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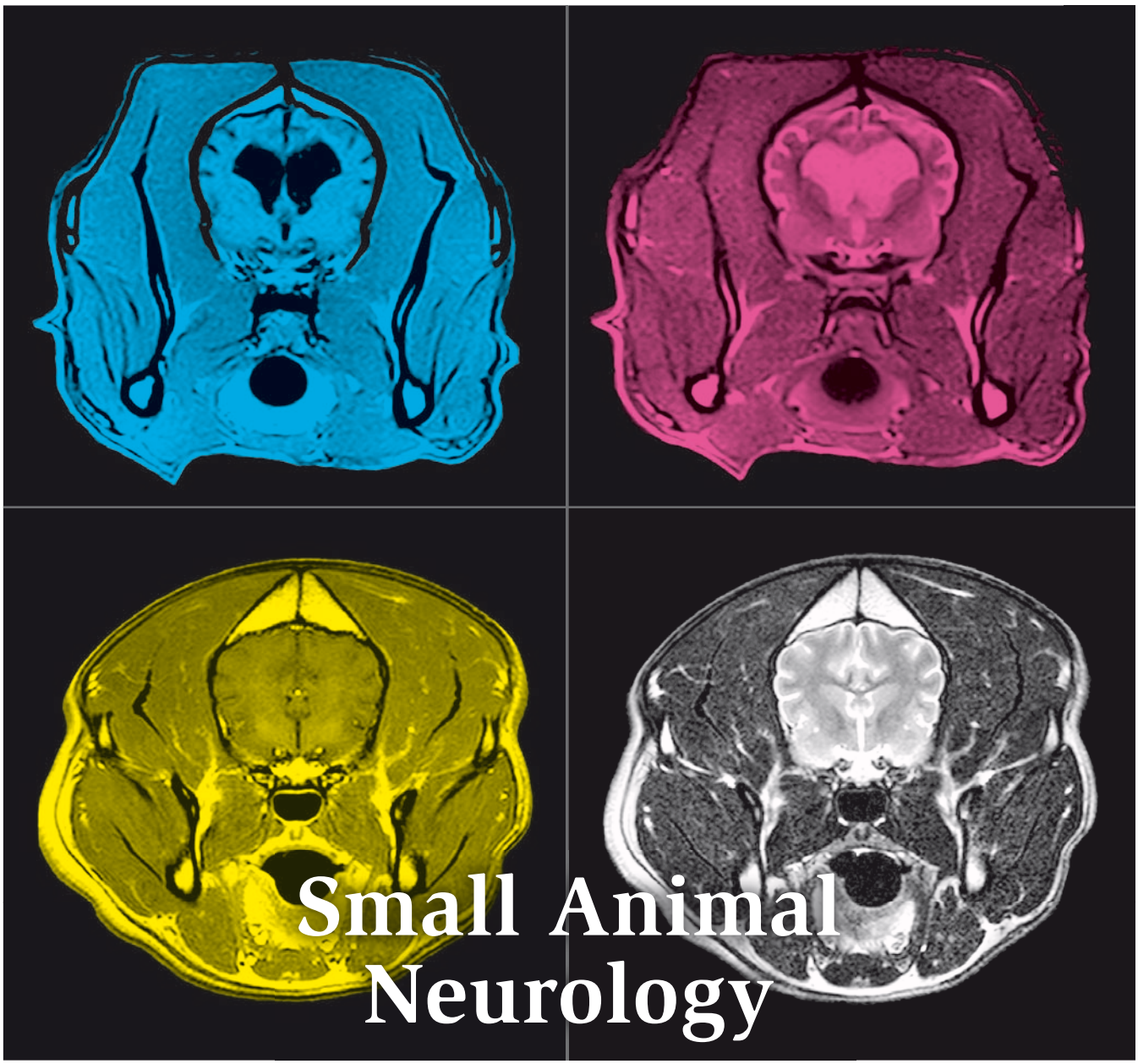

Small Animal Neurology

Intracranial tumors in dogs • How I approach...The circling cat • Vestibular syndrome in dogs • Descriptive epidemiology of idiopathic seizures in dogs • Acquired canine metabolic encephalopathies • Canine lysosomal storage diseases • Feline cognitive dysfunction syndrome • Cut-out and keep guide...Nerve injury and pain

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EDITORIAL

"I think, therefore I am". So wrote René Descartes in 1637, and whilst the French philosopher intended it as a clinching argument to prove that in order to have the capacity to think, one must exist, we can also argue that to think requires a functioning (and indeed highly sophisticated) nervous system – something that Descartes seems to have taken for granted. Certainly the nervous system is the most complex organ in the body; the human brain contains around one hundred billion neurons and one hundred trillion synapses, numbers that we simply cannot comprehend with any real understanding, and yet we read this journal without stopping to think how incredible it is that we have the ability to do so. And since the nervous system is without doubt the overarching controller, coordinating all voluntary and involuntary activity, no animal can function effectively if the system does not work properly – and whilst we may not know if our domesticated pets are capable of philosophical ponderings, they are surely capable of rational thought, behavior and action, and clinicians are all too aware of the problems that can develop when something goes wrong.

Yet neurology may be seen to suffer from a paradox – we are typically unaware or unappreciative of the complexities at cellular and molecular levels that a "simple" task, such as walking in a straight line, requires, and yet we tend to regard the nervous system as the most difficult of the various veterinary disciplines. All too often, we perhaps have a mental block when faced with a neurological illness, intuitively concluding that it must be difficult to diagnose and treat. Thus the challenge of making sense of all this complexity is formidable, but from the myriad of available topics we present a few choice neurological problems in the pages ahead for our readers; to educate them, to challenge their assumptions, and – of course – to make them think.

