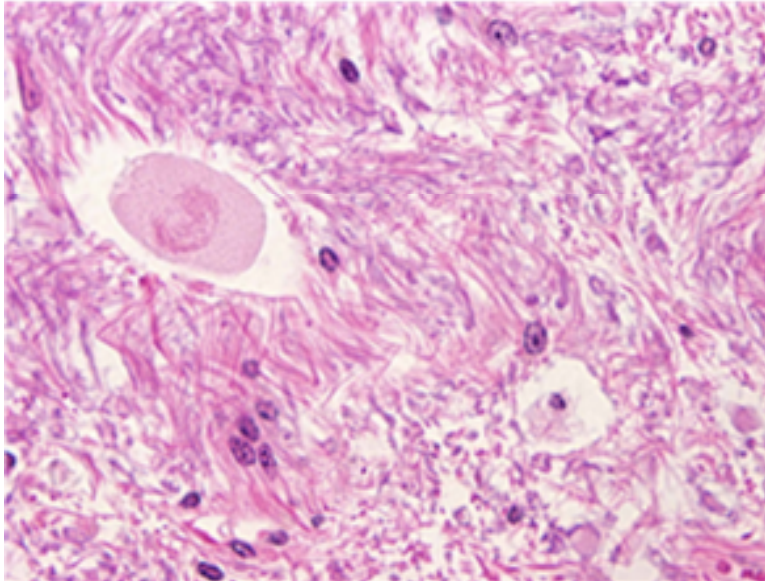
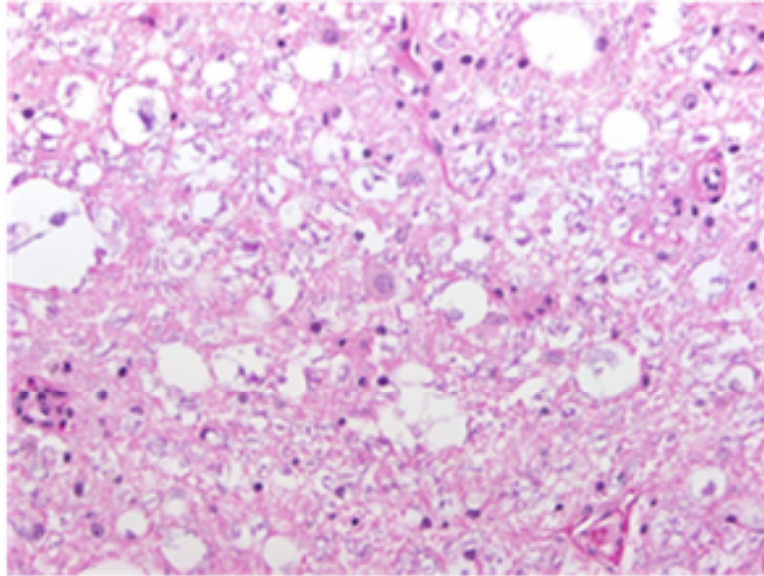
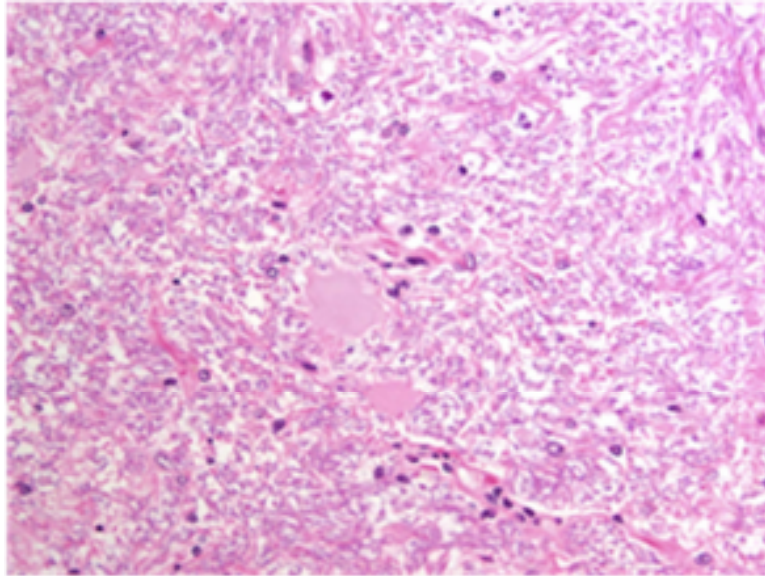
- vertebral fracture
- vertebral abscess
- vertebral malformation eg 'wobbler', occipital condylar dysplasia (Jacob sheep), atlanto-axial-occipital malformations
- epidural fat nodules (Texel, Beltex sheep 'wobblers', often caudal cervical region - C6-C7)



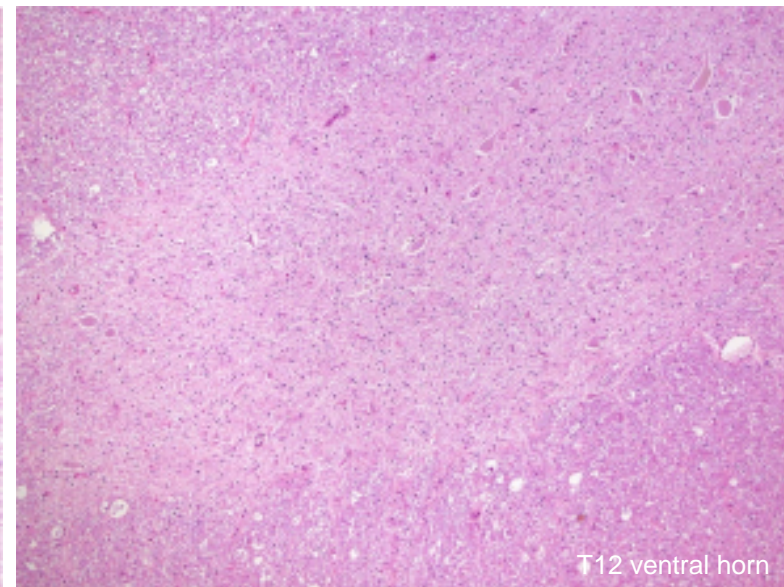
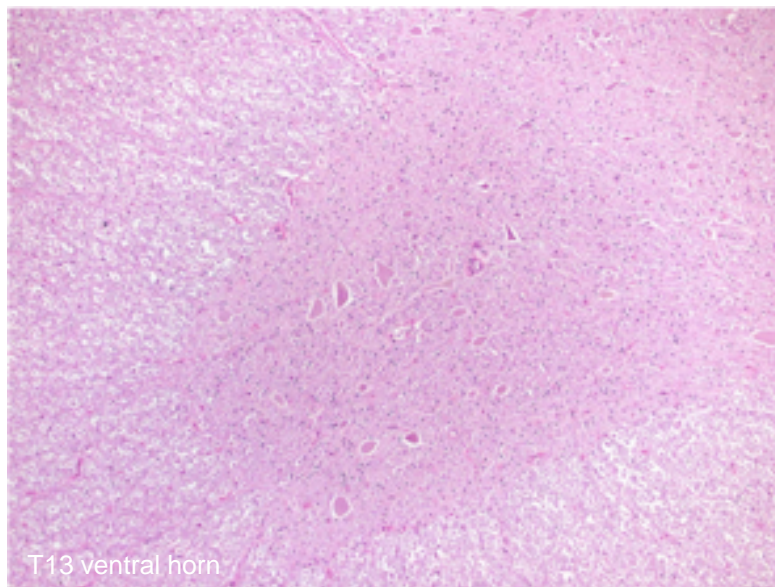
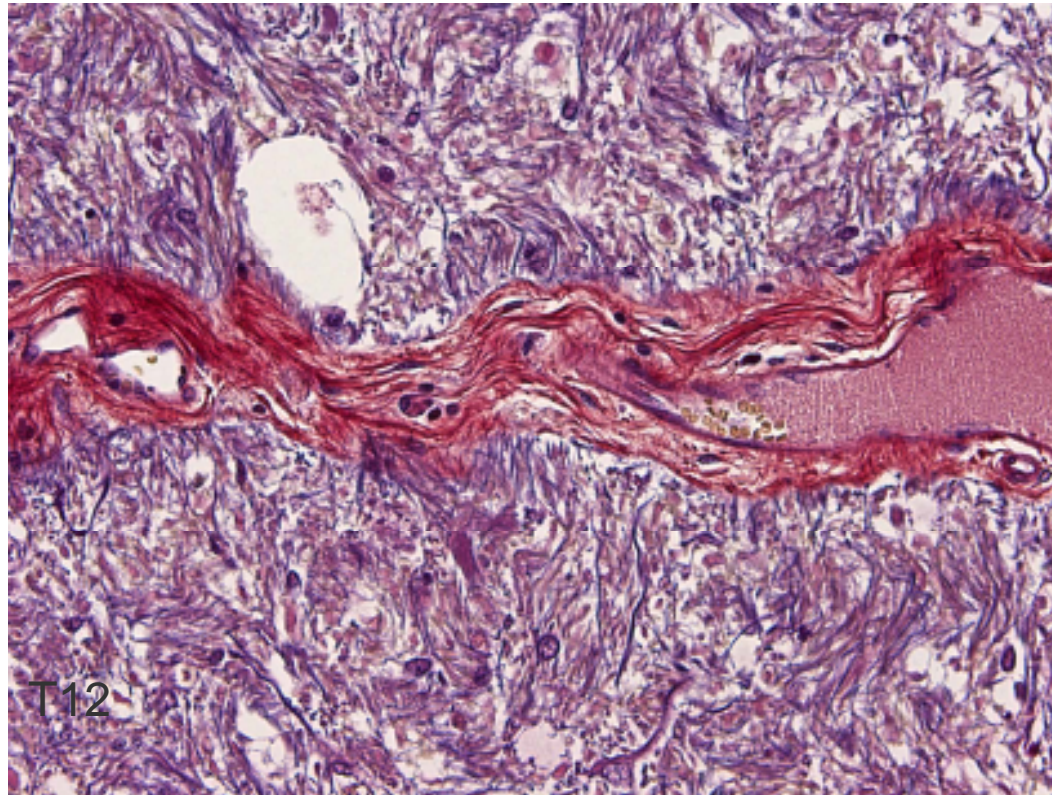
Compressive lesion in a 12 years old steer

