SASAP

UDRUŽENJE VETERINARA MALE PRAKSE SRBIJE

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LeCouteur received his veterinary degree (BVSc) in 1975 from the University of Sydney in Australia. After a year in small animal practice in Sydney, he did an internship and a residency in surgery at the University of Guelph in Canada (1976 to 1978). He completed his neurology/neurosurgery residency training and a PhD in comparative pathology at the University of California, Davis. From 1984 to 1989 he served on the faculty at Colorado State University. In 1989, he returned to Australia and established a neurology/neurosurgery specialty practice in Sydney. LeCouteur returned to the USA in 1995 to assume the position of Professor of Neurology/Neurosurgery at the University of California – Davis. In 1996 he became the Director of the Neuromuscular Disease Laboratory and Clinical Electrophysiology and Radiological Sciences from 2000 to 2004. LeCouteur is a Diplomate of the American College of Veterinary Internal Medicine (Neurology) and a Diplomate of the European College of Veterinary Neurology. >From 1996 to 1999 he was President of the ACVIM specialty of Neurology, and is currently the President of ACVIM. LeCouteur's research interests include brain tumors and neuromuscular disease. Dr. LeCouteur has three orange cats (Sam, OB and Benito).

Update on Brain Tumors

Richard A.leCouter, professor BVSc, PhD Dipl.ACVIM (USA)

Update on Brain Tumor Management

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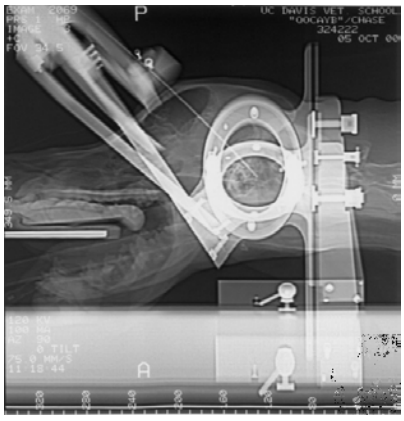
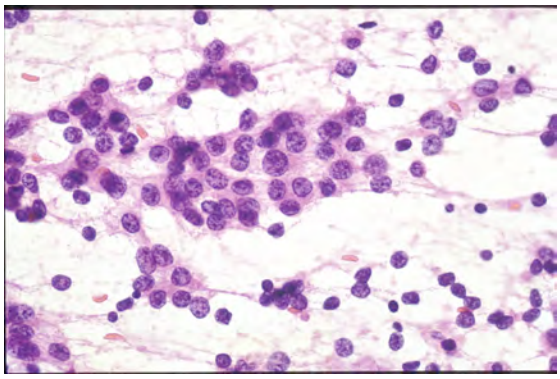
Key Facts

- Primary brain tumors are a significant cause of morbidity and mortality in small animal companion animals, particularly in dogs
- With more widespread availability of advanced imaging techniques, the number of animals being diagnosed with intracranial mass lesions has increased significantly
- The most commonly diagnosed tumors are meningioma, followed by glial tumors (astrocytoma, oligodendroglioma) and choroid plexus tumors
- Information relating to imaging characteristics of specific tumor types has been published, **however imaging can never provide a specific diagnosis**
- As with neoplastic disease affecting any other organ system in the body, definitive diagnosis has been historically confirmed primarily based on the results of biopsy, histopathology and immunohistochemistry
- Biopsy of primary brain tumors presents a number of location specific problems, primarily involving the relative inaccessibility of lesions, together with the significant risks associated with surgical biopsy in many cases
- Although limited in availability at this time, recent advances in the development of stereotactic CT guided biopsy of tumors has done much to improve the likelihood of obtaining an accurate ante mortem diagnosis, allowing for a more appropriate and informed approach to therapeutic planning





CT guided stereotactic brain biopsy

Conventional therapy

- In general, conventional therapeutic approaches to brain tumors in people and animals have involved a combination of surgical debulking/resection, chemotherapy, and radiation therapy
- A large body of clinical data exists in human medicine pertaining to the relative efficacy of these therapies for specific tumors, together with the expected prognosis
- Very little similar objective information is available for the dog, even relating to the normal progression of brain tumors in the absence of treatment
- Small case study series, lack of ante mortem (or post mortem) diagnoses, differing treatment plans, the high degree of variability associated with an end point often defined by euthanasia, and variation in clinical severity at presentation have made the comparison of canine and human data very difficult
- In general, the majority of meningiomas in humans are treated surgically with a mortality rate of less than 10%
- Recurring tumors (and aggressive tumors) may be treated with radiation and repeat surgical resection
- Human gliomas, grades I-II, II and IV are generally treated with surgical resection followed by radiation and chemotherapy, particularly with high grade tumors
- The prognosis for these tumors varies from a 15 year survival rate of ~ 15% for Grade I,II tumors to a median survival of 4-16 months for high grade tumors
- In fact, despite improvements in surgical techniques, radiation therapy (including radio surgery) and new chemotherapeutic agents, the prognosis for human patients with high grade gliomas has not altered significantly over the last 20 years!
- With the exception of meningiomas in cats, and sometimes in dogs, the prognosis for the majority of primary brain tumors (particularly intra axial tumors) even with conventional treatments is guarded to poor
- Survival with symptomatic treatment alone is often measured in terms of weeks in most cases
- Meningiomas treated with surgery +/- radiation or radiation alone may have a survival in the region of 6m-3 years in dogs
- Survival times are often significantly less for intra-axial tumors regardless of the treatment used

Advances in Conventional Therapy

- Improved pre surgical imaging capabilities, together with improved surgical techniques and equipment are likely to lead to some modest improvements in prognosis, particularly for readily accessible extra axial tumors
- Conventional chemotherapy has advanced very little in both the human and veterinary fields in the last 2 decades
- Use of adjunctive chemotherapy such as hydroxyurea in the treatment of meningioma, either following surgery or following recurrence post surgery may be beneficial, however objective data are lacking at this time

- The only “new” chemotherapeutic agent to be approved for the treatment of human glioma in the last 2 decades is the alkylating agent temozolamide (Temodar); however clinical gains are small
- It is unclear whether Temodar offers any significant advantages over standard (much less expensive!) alkylating agents such as CCNU in dogs with gliomas
- Although little data are available to make specific conclusions, radiation therapy is generally accepted to be the most useful adjunctive or sole therapy (where surgery is not possible), particularly for intra-axial tumors
- Standard radiation treatment involves 15-20 fractionated doses of radiation over a 3-4 week treatment course, and significant expense
- Advances in the ability to deliver radiation to tumors while sparing normal brain (e.g., intensity modulated radiation therapy, IMRT) are likely to result in improved survival, and are becoming available at a limited number of veterinary institutions
- More advanced stereotactic radiosurgical techniques such as the Gamma Knife and LINAC knife deliver very high doses of radiation to tumors in a single treatment while sparing normal tissues
- These facilities are available to veterinarians at only a small number of research facilities, however this is likely to change in the next several years
- Radiation involving a single treatment, and therefore a single anesthesia, has many potential benefits for veterinary patients
- Preliminary studies in dogs with brain tumors suggested that single dose radiosurgery can be as effective as standard fractionated radiation treatment in selected tumors

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Molecular Diagnostics and Targeted Therapy

Over the past 15- 20 years, there has been a large effort to understand the specific molecular abnormalities underlying the development and progression of human primary brain tumors. Many of these abnormalities involve tumor suppressor genes, oncogenes and pathways involved in cell cycle regulation and angiogenesis. This has had an impact in two major ways.

1) By defining tumors in terms of their molecular characteristics, it has been possible to further classify apparently histologically identical tumors into separate groups. This has had a major impact on the ability to predict prognosis and response to conventional therapies. For example: Many oligodendroglial tumors exhibit loss of chromosomes 1p and 19q. Loss of 1p or combined loss of 1p and 19q is associated with increased chemosensitivity and increased survival. Over expression of the epidermal growth factor receptor (EGFR) insulin like growth factor receptor (IGF1R) in gliomas is associated with radio resistance; similarly, over expression of the vascular endothelial growth factor (VEGF) and its receptors (VEGFR) is associated with a poor prognosis. The ability to predict response to treatment based on the presence or absence of specific molecular markers has taken clinical pathology/histology to a new level and not only helps to select appropriate patients for specific treatments, but also helps to more realistically assess efficacy of therapeutic regimens which may have appeared ineffective when applied to a “mixed” population of uncharacterized and potentially inappropriate tumors.

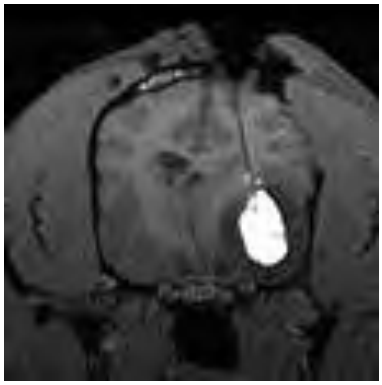
2) Because of the relatively poor response of many primary brain tumors to conventional therapies, many novel approaches have been designed. Many of these approaches target the

molecular abnormalities known to be present in specific tumors such as replacing abnormal or absent tumor suppressor gene function (eg TP53), or inhibiting growth factors known to be important in angiogenesis or tumor growth (eg VEGF, EGF). If appropriate pathways are present, such targeted treatments can be extremely effective, as has been shown in the remarkable success of ST1571 ("Gleevac") in the treatment of chronic myeloid leukemia. (ST1571 targets the constitutively activated BCR-ABL tyrosine kinase receptor) Many similar treatments are currently in development and clinical trials in brain tumor patients. Additionally, over expression of markers specific to brain tumors can be used to target non specific therapeutics such as toxins or more conventional chemotherapeutic agents. Gene therapy using viral vectors such as adenovirus, retrovirus and adeno-associated virus has also been assessed in both experimental and clinical tumors. The ability of many viruses to transduce tumor cells (or normal brain) depends on many factors including appropriate cell surface targets. Generation of promoter specific viral constructs also adds an additional targeting step helping ensure that therapeutic gene expression occurs only in the appropriate cell types.

There is little published data documenting the molecular characteristics of canine brain tumors, however several research groups are currently involved in work in several areas including expression and altered regulation of growth factor pathways; tumor suppressor gene function; telomerase activity, gene array expression profiling and chromosomal alterations. The recent release of the canine genome data will help enormously in promoting this basic research and help ensure that the veterinary profession is able to benefit from current and future advances in human brain tumor therapy, as well as potentially playing an integral part in both basic and applied clinical research.

Delivery of Therapeutic Agents

A wide variety of methods have been employed to deliver therapeutic agents to brain tumors. Many strategies have involved systemic delivery of agents either orally or intravenously. Some drugs (eg standard chemotherapeutic agents) are relatively non specific with respect to their potential targets, whereas others (eg small molecule tyrosine kinase inhibitors such as Gleevac) may have a more precisely defined target despite the systemic delivery. Even with the use of targeted therapies, the likelihood of significant systemic side effects is a major concern with drugs delivered in this manner. Ability of drugs to cross the blood brain barrier is also a factor that can significantly limit the efficacy of systemically delivered therapies, and many factors such as molecular weight, permeability of vasculature, drug stability and diffusion characteristics as well as tumor related factors are critical to attain effective cellular levels of anti tumor drugs. Local "targeted" delivery of therapies directly into tumor tissue has been advocated as a way to increase both the efficacy of many therapeutic agents whilst at the same time decreasing the likelihood of significant systemic toxicity. Therapeutic agents may be delivered directly at surgery following excision/debulking of tumors, or by stereotactic injection. Recent advances in injection of agents by convection enhanced delivery (CED) (over several hours), have shown great promise, and may allow highly accurate and comprehensive delivery of therapeutics to a defined area of tumor and/or surrounding brain.
Preliminary results with CED using a novel chemotherapeutic agent CPT-11 (topoisomerase I inhibitor) in an ongoing clinical trial in dogs with spontaneous gliomas are encouraging, and demonstrate the feasibility of targeted delivery in veterinary patients.



CED of CPT-11 chemotherapy in a canine glio

Advanced Diagnostics for Cerebral Neoplasia

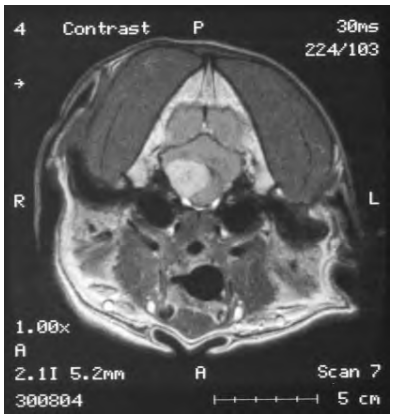
Magnetic Resonance Imaging (MRI)

- In general, many neoplastic lesions have similar imaging characteristics on T1 and T2 weighted images
- Most tumors will be iso-hypo intense on T1W images and hyperintense on T2W images
- Hemorrhage associated with higher grade tumors may result in areas of hyperintensity on T1 weighted precontrast images (see below) and hypointensity on T2 weighted images
- Many tumors are associated with a significant amount of peritumoral edema
- This is typically of a vasogenic nature and is most often seen predominantly involving the white matter tracts in the surrounding tissue
- Edema is most easily seen on T2 or FLAIR images as a hyperintense signal. Animals with brain tumors and significant edema suggested on T2 images are likely to respond favourably to anti-inflammatory doses of glucocorticoids
- Contrast enhancement can be extremely variable and is thought to be secondary to abnormal tumor vasculature or disruption of normal vasculature in the region of the tumor
- Typical contrast patterns are seen with, but are NOT diagnostic of, certain tumor types. (see below)

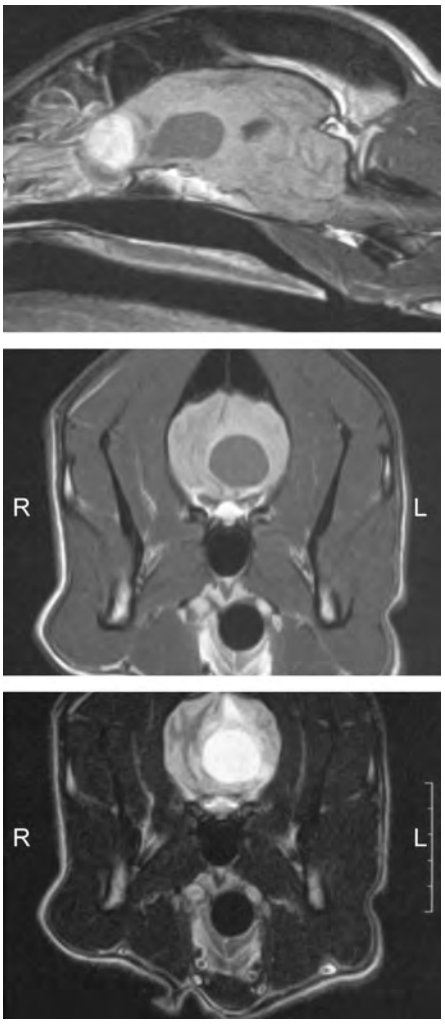
Primary CNS tumors

Meningioma

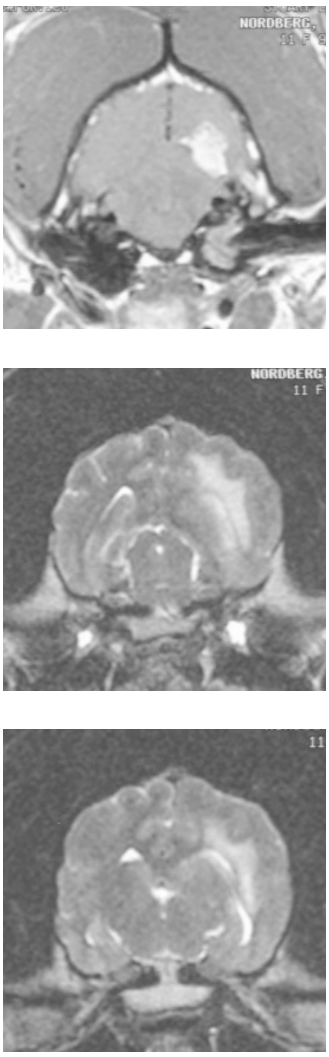
- Tumors are extra-axial and may arise rostrally involving the cerebral convexities, falx, ventrally, within the caudal fossa, or spinal cord
- There may be considerable variation in appearance form well circumscribed mass lesions to plaque like tumors
- Spinal cord meningiomas are most commonly found in the cervical region
- Meningiomas are usually uniformly contrast enhancing although this can be variable
- Significant cystic components may be present
- Presence of a “dural tail” on post contrast T1W images is a common finding, though not diagnostic
- Many tumors have associated edema that may be severe in some cases



T1W +C
Extraaxial uniformly contrast enhancing meningioma with mass effect



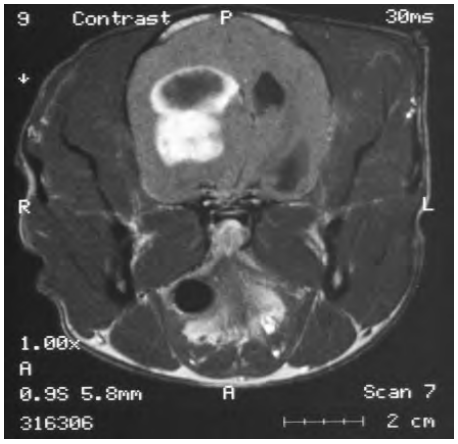
T1W +C (top, middle), T2W (bottom)
Cystic meningioma



TI1W +C (top), T2W (middle, bottom)
Vasogenic edema following the white matter tracts is visible rostral to the tumor on T2W images (meningioma)

Oligodendroglioma

- These glial tumors are intra-axial and most often affect the cerebrum
- Most tumors are high grade (III) tumors characterized by varying degrees of contrast enhancement, often in a ring pattern
- Lower grade (II) tumors may have no contrast enhancement
- Tumors are often grossly gelatinous in nature and can appear markedly hypointense on T1W images and hyperintense on T2W images
- Invasion of ventricular structures with subsequent ventriculomegally is common

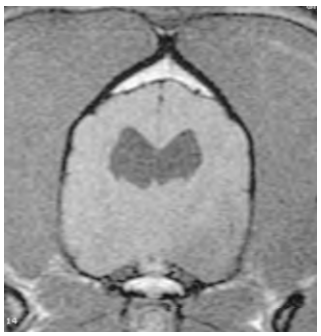


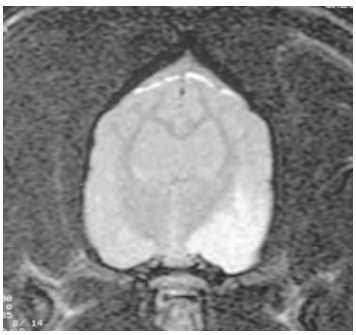
T1W +C

Intraaxial ring enhancing mass with a hypointense center typical of a high grade oligodendroglioma. There is marked mass effect with deviation of the falx and effacement of the right lateral ventricle.

Astrocytoma

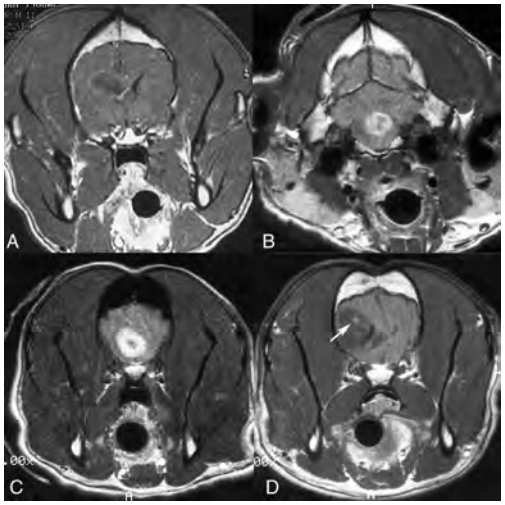
- Low grade (II) tumors are infiltrative and often have little mass effect
- They are rarely contrast enhancing and may only have mild hypointensity on T1 weighted images
- Marked edema is not common
- High grade astrocytomas (III, IV/glioblastoma) have imaging characteristics that can be very similar to high grade oligodendrogliomas, and are usually contrast enhancing with varying amounts of peritumoral edema

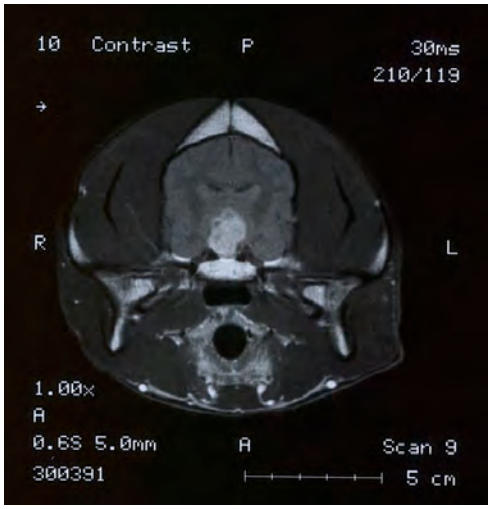




T1W +C *T2W*

Low grade infiltrative astrocytoma with minimal mass effect and no contrast enhancement



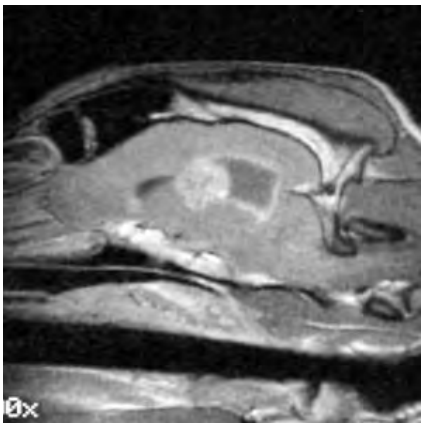


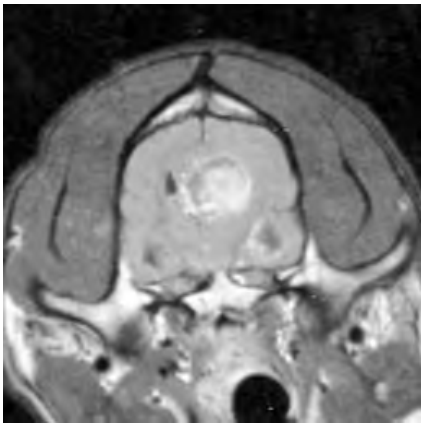
T1W +C *T1W +C*

High grade (IV) glioblastoma multiforme. Variable contrast enhancement is present with significant mass effect.

Choroid plexus tumor

- These tumors (papillomas and carcinomas) are characterised by their location within the ventricular system, often resulting in secondary hydrocephalus
- Most tumors are uniformly strongly contrast enhancing
- Choroid plexus carcinomas can metastasise down the ventricular system resulting in multiple contrast enhancing lesions and/or enhancement of the ventricular system due to multiple micrometastases



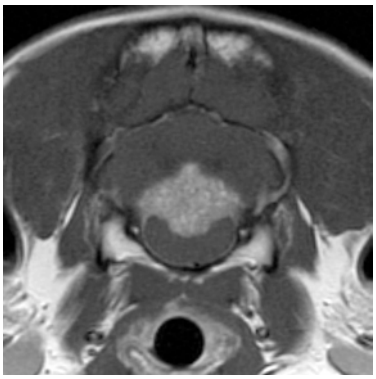


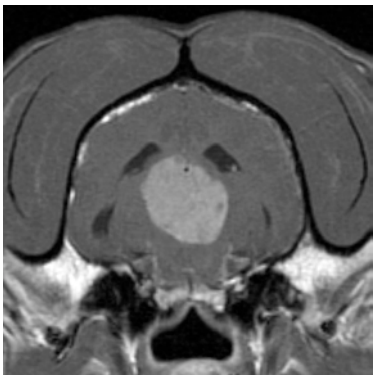
T1W +C *T1W +C*

Choroid plexus carcinoma. Strongly contrast enhancing mass lesion within the lateral ventricle. Multiple "drop metastases" have resulted in contrast enhancement of the lining of the ventricle.

Ependymoma

- These tumors are also associated with the ventricular system due their origin in the lining cells of the ventricles
- They also tend to be uniformly contrast enhancing. Ependymomas appear to less common than choroids plexus tumors and rarely metastasize



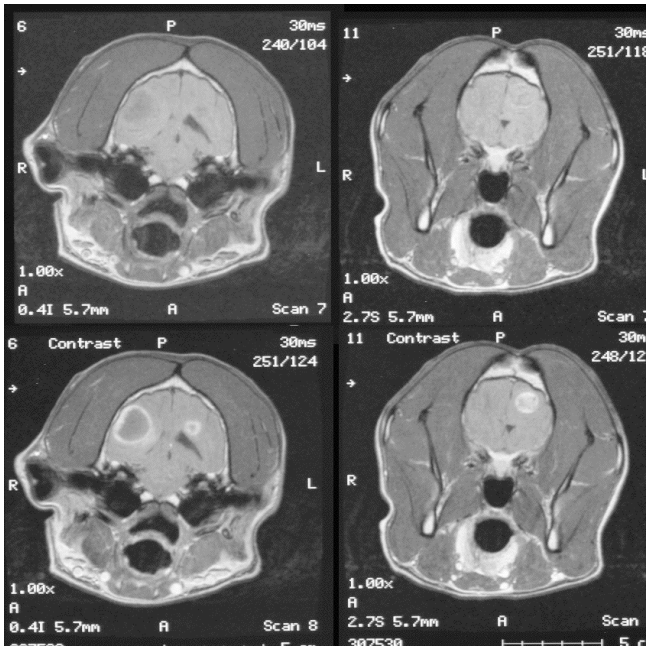


T1 +C *T1 +C*

Uniformly contrast enhancing ependymomas involving the 4th and 3rd ventricles

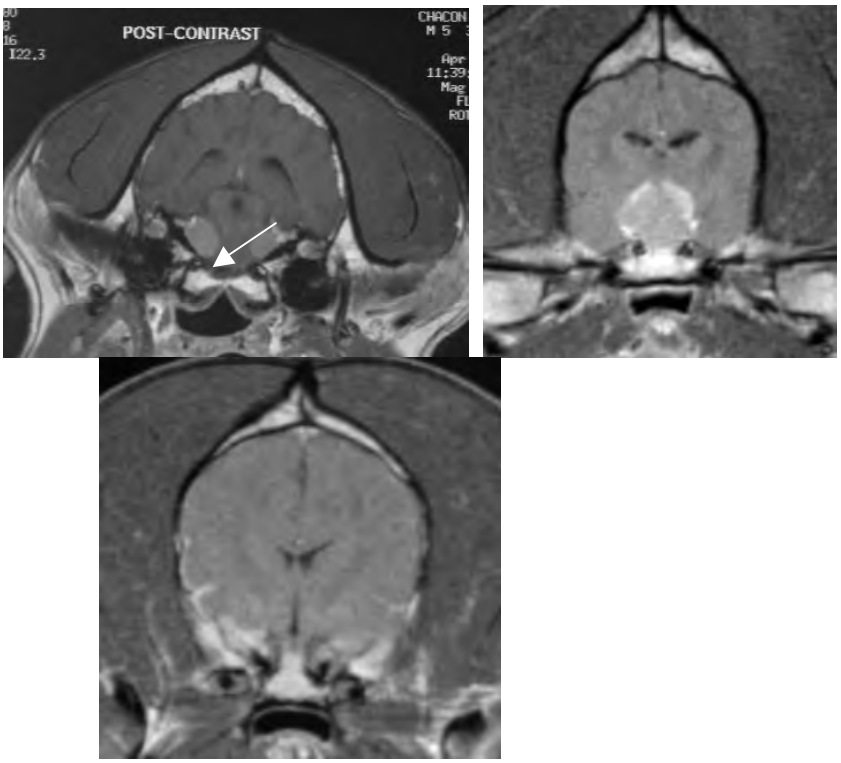
Secondary/metastatic tumors

- Metastatic spread of neoplastic lesions to the CNS is relatively uncommon in the dog and cat
- In the author's experience, the most frequently recorded tumors are haemangiosarcoma, histiocytic sarcoma, melanoma and lymphoma
- Metastatic lesions may be multiple or solitary, and often have a predilection for the grey/white matter junctions of the cerebrum
- Marked edema is a common finding with many metastatic lesions such as haemangiosarcoma
- Many metastatic lesions are contrast enhancing. Lymphoma can present with a variety of imaging characteristics
- It is usually contrast enhancing and may involve the meninges and nerve roots
- It may present as a solitary mass lesions or as multifocal disease or diffusely infiltrative disease



T1W (upper), T1W +C (lower)

Metastasis of haemangiosarcoma to the cerebrum. Another example of a ring enhancing lesion!



T1W +C
Three different imaging presentations of CNS lymphoma affecting cranial nerves,
a) Infiltration of cranial nerves (arrow)
b) Mass lesion (diencephalons)
c) Meningeal infiltration (arrow)

Special Sequences

Note: There are often many different acronyms and variations for each type of sequence, often vendor specific.

Fat suppression

- Fat generally appears hyperintense on standard T1 weighted images and grey on T2 weighted images
- Fat can be useful for highlighting structures it surrounds such as nerve roots of the cauda equina, however it can also make it difficult to interpret other adjacent hyperintense findings such as contrast enhancing lesions, hemorrhage and adjacent fluid structures (e.g., subarachnoid space) and cystic structures
- Fat suppression techniques result in fat appearing dark resulting in better definition of adjacent hyperintense structures

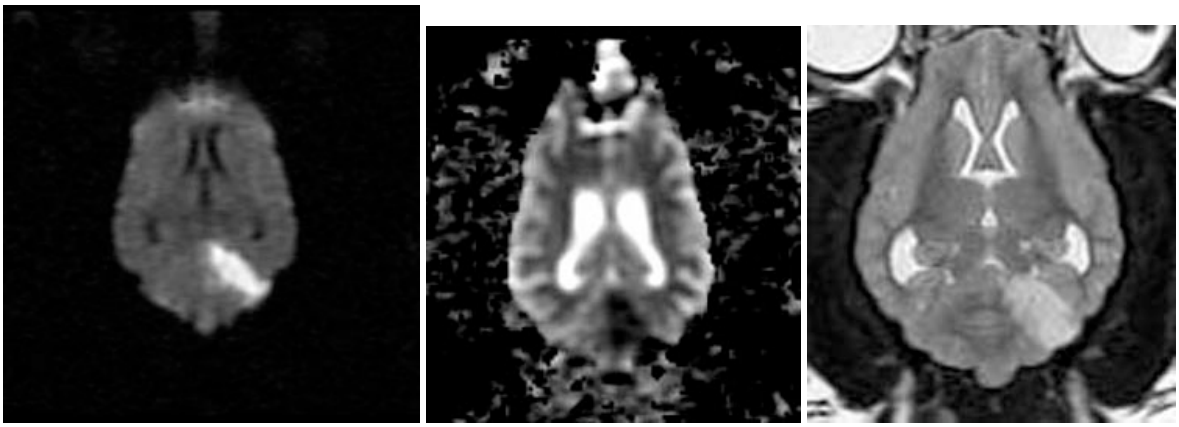
Fluid attenuated inversion recovery (FLAIR)

- This technique nulls the bright fluid signal from free water and CSF
- This can be very useful when hyeprintense lesions are adjacent to fluid filled structures such as ventricles
- It can also help distinguish whether cystic structures contain CSF or necrotic/proteinaceous material

Diffusion weighted images (DWI)

- DW scanning detects random diffusion of water molecules
- Increased diffusion results in loss of signal therefore hypointensity
- An apparent diffusion coefficient map (ADC map) can be computed such that image intensity is proportional to the level of diffusion i.e., increased diffusion results in hyperintensity

a) Vascular infarction results in cytotoxic edema which decreases random diffusion and therefore gives hyperintensity on DWI. (DWI is particularly sensitive for detection of infarction within the first few days). Both cytotoxic and vasogenic edema will appear hyperintense on standard T2 weighted images due to both having increased water content. Using DWI and ADC maps together helps to distinguish cytotoxic edema associated with infarction for vasogenic edema that can be associated with eg neoplasia, infection.
b) Cysts containing highly diffusible fluids (e.g., CSF in an arachnoid cyst) will be hypointense. Cysts containing less diffusible water (eg puss in an abscess) will be hyperintense.



A) *B)* *C)*

A) DWI, B) ADC map, C) T2 weighted image. Infarction of the cerebellum resulting in decreased diffusion of water molecules and therefore increased signal on DWI (Images courtesy of L Garrosi)

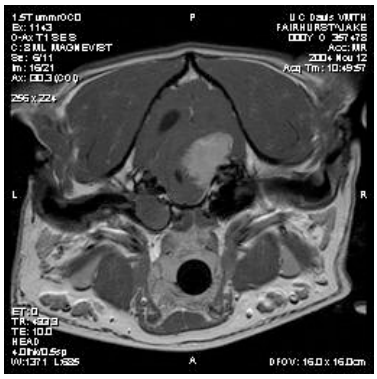
Perfusion imaging

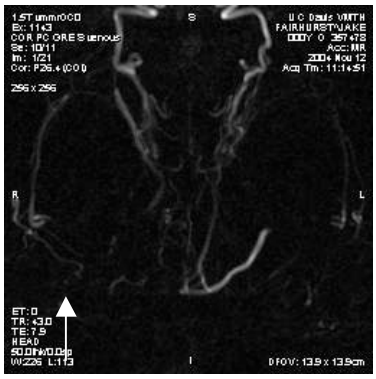
- Perfusion scans are functional scans that assess the delivery of blood to the tissue.

a) Tumors often have increased signal due to their high vascularity and may be distinguishable from radiation necrosis post operative scar tissue which has low signal (perfusion).
b) Infarcts have low signal due to loss or reduction in blood flow

Magnetic resonance angiography (MRA)

- A variety of techniques can be used to outline either the arterial or venous circulation by utilizing the fact that there is flow of proton containing material within the vessels
- MRA is non invasive and therefore less risky than conventional angiography and 3D reconstruction can be done
- MRA may be useful for surgical planning to determine blood supply to, or in the vicinity of, a lesion, and to define vascular abnormalities and malformations

A) 

B) 

A) MRI (T1W post contrast) cerabellopontine angle meningioma in a 7yr MC Boxer. B) Occlusion of the right transverse sinus (arrow) is apparent on MRA (arrow). This information is useful for surgical planning since the surgical approach to this site involves occlusion of the transverse sinus.

Magnetic Resonance Spectroscopy (MRS)

- MRS can be used to quantify specific metabolites in chosen areas of the brain
- Spectroscopy can provide more specific characterisation of lesions such as storage diseases, brain tumors and also provides the potential to non invasively monitor progression of disease or response to specific therapies
- The most common type of clinically utilised spectroscopy is proton spectroscopy
- Usually a single voxel of brain tissue is selected

The most commonly measured metabolites are:

Lactate	Increased in stroke, brain tumors.
Creatine, Phosphocreatine	Important for energy metabolism
Choline (Cho)	Cell membrane precursor, increased with myelin damage and neuronal death. Increased in human glial tumors.
Myoinositol (mI)	Increased in gliosis, human ependymomas
N-acetyl aspartate (NAA)	Decrease indicative of neuronal death (often the dominant peak)

Glutamate	Increased in hypoxia

Ratios of the individual peaks may also be used to characterise lesions.

Functional MRI (fMRI)

- FMRI detects areas of increased blood flow and therefore oxygenation to areas of the brain. Increased oxygen means less deoxyhaemaglobin and more oxyhaemaglobin
- Deoxyhaemaglobin is paramagnetic so that loss causes a decrease in T2 relaxation. (See hemorrhage)

Magnetic transfer imaging (MTI)

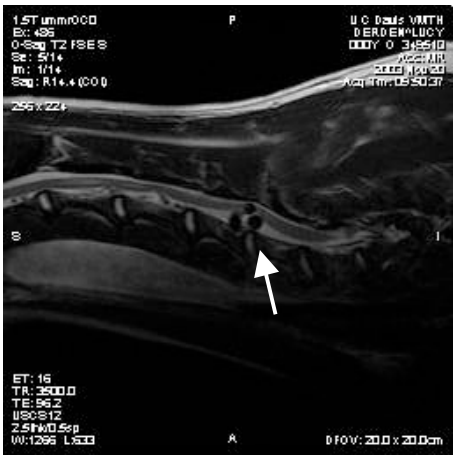
- MTI examines the non water components of the brain and has been used amongst other things, to more specifically characterise disease affecting white matter (myelinated axons), neurodegeneration , trauma and neoplastic lesions

Real-time MRI guided Convection enhanced Delivery (CED)

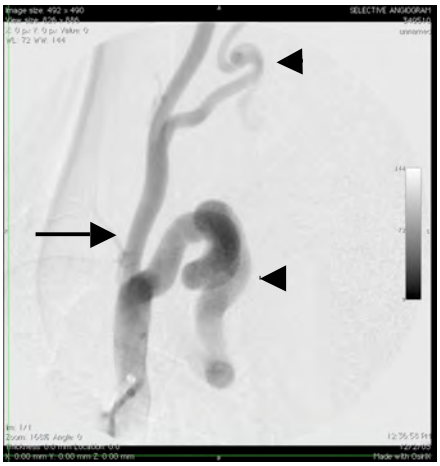
- Infusion of therapeutic agents into the brain using convection enhanced delivery utilizes bulk flow of infusates through the interstitial space
- Large volumes of brain can be "covered", and by using simultaneous infusion of contrast agents such as gadolinium, real-time monitoring of the infusion can be done to ensure optimal infusion while minimizing potential toxicity to non targeted tissues

Angiography

- Initial use of positive contrast cerebral angiography in small animals was essentially for the delineation of intracranial lesions, rather than as a tool to investigate primary vascular disease
- Space occupying masses could be identified based on their secondary effects on local vasculature
- Both venous and arterial contrast techniques can be used in the dog (arterial angiography is extremely difficult in the cat due to lack of a patent internal carotid artery and "reversal of flow in the basilar artery)
- The advent of CT and MRI has essentially supplanted angiography and other related techniques such as pneumoventriculography in the diagnosis of intracranial mass lesions
- Use of positive contrast angiography is currently restricted to cases where specific vascular disease such as arteriovenous malformation is suspected
- Iodinated contrast agents may be visualised using fluoroscopy/radiography, or CT
- Use of magnetic resonance angiography (see below) is likely to replace standard contrast angiography in the future in most cases



A)



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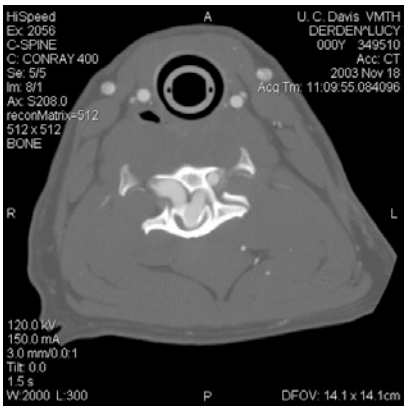

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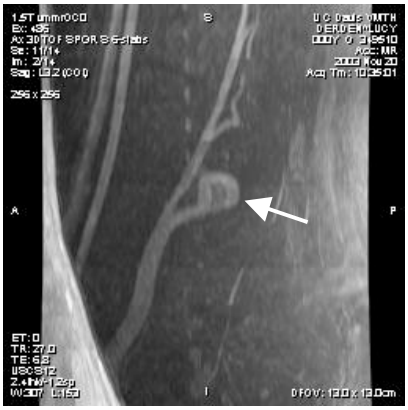

D)

Cervical myelopathy resulting from dilation of spinal branches of the left vertebral artery secondary to congenital non patency of the right proximal subclavian artery.
A) Large flow voids are present on the T2W sagittal MR image due to rapid blood flow in the dilated vessel
B) Selective digital angiography via the femoral artery. The dilated spinal branches are apparent (arrow heads) arising from the left vertebral artery (arrow). Note the lack of orthograde flow in the (non visualised) right vertebral artery
C) Positive contrast CT myelogram demonstrating marked compression of the spinal cord by the tortuous vessels
D) MRA demonstrating a dilated spinal branch arising from the left vertebral artery (arrow)

Ultrasonography

- Use of ultrasound is of limited value in the evaluation of neurological disease due to the presence of the skull and vertebrae. Specific indications include:

1) Identification of hydrocephalus/congenital anomalies (requires open fontanelle)
2) Assessment of soft tissue structures outside the skull/vertebral column e.g., peripheral nerve sheath tumors
3) Assessment of blood flow (eg in basilar artery by Doppler ultrasonography)
4) Assessment of parenchymal architecture intraoperatively. (eg location of intraaxial mass lesions following craniotomy, hemilaminectomy)

Scintigraphy

- Conventional scintigraphy identifies the accumulation of radioactive nuclides (most commonly technetium-99m-DTPA) within the nervous system due to compromise of the blood brain barrier
- Its use has largely been supplanted by CT and MRI and PET

Brain Tumors - Diagnosis and Therapy

Richard A.leCouter, professor BVSc, PhD Dipl.ACVIM (USA)

BRAIN TUMORS: DIAGNOSIS & THERAPY

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The Past: Surgery, Irradiation and Chemotherapy

The major goals of therapy for a brain tumor have been to control secondary effects, such as increased intracranial pressure or cerebral edema, and to eradicate the tumor or reduce its size. Beyond general efforts to maintain homeostasis, palliative therapy for dogs or cats with a brain tumor has consisted of glucocorticoids for edema reduction, and in some cases (e.g., lymphoma), for retardation of tumor growth. Some animals with a brain tumor will demonstrate dramatic improvement in clinical signs for weeks or months with sustained glucocorticoid therapy. Should anti-seizure medications be needed, phenobarbital or bromide are the drugs best suited for the control of generalized seizures.

Three major methods of therapy for a brain tumor have been available for use in dogs and cats: surgery, irradiation, and chemotherapy.

Surgery

In association with the availability of CT and MRI, and the development of advanced neurosurgical, anesthetic, and critical care techniques, complete or partial surgical removal of intracranial neoplasms is being practiced with increasing frequency. Neurosurgical intervention is an essential consideration in the management of intracranial neoplasms of cats or dogs, whether for complete excision, partial removal, or biopsy.

Radiation Therapy

The use of radiation therapy for the treatment of primary brain tumors of dogs and cats is well established. Irradiation may be used either alone or in combination with other treatments. Radiation therapy also is recommended for the treatment of secondary brain tumors. Metastases, pituitary macroadenomas or macrocarcinomas, and skull tumors have been successfully managed by means of either radiation therapy alone or as an adjunct to surgery. Lymphoma may also be sensitive to radiation therapy.

Chemotherapy

Traditionally, cytotoxic drugs have had a limited role in the treatment of dogs or cats with brain tumors, and progress in the development of truly effective chemotherapeutic protocols for humans or companion animals has been slow. Several factors affect the use of chemotherapeutic agents for the treatment of brain tumors in dogs or cats. The first, unique to the brain, is that the blood-brain barrier (BBB) may prevent exposure of all or some of the tumor to a chemotherapeutic agent injected parenterally. Second, tumor cell heterogeneity may be such that only certain cells within a tumor are sensitive to a given agent. Third, a tumor may be sensitive only at dosages that are toxic to the normal brain or other organs (kidney or liver).

The Present: Therapeutic Delivery Strategies for Canine Brain Tumors

The use of Surgery, irradiation and chemotherapy remiains the mainstay of brain tumor therapy today.

Development of novel therapeutic strategies to combat primary brain tumors has followed closely behind elucidation of the basic molecular and genetic mechanisms underlying both tumorigenesis and subsequent progression. Despite the wealth of data documenting successful treatment of experimental tumors, translation into the clinical setting has been slow. Many existing therapeutics are rendered ineffective in the treatment of brain tumors due to the inability to effectively deliver and sustain them within the brain. The major obstacle to therapeutic delivery via the vascular route (following either orally administration or direct vascular administration) is the BBB.

Transport across the brain vascular endothelium is essentially trans-cellular, therefore the ideal substance to be transported should be:

- Small (< 400Da)
- Lipophilic (lipid soluble)
- Non-polar at physiological pH
- Non-protein bound

Unfortunately, a majority of chemotherapeutic agents are large positively charged, hydrophilic molecules. Many therapeutic molecules such as cyclosporine, doxorubicin and vincristine have poor BBB penetration despite being lipophilic (cyclosporine A is more lipophilic than diazepam). This is the result of additional “barriers” such as high levels of degrading enzymes within the endothelial cells, and high concentrations of efflux transporter proteins such as P-glycoprotein, multiple organic anion transporter proteins (MOAT) and multi-drug-resistance proteins (MRP).

In addition to barriers preventing movement of therapeutic agents from the blood into the brain parenchyma, mechanisms are also present to limit movement into the cerebrospinal fluid (CSF). Passage of substances through the arachnoid membrane is prevented by tight junctions and is generally impermeable to hydrophilic molecules. While the capillaries of the choroids plexus are fenestrated, non-continuous and allow free movement of small molecules, the adjacent choroidal epithelial cells form tight junctions preventing the passage of most macromolecules. An active organic acid transporter system in the choroid plexus also is capable of driving therapeutic organic acids such as penicillin or methotrexate back into the blood from the CSF. Entry of drugs into the CSF does not necessarily guarantee that they will reach the interstitial fluid in the brain, suggesting the presence of the so-called CSF-brain barrier, mainly attributed to insurmountable diffusion distances required to equilibrate CSF with brain interstitial fluid.

Although the BBB may be inconsistently compromised in tumor vasculature, a variety of obstacles still restrict delivery of therapeutic agents. Tumor microvascular supply often is heterogeneous and chaotic, with significant areas of inefficient or poor blood flow, vascular shunting, blind-ending vessels, etc., resulting in erratic distribution of drugs that are able to penetrate the BBB.

Improving delivery of therapeutic agents to brain tumors in the face of these obstacles has focused on the following areas of research:

- ***Improve entry through the BBB by modification of therapeutic drugs***

    a. Increase influx
    b. Decrease efflux
    c. Utilization of carriers/receptors

- ***Disruption of the BBB***

    a. A variety of approaches have been used to disrupt BBB integrity including:
        i. Chemical (often toxic), DMSO, ethanol, aluminium, irradiation, hypertension, hypercapnia, hypoxia
        ii. Osmotic agents such as mannitol and arabinose
        iii. Biochemical agents such as leukotriene C4, bradykinin, histamine etc.

- ***Circumventing the BBB***

    a. Using non-vascular delivery of therapeutic agents directly into the CNS is appealing in many ways. Apart from removing the BBB as a restriction to delivery of many potent anticancer therapies, targeting the drugs directly potentially reduces systemic toxicity, degradation and immunological stimulation (particularly with protein and virally based therapies). However strategies are generally more invasive requiring craniotomy or insertion of catheters
        i. Intraventricular/intrathecal infusion
        ii. Wafers/microspheres/microchips
        iii. Delivery from biological tissues (Gene Therapy)
    b. Delivery of therapies directly from living cells within the brain or tumor itself can provide sustained levels of drugs in specific targeted regions. The two main strategies examined to date are:
        i. Implantation of transfected cell lines
        ii. Transduction of resident CNS cells or brain tumor cells with gene therapy constructs

- ***Interstitial delivery***

    a. Both gene therapies and direct acting drugs, such as chemotherapeutics, can be delivered directly into tumor or brain parenchyma. AAV vectors carrying thymidine kinase suicide constructs and antiangiogenic agents have been shown to be efficacious in both *in vitro* and *in vivo* models, and direct injection into canine primary brain tumors has been done. Results in clinical tumors however have been disappointing mainly due to limited distribution of the therapy beyond the local region of the injection site

The Future: Brain Biopsy and Convection Enhanced Delivery (CED)

Brain Biopsy

Biopsy remains the sole method available for the ante mortem definitive diagnosis of brain tumor type in cats or dogs, and is an essential step prior to consideration of any type of therapy. However, biopsy is not always attempted because of practical considerations, such as cost and morbidity. The most recent advance in the biopsy of brain tumors of dogs and cats has been the development of CT-guided stereotactic brain biopsy systems for use in cats and dogs. These CT-guided stereotactic biopsy systems provide a relatively rapid and extremely accurate means of tumor biopsy, with a low rate of complications. Cytological evaluation of brain tumor smear preparations, rapidly fixed in 95% alcohol and stained with hematoxylin and eosin, may be done within minutes of biopsy collection. Diagnostically accurate information from this rapid technique is generally available from both primary and metastatic nervous system tumors.

Convection enhanced delivery (CED)

CED is a local delivery technique that utilizes a bulk-flow mechanism to deliver and distribute macromolecules over clinically relevant volumes of targeted tissue. Unlike local injection techniques, CED uses a pressure gradient established at the tip of an infusion catheter that pushes the infusate through the interstitial space. Volumes of distribution of infused molecules are significantly increased compared to local injection or surgical implantation methods that rely primarily on diffusion and are limited by concentration gradients and molecular weight of the delivered substance. Distribution of infusates over centimeters, rather than millimeters, has been reported in a variety of experimental model systems using CED. Real time *in vivo* imaging of CED is an essential consideration if adequate drug distribution is to be confirmed ante mortem. Additionally, the ability to detect and minimize distribution or leakage of drugs to normal tissues during delivery has the potential to significantly decrease toxicity and increase therapeutic effectiveness. Several surrogate marker systems have been described, facilitating image-guided CED, including magnetic resonance imaging (MRI) systems utilizing T2 imaging correlated with ^{123}I-labelled serum albumin, single photon emission computed tomography (SPECT), and liposomes co-labeled with gadolinium. Liposomes are phospholipid nanoparticles composed of a bi-layered membrane capable of encapsulating a variety of therapeutic molecules. Liposomal encapsulation of a variety of drugs, including chemotherapeutics, has been shown to result in prolonged half-life, sustained release, and decreased toxicity. CED of liposomes, containing therapeutic drugs, directly into targeted brain tissue offers several advantages over systemic delivery of un-encapsulated drug, including bypassing of the BBB, increased volume of distribution within the target tissue, and increased therapeutic index as a result of both liposomal encapsulation and minimal systemic exposure. Irinotecan/CPT-11 is a camptothecin derivative and topoisomerase I inhibitor with activity against a variety of cancer types, including brain tumors. The efficacy and safety of direct delivery of liposomally encapsulated camptothecin analogs in rodent models of glioma has been reported. Translation of this promising therapeutic approach into clinical trials will require demonstration of the safety and efficacy of combined real time gadolinium based imaging and liposomally encapsulated CPT-11 treatment in a large animal model system. The advantages of a canine model system over established rodent and primate models are several and include the ability to investigate aspects of feasibility and toxicity on a scale

relevant to human clinical patients, and the unique potential to investigate CED efficacy, and adverse effects in large, spontaneously occurring tumors.

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Brain Biopsy in Dogs and Cats

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BRAIN BIOPSY IN DOGS & CATS

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The detection, localization and characterization of brain lesions has been greatly improved through the use of computed tomography (CT) and magnetic resonance (MR) imaging. However, there remains a need to obtain an intra-operative neuro-pathological diagnosis from tissue samples of the lesion. The intra-operative cytological evaluation of smear preparations of brain lesions has become a routine procedure, providing a rapid, highly accurate diagnosis. In addition, future therapies may involve intra-lesional administration of drugs, following results of a brain biopsy. The need to obtain biopsy material for diagnosis and/or to deliver therapeutic agents with precision and without an invasive surgical procedure has stimulated the development and refinement of image-guided brain biopsy.

Neoplastic, vascular, infectious, or inflammatory diseases of dogs and cats frequently result in focal brain involvement. Although CT and MRI are sensitive in determining location, extent, and relationships to adjacent structures, of brain lesions, both have limited specificity. For example, non-neoplastic lesions (such as those seen in association with infectious, inflammatory, or vascular diseases) may mimic the CT or MRI appearance of a neoplasm. In most instances, results of CT or MRI provide only a broad list of differential diagnoses for a focal brain lesion. Accurate histologic diagnosis of an intracranial lesion is critical before recommending a specific management or treatment strategy.

CT-Guided Stereotactic Brain Biopsy

Contraindications

Brain biopsy should be approached with caution in animals with underlyiong coagulopathies, clinical signs consistent with increased intracranial pressure (ICP), animals with brainstem lesions, or systemic problems that result in increased anesthetic risk.

Equipment & Anesthetic Considerations

Essentially all closed stereotactic brain biopsy methods rely on the three-dimensional CT-generated coordinates identifying the lesion location. These coordinates are used to plot an optimal trajectory and depth needed for a biopsy needle to reach a target and obtain a diagnostic tissue sample.
Technical impediments exist to the direct application of most human stereotactic systems to dogs and cats. Most commercially available systems use a cumbersome head-frame and localizing system, designed specifically for the human skull, and require dedicated, expensive computer software for the planning phase. Several different systems for image-guided stereotactic brain biopsy have been reported for use in dogs and cats.
General anesthesia is required for stereotactic brain biopsy. Typically, premedication utilizes an opioid (a pure *mu* agonist because of using fentanyl in the maintenance phase). The dose and use of this drug will depend on the concern over changes in ICP and the mental status of the patient. Anesthesia usually is induced with propofol (± a

benzodiazepine). Propofol (0.1-0.4 mg/kg/minute) and fentanyl (0.3-0.7 µg/kg/minute) are recommended for maintenance. . Animals should be ventilated to maintain ETCO2 at a value of 30-35 mmHg. For recovery the fentanyl should be stopped about 30 minutes before the end of the procedure.

Anticipated Time

Two to three hours depending on the number of biopsy specimens collected and the number of trajectories planned.

Animal Preparation

Stereotactic biopsy begins with proper patient selection. The possibility of non-neoplastic disorders such as infection, cerebral infarction, or vasculitis, must be considered and investigated with other tests in appropriate patients prior to biopsy. When the differential diagnosis list is long and may include neoplasms and inflammatory lesions, the appropriate handling of tissue samples should be discussed with a neuropathologist in advance of the procedure. All patients should be tested for coagulation parameters (prothrombin time [PT], partial thromboplastin time [PTT]) prior to the procedure and should have a platelet count greater than 100,000. Patients should not receive aspirin products for 1 week before surgery. Ideally, MRI or CT images should be completed within five days prior to completion of the biopsy procedure.

Possible Complications

Although stereotactic brain biopsy is minimally invasive (compared to open biopsy procedures), complications may occur. Morbidity may include seizures, hemorrhage, development of biopsy-induced neurologic deficits, brain infection, tumor seeding, and lack of definitive diagnosis.

Procedure

Biopsy generally is done on the CT-scanner table. For those lesions not well identified on CT images, MRI images that demonstrate a lesion may be used to localize the lesion on CT images, using well-defined anatomic landmarks (e.g., lateral ventricles). Transverse CT images are used to define the CT coordinates of reference markers and the biopsy target. Dorsal or sagittal images may be used for trajectory planning. An entry point should be selected that is associated with a low risk for neurologic deficit or hemorrhage (e.g., avoidance of dorsal sagittal sinus). Ependymal puncture should be avoided where possible. A small craniotomy (2-mm diameter) is made by means of a twist drill, the dura mater is punctured with an 18-gauge needle, and biopsies may be done with a side-cutting aspirator biopsy needle (Nashold Biopsy Needle, Integra Radionics, Burlington MA) with a 10-mm side opening. On average, one to three specimens are harvested from each biopsy site.

The intra-operative goal should be to confirm by means of smear or touch preparations whether tissue satisfactory for an eventual diagnosis has been obtained. A specific histologic diagnosis may require routine formalin fixation and paraffin embedding of the biopsy tissue. At the conclusion of the biopsy procedure, the needle is withdrawn in increments to assess

any possibility of hemorrhage. In the case of hemorrhage, blood should be permitted to egress from the needle spontaneously until the bleeding stops.

Post-Procedure Considerations

A series of CT images of the brain should be completed immediately following completion of the brain biopsy procedure in order to assess the possibility of intracranial hemorrhage. Animals should recover from anesthesia in sternal recumbency with the head elevated slightly above the level of the heart. Animals should be closely monitored for 12 hours post-biopsy before being discharged from the hospital.

Relative Merits of Alternative Brain Biopsy Procedures

Open (surgical) brain biopsy may be appropriate in certain clinical situations in which cortical architecture needs to be preserved, for leptomeningeal sampling, for superficially located lesions, and when a decompressive craniectomy with good cortical visualization may be helpful in addition to obtaining a biopsy sample.

Intra-operative Diagnosis Using the Smear Technique

The rapid cytological evaluation of a brain lesion from a biopsy sample can provide crucial information on operative management, medical management, chemotherapy, or radiation therapy. In people intra-operative cytological evaluation of smear preparations of brain tumors, supported by frozen and paraffin-embedded tissue, has become a routine procedure, and cytological profiles of smears of various types of human brain tumors have been well described. Smear preparations are generally wet fixed in 95% alcohol and stained with hematoxylin and eosin although toluidine blue, Geimsa, or Papanicolaou's stain may also be used.

In a recent study, tissue samples were obtained from lesions either by CT-guided stereotactic brain biopsy (44 samples) or intra-operatively during craniotomy (49 samples) and the results from the smear technique compared with those from sections of paraffin-embedded tissue. The overall diagnostic accuracy from samples obtained by both craniotomy and stereo-biopsy was about 80%. This compares favorably with the 69-94% accuracy reported in some large series of human cases. The main advantages of this method of intra-operative diagnosis are speed, ease of preparation, technical simplicity, need for minimal equipment, high degree of cytological resolution compared to frozen preparations, low cost and small sample size required. A limitation of this system is that it is difficult to prepare adequate smear preparations in certain tough and coherent tumors (e.g., Schwannomas, fibrillary astrocytomas, and some meningiomas). Smear preparations provide excellent cytologic detail, however these differ from the conventional histologic appearance of HE-stained paraffin-embedded tissue. Experience is required in the correct interpretation of smear preparations.

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Neuromuscular Disorders

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Neuromuscular Disorders of Dogs and Cats

Richard A. LeCouteur, BVSc, PhD, Dip ACVIM (Neurology), Dip ECVN

Suggested Reading

1. Neuromuscular Diseases. The Veterinary Clinics of North America -Small Animal Practice (ed. GD Shelton) 32:1, January 2002.
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Introduction

Neuromuscular diseases are disorders of the motor unit (the basic functional and anatomical organization of neurons and muscle fibers). Neuromuscular diseases involve pathologic processes that primarily are directed against, and are limited to, one or more subdivisions of the motor unit:

A veterinarian encountering an animal with suspected neuromuscular dysfunction is faced with three basic challenges:

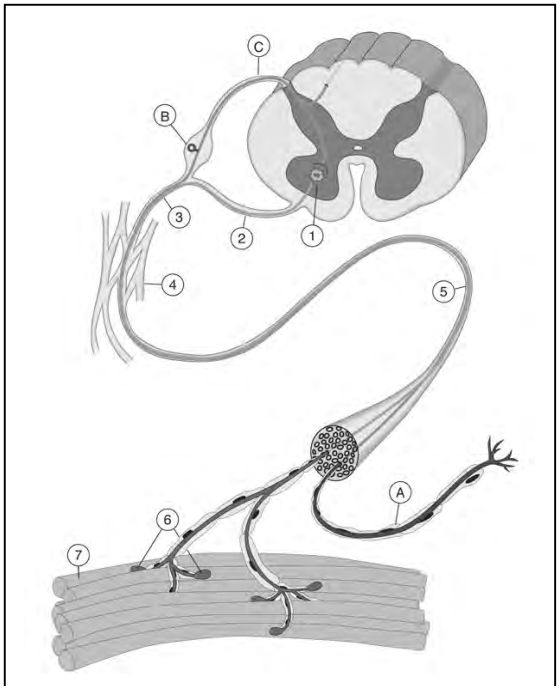
1. To determine whether the animal's presenting complaint and physical findings are the result of a neuromuscular disorder, as similar clinical signs may result from disorders of the brain, spinal cord, ventral horn cells, peripheral nerves, neuromuscular junctions, or muscle;
2. To formulate a complete list of differential diagnoses that will lead to proper identification of the type and cause of the neuromuscular disorder; and,
3. To institute the appropriate therapy (pharmacologic if available) and supportive care to modify the basic disease process and improve the animal's quality of life.

The management of an animal suspected to have a neuromuscular disease may be extremely frustrating, as there is a narrow range of presenting clinical signs for the numerous disorders affecting the neuromuscular system. These clinical signs frequently are common to many different disorders, regardless of the cause.

Anatomy

Each motor unit is composed of a single motoneuron, and a variable number of skeletal myofibers innervated by a single motoneuron. The essential components of each motor unit include:

1. A motoneuron consisting of its cell body (located within the CNS, either in the cranial nerve nuclei of the brainstem, or in the ventral horns of grey matter in the spinal cord) and its peripheral axon, supported by Schwann cells;
2. Neuromuscular junctions; and,
3. Myofibers innervated by the motoneuron.



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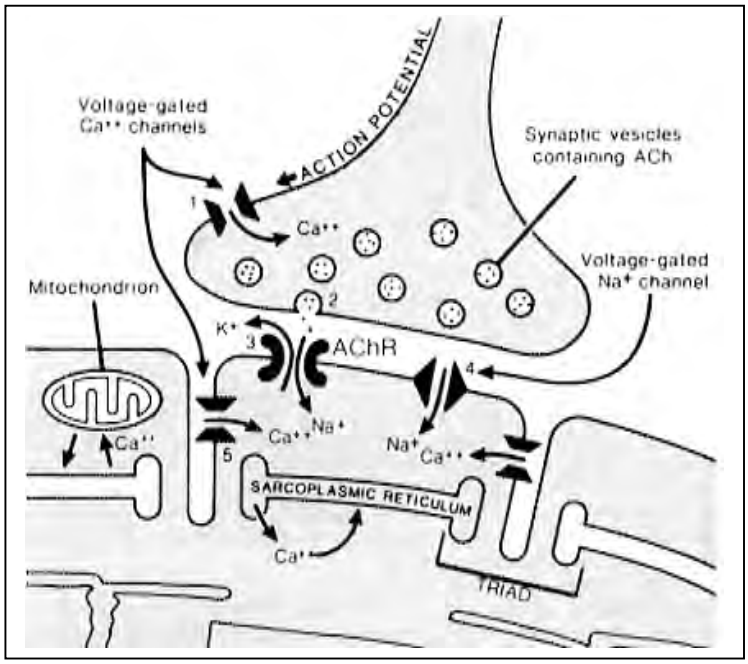
A: Sensory nerve fiber
B: Dorsal root ganglion
C: Dorsal nerve root
1: Motor neuron
2: Ventral nerve root
3. Spinal nerve
4. Plexus
5. Mixed nerve
6. Neuromuscular junctions
7. Muscle fiber

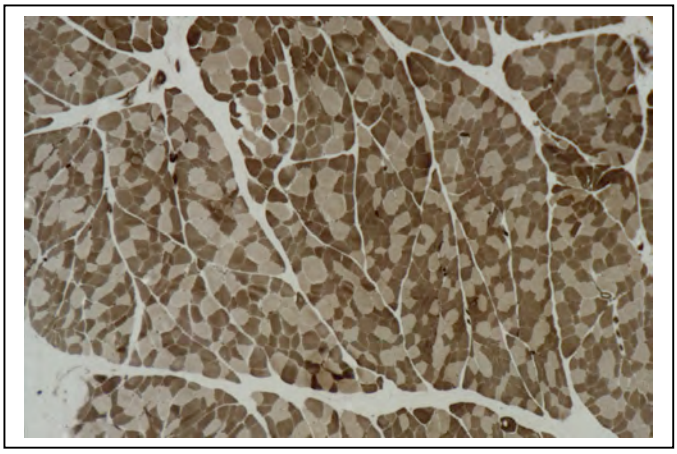


←
The arrival of impulses at the axon terminal (1) causes a calcium dependent, exocytotic release of acetylcholine (ACh) from the presynaptic axon terminals (2). This liberated ACh diffuses across the synaptic cleft to become complexed with specific ACh-receptor sites located on the postsynaptic sarcolemma (end-plate) of the myofiber. The formation of ACh-receptor complexes increases the permeability of the end-plate to Na+ and K+ ions (3), and results in a local depolarization of the end-plate, which in turn generates muscle action potentials over the entire sarcolemmal surface of each myofiber. Opening of Na+ channels (4), and Ca++ channels in the transverse tubules and sarcoplasmic reticulum(5), follows. The sudden increase in sarcoplasmic Ca++ mediates contraction of myofibrils.