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Printed in the European Union
ISSN 1354-0157
Circulation: 70,000 copies
Legal deposit: June 2014
Cover: Images John Rossmeisl Jr.

Veterinary Focus is also published in French, German, Chinese, Italian, Polish, Spanish, Japanese & Russian.

Intracranial tumors in dogs

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Introduction

Intracranial neoplasia is a major cause of morbidity and mortality in companion animals, predominantly in dogs. Increased availability of advanced imaging modalities and specialized surgical equipment, together with a growing understanding of the basic biology of these tumors, has provided the opportunity to significantly advance patient care. This review will summarize clinical, diagnostic and therapeutic aspects of canine intracranial tumors, and briefly introduce novel areas of research and therapy currently in clinical trials.

KEY POINTS

- **Primary intracranial tumors are over-represented in certain breeds such as Boxers, Bulldogs, Boston Terriers and Golden Retrievers.**
- **A comprehensive diagnostic plan is important when intracranial neoplasia is suspected due to the frequency of secondary intracranial tumors and additional unrelated neoplasia.**
- **Advanced imaging is the mainstay of diagnosis, but cannot replace histopathology for optimal therapeutic planning.**
- **Palliative therapy can provide quality of life in the short term (weeks to several months).**
- **Although diagnostic imaging, biopsy and definitive therapies are expensive, they may result in prolonged survival times of one or more years, particularly for rostrotentorial tumors.**
- **Molecular genetic investigations are likely to improve incidence and outcomes through selective breeding and targeted therapies.**

Incidence of intracranial tumors

Accurate data for true incidence of brain tumors in dogs is limited to references from a study in the 1960s and 70s in Northern California which determined the incidence of all nervous system tumors to be 14.5 cases per 100,000 dogs (1). This is similar to human data with an incidence of primary CNS tumors of 20.59 per 100,000 in the US (2). A more accurate comparison may be based on necropsy data, where intracranial/nervous system neoplasia has been reported in approximately 2-4.5% of dogs (compared to ~ 2% of human patients) (3,4). Intracranial tumors are generally classified as either primary ***(Figure 1)*** – originating within the cranial vault, or secondary – invading the cranial vault or metastasizing from distant sites. Secondary neoplasia accounts for approximately 50% of all intracranial tumors, with the most common types being hemangiosarcoma, pituitary tumors, lymphoma, metastatic carcinoma, extension of nasal neoplasms, and histiocytic sarcoma (5). The frequency of specific primary tumor types varies somewhat between studies, but generally meningiomas compromise approximately 50% of primary tumors, with gliomas and choroid plexus tumors being the next most common (6). Most intracranial tumors occur in older (> 5 years of age) adult dogs, with the median age for meningiomas, gliomas and choroid plexus tumors reported as 10-11 years, 8 years and 5-6 years respectively (3,6-8), although occasionally primary tumors, particularly gliomas, may be seen in younger dogs. Whilst no significant sex predisposition has been reported, it has been suggested that brain tumors in general are overrepresented in the larger breeds and that meningiomas are over-represented

in Golden Retrievers, Boxers and Miniature Schnauzers, gliomas are highly over-represented in the brachycephalic breeds (Boxers, Boston Terriers and Bulldogs) and choroid plexus tumors are over-represented in Golden Retrievers (3,6-8). Specific genetic factors associated with breed predisposition have not been definitively identified, but brachycephaly has been provisionally associated with the SMOC-2 and Thrombospondin-2 genes on canine chromosome 1, and a component of glioma susceptibility has been provisionally mapped to a region on canine chromosome 26 (9).

Clinical signs

Presenting clinical signs are dependent on the neuroanatomical location of the tumor, and secondary sequelae such as hydrocephalus (as a result of ventricular outflow obstruction), peritumoral edema, hemorrhage, vascular obstruction, and elevation of intracranial pressure. Elevated intracranial pressure may result in more global signs of cerebral or brainstem dysfunction, or signs secondary to herniation of CNS tissue. As such there are no neurological signs that are exclusive to tumors rather than any other neurological disease.

Since the majority of all intracranial tumors are supratentorial, affecting the forebrain (cerebrum and thalamus), the most commonly encountered clinical signs include those associated with these locations; namely, seizures, mentation changes, circling, compulsive behavior, head pressing, postural deficits, and visual deficits. Tumors affecting the infratentorial structures (cerebellum and caudal brainstem) are more likely to result in ataxia, paresis, and specific vestibular signs (*e.g.*, head tilt and nystagmus (5,6,10)). Apparent cervical pain is an additional clinical sign reported with intracranial disease that should not be overlooked (5).

Diagnosis

Definitive diagnosis of intracranial neoplasia is based on histopathological assessment of either surgical or biopsy tissue. In a minority of cases, neoplastic cells may be identified following cerebrospinal fluid (CSF) analysis, most commonly with specific neoplasms such as choroid plexus tumors, lymphoma, and histiocytic sarcoma (6,8). Various factors involved in the diagnosis and management of intracranial neoplasia are expensive, and many clinicians will provisionally diagnose specific types of intracranial neoplasia based on computed tomography (CT) or magnetic resonance imaging (MRI) characteristics, and plan treatment based on these data. It is however critical that owners are aware of the potential major