- Holstein-Friesian steer culled at 149 months of age because of study termination.
- Gait abnormalities were first noticed 13 months earlier (at 136 months of age):
 - poor hind limb foot placement,
 - excessive adduction of the hind limbs on the forward stride with occasional knuckling of the hind fetlocks and hind limb ataxia.
 - Behaviour and cranial nerve assessments were unremarkable.
- A spinal cord lesion, likely between T2 and S2 suspected
 - However no significant progression and no treatment was required.
- No abnormality was found post mortem in the hind limb joints. The vertebral column would have been inspected during extraction of the spinal cord but no obvious abnormalities were present.

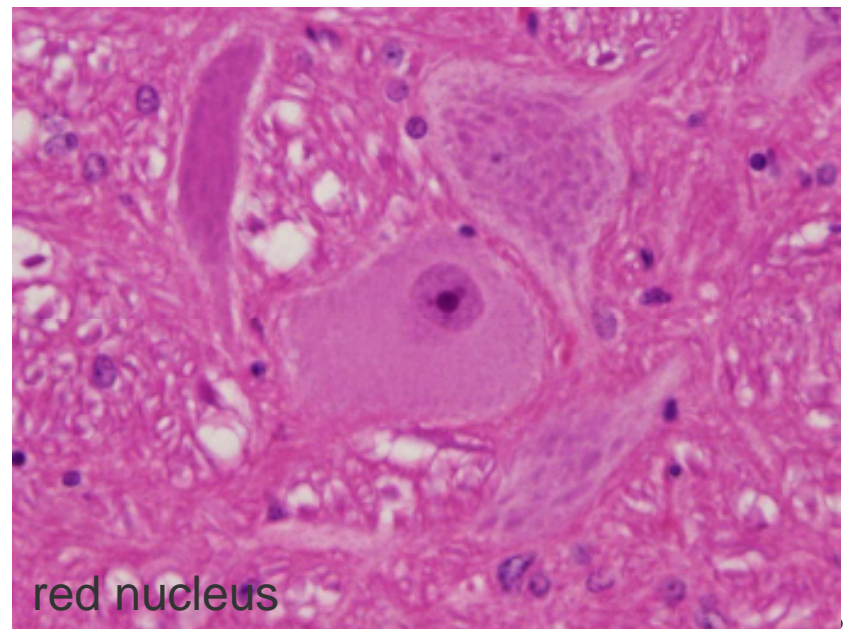
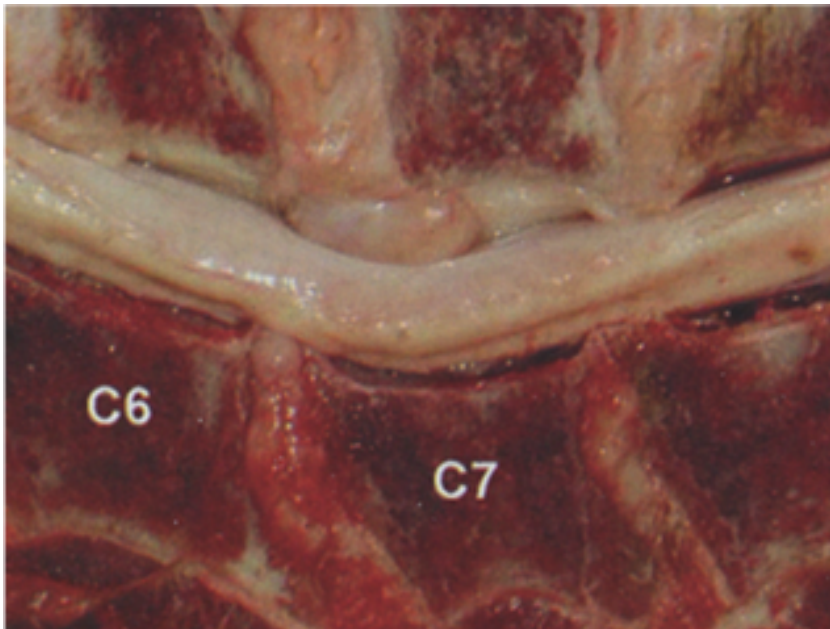
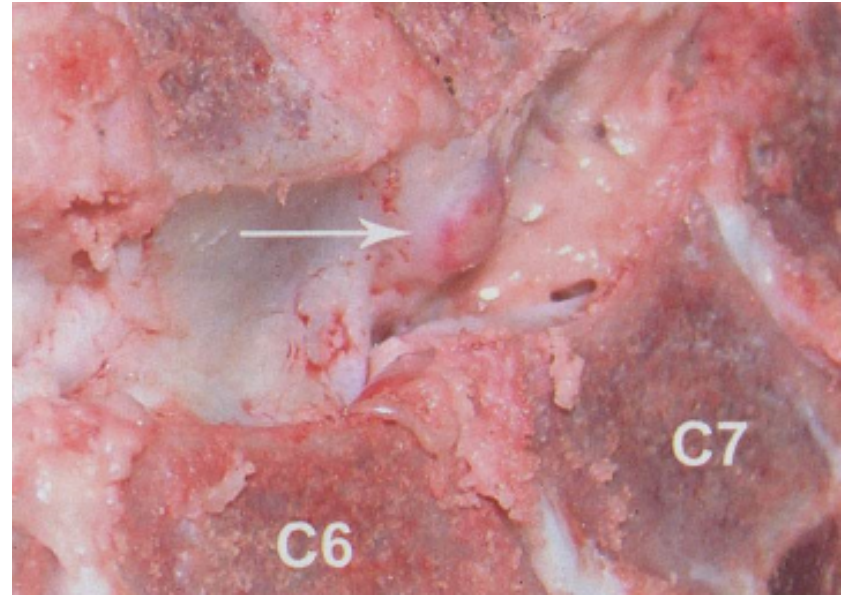
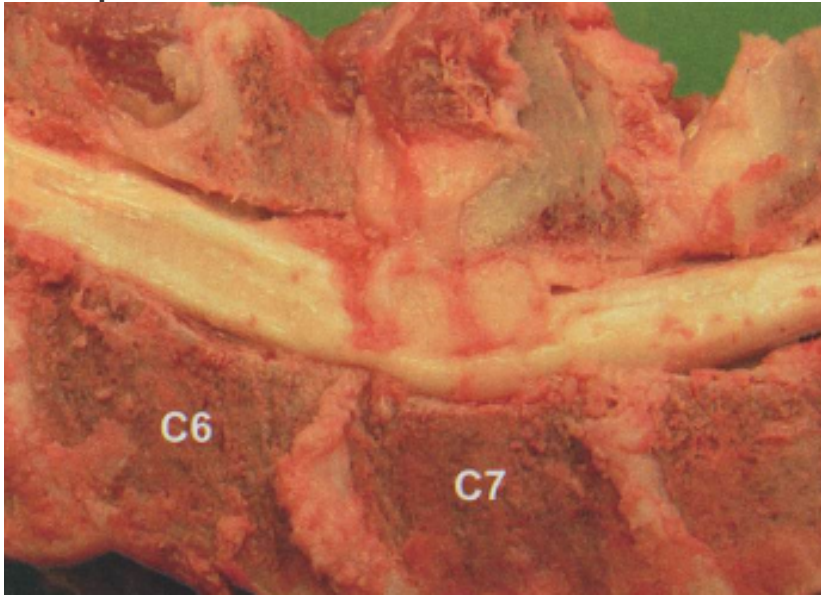
Compressive lesion elderly steer