The action of ACh is reversed by its diffusion away from ACh-receptor sites and its hydrolysis by acetylcholinesterase (AChE) present in the synaptic cleft. The contraction of each myofiber involves the interaction (sliding) of *actin* and *myosin* myofilaments coupled with the hydrolysis of ATP. The interaction of the actin and myosin myofilaments is modulated by the regulatory proteins troponin and tropomyosin, and the rate of their interaction (speed of shortening) is catalyzed by the activity of myosin ATP-ase.

All motor units are not alike and may vary with regard to:

1. Size (the number of myofibers innervated by a single motoneuron),
2. Histochemical properties of the myofibers, and,
3. Functional properties related to their speed of contraction and resistance to fatigue.



There are at least three and possibly five basic types of motor units based on their contractile and histochemical properties. The myofiber type composition of motor units is homogeneous. Each motor unit is composed of a single histochemical myofiber type, and not a mixture of myofiber types. Individual muscles usually are composed of a mixture of motor unit (myofiber) types, and the relative proportions of each may vary considerably between muscles. Individual myofibers of each motor unit are uniformly distributed throughout a relatively large area in a muscle and myofibers of the same motor unit rarely are contiguous. This scattered distribution results in a mosaic pattern of myofiber types within transversely sectioned and stained muscles. For a given muscle within the same species, the myofiber type composition, and mosaic distribution pattern within a muscle, appear to be reasonably constant and characteristic for that muscle.

Classification of Neuromuscular Disorders

A useful classification scheme of neuromuscular diseases is based on the anatomic motor unit components that are primarily involved in the pathogenesis of the muscle weakness. Using this classification, neuromuscular diseases are broadly subdivided into:

1. Neuropathies - disorders of the neuron, its cell body, axon, and/or Schwann cells (myelin)
2. "Junctionopathies" - disorders of neuromuscular junctions
3. Myopathies - disorders of muscle fibers
4 Neuromyopathies - disorders of both the neurons and muscle fibers.

Pathoanatomic Classification of Neuromuscular Diseases

General Classification	Motor Unit Component Involved
NEUROPATHIES	**LOWER MOTOR NEURONS**
Central:	
Motoneuron Diseases	Neuronal Cell Bodies
Peripheral:	
Axonopathies	Axons
Demyelinating Diseases	Schwann Cells
Mixed Axonal/Demyelinating	Both Axons & Schwann Cells
"JUNCTIONOPATHIES"	**NEUROMUSCULAR JUNCTIONS**
Presynaptic	Transmitter Synthesis &/or Release
Synaptic	Acetylcholinesterase
Postsynaptic	Acetylcholine Receptors
MYOPATHIES	**MYOFIBERS**
	Sarcolemma
	Transverse Tubules
	Organelles
	Myofilaments
	Inclusions
NEUROMYOPATHIES	**ELEMENTS OF BOTH MOTONEURONS & MYOFIBERS**

Clinical Signs of Neuromuscular Disorders

Dysfunction of the motor unit results in lower motor neuron signs, seen clinically as *muscle weakness*. The expression of this weakness may vary considerably, and may include: paresis/paralysis, gait abnormalities, exercise related weakness, dysphagia, regurgitation, dyspnea, and dysphonia. The distribution of involvement may be local, regional, or generalized. In addition there may be gross deformities of muscle mass (i.e., atrophy, hypertrophy, and skeletal deformities). Any patient presented with some form of clinical weakness, should be viewed as potentially having a motor unit disorder.

Clinical Signs of Neuromuscular Disorders

1. Generalized or localized muscular weakness

2. Functional manifestations:
   - Paresis/paralysis
   - Gait abnormalities
   - Exercise related weakness
   - Dysphagia
   - Regurgitation
   - Dyspnea
   - Dysphonia

3. Physical manifestations:
   - Muscle atrophy/hypotrophy
   - Muscle hypertrophy
   - Skeletal deformities

Conclusions that the patient is "merely weak because it is sick" should not be readily assumed without meticulous evaluation of the motor unit.

Cervical ventroflexion is a dramatic sign of generalized neuromuscular weakness in cats. The chin usually rests near the thoracic inlet, with the eyes positioned dorsally to maintain a straight-ahead gaze. Other common physical examination findings are a slight protrusion of the dorsal aspects of the scapulae when weight is placed on thoracic limbs, and a stiff thoracic limb gait. A crouched, wide-based stance is often seen in pelvic limbs. Possible causes to consider for this posture are: subacute or chronic organophosphate toxicity, potassium-depletion myopathy, thiamine-responsive neuromuscular weakness, hyperthyroidism, immune-mediated (idiopathic) polymyositis, myasthenia gravis, polyneuropathy, hypernatremic polymyopathy, ammonium chloride toxicity, hereditary myopathies (Burmese, Devon Rex), hypocalcemia, and portosystemic encephalopathy.

Diagnosis of Neuromuscular Disorders

Establishing a diagnosis requires an informed and coordinated approach to defining a problem list through associations and direct observations (i.e. a *diagnostic plan*).

1. Signalment, History, Physical and Neurological Examinations

   Signalment: species, breed, age, sex, use.
   History: congenital/acquired, course of complaint, response to treatment, exposure to toxins, etc.
   Findings: presence and distribution of abnormal findings on physical and neurological examinations.

2. Minimum Data Base

   Minimum data base: CBC, serum biochemistry panel, urinalysis, thoracic radiographs, and abdominal ultrasound.
   Measurement of muscle specific serum enzymes such as creatine kinase (CK,) as well as aspartate aminotransferase (AST), and lactic dehydrogenase (LDH), is very helpful in identifying neuromuscular disorders in which *myonecrosis* is a principal pathologic feature. Elevated serum enzyme activities help to differentiate myopathies from other neuromuscular disorders. Also immunologic procedures for the detection of myoglobin are becoming available, and should be a sensitive means of detecting myolysis in the future.

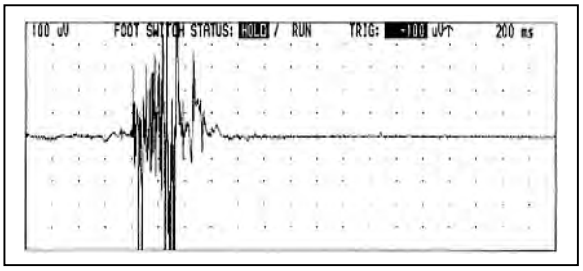
3. Specific Diagnostic Tests - Electrodiagnostic Testing

   a. Electromyography (EMG) - involves the detection and characterization of electrical activity (potentials) recorded from the patient's muscles. A systematic study of individual muscles permits an accurate determination of the distribution of affected muscles. EMG electrodes detect potentials, which are then amplified and displayed on an oscilloscope and a printed record. Potentials also are amplified through an audio amplifier to record sounds, that often have frequencies and amplitudes characteristic of certain disorders.

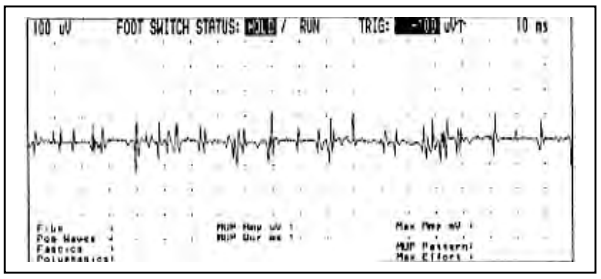
In animals, EMG examinations usually are conducted with the muscles at rest, (i.e. not contracting) and usually under general anesthesia. Under these conditions, resting potentials across muscle fiber membranes are maintained, and hence, normal muscles at rest are "electrically silent".

With depolarization of muscle fiber membranes, potentials are generated that have a wave form usually consisting of negative and positive phases. The potentials generated are evaluated for amplitude, duration, number of phases and polarity, frequency and repetition.

i) Insertional activity - brief bursts of electrical activity (potential changes) are induced by irritation of single muscle fibers caused by insertion of the EMG needles. After insertion and cessation of needle movement, normal muscles become electrically silent. Increased insertional activity (an increase in amplitude and prolonged duration) may be observed in neuromuscular diseases. Affected muscle fibers are hyperexcitable, having a lowered threshold due to diminished membrane potentials.

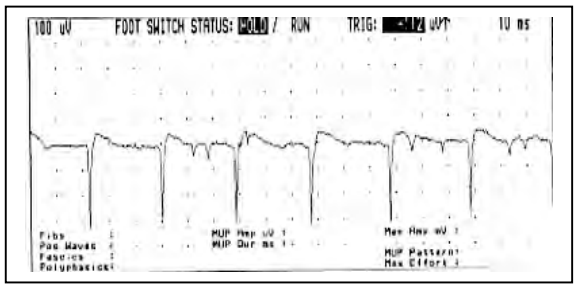


ii) Spontaneous activity - is the spontaneous generation of potentials that are independent of mechanical stimulation. Spontaneous activity is an abnormal finding. The potentials generated include muscle action potentials generated by individual fibers (fibrillation potentials and positive sharp waves), and motor unit potentials generated by fibers of a motor unit (fasciculation potentials).



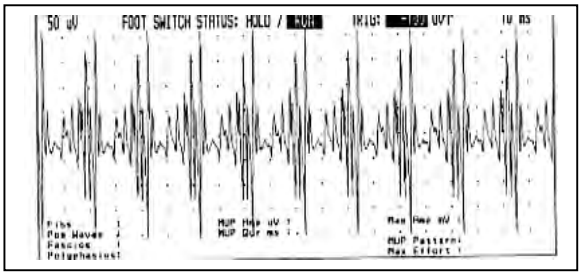
← Fibrillation potentials or “fibs”

Positive sharp wave or “sharps” →



Pronounced and prolonged spontaneous activity may be encountered in which there are repetitive, high frequency potentials generated with needle insertion, or other mechanical stimulation of muscle such as percussion (complex repetitive discharges). In myotonia, a condition of delayed relaxation of muscle fibers, there are phases of increasing amplitudes and frequencies of discharges, followed by decreasing amplitudes and frequencies, which convey the sound of diving propeller driven airplanes. These so-called "dive bomber" potentials, also are referred to as "myotonic" potentials.

When the tip of the EMG needle is placed near the end-plate region, spontaneous small amplitude (miniature) end-plate potentials ("mepp's") may be detected. These are normal potentials due to the spontaneous release of individual quanta of ACh. This activity is also referred to as end-plate "noise".



b. Motor Nerve Conduction Velocity - provides information about the integrity of nerve fibers in peripheral nerves. Recordings are conducted while the patient is anesthetized. Demyelinating disorders cause slowed conduction in peripheral nerves. Ulnar and sciatic (peroneal-tibial) nerves most often are employed for evaluation.

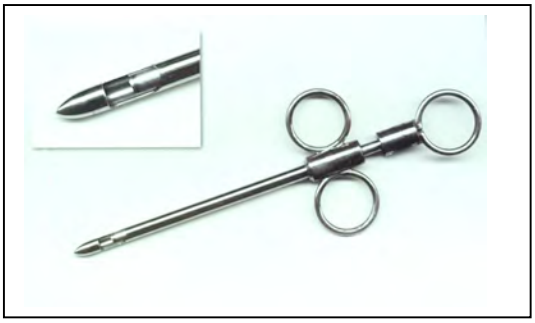
c. Evoked Potential Recordings - with repetitive nerve stimulation provides information about the integrity of neuromuscular transmission (see myasthenia gravis).

4. <u>Specific Diagnostic Tests - Nerve and Muscle Biopsy Examination</u>

These procedures provide an opportunity to evaluate the morphology of portions of the motor unit and differentiate between neuropathies, “junctionopathies”, and myopathies, and in some instances, provide a definitive diagnosis. Since general anesthesia is required for EMG examination and nerve conduction measurements, muscle biopsy procedures should be done at the same time so that a second anesthesia is not needed.

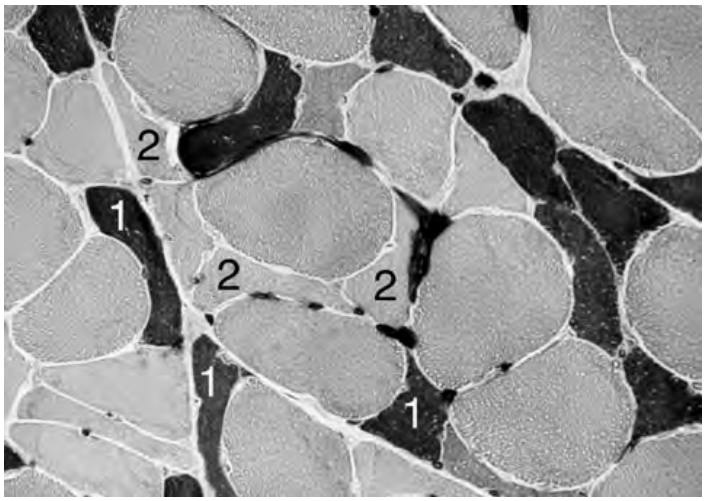
Selection of Muscle/Nerve Biopsy - EMG examination aids in identifying affected muscles/nerves for biopsy. Select involved but not "end-stage" muscle. Knowledge of normal muscle fiber type composition for muscles and species is required for biopsy interpretation.

Biopsy Procedures - special methods of handling and processing are required for proper evaluation of muscle and nerve biopsies. Fresh frozen sections and special staining techniques are essential for light microscopic studies of both muscle and nerve. In addition, special fixatives are required for electron microscopic studies of muscle as well as "teased" nerve fiber studies. Use of formalin fixation of specimens is of limited value and borders on "malpractice". "Open" biopsy techniques are preferred in small animals and "punch" biopsy techniques are preferred in large animals.



HISTOPATHOLOGICAL FEATURES OF NEUROPATHIES

1. General Features



a. Angular Atrophy. The hallmark of denervation consists of characteristic patterns of myofiber *atrophy*. Myonecrosis is an uncommon reaction to denervation. With minimal denervation, in which only a few myofibers are denervated, the denervated myofibers undergo atrophy and these atrophied myofibers tend to be *angular* in appearance. These angular atrophied type 1 and type 2 myofibers ("angular atrophy points to denervation") tend to be scattered throughout the section and they are present in many fasciculi. It appears that this sign of denervation takes several weeks to develop after the denervating event.

The angular morphology develops as a consequence of fiber atrophy occurring between normal or hypertrophied fibers. With greater involvement and progressive course, the angular atrophied fibers become more numerous and tend to occur in small groups (i.e. *small grouped atrophy*). As denervation progresses, healthy muscle fibers undergo compensatory hypertrophy. As a result, biopsies contain a mixture of very small and large fibers.

When most or all fibers in a muscle are denervated at about the same time (e.g., trauma to a muscle's nerve, avulsions, acute severe disorders such as Coonhound paralysis), all fibers undergo atrophy (panatrophy) and the angular morphology does not develop. Instead the fibers have a more uniform "puckered" or "scalloped" appearance (i.e. *large grouped atrophy*).

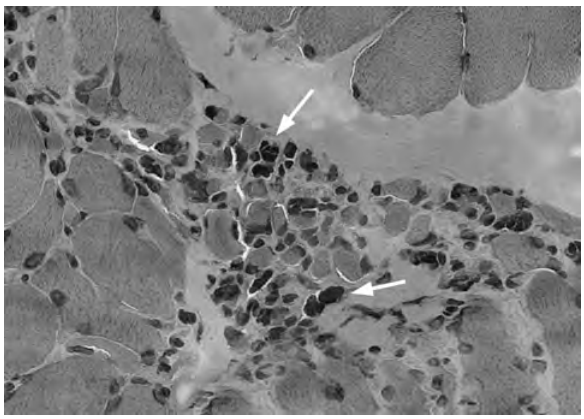
Differentiation of Neurogenic Atrophy from Other Types of Muscle Fiber Atrophy - atrophy of muscle fibers is a common, though non-specific, reaction to a variety of disease states and activity levels. As previously described, when the fiber atrophy is selective, fibers undergoing atrophy may be angular to anguloid in appearance, while in non-selective atrophy involving all/most fibers, myofibers tend to be more rounded to polygonal in shape.

i) Cachetic/Disuse Atrophy - tend to affect all fiber types resulting in a rather uniform decrease in fiber size of most fibers; however, quantitative data suggest that type 2 fibers are proportionally more affected.

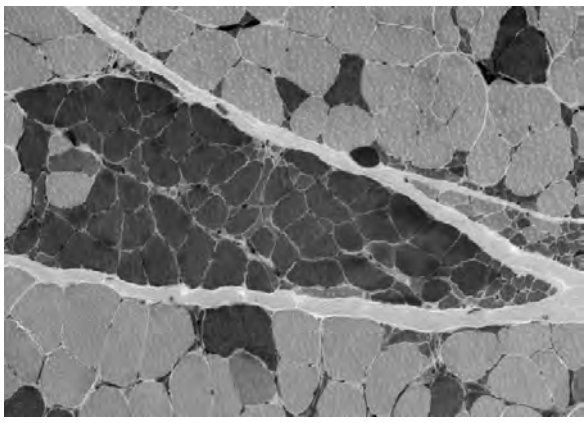
ii) Fractures/Tenotomy - shortening of a muscle's resting length secondary to trauma results in selective/preferential atrophy of type 1 fibers.

iii) Type 2 fiber atrophy - selective type 2 fiber atrophy which may be angular to anguloid develops secondarily in the presence of excess glucocorticoids. The condition is frequently referred to as steroid myopathy. This change has been seen in patients with Cushing's Disease and patients receiving long-term steroid medication for other disorders. Grossly, muscle atrophy may become severe, particularly in the muscles of mastication of dogs, and may result in profound weakness.

b. Pyknotic nuclear clumps - represent the end-stage of denervation and develops if denervated fibers are not reinnervated. These result from a drastic loss of myofibrils with clumps of myonuclei enclosed within the sarcolemma. A chronic change which takes some months to develop.



c. Myofiber Type Grouping - represents reinnervation of previously denervated muscle fibers. Collateral sprouting of surviving axons reinnervate denervated fibers. If the new axon is of a different motor unit type than the denervated fiber, the reinnervated fiber will assume the characteristics of the new motor unit (e.g., denervated fast-twitch, type 2 fibers reinnervated by axonal sprouts of slow-twitch motoneurons will convert to the slow-twitch type 1 fibers). These conversions alter the normal mosaic distribution pattern to groups of like fiber types (i.e. myo-fiber "type grouping"). Collateral sprouting and reinnervation results in the formation of larger than normal motor units. The motor unit potentials generated by these enlarged motor units are referred to as "giant" motor unit potentials. Type grouping may be thought of as the morphologic equivalent of these giant potentials. These changes take 6 months or more to develop, and they are indicative of a chronic disorder. Denervation of giant motor units results in "large grouped atrophy" in histologic sections.



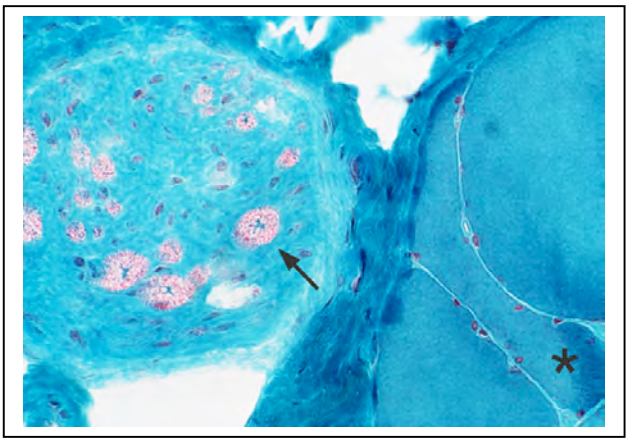
2. Special Features

a. Myofiber Type Predominance or Paucity - describes the predominance of one fiber type over another in a section. This may be normal or abnormal, depending on the specific muscle and the species of animal. In the abnormal state, this may represent an excess or a deficiency of a given fiber type. While the mechanisms for this condition are not fully understood, there are two instances in which muscles commonly have fiber type predominance/paucity.

i) Growing and Developing Muscle - the onset of neuromuscular disease, particularly neuropathies, superimposed on the early growth and differentiation of developing muscle frequently results in type 1 fiber predominance/type 2 fiber paucity.

ii) Thyroid Function - also affects the proportion of fiber types in a muscle. Hypothyroid states result in a transformation of type 2 fibers to type 1 fibers, leading to type 1 fiber predominance. Conversely hyperthyroid states result in the opposite effect (type 1 fibers transform to type 2) leading to type 2 fiber predominance. Polyneuropathies in dogs with hypothyroidism are not uncommon and biopsies from these patients often have type 1 fiber predominance.

b. Intramuscular Nerve Branches - are available for evaluation in approximately 40% of muscle biopsies. Staining techniques applicable to sections of peripheral nerve provide similar opportunities for evaluation of nerve branches in the muscle biopsy specimen.

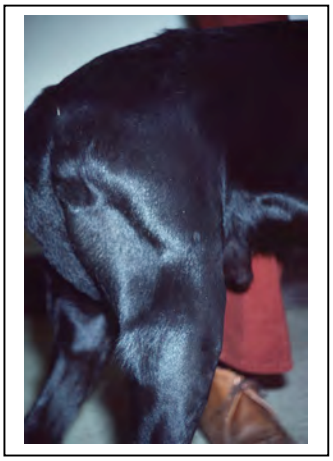


Specific Neuropathies

1. Motoneuron Disorders

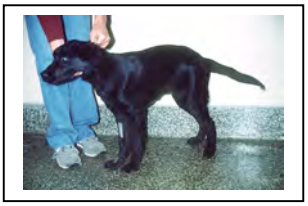
Hereditary and acquired motoneuron disorders have been described in dogs (Spinal muscular atrophy of Brittany spaniels), horses (equine motoneuron disease), and cattle.

2. Peripheral Neuropathies
   a. Mononeuropathies
   b. Multiple mononeuropathies
   c. Polyneuropathies

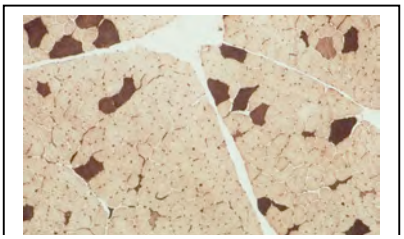


Polyneuropathies represent the single largest group of neuromuscular disorders. Many are idiopathic (i.e. our diagnostic skills are insufficient to establish etiology). Disorders include: acute and recurrent polyradiculoneuritis, metabolic (diabetes, hypothyroidism, hypoadreno-corticism, hyperinsulinism), toxic, lysosomal storage disorders (e.g., Krabbe's globoid cell leukodystrophy or galacto-cerebrosidase deficiency, and Niemann-Pick disease or sphingomyelinase deficiency).

3. Undetermined



A developmental neuromuscular disorder in Labrador retrievers ("type 2 myofiber deficiency") is characterized by type 1 fiber predominance or type 2 paucity. It is inherited as an autosomal recessive trait. Signs are first manifested by 5-7 weeks of age (weaning). The degree of muscle weakness may vary from mild to severe. Likewise the development of muscle mass varies. The disorder is largely benign, seemingly not progressive after 1 year of age, and afflicted dogs must adopt a modified lifestyle commensurate with their strength. This disorder has been referred to as a "muscular dystrophy" by some authors. However, the histopathological features are suggestive of a developmental neuropathical disorder.



HISTOPATHOLOGICAL FEATURES OF "JUNCTIONOPATHIES"

Histopathological changes usually are absent or non-specific in disorders of the neuromuscular junction. Diagnoses usually are based on biochemical, immunological, toxicological, electrodiagnostic, and/or immunological testing.

Classification of "Junctionopathies"

1. Pre-Synaptic Disorders
   a. Reduced Ach Release
      i) Hypocalcemia
      ii) Botulism
      iii) Tick Paralysis
      iv) Aminoglycoside Antibiotics
   b. Increased Ach Release
      i) Hypomagnesemia
      ii) Envenomations
2. Synaptic Cleft Disorders
      i) Cholinesterase Inhibitors
      ii) Organophosphates
3. Post-Synaptic Disorders
   a. Myasthenia Gravis
      i) Acquired
      ii) Congenital
   b. Muscle Relaxants
      i) Non-Depolarizing
      ii) Depolarizing

Specific "Junctionopathies"

1. Presynaptic Disorders
   a. Reduced ACh release - weakness induced by inability to activate sufficient numbers of ACh receptors.

      i) Hypocalcemia - exocytotic release of ACh from axon terminals is calcium ion dependent. Hypermagnes-emia causes same effect and stabilizes postsynaptic membrane as well.
      Cows - postparturient paresis (milk fever), flaccid paralysis. Principal signs referable to effects on neuromuscular transmission.
      Dogs - puerperal tetany (eclampsia). Principal signs referable to hypocalcemic effect on lowering threshold of resting membrane potential in neurons thereby causing spontaneous depolarization of neurons and overriding blockade of ACh release.

      ii) Botulism - (Clostridium botulinum) - toxin irreversibly binds to presynaptic membrane and blocks release of ACh. Results in functional denervation of all muscle fibers. Tick paralysis may be similar but is reversible upon removal of the tick.

      iii) Tick Paralysis
      Etiology & Pathogenesis

Tick Paralysis is a flaccid, afebrile ascending motor paralysis produced by a neurotoxin generated by some but not all strains of certain species of ticks. Not all infested animals become paralyzed. Cats in the U.S. appear to be relatively resistant to tick paralysis, although signs of paralysis have been reported. In North America, the common wood tick, *Dermacentor variabilis*, and *Dermacentor andersoni* (the Rocky Mountain wood tick) are incriminated most often. In Australia, especially along the east coast, *Ixodes holocyclus* is the most important species. Other species that occasionally cause paralysis are *Ixodes cornuatus* and *Ixodes hirsti*. *Ixodes scapularis*, the principal vector of the agent of Lyme disease (*Borrelia burgdorferi*) in the Northeast, Midwest, and Southeast of the United States, also may cause tick paralysis in dogs. This tick also is a primary vector of the agent of human and rodent babesiosis. *Ixodes pacificus* has also been incriminated in dogs in the Grass Valley area of northern California. In Australia, *Ixodes holocyclus* is the vector for Lyme disease and spotted fever, caused by *Rickettsia australis*. There is circumstantial evidence that some dogs bitten by *Ixodes holocyclus* develop signs of chronic illness similar to Lyme disease. With tick paralysis, adult ticks, especially females, produce a salivary neurotoxin that circulates in the host animal and interferes with acetylcholine liberation at the neuromuscular junction and/or impulse propagation along motor axon terminals. In Australia, heavy infestations with nymphs or larvae may result in paralysis.

Clinical Signs

Onset of clinical signs is gradual, paralysis first becoming evident as an incoordination in the pelvic limbs, resulting in an unsteady gait. Altered voice, cough, and dysphagia can be early signs. Dogs become recumbent in 24 to 72 hours. Reflexes are lost but sensation is preserved. Jaw muscle weakness and facial paresis may be present. Death may occur within several days from respiratory paralysis.

Diagnosis

Electromyographic studies reveal absence of spontaneous potentials and lack of motor unit action potentials. No muscle response follows direct nerve stimulation. Motor and sensory nerve conduction velocity may be slower that normal.

Treatment

Prognosis usually is good, with recovery occurring in 1 to 3 days following tick removal or dipping the animal in an insecticide solution. Administration of a systemic insecticide (e.g., cythioate, 3 - 6 mg/kg, PO) ,ay be used to kill any hidden ticks on dogs. Assisted ventilation is necessary in cases with respiratory failure.

iv) Aminoglycoside Antibiotics - inhibit ACh release (neomycin>kanamycin>gentamycin and possibly streptomycin). These antibiotics also decrease ACh sensitivity of postsynaptic membrane and are contraindicated for use in patients with postsynaptic disorders such as myasthenia gravis.

b. Increased ACh release - weakness induced by continued depolarization (hyperexcitability) of postsynaptic membrane.

i) Hypomagnesemia - grass and transport tetany of sheep and cattle. Hypercalcemia produces similar effect.

ii) Black Widow Spider Toxin - binds to presynaptic membrane and stimulates ACh release.

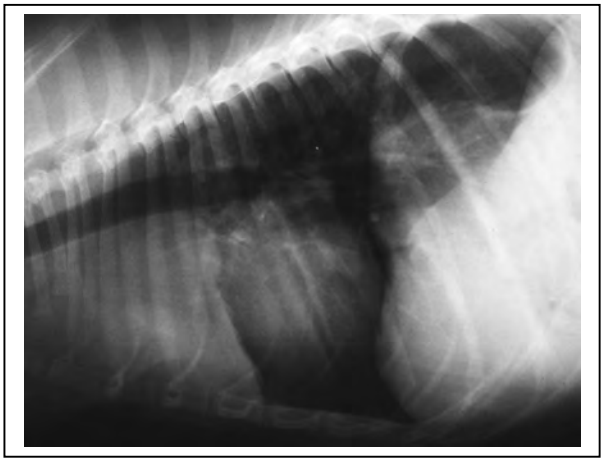
2. Synaptic Cleft Disorders

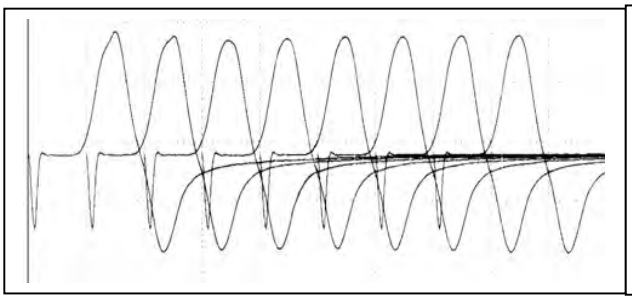
Cholinesterase Inhibitors - inhibit breakdown of ACh and thereby prolong action of ACh on postsynaptic membrane. Important pharmacologic agents include edrophonium chloride (Tensilon; ultrashort acting, minutes), pyridostigmine bromide (Mestinon; short acting, hours), and neostigmine bromine (Prostigmin; medium acting, hours).

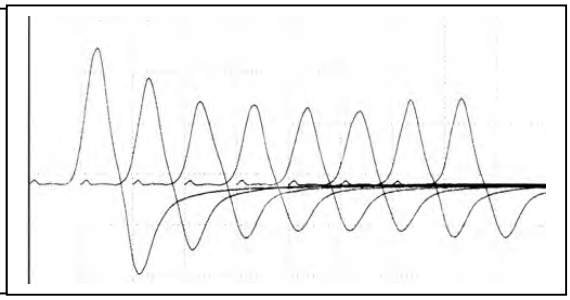
Also organophosphates commonly used in insecticides inhibit acetylcholinesterase and some intoxications may cause neuropathies as well.

3. Postsynaptic Disorders
   a. Myasthenia Gravis (MG)
      Basic lesion is a deficiency of ACh-receptors on the postsynaptic membrane. Both congenital and acquired forms of this condition occur in dogs, cats, and humans. To date, studies suggest the pathophysiology of these conditions are similar among these species.

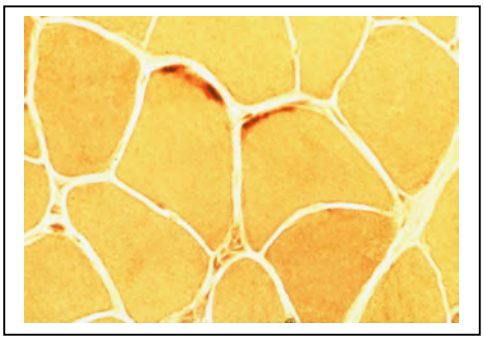
      i)Acquired Myasthenia Gravis
      Etiology & Pathogenesis
      Acquired (immune-mediated) MG is due to antibody mediated destruction of ACh-receptors. Common neuromuscular disorder in dogs. Many reports of the condition in cats. While the immune-mediated destruction of ACh-receptors is well documented, the afferent limb of this immune-mediated disorder is unknown and represents a major problem in modern biology and medicine.
      History and Clinical Signs
      Acquired MG affects numerous breeds of dog older than 1 year of age. There appears to be a bimodal, age-related incidence, with peaks at 2-4 years and 9-13 years. Signs of muscular weakness may be *focal* with selective involvement of the esophageal, pharyngeal, and facial muscles, or *diffuse*, with signs of generalized muscle weakness. In one study it was estimated that one fourth of the canine patients present with idiopathic megaesophagus, had focal MG. Signs of generalized muscle weakness may vary considerably, ranging from some intolerance to exercise, which improves with rest, to acute tetraplegia. Patients with focal or generalized signs, and megaesophagus, often present with pneumonia secondary to aspiration. Evaluation of the thorax may reveal the presence of thymoma, which may be implicated in the etiology of this immune disorder.
      Diagnosis
      Pharmacological Testing - the IV administration of 1-10mg of edrophonium chloride ("Tensilon response test"). A presumptive positive test results in transient improvement in the clinical weakness. Sometimes objective criteria for this test are difficult to establish.
      Electrodiagnostic Testing - involves recording evoked muscle action potentials during repetitive nerve stimulation at 2-10 Hz. A decline in the amplitude of successive potentials (decremental response), provides a presumptive positive test for MG. Also, single fiber EMG may be used.

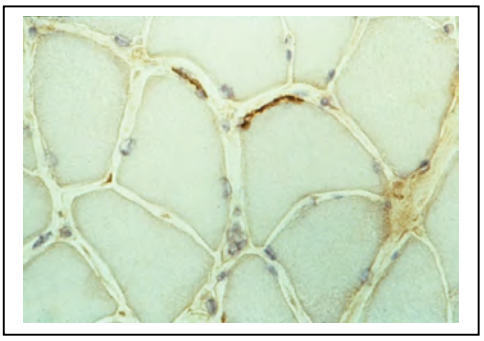






Immunological Testing - screening tests involve: a) incubating the patients biopsy with the immunoreagent SPA-HRP (Staphylococcal protein A conjugated to horseradish peroxidase), to stain for IgG localization at neuromuscular junctions, and b) incubating the patient's sera on sections from a healthy dog and subsequently incubating the section with SPA-HRP to detect fixation of circulating IgG to neuromuscular junctions. *Specific testing involves the use of an immunoprecipitation radioimmunoassay for the determination of ACh receptor antibody titers in serum ("AchRAb titers").*





Treatment

This involves improving neuromuscular transmission through the use of cholinesterase inhibitors (Mestinon, 0.5-1 mg/kg per os, BID to TID as needed) and/or suppression of the immune response with glucocorticoids, (Prednisone, 2 mg/kg BID). Monitor treatment with pyridostigmine (Mestinon) for signs of excessive cholinergic stimulation (salivation, defecation, weakness, etc.). It is not uncommon for dogs to spontaneously abort their immune response, and fully recover without treatment (spontaneous remission). This disorder in cats appears to be more difficult to manage.

ii) Congenital Myasthenia Gravis

Etiology & Pathogenesis

An hereditary disorder resulting in deficiency of Ach receptors on the postsynaptic membrane.

History and Clinical Signs

Reported in Jack Russell terriers, Springer spaniels, and Smooth Fox terriers. Onset is usually apparent at 6-8 weeks of age, with signs of generalized muscular weakness associated with exercise. Megaesophagus is not common. Weakness becomes progressively severe, leading to tetraplegia and death. Congenital MG has also been reported in cats.

Diagnosis

Pharmacological and electrodiagnostic testing only.

Treatment

Prognosis is very poor. Treatment with pyridostigmine is helpful and some animals have been maintained for 12-24 months. Genetic counselling is important since the disorder appears to be inherited as an autosomal recessive condition.

b. Pharmacologic Use of Neuromuscular Blocking Agents (Muscle Relaxants)
The effects of 2 classes of neuromuscular blocking agents commonly used as muscle relaxants during anesthesia deserve mention here.

i) Non-depolarizing agents: include d-Tubocurarine, gallamine, and pancuronium. These agents compete with ACh for the ACh-receptor. When bound to the receptor, the ion channel does not open, preventing depolarization of the membrane.

ii) Depolarizing agents: include succinylcholine and decamethonium. These agents compete with ACh for the ACh-receptor. When bound to the receptor the ion channel opens, causing depolarization of the membrane.

HISTOPATHOLOGICAL FEATURES OF MYOPATHIES

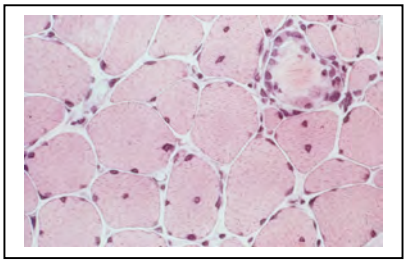
In small animals, myopathies are relatively uncommon and encountered less frequently than neuropathies and junctionopathies, while the converse generally is true in large animals. Myopathies may be subdivided into *non-inflammatory* and *inflammatory* myopathies.

Classification of Myopathies

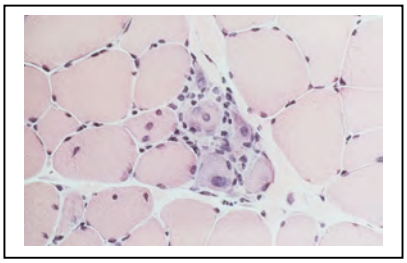
1. Non-Inflammatory Myopathies
   a. X-linked Muscular Dystrophy
   b. Metabolic Muscle Disorders
      i) Malignant Hyperthermia
      ii) Myotonia
      iii) Glycogen Storage Disorders
      iv) Lipid Storage Myopathies
      v) Electrolyte Myopathies
      vi) Mitochondrial Disorders
2. Inflammatory Myopathies
   a. Masticatory Muscle Myositis
   b. Polymyositis
   c. Dermatomyositis
   d. Protozoal Myositis
3. Idiopathic Myopathies
   a. Fibrotic Myopathy
   b. Infraspinatous Contracture
   c. Myositis Ossificans
4. Neoplastic Myopathies

1. Non-Inflammatory Myopathies

Non-inflammatory myopathies are relatively uncommon.



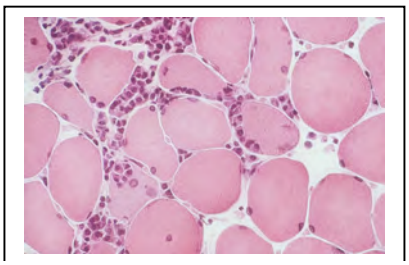
The histopathological changes in non-inflammatory myopathies usually involve the spectrum of myonecrosis, phagocytosis, and regeneration, *in which the degree of cellular infiltration is proportional to the extent of myonecrosis present*, and its distribution is largely limited to necrotic fibers.



Macrophages constitute the principal cell type.

Central nuclei are common.

In chronic myopathies there may be a mixture of atrophied and hypertrophied fibers, with their morphology being more "anguloid" than angular, and increased endomysial connective tissue.



Occasionally necrotic fibers may be calcified.

All these changes are relatively non-specific and secondary to agents that result in myonecrosis. In metabolic myopathies the

fibers frequently contain storage products that appear as vacuoles.

a. X-Linked Muscular Dystrophy of Dogs and Cats

Etiology and Pathogenesis

This is an hereditary myopathy in which there is a deficiency of dystrophin, a cytoskeletal protein associated with the inner surface of the sarcolemma. The pathobiology of this disorder appears to be identical to Duchenne muscular dystrophy, affecting young male children. The condition also occurs in mice.

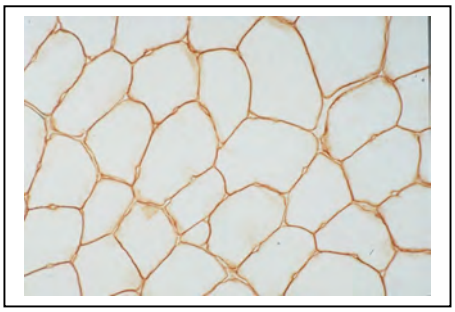
History and Clinical Signs

The disorder is best characterized in Golden Retrievers. Other breeds of dog affected include Rottweilers, Samoyeds, and possibly Irish Terriers. In cats it has been documented in domestic short hair cats. In dogs the disorder usually is recognized between 8 and 10 weeks of age. Signs may include generalized weakness, a stiff-limbed, short strided, shuffling gait, some reduced mobility of the jaws, and difficulty with chewing and swallowing associated with excess salivation. The weakness and signs are progressive, with poorly developed muscle mass, body stature, and spinal curvature. In advanced stages some muscle groups may appear grossly hypertrophied. Cardiac muscle may also become involved.

Recognition of this disorder in cats is more recent and the findings are similar to those in dogs. While the onset is likely similar to that in the dog, reported cases have been somewhat later in onset, 5 to 25 months of age. *Gross hypertrophy of the tongue and diaphragm have been a common finding in cats.*

Diagnosis

These include serum CK, which may be elevated to 300 times normal; EMG examination which reveals repetitive, high frequency discharges; and muscle biopsy examination which reveals multifocal areas of necrosis, necrosis and phagocytosis, and regeneration. In the latter stages, muscle fiber hypertrophy and fiber splitting is common along with fibrosis.



Specific information is provided through the use of immunocytochemical staining techniques to detect dystrophin (or lack thereof) in sections and/or the muscle may be assayed for the presence of dystrophin.

Treatment/Prognosis

Currently there is no cure and lifespan is shortened due to secondary complications. Future research advances in this area will have widespread benefits for both animals and humans.

b. Metabolic Muscle Disorders

These are relatively uncommon disorders of carbohydrate, lipid, and oxygen metabolism that generally induce muscle weakness by supplying insufficient energy (ATP) to sustain muscle contraction, and other cellular functions with a high energy requirement (e.g., maintenance of active transport and ion gradients across the cell membrane).

i) Malignant Hyperthermia

Etiology & Pathogenesis

Malignant hyperthermia (MH) is a life-threatening hypermetabolic and contractile condition that is triggered in humans, pigs, dogs and cats by certain anesthetic agents (e.g., halothane and succinylcholine). The underlying defect in calcium (Ca) homeostasis occurs at the level of the skeletal muscle sarcoplasmic reticulum where there is hypersensitive and heightened ligand-gating of the Ca-release channel. The Ca channel is readily opened by certain drugs, such as caffeine and halothane. Caffeine- or

halothane-induced muscle contracture develops as a result of sustained increase in cytoplasmic Ca levels and subsequent activation of the actin-myosin contractile proteins. In addition, calcium uptake is reduced. The continuous contraction results in depletion of glycogen stores, hypoxemia, and accumulation of heat, hyperkalemia, lactic acid, and metabolic and respiratory acidosis. In people, as a consequence of severe muscle necrosis, CK levels may rise 100-fold and myoglobinuria and disseminated intravascular coagulation may occasionally occur, which may lead to renal failure. Recent reports in dogs and horses indicate that malignant hyperthermia in these species is caused by a mutation in the gene encoding the skeletal muscle calcium release channel (RYR1), similar to that found in pigs and humans.

Clinical Findings

Malignant hyperthermia has been reported in various breeds of immature and mature dogs: St. Bernard, Border Collie, Labrador Retriever, Pointer, Spaniel, Greyhound and animals crossbred with Doberman Pinscher. MH in some colony-bred dogs is inherited as an autosomal dominant trait. Dogs susceptible to MH may be nervous and difficult to handle. Their muscles may be hypertrophic with greater than normal muscle tone and strength. Resting body temperature may be high normal or slightly above and serum CK and aspartate transaminase levels may be mildly elevated. While Greyhounds are often reported with MH, some studies indicate they may not be specifically MH susceptible. MH has been reported only sporadically in cats.

Reports of MH in dogs and cats are most often associated with halothane anesthesia. It should be noted that this disorder does not always occur during the first exposure to halothane anesthesia. Clinical signs can include hyperthermia, tachycardia, tachypnea, severe limb rigidity, and trismus, followed by respiratory and cardiac arrest. In some animals, extreme trismus and generalized muscle rigidity occur immediately after death. Succinylcholine and enflurane, but not methoxyflurane, have also been implicated as triggers of MH in the dog. A MH-like episode was reported in a 5 year old Greyhound anesthetized with thiamylal sodium and also given lidocaine for premature ventricular contractions. In another adult Greyhound, two episodes of malignant hyperthermia occurred at 20 and 44 hours post-surgery following anesthesia with fentanyl-droperidol and sodium pentobarbital.

Diagnosis

Histopathological features in skeletal muscle tend to be fairly non-specific and include fiber size variation, fiber hypertrophy, and increased numbers of internal nuclei in muscle cells. Occasional perivascular infiltrates of lymphocytes with infrequent perimysial and epimysial neutrophils have also been noted. In some patients, muscle biopsies are normal. Ultrastructurally, there may be loss of mitochondria, presence of moth-eaten fibers, cores, and Z-line streaming. Cardiac histomorphometric parameters are normal in MH-susceptible dogs.

Diagnosis of fulminating MH can be suggested by historical data relating to breed or colony susceptibility, and by development of characteristic clinical signs while under or following (see above) anesthesia. Signs may occur after 30 to 300 minutes of halothane exposure.

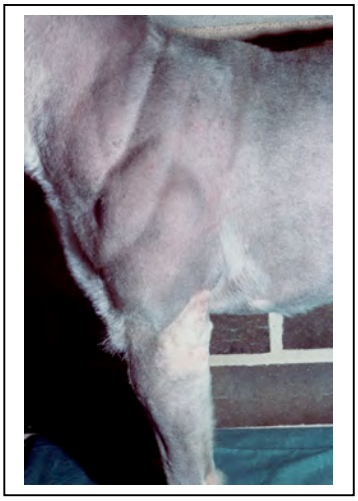
Treatment

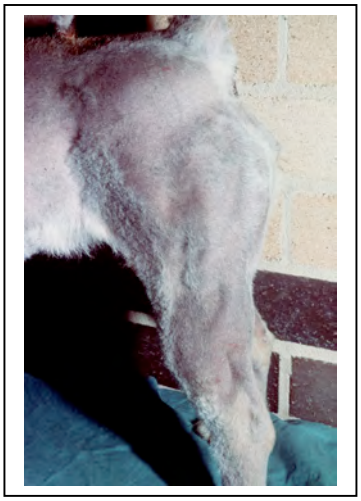
Prognosis is guarded. Removal of triggering agents and treatment of clinical signs (total body cooling, corticosteroids, sodium bicarbonate, intravenous fluids) usually are ineffectual in reversing MH episodes, although hyperventilation with 100% oxygen, stomach lavage with iced water, body surface cooling, and IV administration of cold isotonic saline solution was successful in one report. Dantrolene is the drug of choice for treating affected animals.

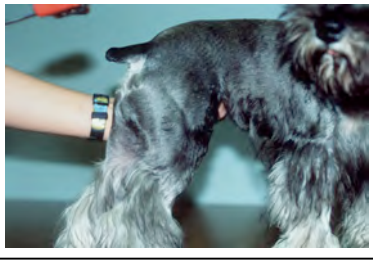
In instances where MH is suspected, susceptible animals can safely undergo anesthesia if triggering agents are avoided. Screening tests for animals susceptible to MH include caffeine/halothane-contracture tests (CCT), erythrocyte osmotic fragility test (EOFT), lymphocyte Ca test, and biochemical tests for defective Ca-transport in sarcoplasmic reticulum isolated from skeletal muscle. Several reports have noted that the initial sign of

a MH episode was a rapid increase in end tidal partial pressure of carbon dioxide before any increase in rectal temperature or muscle tone.
It is now established that the Ca channel may also be triggered by stressors such as excitement, fighting for dominance, and sudden increase in ambient temperature in pigs, and by exercise, in dogs. This *exercise-induced hyperthermia* has been termed "canine stress syndrome" and has been reported in several breeds including an English Springer Spaniel and a Greyhound. In susceptible dogs, the stress of moderate exercise can cause a reversible MH-like syndrome characterized by hyperthermia (e.g., 42ºC), muscle cramping, dyspnea (labored stertorous breathing), panting (e.g., respiratory rate > 200 breaths/minute), hemoconcentration, hyperlactemia, respiratory alkalosis, and raised levels of muscle enzymes. *Similar findings have been reported in Labrador Retrievers following strenuous exercise*. Dogs with the exercise-induced hyperthermia are clinically normal but reportedly have a hyperactive temperament. Absence of myoglobinuria rules out a diagnosis of exertional rhabdomyolysis. Hypercontracted myofibers have been observed in muscle biopsies. Recovery can be relatively rapid (e.g., within 30 minutes of rest) and this condition may represent "mild aborted malignant hyperthermia". A suggested diagnostic protocol for animals with canine-stress syndrome includes exercise/challenge testing, EOFT, and serum CK levels. In susceptible animals, CCT and EOFT are not always positive . The halothane-challenge test is likely risk prohibitive. Note that in dogs with exercise-induced hyperthermia, administration of dantrolene prior to exercise may not prevent the stress syndrome occurring.

ii) Myotonia

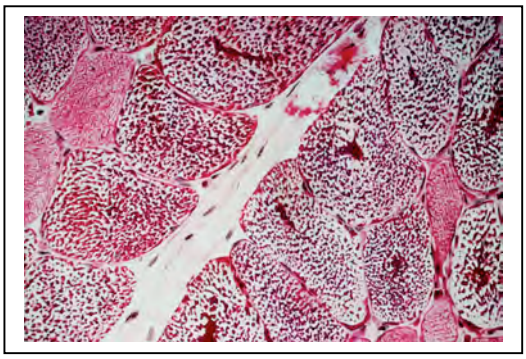






Myotonia is a disorder in which there is sustained (tetanic) muscle contraction associated with repetitive depolarization of muscle fibers. In affected individuals, the is involuntary contraction of a muscle that persists after voluntary movement or stimulation. Congenital myotonias occur in goats, dogs, (Chow Chow, Cocker spaniel, miniature Schnauzer, Labrador retriever, Samoyed, Staffordshire terrier, West Highland white terrier), horses, cats and humans. The main defect is an *altered chloride conductance*, associated with a genetic defect in the chloride channels of the t-tubules. Low membrane chloride conductance and accumulation of potassium in the tubular system may cause post-excitement depolarization of the muscle membrane and continued contraction of the muscle. Clinical signs include abnormal stiff gait, abduction of forelimbs, muscle hypertrophy and a characteristic myotonic dimple which persists for 30-40 seconds after direct muscle stimulation (tongue or shaved limb). EMG findings include high-frequency myotonic discharges with continuous insertional activity and possible decremental response. Nerve conduction velocity is normal and muscle biopsy variable (hypertrophy, atrophy

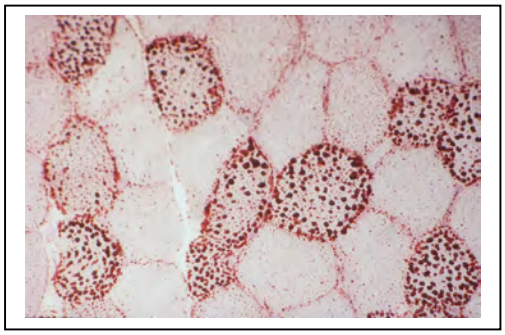
and degeneration). There is no treatment for the disease other than avoiding prolonged exercise. The disease is not progressive.



iii) Glycogen Storage Disorders

- Type II: amylo-1,4-glucosidase (acid maltase) deficiency, reported in cattle, Swedish Lapland dog, Japanese quail, and sheep. A lysosomal storage disorder. Excess glycogen accumulation in skeletal and cardiac muscle as well as CNS.
- Type IV: a-1,4-glucan transferase and a-1,6-glucosidase (debranching enzyme) deficiency has been reported in dogs and cats with diffuse organ involvement.
- Type V: myophosphorylase deficiency has recently been reported in Charolais cattle. Affected calves exhibit exercise related weakness and muscle cramping with exercise.
- Type VII: Phosphofructokinase deficiency reported in Springer spaniel dogs. Hemolytic episodes are predominant signs.
- Polysaccharide Storage Myopathy (PSSM) - in horses with recurrent episodes of muscle stiffness and myoglobinuria. Has appearance of glycogen storage disorders described in other species, but specific enzyme deficiency has not been documented to date.

iv) Lipid Storage Myopathies



Sporadic cases have been reported in dogs with lipid storage in type 1 fibers. In humans, carnitine deficiency results in lipid storage within type 1 fibers. Carnitine serves as a carrier molecule for long chain fatty acid transport through the inner mitochondrial membrane for subsequent beta oxidation in the mitochondrial matrix. While a similar pattern of lipid storage occurs in dogs, carnitine deficiency has not been established as a cause.

v) Electrolyte Myopathies (Periodic Paralyses)

Abnormalities of potassium metabolism involving both *hypo- and hyperkalemic states*, frequently result in accumulation of fluid filled vacuoles. Hypokalemic periodic paralysis is not well documented in animals, but has been occasionally seen in association with "downer" cows.

• Potassium Depletion Polymyopathy of Cats

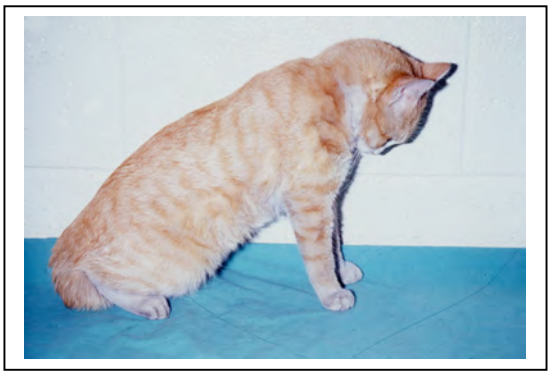
Etiology and Pathogenesis

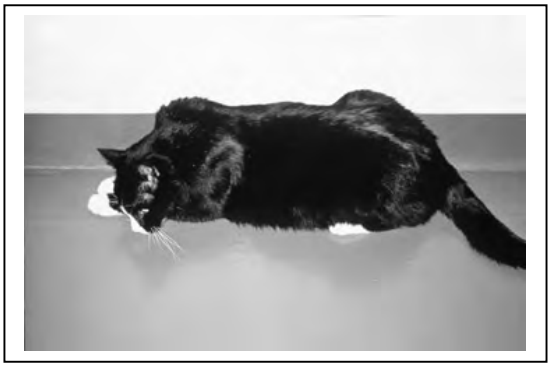
Hypokalemic myopathy is a metabolic disorder of older cats that has been linked with chronic renal disease and excessive urinary potassium loss. Synonyms are feline kaliopenic polymyopathy-nephropathy syndrome, and sporadic feline hypokalemic polymyopathy. Low dietary potassium intake secondary to inadequate potassium levels in certain commercial rations has been associated with episodic hypokalemic myopathy. Additionally, potassium urinary loss may be exacerbated by some diets that are acidified to reduce development of crystalluria and urolithiasis. It has been suggested that increased potassium loss induced by renal dysfunction may represent a phenomenon peculiar to cats. Furthermore, chronic potassium depletion (e.g., from deficient rations) may lead to progressive renal disease (associated with renal ischemia, increased renal ammoniagenesis, activation of the alternate complement pathway, and tubulointerstitial

injury) as well as sudden changes in muscle membrane sodium permeability. Decreased extracellular potassium levels will produce an increase in resting membrane potential, resulting in a greater difference between resting and threshold potential necessary for muscle contraction. This lessened state of electrical excitability underlies the muscle weakness. Additionally, hypokalemia may negatively affect insulin release and end-organ sensitivity to insulin. Other causes of hypokalemia include gastrointestinal loss of potassium, post-obstructive diuresis following relief of urethral obstruction in cats, administration of loop or thiazide diuretics, and rarely, mineralocorticoid excess.

History and Clinical Signs

Clinical signs are characterized by acute onset of a stiff-stilted gait, reluctance to walk, exercise intolerance, ventroflexion of the neck, and muscle pain. Spinal reflexes may be depressed.





Diagnostic Tests

Serum CK levels are moderately to markedly elevated, while serum potassium values are low (e.g., < 4.0 mEq/L). Serum creatinine levels may be markedly increased. Mild, diffuse electromyographic changes have been recorded in various skeletal muscles. Light microscopic evaluation of muscle samples is usually normal, although myofiber vacuolation and mild myonecrosis occasionally may be observed. Rhabdomyolysis in severe hypokalemia might be related to osmotic expansion of cells due to increased intracellular sodium and chloride levels or reflect ischemic myonecrosis due to decreased muscle blood flow associated with impaired potassium metabolism during muscle contraction/exercise.

Treatment

Prognosis is guarded to favorable and may depend upon the severity of the underlying renal disease, if present. Most cats reportedly show significant improvement in muscle strength within 2 to 3 days of initiation of treatment. Oral potassium supplementation (e.g., potassium gluconate - Tumil-Ktm, Daniels Pharmaceuticals), at 5 to 10 mEq/ cat /day, divided bid, is recommended for severely hypokalemic cats. For less severely affected animals, 2 to 4 mEq/day is usually adequate. Permanent daily supplementation with regular re-evaluation of serum potassium, serum creatinine, and urinary potassium loss is recommended, since cats that are not supplemented have a tendency to become hypokalemic again.

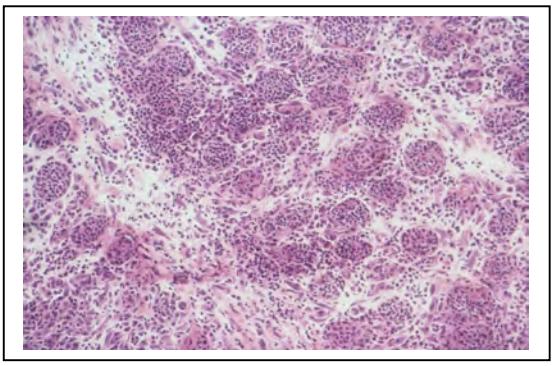
[Note. A second type of hypokalemic myopathy has been reported in young *Burmese kittens*, 2 to 6 months of age, although the disorder has also been reported in a 2 year old Burmese cat. This condition is considered to be a homozygote recessive hereditary disease and is characterized by periodic muscle weakness and ventroflexion of the neck

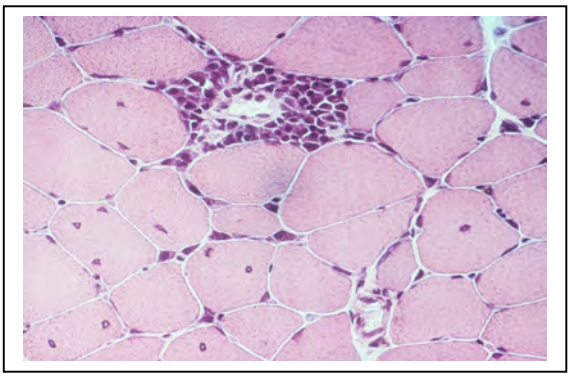
associated with intermittent hypokalemia (e.g., < 3.0 mE/L) and increased serum creatine kinase values, sometimes reaching very high values, e.g., > 50,000 - 90,000 IU/L. The condition has also been termed periodic hypokalemic myopathy. Attacks occur suddenly and are transient and may be precipitated by stress or vigorous exercise. The variable clinical course is characterized by improvement followed by relapse, and there may be weeks between episodes. A head tremor is seen in some cats. Cats are reluctant to walk and tire easily, have a stiff, stilted gait with thoracic limb hypermetria, and a wide-based stance in the hind limbs. Carpal knuckling can be a distinctive clinical feature and some cats sink on their hocks. There are only minor electromyographic and histopathologic changes seen in muscle. Neither decreased potassium intake nor increased renal potassium loss have been found in affected Burmese cats. Continued dietary supplementation of oral potassium usually produces a favorable response (e.g., potassium gluconate solution at 2 to 4 mEq or mmol/cat PO daily, until serum potassium levels are stable) [133]. Some kittens improve without treatment. The periodic hypokalemic attacks in these cats are similar to those seen in humans with hypokalemic periodic paralysis, an inherited calcium channelopathy disorder associated with abnormal muscle membrane excitability and influx of potassium into the muscle fiber that causes muscle fiber depolarization and inexcitability.]

• Hyperkalemic Periodic Paralysis (HYPP)
This is an autosomal dominant disorder of humans and horses (Quarter Horses, Appaloosas and Paints), in which episodes of weakness, muscle fasciculations, myotonia, and recumbency develop in association with hyperkalemia (5.0 to 11.0 mEq K+/L; normal = 3.0 to 4.0 mEqK+/L). Attacks occur following diet changes, fasting, stress, alfalfa consumption and the consumption of other high potassium diets. Muscles are hyperexcitable due to an increase in permeability to sodium ions as a result of an abnormality of voltage-gated sodium channel alpha-subunits of the sarcolemma. The condition appears to be analogous to the human disorder, which is due to a single base pair change in the sodium ion channel gene. The physiological defect appears to be impaired inactivation of the sodium channel. Molecular diagnostic methods are now available. Muscle biopsy changes include vacuolar changes.

vi) Mitochondrial Disorders
Mitochondrial disorders appear to be rare. However, a deficiency of Complex I respiratory chain enzyme has been documented in an Arabian horse with exercise intolerance. Lactic acidosis develops in response to exercise. Also, a recent case of lactic acidosis has been described in an Old English Sheepdog. More details and characterization of these metabolic problems likely will be forthcoming over the next few years.

2. Inflammatory Myopathies





The inflammatory myopathies possess many of the changes described for non-inflammatory myopathies. However, in addition, they are characterized by a *disproportionate number of infiltrating cells* that may include lymphocytes/plasma cells, polymorphonuclear leukocytes and/or eosinophils in addition to macrophages. In these disorders, the cellular infiltrates comprise an integral part of the disorder's pathogenesis and not merely a secondary response to cell death.
The infiltrating cells often have a *perivascular distribution*.
Identification and characterization of the infiltrating cell type assists in the definition and recognition of these disorders.
The use of the term "*myositis*" is reserved for inflammatory myopathies. Inflammatory myopathies may be caused by infectious or immune-mediated disorders.

a. Masticatory Muscle Myositis
Etiology and Pathogenesis
An inflammatory muscle disorder limited to the muscles of mastication in dogs. Muscles of mastication in dogs are composed predominantly of 2M fibers, which differ from the 2A fibers in limb muscles. Type 2M fibers are selectively affected in this disorder. Old literature refers to this condition as "eosinophilic" and/or "atrophic" myositis. An immune response has been identified in which antibodies are selectively produced against type 2M fibers. Masticatory muscles are antigenically different from other skeletal muscles and autoantibodies have been demonstrated that are specifically directed against the fiber proteins found in masticatory muscles. The afferent limb of the immune response has not been determined.
History and Clinical Signs
The disorder may be acute or chronic. Acute onset usually presents with bilateral swelling of the temporalis and masseter muscles, and possibly exophthalmia, due to swelling of the pterygoid muscles. It usually affects large-breed dogs, with no age or gender predilection. Affected dogs may be febrile with conjunctivitis, enlarged lymph nodes, tonsils, and splenomegaly.

Trismus frequently is present, and patients exhibit pain when jaws are manipulated and mouth opening is attempted. Onset may be insidious or acute. Repeated acute bouts may occur. Dogs present with masticatory muscle atrophy, that may be severe, leaving the patient with a "skeleton-like" appearance to the skull .
Diagnostic Tests
These include measurement of CK; however, elevations may be modest, due to limited involvement of masticatory muscles. EMG examination helps define distribution of involvement, but may be difficult to perform in severely atrophied muscles. Muscle biopsies

detect lesions and presence of IgG in type 2M fibers while serologic testing confirms presence of circulating antibodies against 2M fibers.