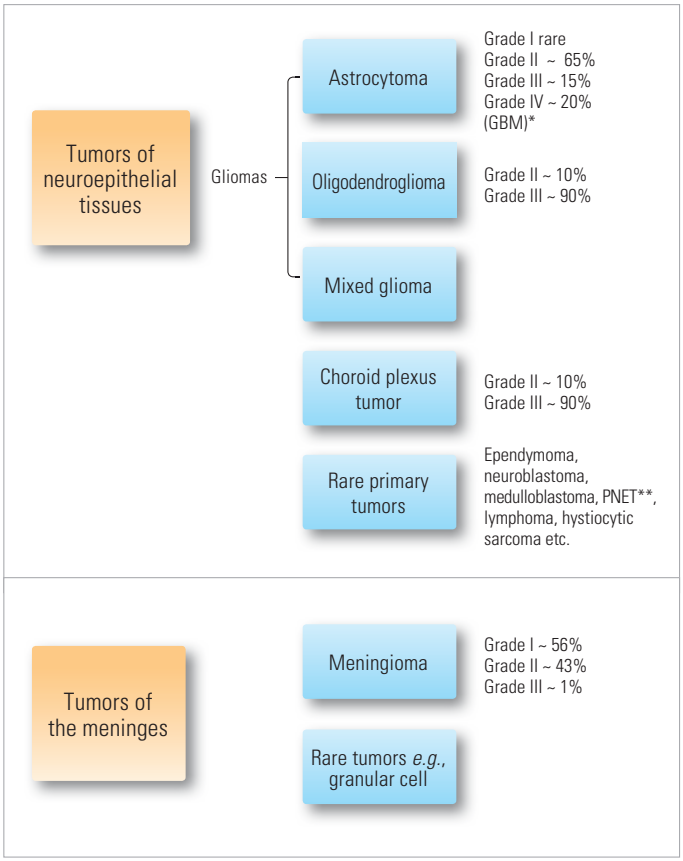

Figure 1. Classification of the major canine primary intracranial tumors. Approximate incidence of specific tumors and tumor grades are based on data from the author's institution.

* GBM = Glioblastoma multiforme

** PNET = Primitive neuroectodermal tumor

pitfalls associated with this approach. While many retrospective imaging studies have shown high degrees of sensitivity, and even specificity, in the classification of tumor types, application to individual animals in a prospective manner in the clinic is more challenging; many different tumor types, and even non-neoplastic disease processes, can have very similar imaging characteristics, and optimal therapeutic plans depend on an accurate knowledge of both the tumor type and grade ***(Figure 2)***. Informed discussions must be undertaken with owners in terms of potentially inappropriate or ineffective therapies for misdiagnosed lesions, balanced against the expense, risk and availability of procedures to obtain definitive diagnoses.

Whenever intracranial neoplasia is a major differential, based on signalment, history and neuroanatomical localization, it is essential that the diagnostic plan should involve a comprehensive minimum database, including