Compressive lesion



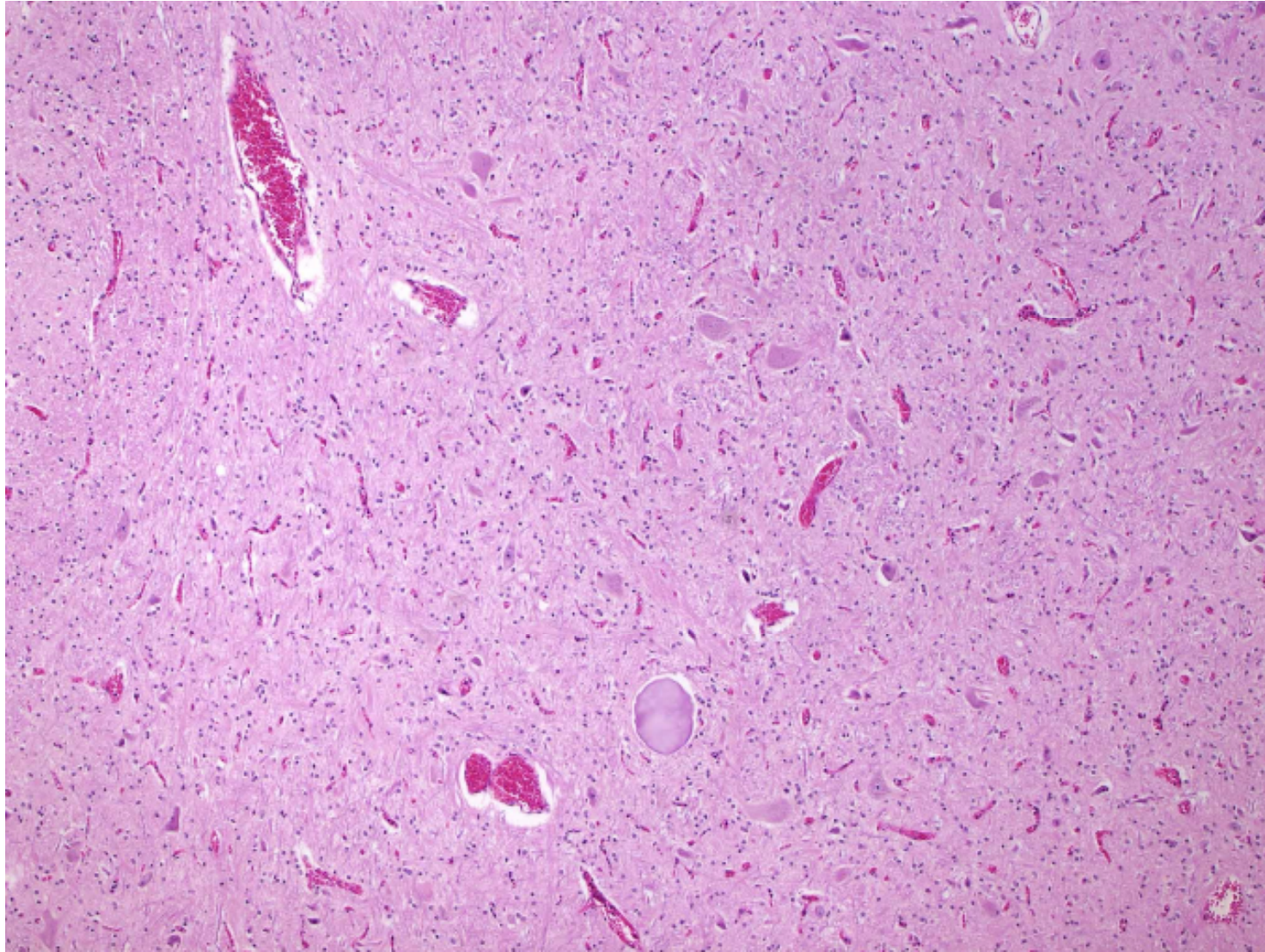
Compressive lesions: Texel 'wobblers'