Treatment

Directed to suppression of the immune response with glucocorticoids. Long-term medication may be needed to maintain remission.

b. Polymyositis

Etiology & Pathotgenesis

Polymyositis is a relatively common myopathic disorder in dogs, but less common in cats. It has been suggested that polymyositis, masticatory myositis and other clinical variations, such as pharyngeal-esophageal and focal appendicular myositis, may represent different clinical and pathological expressions of a single primary muscle inflammatory disease. The cause of polymyositis in dogs is not always known, although the responsiveness of the disease to immunosuppressive therapy suggests that the pathogenesis is immune-mediated. In people with polymyositis, the pathogenesis appear to involve cell-mediated immune mechanisms, with the inflammatory cells being mainly CD8+ T cells. Polymyositis has been reported in dogs with specific autoimmune diseases, including systemic lupus erythematosus, primary lymphocytic thyroiditis, and immune-mediated polyarthritis. Furthermore, it has been seen as an autoimmune paraneoplastic complication of thymoma, usually accompanied by myasthenia gravis. Polymyositis and myasthenia gravis also have been reported in a dog following fetal liver transplant and immunological mechanisms were considered to be involved. Polymyositis also is a feature of dermatomyositis in Collie dogs and Shelties, another suspected immunological disease.

Clinical Signs

Clinical signs are variable and usually are observed in larger breed, mature adults of either gender; however, there are reports in younger animals, including two 7 month old littermates. Onset of signs may be acute or chronic. Signs may include acute vomiting and excessive salivation, weakness of gait with rapid fatigue, megaesophagus, dysphagia, shifting lameness and/or stiffness of gait, muscle swelling and/or pain, pyrexia, muscle atrophy, voice change and depression. Some dogs show signs of cervical ventroflexion. Neurological examination usually is normal.

Diagnosis

Early in the disease, serum levels of CK, aspartate aminotransferase, alanine aminotransferase may be elevated but may not reflect the severity of clinical signs or the underlying muscle pathology. Total serum protein may be elevated associated with increased β- and γ-globulin fractions. Some animals have positive antinuclear antibodies and circulating anti-muscle antibodies. Electrodiagnostic changes include polyphasic motor unit potentials, positive sharp waves, and fibrillation potentials. Motor and sensory nerve conduction velocities are normal. Histopathological findings in skeletal muscle (appendicular and masticatory) are focal/multifocal or diffuse myonecrosis, phagocytosis and lymphoplasmacytic cellular infiltrates, endomysial/perimysial fibrosis, considerable fiber size variation, and areas of fiber regeneration. Rarely, eosinophilic cells may predominate. Deposition of immunoglobulin G (but not C3 component) on sarcolemmal membranes has been demonstrated. In dogs with polymyositis associated with leishmaniasis, IgG immune complexes are detected in muscle samples. Diagnosis is based on clinical signs, increased serum levels of muscle enzymes, electromyographic abnormalities, and histopathological evidence of muscle necrosis and inflammatory cell infiltrates. Not all of these criteria may be

found in any one animal. Diagnosis is definite if all criteria are present, probable if three are present, and possible if two are found. Muscle enzyme activity is an unreliable index of polymyositis.

Treatment

Prognosis usually is favorable for animals with polymyositis, provided inhalation pneumonia is not a complication, and severe damage has not occurred in esophageal and laryngeal muscles. The disease usually is responsive to corticosteroids, e.g., prednisolone at 1 to 3 mg/kg PO sid or bid. The dose is reduced after remission and gradually withdrawn using alternate day therapy. In some instances, long-term therapy for 12 months or longer may be required. Azathioprine may also be used in combination with corticosteroids and has a steroid-sparing effect. Repeated clinical episodes are not uncommon. A fentanyl patch (25 - 50 mg/h) for pain relief during the first 2 to 3 days has been recommended. Prognosis is guarded in animals with thymoma because of the potential for malignancy and occurrence of other non-thymic tumors.

[Note. Feline Idiopathic Polymyositis

An acquired diffuse inflammatory disorder of feline skeletal muscle that is suspected to have an immune-mediated basis has been described in cats. In one report, three of eleven cats with thymoma were confirmed to have an associated polymyositis. Feline idiopathic polymyositis is similar in many respects to canine idiopathic polymyositis. Affected cats are 6 months to 14 years of age, and exhibit a sudden onset of weakness with pronounced cervical ventroflexion, an inability to jump, and a tendency to sit or lie down after walking short distances. Apparent muscle pain may be evident in some affected cats. Feline idiopathic polymyositis is suspected based on clinical findings, elevation of serum CK, and multifocal abnormal EMG findings. Muscle biopsy is the key to diagnosis, revealing myofiber necrosis and phagocytosis, myofiber regeneration, variation in myofiber size, and mononuclear cell (lymphocytes and macrophages) infiltration. These alterations are more severe than the mild myonecrosis reported in cats with hypokalemic polymyopathy. Serum titers for *Toxoplasma gondii*, and tests for FeLV and FIV, may be evaluated in cats suspected to have idiopatic polymyositis. Spontaneous remission or recovery has been observed in some cats with idiopathic polymyositis. Some affected cats may be hypokalemic, making differentiation from hypokalemic polymyopathy difficult. Correction of hypokalemia (if present) is recommended prior to proceeding with an extensive workup for feline idiopathic polymyosistis. If an infectious cause of the polymyopathy cannot be identified, glucocorticoids should be administered (prednisone 4-6 mg/kg/day initially and tapered over 8 weeks). Several authors have recommended administration of clindamycin (12.5 to 25 mg/kg PO BID) for seven days prior to the initiation of immunosuppressive therapy. These authors state that if dramatic improvement is observed, a presumptive diagnosis of *T. gondii* myositis should be made, and that clindamycin should then be continued for four to six weeks in the absence of glucocorticoids. The prognosis for idiopathic polymyositis in cats that do not have megaesophagus generally is good. Long-term glucocorticoid administration may be necessary in some cats.]

[Note. Extraocular Myositis

This condition has been reported in dogs aged between 6 months and 3 years. It appears to be more often reported in Golden Retrievers, but other breeds include Doberman Pinscher,

German Shepherd and mixed-breed dogs. Male and female dogs may be affected. The dominant clinical sign is acute bilateral exophthalmos, although unilateral involvement has been noted. Clinically, abnormalities are restricted to the extraocular muscles with sparing of the masticatory muscles and limb muscles. An immune mechanism directed against specific muscle fiber antigens in the extraocular muscles is suspected. EMG studies reveal presence of fibrillation potentials and positive sharp waves. Fine needle aspirate biopsies can be diagnostic. Oral corticosteroid therapy for two weeks usually results in complete resolution of signs. Relapses may occur but usually respond well to a second treatment. Surgical correction may restore eye position and vision in dogs with restrictive strabismus.]

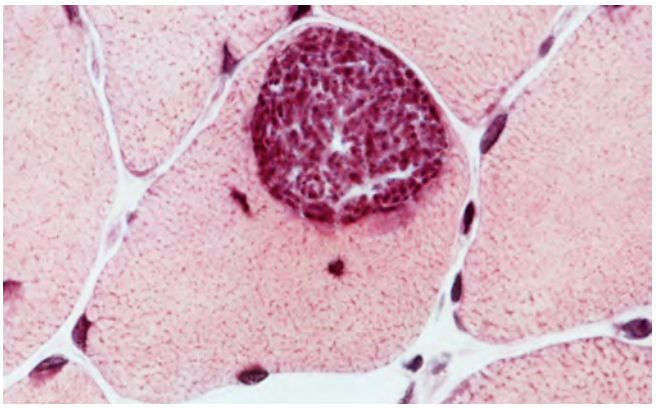
c. Dermatomyositis

Dermatomyositis occurs as a familial disorder in Collies, and possibly Shetland Sheepdogs. Dermatitis involves the face, ears, and distal extremities. Muscle lesions have been described in muscles of mastication and distal limb muscles.

d. Protozoal Polymyositis

Etiology and Pathogenesis

Toxoplasma gondii is the most common cause of infectious myositis. Neospora caninum causes similar signs and may have been called toxoplasmosis in the past. Both organisms tend to cause more severe signs in very young animals and have an increased likelihood of causing signs in immunosuppressed animals. Toxoplasmosis often is associated with canine distemper infection whereas neosporosis most often is not associated with concurrent infection.



History and Clinical Signs

Gait abnormalities are present and include a hopping gait, progressive pelvic limb paresis, rigid extension of the pelvic limbs (progressive ascending paralysis is more common with neosporosis), initially severe muscle pain, and atrophy as the disease progresses. Stupor, seizures, and chorioretinitis may occur with CNS disease.

Diagnostic Tests

Creatine kinase is elevated in the active phase of the disease. Histopathological changes in muscle include: pronounced fiber atrophy, severe multifocal necrosis, mononuclear granulomatous inflammation, and severe interstitial fibrosis in chronic cases. The presence of organisms, free or in cysts, is definitive, but these are not always found. Single antibody titers are not diagnostic, but rising titers support the diagnosis. Serum with antibodies to N. caninum does not react with T. gondii organisms, and vice versa. CSF analysis may reveal mixed pleocytosis, and a high protein content. Indirect fluorescent antibody testing of serum, CSF, or tissue may aid in differentiating N. caninum from T. gondii.

Treatment

Clindamycin or trimethoprim/sulfadiazine are the treatment of choice, and animals with acute systemic disease may respond well.

3. Idiopathic Myopathies
   a) Fibrotic Myopathy

Etiology and Pathogenesis

Fibrotic myopathies are chronic, progressive disorders that result in severe muscle contracture and fibrosis. This condition has been reported in the semitendinosus, quadriceps, supraspinatus, infraspinatus, rectus femoris, and gracilis muscles of the dog and the semitendinosus muscle in the cat. The cause is not known and the condition may be the result of primary neuropathy or myopathy, frequent intramuscular injections, exercise-induced trauma, or chronic trauma with tearing and stretching of muscle fibers, or it may be congenital. Muscle is replaced by dense collagenous connective tissue, resulting in a taut fibrous band.

History and Clinical Signs

The limb involved develops a nonpainful, mechanical lameness, the severity of which depends on which muscle is involved and the extent of the fibrosis.

Diagnostic Tests

On physical examination a thin fibrous band may be palpated, that replaces the muscle belly. Histopathology of affected muscles reveals dense collagenous connective tissue replacing muscle fibers and there is minimal inflammation. EMG activity is not detected from the fibrous band and bizarre high-frequency discharges may occur with incomplete replacement of muscle fibers.

Treatment

Surgery is not recommended unless the lameness is disabling. If surgery is undertaken the goal is to release the fibrous band. Prognosis is guarded because of the likely recurrence of the fibrous band within 3-8 months.

b) Infraspinatous Muscle Contracture

Etiology and Pathogenesis

Fibrosis of the infraspinatous muscle occurs primarily in hunting or working breeds of dogs and is usually unilateral, but may be bilateral. The cause is not known, but it is thought to be a primary muscle disorder. It may be associated with trauma, either self-induced or external. Trauma is thought to cause incomplete rupture of the muscle, resulting in progressive fibrosis and contracture over 2-4 weeks.

History and Clinical Signs

Initially, the dog has an acute onset of pain in the shoulder during or soon after exercise. The lameness gradually subsides, but never resolves. Two to four weeks after the initial injury, a nonpainful mechanical lameness of the thoracic limb develops and the gait is characterized by adduction of the elbow and abduction of the limb, with outward rotation of the antebrachium and carpus. The limb is laterally circumducted with each stride, and the foot "flips" forward.

Diagnosis

Palpation of the thoracic limb reveals that the humerus rotates outward when the elbow joint is flexed and range of motion in the shoulder joint is limited. Disuse atrophy of the infraspinatus, supraspinatus, and deltoid muscles is evident from the prominent scapular spine.

Treatment

Tenotomy of the tendon of insertion of the infraspinatous muscle should allow the thoracic limb to be more easily adducted and the shoulder range of motion is improved. Activity should be limited for 1-2 weeks after surgery and prognosis for a full recovery is excellent.

c) Myositis Ossificans

Etiology and Pathogenesis

Myositis ossificans is the heterotropic formation of bone in muscle. There is usually minimal inflammation, and muscle is not always involved. Generalized and localized forms have been described based on clinical behavior. The localized form is characterized by heterotopic, nonneoplastic bone formation in one muscle or a group of muscles. It is reported in dogs and cats and has been well described in Dobermans where some authors believe it may be a separate disease entity (von Willebrand heterotopic

osteochondrofibrosis in Doberman pinschers). Progressive or generalized myositis ossificans is also known as progressive ossifying fibrodysplasia or progressive or generalized ossifying myositis. It is characterized by the development of excessive fibrous connective tissue, which results in widespread muscle degeneration and ultimately leads to dystrophic calcification and ossification. It has been reported in young to middle-aged cats. The cause is not known and the localized form may be associated with trauma, infection, ossifying hematoma, and metaplasia of muscle and connective tissue to cartilage and bone. In Doberman pinschers, it is speculated that the combination of bleeding tendencies associated with von Willebrand's disease and trauma results in microvascular bleeding with subsequent fibrosis or mineralization. The progressive form is thought to be congenital or hereditary and may be a defect of fibroblasts in collagenous connective tissue with secondary degeneration of muscle, rather than a primary muscular lesion.

History and Clinical Signs

Localized ossifying myositis results in a palpable, firm enlargement in affected muscles, with chronic lameness, pain after exercise and muscle atrophy. Progressive ossifying fibrodysplasia occurs in young to middle-aged cats and results in firm nodules anywhere on the body, but predominantly on the neck and back. Limbs, especially the pelvic limbs, may be stiff which may progress to difficulty walking. Proximal limb musculature is enlarged and firm, painful, and has limited range of motion. Affected cats may be disabled within 2 weeks to several months.

Diagnostic Tests

Radiographs of affected areas show multiple mineralized densities. Soft tissue mineralization occurs within 3-6 weeks of injury and mature bone in soft tissue after 2-6 months. There may or may not be a periosteal reaction. On histopathology of the lesion, "zone phenomena" occur, with progression of bone maturation centrally to peripherally. The central zone contains undifferentiated cells and fibroblasts and may resemble a sarcoma, the intermediate zone contains osteoid and some areas of immature bone, and the peripheral zone contains mature bone. It does not invade the surrounding soft tissue. Affected muscle has excessive connective tissue between muscle fibers, mononuclear infiltration and muscle atrophy and hyaline degeneration.

Treatment

If clinical signs are minimal, treatment is not recommended for localized ossifying myositis. Rest, compressive bandages, and aspirin may help to relieve the acute pain. Surgical excision may be indicated to alleviate discomfort and restore normal limb function. In humans if surgery is performed within 6 months (i.e. when the lesion is immature) there is a high rate of recurrence. Post operative physical therapy is important. There is no effective treatment for progressive ossifying fibrodysplasia.

4. Neoplasia

Muscle tumors may be primary, originating from skeletal muscle (rhabdomyoma, rhabdomyosarcoma), or secondary (metastatic spread from tumors originating elsewhere, or local invasion of tumors into muscle from rapidly expanding cutaneous or bone tumors). Age of onset is variable although secondary tumor spread usually occurs in middle-aged animals. Clinical signs depend on the muscle group affected. Firm, nonpainful swelling, distortion of the area, and lameness are common. Diagnosis is confirmed by histopathologic assessment of biopsy material. Staging of the disease with lymph node biopsy and thoracic radiographs is important.

For primary neoplasia, surgical excision is preferred, but may be ineffectual if the neoplasm is difficult to reach or invasive. Amputation of the limb may be necessary to attain adequate surgical margins. Treatment of secondary neoplasia depends on the therapy indicated for the primary tumor.

Involuntary Movement Disorders

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Involuntary Movement Disorders

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KEY FACTS

- A variety of unusual movement disorders exist in cats and dogs
- From benign sleep-related muscle twitches to life-altering tremors, these movements are representative of a range of underlying neuropathology, toxicology, neuro-degeneration, or even normal behaviors
- Movement disorders include a wide range of neurologic disturbances characterized by:
  - ***Excess Movements*** (hyperkinesia) or
  - ***Reduced Movements*** (bradykinesia)
- Abnormal involuntary movements include a number of muscle jerks, twitches, postures, and oscillations that have been classified in human neurology with terms such as tic, chorea, tremor, dystonia, and myoclonus
- Uncontrolled muscle contractions may be of muscle or neuronal origin
- Many of these disorders are the result of neurodegenerative changes of the basal ganglia in people, a condition not well documented in non-primate species
- The purpose of this lecture is to review and discuss the clinical presentation of movement disorders with emphasis on *tremors* and *fasciculations*

Summary of Abnormal Involuntary Movements in Cats & Dogs

A. Hyperkinetic abnormal involuntary movements

1. Neuromuscular disorders

a. Myotonia
b. Tetany and tremor
   Hypocalcemia
c. Fasciculations
   i. Benign
      Exercise
      Stress
d. Toxicity
e. Metabolic: hypercalcemia
f. Other causes of neuropathy
g. Myokymia
h. Environmental (hypothermia)

2. Central nervous system disorders

a. ***Noncerebellar-related tremor disorders***

i. Myoclonus
    - Spinal
    - Proprioceptive
    - Epileptic
    - Toxicity

ii. Tetanus

iii. Tremor
    - Essential

iv. Toxicity

v. Idiosyncratic drug-induced

vi. Metabolic
    - Hypoglycemia
    - Hepatic or uremic encephalopathy

vii. Degenerative disease

b. ***Cerebellar-related tremor disorders***

i. Congenital
    - Neonatal syndromes
        - Hypoplasia
        - Malformation
        - Granuloprival degeneration
        - Hypodysmyelinogenesis
        - Axonopathy
    - Postnatal syndromes
        - Abiotrophy
        - Lysosomal storage diseases

II. Acquired
    - Inflammatory
        - Infectious
        - Immune-mediated
    - Neoplasm
    - Vascular/traumatic
    - Toxin
    - Idiopathic

B. Hypokinetic abnormal involuntary movements

1. Parkinsonian syndromes
- Primary
- Secondary: drug reaction

C. Paroxysmal abnormal involuntary movements

1. Epileptic seizures

2. Nonepileptic seizures

3. Sleep-related movements

Clinical History

- Dealing with movement disorders is a challenging diagnostic prospect
- The saying ‘‘a picture is worth a thousand words’’ is made for movement disorders
- A detailed history should be combined with visualization of the characteristics of Abnormal Involuntary Movements in order to characterize the nature of the movement disorder
- Essential in the determination of the neuroanatomic localization and potential etiology of Abnromal Movement Disorders is information regarding:
    - Anatomic distribution
    - Rhythmicity
    - Amplitude
    - Frequency
    - Speed of onset and “offset” of the movement
    - Relation to posture and activity
    - Situations that alleviate or exacerbate the movement
    - Presence or absence during sleep, and
    - Affected littermates
- If the movement disorder is not present at the time of the examination, owners should be encouraged to videotape the events for future review
- Many times, the initial few minutes of observation solidify the clinical perspective, allowing an accurate diagnostic and therapeutic course of action to proceed
- There are three diagnostic methods of approach for movement disorders:
    - 1. Pattern recognition. This method is available to a select group of experienced and highly trained senior neurologists who can recognize the underlying disease just by history and evaluation. This method is by no means ‘‘foolproof’’
    - 2. Irrational method. Here, the clinician relies on as many diagnostic tests as possible to try to screen out as many underlying diseases as possible. This method is neither cost-efficient nor practical for the patient or the client
    - 3. Rational diagnostic approach. The goal for this method is to identify the type of movement disorder, to neuro-localize the lesion as to whether the signs are more suggestive of peripheral nervous system (PNS) or central nervous system (CNS) disease, to perform the proper diagnostic testing for this neuro-localization, and then to implement the associated treatment plan. Many movement disorders are early hallmark signs of diseases that can potentially progress to life-threatening situations, emphasizing the importance of proper identification of an underlying cause

Review of Voluntary Control of Motor Unit Activity

- Most movement disorders are the outcome of loss of normal voluntary muscle control
- Review of normal voluntary control of the motor unit is important to an understanding of the origin of movement disorders

- The neuromuscular system consists of an efferent component and an afferent component
- The efferent neuron of the PNS connecting the PNS with the CNS is known as the lower motor neuron (LMN)
- The afferent neuron is the first sensory neuron in the ascending spinal cord pathways, or the dorsal root ganglion
- There are three divisions of the LMN system:
    - 1. General somatic efferent (GSE) system, that innervates striated voluntary muscle of the tongue, extraocular apparatus, and limbs;
    - 2. Special visceral efferent (SVE) system, that innervates striated voluntary muscle associated with the respiratory and digestive systems; and
    - 3. General visceral efferent (GVE) system, that innervates the involuntary smooth muscle associated with autonomic function.
- The SVE system cell bodies are located in cranial nerve nuclei V, VII, IX, X, and XI
- The GVE system is divided into sympathetic and parasympathetic autonomic systems with a thoracolumbar and craniospinal location, respectively
- The GSE cell bodies are located in cranial nerve nuclei III, IV, VI, and XII along with spinal motor neurons that innervate appendicular and axial skeletal muscles
- The motor unit is composed of the LMN (GSE cell body, its axon, and neuromuscular junctions) and the muscle innervated
- Lesions of these LMN systems could include involvement of any component of the motor unit: neuronal cell bodies in the spinal cord or cranial nerve nuclei, spinal or cranial nerve roots, spinal or cranial nerves, peripheral nerves, neuromuscular junction, and muscle
- In the spinal cord, these cell bodies are located in the ventral gray column, with the axial musculature arranged medially and the appendicular musculature located laterally
- Proximal limb muscles are arranged along the ventral aspect, whereas the distal limb neurons are in the dorsal aspect of the lateral ventral gray column
- The respective axons course from the dendritic zone in the gray matter to course distally as the ventral root, spinal nerve, and peripheral nerve to innervate the appropriate muscle
- Each axon divides into branches to terminate on a motor end plate at the muscle cell
- The final branching occurs at the neuromuscular junction
- The number of muscle cells innervated by one motor neuron varies according to the muscle group
- In general, the greater the degree of coordination involved, the smaller is the motor unit
- Voluntary movement is finalized with the coordinated firing of the motor neuron, which produces depolarization of all muscle fibers within a motor unit
- The initial information for excitation of the motor neuron derives from input from the upper motor neurons in the brain, which descends via white matter pathways in the spinal cord to terminate at either the cervical C6–T2) or lumbosacral (L4–S1) spinal segments
- The depolarization then spreads throughout the muscle fiber, followed by release of calcium, and culminates in the contraction of myofibrils

- Muscle fibers are composed of myofibrils that contain the myofilaments actin (thin) and myosin (thick), which are attached to the muscle cell membrane (sarcolemma) by cytoskeletal proteins
- Cytoskeletal proteins give muscle fibers their shape and transmit the force of muscle contraction to the sarcolemma
- Muscle contraction and relaxation are active energy-dependent processes that result from either shortening or lengthening of the myofibrils, respectively
- Calcium acts as a ‘‘security’’ system and must be released for muscle contraction
- Free fatty acids are the major energy substrate for muscle metabolism
- These free fatty acids enter muscle mitochondria via a carnitine-dependent transport process for oxidative phosphorylation to take place
- Thus, the process of initiation and completion of voluntary movement is a complex one that relies on coordination of serial communications between multiple components of the CNS and PNS
- ***Failure of ANY ONE of these multiple components to complete their assigned tasks can result in loss of the desired movement or excessive abnormal movements***

Hyperkinetic Movement Disorders

Myotonia

- Myotonia is a sustained muscle contraction with delayed relaxation
- Myotonia congenita has been reported in the Chow Chow and Miniature Schnauzer breeds and seen sporadically in a number of other breeds
- The disease is caused by a failure of normal myocyte chloride conductance, resulting in delayed muscle hyperpolarization, and thus delayed relaxation
- As an inherited autosomal recessive disease, puppies are affected from birth
- Clinical signs are seen within the first few months of life and are characterized by a stiff ‘‘sawhorse’’ stance on ambulation, with improvement in gait as exercise time increases
- Some dogs may suffer from dysphagia and respiratory problems caused by contraction of the tongue and oropharyngeal muscles
- Affected dogs have hypertrophied glossal and proximal appendicular muscles that exhibit percussion dimpling on being struck with a percussion hammer
- Electromyography (EMG) recordings demonstrate the classic myotonic discharge of a high-frequency waxing-waning spontaneous discharge that produces a ‘‘dive-bomber’’ or revving motorcycle sound
- Muscle biopsy is usually normal, although a type 1 fiber predominance or fiber hypertrophy may be found
- Treatment consists of trial with an antiarrhythmic drug, such as mexiletine (2 mg/kg administered two or three times daily) or procainamide, but it may not alleviate the clinical signs
- Many dogs can have a good quality of life by avoiding excessive exercise in the cold and maintaining a normal exercise routine
- Acquired myotonic myopathy has been reported secondary to exposure to herbicides containing 2,4-dichlorophenoxyacetic acid (2,4-D) or 2-,methoxy-3,6-

dichlorobenzoic acid (dicamba) [8–10] and as an idiopathic,condition associated with a myotonic dystrophy–like disorder in a Rhodesian Ridgeback dog. The clinical signs are similar to those of the congenital form of myotonia

Tetanus and Tetany

Tetanus

- Tetanus is a continuous sustained extensor muscle contraction
- The cause is the tetanus toxin released by Clostridium tetani bacterial infection of domestic animals. The disease occurs when the tetanus spores localized to an anaerobic environment, such as a necrotic wound, transform into the toxin-producing form
- The exotoxin, tetanospasmin, travels from the infected site via peripheral nerves to the CNS
- The toxin prevents the release of the inhibitory neurotransmitter glycine from interneurons in the spinal cord and brain, resulting in excessive excitation of brain stem and motor neurons
- Cats and dogs are fairly resistant to tetanus; however, when infected, they can exhibit an extreme stiffness progressing to extensor rigidity of all limbs, spastic facial muscles, and trismus within 5 to 10 days of infection
- A ‘‘grimacing’’ expression with the ears pulled back is usually seen
- Occasionally, localized tetanus may affect only a single limb or be confined to the facial muscles
- Many animals are hypersensitive to external stimuli
- The diagnosis is based predominantly on a history of recent wounds and clinical signs
- Initial treatment consists of aggressive wound debridement,mparenteral penicillin or metronidazole treatment, muscle relaxant therapy (diazepam continuous rate infusion at 0.3 mg/kg/h or pentobarbital, 3–10 mg/kg, administered intravenously [IV] to effect), and nutritional support
- Tetanus antitoxin (100–1000 IU/kg administered IV) has been reported useful to reduce the duration of clinical effects. A test dose of 0.2 mL administered subcutaneously (SC) should be given first, with observation for anaphylactic reaction
- Careful attention should be given to hydration and nutritional support, because the trismus can prevent adequate fluid and food intake
- Complete remission of clinical signs usually occurs within several weeks to months

Tetany

- Tetany is a variable and intermittent extensor muscle contraction
- It may accompany CNS and PNS diseases
- In dogs, tetany is most commonly seen with hypocalcemia-associated parturition or hypoparathyroidism
- Total calcium is typically below 7.0 mg/dL. Dogs often suffer from an inability to rise, extensor muscle contractions, and hyperthermia (from muscle contractions)
- Secondary hypoglycemia may also be seen because of the excessive muscle movements

- Treatment is focused on initial muscle relaxation with benzodiazepines, followed by calcium and vitamin D supplementation

Myoclonus

- Myoclonus is defined as a sudden, rapid, involuntary muscle movement of short duration caused by active muscle contractions (positive myoclonus) or pauses in muscle activity (negative myoclonus)
- Classification can be based on clinical presentation, site of origin, or etiology. Reflex myoclonus to auditory stimuli has been reported in the retriever dog breeds
- Spinal myoclonus arises from abnormal neuronal discharges originating in the spinal cord and is of two main types: segmental and propriospinal
- Segmental myoclonus can occur in dogs infected with canine distemper, producing a repetitive myoclonic jerk motion of one or more limbs, even during sleep
- Epileptic myoclonus and drug-induced myoclonus in dogs are examples of etiologic classification

Fasciculations and Myokymia

Fasciculations

- Muscle fasciculations are spontaneous contractions of muscle fibers within a motor unit and arise from ectopic electrical activity in the distal axon
- Fasciculations typically are the manifestation of irritability of the neuronal cell body (motor neuron) or its accompanying axon
- As such, they are most often associated with motor neuron disease and peripheral nerve disorders
- Fasciculations can be more readily observed in the distal appendicular muscles and the tongue but can be difficult to detect in more obese animals
- One can usually detect a fine ‘‘rippling’’ movement of the muscle as a sign of fasciculation
- The differential diagnoses of muscle fasciculations range from benign to more severe neuromuscular disease
- Benign contraction fasciculations can be seen after strenuous exercise and possibly in tense animals
- Other transient muscle fasciculations can be associated with hypercalcemia, hypomagnesemia, and certain toxic drug reactions to theophylline, terbutaline, caffeine, and methylxanthine (chocolate toxicity), for example, as well as with reactions to anticholinesterase agents (ie, pyridostigmine and neostigmine used for the treatment of myasthenia gravis)
- Fasciculations associated with neuromuscular disease are most likely to be present after the onset of clinical signs of weakness
- Degenerative feline and canine motor unit disease and more advanced cases of distal axonopathy in the dog are conditions that are more likely to be associated with muscle fasciculations

Myokymia

- Myokymia is a pattern of abnormal muscle contraction that produces a rippling or ‘‘writhing’’ appearance of the area involved
- The change is the result of spontaneous discharges of large motor units
- Myokymia is an indication of neuronal disease, followed by sprouting of the motor unit territory in response to the denervation
- Myokymia or myokymia-like syndrome has been described in Jack Russell Terriers and is associated with hyperthermia and collapse

Tremor Syndromes

- A number of tremor syndromes that have been described in human beings are also seen in small animals
- Tremor is classified according to its anatomic distribution as well as frequency and amplitude during rest, postural maintenance, movement, intention, and the performance of specific tasks
- The degree of tremor (amplitude) is often variable and can be exacerbated with emotional (anxiety) and physical activity
- The two main types of tremor are known to occur at rest or with action
- 1. Resting tremor describes an involuntary rhythmic oscillation of a body part completely supported against gravity. This tremor can be seen in a leg, with the animal lying down and not supporting weight
- 2. Action tremor occurs during voluntary contraction of skeletal muscle and is classified as postural, kinetic, isometric, or task specific
- Postural tremor describes oscillation of a body part that is voluntarily maintained against gravity. This tremor type is rare in small animals
- Kinetic tremor describes oscillation during guidedmvoluntary movement. This intentional tremor is the most common typemseen with cerebellar disease in small animals
- Isometric tremors and task-specific tremors are seen with primate species that can hold objects andminitiate specific movements of the hands and arms

Essential Tremors

- Physiologic and essential tremor syndromes are the most common syndromes in people and can occur in older dogs, particularly in aging terrier breeds
- In affected people, such a syndrome is believed to be an autosomal dominant inherited trait with variable penetrance
- It is a pure clinical syndrome characterized by progressive action tremor of pelvic limbs that worsens with activity and excitement
- Severity can range from barely perceptible tremor to altered gait and balance problems
- Signs can progress as the dog ages

Tremor associated with Neuromuscular Disease

- Tremor attributed to weakness is almost always associated with underlying nerve disease

- Most likely, this type of tremor is an exaggeration of the normal physiologic tremor that results from the synchronized discharge of enlarged motor units in patients that have a reduced number of surviving motor neurons
- Dogs with advanced peripheral neuropathies can present with this type of tremor in the pelvic limbs
- The tremor is exaggerated after exercise and while standing
- Other conditions that directly affect nerve function with this type of tremor include compressive neuropathy from lumbosacral disk disease or stenosis, nerve sheath tumors, and other mass effects or entrapment syndromes involving the nerve

Drug-Induced Tremors

- Drug-induced tremor has been reported in the cat and dog
- Predictable tremor can be seen with stimulant toxicity (eg, caffeine, amphetamines, cocaine)
- Other potential drugs that have induced tremor in human beings include valproic acid, amiodarone, procainamide, and lithium
- Tardive dyskinesia represents a wide variety of involuntary movements in human beings, including chorea, dystonia, akathisia, myoclonus, tremor, and stereotypies
- Stereotypy, or rhythmic involuntary movement, is the most common manifestation resulting from exposure to dopamine receptor–blocking agents, such as phenothiazine (eg, acepromazine) or antiemeticmdrugs (eg, metoclopramide)
- Loss of D2 receptors in the neostriatum is postulated to contribute to the pathophysiology

Cerebellar-Related Tremors

- By far, the most common cause of tremor in small animals is cerebellar syndromes and disease
- Cerebellar diseases are often associated with a conglomeration of signs related to abnormal motor activity to include any or all of the following: tremors, bilaterally symmetric ataxia without paresis, dysmetria, vestibular signs (e.g., head tilt, nystagmus, falling), absent menace with preservation of vision, and pupillary changes
- An altered resting posture is often present, with affected animals demonstrating truncal ataxia (swaying of the body back and forth or side to side) and a compensatory broad-based stance for balance
- Cerebellar tremors are associated with diffuse cerebellar cortical diseases
- These intention tremors are characterized by a fine head tremor that worsens with initiation of voluntary head movements
- ‘‘Titubation’’ is a cerebellar postural tremor that affects the head and trunk.
- The more acute-onset diseases affecting the cerebellar cortex usually result in more pronounced tremor disturbances
- Severe tremors may affect the entire body, with complete loss of all muscular coordination, failure to posture, and failure to prehend food
- Ensuing hyperthermia, rhabdomyolysis, and related complications from continuous muscle activity require that these patients be aggressively treated on an emergency basis (see below)

- Fortunately, many ‘‘pure’’ cerebellar diseases can be treated or compensated for by the patient
- Cerebellar syndromes associated with tremor can be divided into congenital and acquired diseases
- Congenital neonatal syndromes represent diseases of the newborn animal in which the clinical signs are present from birth and are non-progressive
- In contrast, the clinical signs of congenital postnatal diseases begin in the pediatric animal after birth and are slowly progressive
- Acquired cerebellar diseases can be acute or chronic in onset, with rapid progression most commonly seen with inflammatory diseases and toxic exposures (eg, mycotoxins, metaldehyde, macadamia nuts)

Hypokinetic Movement Disorders: Parkinson Syndromes

- Parkinson disease is a neurodegenerative disease of the nigrostriatal dopaminergic system in human beings
- A parallel naturally occurrindisease has not been reported in nonprimate species.
- Secondary parkinsonism, however, can occur in a number of species
- Potential causes of secondary disruption of normal dopaminergic function can be classified as drug induced, toxin induced, associated with a metabolic disorder, vascular-related disease, postencephalitic/postinfectious disease, and posttraumatic events
- Drug-induced parkinsonism is the most common cause of symptomatic parkinsonism in human beings and can occur in animals
- Because of the ability of neuroleptics (eg, haloperidol, droperidol) to block dopamine receptors, a higher prevalence is reported with longer treatment
- Doberman Pinschers seem to be sensitive to an acute-onset type of secondary parkinsonism with tremor that is reversible
- Other potential drugs include metoclopramide, prochlorperazine, calcium channel blockers, fluoxetine, pyridostigmine, and meperidine

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Paroxysmal Movement Disorders

- Paroxysmal movement disorders can be classified as seizure disorders that can be caused by an associated epileptic change in brain activity (epileptic seizures) or can occur without such a change (nonepileptic seizures)
- These sudden changes take the form of many manifestations of body position, motion, ability to stand, facial expressions, and limb movements, for example. Severity varies from involvement of the whole body to movement of only a single muscle group
- It is important for the clinician to recognize the presence of these movements as benign or suggestive of more serious underlying neurologic problem

Epileptic Seizures

- Epileptic seizure types can be classified into two major categories: partial and generalized
- Partial seizures are the manifestation of a focal epileptogenic event in the cerebral cortex
- With simple partial seizures, there are usually asymmetric motor or sensory signs without a change in consciousness. Examples include facial focal seizures or excessive pawing or biting of a body part
- Animals with complex partial seizures, also termed psychomotor seizures, have impaired consciousness, often with bizarre behavioral activity and possible motor disturbances
- Generalized seizures are subdivided into convulsive (‘‘grand mal’’) and nonconvulsive (‘‘petit mal’’) seizures
- These seizures are characterized by impaired consciousness coupled with bilateral motor signs of a tonic-clonic, tonic, myoclonic, or even atonic nature
- The major form of nonconvulsive seizure is them‘‘absence’’ variety manifested as impaired consciousness only. This seizure type is poorly documented in animals

Nonepileptic Seizures

- Many events may mimic epileptic seizures
- Two major categories of nonepileptic seizures in people are psychologic and organic
- Veterinarians are fortunate in not having to determine the presence of hysterical seizures in cats and dogs
- Behavioral disorders, however, may obscure this distinction
- In particular, obsessive-compulsive behaviors, such as tail-chasing and repetitive licking, can occur and end suddenly
- The organic nonepileptic seizures can be broken down into nonneurologic and neurologic causes
- More common causes of nonneurologic and nonepileptic seizures are syncope of cardiac origin, metabolic disturbances (eg, transient hypoglycemia, endocrine diseases), and toxicities
- Two major neurologic causes of nonepileptic seizures are acute vestibular attacks (often peripheral in nature) and narcolepsy
- In practically all instances, dogs with non- epileptic seizures do not exhibit postictal effects

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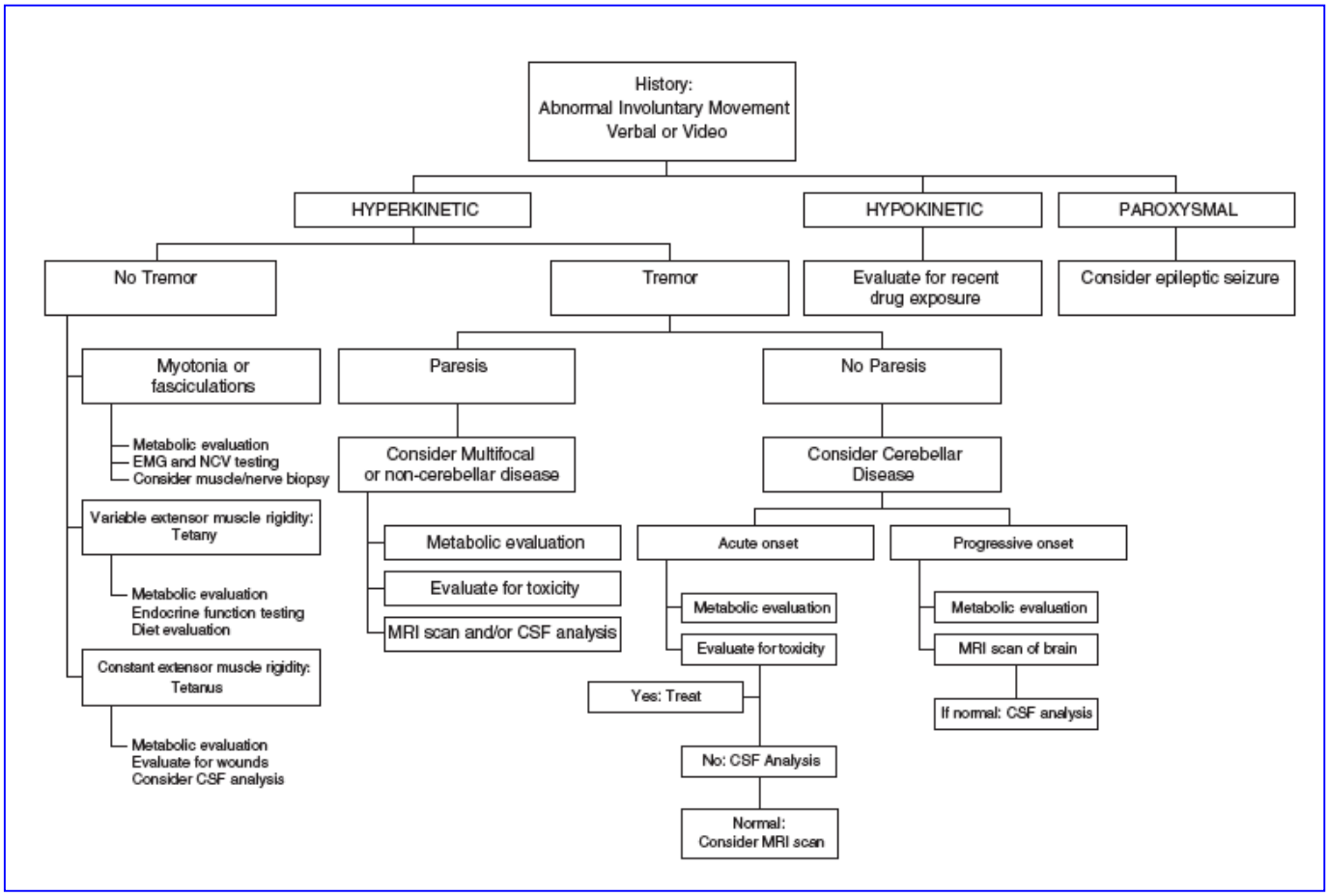
Diagnostic Approach

- The diagnostic approach to an animal with AIMs starts with an evaluation of whether the movement disorder is hyperkinetic, hypokinetic, or paroxysmal
- The next step is to determine if the animal exhibits any signs of tremor of the head, neck, or other areas of the body
- Animals without tremor should then be evaluated for signs of excessive rigidity or stiffness
- Constant extensor muscle rigidity is more likely to be a sign of tetanus, whereas variable extensor muscle rigidity is associated with tetany

Algorithm for the Diagnostic Approach to Abnormal Involuntary Movements in Cats & Dogs



- An initial metabolic evaluation, including a complete blood cell count, serum chemistry panel, ionized calcium measurement, and creatine kinase measurement, should be performed
- Tetanus is diagnosed based predominantly on clinical signs and history, whereas tetany is typically diagnosed based on the presence of hypocalcemia or another metabolic disorder
- If no extensor muscle rigidity is detected, signs of abnormal muscle movement, including myotonia, fasciculation, and myokymia, should be suspected
- These signs are all indicators of underlying neuromuscular disease; as such, they merit further specific diagnostic testing for peripheral neuropathy or myopathy
- Again, an initial metabolic evaluation, including a complete blood cell count, serum chemistry panel, ionized calcium measurement, and creatine kinase measurement, should be performed
- The next level of testing is electrodiagnostic evaluation with EMG and nerve conduction testing
- EMG tests the stability of the muscle membrane
- Major causes for muscle membrane instability resulting in spontaneous firing, or activity of muscle cells, are denervation, inflammation, or intrinsic or extrinsic metabolic abnormalities

- The type of activity pattern is useful in categorizing the etiology
- Motor and sensory nerve conduction velocity testing is often done in conjunction with EMG to evaluate peripheral nerve function
- Reduced velocity is more indicative of a demyelinating process, whereas decreased amplitude of evoked motor or sensory action potentials is more representative of a primary axonopathy
- If tremor is present as part of the history or clinical examination, the next step is to determine if any paresis is present
- Care must be taken not to confuse weakness with falling from incoordination
- A reliable test is to hop an animal on each leg individually to see if it collapses on that leg during the testing
- A weak animal cannot support weight on that limb, whereas an incoordinated one can. If paresis is present, one should consider a multifocal or noncerebellar CNS disease
- A history of possible toxic exposure should be ruled out before pursuing more advanced testing
- If the metabolic evaluation is normal as stated previously, an MRI scan of the brain or spinal cord, with possible cerebrospinal fluid (CSF) analysis, is warranted to evaluate for the underlying etiology
- If paresis is not present with the tremor syndrome, it is most likely that the animal is suffering from a pure cerebellar disease process
- An acute onset of clinical signs is more suggestive of a toxic reaction or inflammatory disease process
- If toxicity is documented, no further diagnostic testing may be needed and symptomatic therapy can be instituted
- If toxicity cannot be documented, CSF analysis is recommended. If the CSF is normal, MRI scanning of the brain may be necessary
- If the disease process is more chronic and progressive in nature, the patient should be evaluated for a possible mass lesion of the cerebellum with a MRI scan before collection of CSF for analysis
- For hypokinetic movement disorders, the most likely scenario is a possible reaction to recent drug therapy or exposure
- Owners should be questioned about any possible accidental exposure to their own medications
- Paroxysmal movement disorders have a history of an animal going from a normal state to a sudden change of body movement for a finite period of time, followed by either an immediate return to normalcy or a period of postictal changes for epileptic seizures

Treatment Approaches

- The goal for the control of tremors in small animals is to determine the etiology, remove any inciting cause (toxin or iatrogenic), and provide immediate and prolonged symptomatic relief for acquired diseases
- A number of treatments for essential chronic tremor disorders have been proposed for people, with varying results

- First-line treatments useful in the dog include phenobarbital, 2.5 mg/kg, administered orally (PO) twice daily or a *b*-adrenergic antagonist (eg, propranolol, 2.5–10 mg, administered PO two to three times daily)
- Benzodiazepines do not seem to be effective in human beings [39] or dogs (personal experience)
- Clozapine, a D2 dopamine receptor antagonist, significantly reduced tremor severity in human patients with essential tremor with chronic dosing between 18 and 36 mg/day
- Topiramate, a new antiepileptic drug, has recently been shown to be efficacious in refractory essential tremor cases in human beings at a dose range between 100 and 200 mg/day
- Documentation of the success of these therapies in animals is not currently available

- Recommended emergency treatment for acute onset of suspected acquired tremor disease (i.e., steroid-responsive tremor syndrome or toxicity) is listed below
- This situation can be a life-threatening disease; as such, it requires a rapid therapeutic approach
- Care should be given to avoid the use of corticosteroid therapy, because this treatment can alter the ability to obtain a diagnosis of an inflammatory disease with CSF analysis

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Insights

- Abnormal Involuntary Movement disorders are common neurologic problems in small animals
- Most animals exhibit hyperkinetic uncontrolled movements that are the result of underlying cerebellar or neuromuscular diseases
- Using precise historical and examination information, a well-planned diagnostic approach can be formulated
- Most important for the clinician is the ability to discern if a primary brain or neuromuscular disease is present
- The use of a guiding algorithm has been presented to aid in this decision-making process
- Advanced diagnostic testing with electrodiagnostic testing or biopsy of the PNS or imaging or CSF fluid analysis of the CNS is critical in the definitive diagnosis of many of the diseases associated with Abnormal Involuntary Movements in small animals
- Fortunately, with proper diagnostic testing that leads to appropriate treatment strategies, many animals affected by these often unusual problems can go on to lead quality lives

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Emergency treatments for acute-onset tremors in the dog

1. Intravenous bolus injection of diazepam, 0.5 mg/kg, administered intravenously. If an intravenous route is not possible immediately, a per rectal injection at a rate of 1 mg/kg can be given.
2. If tremors continue or return, start diazepam at a continuous rate intravenous infusion of 0.25 mg/kg/h in 0.9% saline at a maintenance fluid rate. This rate can be increased to 0.5 mg/kg/h.
3. If the tremors are not controlled, give an intravenous bolus of phenobarbital, 20 mg/kg, followed by 2 mg/kg administered orally every 12 hours.
4. If the tremors continue, a continuous intravenous infusion of a barbiturate should be used.
    a. Propofol intravenous continuous rate infusion at a rate of 5 to 10 mg/kg/h to effect to stop tremors, or
    b. Pentobarbital administered intravenously at a rate of 2 to 5 mg mg/kg/h to effect to stop tremors
    c. Continue a balanced electrolyte solution for fluid therapy to avoid hypotension
5. Monitoring and supportive care
    a. Maintain normal ventilation and blood oxygenation
    b. Maintain normal body temperature
    c. Provide proper intravenous fluid therapy to avoid hypotension and dehydration
    d. Maintain normoglycemia
    e. Maintain normotension

These notes are adapted from the following article written by Dr. Michael Podell:
Tremors, Fasciculations and Movement Disorders, *Vet Clin Small Animal* 34:1435-52, 2004

Marc Vandevelde, Dr. med.vet. DECVN

- 1965-1971: Studies veterinary medicine, Univ. Gent, Belgium: Dr. med.vet.
- 1972-1974: Training in comparative neuropathology at the Bunge institute (Antwerp, Belgium) and institute of comparative neurology, University of Bern, Switzerland.
- 1974-1979: Assistant professor for neuropathology at the Scott-Ritchey foundation, Auburn university USA
- 1979-1984: Assistant professor in institute of comparative neurology, Univ. of Bern, Switzerland. Habilitation and appointment as Privatdozent.
- 1985: Appointment as full professor and head of the institute of animal neurology, University of Bern
- 1995: Diplomate of the European college of veterinary neurology
- 1994 -1996: Dean of the faculty of veterinary medicine, univ. of Bern
- 2000-2005: Director of the department of clinical veterinary medicine, univ. of Bern
- 2006-2012: Chief of neurology section, teaching, research, diagnostic work
- 2012- : Prof emeritus and part time assignement for research at the division of neurological sciences, Vetsuisse faculty Bern.

Special Interest

Pathogenesis of infectious diseases of the nervous system. Neuropathology, neurovirology, neuroimmunology.

Memberships

- Diplomate European college of veterinary neurology
- Board of Directors, European Association for Veterinary Specialization
- Swiss neuropathological society
- World association for neuropathology
- European Society for Veterinary Neurology (ex President)
- Editorial Board Acta Neuropathologica
- Editorial board The veterinary journal.
- Editorial board Ann. Med. Vet.

Grants obtained from Swiss National science foundation,Swiss federal veterinary office, Swiss Multiple Sclerosis Society, European Union.

Awards

- Honorary member of the Italian society for veterinary science.
- WSAVA international award for scientific achievement 2004
- Dr. honoris causa of the Faculty of veterinary medicine of Hannover Germany 2012

Publications

Ca. 300 Publications in peer reviewed journals, bookchapters, books

Cranial trauma

Marc Vandevelde, Dr. med.vet. DECVN

Cranial trauma

- Very common
- Caused by car accidents, falls, fights…..
- A clear history is often lacking:

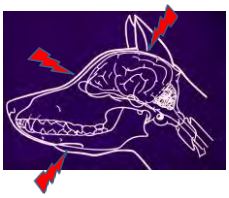
  "Animal found with neurological signs, the animal was normal a few hours ago….."

Always think about trauma

Pathogenesis

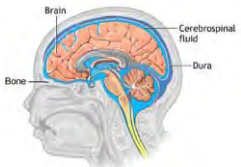
Is very complex because:

- Primary damage at the moment of impact
  - Direct mechanical injury
  - Indirect mechanical injury
- Secondary damage in the following hours/days

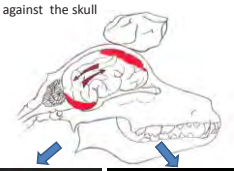


Coup – contrecoup

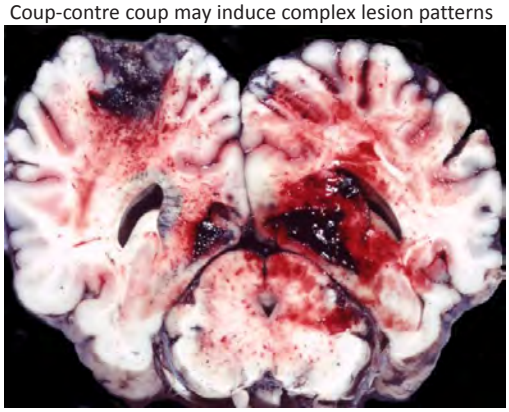
The brain is suspended in spinal fluid



Trauma: Inertia will cause the brain to bounce against the skull



Coup-contre coup may induce complex lesion patterns



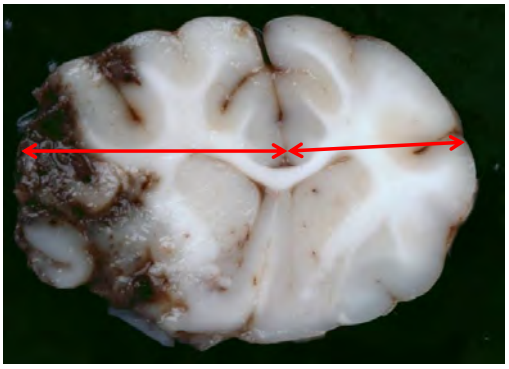
Secondary injury

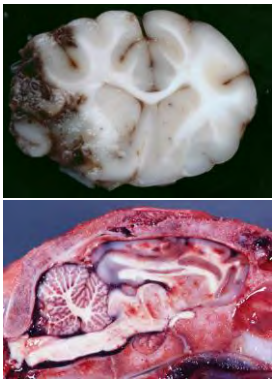
Several interlocking pathways

- Excessive production of excitatory aminoacids
- Excessive generation of reactive oxygen radicals
- Induction of inflammatory molecules such as protaglandins

Effect on cells:	Effect on bloodvessels
-Cell damage	-Blood brain barrier damage
-Cell death	-Decreasing Perfusion
	-Disruption of autoregulation

The brain swells





The swollen brain quickly fills all available space

↓ Intracranial pressure ↑

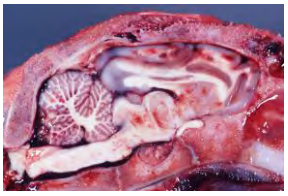
↓ Vascular perfusion ↘

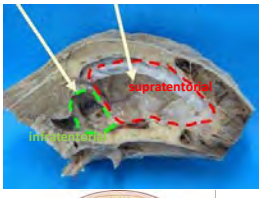
↓ Edema

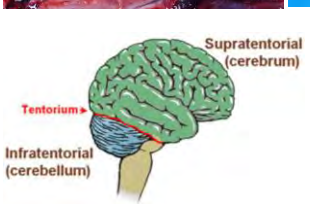
↓ Intracranial pressure ↑↑

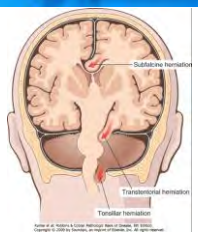
↓

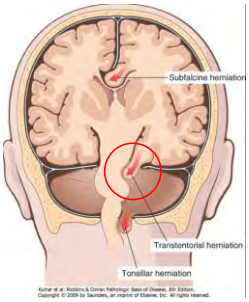
Braintissue starts to herniate

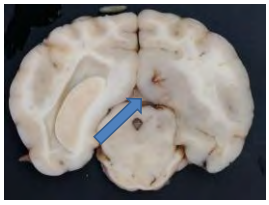


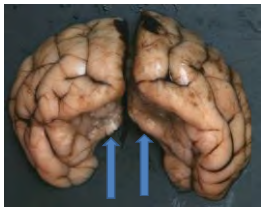




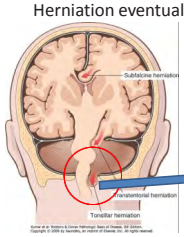


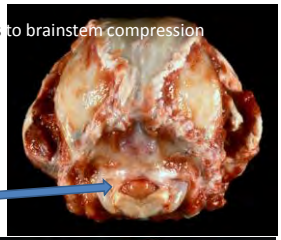


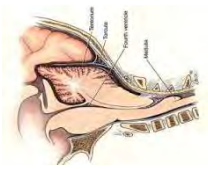




Herniation eventually leads to brainstem compression





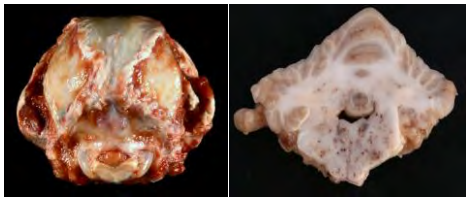


Immediate care

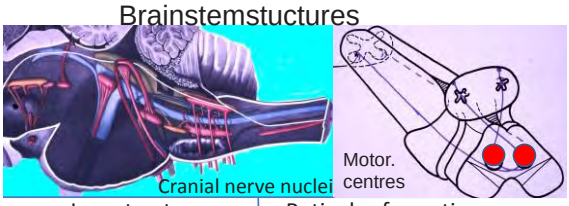
1. Danger of hypovolemic shock
   - Check respiration and heart rate
   - Bloodpressure
   - Hematocrit PCV
   - Glucose/ Electrolytes
2. Check for other injuries
3. Neurological examination

Neurological examination

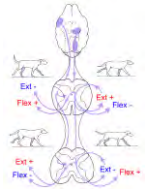
- General assessment of neurological status
- How bad is the damage?
- Focus on Brainstem function



Brainstemstuctures



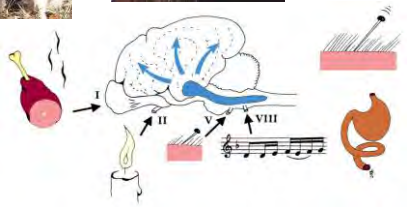
Long tracts



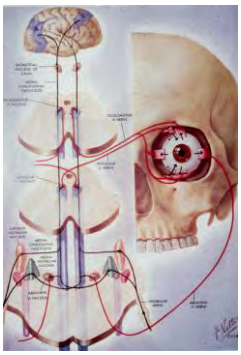
Reticular formation

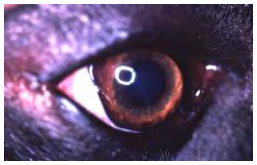
Level of consciousnes: Alert/depressed/stuporous/comatose



Eye movements and pupillary function

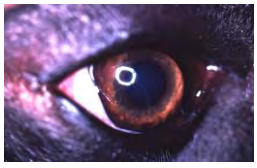




Normal pupils

Constricted pupil(s)

Dilated non-responsive pupil(s)

Motor dysfunction

- Many different presentations
- Ambulatory- complete recumbency

Severe Trauma
Decerebrate rigidity

Example of cranial trauma

- 4 y old dog hit by car

Modified Glasgow Coma Scale

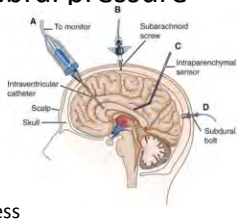
Platt SR, Radaelli ST, McDonnell JJ. The prognostic value of the modified Glasgow coma scale in head trauma in dogs. J Vet Int Med 2001; 15(6):581–584.