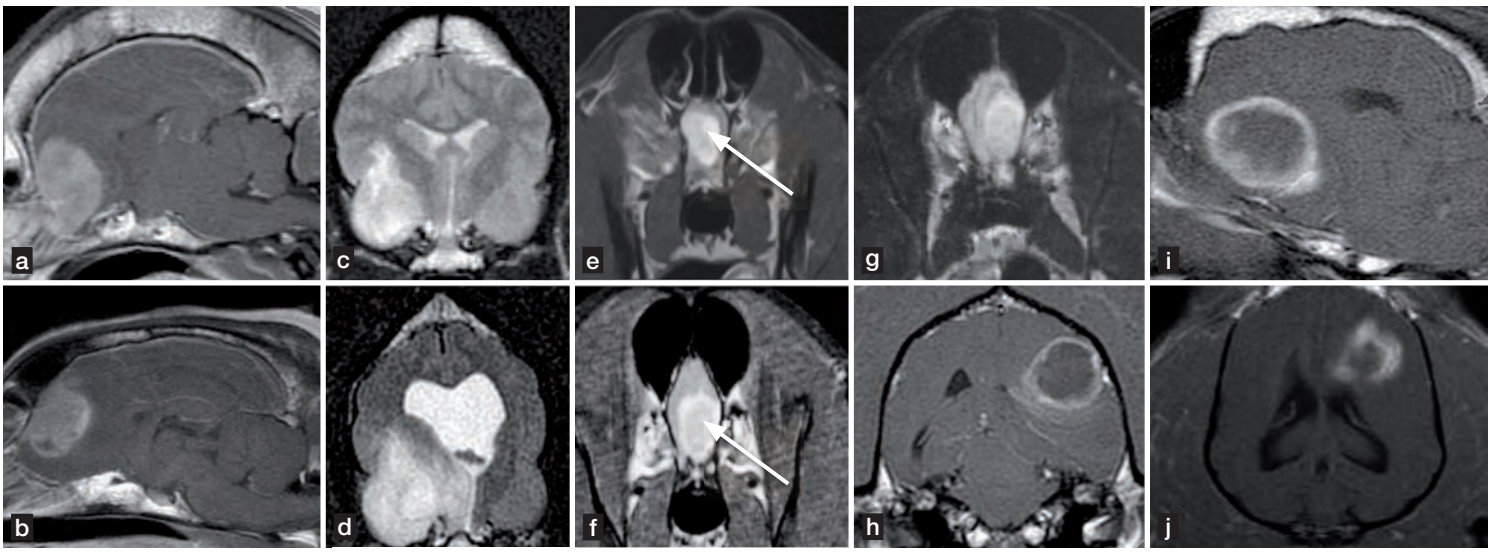

Figure 2. Limitations of diagnostic imaging. Some examples of masses of widely differing histological diagnoses but with similar typical MRI characteristics are shown.
(a,b) T1 weighted post-contrast sagittal images show uniformly contrast-enhancing extra-axial masses involving the olfactory bulb/frontal lobe. **(a)** Primary CNS histiocytic sarcoma, **(b)** grade I meningothelial meningioma. Histiocytic sarcomas carry a much poorer prognosis and, unlike meningiomas, are often poorly responsive to surgical cytoreduction and/or radiation therapy.
(c,d) T2 weighted transverse images of non-contrast enhancing intra-axial lesions involving the piriform/temporal lobes. **(c)** Focal, non-infectious inflammatory disease, **(d)** grade II astrocytoma. Temporal/piriform lobe is a predilection site for low-grade diffuse astrocytomas.
(e,f,g) T1 weighted post-contrast transverse images of strongly contrast enhancing olfactory bulb masses. **(e)** Grade I meningioma, **(f)** granuloma caused by a foreign body (plant material), **(g)** metastatic carcinoma.
(h,i,j) T1 weighted post-contrast images of intra-axial ring enhancing lesions. **(h)** Solitary metastatic hemangiosarcoma, **(i)** grade III oligodendroglioma, **(j)** non infectious focal inflammatory disease.
While imaging characteristics are practically used for presumptive diagnoses and therapeutic planning, their limitation must be recognized and discussed with owners. Therapeutic recommendations derived from studies based only on imaging diagnoses are generally of limited value.

a complete blood count, serum biochemistry, urinalysis, thoracic radiographs and abdominal ultrasound. Approximately 50% of intracranial neoplasia may be secondary, and around 25% of all dogs with primary intracranial neoplasia will have other neoplasms unrelated to the primary tumor (5,6).

Brain biopsy

Ideally all intracranial lesions should have a histological diagnosis prior to therapeutic planning, but cost, availability and potential adverse events are realistic considerations in the clinical setting. Specific indications for brain biopsy include:

- Lesions with atypical imaging characteristics.
- Lesions where the presumptive imaging diagnosis is not consistent with signalment and history.
- Lesions where major imaging differential diagnoses may be associated with markedly different prognoses or therapeutic recommendations.
- Where definitive histological and/or other molecular/genetic classification is required because of possible targeted therapies.

Stereotactically-guided brain biopsy is the preferred method, unless surgical cytoreduction of the lesion has been determined to be the primary therapeutic option based on imaging. A variety of purpose-made CT-based systems have been described (11,12), but only one commercially available MRI system is currently available (13). CT methods generally allow for quicker imaging and real-time assessment intraoperatively, while MRI systems have superior resolution of parenchymal lesions, particularly when contrast enhancement is not present. Fusion of CT and MR images provides the benefits of both modalities ***(Figure 3)***.