Spheroid formation

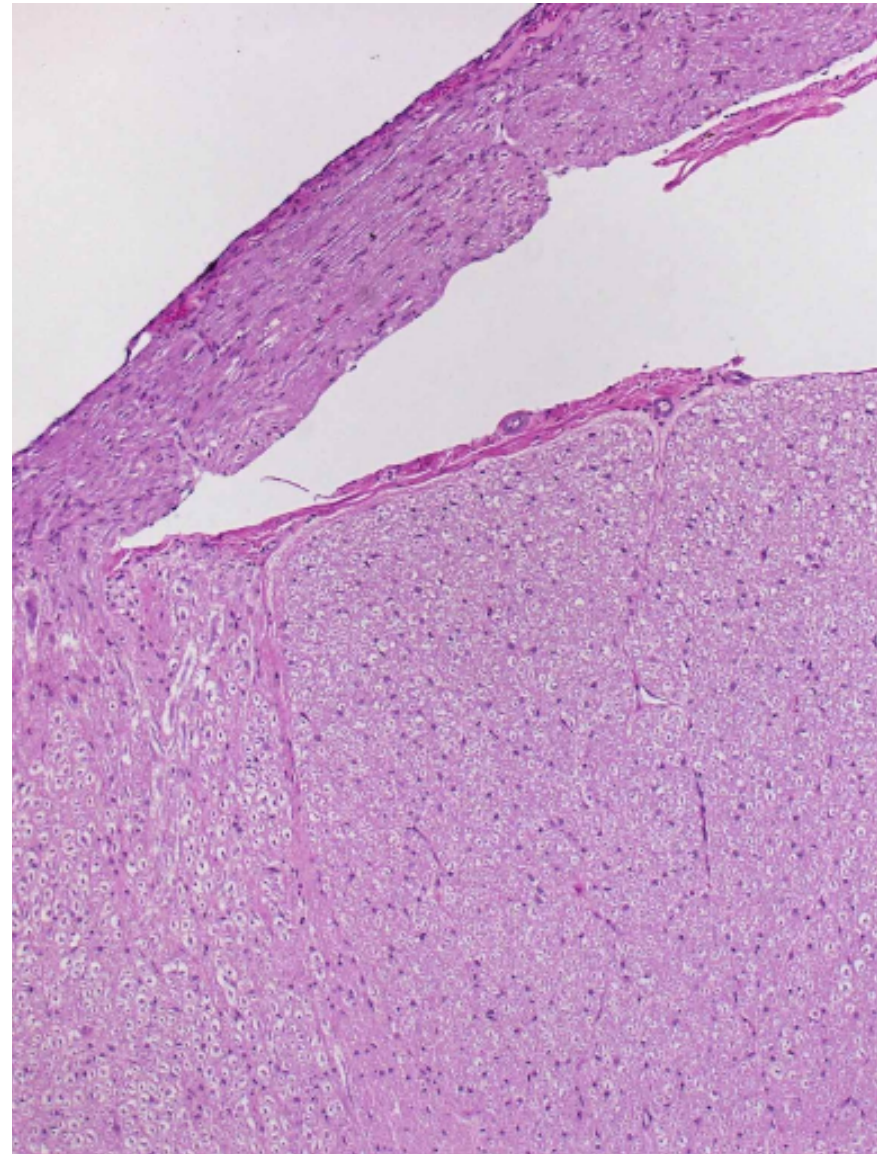
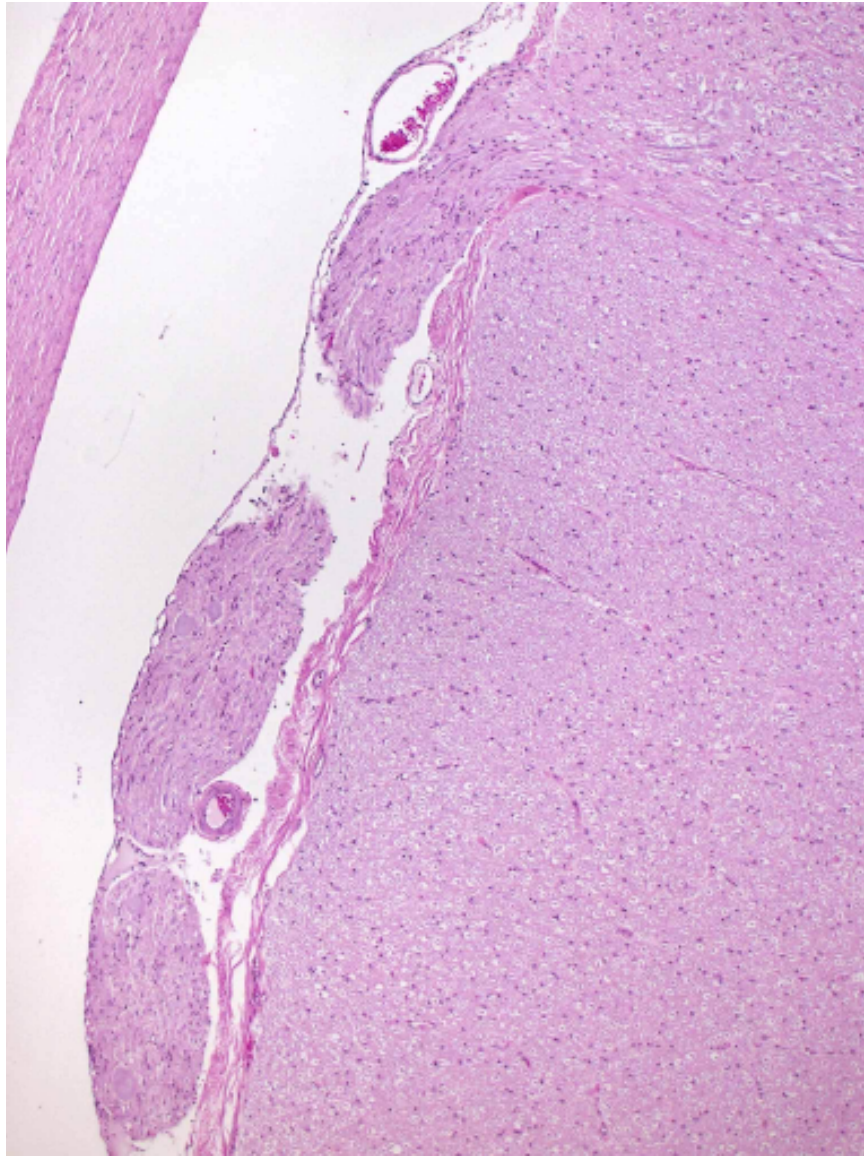
- Proximal axonopathies (GM – especially motor neurones)
 - Primary hyperoxaluria cats – large spheroids in proximal axons SMn, ventral roots, DRG, some WD peripheral nn
 - Some MNDs - Brittany spaniel SMA; Horned hereford motor neuronopathy; Motor neurone disease of Romney sheep
 - Congenital axonopathy of Coopworth sheep
 - 3,3"-iminodipropionitrile toxicity
 - Sorghum intoxication, sheep – brainstem and cerebellar nuclei and ventral horns spinal cord, swelling of proximal axon segments
- Neuroaxonal dystrophy (GM – relay nuclei especially sensory)
 - Breed related (separate list)
 - Vitamin E deficiency
 - OP toxicity
- Site of compression of spinal cord (mainly white matter)
- Other axonopathies
 - Breed related – Merino axonopathy (widespread in WM); progressive axonopathy of Boxer dogs; Giant axonal neuropathy, German shepherd dog; chichuahua dog (white matter); Collie sheep dogs (cerebellar WM); Labrador Retriever : agenesis corpus callosum and other developmental anomalies, WM spheroids particularly in dorsal funiculus, chromatolysis and spheroids in olivary nucleus.
 - May be prominent feature of lysosomal storage diseases (and formation may precede extensive lysosomal storage)
 - Swainsonine toxicity - spheroids may persist in large numbers in cerebellar roof and caudal brainstem even when neuronal storage has decreased
 - Other toxicities eg Cycad toxicity in cattle, Astragalus
 - Coyotillo (Karwinskia toxicity) – peripheral neuropathy dominates, spheroids recorded in cerebellum and spinal cord
 - Small numbers spheroids common component many axonopathies in which Wallerian degeneration is predominant
 - Common feature of cerebellar Purkinje cell degeneration (torpedoes)
- Caution
 - Spheroids common incidental age-related finding in cuneate nuclei (except in cattle)
 - stretch distortion artefact due to excessive tugging of spinal roots especially dorsal
 - occasional spheroids common in medulla of lambs and especially calves (vestibular complex)