- Level of conciousness
  alert-deep coma 6-1 points
- Eye movements and pupils
  Normal – bilat. dilated unresponsive 6-1 points
- Motor function:
  normal gait- recumbency/no reflexes 6-1 points

Total points:	3-8:	Bad prognosis
	8-15:	Guarded
	15-18:	Good

Monitoring intracerebral pressure

- Direct measurement
  - Limited experience in veterinary medicine
  - Fibre optics quite expensive
- Indirect
  - Transcranial Doppler to assess cerebral bloodflow
  - MRI
    - edema
    - contrast behaviour



Monitor the patient

- Repeat neurological assessment at regular intervalls
- Coma scale helps to detect changes: deterioration/improvement

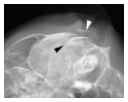
Diagnostic imaging

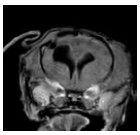
- To get more precise information on the damage
- When the patient does not improve/deteriorates
- When surgery is planned

➡ **the patient must be stable**

Diagnostic imaging

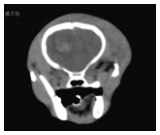
Radiology
-Rarely productive
-Fractures,dislocations



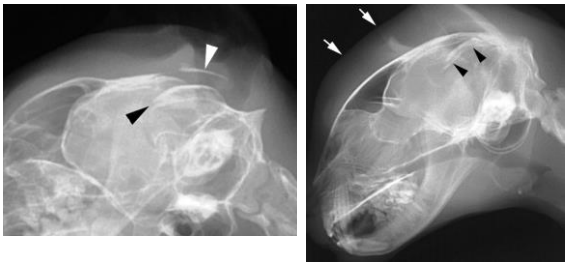


Magnetic resonance imaging
-long examination time
-very high soft tissue contrast;
-morphology of brain including brain pathology
-subacute /chronic intracerebral haemorrhage

Computed tomography
-short examination time (spiral CT)
-fractures, dislocations
-acute (<24h) haemorrhage (subarachnoidal)

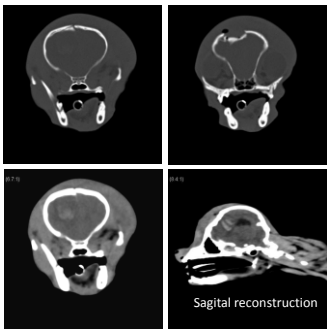


Radiology of skull fractures



Courtesy Prof. J. Lang DECVDI Univ. Bern

Use of computerized tomography to detect traumatic lesions

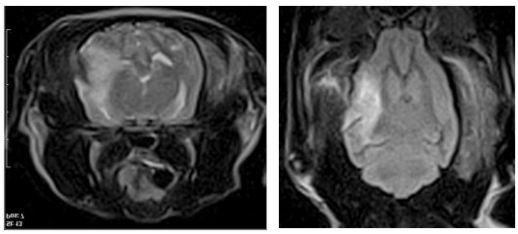


CT Bone window
Shows **fractures** nicely

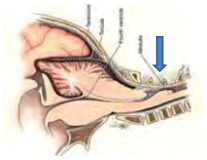
CT Soft tissue window
Shows **hemorrhage**

Courtesy Prof. J. Lang DECVDI Univ. Bern

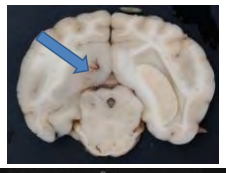
Magnetic Resonance Imaging findings in
Impression fracture and open wound after dog fight

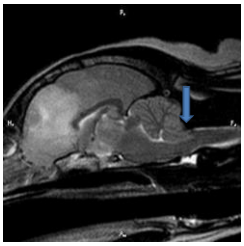


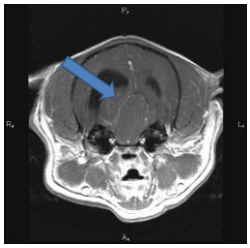
Courtesy Prof. J. Lang DECVDI Univ. Bern



MRI
Detection of
Herniation



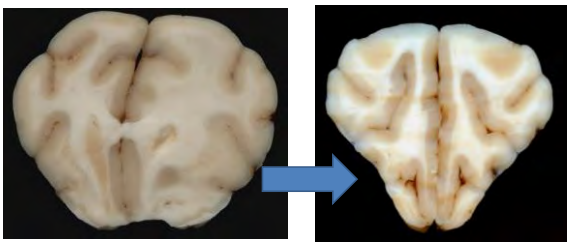




Treatment

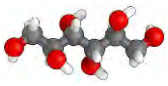
- Place animal with head elevated
- Provide oxygen (incubator/nasal tube)
- Restore+maintain blood volume/ cerebral blood volume, cerebral blood flow
  - Hypertonic salt solution
  - Colloids, cristalloids
- Combat brain swelling

Reduce brain swelling



By application of hyperosmotic agents

Combat brain swelling



Indications:
- Animals with severe Trauma (low MGCS)
- Normovolemic
- Followed by crytalloid infusions

Dose
- Mannitol bolus: 0.5-1.5 g/Kg within 15 min

Effect
- Reduces pressure while maintaining blood flow
- Reduces edema
- Effect lasts for 6-8 hours

Surgical therapy

- Craniectomy and decompression
- Indications:
  - Worsening despite conservative treatment (hematoma)
  - Severe impression/open fracture
  - Foreign body
- Should be done by neurosurgeons

Seizures

- May be induced by cerebral trauma
- Aggravate ICP → Must be treated
- Treatment
  - Status epilepticus/cluster seizures : Diazepam IV
  - Phenobarbital 20 mg/Kg loading dose/ maintenance: 2-3 mg/Kg BID
- Prophylactic use of barbiturates is controversial

Prognosis

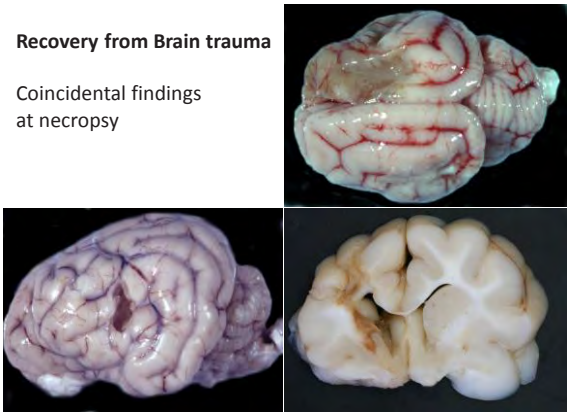
- Prognosis becomes favorable when improvement within one week after trauma
- Assesment of remaining neurological deficits
  - Neurological examination
  - **Localization**
- **Forebrain lesions : remarkable ability to recover**
- **Brainstem lesions : persisting neurological signs**

Example of brain trauma

- 2 y old cat hit by car

Recovery from Brain trauma

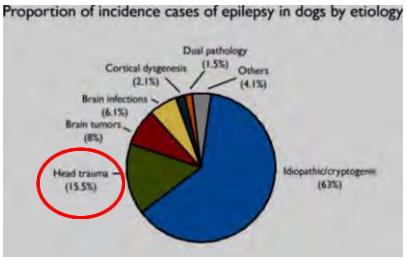
Coincidental findings
at necropsy



Post-traumatic seizures

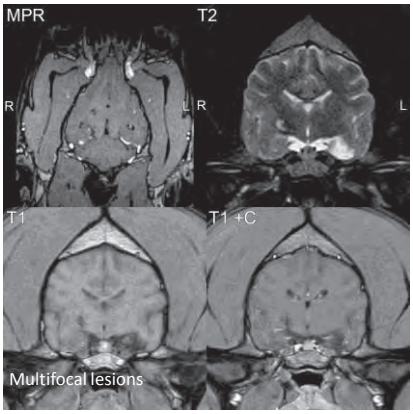
More frequent than previously thought

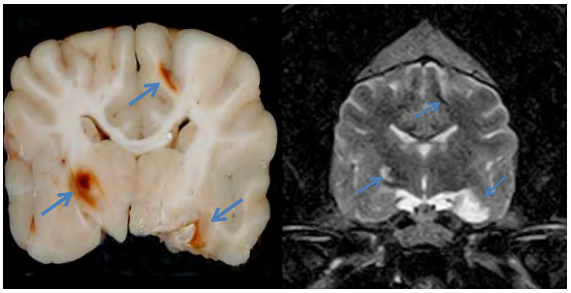
Steinmetz S, Tipold A, Löscher W. Epilepsy after head injury in dogs: a natural model of posttraumatic epilepsy. Epilepsia. 2013;54:580-8



Example of post traumatic seizures

- 3.5 y old golden retriever
  - seizures since one year
  - Treated with phenobarbital and bromide
  - Seizure frequency increases
- CSF normal





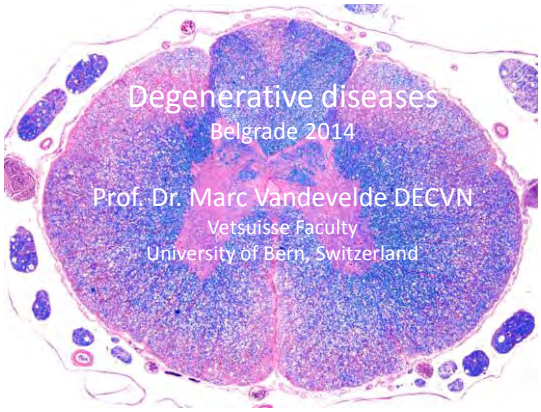
Comparaison with post mortem specimen.
The lesions represent old trauma

Cranial trauma

- Is an emergency situation
- Check whole animal
- Stabilize circulation/respiration
- Monitor neurological function
- Combat brain swelling
- Animals have remarkable ability to recover

Degenerative diseases

Marc Vandevelde, Dr. med.vet. DECVN



Degeneration in the NS

Specific defect of molecules that occur in specific cells

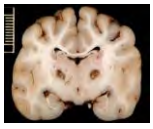
⇩

These cells degenerate and die

⇩

Selective slow atrophy of targeted areas

Anatomical Targets of degenerative disease

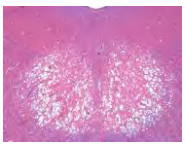


- grey matter: e.g. Alaskan husky encephalopathy
- white matter: e.g. Afghan dog myelopathy

- focal: e.g. cerebello cortical degeneration
- diffuse: e.g.: lysosomal storage disease

Degenerative lesions

- Degeneration is usually slow
- Process is progressive
- Irreversible
- The lesions are bilaterally symmetrical



Classification

Hundreds of different diseases have been described

- Classification according to pathological anatomical criteria
- Molecular classification depending on the primary defect

Anatomo-pathological classification

- Neuronal degenerations
  - Motor neurons
  - Cerebellar cortex
  - Others
- Axonal degenerations
  - Wallerian type
  - Axonal dystrophy
- Myelin degenerations
  - Leukodystrophy
  - Dysmyelination
- Lysosomal storage diseases
- Spongiform encephalopathies
- Spongy degenerations
- Selective symmetrical encephalomalacias

Degenerative diseases general clinical aspects

- Juvenile animals (sometimes late onset)
- Family history
- Hereditary in specific breeds
- Slowly progressive
- Symmetrical signs
- Neurological signs depend on localization:
  =Target of the degenerative process

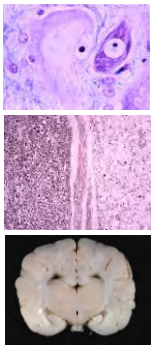
Diagnosis

- History, species, breed, genetic background
- Neurological examination
  - May reveal localisation
  - Hardly truly specific signs
- Diagnostic imaging
  - Detection of bilateral lesions
  - Distribution pattern
- Consult the lists of hereditary diseases
- Molecular genetics: tests are increasingly available

Degenerative diseases

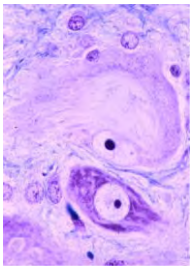
examples

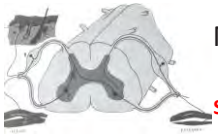
- Neuronal degenerations
  - *Cerebello-cortical degeneration*
  - *Neuronal vacuolation*
- Lysosomal storage diseases
  - *Ceroid lipofuscinosis*
- Axonal diseases
  - *Degenerative myelopathy*
- Myelin diseases
  - *Congenital tremor*
  - *Leukoencephalomyelopathy*
- Spongy degenerations
- Selective symmetrical encephalomalacias

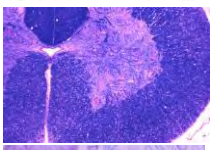


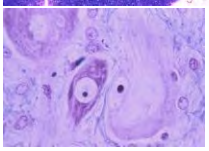
Degenerative diseases

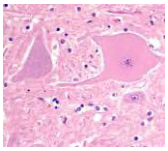
- Neuronal degenerations
- Lysosomal storage diseases
- Axonal diseases
- Myelin diseases
- Spongy degenerations
- Selective symmetrical encephalomalacias









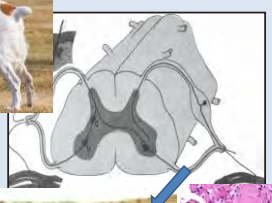


Motor neuron diseases

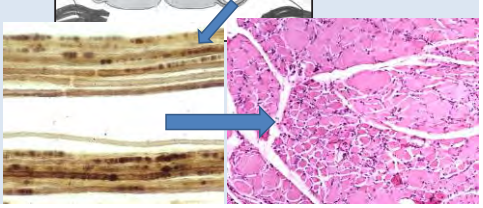
Spinal Muscular Atrophy in:
- Britanny Spaniels
- Lapland dogs
- Rottweilers
- .....

Neurons degenerate In spinal cord and brainstem

Spinal Muscular Atrophy

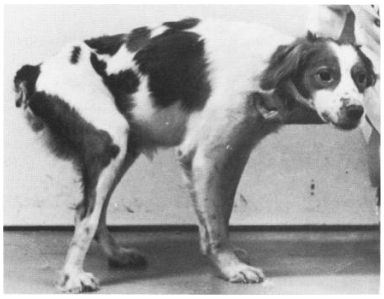


Neurogenic Atrophy

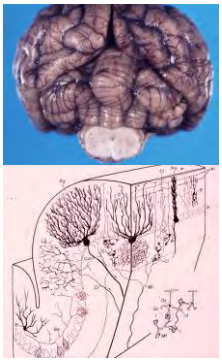


Signs of motor neuron diseases

- Weakness, paresis, paralyis of limbs, trunc, cranial nerves
- Loss of spinal reflexes
- Neurogenic atrophy



Cork LC, Griffin JW, Munnell JF, Lorenz MD, Adams RJ.
Hereditary canine spinal muscular atrophy.
J Neuropathol Exp Neurol. 1979 May;38(3):209–221..

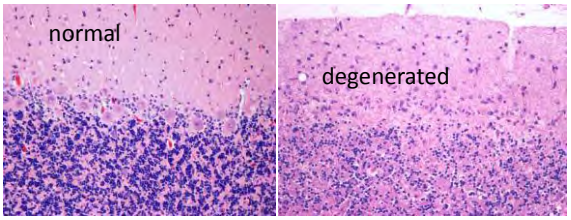


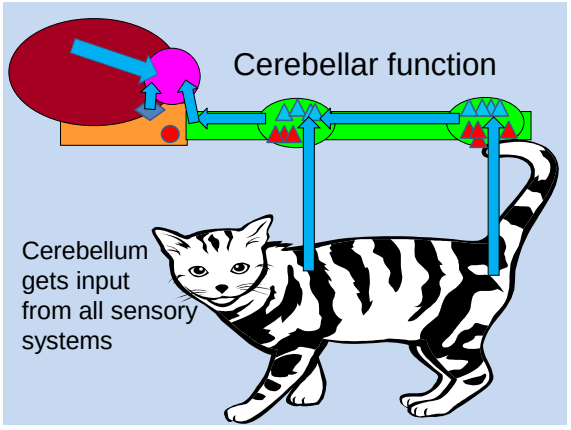
Purkinje cell degenerations

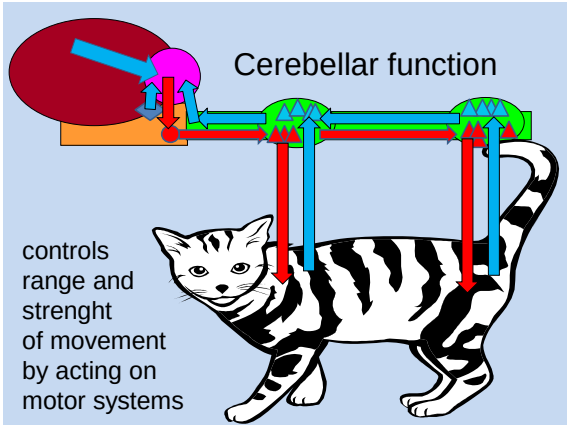
- very large spectrum
- dog, cat
- ca. 40 breeds affected

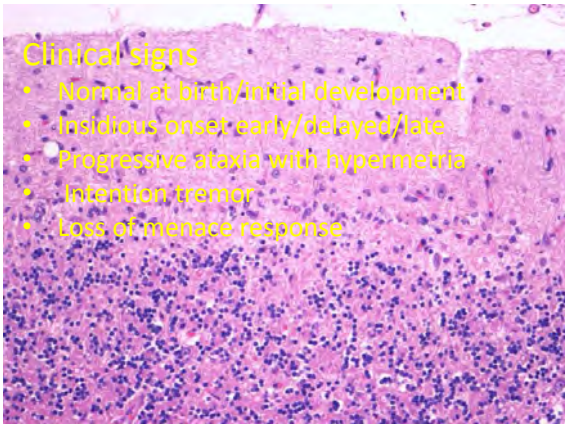
Purkinje cell degeneration

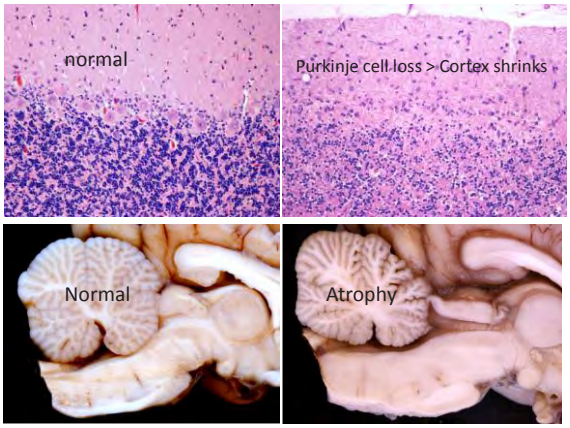
-Purkinje cells die and are lost
-Cerebellar cortex shrinks



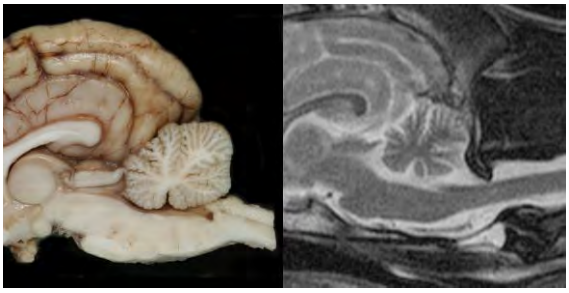








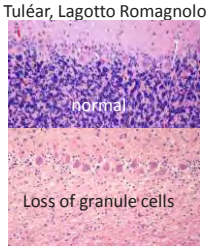
Detection of atrophic cerebellum on MRI



- To much empty space between cerebellum-occipital lobe
- Widening of sulci in cerebellar cortex

Variations of cerebellar degeneration

- **Granule cell degeneration**
- Collies, Border collies, Britanny spaniel, Coton de Tuléar, Lagotto Romagnolo



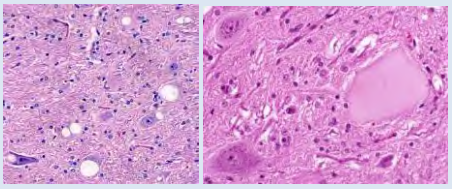
Canine multiple system degeneration

- Kerry blue terrier, Chinese crested dog
- Cerebellum+ olivary nuclei +basal nuclei

Park2 gene defect

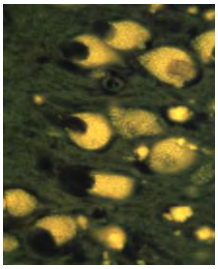
Further examples of neuronal degenerations

- Multisystem degeneration in Cocker Spaniel
- Neuronal vacuolation in Rottweiler dogs/Huskies
- Dementia/old age



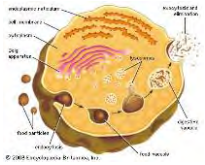
Degenerative diseases

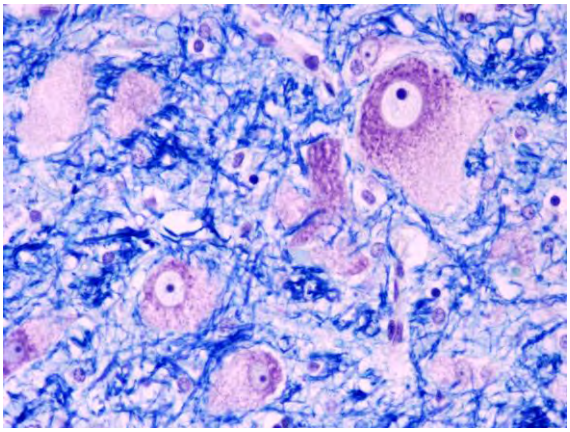
- Neuronal degenerations
- **Lysosomal storage diseases**
- Axonal diseases
- Myelin diseases
- Spongy degenerations
- Selective symmetrical encephalomalacias



Lysosomal storage diseases

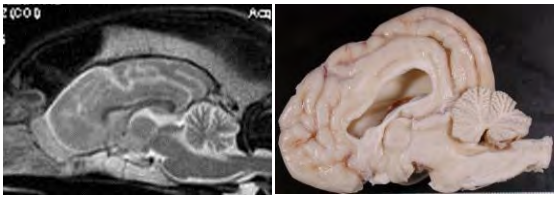
- Genetic defects of lysosomal enzymes
- Enzyme substrate is no longer degraded
- And accumulates in the lysosome



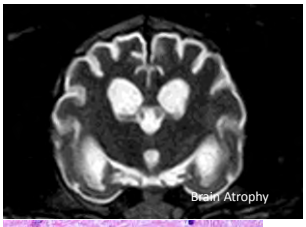


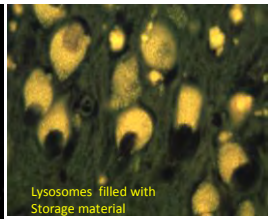
Examples of Lysosomal storage diseases

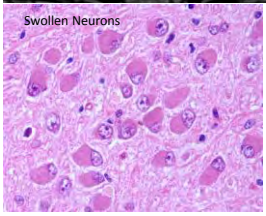
Disease	Breed	Age at onset of symptoms
GM1 Gangliosidosis	Beagle, Siamese, domestic cat	3 to 6 months
GM2 Gangliosidosis	German Pointer (male), Japanese and Springer Spanie; domestic cat	6 - 12 months
Sphingomyelinosis	Poodle; Siamese, Domestic cat	4 - 6 months
Glucocerebrosidosis	Silky Terrier	6 - 8 months
Globoid-Cell-Leukodystrophy (Krabbe)	Westhighland White and Cairn Terrier, Beagle. Poodle; Domestic Cat	6 - 12 monbths
Ceroid Lipofuscinosis	Chihuahua, Saluki,English Setter, Dachshound, **Am. Staffordshire Terrier**	6 months to 2 years (sometimes later)
Fukosidosis	Springer spaniel	2 - 3 years
Glycoproteinosis	Beagle, Basset, Poodle	2 - 12 months
Mannosidosis	Persian Cat, Domestic cat	1 - 3 months



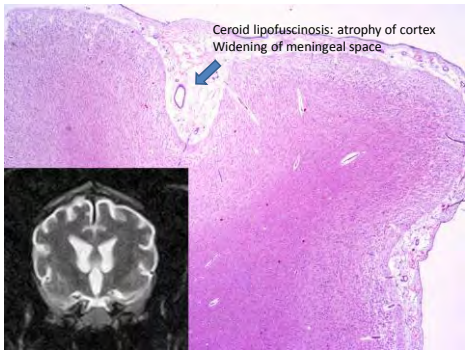
Ceroid lipofuscinosis in Staffordshire Terrier:
Marked atrophy of the cerebellum seen in MRI





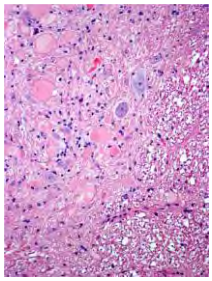


Example of Storage disease:
Ceroid lipofuscinosis in Tibetan Terrier



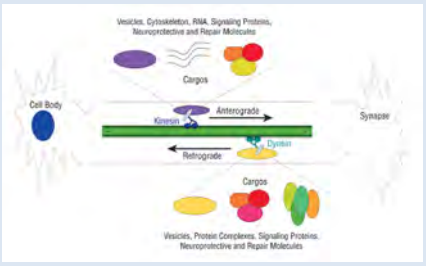
Degenerative diseases

- Neuronal degenerations
- Lysosomal storage diseases
- Axonal diseases
- Myelin diseases
- Spongy degenerations
- Selective symmetrical encephalomalacias



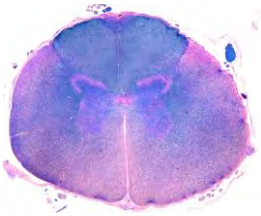
Axonal Transport

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



A lot can go wrong

Clinical signs

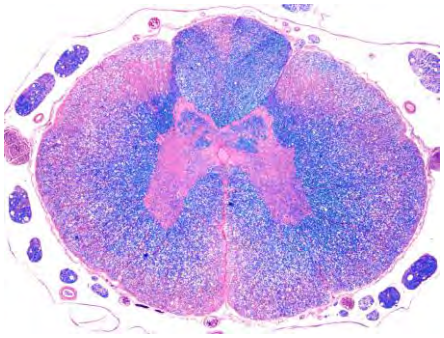


- Insidious onset
- Ataxia
- Hindlimbs progressing to all limbs
- Progressive
- Proprioception but not nociception affected
- In some conditions cerebellar signs

Axonal diseases

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

German shepherd dog ; degenerative myelopathy: diffuse loss of axons (red areas)



Degenerative Myelopathy in large breed dogs

- Large breed dogs, >7 years
- Slow onset and progression of paresis and ataxia in hind limbs
- Diffuse/disseminated loss of axons in spinal cord
- Cause/pathogenesis?
  - Hereditary factors/ SOD 1 mutations?

Degenerative disease groups

- Neuronal degenerations
- Axonal degenerations
- Myelin degenerations
- Lysosomal storage diseases
- Spongiform encephalopathies
- Spongy degenerations
- Selective symmetrical encephalomalacias

Degenerative diseases

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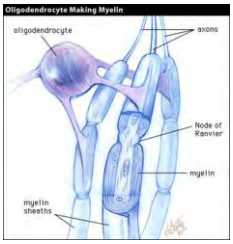
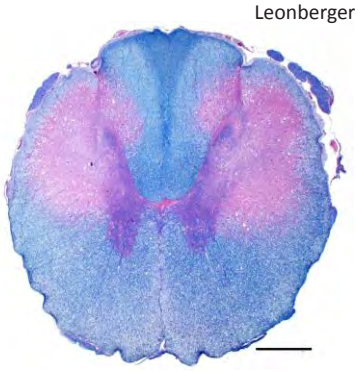


Leukodystrophy

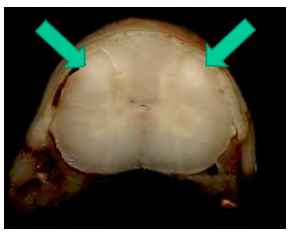
- Lysis of myelin+axons, often bizarre distribution
- Hereditary forms:
  - Cavitating leukodystrophy, Dalmatians
  - Leukomyeloencephalopathy in Rottweiler/Leonberger dogs
  - Fibrinoid leucodystrophy , Labrador ret.
  - Necrotizing myelopathy Afghan, Kooiker dog
  - Globoid cell leucodystrophy (storage disease)

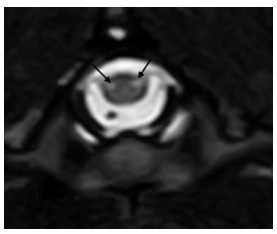
Leonberger



MRI Diagnosis of Leukomyeloencephalopathy

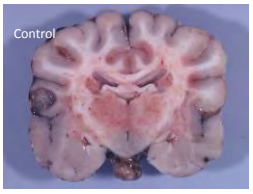
Detection of bilaterally symmetrical lesions
In spinal cord white matter

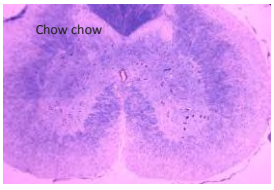


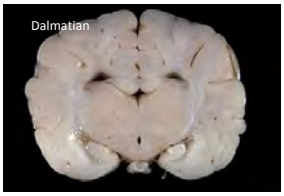


Dysmyelination

Congenital tremor
Lack/deficiency of myelin
Genetic defects in Myelin proteins







Degenerative diseases

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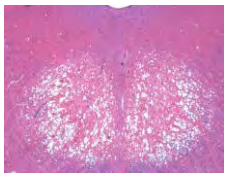

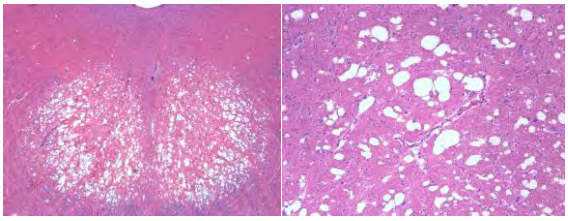

Spongy degeneration : bilaterally symmetrical vacuolation of the tissue

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

Degenerative diseases

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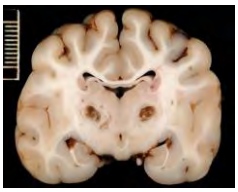
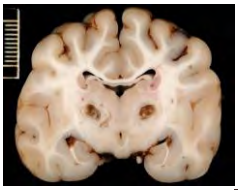
- Spongy degenerations
- Selective symmetrical encephalomalacias



Selective symmetrical encephalomalacias

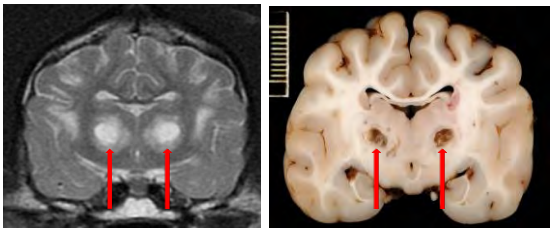


Symmetrical areas of tissue destruction

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

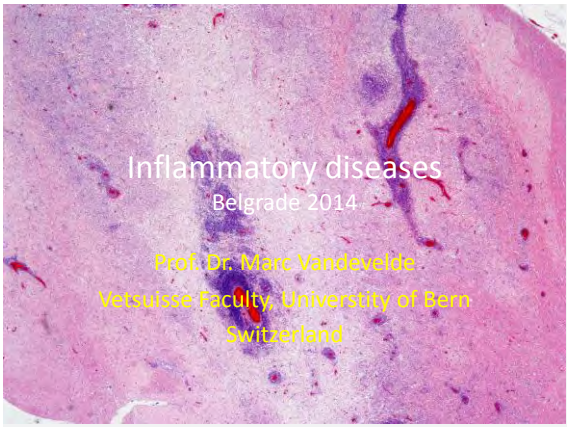
Degenerative diseases

- Juvenile animals, sometimes late onset
- Usually pure bred
- Family history
- Slowly progressive
- Symmetrical
- Normal CSF

Get a post mortem/ save fresh frozen material

Inflammatory diseases

Marc Vandevelde, Dr. med.vet. DECVN



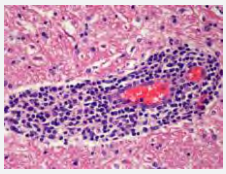
Inflammatory diseases

Inflammation is a very common cause of neurological disease in animals

In many cases inflammation should be considered in the differential diagnosis

Inflammatory diseases

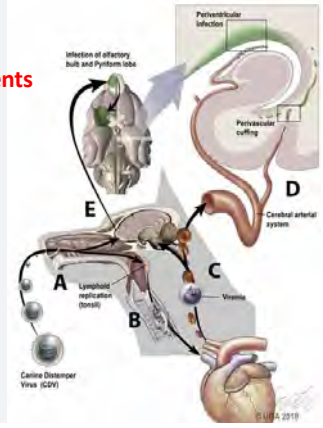
- Lesions are characterized by strong participation of immune cells



- Most are infectious
- Some are (auto)immune diseases

Entry of infectious agents

- Blood
- Nose
- Peripheral nerves



Response to infection

Entry of infectious agent

↓

Recognition by local immune cells

↓

Signals to the immune system

↓

Influx of inflammatory cells from the blood

↓

Immune cells attack infectious agent

Autoimmune diseases

Certain molecules in the nervous system are changed/abnormally presented

↓

Recognized by the immune-system as non-self

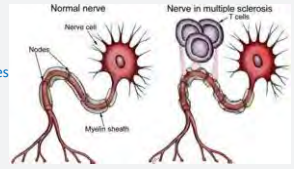
↓

Influx of inflammatory cells from the blood

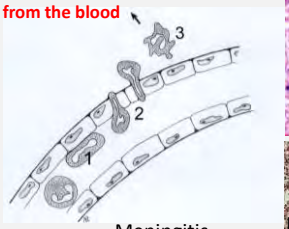
↓

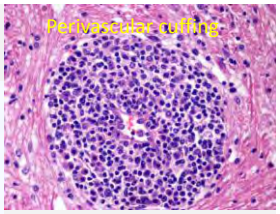
Immune system attacks the nervous system

-White matter
-Grey matter
-Blood vessels
-Meninges
-Peripheral nerves



INFLAMMATION:
Invasion of immunecells in the brain from the blood

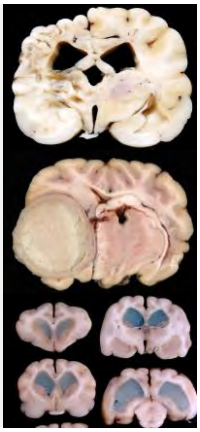




- Meningitis
- Encephalitis
- Myelitis
- Ependymitis
- Chorioiditis

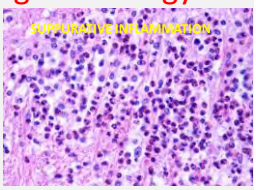
Effects of the inflammatory response

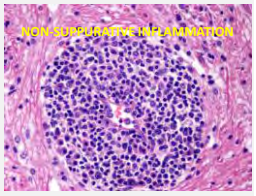
- Tissue destruction
- Space occupying effect
  - Abcess
  - Granuloma
- Obstruction of CSF pathways
  - hydrocephalus
  - Hydromyelia



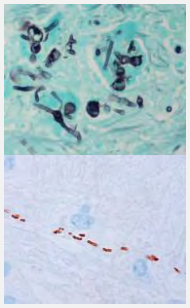
Variations depending on etiology

- Focal-multifocal-dissiminated lesions
- Specific cell compartment
  - Grey matter-white matter
  - CSF pathways
  - Bloodvessels
  - Specific anatomy
- Type of immune response
  - Suppurative
  - non suppurative
  - granulomatous

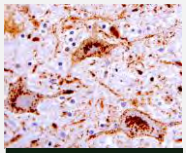


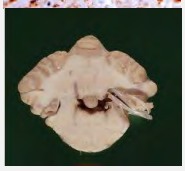


Causes



- Bacterial
- Viral
- Fungal
- Protozoal
- Helmintic
- Autoimmune





Diagnosis of inflammatory diseases

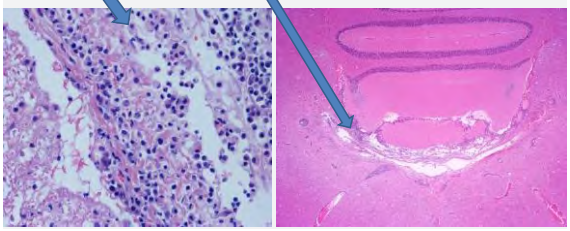
- Species, geography, age, breed
- Onset,course
- Neurological examination: rarely specific
  - Evidence for multifocal lesions
  - Etiology-specific localization
- General examination, hematology sometimes helpful
- Special examination techniques

Special examinations

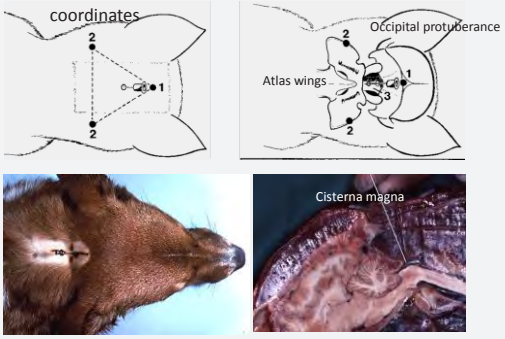
- Cerebro Spinal Fluid
- Diagnostic imaging: CT
  MRI
- Serology
- Demonstration of infectious agent
  - PCR
  - Immunedetection

CSF

The most important aid to detect inflammation since inflammatory cells also invade the meningeal and ventricular spaces

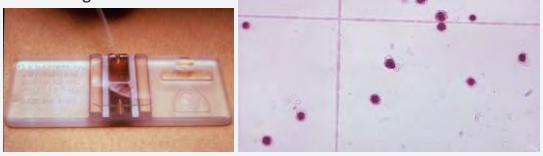


Taking spinal fluid



Cell count

Some CSF + vital dye in Counting chamber



Normal: up to 5 nucleated cells /microliter

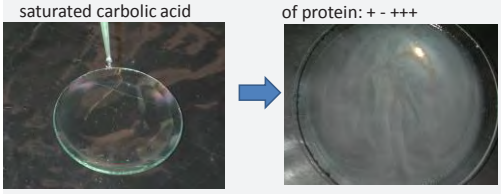
>5 cells/microliter: **pleocytosis**

Protein determination

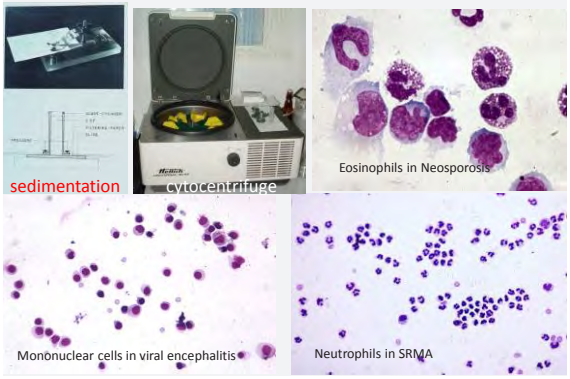
- Several techniques
- Pandy test: simple, cheap, fast, effective

A few drops of CSF in saturated carbolic acid

Turbidity depending on amount of protein: + - +++

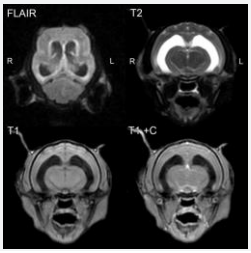


CSF Cytology: type of inflammation



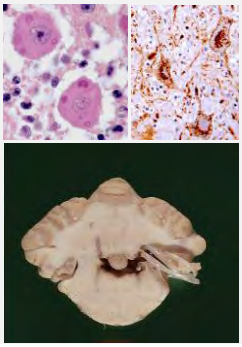
Diagnostic imaging

- Radiology rarely helpful: ear/nose infections
- CT for extensive/space occupying lesions
- MRI : by far the best resolution
  Standard protocol:
  – T1W, T2W, FLAIR,
  – T1W+ contrast



Common infectious diseases

- Viral
  - Rabies
  - Canine distemper
  - Tick born encephalitis
  - FIP
- Bacterial
  - Abscess (otogenic)
  - Embolic bacterial encephalitis
- Fungal/Algal
  - Aspergillosis
  - Cryptococcosis
- Protozoal
  - Neosporosis
  - Toxoplasmosis
- Helmintic
  - Angiostrongylosis
  - Dirofilariosis



Examples of infections

- Canine distemper encephalitis
- Feline infectious peritonitis
- Neosporosis

Example of distemper Puppie mixed breed, M

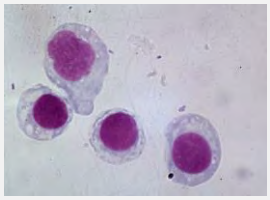
- A few days ago acute onset of gait problems in the hind limbs
- Rapid progression
- Neurological examination:
  - Gen. Paresis/Ataxia
  - Myoclonic Jerks

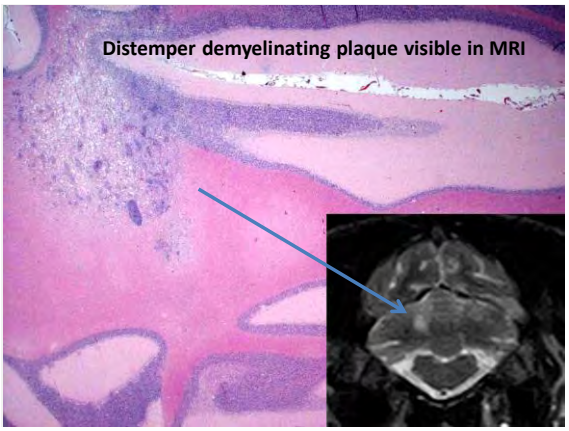
Myoclonus

- Frequent sign in distemper
- Highly diagnostic
- Focal-generalized

Further examinations

- CSF
  pleocytosis (35 cells/microliter)
  elevated protein



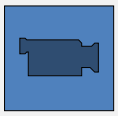


Distemper Prognosis/therapy

- Prognosis guarded
- Treatment palliative

Example of FIP Persian cat 5 Y, F

- Headtilt since a few days and progressive gait disturbance

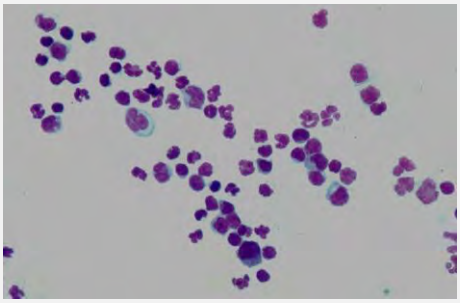


Persian cat 5 Y, F

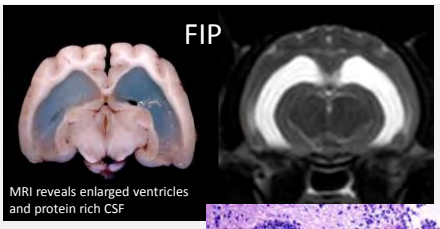
- General exam normal
- Neurological exam
  - Behaviour/conciousness: depressed
  - Gait: severe vestibular ataxia
  - Cranial nerves:head tilt, positional rot. nystagmus, Decreased menace
  - Postural reactions: decreased/assymetrical

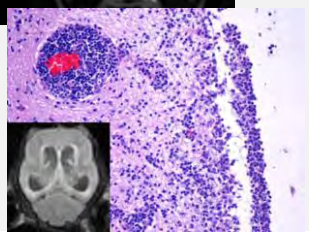
Multifocal

CSF: Mixed pleocytosis



Diagnostic for FIP





MRI shows typical periventricular inflammation hyperintensity of ventricular walls in FLAIR

Prognosis/treatment

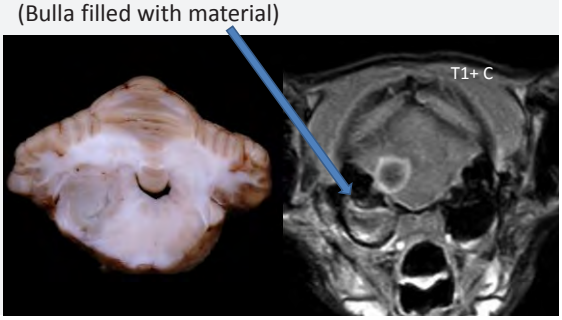
- Prognosis is bad
- Anti inflammatory/immunosupressive

Other infectious diseases

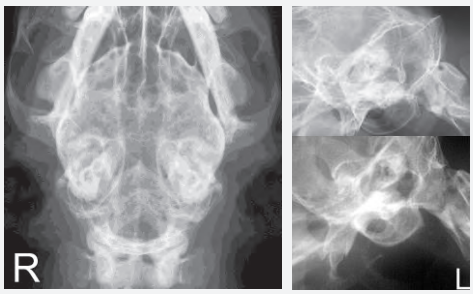
- Bacterial
  - Metastatic from other organs
  - Traumatic
  - Extension from ear or nose
- Fungal
- Protozoal
- Parasitic

Example of bacterial infection

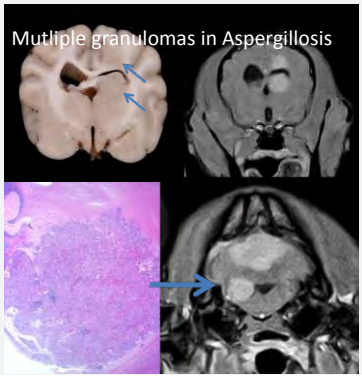
Dog with brainstem abscess resulting from Middle/Inner ear infection
(Bulla filled with material)



Xray: Detection of Otitis media as underlying cause of brain abscess



Example of fungal infection:

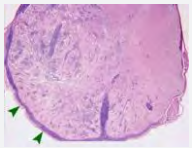


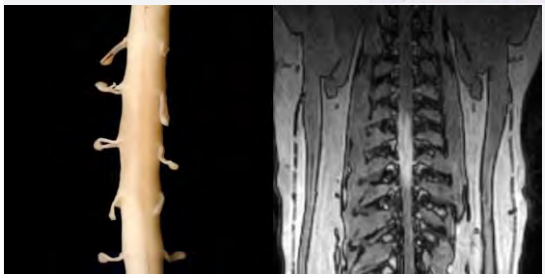
Protozoal infection

- Neospora caninum
- In juvenile dogs CNS + PNS and muscle

Example of young boxer with paresis and painfull atrophic muscles

(rare) example of toxoplasmosis segmental myelitis in a cat the lesion was nicely visible in MRI





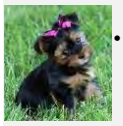
Non-infectious inflammatory diseases

- Mostly in dogs
- Assumed to be (auto)immune diseases
- Target tissue: Brain, Meninges, Bloodvessels, peripheral nerves

  - **Steroid responsive meningitis arteritis**
  - **Granulomatous meningo-encephalitis (GME)**
  - **Necrotizing meningo-encephalitis (NME)**
  - **Necrotizing encephalitis (NE)**
  - **Eosinophilic meningo-encephalitis**
  - ***White shaker syndrome***
  - **Polyneuritis**
  - **Polymyositis**

Canine non infectious encephalitides

- Granulomatous Meningo Encephalitis (GME) in many breeds

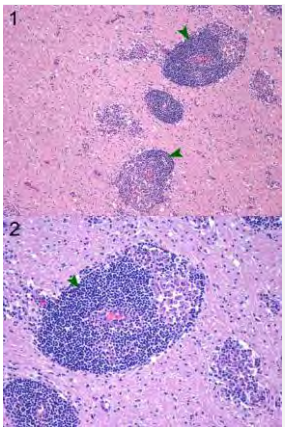


- Necrotizing encephalitis (NE) in Yorkshire terrier, Maltese, Chihuahua,Boston Terrier, Shih Tzu, Coton de Tulear, Papillon

- Necrotizing meningoencephalitis (NME) in Pug dogs, French Bulldog, Pommeranian

Non infectious encephalitides

- Cause is unknown
- Small breeds
- Sporadic
- Epidemiology NME: no riskfactors
- Immunediseases?
  - No infectious agents found
  - Respond to immunosupressive therapy
  - Demonstration of antibodies against CNS antigens
  - There maybe an association with leukocyte antigens

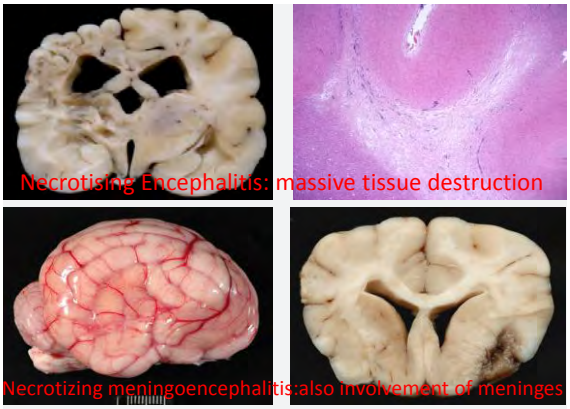


GME

- Adult dogs
- Angiocentric lesions
  Around bloodvessels:
  - Infiltration of inflammatory cells
  - Proliferation of Histioytes
- More in white than in grey matter
- Different forms:
  - Multifocal
  - Focal
  - Eye-Brain

Example of GME

- 5 y old dog with subacute progressive signs
- Marked Forebrain localization with circling

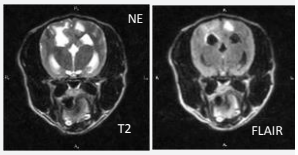


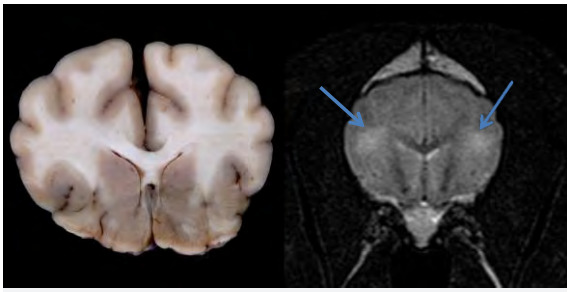
Example of NE

- 9 y old male Yorkshire Terrier
- Chronic neurological signs
- Multifocal; tetraparesis, more marked on the left

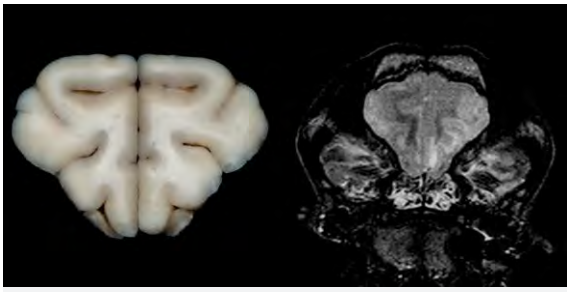
Diagnosis of non infectious encephalitides

- Breed, mostly adults
- Acute-subacute-chronic
- Helpful signs
  - All: multifocal
  - NME: Seizures
  - NE: vestibular signs
  - GME: paraspinal pain
- CSF
- MRI





GME. Hyperintensity of white matter in MRI



NME: cortical superficial involvement well visible in MRI

Treatment

- Concept: Immunosupression/anti-inflammatory
- Large statistically meaningful studies are lacking
- Several small studies
  - Small case numbers
  - Weak diagnosis
- Traditionally: Longterm glucocorticosteroids
- Since a few years: combined with Immunosupressives

Prednisolone

Prednisolone
- 1·5 mg/kg BID/ 3 Weeks
- 1·0 mg/kg BID/ 6 Weeks
- 0·5 mg/kg BID/ 3 Weeks
- 0·5 mg/kg QD/ 3 Weeks
- 0·5 mg/kg every other day indefinitely

(eventuelly reducing to 0.25 mg)

L. R. Talarico & S J. Schatzberg
Journal of Small Animal Practice. 51, 146,2010

Kombinations

Prednisolone

+

cytosine arabinoside
procarbazine
cyclosporine,
lomustine
leflunomide
mycophenolate
mofetil
azathioprine

All seem to work!!

Bern/Zürich/Leipzig

- Prednisolone + Lomustine 50mg/m2
- Regular hematology
- Generelly good results
- But also a few bad complications(Sepsis)

Other targets besides brain tisssue of the immune system

- Meninges/Arteries:
  - Steroid Responsive Meningitis Arteritis (SRMA) in dogs
  - Neckpain, fever, neutrophilia
  - Diagnosis: CSF
  - Effective treatment with steroids
- Peripheral Nerves
  - Polyneuritis
- Muscles
  - Myositis

Polyneuritis

- Most common PNS inflammatory problem
- Acute onset rapid progression
- Lower motor neuron signs
- Prognosis generally good

Example: 10 Y old Mongrel, progressive weakness first hindlimbs then frontlimbs as well

Inflammatory diseases

- Extremely wide spectrum
- Infectious and non-infectious entities
- CSF examination is essential
- Many can be treated

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Holger graduated from the Veterinary School Hanover in 2001 followed by a PhD in Neuropharmacology. He then completed his clinical training at the Royal Veterinary College (RVC) and was then awarded the Diploma of the European College of Veterinary Neurology. He is currently Clinical Director of the RVC's small animal referral hospital, Professor and Head of Veterinary Neurology & Neurosurgery at the RVC and Vicepresident of the European College of Veterinary Neurology.

Canine and feline epilepsy

Holger Volk DVM PGCAP DipECVN PhD FHEA MRCVS

RVC Royal Veterinary College University of London

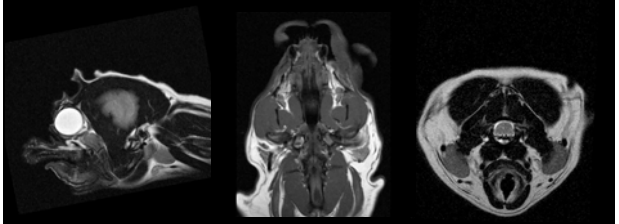
Canine and feline epilepsy

Holger A. Volk DVM, DipECVN, PhD, FHEA, MRCVS
Clinical Director & Professor of Veterinary Neurology & Neurosurgery
Royal Veterinary College

Sharing passions, shaping futures

"Angst"

Complex simplicity



The tools

Your Brain

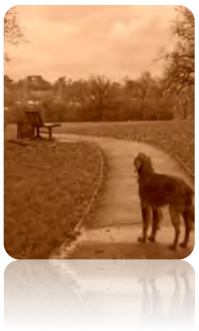
History

Neurological examination

RVC

The path

1. Define the problem
2. Define the system and location
3. Define the lesion



RVC

Presenting Complaint — Problem

History & Physical Exam & NEURO EXAM — System

Define & Refine PROBLEM — Location

Differential Diagnoses

Diagnostic Tests

DIAGNOSIS — Lesion

Treatment Plan

Labrador, 3yrs, FS

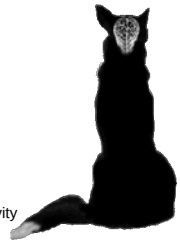
•Poppy had four collapsing episodes in the last month

•The physical examination and neurological examination were unremarkable

RVC

Definition of seizures

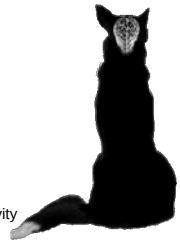
What is the definition of seizures?



- Your current brain activity
- Hopefully not your current brain activity

Definition of seizures

What is the definition of seizures?



- Your current brain activity
- Hopefully not your current brain activity

Definition of seizures

- Transient and involuntary change in behaviour or neurological status due to the abnormal activity of populations of CNS neurons
- Hypersynchronous: “Neurons are firing at the same time”

Seizure?

Royal Veterinary College

Seizure?

Royal Veterinary College

Seizure?

Royal Veterinary College

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Parallel Mapping and Simultaneous Sequencing Reveals Deletions in *BCAN* and *FAM83H* Associated with Discrete Inherited Disorders in a Domestic Dog Breed

Oliver P. Forman[1]*, Jacques Penderis[2]*, Claudia Hartley[1]*, Louisa J. Hayward[1], Sally L. Ricketts[1], Cathryn S. Mellersh[1]

1 Kennel Club Genetics Centre, Animal Health Trust, Kentford, United Kingdom, 2 The School of Veterinary Medicine, University of Glasgow, Glasgow, United Kingdom

- Mutation in *BCAN* ->
  - brevican (Member of hyaluronan- binding chondroitin sulfate proteoglycan family)
  - important in organisation of nodes of Ranvier
- 17/56 homozygous but not affected

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Parallel Mapping and Simultaneous Sequencing Reveals Deletions in *BCAN* and *FAM83H* Associated with Discrete Inherited Disorders in a Domestic Dog Breed

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  - important in organisation of node
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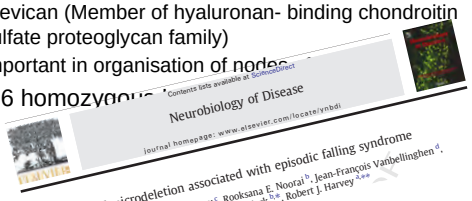

A canine *BCAN* microdeletion associated with episodic falling syndrome

Jennifer L. Gill[a], Kate L. Tsai[b], Christa Krey[c], Rooksana E. Noorai[b], Jean-François Vanbellinghen[d], Laurent S. Garosi[e], G. Diane Shelton[f], Leigh Anne Clark[b,g], Robert J. Harvey[a,**]

RVC

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Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Startle disease in Irish wolfhounds associated with a microdeletion in the glycine transporter GlyT2 gene

Jennifer L. Gill[a], Deborah Capper[b], Jean-François Vanbellinghen[c], Seo-Kyung Chung[d], Robert I. Higgins[e], Mark I. Rees[d], G. Diane Shelton[f,g], Robert J. Harvey[a,g,**]

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Startle disease

ABSTRACT

Defects in glycinergic synaptic transmission in humans, cattle, and rodents result in an exaggerated startle reflex and hypertonia in response to either acoustic or tactile stimuli. Molecular genetic studies have determined that mutations in the genes encoding the postsynaptic glycine receptor (GlyR) α1 and β subunits (*GLRA1* and *GLRB*) and the presynaptic glycine transporter GlyT2 (SLC6A5) are the major cause of these disorders. Here, we report the first genetically confirmed canine cases of startle disease. A litter of seven Irish wolfhounds was identified in which two puppies developed muscle stiffness and tremor in response to handling. Although sequencing of *GLRA1* and *GLRB* did not reveal any pathogenic mutations, analysis of SLC6A5 revealed a homozygous 4.2 kb microdeletion encompassing exons 2 and 3 in both affected animals. This results in the loss of part of the large cytoplasmic N-terminus and all subsequent transmembrane domains due to a frameshift. This genetic lesion was confirmed by defining the deletion breakpoint, Southern blotting, and multiplex ligation-dependent probe amplification (MLPA). This analysis enabled the development of a rapid genotyping test that revealed heterozygosity for the deletion in the dam and sire and three other siblings, confirming recessive inheritance. Wider testing of related animals has identified a total of 13 carriers of the SLC6A5 deletion as well as non-carrier animals. These findings will inform future breeding strategies and enable a rational pharmacotherapy of this new canine disorder.

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Seizure?

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Seizure?

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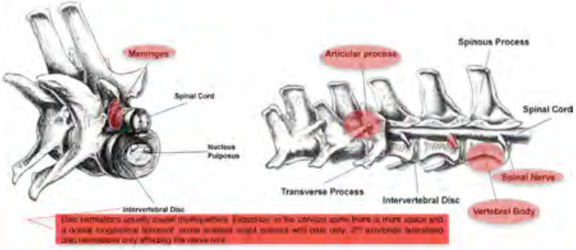
Location of lesion

Which structures could cause pain and surround or are close to the spinal cord?



Seizure?

Royal Veterinary College

Seizure?

Royal Veterinary College

An Inherited Episodic Head Tremor Syndrome in Doberman Pinscher Dogs

Martina Wolf, DVM,[1] Andreas Bruehschwein, PhD,[2] Carola Sauter-Louis, PhD,[3] Adrian C. Sewell, PhD,[4] and Andrea Fischer, PhD[1]*

Movement Disorders,

TABLE 1. Phenomenology of episodic head tremor in Doberman pinschers

Parameter	Description			Comments
Direction	Vertical 24.1%	Horizontal 66.7%	Both directions 9.2%	Direction of head movements never changed during a single episode.
Velocity (Hz)	5.4–8.3 Hz (median: 6.5 Hz)			Velocity and amplitude varied between episodes and dogs, even in a single episode. Sometimes head tremors stopped for less than 1 sec and continued with different velocity and amplitude
Amplitude	Variable			
Duration of an episode	10 seconds to 3 hours (median: 3 minutes)			
Cluster episodes	0 to 20 episodes/day (median: 2 episodes/day)			
Intervals without head tremor	0 to 1800 days (median: 60 days)			

RVC

Movement Disorders,

RESEARCH ARTICLE

Idiopathic Head Tremor in English Bulldogs

Julien Guevar, DVM,[1,2] Steven De Decker, DVM, PhD,[2] Luc M.L. Van Ham, DVM, PhD, DECVN,[3] Andrea Fischer, DVM, PhD, DECVN,[4] and Holger A. Volk, DVM, PhD, DECVN[2]*

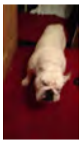


TABLE 1. Phenomenology of idiopathic head tremors in English bulldogs

Parameters	Results
Direction	Vertical/horizontal
Frequency range	4.8-6.2 Hz (median, 5.75 Hz)
Duration	Seconds to 3 hours
Episodes per day	1–11 (median, 2)

TABLE 2. Comparison of movement characteristics of idiopathic head tremors (IHTs) in English bulldogs (EBs) and Doberman pinschers (DPs) with some human movement disorders

Movement disorder	Essential tremor	Dystonic tremor	Cerebellar tremor	Paroxysmal dyskinesia	Clonus	IHT in EBs	IHT in DPs
Localization	Hands, head, vocal cords			Head: not reported	Generally involves extremities	Head	Head
Head localization	Yes (infrequent)[a,b]	Yes	Yes	N/R	Yes	Yes (only)	Yes[c]
Movement driven	No	No	Yes	No	No	No	
Paroxysmal	No	No	No	Yes	No	Yes	Yes
Frequency (Hz)	4–8	3–12	2–4	4–7	N/A	4–7	5–9

N/R, not reported; N/A, not applicable.
[a]Inclusion of isolated head tremor in essential tremor is controversial and a notion of duration (3–5 years) is included in order to distinguish from other tremor syndromes.
[b]In general, head tremor is associated with mild arm tremor, and isolated head tremor is very rare.[18-20]
[c]Coexistent cervical dystonia reported.

Seizure?

Royal Veterinary College

Seizure?

Courtesy of Dr. Katia Marioni

Seizure?

Courtesy of Dr. Katia Marioni

Phenotypic characterisation of canine epileptoid cramping syndrome in the Border terrier

V. Black*, L. Garosi*, M. Lowrie*, R. J. Harvey† and J. Gale‡

*Davies Veterinary Specialists, Higham Gobion
†Department of Pharmacology, UCL School of Pharmacy, London
‡Hythe, Southampton
V. Black's current address is Department of Clinical Veterinary Science, University of Bristol, Langford House, Langford, Bristol BS40 5DU

Objectives: To characterise the phenotype of Border terriers suspected to be affected by canine epileptoid cramping syndrome and to identify possible contributing factors.

Methods: Owners of Border terriers with suspected canine epileptoid cramping syndrome were invited to complete an online questionnaire. The results of these responses were collated and analysed.

Results: Twenty-nine Border terriers were included. Most affected dogs had their first episode before 3 years of age (range: 0·2 to 7·0 years). The majority of episodes lasted between 2 and 30 minutes (range: 0·5 to 150 minutes). The most frequent observations during the episodes were difficulty in walking (27 of 29), mild tremor (21 of 29) and dystonia (22 of 29). Episodes most frequently affected all four limbs (25 of 29) and the head and neck (21 of 29). Borborygmi were reported during episodes in 11 of 29 dogs. Episodes of vomiting and diarrhoea occurred in 14 of 29, with 50% of these being immediately before or after episodes of canine epileptoid cramping syndrome (7 of 14). Most owners (26 of 29) had changed their dog's diet, with approximately 50% (14 of 26) reporting a subsequent reduction in the frequency of episodes.

Clinical Significance: This study demonstrates similarities in the phenotype of canine epileptoid cramping syndrome to paroxysmal dystonic choreoathetosis, a paroxysmal dyskinesia reported in humans. This disorder appears to be associated with gastrointestinal signs in some dogs and appears at least partially responsive to dietary adjustments.

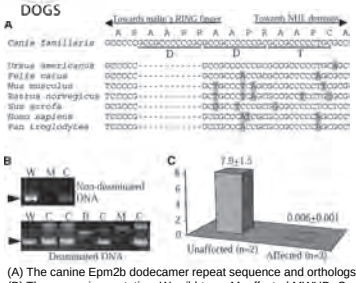
Seizure?

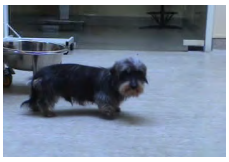
Courtesy of Dr. Clare Rusbridge

Royal Veterinary College

Expansion mutation

LAFORA DOGS





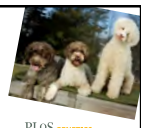
H Lohi et al. Science 2005;307:81-81

(A) The canine Epm2b dodecamer repeat sequence and orthologs.
(B) The expansion mutation. W, wild-type; M, affected MWHD; C, carrier; B, affected basset hound; arrowheads, normal alleles; other bands, mutant alleles.
(C) Muscle Epm2b mRNA amounts normalized against Gapdh (1).

Published by AAAS

Science AAAS

Genetic Profiling



OPEN ACCESS Freely available online PLoS GENETICS

LGI2 Truncation Causes a Remitting Focal Epilepsy in Dogs

Eija H. Seppälä[1,2], Tarja S. Jokinen[3], Masaki Fukata[4], Yuko Fukata[4,5], Matthew T. Webster[6], Elinor K. Karlsson[7,8], Sami K. Kilpinen[9], Frank Steffen[10], Elisabeth Dietschi[11,12], Tosso Leeb[11], Ranja Eklund[1,2], Xiaochu Zhao[13], Jennifer J. Rilstone[13], Kerstin Lindblad-Toh[6,7], Berge A. Minassian[13,14], Hannes Lohi[1,2]*

OPEN ACCESS Freely available online PLoS one

Identification of a Novel Idiopathic Epilepsy Locus in Belgian Shepherd Dogs

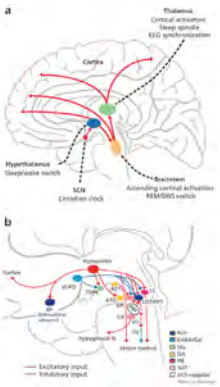
Eija H. Seppälä[1,2,3], Lotta L. E. Koskinen[1,2,3], Christina H. Gullev[4], Päivi Jokinen[1,2,3], Peter Karlskov-Mortensen[5], Luciana Bergamasco[6], Izabella Baranowska Körberg[7], Sigitas Cizinauskas[8], Anita M. Oberbauer[9], Mette Berendt[4], Merete Fredholm[5], Hannes Lohi[1,2,3]*

1 Research Programs Unit, Molecular Medicine, University of Helsinki, Helsinki, Finland, 2 Department of Veterinary Biosciences and Department of Medical Genetics, University of Helsinki, Helsinki, Finland, 3 Folkhälsan Institute of Genetics, Helsinki, Finland, 4 Department of Small Animal Clinical Sciences, University of Copenhagen, Copenhagen, Denmark, 5 Department of Basic Animal and Veterinary Sciences, University of Copenhagen, Copenhagen, Denmark, 6 College of Veterinary Medicine, Kansas State University, Manhattan, Kansas, United States of America, 7 Department of Animal Breeding and Genetics, Swedish University of Agricultural Sciences, Uppsala, Sweden, 8 Referral Animal Neurology Hospital Aisti, Vantaa, Finland, 9 Department of Animal Science, University of California Davis, Davis, California, United States of America

Seizure?

Courtesy of Dr. Annette Wessmann

Narcolepsy



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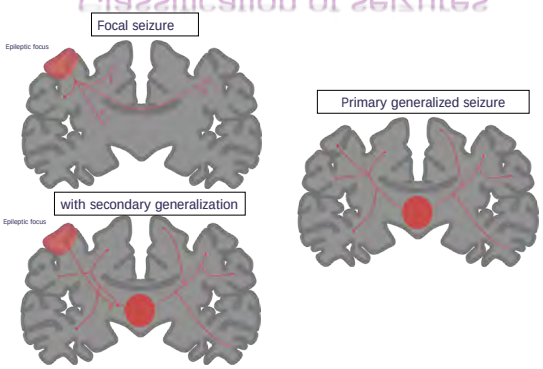
Classification of seizures



Video comparison study

SPECIALISTS VS NON SPECIALISTS

- From Chi-squared analyses:
  - Specialists were LESS LIKELY to categorise the videos as being seizures than non-specialists (specialist: non seizures 32% vs. non-specialist: non seizures 25.3%; X^2: 7.01, p=0.008)
  - Specialists were MORE LIKELY to state that **motor** signs WERE present (specialist: 97.5% vs. non-specialist: 95.2%; X^2: 5.38, p=0.02)
  - Specialists were MORE LIKELY to state that **neurobehavioural** signs WERE present (specialist: 58.9% vs. non-specialist: 53%; X^2: 4.67, p=0.031)
  - There was NO DIFFERENCE between specialists vs. non specialists as to whether **autonomic** signs were present

Events that can mimic seizures

- **Syncope**
  - **Partial or complete loss of consciousness**
  - **Lack of motor activity**
  - **No post-ictal signs**
  - **Shorter in duration**
- **Narcolepsy**
  - **Stimulated often by excitement, food, pharmacologically**
- **Pain**
- **Vestibular syndrome**

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Events that can mimic seizures

- **Movement disorder**
  - Scotty Cramp
  - Cavalier King Charles Spaniel – episodes of tetany, hypertonicity, “deer-stalking”
  - Boxers – paroxysmal dystonic choreoathetosis
  - Bichon frises – similar to Boxers
  - Head bobbing (Bulldogs, Doberman Pinschers)
  - Border Terrier (canine epileptoide cramping syndrome?),….

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History

- Seizures typically last around 1 minute.
- Seizures exhibit several stages
- Seizures often, but not always, occur at rest or out of sleep.
- Clonic movements (rhythmic muscle contractions) are common in both partial and generalized seizures
- Most recurrent seizures respond at least in part to antiepileptic drugs.
- EEG

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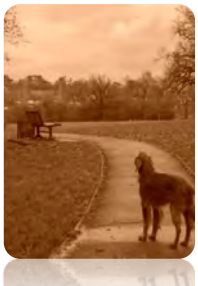
The path



1. Define the problem
2. Define the system and location
3. Define the lesion

RVC

Labrador, 3yrs, FS

- Poppy had four seizures in the last month
- The physical examination and interictal neurological examination were unremarkable

RVC

Have you ever cooked spaghetti?