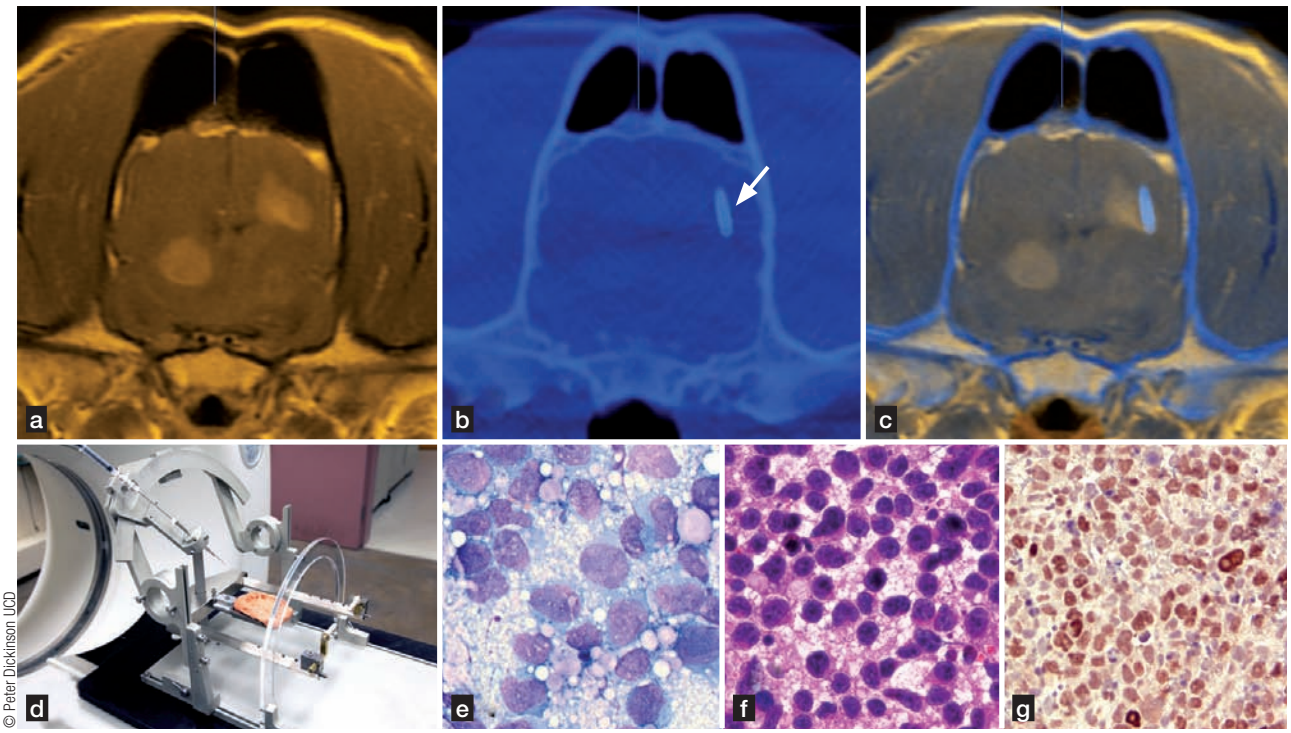

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Figure 3. Various components of stereotactic brain biopsy.
(a) An MRI T1 weighted post-contrast image showing two intra-axial contrast enhancing lesions.
(b) An intra-biopsy CT image showing the biopsy needle (arrow). Note the lesions are not apparent on this image.
(c) MRI/CT fusion images allow for accurate determination of biopsy trajectory and confirmation of needle placement in real time.
(d) Center of arc CT-based biopsy apparatus.
(e,f) Air-dried (Wright-Giemsa stain) and rapid alcohol-fixed (H&E) intra-biopsy smear preparations confirm the acquisition of pathological tissue. Air-dried smears are generally more informative with respect to cellular detail in inflammatory and infectious disease. Alcohol-fixed tissue provides additional detail of vascular and cell morphology.
(g) Paraffin-embedded tissue immunostained with CD79 antibody confirms the lesion as a primary CNS B-cell lymphoma.

Morbidity and mortality associated with biopsy are generally less than 5% at the author's institution, and diagnostic yield is greater than 90%, but many aspects can influence these parameters. Factors increasing morbidity include poor neurological status, untreated peritumoral edema, biopsy of brainstem or infratentorial structures, compromise of ventricular structures, hemorrhage, and operator inexperience. Diagnostic yield is highest for neoplastic lesions, but definitive diagnosis of infectious/inflammatory diseases can be more problematic as the biopsy tissue obtained is relatively small. Intraoperative biopsy assessment ***(Figure 3 e and f)*** greatly helps in determining if additional tissue, or repositioning, is necessary, or if other specific procedures (*e.g.*, microbial culture) are indicated. Post-procedure imaging to check for hemorrhage is important, and this is achieved rapidly and effectively with CT systems.

Treatment

Standard therapies for primary intracranial neoplasia fall into 5 broad categories:

- Palliative therapy
- Surgical cytoreduction
- Chemotherapy
- Radiation therapy
- Novel experimental therapies

Generally, evidence-based data relating to intracranial neoplasia in dogs are limited for most therapies and for many tumor types. This is a reflection of the technical challenges and expense involved, and general acceptance by veterinarians that these tumors carry a poor prognosis. Definitive diagnoses are often not available, and monitoring of progression and outcome can be challenging. However, for specific tumor types and locations,

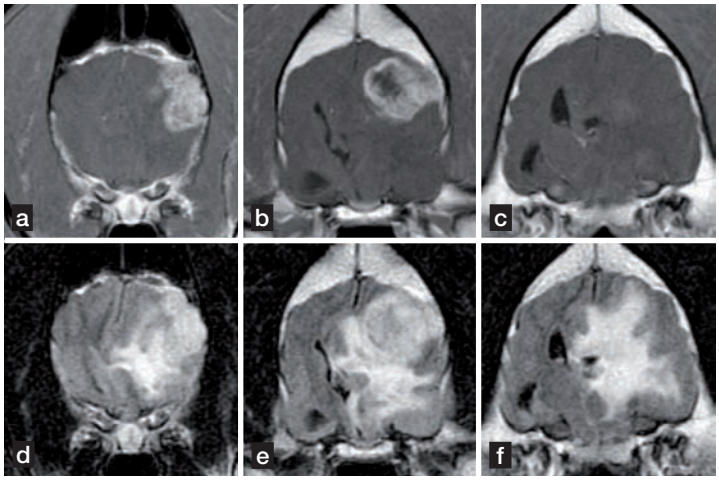


Figure 4. Peritumoral vasogenic edema. Upper row, consecutive transverse T1 weighted post-contrast MR images of a grade I frontal/parietal meningioma. Lower row, consecutive corresponding transverse FLAIR* MR images demonstrating marked hyperintensity (edema) beyond the margins of the contrast enhancing tumor. Predominantly white matter location is suggestive of vasogenic edema. Mass effect of the edema, evidenced by effacement of the lateral ventricle and deviation of the midline falx cerebri, is greater than that of the tumor itself. Dramatic improvement in clinical signs would be expected in this case following corticosteroid administration, as this typically results in resolution of the majority of vasogenic edemata.

* FLAIR = fluid-attenuated inversion recovery

prognosis can be good, particularly in the medium term, and advances in both standard and novel therapies are improving outcomes significantly.

Palliative therapy

The primary goals are to decrease effective tumor mass and to control secondary clinical signs associated with tumor location. Peritumoral and intratumoral edema secondary to release of vasoactive substances, such as vascular endothelial growth factor (VEGF), and presence of aberrant tumor vasculature can dramatically increase the effective volume of intracranial tumors, resulting in elevated intracranial pressure and potential herniation of CNS structures ***(Figure 4)***. Anti-inflammatory doses of corticosteroids can result in marked improvement in clinical signs, particularly when pronounced edema has been found on advanced imaging. Elevated intracranial pressure may also occur secondary to ventricular outflow obstruction and secondary hydrocephalus, and corticosteroids may resolve the primary obstruction and reduce CSF production. In severe cases, placement of an intraventricular shunt may temporarily resolve clinical signs or provide a therapeutic window for more definitive therapy.

Lesions involving the cerebral cortex will often result in seizures as the primary or only clinical sign and anti-epileptic drugs to control the seizures may provide prolonged periods of acceptable quality of life, particularly for slower-growing, rostrotentorial lesions (14). Few data are available describing the natural progression of specific tumor types and grades in dogs, and outcome with palliative care is often influenced by secondary issues such as seizure control and a generally negative attitude to prognosis. Median survival is generally reported to be short (1-10 weeks following presentation (14)), but for many animals with slower growing tumors, particularly those involving the cerebrum, survival times can be several months or even years.