Caution



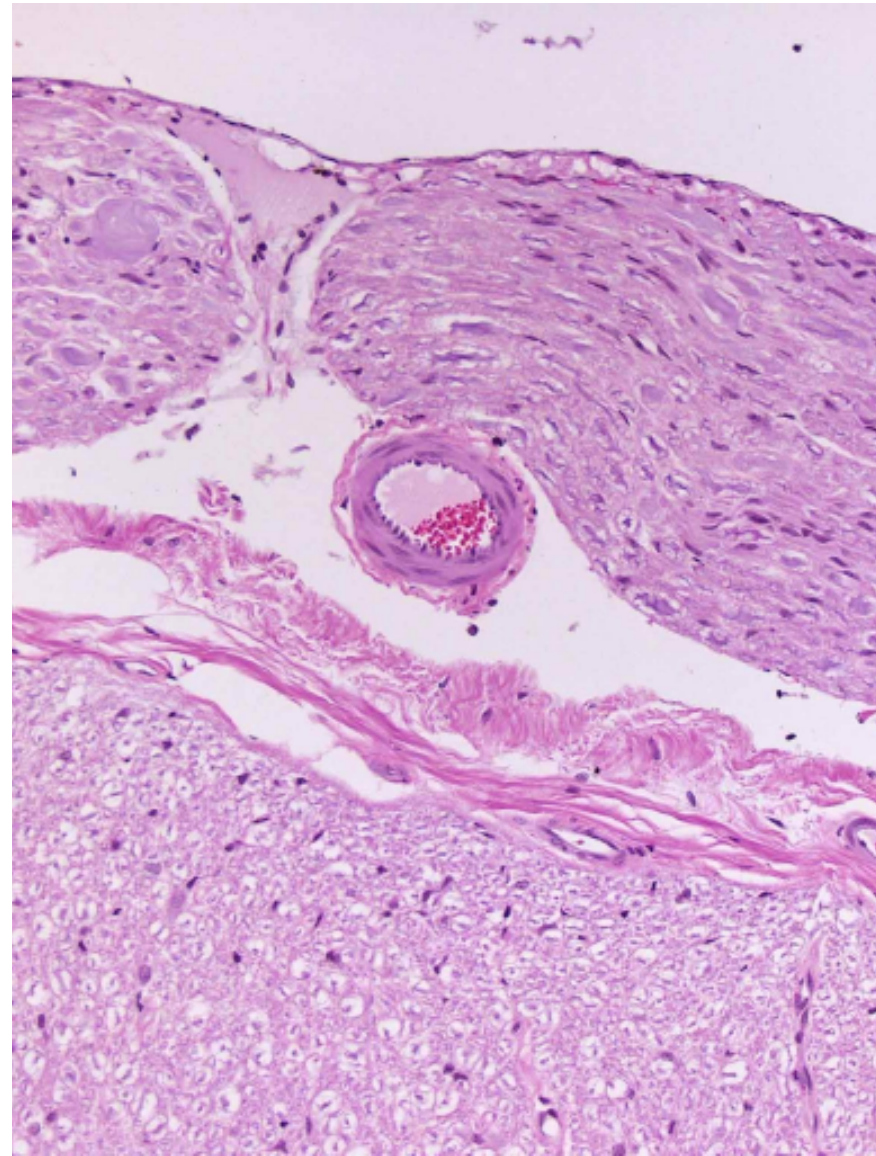
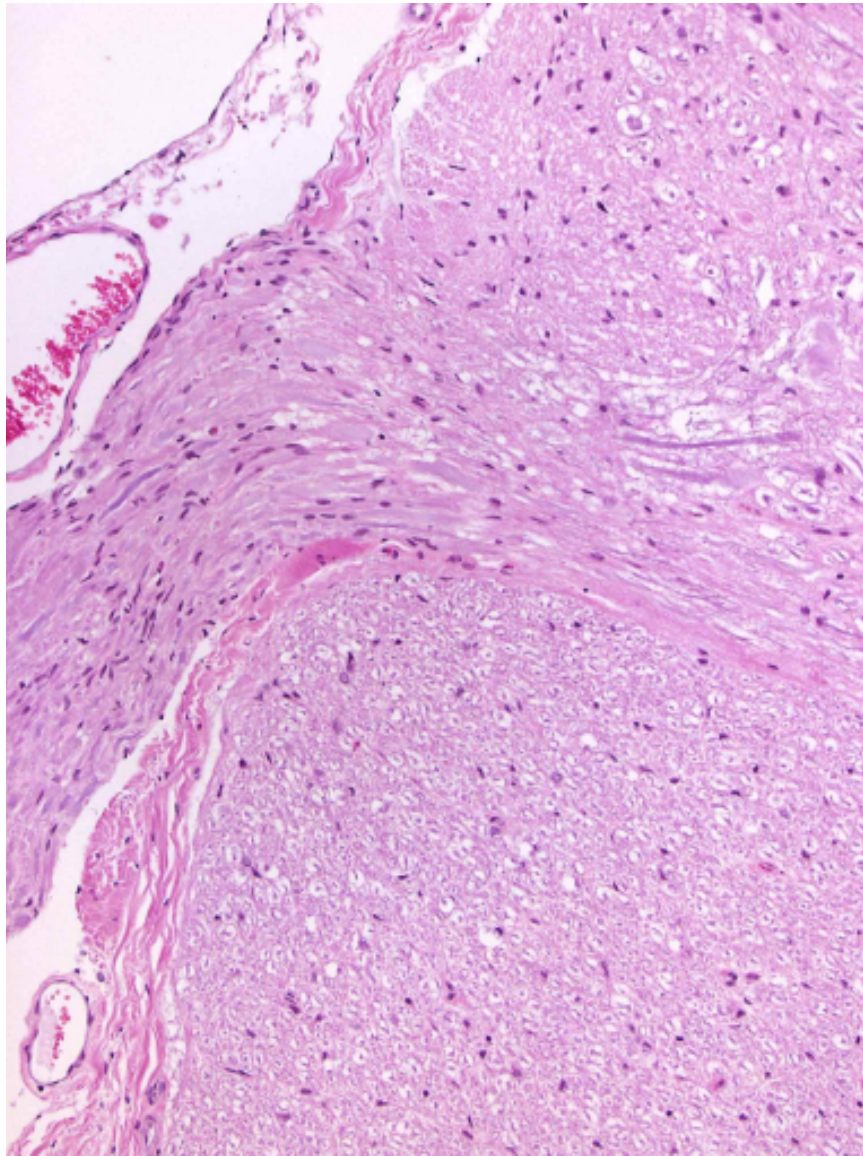
Calf, spheroid medulla (common background)