RVC

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Classification by aetiology

- Symptomatic or secondary seizure
  - Structural brain lesion
- Reactive seizure
  - Metabolic or toxic cause
- Idiopathic or primary epilepsy
  - Suspected genetic cause
- Possible symptomatic or cryptogenic seizure
  - Rule out only via PME…

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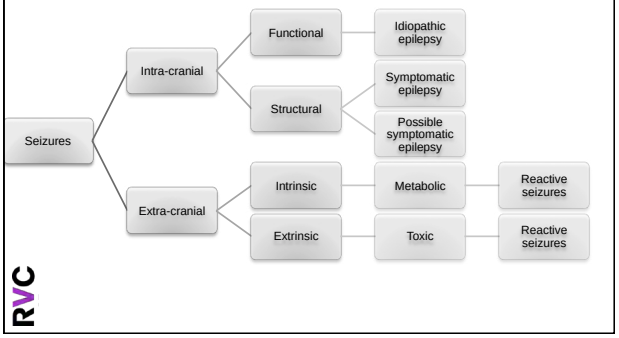
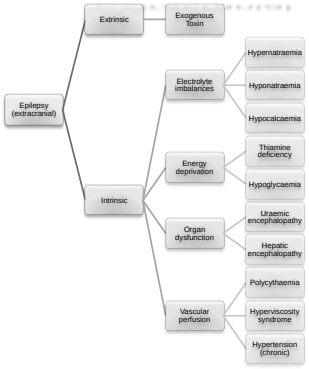
Classification by aetiology



RVC

Extracranial



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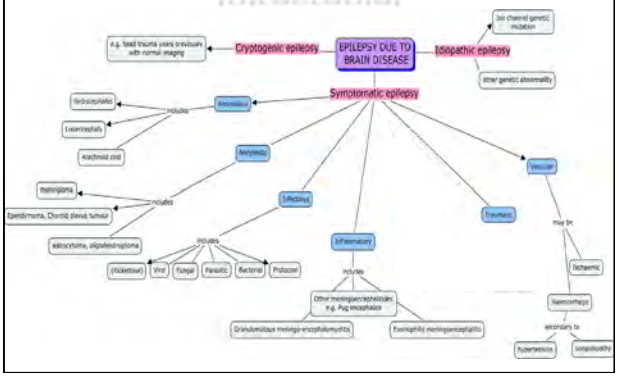
Intracranial

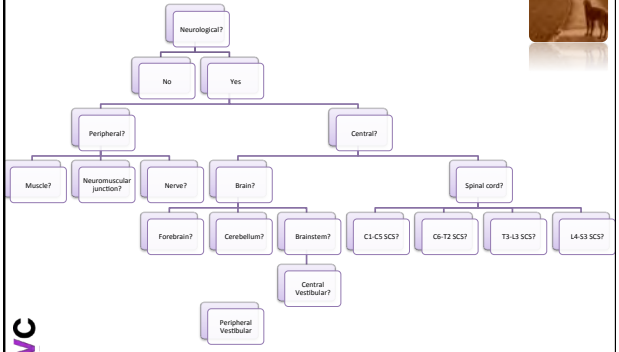


The path

1. Define the problem
2. Define the system and location
3. Define the lesion

RVC

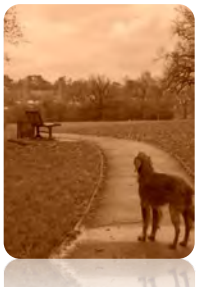
1. **Mentation**
2. **Posture**
3. **Gait**
4. **Postural Reactions**
5. **Cranial Nerves**
6. **Spinal Reflexes**
7. **Palpation**
8. **Nociception**



RVC

The path

1. Define the problem
2. Define the system and location
3. Define the lesion



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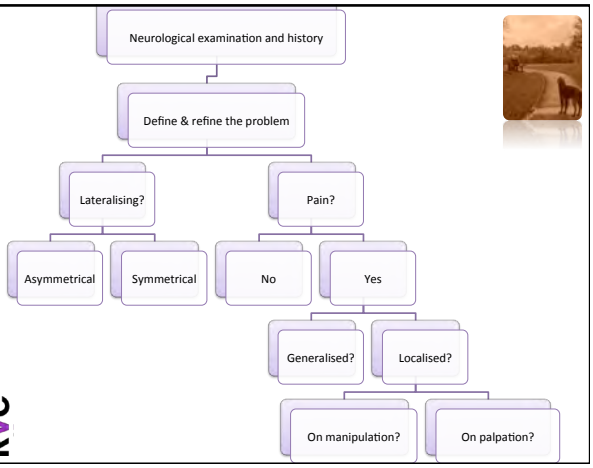

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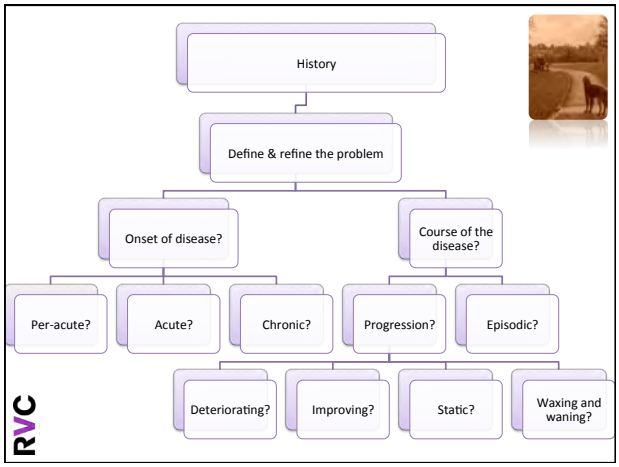
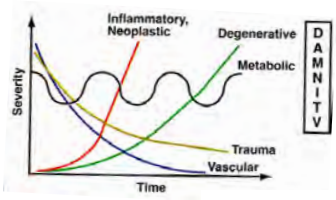


RVC

Differential diagnoses

D	Degenerative
A	Anomalous
M	Metabolic
N	Neoplastic Nutritional
I	Infectious Inflammatory Iatrogenic Idiopathic
T	Toxic Traumatic
V	Vascular



Define & refine the problem

How can we define the lesion now by the neuro-hand rule?

1.Onset, 2.clinical course, 3.pain, 4.lateralising, 5.neurological localisation

Example:
•Acute, onset, non-deteriorating, lateralising, painful forebrain disease

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Do not forget signalment

•Breed
•Age
•Sex

RVC

Inter-ictal neuroexam findings
Normal?
Lateralising?

Normal	Abnormal - symmetrical	Abnormal - asymmetrical
Idiopathic Epilepsy	Metabolic	Neoplasia
Metabolic Wax and wane phenomenon	Toxic	Inflammatory/Infectious
Neoplasia "silent" area of the brain; early in disease process	Hydrocephalus Degenerative disease	Anomalies
Toxic	Midline structural disease (e.g. pituitary neoplasia)	
	!?Postictal?!	

RVC

Seizures
Lateralising?

Symmetrical – generalized onset	Asymmetrical – focal onset
Idiopathic Epilepsy	Inflammatory/infectious
Metabolic	Neoplasia
Toxic	Anomalies
Degenerative	Trauma
Hydrocephalus	Cryptogenic and idiopathic
Trauma	
Midline structural problems (pituitary tumour)	

RVC

Signalment

- **Breed** (Family)
- **Age**

<6 months	6 months- 6 years	>6 years
Metabolic (Portosystemic shunt; hypoglycaemia)	Idiopathic epilepsy	Neoplasia
Infectious diseases (Distemper, Neosporosis, FIP, FeLV)	Inflammatory/infectious	Idiopathic epilepsy (late-onset)
Congenital	Metabolic	Inflammatory/Infectious
Toxic; trauma	Neoplasia; toxic, trauma	Metabolic (HE; hypoglycaemia secondary to beta-cell tumour "Insulinoma")
		Toxic, trauma

RVC

Intracranial structural asymmetrical lesions
Predictors for structural asymmetrical lesions include age of seizure onset >6years, the occurrence of cluster seizures, asymmetrical seizure episodes, a symmetrically abnormal interictal neurological examination and an asymmetrically abnormal interictal neurological examination

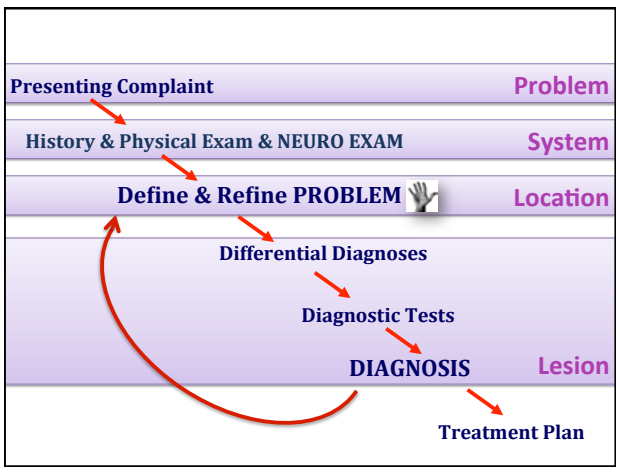
Variable	Maximum Odds ratio		SE	95% CI	*t* Value	*P*-Value
Seizure onset >6years	17.81	±	0.28	9.80-32.39	10.21	<0.0001
Cluster seizure	2.44	±	0.26	1.41-4.21	3.45	0.003
Asymmetrical seizure	3.23	±	0.39	1.41-7.36	3.01	0.008
Neuro exam abnormal symmetrical	9.50	±	0.31	4.94-18.28	7.30	<0.0001
Neuro exam abnormal asymmetrical	27.97	±	0.35	13.38-58.50	9.57	<0.0001

Intracranial structural symmetrical lesions
Predictors for a symmetrical structural lesions are the age of seizure onset and an abnormal symmetrical neurologic examination.

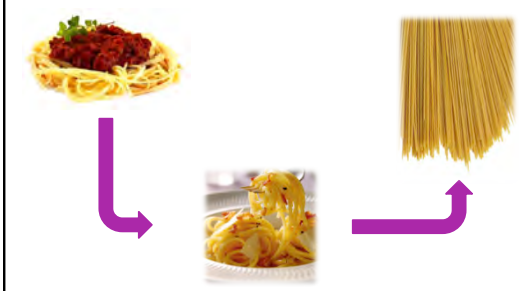
Variable	Maximum Odds ratio		SE	95% CI	*t* Value	*P*-Value
Age of seizure onset	1.06	±	0.02	1.01-1.10	2.69	0.008
Neuro exam abnormal symmetrical	6.06	±	0.64	1.71-21.44	2.81	0.05

Intracranial functional lesions
Predictors for functional intracranial lesions are: age of seizure <6years, occurrence of a single and symmetrical seizure episode and normal interictal neurological examination Combined, these factors can predict the presence on a functional intracranial lesion with a sensitivity of 82.1% and a specificity of 83.9%.

Variable	Maximum Odds ratio		SE	95% CI	*t* Value	*P*-Value
Seizure onset <6years	13.55	±	0.28	7.47-24.58	9.75	<0.0001
Single seizure	1.92	±	0.27	1.06-3.39	2.44	0.035
Symmetrical seizure	2.30	±	0.38	1.00-5.31	2.22	0.051
Neuro exam normal	15.4	±	0.25	8.72 -27.02	10.8	<0.0001



Have you ever eaten Spaghetti?



RVC

Ancillary tests

- Clinical pathology
  - Haematology/biochemistry
  - Endocrine tests
  - Cerebrospinal fluid analysis
  - Serology / PCR for detection of infectious agents
  - Blood pressure
  - Metabolic tests for storage diseases …
- Diagnostic imaging
  - MRI or CT
- Electrophysiology
  - EEG
- …….

The path

1. Define the problem
2. Define the system and location
3. Define the lesion

RVC

How high do you think is the percentage of dogs with epilepsy?

1. 0.1%
2. 0.6%
3. 2%
4. 5%

RVC

How high do you think is the percentage of pharmacoresistance in dogs with epilepsy?

1. 10-15%
2. 20-30%
3. 40-50%
4. 50-60%

RVC

How high do you think is the spontaneous and drug-induced epilepsy remission rate ?

1. 10-15%
2. 20-30%
3. 40-50%
4. 50-60%

RVC

~0.6% - estimated canine epilepsy prevalence in UK's first opinion clinic[1]

UK companion dog population ~9.4 million

⬇

~55.000 dogs with epilepsy

⬇

~44.000 will continue to seizure (AED)

⬇

~10.000 remain poorly controlled (2xAED)

[1]Fleet L, O'Neill DG, Volk HA, et al. VetRec, 2013

Epilepsy treatment – the past, the present and the future

1. Principles
2. "Licensed" AED
3. "Non-Licensed" AED

RVC

Neuropharmacology – new and old AED

1. Principles
    1. Principle 1
    2. Principle 2

RVC

Definition of seizures

What is the definition of seizures?

- Your current brain activity
- Hopefully not your current brain activity

Definition of seizures

What is the definition of seizures?

- Your current brain activity
- Hopefully not your current brain activity

Definition of seizures

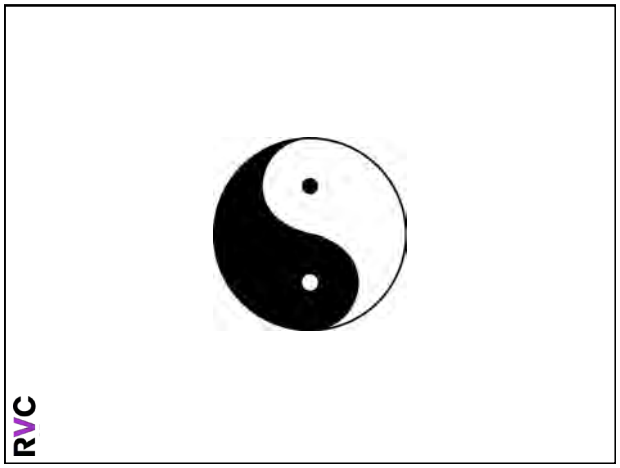
- Transient and involuntary change in behaviour or neurological status due to the abnormal activity of populations of CNS neurons
- Hypersynchronous: "Neurons are firing at the same time"

RVC

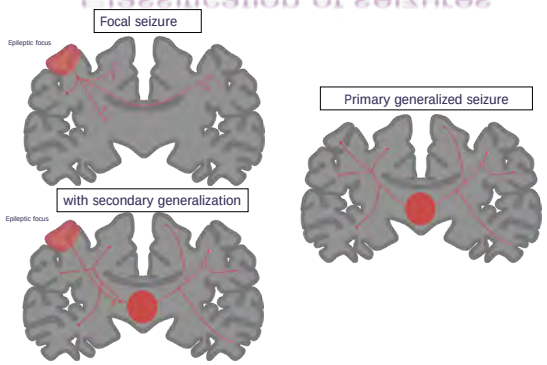
Neuropharmacology – new and old AED

1. Principles
    1. The Queen Principle: Hypersynchronous activity
    2. Principle 2

RVC



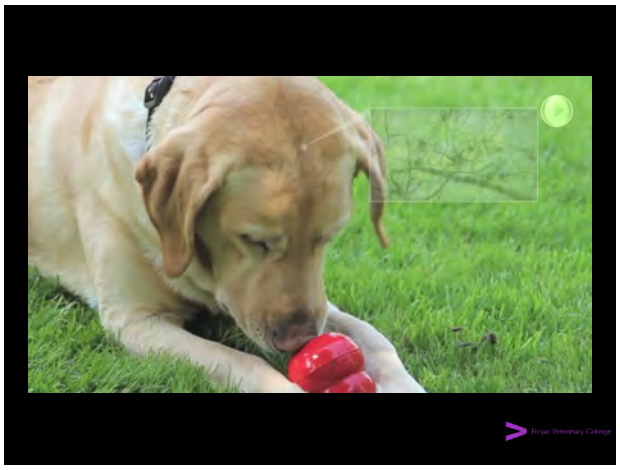
Classification of seizures



Excitation versus Inhibition

Labrador, 3yrs, FS

- Poppy had four seizures in the last month
- The physical examination and interictal neurological examination was unremarkable



Neuropharmacology – new and old AED

1. Principles
    1. The Queen Principle: Hypersynchronous activity
    2. The Yin Yan principle: Inhibition vs. Excitation

RVC

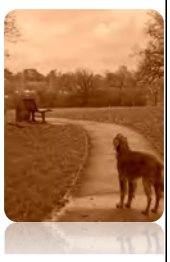
'Idiopathic' epilepsy

•Dog: 6 months to 6 years

Breeds
Beagles, German Shepherd Dogs, Labrador Retrievers, Golden Retrievers, Bernese Mountain Dog, Belgian Tervuerens, Keeshonds, Irish Wolfhounds, Viszlas, English Springer Spaniels, Danish Labradors, Lagotto Romagnolo, Standard Poodles, Finnish Spitz,…

Epilepsy treatment – the past, the present and the future

1. Principles
2. "Licensed" AED
3. "Non-Licensed" AED



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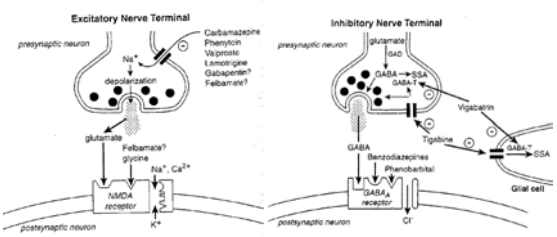
Have you ever cooked spaghetti?

RVC

Therapy – Mode of action



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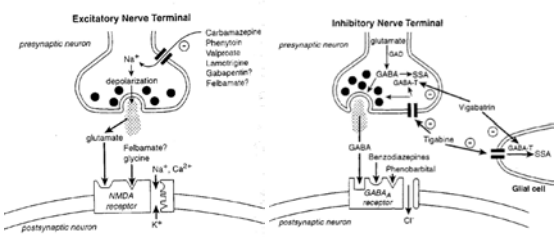
Therapy – Mode of action



Barbiturate increases the **duration** of chloride ion channel opening at the $GABA_A$ receptor. This **increases the efficacy of GABA**.

Benzodiazepines increase the **frequency** of the chloride ion channel opening at the $GABA_A$ receptor. This **increases the potency of GABA**.

RVC

What to expect from an Antiepileptic drug (AED)?

≥ than 50% reduction in seizure frequency

↓

Seizure diary

Anticonvulsant vs. Antiepileptogenic

RVC

What to expect from an Antiepileptic drug (AED)?

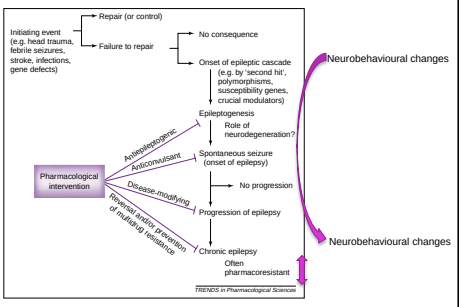
Seizure freedom

↓

Seizure diary

Anticonvulsant vs. Antiepileptogenic

Progression of epilepsy



Löscher, Trends in Pharmacological Sciences, 2002

RVC

What to expect from an Antiepileptic drug (AED)?

Efficacy <-> Tolerability

RVC

When to start treatment…

- Status epilepticus or animals with cluster seizures
- Severe postictal signs
- Identifiable structural lesion
- Increasing seizure frequency or severity

- ?2 or more isolated seizures within 6 m?

RVC

Client education prior to treatment

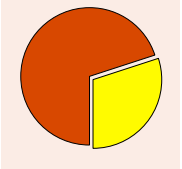
Life-time commitment

"your dog may always have a seizure"

Chart for seizure frequency

Side effects

2/3 of the dogs respond to AED



RVC

Treatment

- Monotherapy
- Seizure frequency may influence choice of AED?
- Monitor plasma levels?
- Owner compliance

RVC

Limitation of AEDs from people

- Toxicity
- Tolerance
- Inappropriate pharmacokinetics
- Expense

RVC

Labrador, 3yrs, FS

- Poppy had four seizures in the last month
- The physical examination and interictal neurological examination was unremarkable
- Bloods and urine were unremarkable
- What would you do?

RVC

Labrador, 3yrs, FS

Do you think it is right to start treatment?

1. Yes
2. No

RVC

Labrador, 3yrs, FS

Which drug would you use first line?

1. Phenobarbitone
2. Imepitoin
3. Potassium bromide
4. Levetiracetam
5. Gabapentin
6. Zonisamide

RVC

Labrador, 3yrs, FS

Which drug would you use first line?

1. **Phenobarbitone**
2. **Imepitoin**
3. Potassium bromide
4. Levetiracetam
5. Gabapentin
6. Zonisamide

RVC

Labrador, 3yrs, FS

When would you check Phenobarbitone serum levels for the first time?

1. 2 days
2. 12 days
3. 30 days
4. 90 days

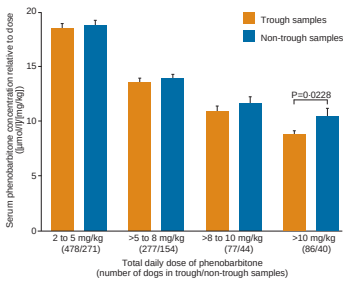
RVC

Phenobarbitone (dog)– First line treatment

- Phenobarbitone (PB)
  - Dose ~2.5 mg/kg BID
  - Peak serum concentration 4-8 hours (oral)
  - Half-life 24-40 hrs
  - Time to steady state 10-14 days
  - Therapeutic range 15.0 – 35 µg/ml
  - Potential side effects Sedation, PU/PD, polyphagia, hepatotoxicity
  - Metabolism liver
  - Drug interaction Can alter serum levels of liver metabolised drugs
  - Obtain plasma level 14, 45, 90, 180, 360 d, then q 6m
- Loading dosage if indicated
  - 12 to 24 mg/kg total dose within 24 hours (equal dose q 30 min to 4 hrs to effect, i.e. no seizures)

SPC Epiphen®; Phenoleptil®

The peak and trough debate



Monteiro et al., 2009, Vet Record

RVC

Phenobarbital – Side effects

- Rare but severe (idiosyncratic reactions):
  - Behavioural alterations
  - Immune-mediated neutropaenia, thrombocytopaenia, anaemia
  - Superficial, necrlolytic dermatitis
  - Idiosyncratic hepatotoxic reactions (rapid elevation of ALT and abnormal bile acids)

  Action: stop drug immediately – load with another AED
- Withdrawal seizures (drug dependence)
  - How to stop?

RVC

Comparison of phenobarbital with bromide as a first-choice antiepileptic drug for treatment of epilepsy in dogs

Dawn Merton Boothe, DVM, PhD, DACVIM, DACVCP; Curtis Dewey, DVM, MS, DACVS, DACVIM; David Mark Carpenter, PhD

Objective—To compare efficacy and safety of treatment with phenobarbital or bromide as the first-choice antiepileptic drug (AED) in dogs.

Design—Double-blinded, randomized, parallel, clinical trial.

Animals—46 AED-naive dogs with naturally occurring epilepsy.

Procedures—Study inclusion was based on age, history, findings on physical and neurologic examinations, and clinicopathologic test results. For either phenobarbital treatment (21 dogs) or bromide treatment (25), a 7-day loading dose period was initiated along with a maintenance dose, which was adjusted on the basis of monthly monitoring. Efficacy and safety outcomes were compared between times (baseline and study end [generally 6 months]) and between drugs.

Results—Phenobarbital treatment resulted in eradication of seizures (17/20 [85%]) significantly more often than did bromide (12/23 [52%]). Phenobarbital treatment also resulted in a greater percentage decrease in seizure duration (88 ± 34%), compared with bromide (49 ± 75%). Seizure activity worsened in 3 bromide-treated dogs only. In dogs with seizure eradication, mean ± SD serum phenobarbital concentration was 25 ± 6 µg/mL (phenobarbital dosage, 4.1 ± 1.1 mg/kg [1.9 ± 0.5 mg/lb], PO, q 12 h) and mean serum bromide concentration was 1.8 ± 0.6 mg/mL (bromide dosage, 31 ± 11 mg/kg [14 ± 5 mg/lb], PO, q 12 h). Ataxia, lethargy, and polydipsia were greater at 1 month for phenobarbital-treated dogs; vomiting was greater for bromide-treated dogs at 1 month and study end.

Conclusions and Clinical Relevance—Both phenobarbital and bromide were reasonable first-choice AEDs for dogs, but phenobarbital was more effective and better tolerated during the first 6 months of treatment. (*J Am Vet Med Assoc* 2012;240:1073–1083)

RVC

Phenobarbital

Epilepsia, 45(9):1141–1149, 2004
Blackwell Publishing, Inc.

Invited Review

Phenobarbital for the Treatment of Epilepsy in the 21st Century: A Critical Review

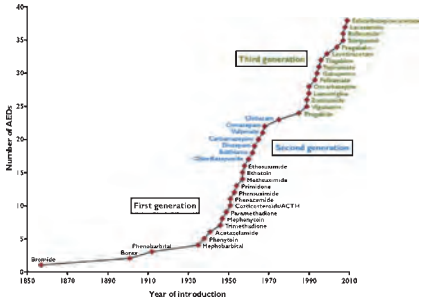
*Patrick Kwan and †Martin J. Brodie

*Division of Neurology, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong; and †Epilepsy Unit, Division of Cardiovascular and Medical Sciences, Western Infirmary, Glasgow, Scotland

Summary: Phenobarbital (PB) is the most widely used antiepileptic drug (AED) in the developing world and remains a popular choice in many industrialized countries. Meta-analyses of randomized controlled trials suggest that few differences in efficacy exist between PB and other established AEDs, but its possible deleterious cognitive and behavioral side effects remain a concern in the developed world. In contrast, high degrees of efficacy and tolerability in everyday clinical use have been demonstrated consistently in observational studies in developing countries. We propose that a pragmatic, comprehensive outcomes program be carried out, perhaps under the aegis of the Global Campaign Against Epilepsy, to optimize the conditions of the use of PB, so that more people around the world can benefit from this cost-effective medication and live more fulfilling lives.

RVC

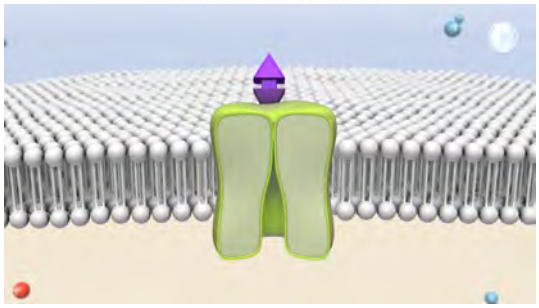
Chronology of human AED market



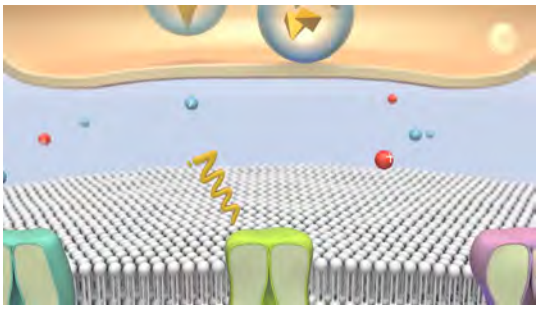
Loscher and Schmidt 2011

RVC

Phenobarbitone (Mode of Action)



Imepitoin Novel mode of action



Epilepsia, **45**(10):1228–1239, 2004
Blackwell Publishing, Inc.

Anticonvulsant Efficacy of the Low-affinity Partial Benzodiazepine Receptor Agonist ELB 138 in a Dog Seizure Model and in Epileptic Dogs with Spontaneously Recurrent Seizures

*Wolfgang Löscher, *Heidrun Potschka, †Susanne Rieck, †Andrea Tipold, and ‡Chris Rundfeldt

*Department of Pharmacology, Toxicology, and Pharmacy, and †Department of Small Animal Medicine and Surgery, University of Veterinary Medicine Hannover; and ‡Elbion AG, Radebeul, Germany

Summary: *Purpose:* Ataxia, sedation, amnesia, ethanol and barbiturate potentiation, loss of efficacy (tolerance), development of dependence, and the potential for drug abuse limit the clinical use of benzodiazepines (BZDs) for long-term treatment of epilepsy or anxiety. BZD ligands that are in current use act as full allosteric modulators of γ-aminobutyric acid (GABA)-gated chloride channels and, on long-term administration, trigger a functional uncoupling between the $GABA_A$ and BZD recognition sites. Partial allosteric modulators, which have a low intrinsic activity at the BZD recognition site of the $GABA_A$ receptor, might eventually overcome the limitations of full agonists such as diazepam (DZP).

Methods: In the present study, the new low-affinity partial BZD-receptor agonist ELB 138 [former name AWD 131-138; 1-(4-chlorophenyl)-4-morpholino-imidazolin-2-one] was evaluated in a dog seizure model and in epileptic dogs with spontaneously recurrent seizures.

Results: ELB 138 was shown to increase potently the pentylenetetrazole (PTZ) seizure threshold in dogs. Prolonged oral administration with twice-daily dosing of ELB 138 with either 5 or 40 mg/kg over a 5-week period was not associated with loss of anticonvulsant efficacy in the PTZ dog model. To study whether physical dependence developed during long-term treatment, the BZD antagonist flumazenil was injected after 5 weeks of treatment with ELB 138. Compared with prolonged treatment with DZP, only relatively mild abstinence symptoms were precipitated in dogs treated with ELB 138, particularly at the lower dosage (5 mg/kg, b.i.d.). In a prospective trial in dogs with newly diagnosed epilepsy, ELB 138 markedly reduced seizure frequency and severity without significant difference to standard treatments (phenobarbital or primidone) but was much better tolerated than the standard drugs. In dogs with chronic epilepsy, most dogs exhibited a reduction in seizure frequency and severity during add-on treatment with ELB 138.

Conclusions: The data demonstrate that the partial BZD receptor agonist ELB 138 exerts significant anticonvulsant efficacy without tolerance in a dog seizure model as well as in epileptic dogs with spontaneously recurrent seizures. These data thus substantiate that partial agonism at the BZD site of $GABA_A$ receptors offers advantages versus full agonism and constitutes a valuable approach for treatment of seizures. **Key Words:** Epilepsy—Antiepileptic drugs—GABA receptors—Benzodiazepines.

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The Veterinary Journal 172 (2006) 86–95

The Veterinary Journal
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Anticonvulsant activity and tolerance of ELB138 in dogs with epilepsy: A clinical pilot study

Susanne Rieck [a], Chris Rundfeldt [b], Andrea Tipold [a,*]

[a] Department of Small Animal Medicine and Surgery, University of Veterinary Medicine, and Center for Systems Neuroscience, Hannover, Germany
[b] Elbion AG, Department of Pharmacology, Radebeul, Germany

Abstract

A new antiepileptic and anxiolytic drug, ELB138, was evaluated in a clinical pilot study in dogs with newly diagnosed or chronic idiopathic epilepsy. The purpose was to verify clinically the anticonvulsant effectiveness of this substance, which had already been demonstrated experimentally. Data from 29 dogs treated with ELB138 were compared with results obtained retrospectively from 82 dogs treated with conventional antiepileptic medication. The reduction in seizure frequency using ELB138 in dogs with newly diagnosed idiopathic epilepsy was comparable to the reduction in dogs treated either with phenobarbital or primidone. In dogs with chronic epilepsy and add-on therapy with either ELB138 or potassium bromide, such supplementation reduced the seizure frequency and the duration and severity of seizures. The most obvious difference between ELB138 treatment and conventional medications became clear in the evaluation of side effects, which in those dogs treated with ELB138 were rare, and consisted mostly of transient polyphagia. This pilot study confirmed that ELB138 has a potent anticonvulsant effect in dogs with idiopathic epilepsy. These results will form the basis for a multicentre, blinded study.

Keywords: Epilepsy; Dogs; New anticonvulsant medication; ELB138; Pilot study

Side-effect Profile (Imepitoin)

- Newly diagnosed dogs: Imepitoin very well tolerated, no sedation or other central side effects, mostly transient polyphagia in 7/12 cases (58%)
- Add on: no additional side effects to the well known effects of phenobarbital
- Regular follow up examinations: clinical and neurological examinations normal, some dogs increased activity
- Anxiolytic effects supported (in earlier studies examined in 4 anxious Beagle dogs)

RVC

Treatment of epileptic dogs: Summary

- Imepitoin appears effective in newly diagnosed and in drug-resistent dogs with epilepsy
- Imepitoin appears well tolerated compared to standard medication used

Data used for power analyses for ⇩

Multiple randomized multicentre studies (Germany, Switzerland, France; ECVN/ESVN)

Results

- Primary efficacy variable: monthly seizure frequency
- Reduction confirmed the non-inferiority of imepitoin in comparison to phenobarbital
- **No correlation of plasma concentration and seizure control**

Table 26 Proportion of generalized seizure-free dogs in the PPS population

Treatment	Generalized seizure-free: no N	no %	yes N	yes %	All N	All %
Imepitoin	34	53.1	30	46.9	64	100
Phenobarbital	37	42.0	51	58.0	88	100

Note: p-value of Fisher's exact test is 0.1913

Results

- Primary efficacy variable: monthly seizure frequency
- Reduction confirmed the non-inferiority of imepitoin in comparison to phenobarbital

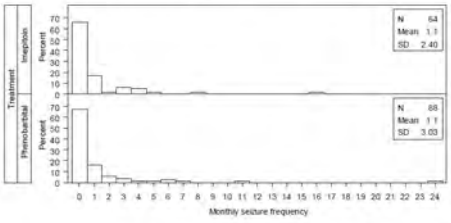


Figure 6 Histograms of monthly seizure frequency in the PPS population (percentage of dogs having certain seizure frequencies)

Side effect profile

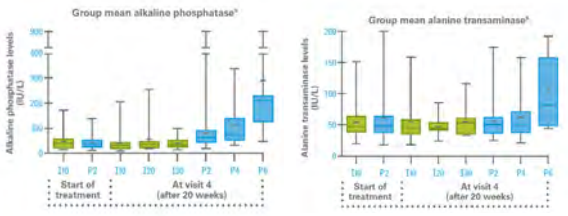
- Imepitoin had a more favourable safety profile than phenobarbital in clinical use

Adverse events:
- Somnolence/sedation
- Polydipsia/polyuria
- Increased appetite

} more cases in phenobarbital group

- Hyperactivity ⇨ more cases in Imepitoin group

Liver enzyme activity induction



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The novel antiepileptic drug imepitoin compares favourably to other GABA-mimetic drugs in a seizure threshold model in mice and dogs

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[b] Center for Systems Neuroscience, Hannover, Germany
[c] Institute of Pharmacology, Toxicology, and Pharmacy, Ludwig-Maximilians-University, Munich, Germany

RVC

Summary (Imepitoin)

Personal recommendation

- Consider as first line treatment for dogs with newly diagnosed idiopathic epilepsy
  - Due to its relatively good side effect profile treatment can be considered in `less severe' epilepsy cases earlier
  - Should currently not be considered for dogs with acute seizures (cluster seizures/status epilepticus) or in cats
- Dogs with severe side effects on Phenobarbitone or other anticonvulsant drugs
- Alternative for dogs with unsatisfying seizure control on Phenobarbitone or other anticonvulsant drugs

RVC

Potential anxiolytic activity (Imepitoin)

Epilepsy & Behavior 21 (2011) 160–167

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Behavioral changes in dogs associated with the development of idiopathic epilepsy

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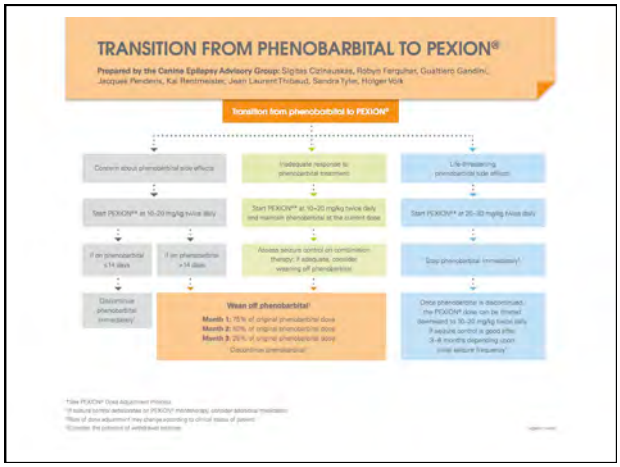
ABSTRACT

Objectives: The aim of the study was to demonstrate behavioral changes with the development of epilepsy in dogs, a species proposed as a naturally occurring animal model for human epilepsy.
Methods: Owners of dogs diagnosed with idiopathic epilepsy (n = 80) completed a modified, previously-validated behavioral and seizure questionnaire. Principal axis factor analysis identified behavioral factors, the scores for which were compared before and after the development of epilepsy.
Results: Drug-naive dogs showed an increase in the behavior factors Fear/Anxiety, Defensive Aggression, and Abnormal Perception. In dogs receiving antiepileptic medication, there were still increases in Fear/Anxiety and Abnormal Perception, but no longer in Defensive Aggression. Additional increases were observed in Abnormal Reactivity, Attachment Disorder, Demented Behavior, and Apathetic Behavior. Pharmacoresistant dogs had larger increases in Controlling Aggression, Abnormal Perception, and Demented Behavior than drug responders.
Conclusion: Our data suggest that dogs, like humans and rodents, exhibit neurobehavioral comorbidities with the development of epilepsy.

RVC

*In case of severe seizures, efficacy is seen within 48h



Labrador, 3yrs, FS

When would you check Imepitoin serum levels for the first time?

1. 2 days
2. 10 days
3. 30 days
4. 90 days

RVC

Labrador, 3yrs, FS

When would you check Imepitoin serum levels for the first time?

1. 2 days
2. 10 days
3. 30 days
4. 90 days
5. **Never**

RVC

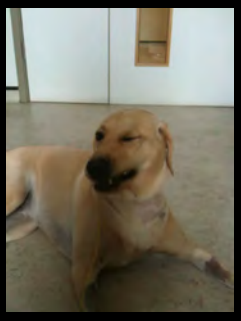
Labrador, 3yrs, FS

One month later the dog had 4 seizures.
What do you want to do now?

1. Check serum levels (PB)?
2. Add potassium bromide or another antiepileptic drug?
3. Refer to a neurologist?
4. Repeat the neurological exam?
5. Ask for a video of the seizures?

RVC

Videos



Labrador, 3yrs, FS

Does this change your plan?

1. Yes
2. No

RVC

Labrador, 3yrs, FS

Does this change your plan?

1. **Yes**
2. No

RVC

Intracranial structural lesions

Variable	Maximum Odds ratio		SE	95% CI	*t* Value	*P*-Value
Seizure onset >6years	17.81	±	0.28	9.80-32.39	10.21	<0.0001
Cluster seizure	2.44	±	0.26	1.41-4.21	3.45	0.003
Asymmetrical seizure	3.23	±	0.39	1.41-7.36	3.01	0.008
Neuro exam abnormal symmetrical	9.50	±	0.31	4.94-18.28	7.30	<0.0001
Neuro exam abnormal asymmetrical	27.97	±	0.35	13.38-58.5	9.57	<0.0001

RVC

Intracranial functional lesions

Variable	Maximum Odds ratio		SE	95% CI	*t* Value	*P*-Value
Seizure onset <6years	13.55	±	0.28	7.47-24.58	9.75	<0.0001
Single seizure	1.92	±	0.27	1.06-3.39	2.44	0.035
Symmetrical seizure	2.30	±	0.38	1.00-5.31	2.22	0.051
Neuro exam normal	15.4	±	0.25	8.72 -27.02	10.8	<0.0001

RVC

Reasons for treatment failure

- Incorrect diagnosis
  - MRI performed?
- Incorrect choice of AED
- Incorrect dosage
- Low AED levels
- Newly developed disease
  - (liver/kidney/pancreatic diseases)

- Change in patient weight
- Patient tolerance to drug
  - PB / benzodiazepine
- Monotherapy is insufficient
- Refractory seizures
- Difficult owner (poor compliance)

RVC

What to do if treatment fails?

- Monitor drug levels – Adjust dose
- If still failure – Monitor drug levels
- If still failure – Add anticonvulsant
- If still failure – Monitor drug levels – Adjust dose
- If still failure – Consider newer drug

RVC

Potassium bromide – add on/first line (not in cats)

- Potassium bromide (KBr)
  - Dose: 30-40 mg/kg SID
  - Half-life: 15-20 days
  - Time to steady state: 100-200 days
  - Therapeutic range: 0.7 – 1.9 mg/ml/2.3 mg/ml
  - Side effects: sedation, weakness, PU, PD, GI irritation, (pancreatitis)
  - Excretion: renal
  - Obtain plasma level: 4 wks, 8-12 wks, then q 6m
- Loading dosage if indicated
  - 600 mg/kg (equal doses over 6 days)+ maintenance dose

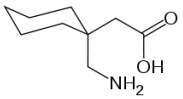
RVC

What's new in the treatment of canine epilepsy

1. Principles
2. "Licensed" AED
3. "Non-Licensed" AED

RVC

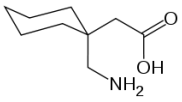
Gabapentin (Neurontin®)



- Pharmacodynamic
  - GABA analogue
  - binding site: α2δ subunit of voltage-activated calcium channels
  - it may enhance GABA synthesis
- Pharmacokinetic
  - ~30% metabolised to N-methylgabapentin in the liver
  - oral bioavailability is 80%
  - plasma protein binding is less than 3%
  - renally excreted
  - Elimination half-life 2-4 hrs

RVC

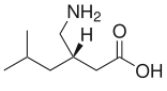
Gabapentin (Neurontin®)



- Veterinary evidence
  - 2 open label trials
  - ≥50% of PB and/or KBr resistant dogs respond to gabapentin (Govendir et al. 2005; Platt et al. 2006)
- Side effects
  - Sedation (mild)
  - Ataxia (mild)
- Dosage
  - Dog 10 mg/kg TID
  - Cats? 5-10 mg/kg BID

RVC

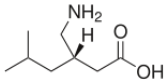
Pregabalin (Lyrica®)



- Pharmacodynamic
  - Binding site: α2δ subunit of voltage-activated calcium channels
  - it may increase GABA synthesis
  - Potentiates benzodiazepines and barbiturates
- Pharmacokinetic
  - renally excreted
  - Elimination half-life 7 hrs

RVC

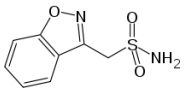
Pregabalin (Lyrica®)



- Veterinary evidence
  - 1 open label trials
  - ≥77% of PB and/or KBr resistant dogs respond to pregabalin (Dewey et al. 2009)
- Side effects
  - Sedation (moderate)
  - Ataxia (mild)
- Dosage
  - Dog 2-4 mg/kg BID or TID

RVC

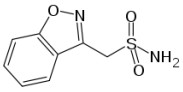
Zonisamide (Zonegran®)



- Pharmacodynamic
  - Carbonic anhydrase inhibitor
  - Blocking of Voltage-gated sodium channel and T-type-calcium channels
  - Allosteric GABA receptor activation
- Pharmacokinetic
  - Good oral bioavailability
  - High plasma protein binding
  - Metabolized in liver
  - Elimination half-life 15-20 hrs

RVC

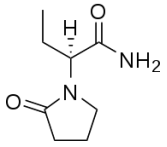
Zonisamide (Zonegran®)



- Veterinary evidence
  - 2 open label trials
  - ~50% of PB and/or KBr resistant dogs respond to zonisamide (Dewey et al. 2004; Kloppmann et al. 2007)
  - "Honeymoon period"
- Side effects
  - Renal calculi
  - Sedation
  - Gastrointestinal disorders
  - Hepatotoxicity (Schwartz et al., 2011)
- Dosage
  - Dog 5-10 mg/kg BID / Cat SID

RVC

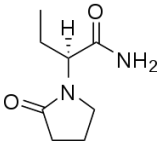
Levetiracetam (Keppra®)



- Pharmacodynamic
  - inhibit high voltage activated neuronal calcium currents
  - act by interfering with negative allosteric modulators of inhibitory GABA and glycine receptors
  - presynaptic vesicle SV2A – impedes nerve conduction across synapses
- Pharmacokinetic
  - oral bioavailability is ~100%
  - plasma protein binding minimal
  - unchanged renally excreted
  - Elimination half-life 3-4 hrs
  - Phenobarbitone increases clearance of levetiracetam

RVC

Levetiracetam (Keppra®)

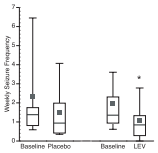


- Veterinary evidence
  - 2 open label trials
  - ≥30% of PB and/or KBr resistant dogs respond to levetiracetam (Steinberg & Faissler 2004; Volk et al. 2008)
  - Effect on acute seizures - 56% response rate (Hardy et al., 2012)
  - Decreased risk of seizures post ligation of portosystemic shunt (Fryer et al., 2011)
  - "Honeymoon period"
- Side effects
  - Sedation (very mild)
- Dosage
  - Dog 20 mg/kg TID

RVC

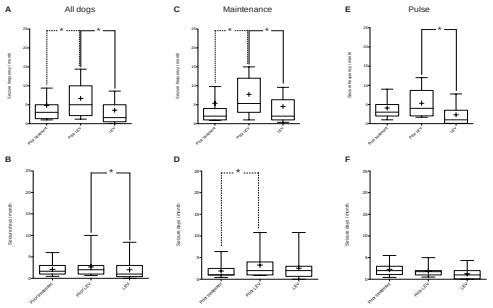
Evaluation of Levetiracetam as Adjunctive Treatment for Refractory Canine Epilepsy: A Randomized, Placebo-Controlled, Crossover Trial

K.R. Muñana, W.B. Thomas, K.D. Inzana, J.A. Nettifee-Osborne, K.J. McLucas, N.J. Olby, C.J. Mariani, and P.J. Early



RVC

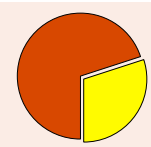
Clinical audit



RVC

Pharmacoresistance (Dogs)

- ~75-85% of dogs with epilepsy continue to have seizures[1-4]
- ~20–30% remain poorly controlled (<50% reduction of seizure frequency) despite adequate treatment with phenobarbitone (PB) and/or potassium bromide (KBr)[6-7]



RVC

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3. Berendt M, Gredal H, Ersbøll AK, et al., J Vet Intern Med 2007;21:754-759.
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Remission rate?

Comparison of phenobarbital with bromide as a first-choice antiepileptic drug for treatment of epilepsy in dogs

Dawn Merton Boothe, DVM, PhD, DACVIM, DACVCP; Curtis Dewey, DVM, MS, DACVS, DACVIM; David Mark Carpenter, PhD

Objective—To compare efficacy and safety of treatment with phenobarbital or bromide as the first-choice antiepileptic drug (AED) in dogs.

Design—Double-blinded, randomized, parallel, clinical trial.

Animals—46 AED-naïve dogs with naturally occurring epilepsy.

Procedures—Study inclusion was based on age, history, findings on physical and neurologic examinations, and clinicopathologic test results. For either phenobarbital treatment (21 dogs) or bromide treatment (25), a 7-day loading dose period was initiated along with a maintenance dose, which was adjusted on the basis of monthly monitoring. Efficacy and safety outcomes were compared between times (baseline and study end [generally 6 months]) and between drugs.

Results—Phenobarbital treatment resulted in eradication of seizures (17/20 [85%]) significantly more often than did bromide (12/23 [52%]); phenobarbital treatment also resulted in a greater percentage decrease in seizure duration (88 ± 34%), compared with bromide (49 ± 75%). Seizure activity worsened in 3 bromide-treated dogs only. In dogs with seizure eradication, mean ± SD serum phenobarbital concentration was 25 ± 6 µg/mL (phenobarbital dosage, 4.1 ± 1.1 mg/kg [1.9 ± 0.5 mg/lb], PO, q 12 h) and mean serum bromide concentration was 1.8 ± 0.6 mg/mL (bromide dosage, 31 ± 11 mg/kg [14 ± 5 mg/lb], PO, q 12 h). Ataxia, lethargy, and polydipsia were greater at 1 month for phenobarbital-treated dogs; vomiting was greater for bromide-treated dogs at 1 month and study end.

Conclusions and Clinical Relevance—Both phenobarbital and bromide were reasonable first-choice AEDs for dogs, but phenobarbital was more effective and better tolerated during the first 6 months of treatment. (J Am Vet Med Assoc 2012;240:1073–1080)

RVC

Impact

Dogs with epilepsy (poorly controlled, high seizure frequency) -> increased risk of[1-4]

- premature death
- behaviour changes
- reduced quality of life (QoL).

Seizures not only affect QoL for affected dogs, but also for owner[3-4].

RVC

1. Berendt M, Gredal H, Ersbøll AK, et al. JVIM 2007.
2. Shihab N, Bowen J, Volk HA. Epilepsy Behav 2011.
3. Chang Y, Mellor DJ, Anderson TJ. JSAP 2006.
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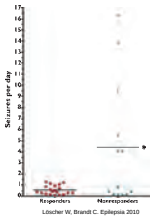
Risk Factors



- **However** (dog, human, rodent) drug responsiveness influenced by[1-5]
  - high seizure frequency
  - cluster seizures
  - status epilepticus
- Seizure severity -> guide clinical reasoning -> severe seizuring patient receive treatment earlier
- Intact male & female dogs have a higher likelihood of having cluster seizures[6].

RVC

1. Heynold Y, Faissler D, Steffen F, et al. J Small Anim Pract 1997
2. Hulsmeyer V, Zimmermann R, Brauer C, et al. J Vet Intern Med 2010
3. Weissl J, Hulsmeyer V, Brauer C, et al. J Vet Intern Med 2012
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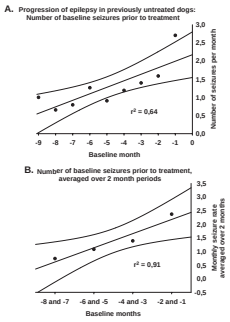
5. Kwan P, Brodie MJ. N Engl J Med 2000
6. Monteiro R, Adams V, Keys D, et al. J Small Anim Pract 2012

Seizure begs another seizure?

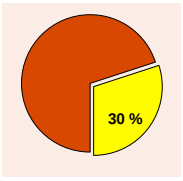


Löscher et al., 2004

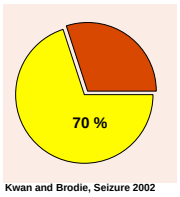
RVC

Risk factor – seizure type

Epilepsy / all types



Temporal lobe epilepsy

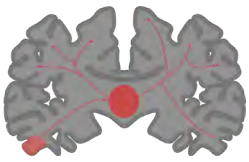


Kwan and Brodie, Seizure 2002

RVC

Temporal lobe epilepsy (human)

•The complex-focal seizure is the most often seen seizure type



•70 – 80 % of the complex-focal seizures have their origin in the temporal lobe (especially in the hippocampus and amygdala)

•Temporal lobe epilepsy (TLE) is often refractory to pharmacological treatment.

RVC

Temporal lobectomy

Pharmacoresistant

↓

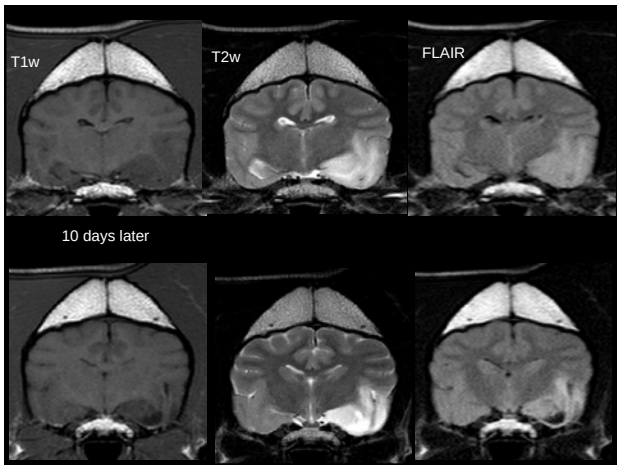
Surgery

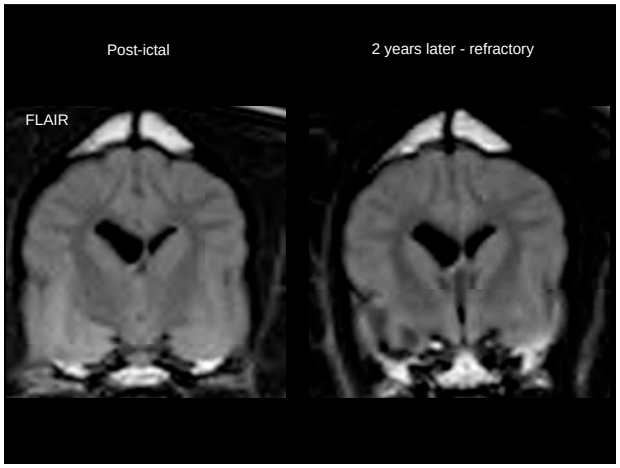
↓

Pharmacoresponder

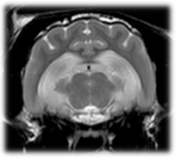
(Rarely cured)

RVC





TLE (dog, cat)?



- **Cats with bilateral hippocampal necrosis ➔ refractory to treatment** (Fatzer et al. 2000; Brini et al. 2004; Schmied et al. 2008)
- **Dogs:**
  - **Reversible MRI changes post prolonged seizure activity** (Mellema et al. 1999)
  - **TLE model in dogs similar changes as human with TLE** (Hasegawa et al. 2002, 2003)
  - **Absence of TLE in dogs with pharmacoresistant epilepsy** (Buckmaster et al. 2002)

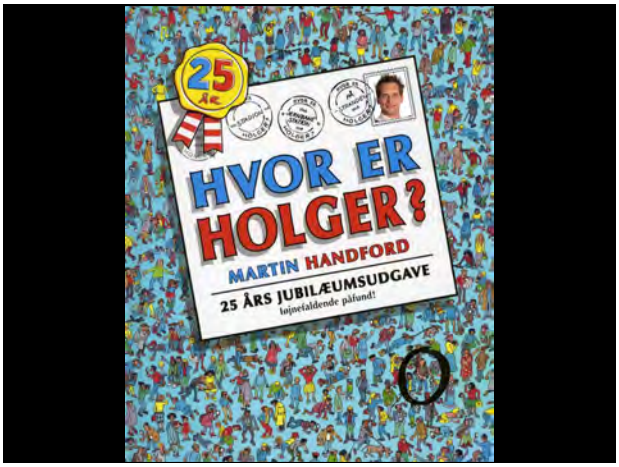
TLE (Cat)?

Brief Communication
J Vet Intern Med 2013;27:212–214

Suspected Limbic Encephalitis and Seizure in Cats Associated with Voltage-Gated Potassium Channel (VGKC) Complex Antibody

A. Pakozdy, P. Halasz, A. Klang, J. Bauer, M. Leschnik, A. Tichy, J.G. Thalhammer, B. Lang, and A. Vincent

Background: Treatment-resistant complex partial seizures (CPS) with orofacial involvement recently were reported in cats in association with hippocampal pathology. The features had some similarity to those described in humans with limbic encephalitis and voltage-gated potassium channel (VGKC) complex antibody.
Hypothesis/Objectives: The purpose of this pilot study was to evaluate cats with CPS and orofacial involvement for the presence of VGKC-complex antibody.
Animals: Client-owned cats with acute orofacial CPS and control cats were investigated.
Methods: Prospective study. Serum was collected from 14 cats in the acute stage of the disease and compared with 19 controls. VGKC-complex antibodies were determined by routine immunoprecipitation and by binding to leucine-rich glioma inactivated 1 (LGI1) and contactin-associated protein-like 2 (CASPR2), the 2 main targets of VGKC-complex antibodies in humans.
Results: Five of the 14 affected cats, but none of the 19 controls, had VGKC-complex antibody concentrations above the cut-off concentration (>100 pmol/L) based on control samples and similar to those found in humans. Antibodies in 4 cats were directed against LGI1, and none were directed against CASPR2. Follow-up sera were available for 5 cats in remission and all antibody concentrations were within the reference range.
Conclusion and Clinical Importance: Our study suggests that an autoimmune limbic encephalitis exists in cats and that VGKC-complex/LGI1 antibodies may play a role in this disorder, as they are thought to in humans.
Key words: Autoimmune limbic epilepsy; Feline.



Royal Veterinary College
University of London

Neurology & Neurosurgery team
Clinical Investigation Centre

Epilepsy clinic

Thank you!
Canine Epilepsy Advisory Group:
Sigitas Cizinauskas, Robyn Farquhar, Gualtiero Gandini, Jacques Penderis, Kai Rentmeister, Jean-Laurent Thibaud, Sandra Tyler

A special thank you to Andrea Tipold Wolfgang Löscher and Chris Rundfeldt

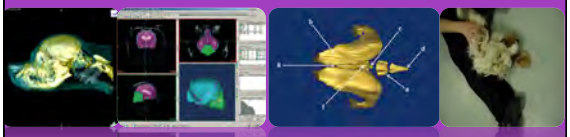
An even more special **thank you to** all the former/current **RVC students, to all referral vets and to the QMHA team!**

Chiari like malformation

Holger Volk DVM PGCAP DipECVN PhD FHEA MRCVS

Royal Veterinary College
University of London

An update on the pathogenesis of syringomyelia secondary to Chiari-like malformations in dogs

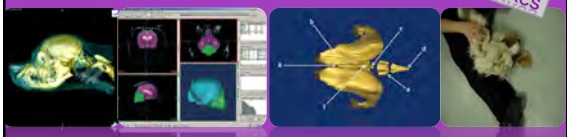


Holger A. Volk
Royal Veterinary College

Royal Veterinary College
University of London

An update on the pathogenesis of syringomyelia secondary to Chiari-like malformations in dogs

CKCS



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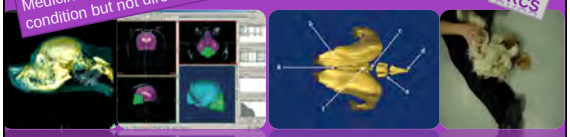
epiphenomenon |ˌɛpɪfəˈnɒmɪnən - noun (pl.**epiphenomena** |-nə|)

a secondary effect or by-product, in particular:

Medicine a secondary symptom, occurring simultaneously with a disease or condition but not directly related to it.

syringomyelia like malformations in dogs

CKCS



Holger A. Volk
Royal Veterinary College

Clinical Investigation Centre

History and Future

The Clinical Investigation Center (CIC) is based at the Hawkshead campus and has expanded considerably in recent years.

Cavalier King Charles Spaniel Clinical Study

The Veterinary Clinical Investigation Center has completed a clinical study evaluating the efficacy of a novel treatment for the control of pain associated with syringomyelia in Cavalier King Charles Spaniels.

The study was part of a collaborative effort between a Pharmaceutical Company, and the Schools of Veterinary Medicine at the University of Minnesota, the University of Pennsylvania and the Royal Veterinary College in the United Kingdom. The study actively recruited patients from November 2007 to October 2008 and after screening 119 dogs a total of fifty two patients participated in the trial.

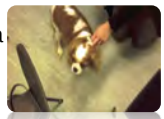
Following statistical analysis the results are promising and there is potential for further development of this new medication to help alleviate the pain associated with syringomyelia.

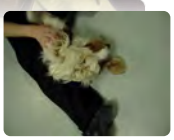
Many Thanks to those of you who took part - your support is much appreciated.

Investigator Dr Holger A Volk DVM DipECVN PhD MRCVS

CKCS with CM/SM

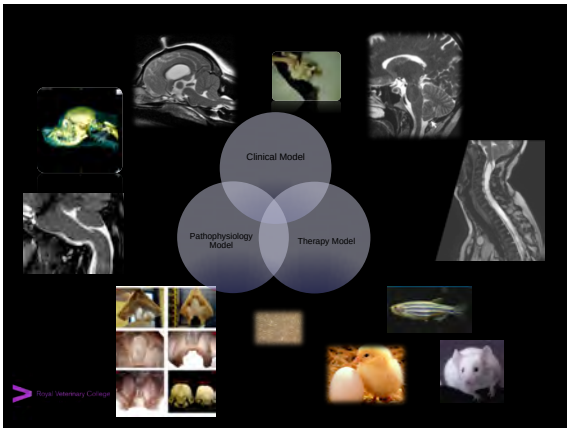
- Neuropathic pain
- Allodynia and dysaesthesia
  - Facial Rubbing
  - Phantom scratching
  - Cervical hyperaesthesia
  - Spontaneous vocalisation





Similarities?

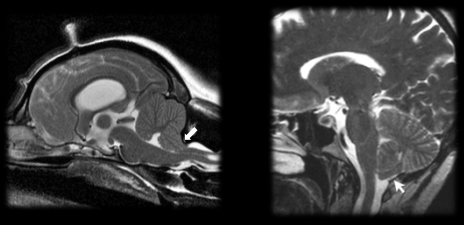
Similarities?



Chiari malformation (CM)

Cavalier King Charles Spaniel (CKCS)

Human



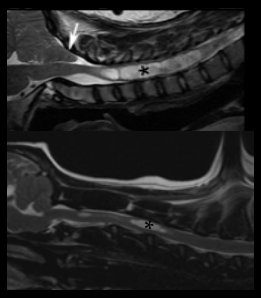
>95%?

1:1280

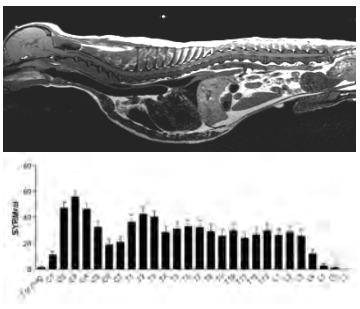
Syringomyelia (SM)

Human

CKCS



Syringomyelia Distribution



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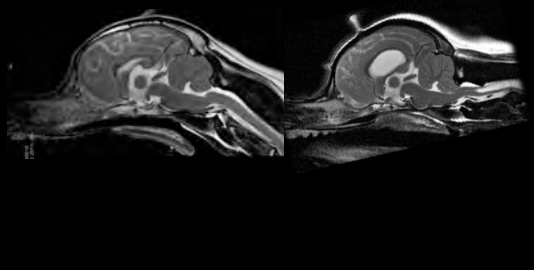
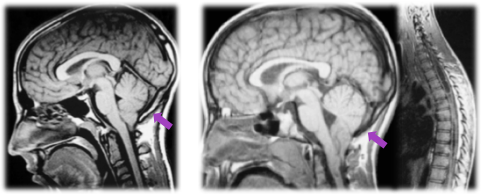
Loderstedt, Benigni, Chandler, Cardwell, Rusbridge, Lamb & Volk 2011

CM <-> CM/SM



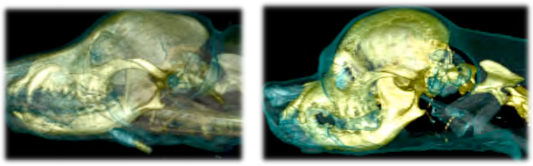
CM/SM Human



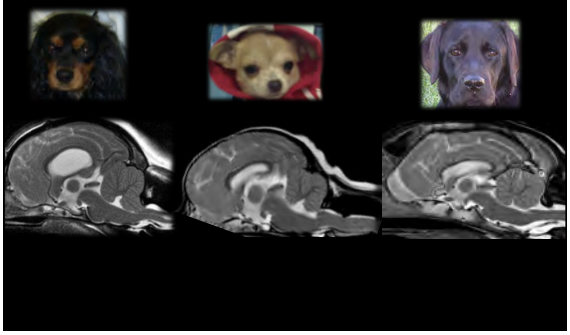
- CM patient (Human) small skull volume around cerebellum (*Fossa posteria cranii)*
- Children with CM and SM smaller *Fossa posteria cranii* (Sgorous et al. 2006)

Skull ↔ Brain

- Smaller caudal cranial fossa in the dog?