Surgery

Most data for canine primary tumors relate to cytoreduction of meningiomas, reflecting their common occurrence and generally more superficial location. Data for intra-axial tumors such as gliomas, or for intraventricular neoplasms such as choroid plexus tumors or ependymomas, are mostly anecdotal, and appropriate "non-treated" controls are absent from most published reports; however, a survival benefit appears to be present (with or without adjunctive therapies), with some animals living for more than a year following surgery (15). Surgical cytoreduction appears to have a survival benefit for meningiomas, and this has increased over time as expertise and access to advanced surgical equipment has improved ***(Figure 5)***. Median survival with cytoreduction alone for meningiomas has been reported to be around 4.5-7 months (16), although the application of cortical resection, ultrasonic aspirators, and intraoperative endoscopic techniques has resulted in widely variable reported median survival times of 16, 41, and 70 months respectively for rostrotentorial meningiomas.

The most common secondary tumors treated by surgery are pituitary microadenomas, nasal tumors extending into the cranial vault, and calvarial neoplasms such as multilobular tumors of bone (MLTB). Specific data are often missing relating to tumors with intracranial involvement, but microsurgical hypophysectomy has been shown to have similar outcomes to medical management for pituitary tumors, although there are size limitations. At this time it is unclear whether debulking of the subset of nasal tumors with intracranial extension resulting in neurological signs will improve overall survival compared to non-surgical treatments. Surgical cytoreduction of MLTBs (which often arise from the frontal or occipital bones) may be curative

(even for very large tumors) if good surgical margins can be achieved.

Chemotherapy

Data for chemotherapeutic treatment of primary or secondary intracranial neoplasia is mostly anecdotal and poorly controlled. The most commonly used agents are those that have been shown to have superior ability to cross the blood-brain and blood-CSF barriers, and include the alkylating agents CCNU/lomustine and temozolomide, the anti-metabolic agent cytosine arabinoside, and the ribunucleotide reductase inhibitor hydroxyurea. Corticosteroids may also be considered as chemotherapeutic agents; they achieve high concentrations within the CNS and may have dramatic, if short-lived, effects in tumors of lymphoid origin ***(Figure 6)***. Response to therapy for CNS lymphoma is poorly documented and can vary from minimal response to prolonged remission of several months. Methotrexate is the cornerstone of therapy for human CNS lymphoma, but practical limitations have so far precluded its comprehensive assessment in canine patients. It is generally accepted that chemotherapy alone has limited efficacy for most primary CNS tumors, and one study involving 71 undiagnosed intracranial masses would support this assumption (17). It is however likely that, following appropriate diagnostic classification and analysis of controlled prospective studies, subsets of tumor types may be shown to be appropriate targets for selected chemotherapeutic protocols.

Radiation therapy

Although published data can be difficult to compare due to different treatment protocols and the lack of appropriate control populations, there appears to be a clear benefit from radiation therapy for many intracranial tumors; standard fractionated radiation therapy has been shown to improve survival in animals with surgically resected tumors (15,16). Although adjunctive radiation therapy has been reported to increase median survival in dogs with surgically resected meningiomas from 4.5-7 months to 16.5-30 months (16,18), as stated above, improvements in technique may result in survival times of 16-70 months with surgery alone in selected cases. In cases where good gross tumor resection is achieved, the potential benefit/cost of adjunctive radiation therapy, in typically older animals, must be balanced with likely survival times as well as potential additional surgical resection. For tumors with challenging surgical approaches (often involving the skull base, ventricles or intra-axial locations), the indications

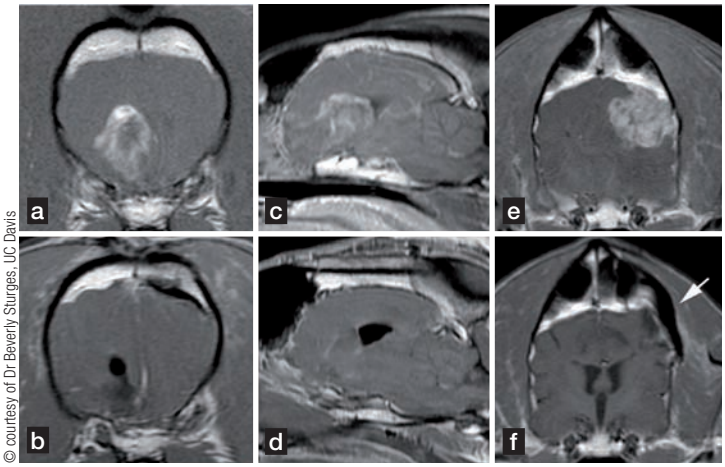
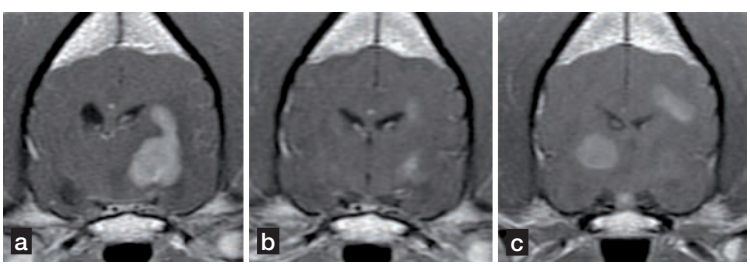


Figure 5. Surgical cytoreduction of intracranial tumors.
(a,b,c,d) Transverse and sagittal T1 weighted post-contrast MR images pre-surgery **(a,c)** and immediately post-surgery **(b,d)** following cytoreduction of a grade III oligodendroglioma via a transfrontal surgical approach. With appropriate surgical equipment and experience, gross total resection of intra-axial gliomas is feasible, and survival times of a year or longer are possible with surgery alone. Adjunctive radiation therapy is generally recommended following cytoreduction due to the invasive nature of these tumors.
(e,f) Transverse T1 weighted post-contrast MR images pre-surgery **(e)** and immediately post-surgery **(f)** following cytoreduction of a grade I transitional meningioma via a rostrotentorial craniotomy. Resected dura is replaced with temporal fascia, and the craniectomy defect is reconstructed using methyl methacrylate bone cement (arrow). Survival times of several years are possible following gross total resection of meningiomas in this location. Adjunctive radiation therapy or repeated resection are possible if tumor regrowth occurs.