Caution

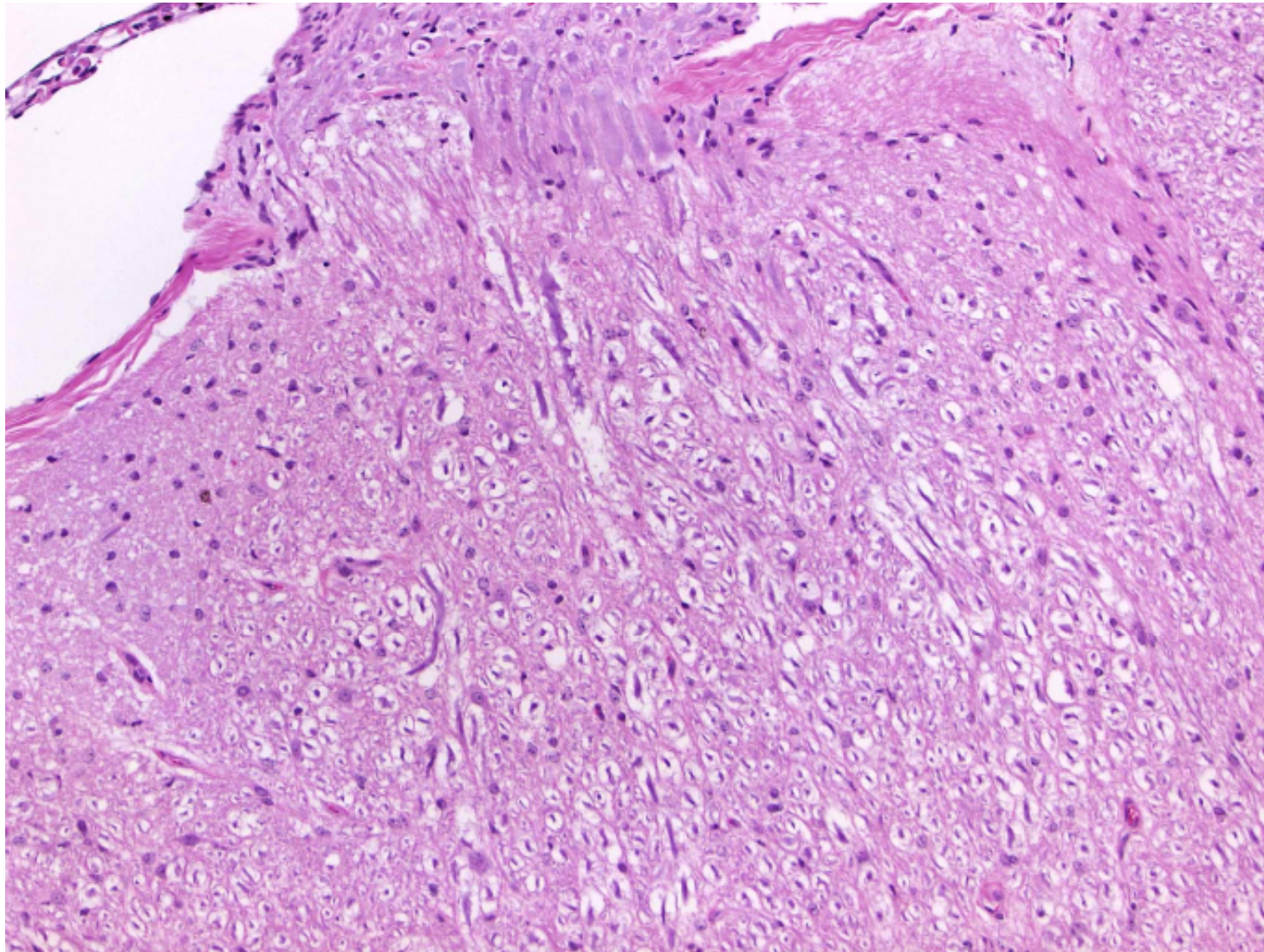


Not spheroid – stretch distortion; dorsal nerve root 'unilateral' in this case

Caution

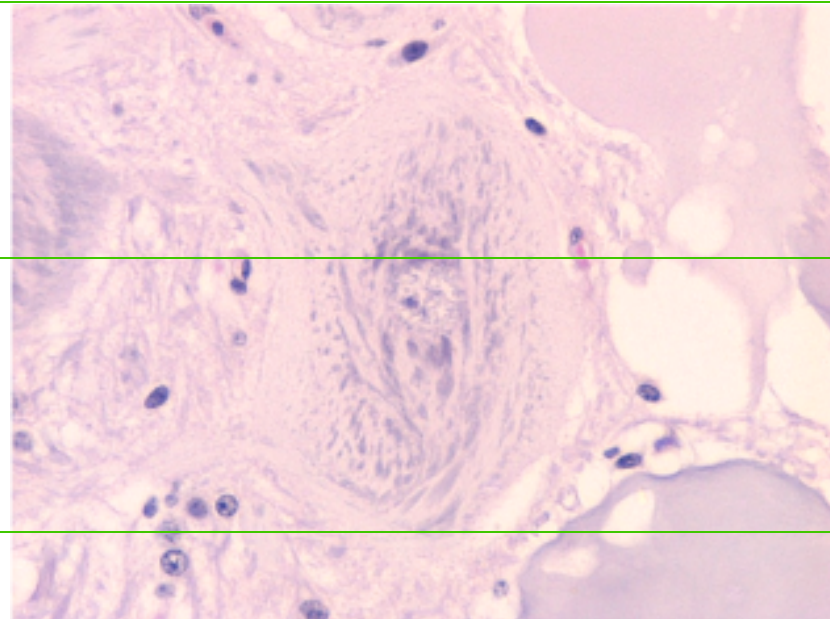
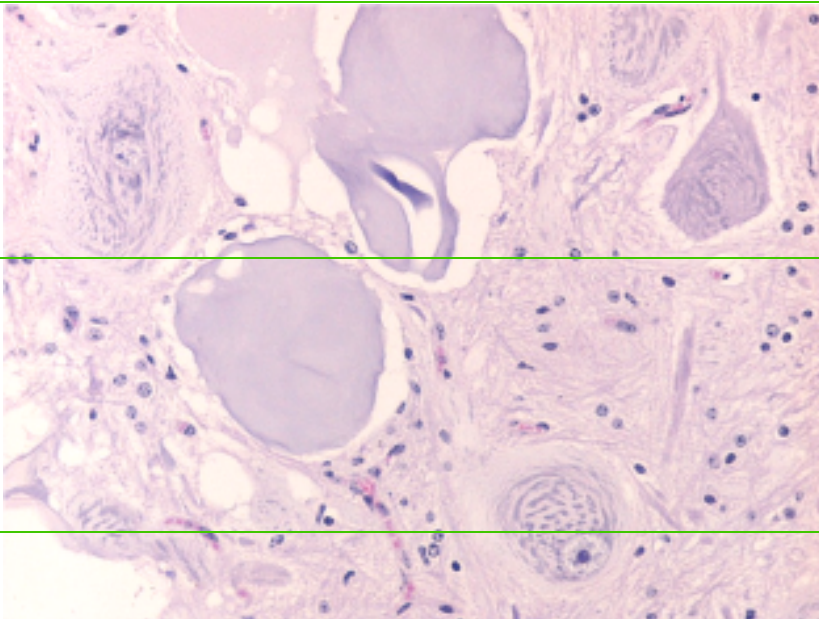
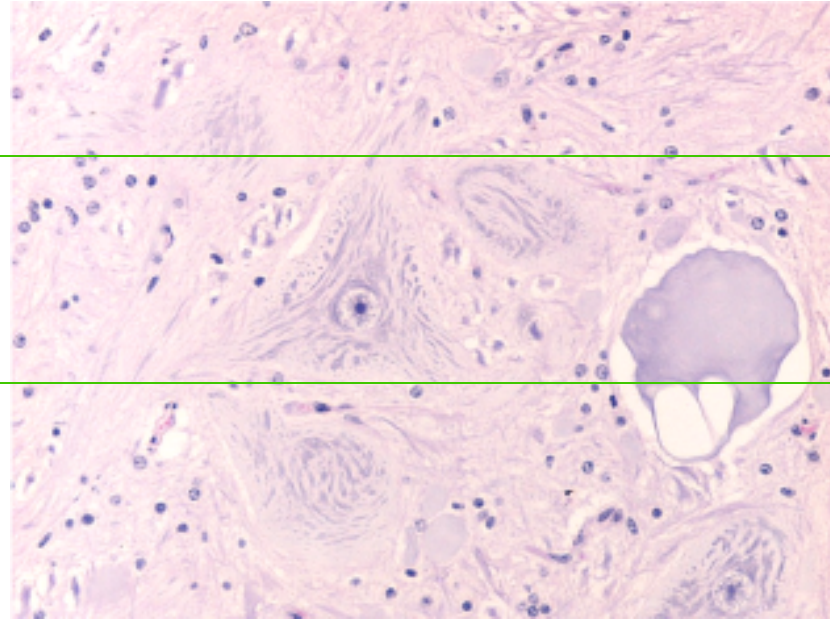
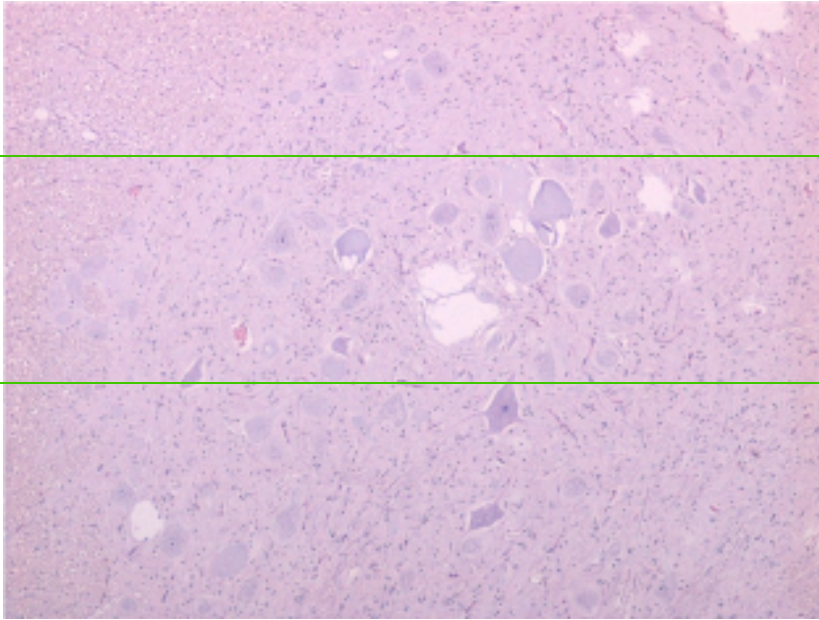