Skull ↔ Brain



Use of magnetic resonance imaging for morphometric analysis of the caudal cranial fossa in Cavalier King Charles Spaniels

Inés Carrera, DVM; Ruth Dennis, VetMB, MA; Dominic J. Mellor, BVMS, PhD; Jacques Penderis, BVSc, PhD; Martin Sullivan, BVMS, PhD

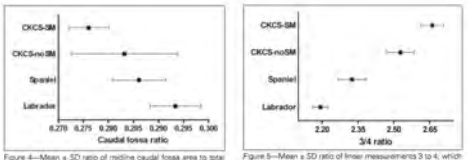


Figure 4—Mean ± SD ratio of midline caudal fossa area to total midline intracranial area for each type of dog. Notice that the ratio for CKCSs with syringomyelia has no overlap with ratios for spaniel-type dogs and Labrador Retrievers, reflecting the smaller caudal fossa in CKCSs with syringomyelia. CKCS-SM = CKCSs with syringomyelia. CKCSnoSM = CKCSs without syringomyelia. Spaniel = Spaniel-type dogs (ie, English Springer Spaniels and Cocker Spaniels). Labrador = Labrador Retrievers.

Figure 5—Mean ± SD ratio of linear measurements 3 to 4, which highlights the length of the ventral aspect of the occipital bone, for each type of dog. Notice that ratios for CKCSs have no overlap with ratios for spaniel-type dogs and Labrador Retrievers. See Figure 4 for key.

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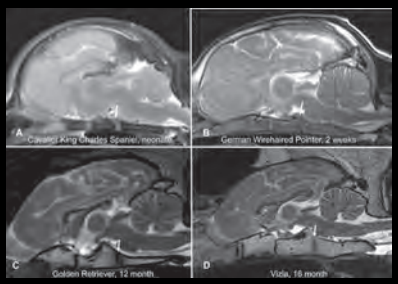
Synchondrosis

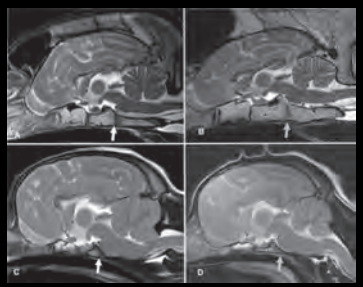


V

Synchondrosis

Labrador

CKCS



V

COMPARISON OF CLOSURE TIMES FOR CRANIAL BASE SYNCHONDROSES IN MESATICEPHALIC, BRACHYCEPHALIC, AND CAVALIER KING CHARLES SPANIEL DOGS

MARTIN J. SCHMIDT, HOLGER VOLK, MELANIE KLINGLER, KLAUS FAILING, MARTIN KRAMER, NELE ONDREKA

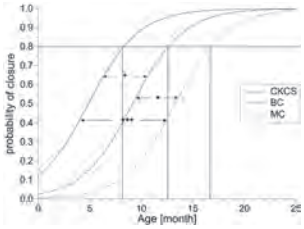


FIG. 3. Plot of logistic regression curves for the probability of spheno-occipital synchondrosis closure and effect of age for the different dog groups, assuming a logistic model without interaction between age and group. The gray lines highlight the time shift points where different groups have a probability of synchondrosis closure of 80%.

Veterinary Radiology Ultrasound, 2013

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Evaluation of the volumes of cranial cavities in Cavalier King Charles Spaniels with Chiari-like malformation and other brachycephalic dogs as measured via computed tomography

Martin J. Schmidt, Dr med vet; Miriam Biel, Dr med vet; Stephan Klumpp, Dr med vet; Matthias Schneider, PD, Dr med vet; Martin Kramer, Dr med vet

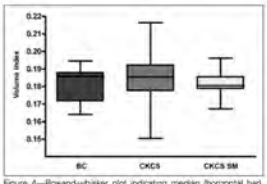

Figure 4—Boxand-whisker plot indicating median (horizontal bar), 25th and 75th percentiles (box), and range (whiskers) of volume index in CKCSs with (n = 14) and without (28) syringohydromyelia (SM) and other brachycephalic (BC) dogs (25).

RVC

CEPHALOMETRIC MEASUREMENTS AND DETERMINATION OF GENERAL SKULL TYPE OF CAVALIER KING CHARLES SPANIELS

M. J. SCHMIDT, A. C. NEUMANN, K. H. AMORT, K. FAILING, M. KRAMER

The general skull morphology of the head of the Cavalier King Charles Spaniel (CKCS) was examined and compared with cephalometric indices of brachycephalic, mesaticephalic, and dolichocephalic heads. Measurements were taken from computed tomography images. Defined landmarks for linear measurements of were identified using three-dimensional (3D) models. The calculated parameters of the CKCS were different from all parameters of mesaticephalic dogs but were the same as parameters from brachycephalic dogs. However, the CKCS had a wider braincase in relation to length than in other brachycephalic breeds. Studies of the etiology of the chiari-like malformation in the CKCS should therefore focus on brachycephalic control groups. As Chiari-like malformation has only been reported in brachycephalic breeds, its etiology could be associated with a higher grade of brachycephaly, meaning a shorter longitudinal extension of the skull. This has been suggested for other breeds. © 2011 *Veterinary Radiology & Ultrasound, Vol. 52, No. 4, 2011, pp 436–440.*

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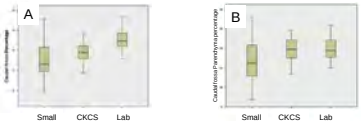
Skull ↔ Brain

A) Caudal cranial fossa
➔CKCS ~ small breed dogs

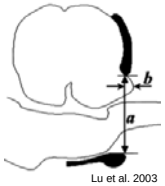
B) Brain volume in caudal cranial fossa
➔ CKCS ~ Labrador



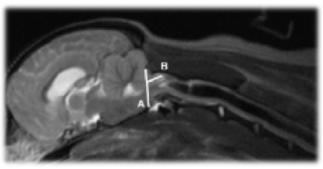
Cross et al. 2009

Cerebellar herniation

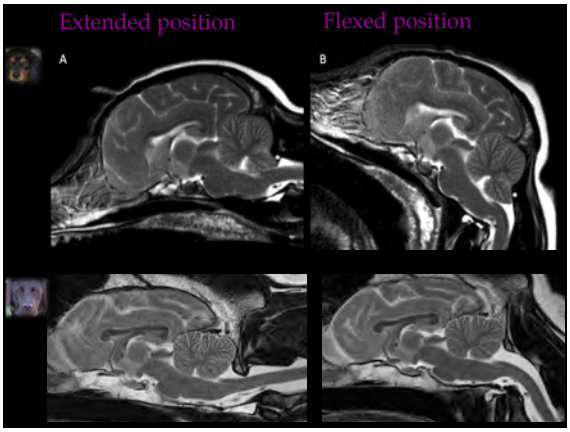
- Degree of cerebellar herniation correlates with syringomyelia (Human medicine)
- CKCS?



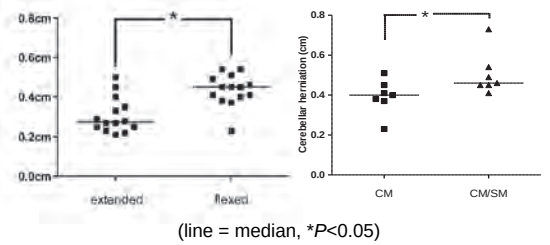
Lu et al. 2003



Cerda-Gonzalez et al. 2009



Cerebellar herniation increases with flexion

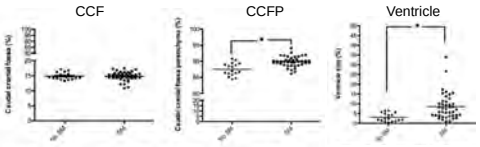


(line = median, *P<0.05)

Upchurch, J.J., Driver, C.J., Butler, L., McGonnell, I.M., Volk, H.A. (2011)

Chiari-like malformation (CM) / Syringomyelia (SM)

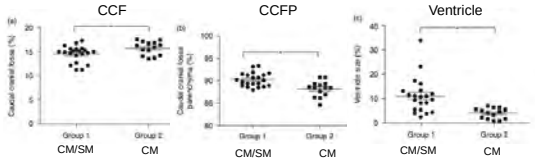
- ↑Increase in brain parenchyma (CCFP) in caudal cranial fossa (CCF)
- ↑Ventricle size in CKCS with CM/SM
- Both factors correlate with syrinx size



Driver, C.J., Rusbridge, C., Cross, H., McGonnell, I.M., Volk, H.A. (2010a)

Comparison of ≤2 years old CKCS with CM/SM versus ≥5 years old CKCS with CM

Additional finding decrease in caudal cranial fossa (CCF) volume

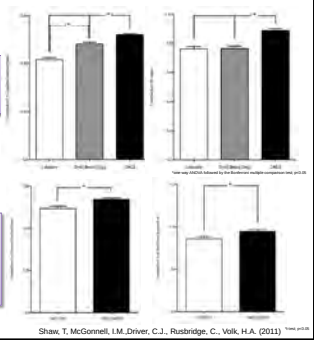


Driver, C.J., Rusbridge, C., McGonnell, I.M., Volk, H.A. (2010b)

Cerebellum increased in size

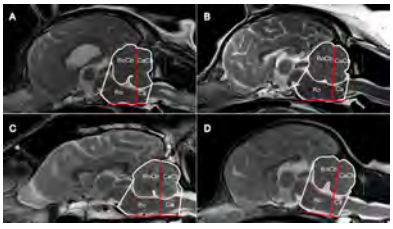
Increase of cerebellar volume in comparison to caudal cranial fossa

Cerebellar enlargement associated with SM



Shaw, T, McGonnell, I.M.,Driver, C.J., Rusbridge, C., Volk, H.A. (2011)

Partitioning of caudal cranial fossa



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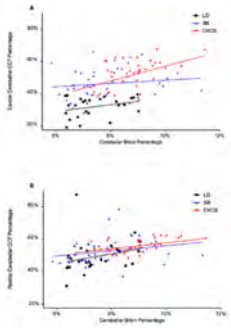
Caudal Compartment affected



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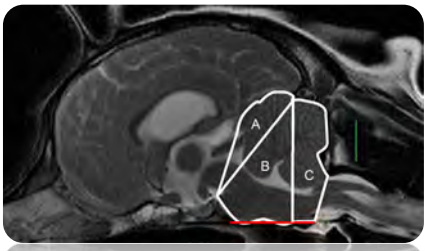
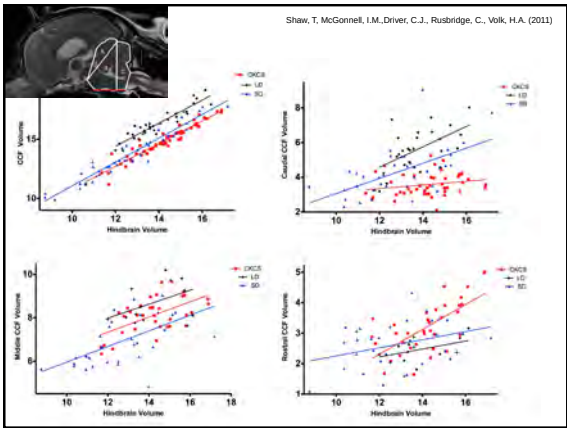
Partitioning of caudal cranial fossa



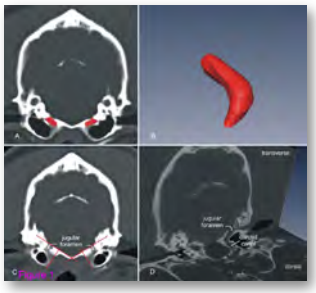
Shaw, T, McGonnell, I.M.,Driver, C.J., Rusbridge, C., Volk, H.A. (2011)

RVC



Shaw, T, McGonnell, I.M.,Driver, C.J., Rusbridge, C., Volk, H.A. (2011)

Decrease in venous drainage?



Schmidt, Ondreka, Sauerbrey, Volk, Rummel, Kramer (2012)

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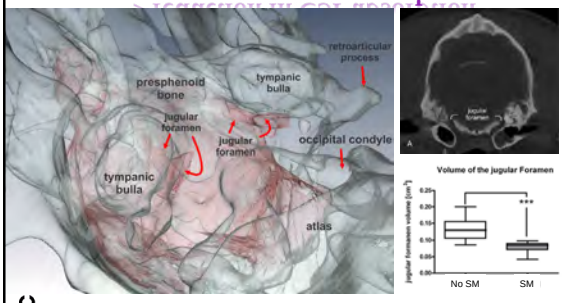
Decrease in venous drainage? -> reduction in CSF absorption



Schmidt, Ondreka, Sauerbrey, Volk, Rummel, Kramer (2012)

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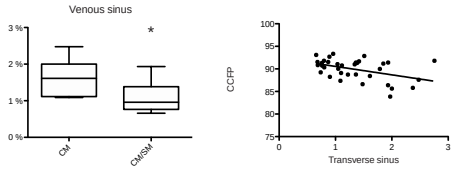
Transverse venous sinus reduced in CKCS with CM/SM – associated with hindbrain size



Fenn, J, Schmidt MJ, Simpson, H, Driver, CJ, Volk HA 2013

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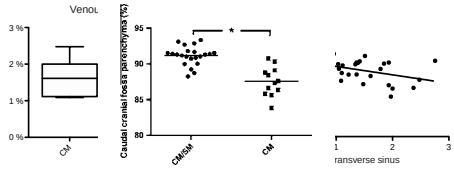
Transverse venous sinus reduced in CKCS with CM/SM – associated with hindbrain size



Fenn, J, Schmidt MJ, Simpson, H, Driver, CJ, Volk HA 2013

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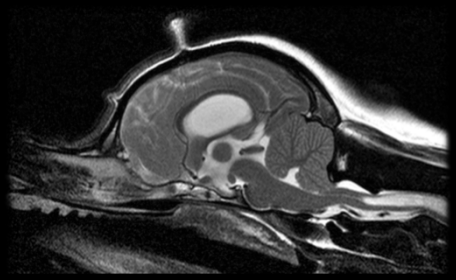
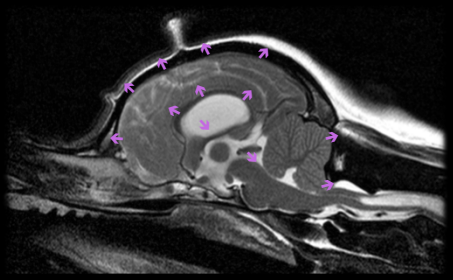
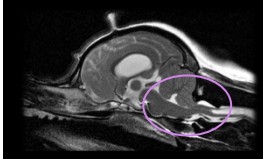
Pulsation

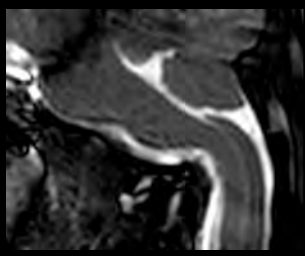


Pulsation



Pulsation





Pulsation more important than pressure

Clinical Neurosurgery • Volume 53, 2006 *Cerebrospinal Fluid Pulsatility and Hydrocephalus: The Fourth Circulation*

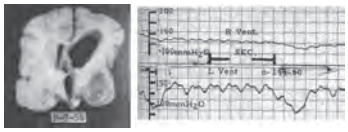


FIGURE 6.5. Results of a dog experiment reported by Bering.[9] In a model of communicating hydrocephalus, as described by Dandy, unilateral choroid plexectomy diminishes the amplitude of pressure pulsations on the plexectomized side, but mean pressure is the same on the two sides. Ventricular dilation occurs primarily on the intact side (with greater pulsations). This favors a view that pulsatile pressure waves can alter ventricular size even when the average pressure is kept constant.

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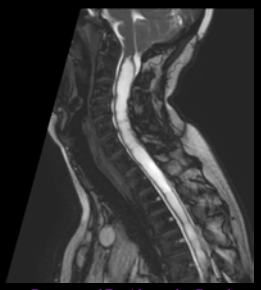
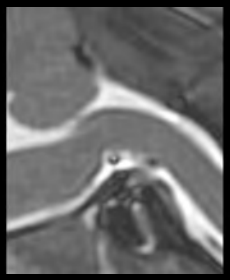
Human

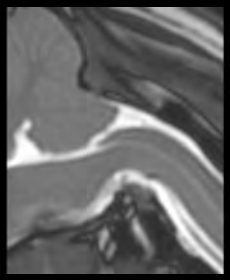


Courtesy of Dr. Alexander Bunck

V

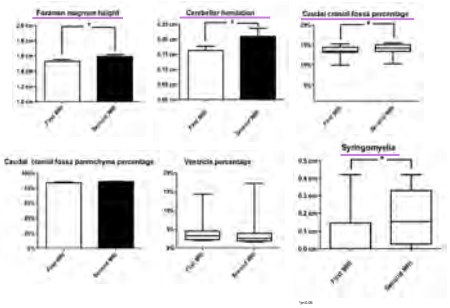
CM CM/SM





V

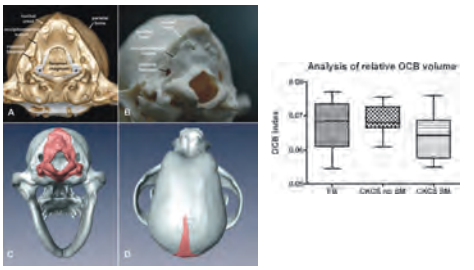
Changes over time



Driver, C.J., DeRisio, L., Hamilton, S., Rusbridge, C., Dennis, R., McGonnell, I.M., Volk, H.A. (2012)

COMPARISON OF THE RELATIVE OCCIPITAL BONE VOLUME BETWEEN CAVALIER KING CHARLES SPANIELS WITH AND WITHOUT SYRINGOHYDROMYELIA AND FRENCH BULLDOGS

M.J. Schmidt, M. Kramer, N. Ondreka



2012 *Veterinary Radiology & Ultrasound*

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Os supraoccipital-changes

- Bone thinning
- Enlargement of the foramen magnum

When does this phenotype first appear?

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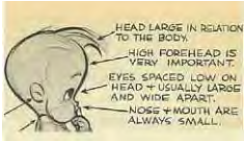
What have we done?

RVC

Paedomorphism



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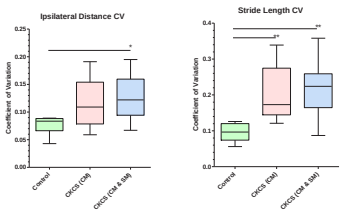
CKCS more variable in gait compared to Border Terriers



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Questionnaire-based behaviour analysis of Cavalier King Charles spaniels with neuropathic pain due to Chiari-like malformation and syringomyelia

Lynda Rutherford [a], Annette Wessmann [b], Clare Rusbridge [c], Imelda M. McConnell [d], Siobhan Abeyesinghe [e], Charlotte Burn [e], Holger A. Volk [a,*]

[a] Department of Veterinary Clinical Sciences, Royal Veterinary College, Hatfield, UK
[b] School of Veterinary Medicine, University of Glasgow, Bearsden, Glasgow, UK
[c] Stone Lion Veterinary Hospital, Guildford Veterinary Group, London, UK
[d] Department of Veterinary Basic Sciences, Royal Veterinary College, London, UK
[e] Centre for Animal Welfare, Department of Veterinary Clinical Sciences, Royal Veterinary College, Hatfield, UK

Table 1
Correlation between neuropathic pain score and behaviour factors and quality of life.

Category	Spearman rank coefficient	P value/FDR threshold*	Description of shown behaviour*
Separation-related behaviour	0.38	<0.0001/0.0045*	Dog displays fear/anxiety behaviour when left on its own
Non-social fear	0.34	0.0002/0.0055*	Dog acts anxious/fearful towards loud/sudden noises, towards unfamiliar/wind-blown objects on walks, or during heavy traffic, thunderstorms or unfamiliar situations generally
Pain sensation	0.29	0.0018/0.0068*	Dog acts anxiously/fearful when treated by veterinarian, groomed, bathed or having claws clipped
Stranger-directed fear	0.28	0.0023/0.011*	Dog acts anxious/fearful when approached by unfamiliar man/woman/child, or when an unfamiliar visitor enters the home
Attachment behaviour	0.24	0.0095/0.015*	Dog shows strong attachment behaviour to a particular member in the household and is attention seeking
Excitability	0.21	0.02/0.022*	Dog overreacts or is excitable when household members/visitors arrive, when the doorbell rings, when it is being taken to a walk or car trip, or during play
Stranger-directed aggression	0.16	0.073/0.034	Dog acts aggressively when approached by an unfamiliar man/woman/child, or when an unfamiliar visitor enters the home
Dog-directed fear or aggression	0.09	0.32/0.05	Dog acts anxious/fearful or aggressive when approached by an unfamiliar dog
Owner-directed aggression	0.08	0.39/0.05	Dog acts aggressively when approached, threatened, punished by owner, especially in relation to grooming, bathing, food or toys
Trainability	0.05	0.6/0.05	Dog responds to commands adequately and immediately, is quick to learn 'tricks' and responds to corrections
Chasing	−0.03	0.71/0.05	Dog acts aggressively and chases cats, squirrels and birds if given the chance

Spearman rank correlations were carried out between NRS scores and the median score for each behavioural category for each dog (n = 122).
* False discovery rate controlling procedure (FDR).
† For details of behaviour traits, see questionnaire of the study of Hsu and Serpell (2003).
P value below the FDR threshold and thus considered to be significant.

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PLOS ONE

Quantitative Analysis of Chiari-Like Malformation and Syringomyelia in the Griffon Bruxellois Dog

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Abstract

This study aimed to develop a system of quantitative analysis of canine Chiari-like malformation and syringomyelia on variable quality MRI. We made a series of measurements from magnetic resonance DICOM images from Griffon Bruxellois dogs with and without Chiari-like malformation and syringomyelia and identified several significant variables. We found that in the Griffon Bruxellois dog, Chiari-like malformation is characterized by an apparent shortening of the entire cranial base and possibly by increased proximity of the atlas to the occiput. As a compensatory change, there appears to be an increased height of the rostral cranial cavity with lengthening of the dorsal cranial vault and considerable reorganization of the brain parenchyma including ventral deviation of the olfactory bulbs and rostral invagination of the cerebellum under the occipital lobes.

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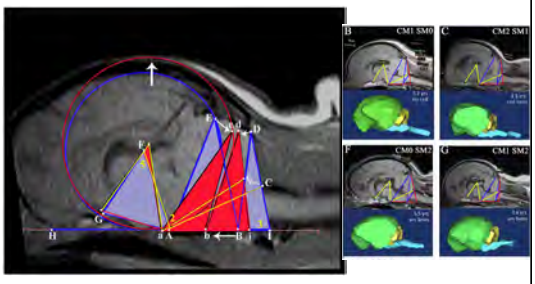

Figure 9. Change in skull and brain conformation in Griffon Bruxellois with CM and syringomyelia. The T1-weighted midsagittal MRI image is from dog A (without CM or syringomyelia) and the framework of lines and angles is indicated in blue and higher case letters with the exception of angles 2 and 5 which are numbered in yellow. The framework of dog D (with CM and syringomyelia) has been superimposed on the image and aligned with baseline HAN and on the F-filametar. The framework of dog D is in red and with lower case letters. Angles 2 and 5 are yellow. It is possible to appreciate how with syringomyelia, the occipital lobe circle and height of cranial fossa increases (red circle). Angles 2 and 5 (yellow) are decreased as a consequence of the cranial base shortening and increased proximity of the atlas to the occiput. In addition the vertexes at E and D (red triangles) are closer together giving an appreciation of the overcrowding and change in shape of the caudal fossa. The white arrows depict the changes between the measurements.
doi:10.1371/journal.pone.0088120.g009

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Summary

- Similarities between human and canine Chiari-malformation and Syringomyelia
- Overcrowding of Caudal Cranial Fossa (too much brain in a reduced space)
- Progressive disease with complex pathophysiology
- Breeding for paedomorphic traits?

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Treatment

1. None
2. Medical
3. Surgical
4. Euthanasia

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Medical

- Nonsteroidal anti-inflammatory drugs (NSAID)
  - COX-2 inhibitors (not as affected for neuropathic pain)
- Corticosteroids
  - Anti-inflammatory
  - Sympathetic modulated pain
  - Decrease of substance P
- Antiepileptic drugs
  - Voltage-gated calcium channels
    - Gabapentin
    - Pregabalin

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Medical

- Opioides
  - Methadone
  - Tramadol
- Ketamine
- Sodium channel blockers
  - Phenytoin, carbamazepine
  - Topiramate
  - Tricyclic antidepressants, e.g. amitriptyline (also serotonine and noradrenaline reuptake inhibitor)
- Sympathetic nervous system
  - Accupuncture
  - Alpha-2 agonist clonidine

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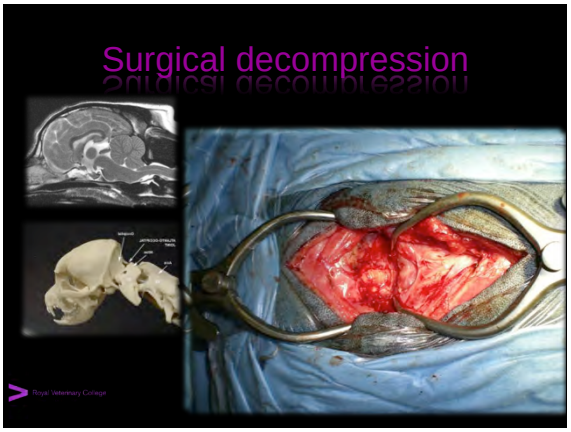
Surgical decompression



RVC Integrated Neurology

Team dog - Team chicken- Team mouse

Imelda McGonnell/Holger Volk
Albert Basson
Colin Driver
Ania Giejda
Danielle Whittaker

RVC Imaging team — Joe Fenn
RVC Neuro team — Thomas Shaw
Emma Buckland — Clare Rusbridge
Emma Jane Suiter — Luisa de Risio
Sarah Hamilton — Dan Preece
Jessica Upchurch — Ruth Dennis
Hannah Cross — Paul Mandiger

Supported by wellcome trust

BBSRC bioscience for the future

THE KENNEL CLUB

Other funding
CKCS breeders etc

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Spinal degenerative diseases

Holger Volk DVM PGCAP DipECVN PhD FHEA MRCVS

Royal Veterinary College
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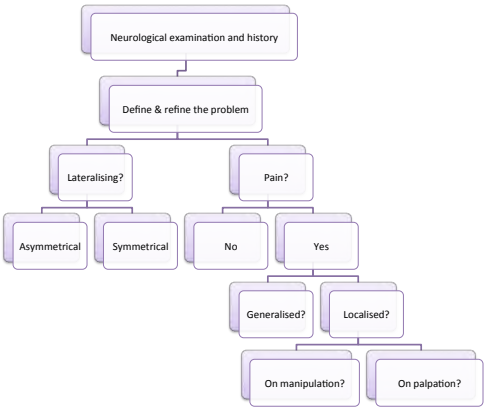
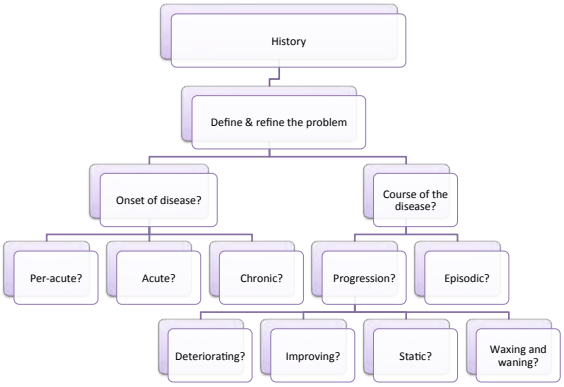
Spinal degenerative diseases

Holger A. Volk DVM, DipECVN, PhD, MRCVS
Neurology & Neurosurgery
The Royal Veterinary College



1. To **appreciate** the importance of clearly defining the problem to differentiate myelopathic versus non-myelopathic diseases.
2. To **appreciate** that 'thinking pathophysiologically' is essential in order to rank your differential list and to define/refine your problem.
3. To **develop** a diagnostic approach to the patient with spinal disease





Define & refine the problem

How can we define the problem now by the neuro-hand rule?

1.Onset, 2.clinical course, 3.pain, 4.lateralising, 5.neurological localisation

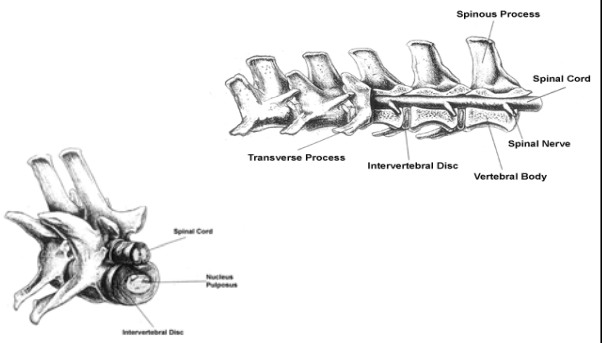
Example:
•Acute, onset, progressive, painful, asymmetrical T3-L3 myelopathy
•Chronic, progressive, non-painful, asymmetrical, forebrain disorder

Boosted by pathology…

DAMNITV scheme:

1. Degenerative
2. Anomaly
3. Metabolic
4. Neoplastic / Nutritional
5. Inflammatory / Infectious / Idiopathic
6. Trauma / Toxin
7. Vascular

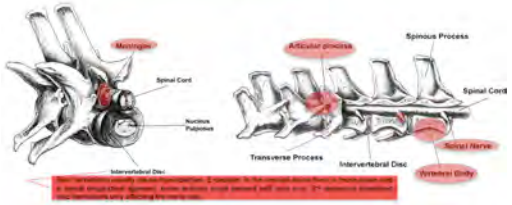
Myelopathic vs. non-myelopathic



Myelopathic vs. non-myelopathic

Location of lesion

Which structures could cause pain and surround or are close to the spinal cord?



Non-myelopathic

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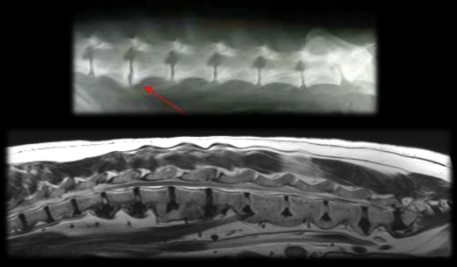
Spondylosis deformans
Diffuse Idiopathic Skeletal Hyperostosis



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SPONDYLOSIS DEFORMANS AND DIFFUSE IDIOPATHIC SKELETAL HYPEROSTOSIS (DISH) RESULTING IN ADJACENT SEGMENT DISEASE

MARIA ORTEGA, RITA GONÇALVES, ALLISON HALEY, ANNETTE WESSMANN, JACQUES PENDERIS

Spondylosis deformans and diffuse idiopathic skeletal hyperostosis (DISH) are usually incidental findings and in most dogs are either asymptomatic or associated with mild clinical signs. Severe spondylosis deformans and DISH can result in complete bony fusion of consecutive vertebral segments. One of the recognised complications following vertebral fusion in human patients is the development of adjacent segment disease, which is defined as degenerative changes, most commonly degenerative intervertebral disc disease, in the mobile vertebral segment neighboring a region of complete vertebral fusion. A similar syndrome following cervical fusion in dogs has been termed the domino effect. The purpose of this retrospective study was to investigate the hypothesis that vertebral fusion occurring secondary to spondylosis deformans or DISH in dogs would protect fused intervertebral disc spaces from undergoing degeneration, but result in adjacent segment disease at neighbouring unfused intervertebral disc spaces. Eight dogs with clinical signs of thoracolumbar myelopathy, magnetic resonance imaging of the thoracolumbar vertebral column, and spondylosis deformans or DISH producing fusion of ≥2 consecutive intervertebral disc spaces were evaluated. Vertebral fusion of ≥2 consecutive intervertebral disc spaces was correlated ($P = 0.0017$) with adjacent segment disease at the neighbouring unfused intervertebral disc space. Vertebral fusion appeared to protect fused intervertebral disc spaces from undergoing degeneration ($P < 0.0001$). Adjacent segment disease should be considered in dogs with severe spondylosis deformans or DISH occurring in conjunction with a thoracolumbar myelopathy. © 2012 *Veterinary Radiology & Ultrasound.*

Key words: Intervertebral disc degeneration, Wobbler, domino, spinal cord, compression

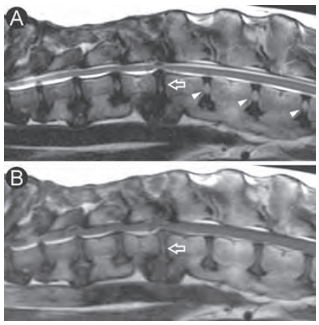
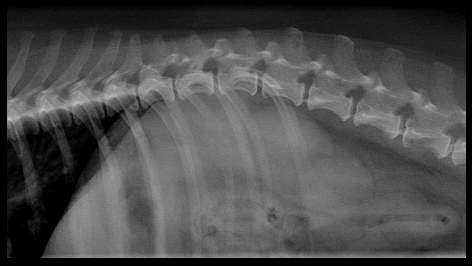


FIG. 3. Midline sagittal plane T2-weighted (A) and T1-weighted (B) magnetic resonance images of the thoracolumbar vertebral column. There is complete bony fusion of the T10–T11, the T12–T13, and the L1–L3 intervertebral disc spaces. The intervertebral disc spaces within the L1–L3 segment of vertebral fusion appear normal (arrowheads), but adjacent to this, there is marked degeneration and protrusion of the unfused T13–L1 intervertebral disc (arrow) with severe spinal cord compression.

?



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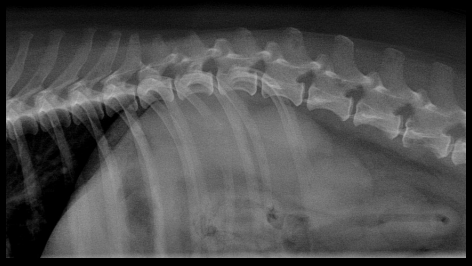
Neoplasia



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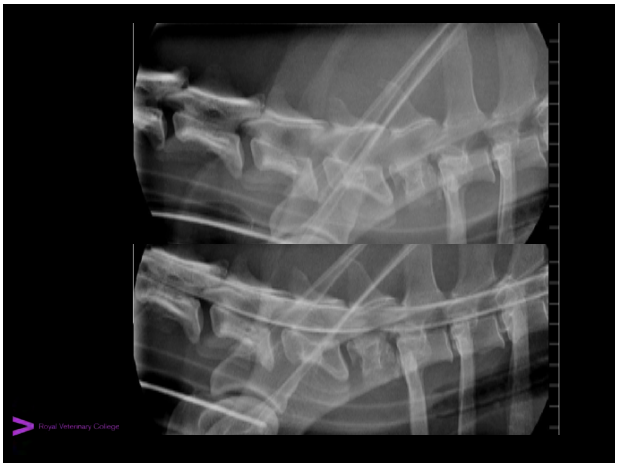

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Myelopathic

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Dachshund, 5yrs, FS

- History:
  - Yesterday the dog fell of the sofa and now it is painful in its back
  - Gina is getting worse and the owner is very worried as Gina is also wobbly
  - The owner thinks only the hind limbs are affected

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Neurological findings

Mentation
Posture
Gait
Postural reactions
Cranial nerves
Spinal reflexes
Palpation
Nociception

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Dachshund, 5yrs, FS

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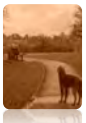

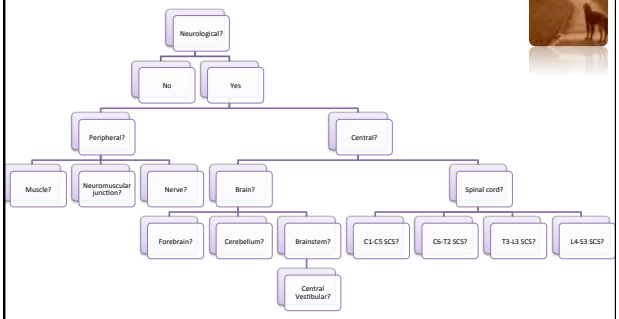

Define & refine the problem

How can we define the lesion now by the neuro-hand rule?

1.Onset, 2.clinical course, 3.pain, 4.lateralising, 5.neurological localisation

Can the signalment help us in this case?

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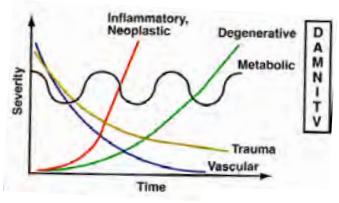
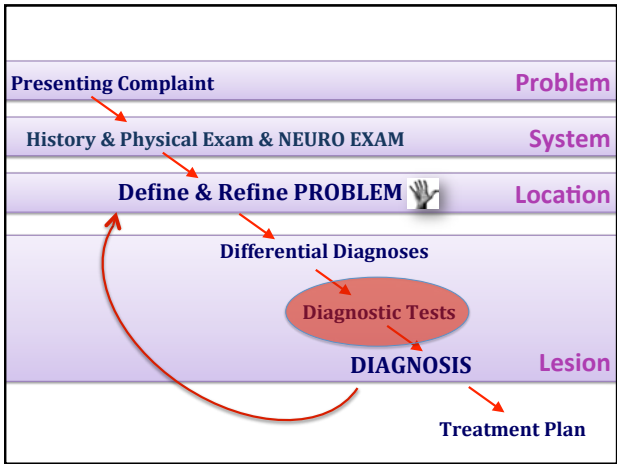
Please write down now your differential list:

D	Degenerative
A	Anomalous
M	Metabolic
N	Neoplastic Nutritional
I	Infectious Inflammatory Iatrogenic Idiopathic
T	Toxic Traumatic
V	Vascular



Category	Acute nonprogressive	Acute progressive	Chronic progressive
Degenerative		Type I disk disease (A, Y)	Lumbosacral stenosis (A,Y) Type II disk disease (A) Degenerative myelopathy (A) Spondylosis deformans (A) Demyelinating diseases (Y) Axonopathies and neuronopathies (Y) Extradural synovial cysts (A) Breed specific myelopathies (such as Afghan hound myelopathy (Y) Storage disease (Y)
Anomalous			Chiari-like malformation& Syringomyelia (Y, A) Vertebral anomalies (Y) Atlantoaxial luxation (Y) Spinal dysraphisms (Y)
Neoplastic		Primary (A) Metastatic (A) Skeletal (A)	Nephroblastoma (Y) Primary (A) Metastatic (A) Skeletal (A)
Nutritional			Hypervitaminosis A (Y,A)
Inflammatory / infectious		Distemper (Y,A) FIP (Y) Protozoal (Y) GME (A) Bacterial myelitis (Y,A) Discospondylitis (Y,A)	Distemper (Y,A) FIP (Y) Protozoal (Y) GME (A)
Traumatic	Fractures (Y,A) Luxations (Y,A) Contusions (Y,A) Traumatic disk (Y,A)	Traumatic disk (Y,A)	
Vascular	Infarction (FCE; Y,A) Septic emboli (Y,A) Hemmorrhage (Y,A) Vascular malformations (Y)		



Diagnostic plan

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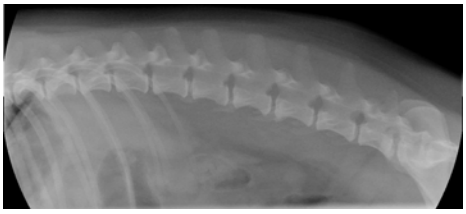
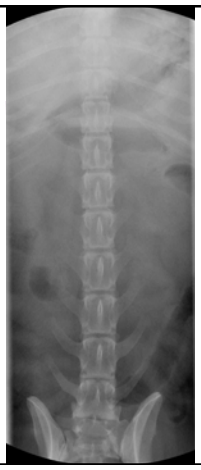
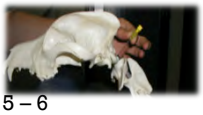
Radiographs





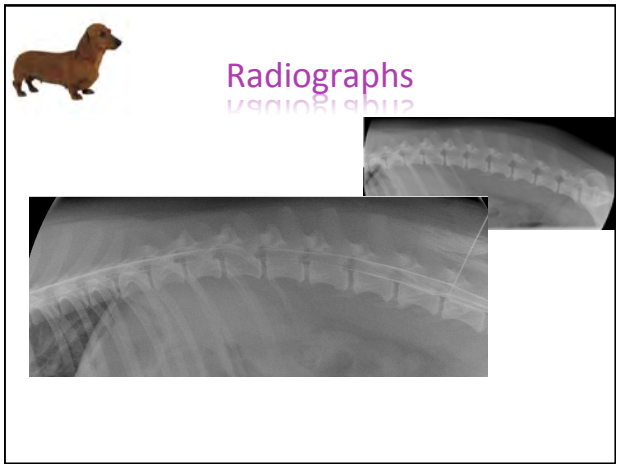
Myelogram

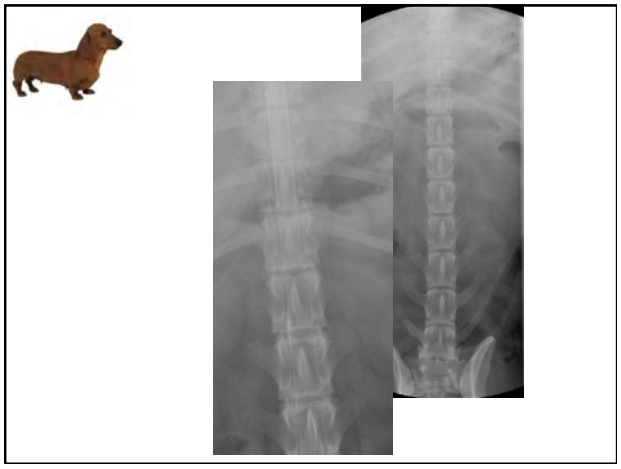
- **Cerebello-medullary cistern**
  - (cisterna magna)
- **Lumbar**
  - Between lumbar vertebrae 5 – 6

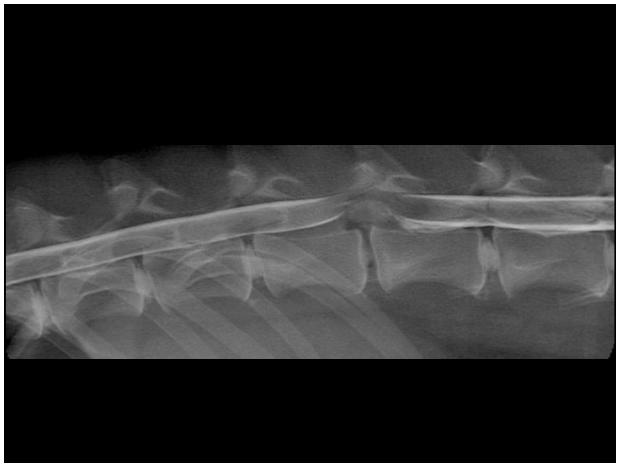


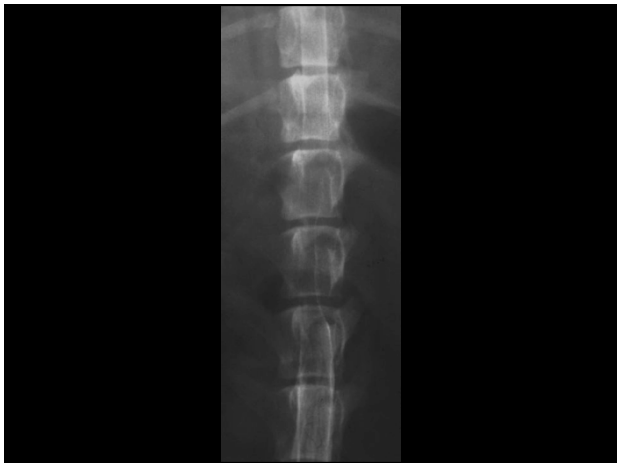
Site for CSF identical

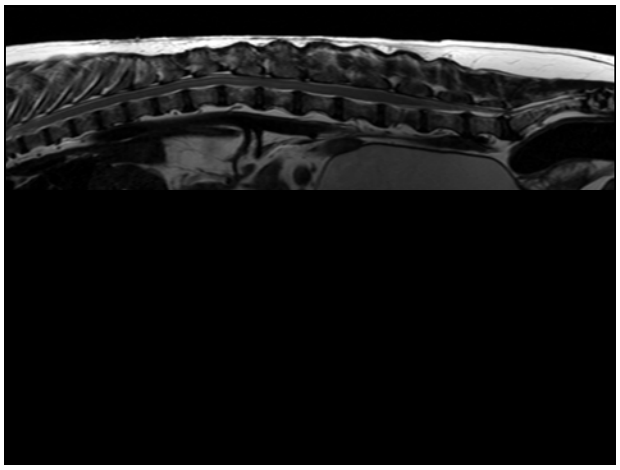
Holger Volk

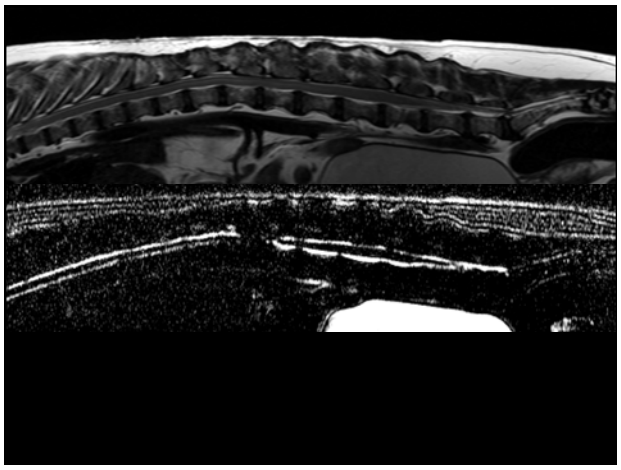

Radiographs

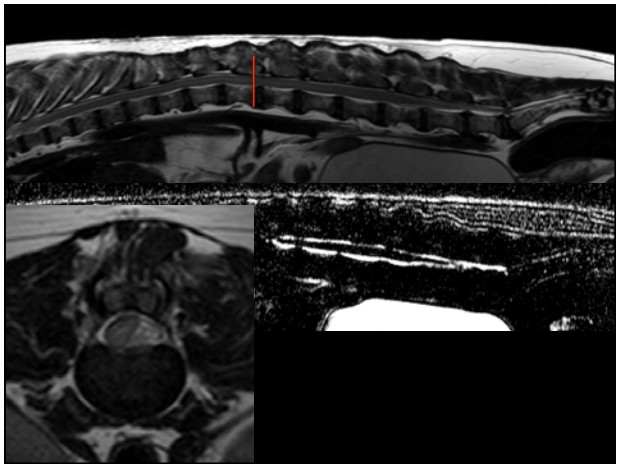






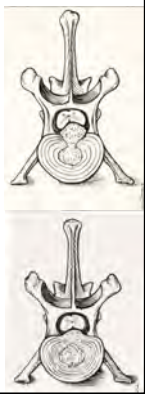




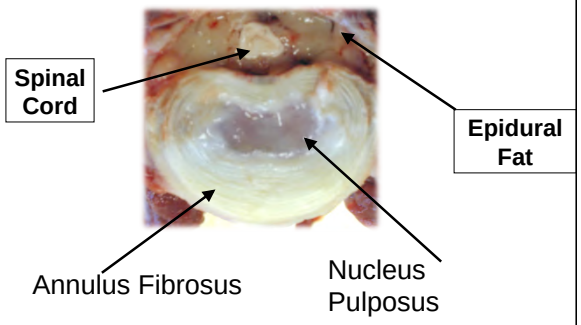


Disc degeneration

- Hansen type I
  - Chondrodystrophoid
  - Disc extrusion
- Hansen type II
  - Non - chondrodystrophoid
  - Disc protrusion

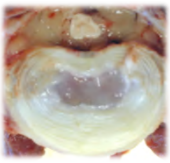


Anatomy

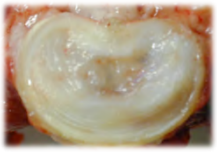


Pathogenesis

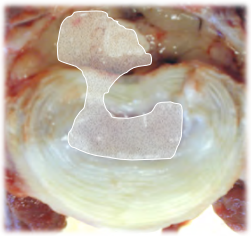
Normal

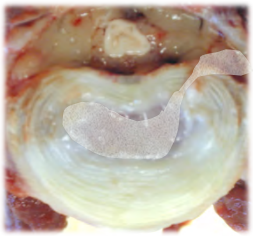


Early Degeneration



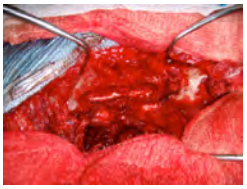
Pathogenesis





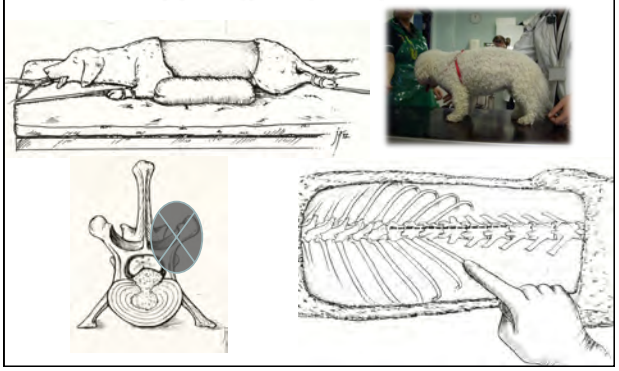
Treatment

- Medical
  - NSAIDs and 4 WEEKS CAGE REST
  - Bladder management if necessary
- Surgical
  - Decompression
  - Bladder management if necessary
  - Rehabilitation
  - Analgesia



- Steroids are NOT indicated in the treatment of disc disease

Hemilaminectomy



The most important: NURSING

COMPASSION

Bedding

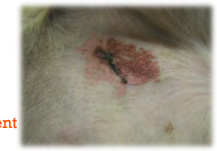
Bladder

Turning

FOOD

Complications

- Urinary tract infections
  - Poor bladder management
- Gastrointestinal disturbances
  - Steroids, NSAIDs
- Wound infection
  - Surgical time, steroids
- Urine scald
  - Poor bladder management
- Decubital ulcers
  - Poor nursing



Prognosis - recovery rate

Grade	Conservative	Decompression
1	100%	100
2	84	100
3	100	95
4	50	90
5 <48 hours	7	50
<24 hours		75
>48 hours		6

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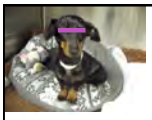

Dachshund, 2yrs, MN

•History:
- •Mischa has been off colour since 2 weeks
- •First he was slowing down and since a week he is falling all over the place

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Neurological findings

Mentation
Posture
Gait
Postural reactions
Cranial nerves
Spinal reflexes
Palpation
Nociception

Holger A. Volk
DVM, PhD, MRCVS

Neurology
The Royal Veterinary College

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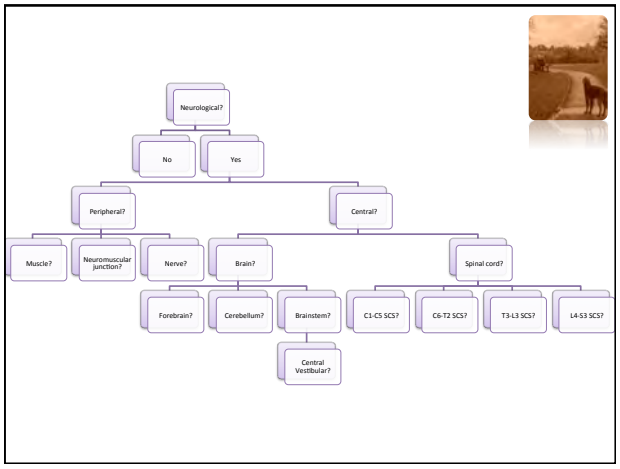

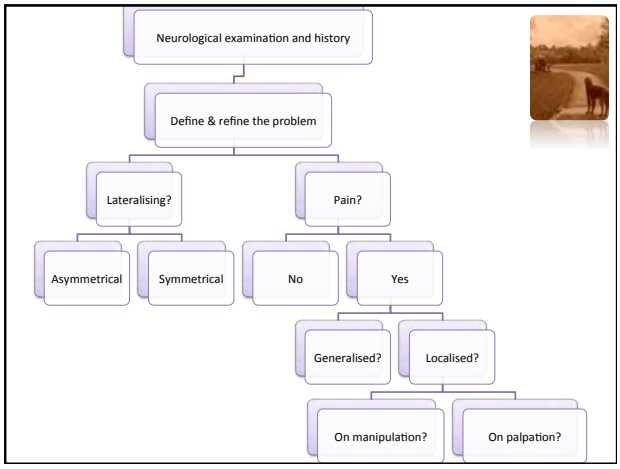

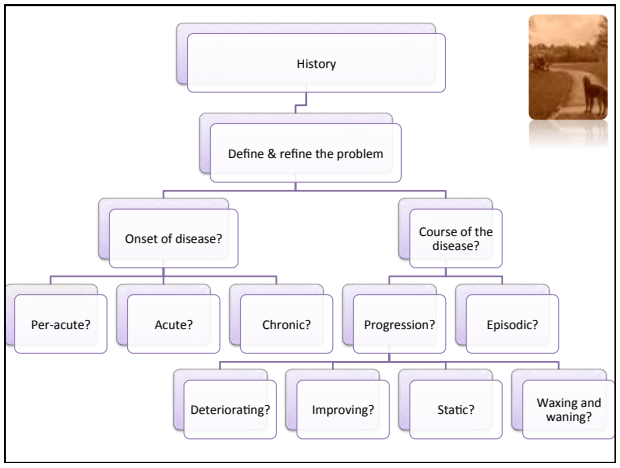

Define & refine the problem

How can we define the lesion now by the neuro-hand rule?

1.Onset, 2.clinical course, 3.pain, 4.lateralising, 5.neurological localisation

Can the signalment help us in this case?

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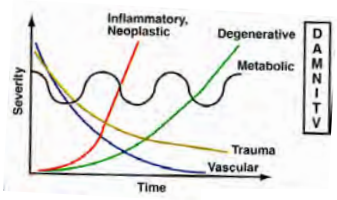
Please write down now your differential list:

D	Degenerative
A	Anomalous
M	Metabolic
N	Neoplastic Nutritional
I	Infectious Inflammatory Iatrogenic Idiopathic
T	Toxic Traumatic
V	Vascular



Category	Acute nonprogressive	Acute progressive	Chronic progressive
Degenerative		Type I disk disease (A, Y)	Lumbosacral stenosis (A,Y) Type II disk disease (A) Degenerative myelopathy (A) Spondylosis deformans (A) Demyelinating diseases (Y) Axonopathies and neuronopathies (Y) Extradural synovial cysts (A) Breed specific myelopathies (such as Afghan hound myelopathy (Y) Storage disease (Y)
Anomalous			Chiari-like malformation& Syringomyelia (Y, A) Vertebral anomalies (Y) Atlantoaxial luxation (Y) Spinal dysraphisms (Y)
Neoplastic		Primary (A) Metastatic (A) Skeletal (A)	Nephroblastoma (Y) Primary (A) Metastatic (A) Skeletal (A)
Nutritional			Hypervitaminosis A (Y,A)
Inflammatory / infectious		Distemper (Y,A) FIP (Y) Protozoal (Y) GME (A) Bacterial myelitis (Y,A) Discospondylitis (Y,A)	Distemper (Y,A) FIP (Y) Protozoal (Y) GME (A)
Traumatic	Fractures (Y,A) Luxations (Y,A) Contusions (Y,A) Traumatic disk (Y,A)	Traumatic disk (Y,A)	
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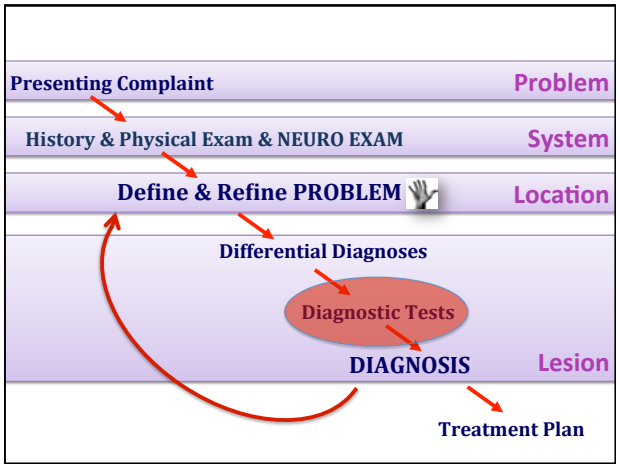

Diagnostic plan

- Haematology:
  - Lymphocytes: 0.52 x10e9/l (RR 1-4.8x10e9/l)
  - Monocytes: 1.56x10e9/l (RR 0.15 - 1.5 10e9/l)
- Biochemistry
  - Creatinine kinase activity 61 umol/l (RR 98-163 umol/l).

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Diagnostic plan

- CSF findings:
  - White blood cell number: 8 /mm^3 (<5/mm^3)
  - Protein content: 0.34 g/l (<0.25 g/l)
  - Cytology: 68% small mononuclear cells; rest mix of large mononuclear cells and neutrophils

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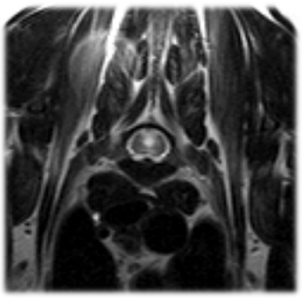
Myelitis



Dalmatian, 7 yrs, FS

- History:
  - The owner reports the dog to be getting more and more wobbly. It all started 3 months ago.
  - Owner thinks dog is painful after a long walk and that excercise makes it worse

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Neurological findings

Mentation
Posture
Gait
Postural reactions
Cranial nerves
Spinal reflexes
Palpation
Nociception

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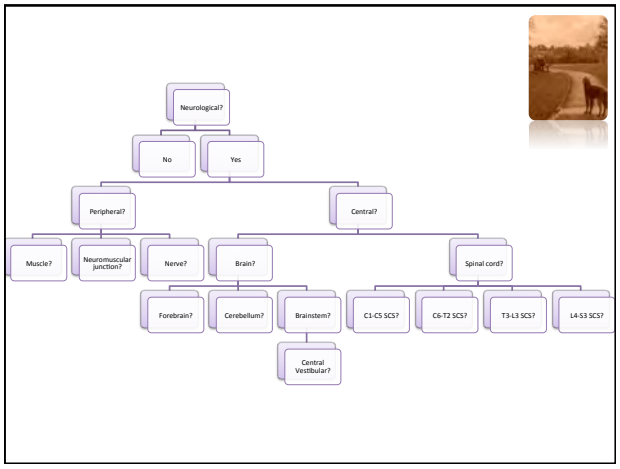

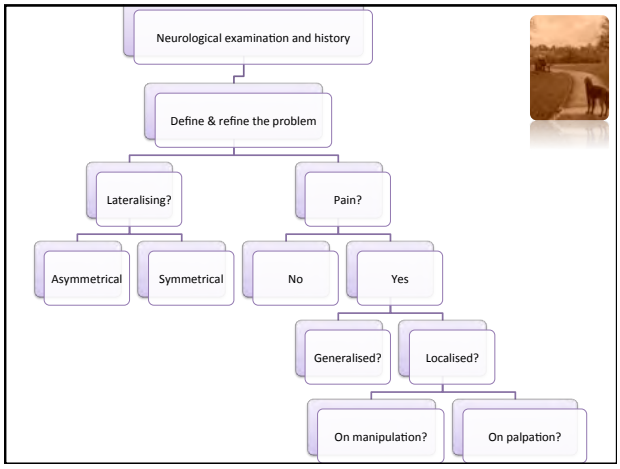

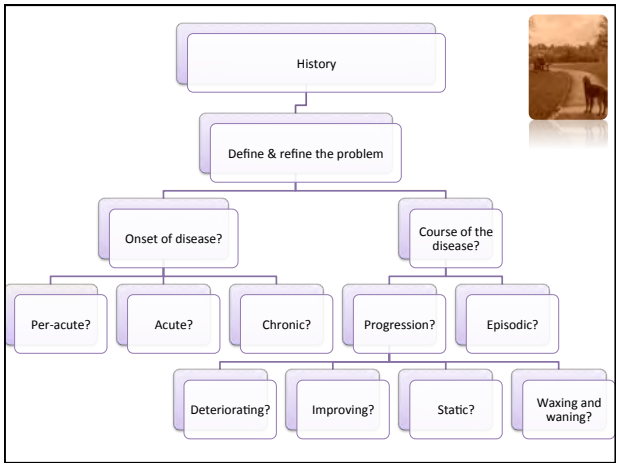

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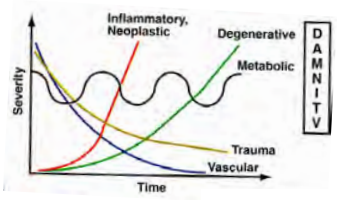

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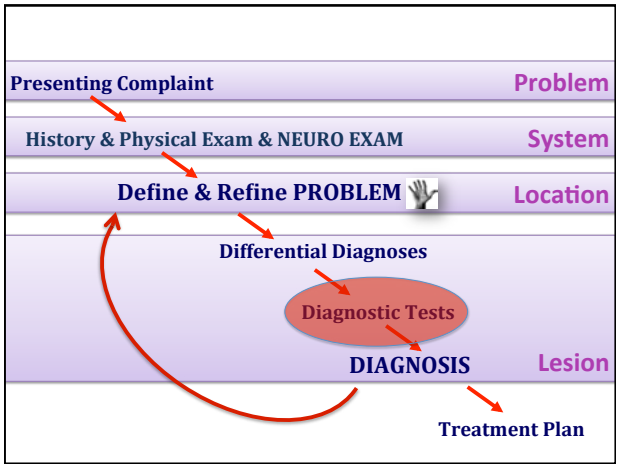

Diagnostic plan

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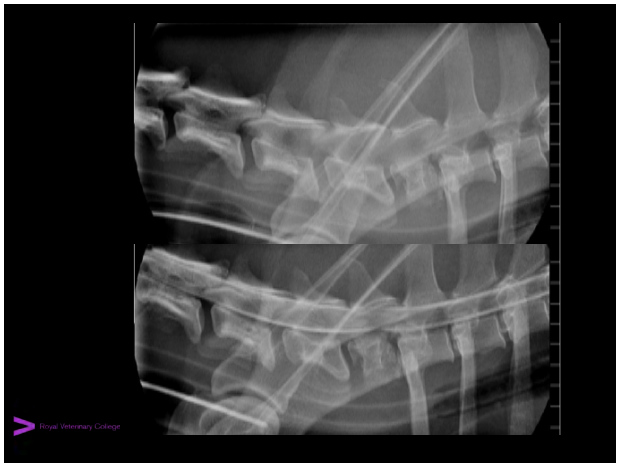

German Shepherd Dog, 9yrs, MN

- History:
  - 5 months history of not jumping into cars
  - Since 1 week very painful, not responding to NSAIDs and rest
  - The dog is now also faecal and urinary incontinent

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Neurological findings

Mentation
Posture
Gait
Postural reactions
Cranial nerves
Spinal reflexes
Palpation
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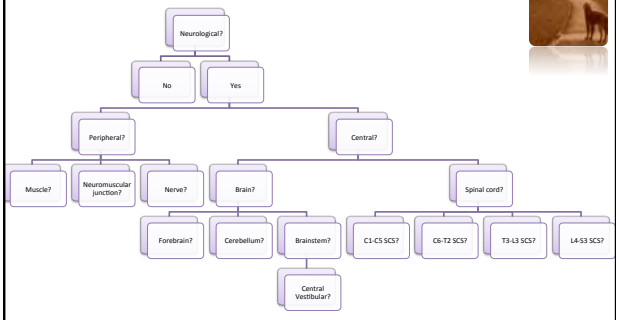

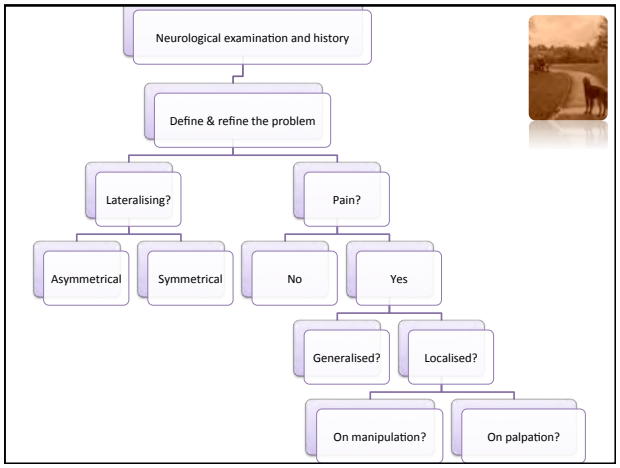

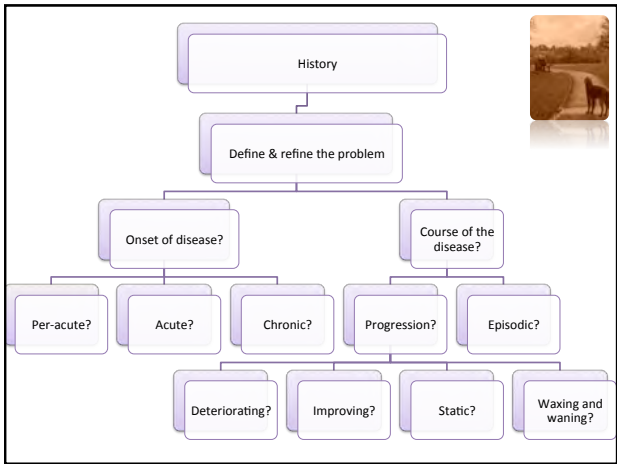

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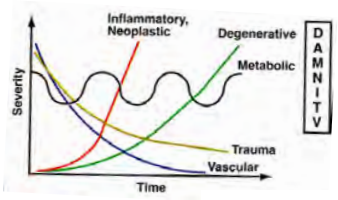

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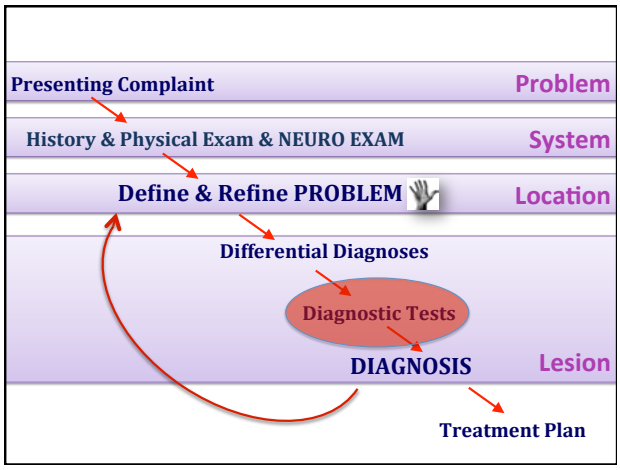

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CLINICAL MEDICINE

Section of Diagnostic Imaging and Radio-Oncology, Department of Small Animals, University of Zurich, Zurich, Switzerland

The Lumbosacral Junction in Working German Shepherd Dogs – Neurological and Radiological Evaluation

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With 4 figures and 3 tables

Received for publication: June 10, 2003

Summary

The clinical and radiological incidence of lumbosacral (LS) disease was studied on 57 German Shepherd dogs (GSDs) used in active service. The study included a clinical history, a neurological examination, and plain radiographs of the caudal lumbar vertebrae. The neurological examinations revealed lower back pain and/or neural deficits in 21 dogs, of which 14 had a history of pain or pelvic gait abnormalities. Radiographic findings were spondylosis at L7–S1, degeneration of L7–S1 disc, LS malalignment, transitional LS vertebrae and/or primary spinal canal stenosis in 15 dogs with neurological abnormalities and/or back pain and in 18 dogs with no clinical signs. No correlation between the neurological and the radiographic findings were found. This study demonstrates that even prominent radiographic LS abnormalities are of minimal value in the evaluation of LS disease in the GSD.