Figure 6. Transverse T1 weighted post-contrast MR images of the B-cell lymphoma shown in ***Figure 3***.
(a) Pre-biopsy image.
(b) Repeated image 14 days following prednisone therapy (0.5 mg/kg BID) to resolve peri-tumoral edema prior to biopsy. Marked resolution of both the edema and the contrast enhancing lesion is seen, consistent with dramatic clinical improvement.
(c) Recheck image taken 37 days after corticosteroid initiation, following clinical deterioration, demonstrates additional new lesions, subsequently biopsied and diagnosed as primary CNS B-cell lymphoma. The potential short-term efficacy of corticosteroids with CNS lymphoma is apparent.



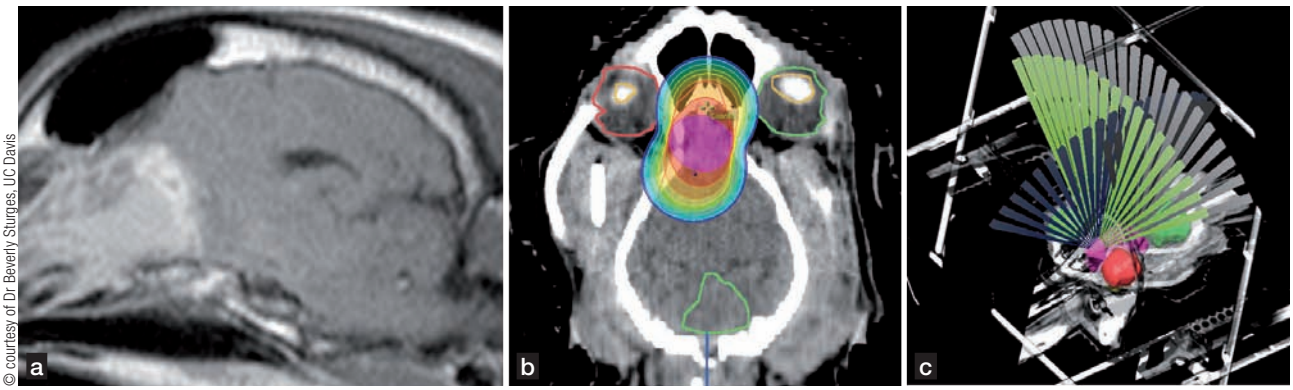


Figure 7. Stereotactic radiotherapy (SRT).
(a) Sagittal T1 weighted post-contrast MR image of an olfactory/frontal lobe mass.
(b,c) SRT planning to deliver a high dose (15 Gy) single treatment to the lesion (as shown by the magenta coloration) using multiple arcs, while minimizing exposure to critical structures such as the eyes (red, green).

for radiation are more logically apparent, although specific data are limited. Reported median survival times, for a variety of protocols and involving a majority of non-diagnosed tumors, are ~33-99 weeks for all masses, ~40 weeks for intra-axial masses, and ~40-49 weeks for extra-axial masses (15,16).

A major development in radiation therapy is the emergence of more precise protocols involving either intensity-modulated radiation therapy utilizing multileaf collimation, or stereotactic radiotherapy (SRT). This latter method delivers radiation to defined tumor volumes utilizing MRI and CT forward-based planning ***(Figure 7)*** and thus spares surrounding brain tissue, allowing total radiation doses to be delivered in ~1-5 treatments (compared to 15-20 treatments commonly used with standard fractionated protocols) with significant practical implications for patients undergoing multiple anesthetic episodes. The size of SRT-treatable lesions is limited compared to standard protocols, and it is generally inappropriate for treatment of post-surgical residual disease. Outcome data are currently limited but encouraging, suggesting that similar outcomes to standard protocols may be possible for non-surgically resectable tumors (19).

Single treatments with high radiation dose fractions (~15 Gy) are referred to as stereotactic radiosurgery (SRS). Although there are obvious advantages to single treatments, it is likely that future protocols may be based around the summated advantages of highly conformal stereotactic delivery combined with a more limited fractionated approach than standard protocols. Fractionated SRT protocols for CNS tissues generally involve two or three 7-8 Gy fractions, compared to standard fractionated protocols of perhaps fifteen 2-2.5 Gy fractions.

Experimental/novel therapies

Advances in the management of intracranial neoplasia in dogs has occurred on many fronts; improved accessibility to, and application of, advanced diagnostic imaging, and surgical and radiation therapy procedures that are standard of care in human neuro-oncology has had a significant impact. Advanced imaging techniques provide not only improved presumptive diagnostic capabilities, but also information such as functional and vascular characteristics of tumors that may be utilized for surgical planning and therapeutic monitoring. Surgical ultrasonic aspirators (20), and availability of intra-operative neuronavigational capabilities ***(Figure 8)*** promises to advance surgical management of more challenging intra-axial tumors (12). Additionally, novel surgical techniques such as intratumoral irreversible electroporation (21) and automated tissue excision systems are in canine clinical trials.