Not spheroid – stretch distortion; dorsal nerve root 'unilateral' in this case

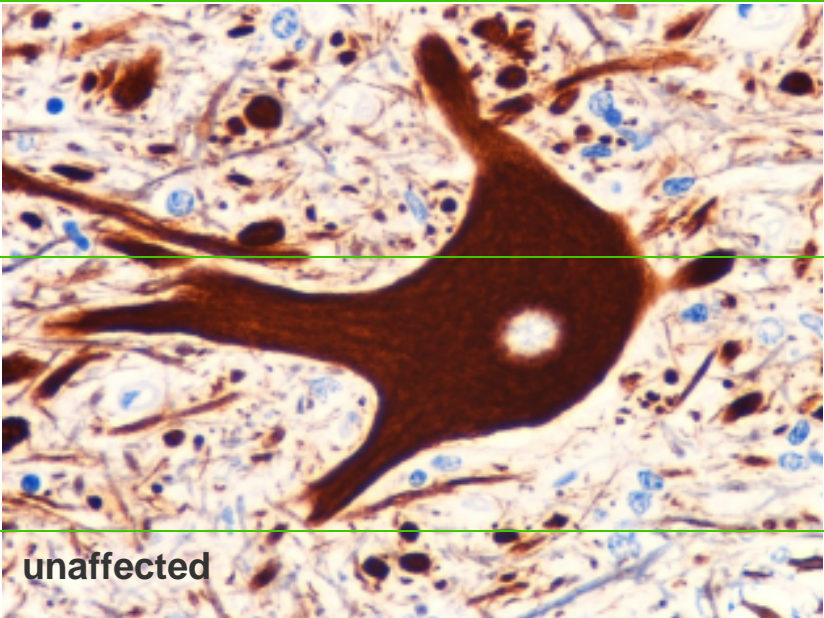
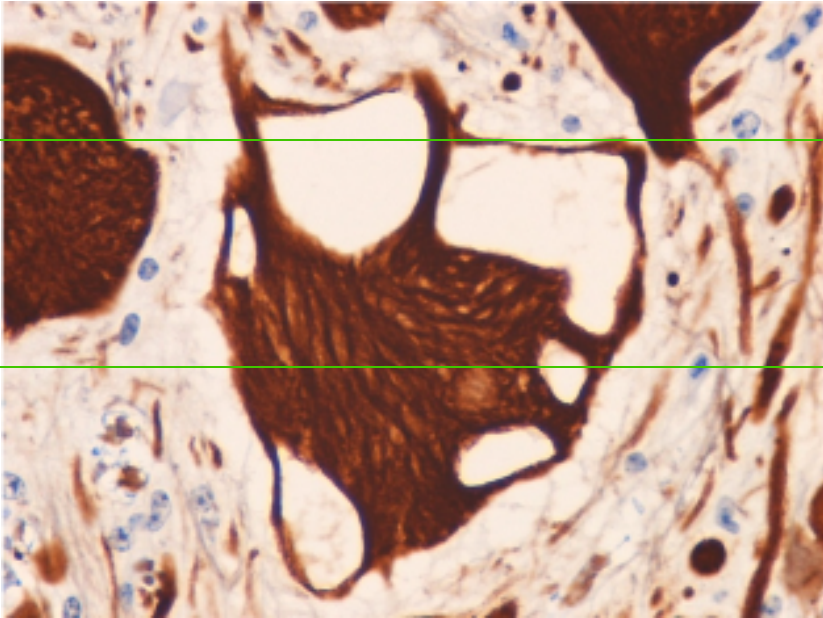
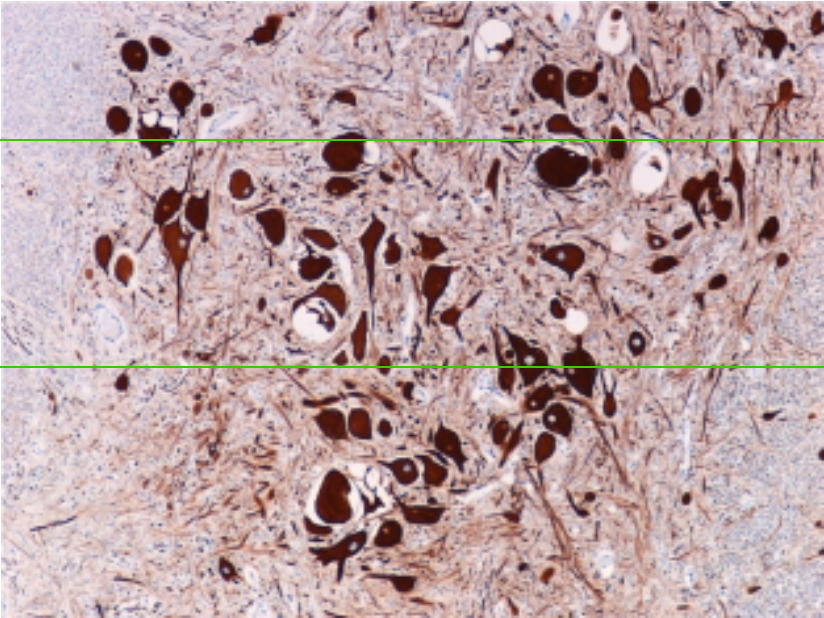


Not spheroid – stretch distortion

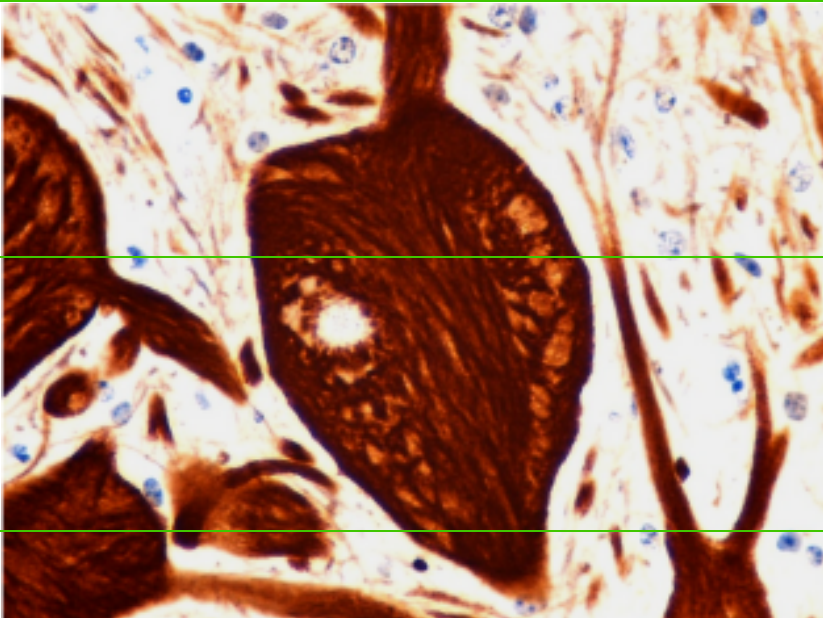
Motor neuronopathy, 3 weeks old pedigree hereford calf



Motor neuronopathy, 3 weeks old pedigree hereford calf



unaffected



Neuroaxonal dystrophy :