Introduction

Canine hip dysplasia (CHD), sacral osteochondrosis (SOC), primary lumbosacral spinal canal stenosis and transitional lumbosacral vertebrae (TLSV) are frequently diagnosed in German Shepherd dogs (Oliver et al., 1978; Tarvin and Prata, 1980; Winkler and Loeffler, 1986; Morgan and Bailey, 1990; Lang et al., 1992; Morgan et al., 1993; De Risio et al., 2000). These heritable diseases are risk factors for the development of cauda equina compression syndrome (CES), a term describing clinical symptoms produced by compression or injury of the caudal lumbar, sacral and/or coccygeal segments of the spinal cord and associated nerve roots (Lang et al., 1992; Morgan et al., 1993; De Risio et al., 2000). Spinal cord diseases and CES in particular are common causes for early elimination of dogs in the USA military dog programme (Moore et al., 2001). Despite this knowledge Swiss police GSDs are rarely examined radiographically prior to training.

The purpose of the study was to correlate the radiographic findings in the LSV and the neurological findings in working GSDs.

Materials and Methods

Between February and May 2001, 60 GSDs from a Swiss police unit were evaluated at the Animal Teaching Hospital of the University of Zurich. Three dogs with behavioural problems were excluded from the study. Fifty males (49 intact/one neutered) and seven females (six intact/one neutered) ranging in age from 1 to 9 years (mean 4.5 years) were evaluated. Their body weights ranged between 28 and 45 kg (mean 37 kg). Fifty-two dogs were used as guard dogs and five were used as drug dogs.

A clinical history was obtained from the owners or handlers. A neurological examination was performed by one of the two neurologists (FS, FG). This examination included the evaluation of posture and gait as well as palpatory manipulation with focus on hypotrophied musculature, tail and anal tone and conscious proprioception. Swaying of the back, incoordinated movements of the pelvic limbs, spastic gait (reduced flexion), dragging of limbs, knuckling of feet and/or scuffing of toe nails are referred to as gait abnormalities in the following. Pain perception was assessed by hyperextending the tail, by LS hyperextension and spinal deep palpation. The spinal reflexes including patellar, cranial tibial and withdrawal reflex were evaluated. Dogs with at least one abnormal neurological finding were considered as clinically abnormal.

For the radiographic examination, the dogs were sedated intravenously with a combination of 5–10 μg/kg medetomidine (Domitor®; Dr E. Gräub AG, Berne, Switzerland) and 0.2 mg/kg butorphanol (Morphasol®; Dr E. Gräub AG). Muscle relaxation was achieved by subsequent intravenous administration of propofol (Propofol 1%®; Fresenius AG, Sarnen, Switzerland) to effect. Three digital radiographs (Fuji AC3-System; Fujifilm AG, Dielsdorf, Switzerland) were taken with the limbs held in position by sand bags and ropes:

1 A left lateral radiograph centred at LS-junction with femora perpendicular to the lumbar spine (Morgan, 1993).

2 A ventrodorsal radiograph centred at LS-junction with femora abducted and the X-ray beam parallel to the LS-endplates, angled cranially by 7–10° (Morgan, 1993).

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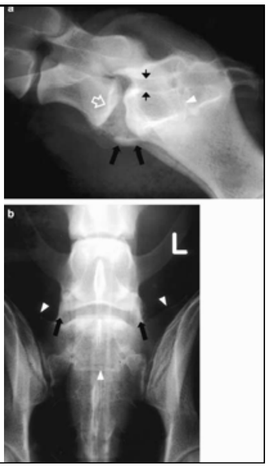

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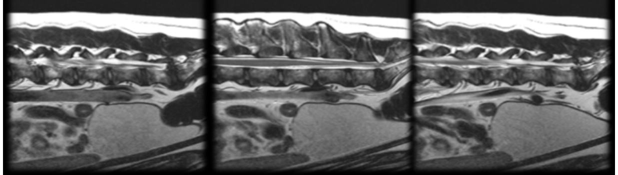
Lumbosacral stenosis



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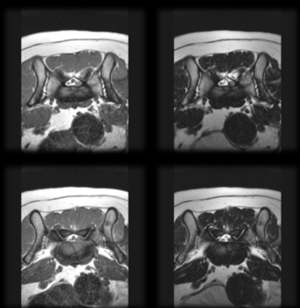
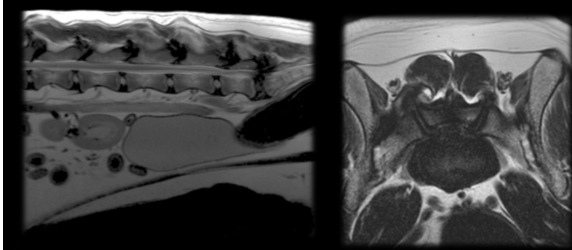
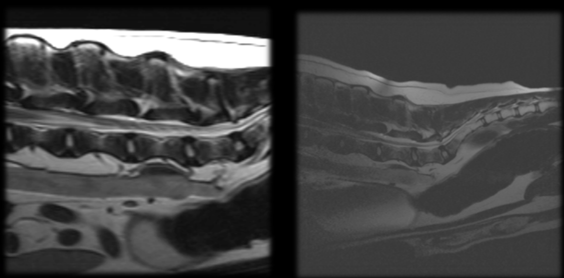


Lumbosacral Stenosis (static)



Lumbosacral Stenosis (dynamic)



Lumbosacral Disease

- Older large breed dogs
  especially German Shepherd Dogs
- Syndrome
- Bladder function; L4-S3 spinal cord segments
- Dynamic <-> Static

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Lumbosacral Disease

Stenosis of the vertebral canal and/or intervertebral foramina and/or the related vasculature

1. Hansen type II disc degeneration and protrusion at the lumbosacral junction
2. Thickening and in-folding of the intearcuate ligament
3. Subluxation of the articular facets
4. Epidural fibrosis
5. Thickened lamina and pedicles
6. Spondylosis, proliferative degenerative changes of the articular facets
7. Instability and misalignment between the last lumbar vertebra and the sacrum

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Pathogenesis

The importance of

1. Motion
2. Anatomic conformation
   a. Articular joint tropism
   b. Straighter facet joints
   c. Level of change of plane
   d. Facet joint angle
3. Congenital & developmental abnormalities
   a. Transitional vertebrae
   b. Osteochondrosis

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Diagnostics

1. The neuro-exam
   1. Pseudo-hyperreflexia
   2. Urinary + faecal incontinence
2. Imaging
   1. Radiographs
   2. Epidurography
   3. Discography
   4. CT
   5. MRI
3. EMG

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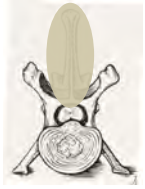
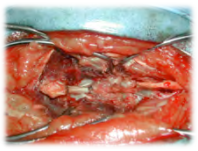
Lumbosacral Stenosis

- Treatment
  - Conservative
    - Restricted excercise 6-8 weeks
    - Anti-inflammatories
    - Pain relief
  - Surgery
    - Dorsal Laminectomy
    - **Dynamic vs non-dynamic**





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Lumbosacral Stenosis

- Post surgical complications
  - Immediate
    - Seroma – haemorrhage
      - > often due to too much movement after surgery
  - Delayed
    - Discospondylitis
    - Lamina formation/Fibrosis
      - > secondary compression

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German Shepherd X, 6yrs, MN

•History:
- •6 months history of slowing down
- •Since 3 weeks Batten is more wobbly in the hind limbs
- •not responding to NSAIDs and rest

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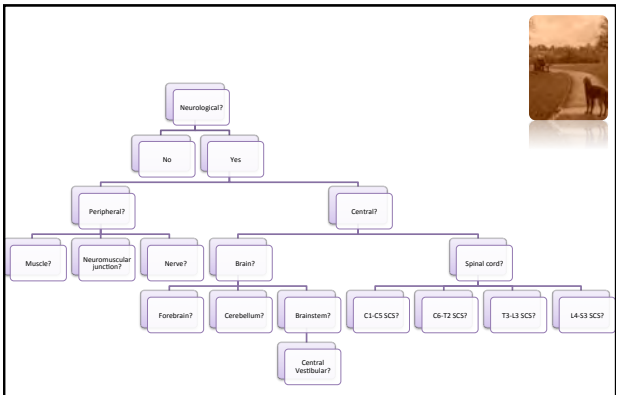

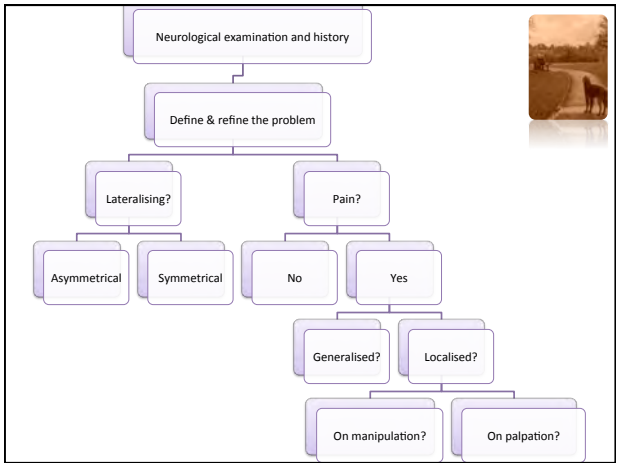

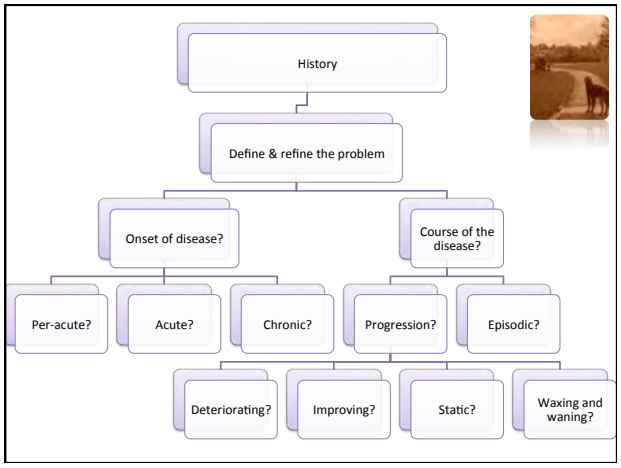

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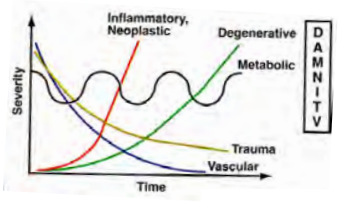
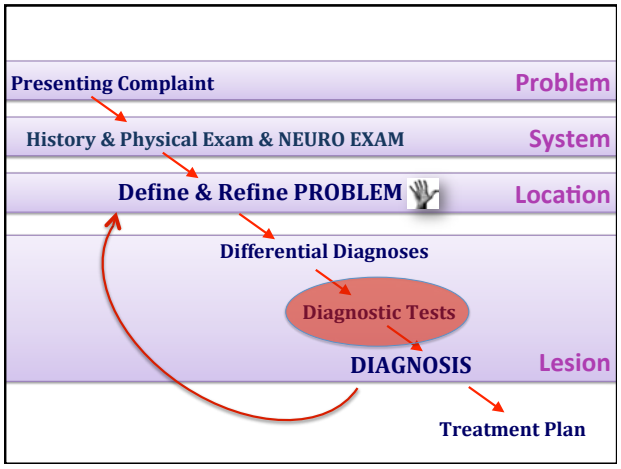


Category	Acute nonprogressive	Acute progressive	Chronic progressive
Degenerative		Type I disk disease (A, Y)	Lumbosacral stenosis (A,Y) Type II disk disease (A) Degenerative myelopathy (A) Spondylosis deformans (A) Demyelinating diseases (Y) Axonopathies and neuronopathies (Y) Extradural synovial cysts (A) Breed specific myelopathies (such as Afghan hound myelopathy (Y) Storage disease (Y)
Anomalous			Chiari-like malformation& Syringomyelia (Y, A) Vertebral anomalies (Y) Atlantoaxial luxation (Y) Spinal dysraphisms (Y)
Neoplastic		Primary (A) Metastatic (A) Skeletal (A)	Nephroblastoma (Y) Primary (A) Metastatic (A) Skeletal (A)
Nutritional			Hypervitaminosis A (Y,A)
Inflammatory / infectious		Distemper (Y,A) FIP (Y) Protozoal (Y) GME (A) Bacterial myelitis (Y,A) Discospondylitis (Y,A)	Distemper (Y,A) FIP (Y) Protozoal (Y) GME (A)
Traumatic	Fractures (Y,A) Luxations (Y,A) Contusions (Y,A) Traumatic disk (Y,A)	Traumatic disk (Y,A)	
Vascular	Infarction (FCE; Y,A) Septic emboli (Y,A) Hemmorrhage (Y,A) Vascular malformations (Y)		



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Diagnostic plan

- CSF findings:
  - White blood cell number: 5 /mm^3 (<8/mm^3)
  - Protein content: 0.41 g/l (<0.3 g/l)
  - Cytology: unremarkable

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Degenerative myelopathy

Genome-wide association analysis reveals a *SOD1* mutation in canine degenerative myelopathy that resembles amyotrophic lateral sclerosis

Tomoyuki Awano[a], Gary S. Johnson[a,1], Claire M. Wade[b,c], Martin L. Katz[c,d], Gayle C. Johnson[a], Jeremy F. Taylor[e], Michele Perloski[b], Tara Biagi[b], Izabella Baranowska[f], Sam Long[g], Philip A. March[h], Natasha J. Olby[i], G. Diane Shelton[i], Shahnawaz Khan[a], Dennis P. O'Brien[k], Kerstin Lindblad-Toh[b,l], and Joan R. Coates[k]

Departments of [a]Veterinary Pathobiology and [e]Veterinary Medicine and Surgery, [g]Mason Eye Institute, and [h]Division of Animal Sciences, University of Missouri, Columbia MO 65211; [b]Broad Institute of Harvard and Massachusetts Institute of Technology, 7 Cambridge Center, Cambridge MA 02141; [c]Center for Human Genetic Research, Massachusetts General Hospital, 185 Cambridge Street, Boston MA 02114; [d]Department of Animal Breeding and Genetics, Swedish University of Agricultural Sciences, Biomedical Center, Box 597, SE-751 24 Uppsala, Sweden; [f]Section of Neurology and Neurosurgery, University of Pennsylvania, Philadelphia, PA 19104; [i]Department of Clinical Sciences, Tufts University, North Grafton, MA 01536; [j]Department of Clinical Sciences, North Carolina State University, Raleigh, NC 27606; [k]Department of Pathology, University of California at San Diego, La Jolla, CA 92093; and [l]Department of Medical Biochemistry and Microbiology, Uppsala University, Box 597, 751 24 Uppsala, Sweden

Communicated by James E. Womack, Texas A&M University, College Station, TX, December 10, 2008 (received for review June 17, 2008)

Cervical Spondylomyelopathy

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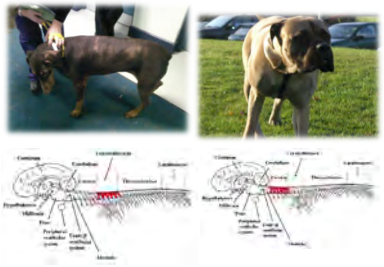
Cervical Spondylomyelopathy



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Cervical Spondylomyelopathy

- Syndrome
- Degenerative changes in upper cervical spine
- Large breed dogs (Great Dane, Mastiff, Basset...)
- <2 years
- Chronic progressive tetraparesis and ataxia
- Neck pain

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Cervical Spondylomyelopathy

Caudal cervical stenotic myelopathy

- Dobermann or Dalmatian
- >2 years (~5-6 years old)
- Chronic progressive
- Caudal neck pain
- Dobermann
  - Dilative cardiomyopathy
  - Hypothyroidism
  - Bleeding disorder (vWF)

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Cervical Spondylomyelopathy

- C6-T2 spinal cord segments
- Worse in the pelvic limbs
- Stiff stilted in the thoracic limbs
- Supraspinatus muscle atrophy
- Elbow abduction with internal rotation of the digits

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Cervical Vertebral Stenosis Associated with a Vertebral Arch Anomaly in the Basset Hound

S. De Decker, L. De Risio, M. Lowrie, D. Mauler, E. Beltran, A. Giedja, P.J. Kenny, I. Gielen, L. Garosi, and H. Volk

Objectives: To report the clinical presentation, imaging characteristics, treatment results, and histopathological findings of a previously undescribed vertebral malformation in the Basset Hound.

Animals and Methods: Retrospective case series study. Eighteen Basset Hounds presented for evaluation of a suspected cervical spinal cord problem. All dogs underwent computed tomography myelography or magnetic resonance imaging of the cervical region.

Results: Thirteen male and 5 female Basset Hounds between 6 months and 10.8 years of age (median: 1.4 years) were studied. Clinical signs varied from cervical hyperesthesia to nonambulatory tetraparesis. Imaging demonstrated a well-defined and smooth hypertrophy of the dorsal lamina and spinous process of ≥2 adjacent vertebrae. Although this bony abnormality could decrease the ventrodorsal vertebral canal diameter, dorsal midline spinal cord compression was predominantly caused by ligamentum flavum hypertrophy. The articulation between C4 and C5 was most commonly affected. Three dogs were lost to follow-up, 10 dogs underwent dorsal laminectomy, and medical management was initiated in 5 dogs. Surgery resulted in a good outcome with short hospitalization times (median: 4.5 days) in all dogs, whereas medical management produced more variable results. Histopathology confirmed ligamentum flavum hypertrophy and demonstrated the fibrocartilaginous nature of this anomaly.

Conclusions and Clinical Importance: Dorsal lamina and spinous process hypertrophy leading to ligamentum flavum hypertrophy should be included in the differential diagnosis of Basset Hounds with cervical hyperesthesia or myelopathy. Prognosis after decompressive surgery is favorable. Although a genetic component is suspected, additional studies are needed to determine the specific etiology of this disorder.

Key words: Bone morphogenetic proteins; Congenital vertebral malformation; Dorsal cervical laminectomy; Spinous

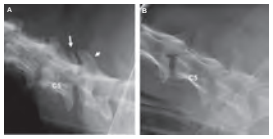

Fig 1. Survey cervical radiographs of a 4-year-old Basset Hound with ambulatory tetraparesis and cervical hyperesthesia (A) and a 4-year-old Basset Hound without a cervical spinal disorder (B). Cranial is left. (A) The caudal part of the dorsal lamina of C5 is well-defined, smooth, and enlarged dorsally (arrow). Also, the spinous process of C6 is enlarged and extends cranially (arrowhead).

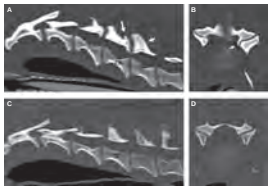

Fig 2. Sagittal reconstructed (A) and C5–C6 transverse (B) cervical CT images of the same clinically affected Basset Hound as Figure 1A. Cranial is left. (A) The caudal part of the dorsal lamina of C5 forms a well-defined and smooth enlarged convex protuberance, which extends dorsally and ventrally (arrow). Also, the spinous process of C6 is enlarged and extends craniaventrally (arrowhead). Sagittal reconstructed (C) and C5–C6 transverse (D) CT images of the same unaffected Basset Hound as Figure 1B.

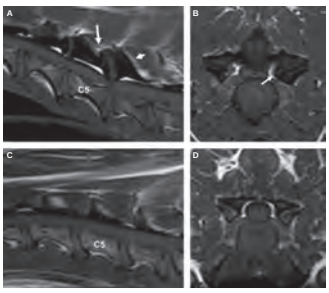

Fig 3. T1-weighted sagittal (A) and C5–C6 transverse (B) MR images of the same clinically affected Basset Hound as Figures 1–3. Cranial is left. (A) The caudal part of the dorsal lamina of C5 forms a well-defined and smooth enlarged convex protuberance, which extends dorsally and ventrally (arrow). Also, the spinous process of C6 is enlarged and extends cranioventrally (arrowhead). Obvious dorsal spinal cord compression is present at this level. Similar abnormalities, but to a lesser extent, are present between C4 and C5. (B) Dorsal midline compression can be appreciated. Sagittal (C) and C5–C6 transverse (D) T1-weigthed MR images of a 7-year-old Basset Hound without cervical spinal disease.

Pathogenesis

Multifactoriel / unclear
1. Nutritional (Calcium supplementation)?
2. Spinal conformation (Longer neck, heavier head)?
3. Genetic?

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Pathogenesis

Multifactoriel / unclear
1. Nutritional?
2. Spinal conformation (Longer neck, heavier head)?
3. Genetic?

Cervical stenosis ⟺ Cervical instability

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Pathogenesis

Multifactoriel / unclear
1. Nutritional?
2. Spinal conformation (Longer neck, heavier head)?
3. Genetic?

Cervical stenosis ⟺ ~~Cervical instability~~

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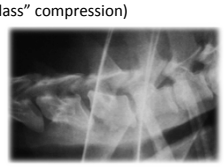
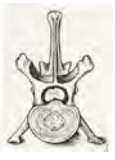
Instability vs. Dynamic

- Instability defined as ‘‘the loss of ability of the cervical spine under physiologic loads to maintain relationships between vertebrae in such a way that there is neither initial nor subsequent damage to the spinal cord or nerve roots, and in addition, there is neither development of incapacitating deformity nor severe pain.’’ (Panjabi et a., 2005)
- Dynamic lesion is one that worsens or improves with different positions of the cervical spine.

Cervical stenosis

CSM involves bone, fibrocartilaginous and ligamentous structures:
1. Congenital vertebral malformation (stenosis of vertebral canal & abnormal articulation of the articular facets)
2. Chronic degenerative disc disease (Type II disc disease)
3. Vertebral instability or "tipping"
4. Hypertrophy of ligamentum flavum & dorsal longitudinal ligament (“hourglass” compression)





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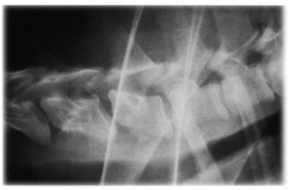
Primary vertebral abnormalities

1. ~25% of Dobermans affected (visible by 16 weeks)
2. Lack of sufficient growth of the cranial vertebral pedicle
3. Decreased compliance of the vertebral canal
4. Articular facets orientation (concave)



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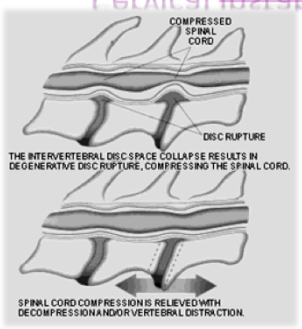
Cervical ~~instability~~



Secondary changes lead to stability

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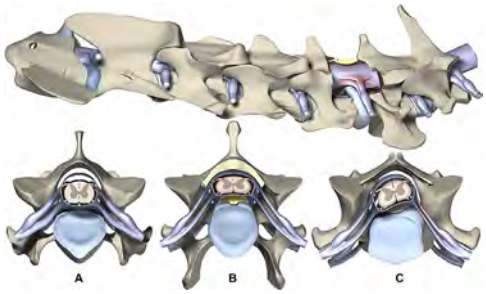


Fig. 1. Disc-associated CSM. (*Top*) Ventral spinal cord compression and nerve root compression at C5-6 caused by intervertebral disc protrusion. Dorsally, hypertrophy of the ligamentum flavum causes mild spinal cord compression. (*Bottom*) (*A*) Transverse section at the level of the C4-5 disc region showing normal spinal cord and vertebral canal. (*B*) Ventral compression at C5-6 region caused by intervertebral disc protrusion and hypertrophy of the dorsal longitudinal ligament (*yellow*) and ligamentum flavum (causing mild dorsal compression). (*C*) Asymmetric intervertebral disc protrusion at C6-7 causing

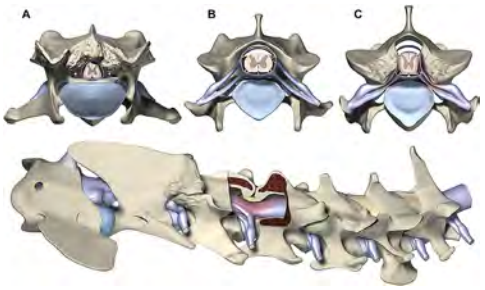
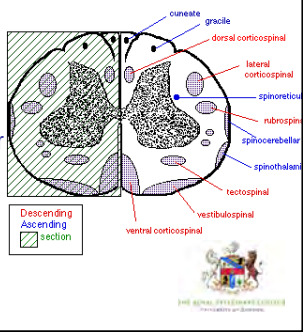


Fig. 2. Osseous-associated CSM. (*Top*) (*A*) Severe dorsolateral spinal cord compression at C2-3 caused by osseous malformation and osteoarthritic changes. (*B*) Normal C3-4 disc region. (*C*) Bilateral compression at C4-5 caused by osteoarthritic changes and medial proliferation of the facets causing absolute vertebral canal stenosis and foraminal stenosis, leading to spinal cord and nerve root compressions, respectively. (*Bottom*) Dorsal spinal cord compression at C3-4 caused by lamina malformation and hypertrophy of the ligamentum flavum. Osteoarthritic changes are also shown at C2-3. (*Courtesy of* The Ohio State University; with permission.)

Cervical Spondylomyelopathy (Wobbler Syndrome)

Proprioceptive pathways

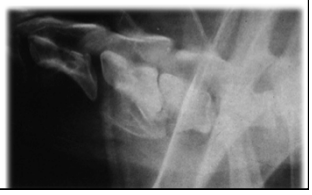
- Receptors in joint, tendon, muscles
- Sensory tracts (blue)
  - CP in dorsal column tr.
  - unCP in spinocerebellar tr.
  - Nociception in spinoreticular & spinothalamic tr.
- Motor response (red)



Diagnostics

Imaging

1. **Radiographs**
2. **Myelogram**
3. **CT**
4. **MRI**



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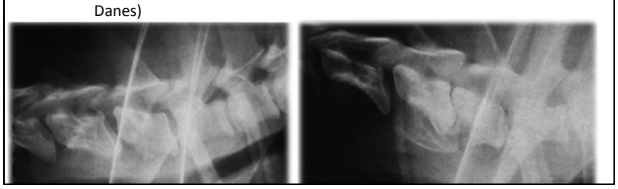
Diagnostics

1. **Tipping** of the craniodorsal aspect of the vertebral body into the spinal canal which may be exaggerated by neck flexion (mainly in Doberman)
2. **Stenosis** of the vertebral canal, especially at the cranial aspect of the vertebrae (large breed dogs)
3. **Malformations** of the vertebral bodies (mainly in Doberman)
4. Narrowed **disk** spaces, often spondylosis deformans
5. **Degenerative** changes in the **articular facets** (mainly in Great Danes)



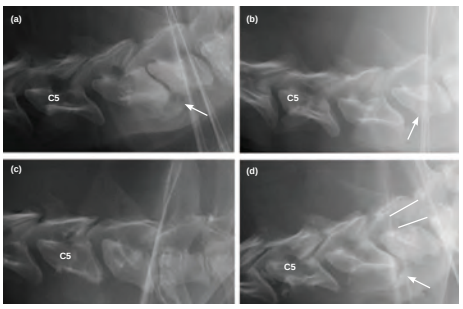


FIG 1: Radiographic abnormalities in four different dogs with disc-associated cervical spondylomyelopathy (a) Collapsed intervertebral disk space at C6-C7 (arrow) with sclerosis of the vertebral endplates and increased opacity of the vertebral bodies. Spondylosis deformans ventral to intervertebral disk space at C6-C7. (b) Abnormal shape of the vertebral body at C7, consisting of flattening of the craniodorsal border (arrow). (c) Abnormally positioned vertebral body at C6 with craniodorsal tilting into the vertebral canal. Collapsed intervertebral disk space at C6-C7. (d) Funnel-shaped vertebral canal at the level of C7 (indicated by lines) leading to a narrowed cranial orifice. Spondylosis deformans ventral to intervertebral disk space at C6-C7 (arrow). Narrowed intervertebral disk space at C6-C7

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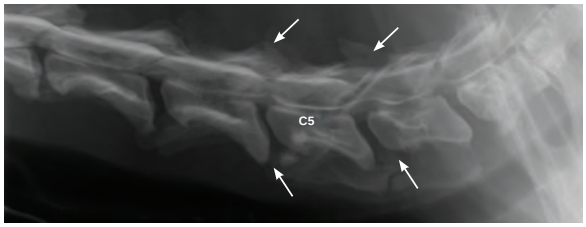
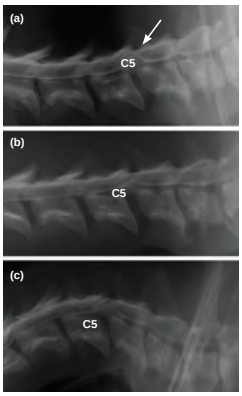


FIG 2: Lateral neutral myelogram in a 10-year-old Dalmatian with ambulatory tetraparesis and cervical hyperaesthesia. Ventral extradural compressive lesions associated with intervertebral disk protrusions are at C4-C5, C5-C6 and C6-C7. Dorsal extradural compressive lesions associated with ligamentum flavum hypertrophy are at C4-C5 and C5-C6 (arrows). Spondylosis deformans from caudal C4 to mid C6 is seen (arrows)

FIG 3:(a) Lateral neutral myelogram, (b) lateral myelogram after linear traction, and (c) lateral myelogram after cervical flexion in a four-year-old dobermann with ambulatory paraparesis. (a) Severe ventral extradural spinal cord compression at C5-C6 (arrow) and minor compression at C6-C7. Collapsed intervertebral disk space with moderate degree of spondylosis deformans at C6-C7. Compressions have largely resolved after linear traction (b) and cervical flexion (c)



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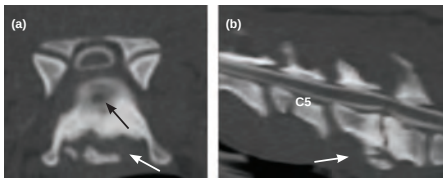
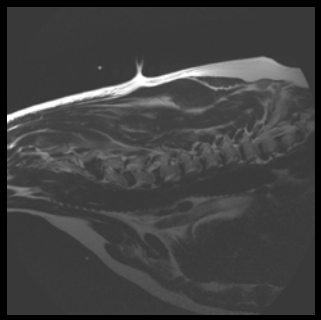
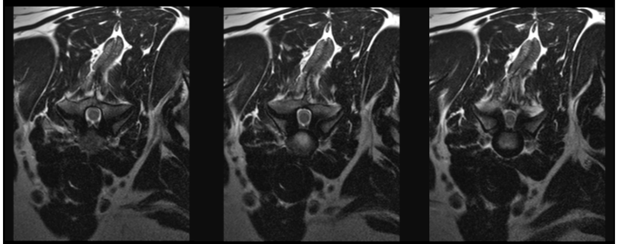


FIG 4: (a) Transverse CT myelogram image (b) at the level of C6-C7 and sagittal reconstruction of an eight-year-old dobermann with ambulatory tetraparesis (same dog as Fig 1a). (a) Attenuation ventral subarachnoid space with dorsal displacement and deformation spinal cord is seen. The vertebral endplate demonstrates a mixed hyperattenuate signal. Hypoattenuating lesion indicating vacuum phenomenon, suggesting intervertebral disk degeneration (black arrow) is also seen along with spondylosis deformans ventral to intervertebral disk space (white arrow). (b) Collapsed intervertebral disk space and extradural spinal cord compression at C6-C7 with increased attenuation in vertebral endplates and vertebral bodies

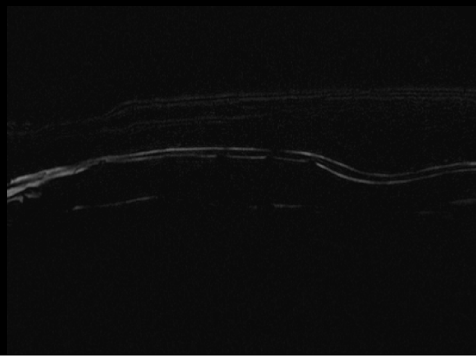
Great Dane, 1yr, MN



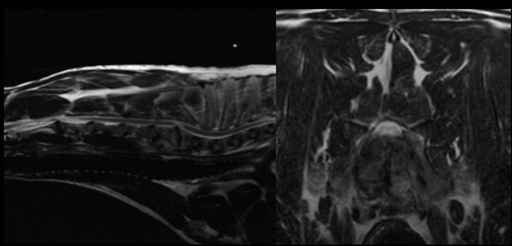
Great Dane, 1yr, MN



Doberman, 7yrs, FN



Doberman, 7yrs, FN



Prognosis & Treatment

Prognosis for complete recovery is poor (Da Costa 2008)

- **Surgery**:
  81% of dogs treated surgically improved, 3% were unchanged and 16% were worse

- **Conservative**:
  54% dogs treated medically improved, 27% were unchanged and 19% were worse

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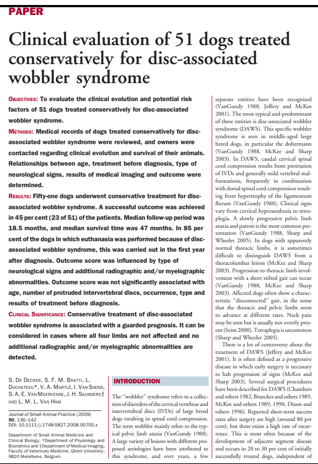

PAPER

Clinical evaluation of 51 dogs treated conservatively for disc-associated wobbler syndrome

OBJECTIVES: To evaluate the clinical evolution and potential risk factors of 51 dogs treated conservatively for disc-associated wobbler syndrome.

METHODS: Medical records of dogs treated conservatively for disc-associated wobbler syndrome were reviewed, and owners were contacted regarding clinical evolution and survival of their animals. Relationships between age, treatment before diagnosis, type of neurological signs, results of medical imaging and outcome were determined.

RESULTS: Fifty-one dogs underwent conservative treatment for disc-associated wobbler syndrome. A successful outcome was achieved in 45 per cent (23 of 51) of the patients. Median follow-up period was 18.5 months, and median survival time was 47 months. In 85 per cent of the dogs in which euthanasia was performed because of disc-associated wobbler syndrome, this was carried out in the first year after diagnosis. Outcome score was influenced by type of neurological signs and additional radiographic and/or myelographic abnormalities. Outcome score was not significantly associated with age, number of protruded intervertebral discs, occurrence, type and results of treatment before diagnosis.

CLINICAL SIGNIFICANCE: Conservative treatment of disc-associated wobbler syndrome is associated with a guarded prognosis. It can be considered in cases where all four limbs are not affected and no additional radiographic and/or myelographic abnormalities are detected.

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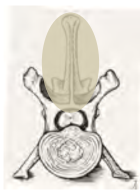
INTRODUCTION

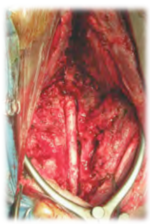
The "wobbler" syndrome refers to a collection of disorders of the cervical vertebrae and intervertebral discs (IVDs) of large breed dogs resulting in spinal cord compression. The term wobbler mainly refers to the typical pelvic limb ataxia (VanGundy 1988). A large variety of lesions with different proposed aetiologies have been attributed to this syndrome, and over years, a few separate entities have been recognised (VanGundy 1988, Jeffery and McKee 2001). The most typical and predominant of these entities is disc-associated wobbler syndrome (DAWS). This specific wobbler syndrome is seen in middle-aged large breed dogs, in particular the dobermann (VanGundy 1988, McKee and Sharp 2003). In DAWS, caudal cervical spinal cord compression results from protrusion of IVDs and generally mild vertebral malformations, frequently in combination with dorsal spinal cord compression resulting from hypertrophy of the ligamentum flavum (VanGundy 1988). Clinical signs vary from cervical hyperaesthesia to tetraplegia. A slowly progressive pelvic limb ataxia and paresis is the most common presentation (VanGundy 1988, Sharp and Wheeler 2005). In dogs with apparently normal thoracic limbs, it is sometimes difficult to distinguish DAWS from a thoracolumbar lesion (McKee and Sharp 2003). Progression to thoracic limb involvement with a short stilted gait can occur (VanGundy 1988, McKee and Sharp 2003). Affected dogs often show a characteristic "disconnected" gait, in the sense that the thoracic and pelvic limbs seem to advance at different rates. Neck pain may be seen but is usually not overtly present (Seim 2000). Tetraplegia is uncommon (Sharp and Wheeler 2005).

There is a lot of controversy about the treatment of DAWS (Jeffery and McKee 2001). It is often defined as a progressive disease in which early surgery is necessary to halt progression of signs (McKee and Sharp 2003). Several surgical procedures have been described for DAWS (Chambers and others 1982, Bruecker and others 1989, McKee and others 1989, 1990, Dixon and others 1996). Reported short-term success rates after surgery are high (around 80 per cent), but there exists a high rate of recurrence. This is most often because of the development of adjacent segment disease and occurs in 20 to 30 per cent of initially successfully treated dogs, independent of

Caudal spondylomyelopathy

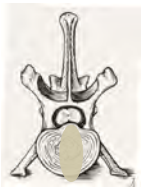
- Treatment
  - Conservative
    - Restricted excercise
    - Anti-inflammatories
  - Surgery
    - Dorsal laminectomy





Caudal spondylomyelopathy

- Treatment
  - Conservative
    - Restricted excercise
    - Anti-inflammatories
  - Surgery
    - Ventral Slot
    - **Dynamic vs non-dynamic**



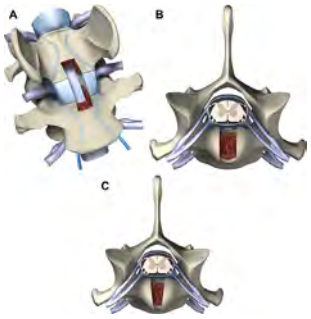


Fig. 10. Ventral slot at C6-7. (*A*) Ventral view. (*B*) Transverse view. The slot width and length should ideally be kept at about one-third of the vertebral bodies. The internal vertebral venous plexus are represented by the blue vessels running in the ventral aspect of the vertebral canal. (*C*) Inverted cone slot; this is a modification of the traditional ventral slot that minimizes the risk of hemorrhage and subluxation. (*Courtesy of* The Ohio State University; with permission.)

Fig. 13. The technique of pins and PMMA combined with a partial slot. Note the location of pin insertion avoiding the transverse foramina and vertebral canal. (*Courtesy of* The Ohio State University; with permission.)

Post surgical decompression

- Physiotherapy!

Priv.-Doz. Dr. Thomas Flegel

Veterinary Training

Humboldt-University Berlin, Germany	1986-1992

Working Experience

Working experience in large and small animal medicine at Free University of Berlin as well as in private practice in Berlin	1992-1998
Department of Companion Animals and Special Species College of Veterinary Medicine, North Carolina State University, USA Clinical Instructor in Veterinary Neurology	1998-1999
Department of Veterinary Clinical Sciences, The Ohio State University, USA Residency in Veterinary Neurology and Neurosurgery	1999-2001
Department of Small Animal Medicine, University of Leipzig, Germany Head of the section of neurology and neurosurgery	**since November 2002**

Veterinary and Academic Qualifications

Doctor medicinae veterinariae (summa cum laude)	1994
Master of Veterinary Sciences (The Ohio State University, USA)	2001
Diplomate American College of Veterinary Internal Medicine (Neurology)	2003
Diplomate European College of Veterinary Neurology	2005
European Specialist in Veterinary Neurology	2008
Dr. med. vet. habilitatus (small animal surgery and small animal neurology)	2010
Secretary of the European College of Veterinary Neurology	since 2012

Disorder of eyes and vision

Priv.-Doz. Dr. Thomas Flegel

UNIVERSITY of LEIPZIG, GERMANY

Department of Small Animal Medicine

Disorders of Eyes and Vision

Thomas Flegel

DACVIM (Neurologie), DECVN

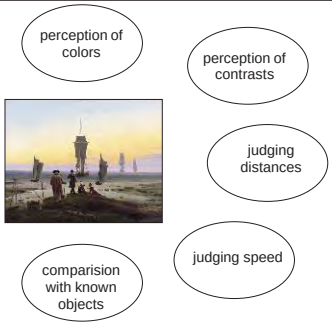
- physiology of vision
- testing the visual system
- neurological diseases resulting in:

  impaired vision

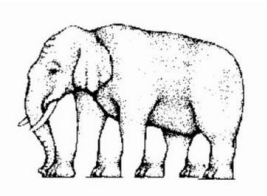
  abnormal eye position/movement

  anisocoria

What do we really see?



Comparison with other objects

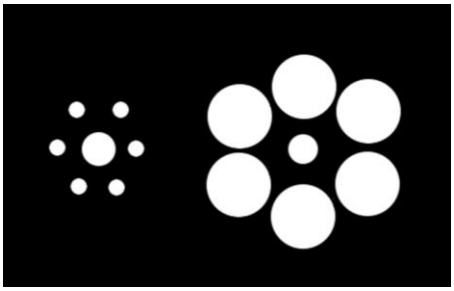


Internal comparison:

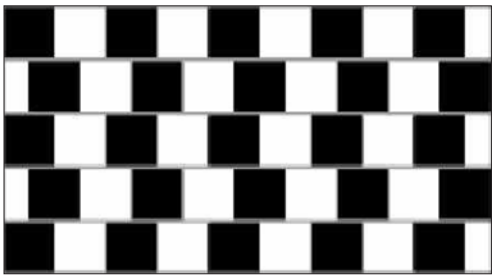
A: elephant

B: quadruped

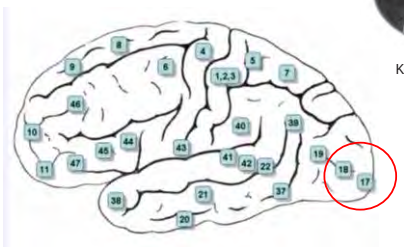
Comparison with other objects: external comparison



Comparison with other objects: external comparison



Brodman Regions



Korbinian Brodman
1868-1918

Primary and secondary visual cortex

Visual cortex

primary	secondary
Processing of direct visual input	Processing of the meaning of things we see
„cortical blindness“	„soul blindness“

Perception of distance

Left eye	Right eye
sees a little bit more of the left side of an object	sees a little bit more of the right side of an object

The discrepancy between those 2 images is the larger the closer the object is

↓

Some fibers carry the same information

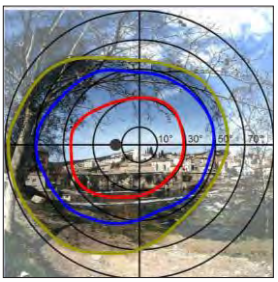
If those are the „2-meter-fibers“: the object is 2 meters away

↓

estimating distances reliably up to 60 meters

Stereopsis *(depth perception)*

Color vision



black/white
in addition: blue
in addition: red

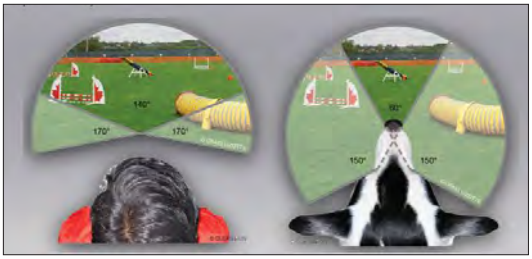
Color vision

Human | Dog (probably)

Dogs:

- differentiate red and blue
- often mix up green and red

Visual field



www.veterinaryvision.com

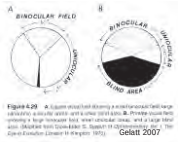
Visual field

	Crossing of optical fibers	Visual field
cat:	65%	200°-285°
dog:	75%	240°
horse:	80-90%	305°
cattle:	80-90%	
birds:	100%	300°
owl:	60-70%	160°
frog:		330°
human:	50%	180 - 200°

Flight animals:

Wide visual field

difficulties to judge distance



Gelatt 2007

hunters:

Smaller visual field

Jadvantage in judging distance

Testing vision

Neurological examination:

- obstacle course
- cottonball test
- menace reaction
- pupillary light reflex
- testing physiological nystagmus

Additional tests:

- ophthalmological examination
- Electroretinogram (ERG)
- visual evoked potentials (VEP)
- MRI
- CSF analysis

Obstacle course

Obstacle Course

Cotton ball test

Wattebauschtest

cotton ball test

Cotton ball test

Cotton Ball Test

negative

Cotton Ball Test

unilateral negative

Visual testing: menace response

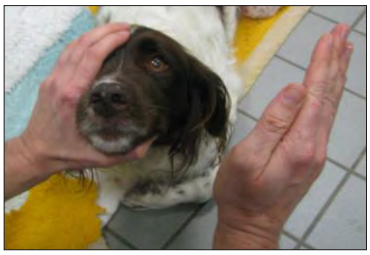
Drohreaktion

Not correct:

Second eye is not covered

Touching the hair

Visual testing: menace response



one hand fixes head and covers one eye

second hand tests vision from different angles

What is a normal response?

Menace response: correct

menace response

Drohreaktion

Age dependent?

You have to learn it:

- foal, calf: from 1-2 weeks on
- puppy: from 10-12 weeks on

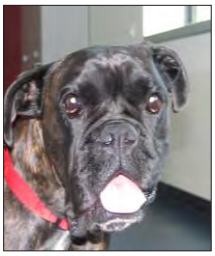
rabbit: no menace response

Which nerves are tested?

menace response

eye, optic nerve	facial nerve
cotton ball test	palpebral reflex
obstacle course	lip retraction
	facial deviation
	asymmetric nares
	reduced tear production

Facial paresis



Boxer, 6 years, male

- drooping of and inability to move ear and lips
- widened palpebral fissure
- absent blink
- absent abduction of nostril during inspiration
- deviation of the nose to the opposite side
- chronic: nose deviated to abnormal side, facial muscle contracted due to fibrosis

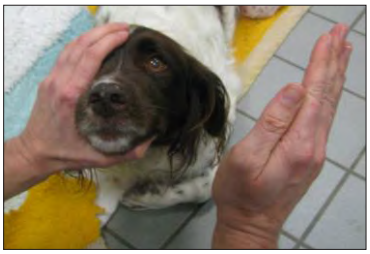
Visual field

1 visual field
2 optic nerve
3 optic chiasm
4 optic tract
5 lat. geniculate body
6 optic radiation
7 primary visual cortex
8 Brodman area 18 (secondary visual cortex)
9 Brodman area 19 (associative visual cortex)

Visual field

Right eye menace from R	Right eye menace from L	Left eye R	Left eye L	
no	no	yes	yes	right: eye, optic nerve
no	yes	no	yes	right: optic tract, visual cortex
no	yes	yes	no	central optic chiasm

Visual testing: menace response



but what is going on if:

- no menace response
- but normal vision

Normal vision- but no menace

Maine Coon "Lona"
female, 6 months

case number: 46885

Normal vision- but no menace

- ataxia
- intention tremor
- hypermetria
- titubation
- nystagmus

- normal conscious proprioception

American Staffordshire Terrier
"Cessy"

intact female, 7 years

case number: 38894

What has the cerebellum to do with it?

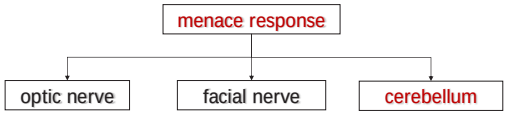
Maine Coon "Lona"
female, 6 months

case number: 46885

Two theories:

- either response is directly transmitted by cerebellum
- or response is indirectly influenced by cerebellum

Differentials for reduced menace response



optic nerve	facial nerve	cerebellum
cotton ball test	palpebral eflex	Other cerebellar deficits?
obstacle course	lip retraction	generalized ataxia
pupillary light reflex	facial deviation	hypermetria
	asymmetric nares	intention tremor
	reduced tear production	titubation

Testing vision

Neurological examination:

- obstacle course
- cottonball test
- menace reaction
- pupillary light reflex
- testing physiological nystagmus

Additional tests:

- ophthalmological examination
- Electroretinogram (ERG)
- visual evoked potentials (VEP)
- MRI
- CSF analysis

Visual testing: pupillary light reflex

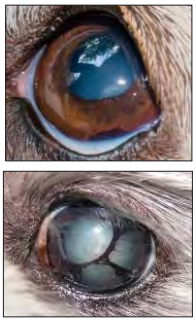
pupillary light reflex

not ideal

pupillary light reflex

correct

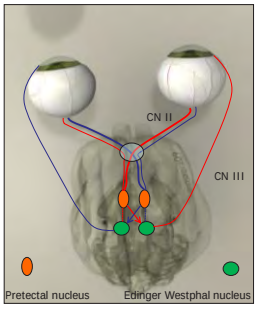
Visual testing: iris atrophy



Iris atrophy may affect pupillary light reflex:

- irregular pupillary margin (scalloped, moth-eaten apperance
- thinning of the stroma
- translucend areas
- openings within iris

Pupillary light reflex (PLR): lesion localisation



blind + no PLR:

- Eye
- Optic nerve
- Optic chiasm
- Brain stem

blind + normal PLR:

- Optic radiation
- Visula cortex (occipital lobes)

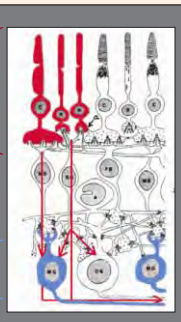
Testing iris function: IRIS-VET

Courtesy of Sabine Sahr

Testing iris function

Rhodopsin

Melanopsin



- photoreceptor mediated
- responding to red light
- fast reaction, very light sensitive

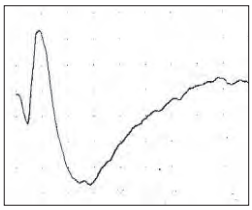
- menalopsin mediated
- responding to blue light
- slow reaction, high light intensity necessary

Melan-100

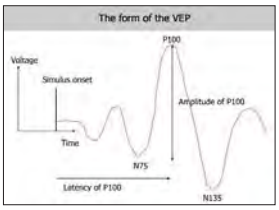
Conditions which frequently cause loss of vision and pupil light reflex abnormalities

Condition	Menace/ Vision	Dazzle	Pupil light reflex using (Melan- 100) RED	Pupil light reflex using (Melan- 100) BLUE	ERG
SARDS	- -	+			-
Immune-mediated retinitis	-/+ -/+ OR	+			+ OR -/+
Retinal degeneration (hereditary)	-/+ -/+ OR	+			+ OR -/+
Chorio-retinitis/ retinitis	-/+ -/+ OR	+ OR - -			-/+
Retinal detachment	-/+ -/+ OR	-/+	OR	OR	-/+ OR -
Glaucoma	-/+ -/+ OR	-/+			-/+
Optic neuritis/ meningitis, pituitary tumor, chiasmal tumor	- - OR -/+ -/+	-			+
Brain tumor/ visual cortex damage	- -	+			+
Ophthalmoplegia interna/ externa	+ +	+			+

Electrodiagnostics



Electroretinogram (ERG)



Visual evoked potentials (VEP)

http://totaleyecare.files.wordpress.com/2012/10/vepimage1.jpg

- physiology of vision
- testing the visual system
- neurological diseases resulting in:

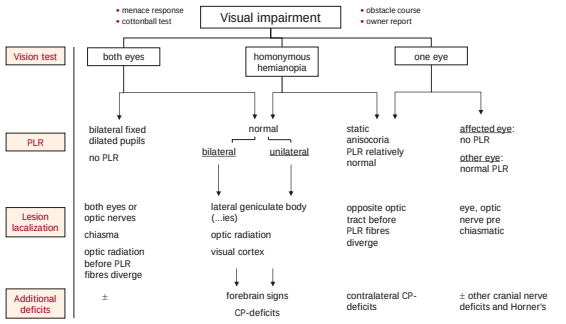
  impaired vision

  abnormal eye position/movement

  anisocoria

Algorythm visual deficits:

adopted from Gelatt: Veterinary Ophthalmology, 2007



Algorythm visual deficits:

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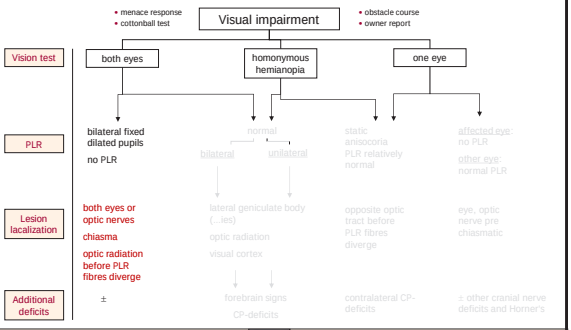
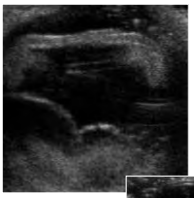
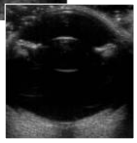
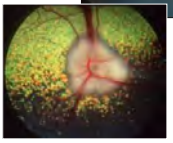


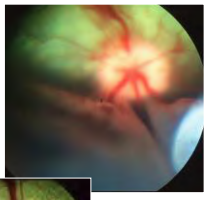
Ocular lesion: retinal detachment





ultrasound of the eye





funduscopic examination

Ocular lesion: retinal detachment

Often caused by systemic hypertension due to:

- renal failure
- hyperthyroidism (cat)

Less commonly caused by systemic hypertension due to:

- hyperadronocorticism
- phaechromocytoma
- hypercorticism
- hyperaldosteronism
- diabetes mellitus
- essential hypertension (primary)

Ocular lesion: SARDS

Sudden Aquired Retinal Degeneration Syndrome:

- idiopathic
- acute retinal blindness without in the absence of funduscopic disease
- clinical signs suggestive of metabolic disease (i.e. 15% Cushing)
- no menace
- dilated pupils, slugish to no PLR
- sometimes dazzle-reflex preserved

Optic „nerve“

- axons are myelinised by oligodendrocytes
- astrocytes between fibres
- surrounded by meninges with subarachnoid space

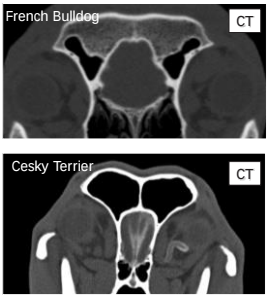
It's not really a nerve but
an extension of the brain

↓

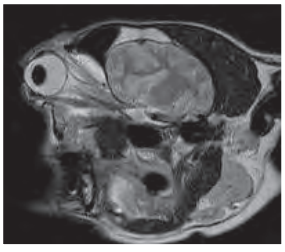
Not involved in generalized neuropathies

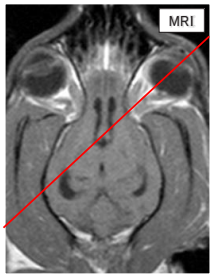
But may be involved in brain disease

Optic nerve

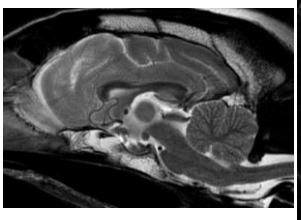


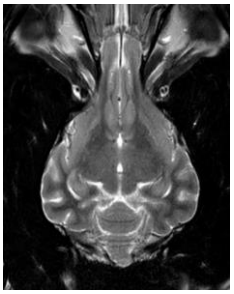
Optic nerve





Optic nerve





MRI



MRI is only as good as:

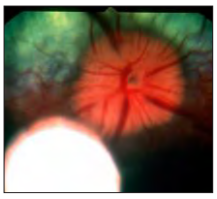
1. the knowledge of the examiner of all relevant diseases
2. the ability of the examiner to visualize those diseases

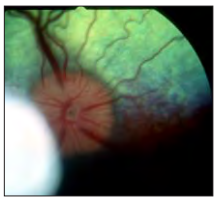
Optic nerve

Fibers of the Macula are localized centrally

Central lesion	Peripheral lesion
axial neuritis	*Druck von außen*
Reduced visual acuity	Narrowed visual field
No blindness	No impairment of visual acuity

Optic nerve lesion: neuritis

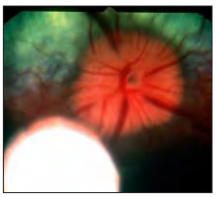

neuritis


opposite (normal) eye

- disc appears swollen and edematous
- blurry disc margins

Courtesy of Andrea Steinmetz

Optic nerve lesion: neuritis


neuritis

- disc appears swollen and edematous
- blurry disc margins

infectious:	distemper, toxoplasmosis tick-borne-encephalitis ehrlichiosis fungal FIP
inflammatory:	GME, NME?
others:	traumatic vitamin A deficiency toxic neoplastic

Lesion at the optic chiasm


Acute postretinal blindness: ophthalmologic, neurologic, and magnetic resonance imaging findings in dogs and cats (seven cases)

Seruca et al., Vet Ophthalmology, 2010

Neuroanatomic localisation:

- optic chiasm 5/7
- optic nerve: 1/7
- optic tract: 1/7

Etiology:

- neoplasia: 5/7
- optic neuritis: 1/7

Ocular lesion: lesion at the optic chiasm


Acute postretinal blindness: ophthalmologic, neurologic, and magnetic resonance imaging findings in dogs and cats (seven cases).

Author information

Abstract

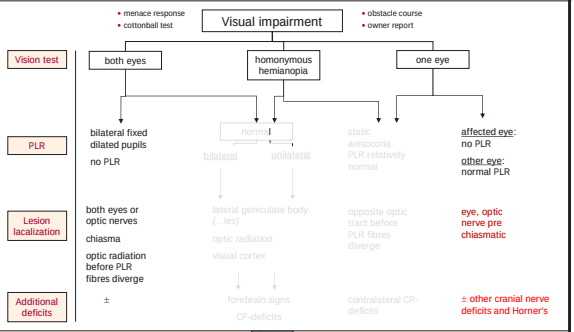
OBJECTIVE: To describe the ophthalmologic, neurologic, and magnetic resonance imaging (MRI) findings of seven animals with acute postretinal blindness as sole neurologic deficit.

METHODS: Medical records were reviewed to identify dogs and cats with postretinal blindness of acute presentation, that had a cranial MRI performed as part of the diagnostic workup. Only animals lacking other neurologic signs at presentation were included. Complete physical, ophthalmic, and neurologic examinations, routine laboratory evaluations, thoracic radiographs, abdominal ultrasound, electroretinography, and brain MRI were performed in all animals. Cerebrospinal fluid analysis and postmortem histopathologic results were recorded when available.

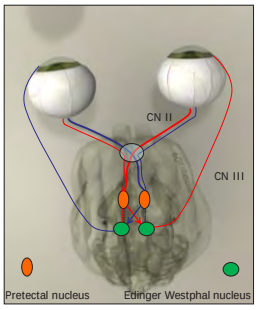
RESULTS: Four dogs and three cats met the inclusion criteria. Lesions affecting the visual pathways were observed on magnetic resonance (MR) images in six cases. Location, extension, and MRI features were described. Neuroanatomic localization included: olfactory region with involvement of the optic chiasm (n = 4), pituitary fossa with involvement of the optic chiasm and optic tracts (n = 1), and optic nerves (n = 1). Of all lesions detected, five were consistent with intracranial tumors (two meningiomas, one pituitary tumor, two nasal tumors with intracranial extension), and one with bilateral optic neuritis that was confirmed by cerebrospinal fluid analysis. Histologic diagnosis was obtained in four cases and included one meningioma, one pituitary carcinoma, one nasal osteosarcoma, and one nasal carcinoma.

CONCLUSIONS: Central nervous system (CNS) disease should be considered in dogs and cats with acute blindness, even when other neurologic deficits are absent. This study emphasizes the relevance of MRI as a diagnostic tool for detection and characterization of CNS lesions affecting the visual pathways.

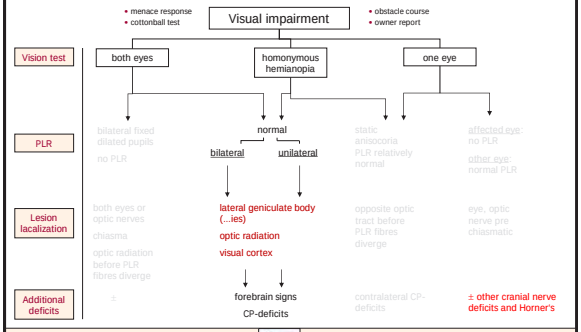
Algorythm visual deficits:
adopted from Gelatt: Veterinary Ophthalmology, 2007



Unilateral lesions with impaired PLR



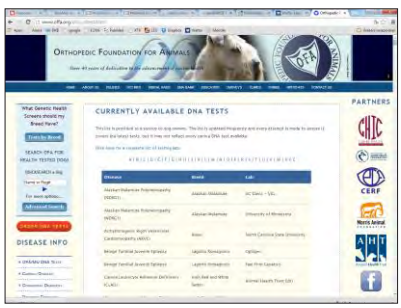
Algorythm visual deficits:
adopted from Gelatt: Veterinary Ophthalmology, 2007



Forebrain lesion

V	hemorraghe, infarct, global ischemia, mouth gag
E	infection, non-infectious encephalitis
T	
A	hydrocephalus
M	
I	
N	primary or metastatic neoplasia
D	Ceroid lipofuscinois, Mucopolysacharidosis Typ II

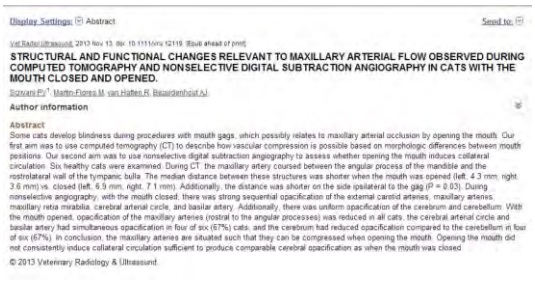
Genetic diseases



http://www.offa.org/dna_alltest.html

Forebrain lesion

Forebrain lesion



Display Settings: Abstract Send to:

Vet Radiol Ultrasound. 2013 Nov 13. doi: 10.1111/vru.12118. [Epub ahead of print]

STRUCTURAL AND FUNCTIONAL CHANGES RELEVANT TO MAXILLARY ARTERIAL FLOW OBSERVED DURING COMPUTED TOMOGRAPHY AND NONSELECTIVE DIGITAL SUBTRACTION ANGIOGRAPHY IN CATS WITH THE MOUTH CLOSED AND OPENED.

Scrivani PV[1], Martin-Flores M, van Hatten R, Bezuidenhout AJ

Author information

Abstract

Some cats develop blindness during procedures with mouth gags, which possibly relates to maxillary arterial occlusion by opening the mouth. Our first aim was to use computed tomography (CT) to describe how vascular compression is possible based on morphologic differences between mouth positions. Our second aim was to use nonselective digital subtraction angiography to assess whether opening the mouth induces collateral circulation. Six healthy cats were examined. During CT, the maxillary artery coursed between the angular process of the mandible and the rostrolateral wall of the tympanic bulla. The median distance between these structures was shorter when the mouth was opened (left, 4.3 mm; right, 3.6 mm) vs. closed (left, 6.9 mm; right, 7.1 mm). Additionally, the distance was shorter on the side ipsilateral to the gag ($P = 0.03$). During nonselective angiography, with the mouth closed, there was strong sequential opacification of the external carotid arteries, maxillary arteries, maxillary retia mirabilia, cerebral arterial circle, and basilar artery. Additionally, there was uniform opacification of the cerebrum and cerebellum. With the mouth opened, opacification of the maxillary arteries (rostral to the angular processes) was reduced in all cats, the cerebral arterial circle and basilar artery had simultaneous opacification in four of six (67%) cats, and the cerebrum had reduced opacification compared to the cerebellum in four of six (67%). In conclusion, the maxillary arteries are situated such that they can be compressed when opening the mouth. Opening the mouth did not consistently induce collateral circulation sufficient to produce comparable cerebral opacification as when the mouth was closed.

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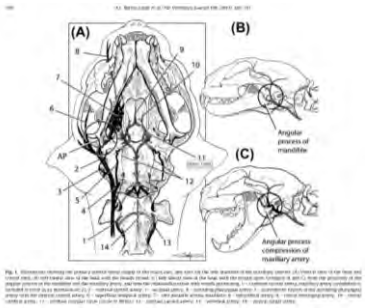
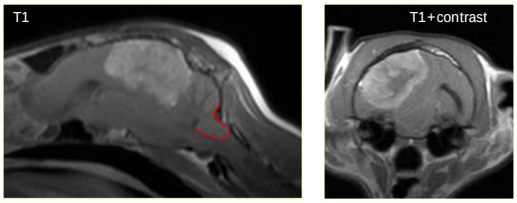
Forebrain lesion



MRI: occipital meningioma



Domestic shorthair cat „Strolchie", 12 years, neutered male

mean arterial blood pressure: 230 mm Hg

Hypertension: keep your hands off the blood presssure until...

CONCERNING A DEFINITE REGULATORY MECHANISM OF THE VASO-MOTOR CENTRE WHICH CONTROLS BLOOD PRESSURE DURING CEREBRAL COMPRESSION.

By Harvey Cushing, M. D.

Archieves Italiennes de Biologie 1901

Harvey Cushing

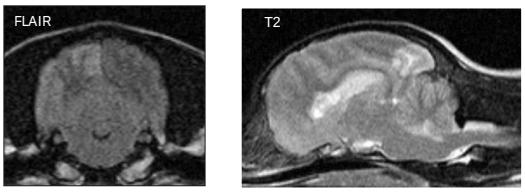
Cushing-Reflex

bradycardia

⇑ Systemic blood pressure

⇑ Intracranial pressure

Occipital infarct



CKCS „Tina", 5 Jahre

Caudal cerebral artery

Global brain ischemia

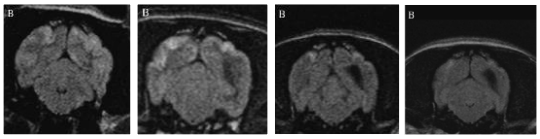
J Small Anim Pract. 2008 Aug 49(8):408-12. Epub 2008 May 12.

Sequential magnetic resonance imaging changes after suspected global brain ischaemia in a dog.

Timm K, Flegel T, Oechtering G.

Department of Small Animal Medicine, University of Leipzig, An den Tierkliniken 23, 04103 Leipzig, Germany.

Pug, 2 years, female: surgery for brachycephalic syndrome



3 hours | 6 weeks | 7 months | 18 months

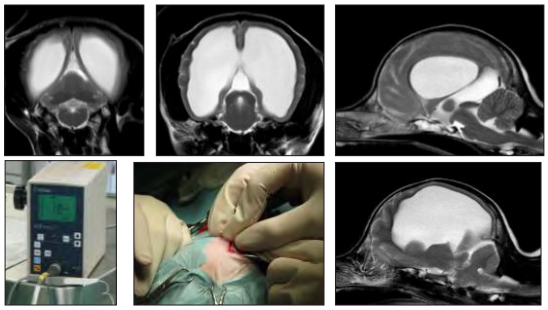
Hydrocephalus

Bolognese
"Minchen"

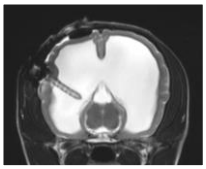
intact female, 3 years

case number: 83862

Hydrocephalus: „Minchen“



Hydrocephalus: „Minchen“



Necrotising meningoencephalitis: Pug

Pug Dog "Moppi"

intact male
1,5 years

case number: 74170

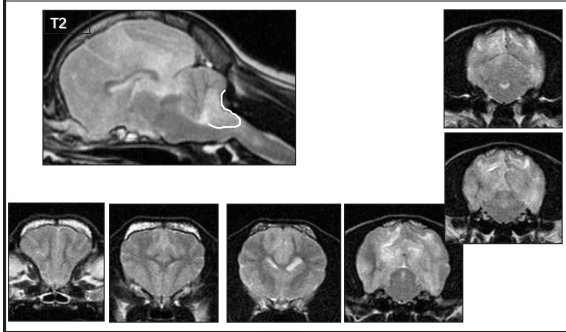
Pug dog "Philine"

female, 1 year

case number: 48404

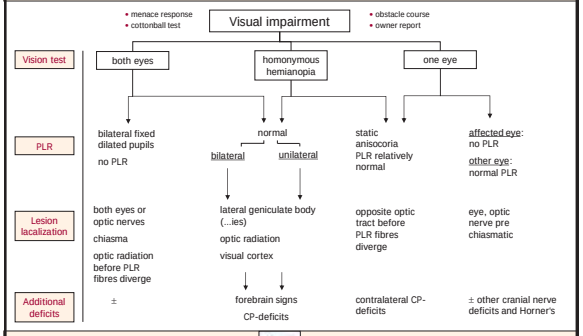
- seizures (often partial)
- reduced conscious proprioception
- central blindness

Necrotising meningoencephalitis: Pug



Algorythm visual deficits:

adopted from Gelatt: Veterinary Ophthalmology, 2007

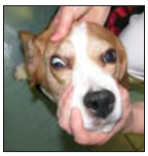


- physiology of vision
- testing the visual system
- neurological diseases resulting in:

  impaired vision
  abnormal eye position/movement
  anisocoria

Neurological causes of strabism

- congenital strabism (brachycephalic dogs, siamese cats, albinos)
- peripheral vestibular syndrome (ventrolateral strabismus)
- hydrocephalus (bilateral ventrolateral strabism: „setting sun sign“)
- forebrain lesion (ipsilateral ventrolateral strabismus)



Platt, Olby

Duane Syndrome

Labrador Retriever
"Happy"
female, 10 years
"Duane retraction syndrome"
case number: 81634

Duane retraction syndrome

Alexander Duane (1858 – 1926)

The characteristic features of the syndrome are:

- limitation of abduction (outward movement) of the affected eye
- less marked limitation of adduction (inward movement) of the same eye
- retraction of the eyeball into the orbita on adduction, with associated narrowing of the palpebral fissure

Duane retraction syndrome

Alexander Duane (1858 – 1026)

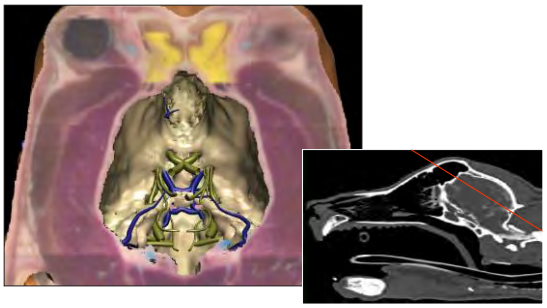
causes:

- abducens nucleus and nerve are absent or hypoplastic
- lateral rectus muscle is innervated by a branch of the oculomotor nerve

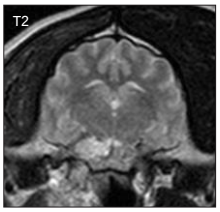
Cavernous sinus syndrome

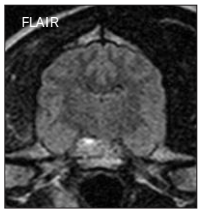
Labrador Retriever
"Lena"
female, 8 years
case number: 47681

Cavernous sinus syndrome



Cavernous sinus syndrome





Labrador „Lena“ , 11 years, female

Cavernous sinus syndrome

Deficits of the following cranial nerves:

CN III	oculomotor
CN IV	trochlear
CN VI	abducens
CN V	trigeminal (first 2 branches)

Deficits on the following test:

- physiological nystagmus (external ophthalmoparesis/plegia)
- retractor oculi reflex
- palpebral reflex
- testing nasal sensation
- drooping of the upper eyelid
- direct and indirect pupillary light reflex (internal ophthalmoparesis/plegia)

Cavernous sinus syndrome

Bilateral cavernous sinus syndrome in dogs: 6 cases (1999–2004)

John H. Rossmeisl Jr, DVM, MS, DACVIM; Michael A. Higgins, DVM; Karen D. Inzana, DVM, PhD, DACVIM; Tao P. Herring, DVM, MS, DACVO; David C. Grant, DVM, MS, DACVIM

Results—5 dogs were evaluated because of problems referable to abnormal ocular motility or pupillomotor dysfunction, and 1 dog was evaluated because of partial motor seizures involving the face and bilateral mydriasis. Four dogs had neurologic signs referable to an extrasinusoidal lesion at the time of initial examination, and the remaining 2 dogs eventually developed extrasinusoidal signs. Besides neuroanatomic location, the only consistent neuroimaging feature was variably intense, heterogeneous enhancement of cavernous sinus lesions. Neoplasia was histologically confirmed as the underlying cause in 5 of the dogs and was suspected in the remaining dog. Median survival time for the 4 dogs that were treated was 199 days (range, 16 to 392 days).

JAVMA 2005

- physiology of vision
- testing the visual system
- neurological diseases resulting in:

  impaired vision

  abnormal eye position/movement

  anisocoria

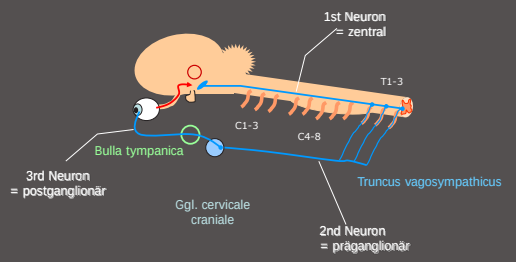
Horner's Syndrome

Sympathic Innervation:
- M. ciliaris
- M. orbitalis
- M. dilatator pupillae
- M. tarsalis superior (Müller-Muscle)

Loss of sympathic innervation to the eye:

- ptosis: „smaller eye“
- miosis: smaller pupil
- enophthalmus: sunken in eye ball
- 3rd eye lid protrusion

Sympathetic nerve: the long way back



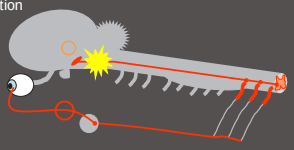
Dr. Kaspar Matiasek
The Animal Health Trust, Newmarket

Localisation: brain stem

Complex deficits pointing towards brain lesion

Other symptoms:

- multiple cranial nerve deficits
- paresis/paralysis
- reduced conscious proprioception
- vestibular deficits



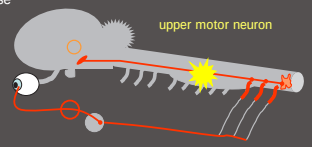
Dr. Kaspar Matiasek
The Animal Health Trust, Newmarket

Localisation: cervical spinal cord

tetra-/hemiparesis/plegia

Differentials:

- intervertebral disc disease
- FCE
- trauma

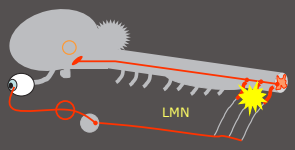


Dr. Kaspar Matiasek
The Animal Health Trust, Newmarket

Localisation: brachial plexus

Other symptoms:

- monoparesis/plegia
- unilaterally reduced panniculus reflex



Dr. Kaspar Matiasek
The Animal Health Trust, Newmarket

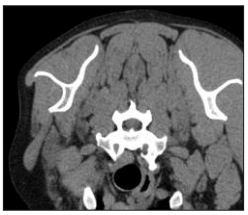
Localisation: brachial plexus

Labrador Retriever
"Hektor"

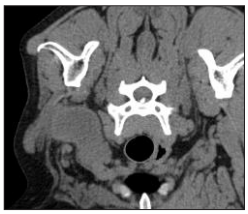
7 years, male

case numer: 35463

Localisation: brachial plexus



Rottweiler Mix „Cora“ 7 years

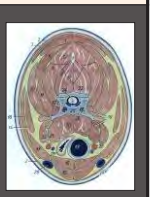


- neoplasia
- stick-injury
- biting injury

Localisation: vagosympathetic trunc

Other symptoms:
- laryngeal paralysis
- Megaösophagus

Differentials:
- pulling on the leash
- neoplasia
- injection, taking blood
- biting, infection



carotid sheath:
- arteria carotis communis
- Vagosympathicus trunc
  - vagal nerve
  - sympathic nerve

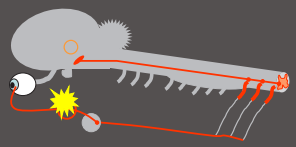
Dr. Kaspar Matiasek
The Animal Health Trust, Newmarket

Localisation: middle ear

- head tilt
- nystagmus
- ataxia
- ± CN VII defizit

peripheral vestibular syndrome

Differentials:
- otitis media/interna
- polyp
- iatrogen



(Aus dem pharmakologischen Institut der Reichsuniversität Utrecht.)

Sympathicuslähmung durch Abkühlung des Mittelohres beim Ausspritzen des Gehörganges der Katze mit kaltem Wasser.

Von

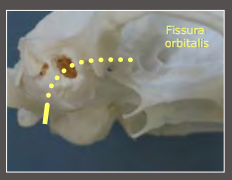
Dr. A. de Kleijn und Prof. R. Magnus.

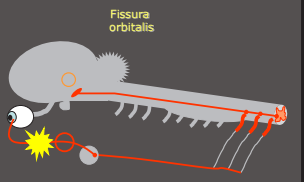
Graefe's Archieve for Clinical and Experimental Ophthalmology, 1918

Dr. Kaspar Matiasek
The Animal Health Trust, Newmarket

Localisation: media cranial fossa

- cranial nerve deficits
- reduced mentation





Diabetes mellitus

Dr. Kaspar Matiasek
The Animal Health Trust, Newmarket

Horner's Syndrome: Diabetes mellitus

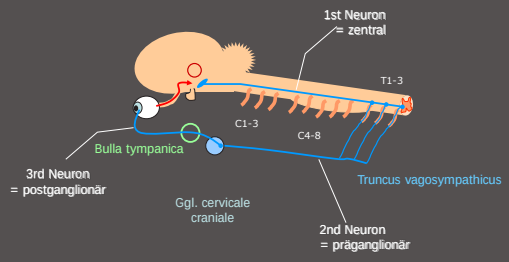
Bilateral Horner's syndrome in a dog with diabetes mellitus

C. Mellor

History: weakness
polydipsia
bilateral Horner's syndrome

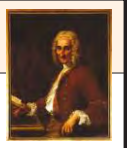
Neuroexam:
delayed conscious proprioception
reduced segmental spinal reflexes in rear limbs

Sympathetic nerve: the long way back



Dr. Kaspar Matiasek
The Animal Health Trust, Newmarket

Pourfour-le-Petit-Syndrome



1664-1741

Boydell: Journal of Small Animal Practice 2000 (41): 202-203

FIG 1. Pourfour du Petit syndrome in a cat exhibiting the characteristic pupillary and mild exophthalmos of the right eye

Table 1. Case details for the three cats with iatrogenic pupillary dilation

Case	Breed	Age (years)	Gender	Pupillary changes
1	DSH	6	MN	Mydriasis post-procedure. Resolved within 24 hours
2	DSH	7	MN	Mydriasis post-procedure. Resolved four to seven days later (see Fig 1)
3	DLH	11	FN	Mydriasis post-procedure. Miosis four days later. Resolved spontaneously after five weeks

DSH Domestic shorthaired cat, DLH Domestic longhaired cat, M Male, F Female, N Neutered

Vestibular desease

Priv.-Doz. Dr. Thomas Flegel

Vestibular Syndrome

Thomas Flegel
DACVIM (neurology), DECVN

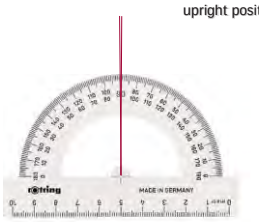
UNIVERSITY of LEIPZIG, GERMANY
Department of Small Animal Medicine

Why do we have a vestibular system?

- supports body against gravitation
- supports body during acceleration
- coordination of body movements and eye movements

Why do we have a vestibular system?

0.5° deviation from the upright position



Why do we have a vestibular system?

supports body against gravitation	supports body during acceleration	coordinates movements of eyes
difficulties standing rolling, falling to the side, circling, head tilt	falling over, loss of coordination, ataxia	blurred vision, whenever you move your head nystagmus

Anatomy of the vestibular system

peripheral:
inner ear

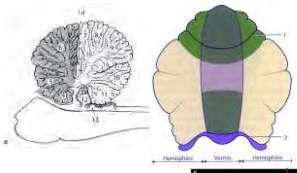
central:
brain stem
cerebellum

vestibulocochlear nerve (VIII)

connecting tracts:
to the eyes: medial longitudinal fasciculus
to limb muscles: vestibulospinal tract (mainly ipsilateral)

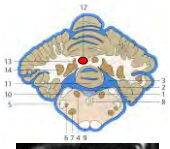
„Vestibulocerebellum“

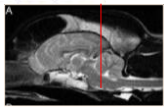
Flocculonodular lobe

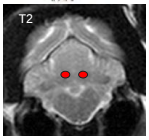


Stoffel: Funktionelle Neuroanatomie für die Tiermedizin, 2011

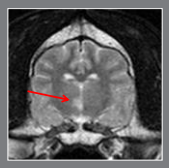
Fastigial nucleus







„Vestibulothalamus“



mixed breed „Lino“
9 years

„Vestibulo-spinal cord“

Lesions in the upper cervical spine may cause vestibular symptoms:

- transection of dorsal roots of the first 3 cervical segments
- lesions interfering with the cervicospinovestibular tracts of those segments (S. 225)

Testing physiological nystagmus?

Test:
physiological nystagmus

Test:
physiological Nystagmus
"light"

Innervation of extraocular muscles

http://www.csdl.tamu.edu/~sam/pictures/eye_muscles.gif

$(LR_6SO_4)^3$

oculomotor n. (3)
trochlear n. (4)
abducens n. (6)

Lateral Rectus muscle
Superior Oblique muscle

Why do we have a vestibular system?

supports body against gravitation	supports body during acceleration	coordinates movements of eyes
difficulties standing rolling, falling to the side, circling, head tilt	falling over, loss of coordination, ataxia	blurred vision, whenever you move your head nystagmus

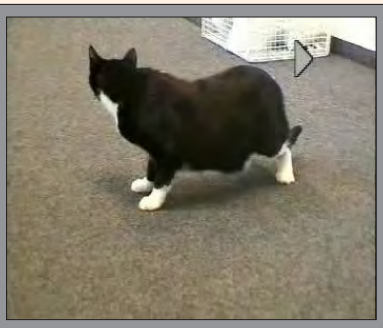
Ataxia

Mixed breed dog
"Ciara"

intact female, 14 years

case number: 94738

Circling, head tilt, ataxia



Bilateral vestibular lesion

DSH cat "Ernie"

neutered male, 5 years

case number: 44052

Bilateral vestibular lesion

CKCS "Queeny"

intact female, 5.5 years

case number: 66033

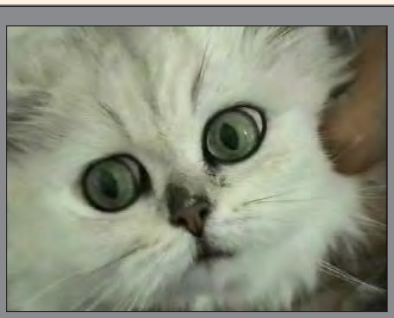
Nystagmus

physiological versus pathological

3 types of pathological nystagmus:

- horizontal
- vertical
- rotatory

Nystagmus: horizontal



Dr. Konni Jurina

Nystagmus: vertical

Nystagmus: rotatory

German-Shepherd-Mix
"Loewe"

male, 13 Jahre

case number: 49898

Nystagmus: „rabbitory“

Rabbit "Paula"

female, 5 years

case number: 66971

Nystagmus?

Colorpoint Katze "Flavia"

10 Jahre, weiblich kastriert

case number: 57962

Most important question in „vestibular neurology“

„Ear or brain: That is the question.“

W. Shakeseare

- Diifferentials
- Diagnostic tests
- Prognois
- cost

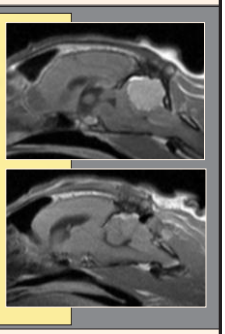
Nystagmus: positional

British Shorthair Cat
"Leonardo"

postitional vertical nystagmus

intact male, 11 years

case number: 17731



Nystagmus

When do we see nystagmus?

permanent:	peripheral
positional:	central

What about the frequency?

>60 beats/min	peripheral
<60 beats/min	central

Troxel et al.. Signs of neurological dysfunction in dogs with central versus peripheral vestibular disease. *J Am Vet Med Assoc* 2005;**227**:570-574.

peripheral versus central

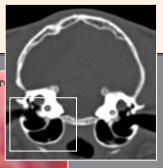
	peripheral	central
mentation	normal	can be abnormal
bahavior	normal	can be abnormal
nystagmus	horizontal, rotatory	horizontal, vertical, rotatory
cranial nerve deficits	only VII	several possible
Horner's syndrome	yes	no
proprioception	normal	can be abnormal

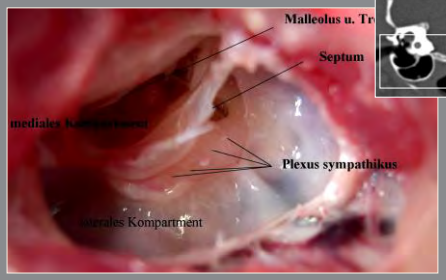
Horner's Syndrome

Loss of sympathic innervation to the eye:

- ptosis: „smaller eye“
- miosis: smaller pupil
- enophthalmus: sunken in eye
- 3rd eye lid protrusion

Horner's Syndrome





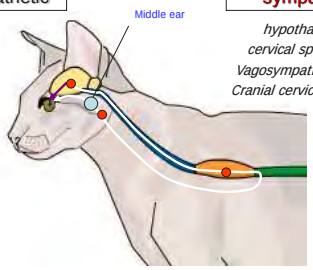
Stefan Rupp, Hofheim, Germany

Sympathetic innervation of the eye

parasympathetic

sympathetic

hypothalamus
cervical spinal cord
Vagosympathetic trunc
Cranial cervical ganglion

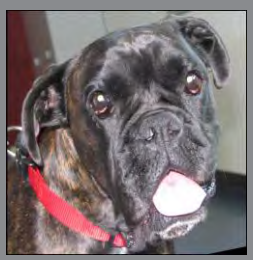


Innervation:
Ciliar muscle
Orbital muscle
dilatator pupillae m.
tarsalis superior m.
(Müller-muscle)

Here comes a little bit of history

François Pourfour du Petit	1712	sympathetic innervation of the eye comes not directly from the brain
1664-1741 	1728	oculofacial syndrome following transection of intercostal nerves
Edward Selleck Hare	1838	ocular syndrome in a patient with cervical spinal tumor
Claude Bernard	1852	Trias
Mitchell, Keen, Morehouse	1864	
Jonathan Hutchinson	1865	case report of a woman with
Johann Friedrich Horner	1868	detailed report of the Hutschinson case

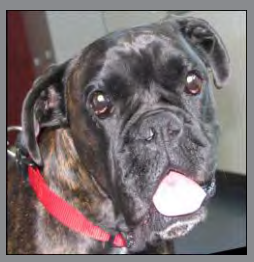
Facial paresis

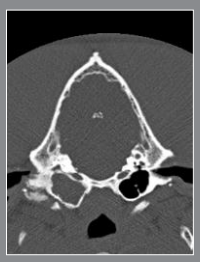


Boxer, 6 years, male

- drooping of and inability to move ear and lips
- widened palpebral fissure
- absent blink
- absent abduction of nostril during inspiration
- deviation of the nose to the opposite side
- chronic: nose deviated to abnormal side, facial muscle contracted due to fibrosis

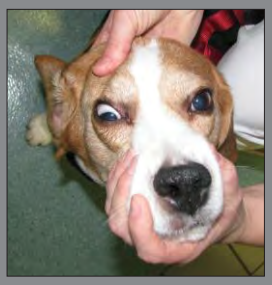
Facial paresis





Boxer, 6 years, male

Vestibular strabism: positionally ventral



MRI findings in vestibular syndrome

Results of magnetic resonance imaging in dogs with vestibular disorders: 85 cases (1996–1999)

Clinical symptoms of peripheral vestibular disease

- MRI abnormalities of the ear: 67%
- intracranial lesion: 7%
- no MRI abnormalitiy: 26%

Clinical symptoms of central vestibular disease

- MRI abnormalities in the brain: 100%

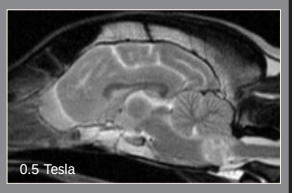
Paradoxical vestibular syndrome

If nystagmus/head tilt and reduced conscious proprioception do not fit with a brain stem disease on one side

Than you are dealing with:

1. a lesion involving brainstem and caudal cerebellar peduncle
2. the lesion is on the side of reduced CP
3. often serious disease

Paradoxical vestibular syndrome



- lesions affecting the brain stem and caudal cerebellar peduncle ipsilateral (cerebellopontine angle)
- encephalitis, neoplasia, infarction

Paradoxical vestibular syndrome

Results of magnetic resonance imaging in dogs with vestibular disorders: 85 cases (1996–1999)

25% of dogs with vestibular lesion suffered from paradoxical vestibular syndrome

peripheral versus central

	peripheral	central
mentation	normal	can be abnormal
bahavior	normal	can be abnormal
nystagmus	horizontal, rotatory	horizontal, vertical, rotatory
cranial nerve deficits	only VII	several possible
Horner's syndrome	yes	no
proprioception	normal	can be abnormal

Differentials

- encephalitis
- brain stem neoplasia
- extension of otitis
- infarction
- trauma
- thiamine deficiency

→ central

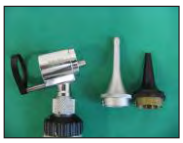
→ peripheral

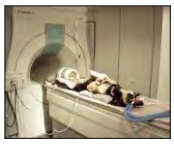
- otitis media/interna
- polyps
- hypothyroidism
- idiopathic
- congenital
- medications

Diagnostics

- MRI
- CT
- CSF analysis

→ central





→ peripheral

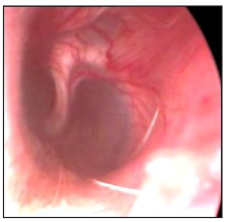
- otoscopy
- bulla radiographs
- CT/MRI
- fT4/TSH

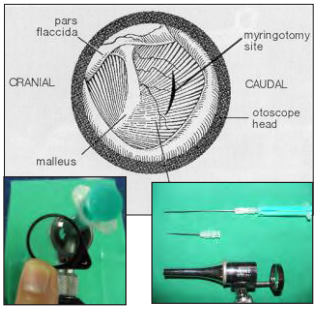
Otoscopy

- otitis externa: redness, swelling
- neoplasia: (polyp)
- foreign body
- intact ear drum?
- how does the intact ear drum look alike?

pale-bluish	normal
yellowish	pus in the middle ear
red	inflammation

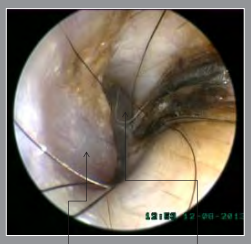
Otoscopy: myringotomy

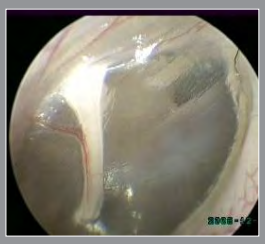




- cytology
- bacterial culture

Otoscopy: ear drum

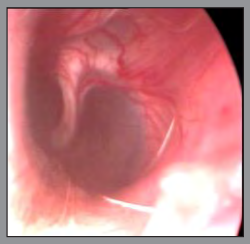
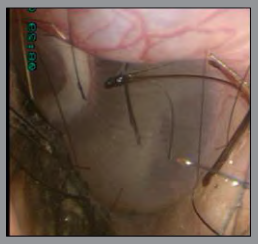




Pars flacida Pars tensa

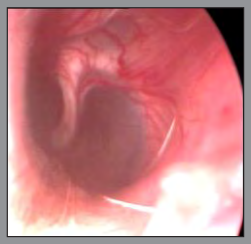
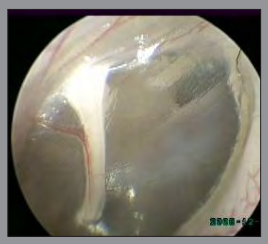
courtesy of S. Pohl

Otoscopy: ear drum

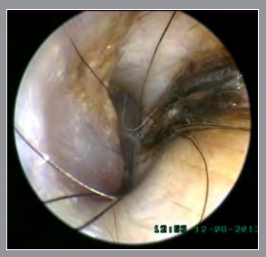
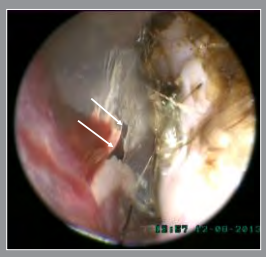
courtesy S. Pohl

Otoscopy: ear drum

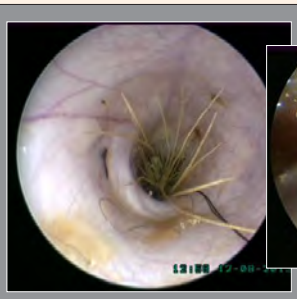
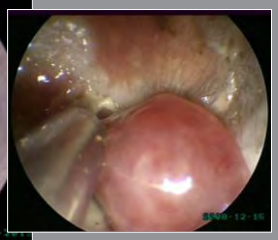
courtesy S. Pohl

Otoscopy: ruptured ear drum

courtesy S. Pohl

Otoscopy: foreign body, polyp

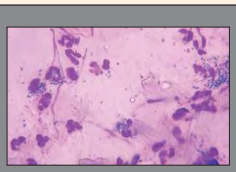
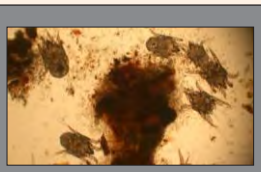



Courtesy of S. Pohl

Grass awn

Polyp

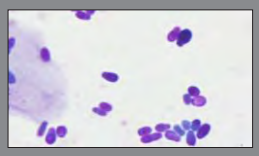
Otoscopy: cytology

bacterial otitis

Wright-Giemsa stain

ear mites

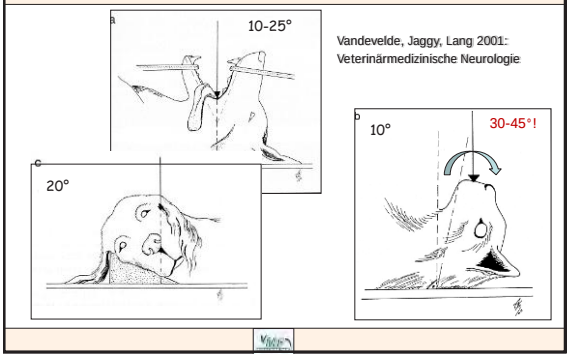


Malessezia

Imaging

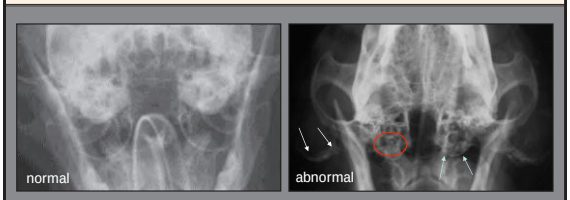
- radiography
- computed tomography
- magnetic resonance imaging

Radiographs: middle ear



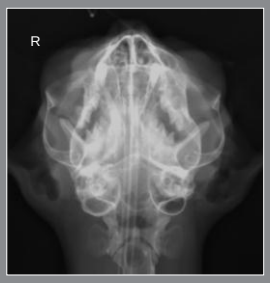
Vandevelde, Jaggy, Lang 2001:
Veterinärmedizinische Neurologie

Radiographs: middle ear ventrodorsal



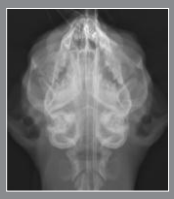
- mineralization of external ear canal
- loss of radiolucency of tympanica bulla
- lysis or proliferation of bulla wall

radiographs: middle ear ventrodorsal

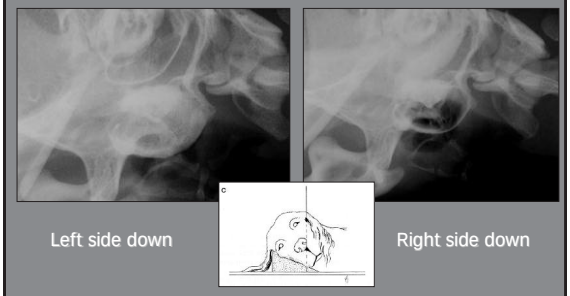


DSH-cat, 1 year

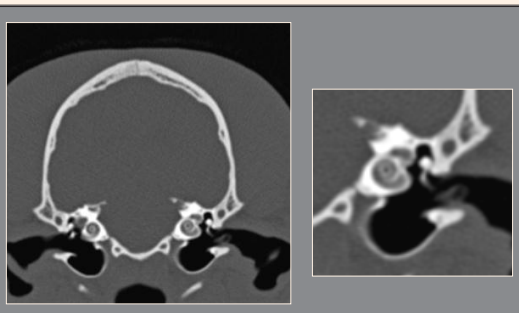
- opaque material in right bulla
- thickened bulla wall



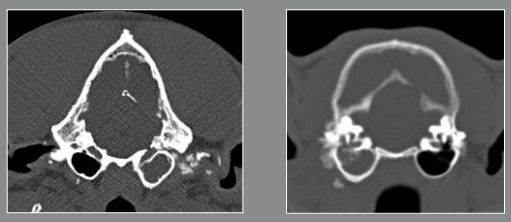
Radiographs: middle ear oblique view



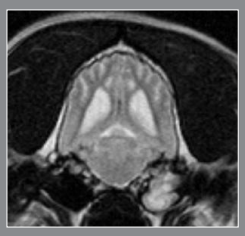
CT: middle and inner ear



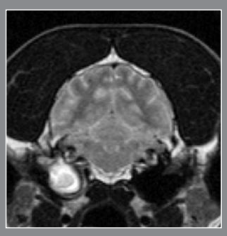
CT: otitis media



MRI: Otitis media (interna?)

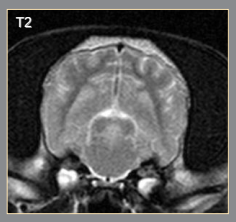


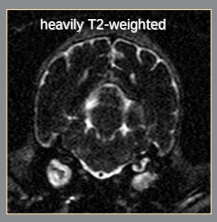
Boxer, 8 years



Doberman, 3 years

MRI: Otitis media/interna





Primary secretory otitis media (PSOM)

Fluid filled middle ear without associated clinical signs (PSOM)
Katrin Truar

Pug Dog (n=41)

unilateral:	14.6%
bilateral:	9.8%
total:	24.4%

French Bulldog (n=41)

unilateral:	24.4%
bilateral:	29.3%
total:	53.7%

MRI: PSOM

J Small Anim Pract. 2003 Jun;44(6):253-8

Primary secretory otitis media in the Cavalier King Charles spaniel: a review of 61 cases.

Stein-Berthold IV[1], Rikstrin L, Håkanson NW

Author information

Abstract

Sixty-one episodes of primary secretory otitis media (PSOM) were diagnosed in 43 Cavalier King Charles spaniels over a 10-year period. The principal findings were signs of moderate to severe pain localised to the head or cervical area, and/or neurological signs. Diagnosis was made by examination of the tympanic membrane and middle ear with the aid of an operating microscope under general anaesthesia. A bulging, but intact, tympanic membrane was found in most cases. Following myringotomy, a highly viscous mucus plug was found filling the middle ear. Treatment, consisting of removal of the mucus plug, flushing of the middle ear, and local and systemic medical therapy, had to be repeated between one and five times. The prognosis was good in all cases. PSOM is an important differential diagnosis in Cavalier King Charles spaniels with signs of pain involving the head and neck, and/or neurological signs.

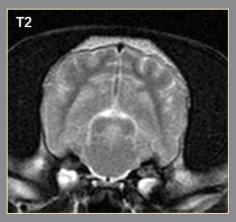
Subclinical middle ear disease

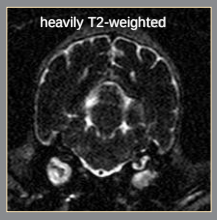
PREVALENCE OF CLINICAL AND SUBCLINICAL MIDDLE EAR DISEASE IN CATS UNDERGOING COMPUTED TOMOGRAPHIC SCANS OF THE HEAD

MIRIAM SHANAMAN, GABRIELA SEILER, DAVID E. HOLT

Three hundred and ten cats that had CT imaging of the head between January 2000 and December 2007 were evaluated retrospectively. Data that were recorded included signalment, presenting complaint, clinical signs, presence of upper respiratory tract disease, and CT findings. One hundred and one cats had evidence of middle ear disease on CT. Thirty-four of the 101 cats (34%) did not have a primary complaint of ear-related disease, clinical signs or physical findings consistent with ear disease, suggesting that the middle ear disease was subclinical. Twenty-seven of the 34 cats (79%) had concurrent nasal disease. Middle ear lesions were chronic in appearance. With the exception of tympanic bulla lysis, CT findings were similar in cats presenting with primary aural disease versus cats with presumptive subclinical middle ear disease. The majority of the cats did not return for treatment of the identified middle ear abnormalities. Subclinical middle ear disease is relatively frequent in cats undergoing CT imaging of the head. Few cats required subsequent treatment for ear disease although follow up was limited. Identification of subclinical middle ear abnormalities on CT should prompt acquisition of a detailed patient history and bilateral otoscopic examination. © 2012 *Veterinary Radiology & Ultrasound*, Vol. 53, No. 1, 2012, pp 76–79

MRI: Otitis media/interna



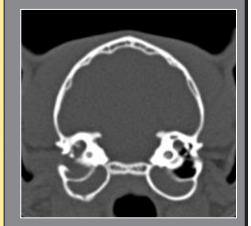


CT „Ernie“: bilateral vestibular syndrome

DSH cat "Ernie"

neutered male, 5 years

case number: 44052

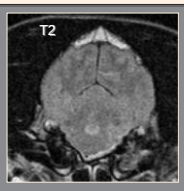


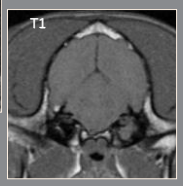
Therapy: Otitis media/interna

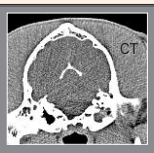
- antibiotics for 6 weeks (at least):
  cephalosporine
  fluroquinolone
  amoxicillin/clavulanic acid
  TMS
- ear cleaning and local antibiatic (if ear drum is intact)
- surgical: bulla osteotomy
  total ear canal ablation (TECA)

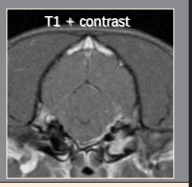
  endoscopic surgery through ear drum

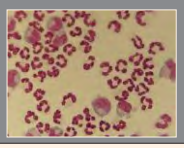
MRI: otitis with brain stem involvement





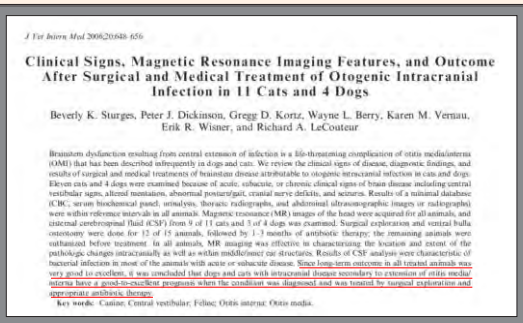






CSF cell count:
881/µl (normal<5)

MRI: Otitis with brain stem involvement



J Vet Intern Med 2006;20:648–656

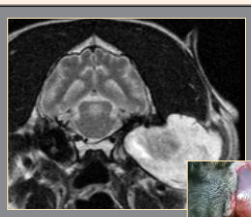
Clinical Signs, Magnetic Resonance Imaging Features, and Outcome After Surgical and Medical Treatment of Otogenic Intracranial Infection in 11 Cats and 4 Dogs

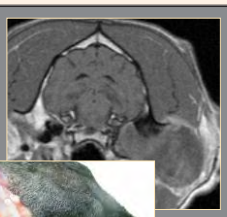
Beverly K. Sturges, Peter J. Dickinson, Gregg D. Kortz, Wayne L. Berry, Karen M. Vernau, Erik R. Wisner, and Richard A. LeCouteur

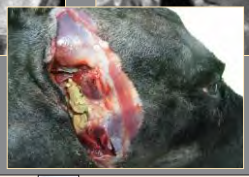
Brainstem dysfunction resulting from central extension of infection is a life-threatening complication of otitis media/interna (OMI) that has been described infrequently in dogs and cats. We review the clinical signs of disease, diagnostic findings, and results of surgical and medical treatments of brainstem disease attributable to otogenic intracranial infection in cats and dogs. Eleven cats and 4 dogs were examined because of acute, subacute, or chronic clinical signs of brain disease including central vestibular signs, altered mentation, abnormal posture/gait, cranial nerve deficits, and seizures. Results of a minimal database (CBC, serum biochemical panel, urinalysis, thoracic radiographs, and abdominal ultrasonographic images or radiographs) were within reference intervals in all animals. Magnetic resonance (MR) images of the head were acquired for all animals, and cisternal cerebrospinal fluid (CSF) from 9 of 11 cats and 3 of 4 dogs was examined. Surgical exploration and ventral bulla osteotomy were done for 12 of 15 animals, followed by 1–3 months of antibiotic therapy; the remaining animals were euthanized before treatment. In all animals, MR imaging was effective in characterizing the location and extent of the pathologic changes intracranially as well as within middle/inner ear structures. Results of CSF analysis were characteristic of bacterial infection in most of the animals with acute or subacute disease. Since long-term outcome in all treated animals was very good to excellent, it was concluded that dogs and cats with intracranial disease secondary to extension of otitis media/interna have a good-to-excellent prognosis when the condition was diagnosed and was treated by surgical exploration and appropriate antibiotic therapy.

Key words: Canine; Central vestibular; Feline; Otitis interna; Otitis media.

Cholesteatoma

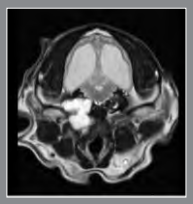


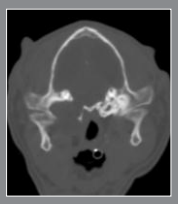




Airdale Terrier „Paula“
female, 12 years

Cholesteatoma





„Epidermoid cysts containing hyperkeratotic squamous epithelium surrounding core of keratin debris“

Banco et al. 2014

Complication of otitis media

French Bulldog „Louis“ 8 years

Cholesteatoma

Aural Cholesteatoma in Twenty Dogs

ELIZABETH M. HARDIE, KEITH E. LINDER, and ANTHONY P. PEASE

Differentials

- encephalitis
- brain stem neoplasia
- extension of otitis
- infarction
- trauma
- thiamine deficiency

central

- otitis media/interna
- polyps

peripheral

- hypothyroidism
- idiopathic
- congenital
- medications

Acute vestibular symptoms in old dogs

Deutscher Schäferhund "Franzis"

15 Jahre, weiblich

case number: 79169

German Shpeherd dog

15 years

History:

acute lack of coordination

Acute vestibular symptomes in old dogs...

In most cases neoplastic disease is supsected:

Euthanasia

No, no, no, no!! –
It is more likely to be
idiopathic vestibular syndrome
or hypothyroidism!!

„Old dog" vestibular disease

Deutscher Schäferhund "Franzis"

15 Jahre, weiblich

- old (> 10 Jahre)
- acute symptomes
- peripheral vestibular syndrome

→ Idiopathic vestibular syndrome

→ Hypothyroidism

⇢ Brain infarct

Geriatric vestibular syndrome: the typical patient

breeds: more often large breed dogs

age: > 10 years of age
but consider normal life expectation

presenting signs: acute severe vestibular syndrome
- head tilt
- generalized ataxia
- nystagmus

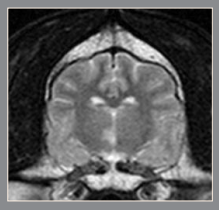
signs of peripheral vestibular lesion

„Old dog“ vestibular disease

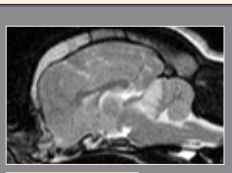
- old (> 10 Jahre)
- acute symptomes
- peripheral vestibular syndrome

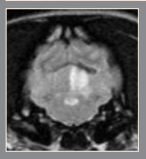
Idiopathic vestibular syndrome | Hypothyroidism | Brain infarct

Infarct



mixed breed dog
female, 9 years





Pug
male, 4 years

„Old dog“ vestibular disease

- old (> 10 Jahre)
- acute symptomes
- peripheral vestibular syndrome

Idiopathic vestibular syndrome | Hypothyroidism | Brain infarct

Hypothyroidism (dog)

Name	Ergebnis	Einheit	Min.	Max	Bemerkungen
free T4	0,5	ng/dl	0,47	3,12	VML 248
TSH (canines)	1,54	ng/ml	0	0,5	VML
Behandelnder TA:	Rodler/				

Specificity: 74% without hypothyroidism have a negative test result

Sensitivity: 98% with hypothyroidsim have a postitive test result

Geriatric vestibular syndrome: differentials

- idiopathic (geriatric) vestibular syndrome
- Hypothyroidism

peripheral

- Infarction

central

Geriatric vestibular syndrome: diagnostics

- idiopathic (geriatric) vestibular syndrome
  - → no test
- Hypothyroidism
  - → fT4, TSH

peripheral

- Infarction
  - → brain MRI

central

Therapy: Idiopathic vestibular syndrome

„The art of medicine consists in amusing the patient while nature cures the disease“

Voltaire (1694-1778)

Geriatric vestibular syndrome: therapy

- idiopathic (geriatric) vestibular syndrome
  - no test — fluids, antiemetics, Karsivan??
- Hypothyroidism
  - fT4, TSH — levothyroxin 20 µg/kg BID
- Infarction
  - brain MRI — probably nothing

peripheral / central

Geriatric vestibular syndrome: prognosis

- idiopathic (geriatric) vestibular syndrome
  - none — fluids, antiemetics (Maropitant), propentofyllin (Karsivan®) ⇨ improvement starts within 3-4 days, begins with less severe nystagmus, might have residual head tilt
- Hypothyroidism
  - fT4, TSH — levothyroxin 20 µg/kg BID ⇨ improvement within days-months
- Infarction
  - brain MRI — probably nothing

Differentials

- encephalitis
- brain stem neoplasia
- extension of otitis
- infarction
- trauma
- thiamine deficiency

→ central / peripheral

- otitis media/interna
- polyps
- hypothyroidism
- idiopathic
- congenital
- medications

Vestibulotoxic substances

Table 8–1 **Ototoxic Drugs and Chemicals**[11]

Antibiotics	Antineoplastics
Aminoglycosides	Cisplatin
Streptomycin	Nitrogen mustard
Dihydrostreptomycin	Diuretics
Gentamicin	Bumetanide
Neomycin	Ethacrynic acid
Kanamycin	Furosemide
Amikacin	Heavy Metals
Tobramycin	Arsenic
Other	Lead
Polymixin B	Mercury
Minocycline	Miscellaneous
Erythromycin	Cerumenolytic agents
Vancomycin	Detergents
Chloramphenicol	Quinine
Antiseptics	Propylene glycol
Ethanol	Salicylates
Iodine and iodophors	
Benzalkonium chloride	
Chlorhexidine	
Centrimide	
Benzethonium chloride	

metronidazol in therapeutic dosage

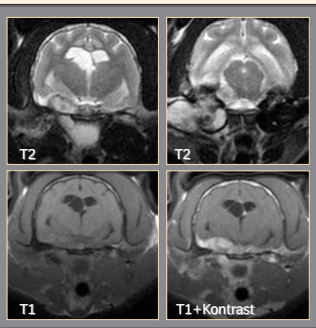
Differentials

- encephalitis
- brain stem neoplasia
- extension of otitis
- infarction
- trauma
- thiamine deficiency

→ central / peripheral

- otitis media/interna
- polyps
- hypothyroidism
- idiopathic
- congenital
- medications

Polyp (cat)



DSH cat „Pablo“
male, 8 years

Differentials

- encephalitis
- brain stem neoplasia
- extension of otitis
- infarction
- trauma
- thiamine deficiency

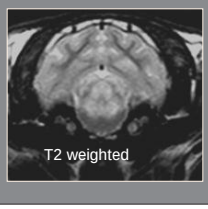
central

peripheral

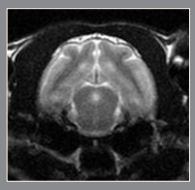
- otitis media/interna
- polyps
- hypothyroidism
- idiopathic
- congenital
- medications

Thiamine deficiency (cat)

thiamine deficiency



normal



- Diagnostics: EDTA-plasma
- Therapy: Thiamine 25-50mg daily

- Fisch diet
- anorexia

Thiamine deficiency (cat)

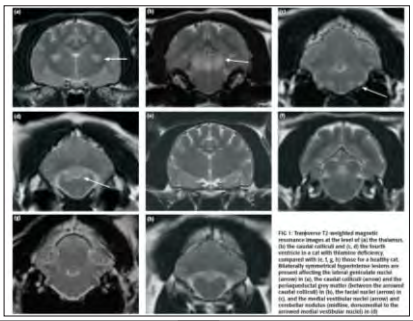
SHORT COMMUNICATIONS

Penderis et al., Vet Record 2007

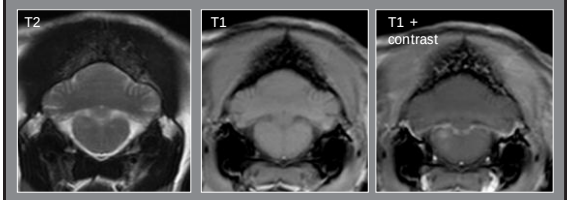
Magnetic resonance imaging features of thiamine deficiency in a cat

J. Penderis, J. F. McConnell, J. Calvin

Thiamine deficiency (cat)



DSH cat „Samira“, female, 7 years



- generalized ataxia, head tilt and circling to the right of 2 days duration
- vertical nystagmus

DSH cat „Samira“, female, 7 years

CSF analysis:

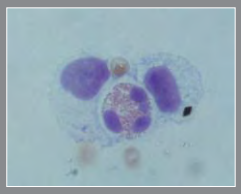
nucleated cell count: 11/µl (normal <5)
total protein: 0.21 g/l (normal <0.25)

Toxoplasmosis Ab-titer:

IgG: 1:1024 (normal 1:32)
IgM: 1:64 (normal 1:16)

Toxoplasmosis Ab-titer 5 weeks later:

IgG: 1:1024 (normal 1:32)
IgM: 1:256 (normal 1:16)



Anything else?

Recurrent vestibular paroxysms associated with systemic hypertension in a dog

R. Timothy Bentley, BVSc, DACVIM, and Philip A. March, DVM, MS, DACVIM

Case Description—A 9-year-old 19.7-kg (43.3-lb) spayed female Australian Shepherd was examined for an increase in frequency of episodic neurologic signs, often occurring upon exercise.

Clinical Findings—Between episodes of neurologic signs, the dog was considered clinically normal on the basis of findings on physical and neurologic examinations. An episode of ataxia with central vestibular signs was induced by exercising the patient in the hospital. All clinicopathologic values were within reference ranges, as were findings on magnetic resonance imaging of the brain and peripheral vestibular system. Systolic blood pressures of 180 to 200 mm Hg were recorded, and systemic hypertension was diagnosed.

Treatment and Outcome—While the dog received amlodipine and enalapril, blood pressure returned to within reference range, and episodes of neurologic signs no longer occurred. When clinical signs later recurred, systolic blood pressure was again found to be high. Following an increase in medication dosage, blood pressure normalized, and only 4 further episodes of neurologic signs were observed during a follow-up period totaling 30 months.

Clinical Relevance—Transient ischemic attack is a common diagnosis in humans but has not been described for dogs. In humans, it is defined as focal brain dysfunction caused by vascular disease that resolves completely in less than 24 hours and is often recurrent. Systemic hypertension is one of the most common preexisting conditions. We propose that the dog in the present report had clinical signs and diagnostic test results supportive of a diagnosis of transient ischemic attack. (*J Am Vet Med Assoc* 2011;239:652–655)

Novi vid zaštite

protiv buva i krpelja u trajanju do **8 meseci**

Ima repelentno dejstvo na krpelje, ubija buve i krpelje u trajanju do **8 meseci**

- **Inovativna ogrlica** obezbeđuje kontinuiranu zaštitu za mačke i pse
- Polimerni matrix obezbeđuje sporo i kontinuirano oslobađanje imidakloprida i flumetrina **u niskim dozama**
- **Smanjuje rizik transmisije** vektorskih bolesti
- **Vodootporna ogrlica bez mirisa**

Do 8 meseci zaštite

Foresto ogrlica za mačke i male pse, 1x1,(br. dozvole 365-2010-14-01-001 od 13.10.2011, datum revizije teksta Oktobar 2011.). **Foresto ogrlica za velike pse**, 1x1 (br.dozvole 366-2010-14-01-001 od 24.10.2011., datum revizije teksta oktobar 2011.). **Način izdavanja:** lek se može izdavati samo na recept veterinara. **Indikacije:** tretman i prevencija infestacije buvama tokom 7 do 8 meseci. Kod infestacije krepljima, proizvod ima postojanu akaricidnu i repelentnu efikasnost tokom 8 meseci. Za tretman infestacije pavašima (*Trichodectes canis*). **Kontraindikacije:** Ne koristiti kod mačića mlađih od 10 nedelja i štenadi mlađe od 7 nedelja. Ne koristiti u slučaju poznate preosetljivosti na aktivne supstance ili na bilo koju pomoćnu suspstancu. **Neželjena dejstva:** Kod životinja koje nisu navikle na nošenje ogrlice, u prvih nekoliko dana nakon postavljanja može doći do pojave blagog svraba i/ili eritema. Može doći do pojave neznatnog opadanja dlake i blagih kožnih reakcija na mestu postavljanja, koje obično nestaju u okviru 1 do 2 nedelje, bez potrebnog skidanja ogrlice. U pojedinačnim slučajevima, preporučljivo je privremeno uklanjanje ogrlice do nestanka simptoma. Kod mačaka se, na početku, retko mogu javiti blage i prolazne reakcije kao što su depresija, promene u uzimanju hrane, salivacija, povraćanje i dijareja. Kao i u slučaju bilo kog proizvoda koji se topikalno primenjuje, kod preosetljivih životinja može se javiti alergijski kontaktni dermatitis.
Za detaljnije informacije pogledati uputstvo za korisnike

foresto®

Do 8 meseci zaštite protiv buva i krpelja

Krpelji Buve Larve Pavaši (samo psi)

Samo za stručnu javnost

Farmina Pet Foods

Vet Life

Veterinary Formulated

Najbolja podrška za dobrobit vašeg psa.

Za svaki problem postoji rešenje, pravo rešenje.

SCIENTIFICALLY TESTED BY: FVR FarminaVETResearch — the Chair of Animal Nutrition and Diet, University of Naples "Federico II".

Struvite
Struvite Management

Prevencija stvaranja i otapanje struvitnih kamenčića.

Struvite i Struvite Management sadrže nizak nivo proteina, kalcijuma, fosfora, magnezijuma i supstancu za zakiseljavanje urina da bi se sprečilo taloženje kristala.

Ossalati

Smanjuje formiranje osalata.

Osalati sadrži smanjen nivo kalcijuma, fosfora i amino kiselina i radi kao alkalinajzer urina, sprečavajući kristalizaciju kalcijum oksalata i uratnih kalkulusa.

Renal

Za prevenciju i terapiju hronične bubrežne i srčane insuficijencije.

Zahvaljujući redukovanom nivou proteina, fosfora i natrijuma smanjuje se mogućnost pojave azatermije, hiperfosfatemije i sekundarnog hiperparatireoidizma. Takođe se kontroliše i visok krvni pritisak i metabolička acidoza.

Growth

Za rast šteneta, oporavak i kod gastro-intestinalnih poremećaja.

Kompletna dijetetska hrana, visoke svarljivosti zbog čega je optimalna za štence kod kojih je uočen poremećaj u rastu, za nutritivni oporavak i pravilan razvoj imunog sistema.

Neutered 1-10kg
Neutered >10kg

Za kontrolu telesne težine, sprečavanje Diabetes mellitusa i urolitijaze.

Pogodan za ishranu ženki pasa i sterilisanih odraslih mužjaka. Pomaže da se spreče neželjena dejstva zbog sterilizacije/kastracije, kao što su gojaznost, rezistencija na insulin i formiranje urolita.

Convalescence

Za odrasle pse kod oporavka od nekih nespecifičnih bolesti.

Posebno pogodna za nutritivni oporavak iscrpljenih pasa zbog visoko kvalitetnih sastojaka uz dodatak antioksidanata i prebiotika.

UltraHypo

Kod alergijskih reakcija na hranu, dijareje i idiopatskog dermatitisa.

Sadrži samo hidrolizovani protein ribe i skrob, čime se ograničava alergijska reakcija na hranu.

Gastro-Intestinal

Kod poremećaja u varenju, radu creva i insuficijencije pankreasa.

Hrana pogodna kod stomačnih i crevnih problema sa poremećajem u apsorpciji, visoko svarljivi i bio-raspoloživi sastojci. Pogodna i kod isuficijencije pankreasa.

Hypoallergenic Egg & Rice
Hypoallergenic Fish & Potato

Kod neželjenih reakcija na hranu.

Hypoallergenic je kompletna, izbalansirana hrana koja sadrži samo jedan izvor proteina (riba ili jaja) i jedan izvor skroba (krompir ili pirinač), namenjena je kao dijeta jedinkama koje imaju alergijske reakcije na hranu, osim na formulaciju koja se nalazi u hrani.

Joint

Za odrasle pse koji imaju poremećaj u lokomotornom sistemu i posle ortopedskih operacija.

Kompletna, izbalansirana hrana sa glukozaminom i hondroitinom za stimulaciju rasta zglobne hrskavice, posebno indukovana za primenu kod pasa koji imaju zapaljenje koštanog tkiva i zglobova i kod metaboličkog poremećaja zglobova.

Obesity

Za kontrolu prekomerne telesne težine i Diabetes mellitusa.

Namenjen je za kontrolu gojaznosti zbog smanjenog sadržaja energije i visokog sadržaja lipida. L- karnitin i visoka kvalitetni proteini doprinose održavanju mišićne mase. Ograničavanjem od rizika gojaznosti doprinosi se kvalitetnijem i dužem životu psa. Zahvaljujući niskom sadržaju skroba može se koristiti u kontroli nastanka i terapiji Diabetes mellitusa.

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fipronil

Rastvor za lokano nakapavanje na kožu
(ATC vet kod: QP53AX15)

Efikasno deluje na

Sastav: Pipeta od 0,67 ml sadrži 67 mg fipronila. Pipeta od 1,34 ml sadrži 134 mg fipronila. Pipeta od 2,68 ml sadrži 268 mg fipronila. Pipeta od 4,02 ml sadrži 402 mg fipronila. Pipeta od 0,50 ml sadrži 50 mg fipronila. **Indikacije:** Lečenje i prevencija infestacije buvama (*Ctenocephalides* spp.) i krpeljima (*Rhipicephalus* spp., *Dermacentor* spp., *Ixodes* spp.) kod pasa i mačaka. Lečenje i kontrola alergija na ujede buva (FAD) kod pasa i mačaka. Prevencija i lečenje infestacije pavašima (*Mallophaga*) kod pasa i mačaka. **Ciljne životinjske vrste:** Psi. Mačke. **Kontraindikacije:** Pošto ne postoje podaci o upotrebi ovog leka, ne upotrebljavajte ga kod štenaca mladih od 8 nedelja ili lakših od 2 kg te kod mladunaca mačaka mladih od 8 nedelja ili lakših od 1 kg. Nemojte primenjivati ovaj lek na obolelim životinjama (sistemska oboljenja, temperatura) niti na životinjama u periodu oporavka. Nemojte koristiti na zečevima zbog opasnosti od neželjenih dejstava ili čak i smrti. Lek za pse, zbog opasnosti od predoziranja, ne upotrebljavajte kod mačaka. **Farmakoterapijska grupa:** Ektoparaziticid za lokalnu primenu. Izdaje se samo na recept veterinara. **Broj rešenja:** 323-01-122-10-001 od 05.04.2011. godine. **Datum revizije teksta:** April 2011.

Samo za stručnu javnost

Za upotrebu u veterinarskoj medicini

Pre propisivanja leka pročitajte kompletan sažetak karakteristika leka.

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