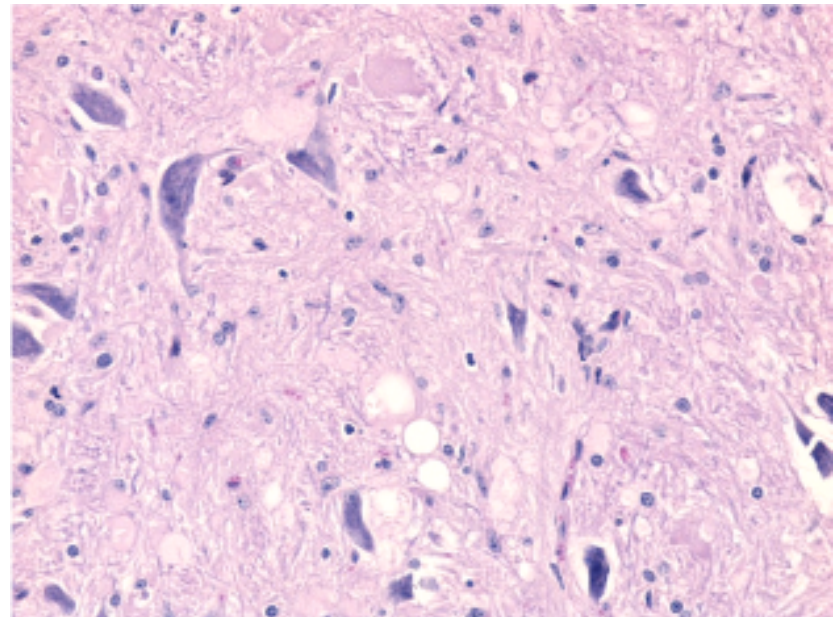
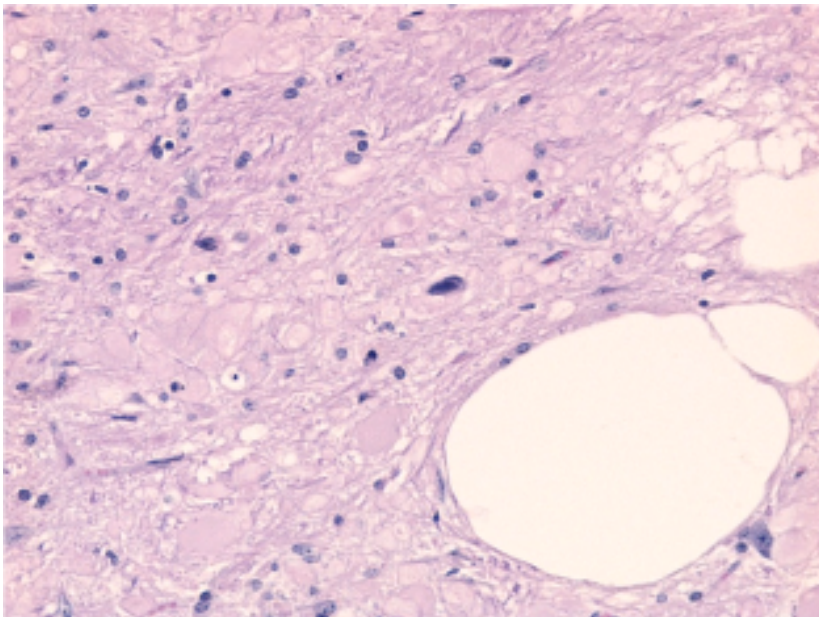
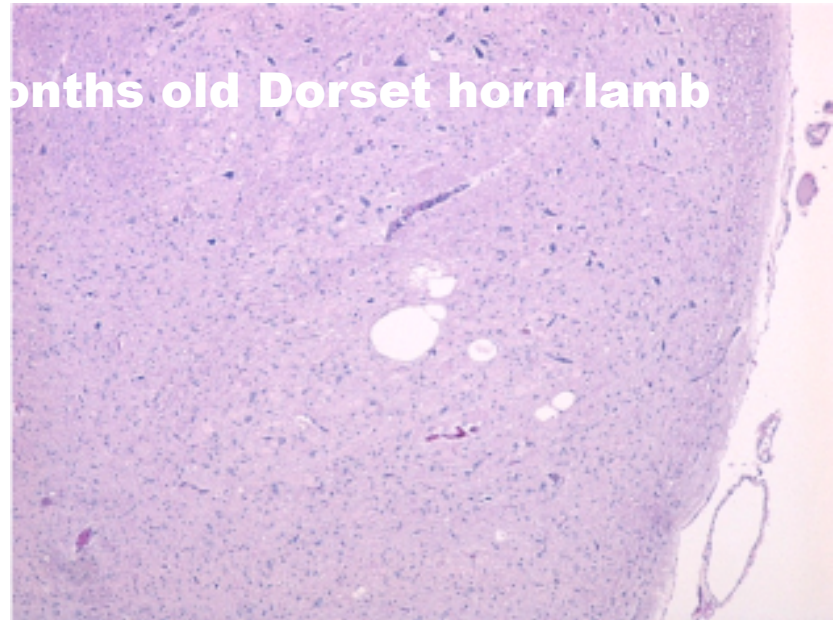
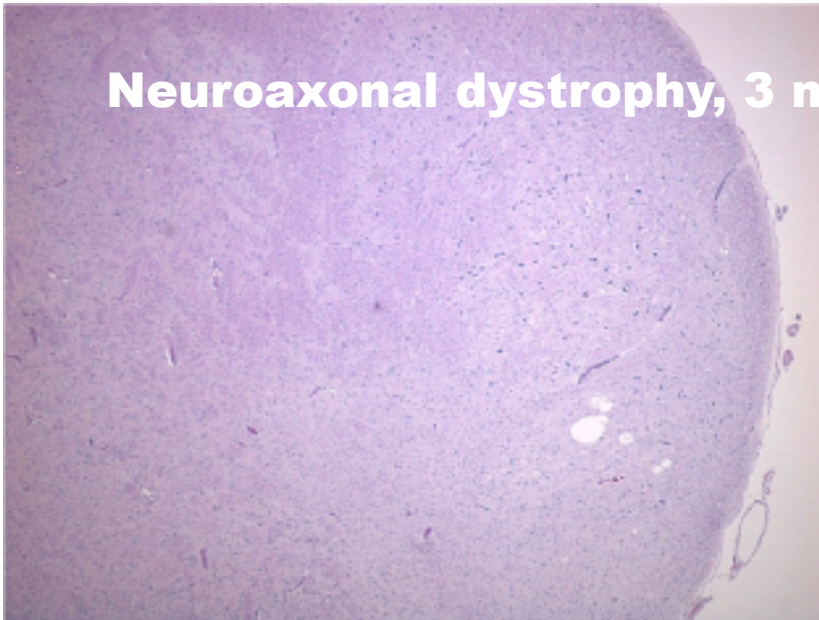
Defining feature is spheroids in pre-terminal portions of axons and in synaptic terminals, particularly involve relay nuclei (proprioceptive, visual), therefore particularly

- Dorsal horn spinal cord
- Cuneate, gracile, vestibular nuclei
- Lateral and medial geniculate bodies
- Nucleus thoracicus
- Breeds reported
 - Rottweiler, Jack Russell terrier (with hydrocephalus) dogs
 - Suffolk, Merino (4-7 month lambs); ? Perendale and South Suffolk sheep
 - Cats associated with coat colour abnormality
 - Sibling Haflinger horses
- Also consider
 - NAD may be a prominent feature of equine degenerative myeloencephalopathy
 - Vitamin E deficiency
 - OP toxicity

Caution

- Age related spheroid development

Neuroaxonal dystrophy, 3 months old Dorset horn lamb



Spinal white matter vacuolation in fibre tract pattern:

- Copper deficiency deer
 - Marked white matter vacuolation in LFT pattern; Wallerian degeneration often not prominent
 - Neuronal chromatolysis 'UMN'
- Spinal myelinopathy in Murray Grey cattle
 - Marked white matter vacuolation in LFT pattern
 - Neuronal chromatolysis nucleus thoracicus and 'UMN'