Canine primary intracranial neoplasia has been recognized for many years as a potentially valuable model for translational therapeutic development. This has been particularly true for the development of targeted approaches to intracranial tumors. Such approaches may involve gross targeting of tumors with techniques bypassing the blood-brain barrier, targeting of aberrant molecular pathways, targeting of toxin/suicide therapies to tumor cells, and immune-based therapies targeting tumor antigens. The use of advanced techniques to deliver specific therapies (including liposomal chemotherapy, viral suicide gene therapy, and targeted nanoparticles (22))

directly to tumors have shown efficacy in selected cases ***(Figure 9)***.

Other than dramatic reductions in human cancers due to improved screening and reduction of environmental factors such as smoking, some of the most dramatic successes in human oncology have been with agents targeting aberrant pathways such as Her2/Neu overexpressing breast cancers, and BCR-ABL positive chronic myelogenous leukemia. A major effort is underway to define chromosomal, molecular genetic and epigenetic abnormalities in canine intracranial tumors to determine appropriate tumor candidates for currently available targeted therapies as well as for development of novel targeted approaches. Two small-molecule tyrosine kinase receptor (TKR) inhibitors (toceranib phosphate and masitinib) are approved in some countries for veterinary use, and several others may enter veterinary trials in the near future for tumors with defined TKR pathways abnormalities. Similarly, clinical trials utilizing defined tumor-specific surface markers such as IL-13 receptor alpha and EGFR are in progress (23).

Immune-based therapies have shown great potential for some human tumor types, and a variety of approaches are being explored in canine intracranial tumors. These include gene therapy involving delivery of immunostimulatory genes encoding for cytokines such as IL-2, 4 and 12, TNF alpha, interferon, and dendritic cell growth factors such as Flt3L, as well as dendritic cell vaccination strategies. The feasibility of these approaches has been demonstrated in canine glioma and meningiomas (24), and preliminary results are encouraging for development of this field.

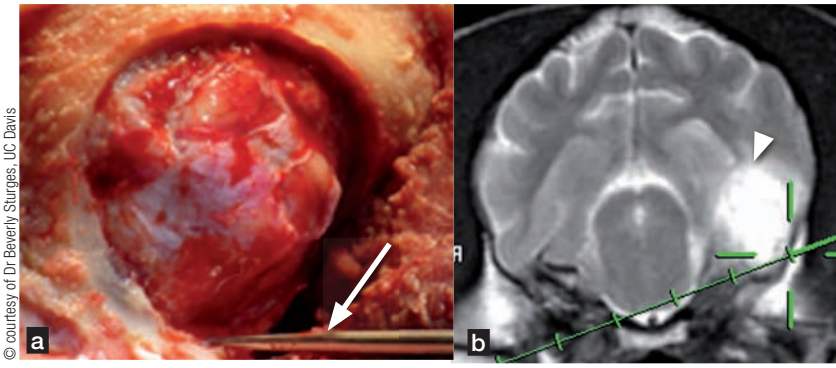
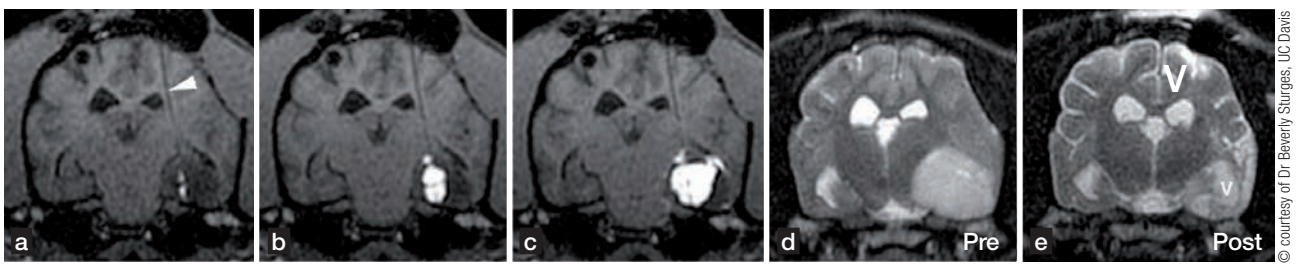


Figure 8. Increased availability of equipment such as stereotactic neuronavigational apparatus has allowed easier identification of tumor tissue during surgery. Here a rostrotentorial craniotomy is being undertaken to remove an anaplastic temporal lobe oligodendroglioma; co-registration of MR/CT images using a commercial camera system allows concurrent assessment of the surgical instruments intra-operatively. The intraoperative image **(a)** shows a surgical pointer (arrow) at the ventral extent of the craniotomy. Position of the tip of the pointer can be seen in real-time on the T2-weighted MR image **(b)** represented by a green crosshair. In this case the surgeon can determine that the craniotomy is positioned adequately to approach the tumor (arrowhead) that is not apparent prior to incision of the meninges and brain parenchyma.

Future advances

Application of proven advanced techniques and therapies from the neuro-oncology field in humans, together with a "one-medicine" translational research focus, promises to allow continued improvement in the treatment of canine intracranial tumors. While it is less likely that major advances, as seen in human oncology, will be made via screening and elimination of environmental factors, the potential for reducing tumor incidence of breed-associated tumors is significant,

Figure 9. Novel delivery methods such as convection enhanced delivery (CED) allow for direct infusion of therapeutic agents (in this case liposomal CPT-11) directly into tumor tissue, maximizing dose while minimizing systemic toxicity. Concurrent infusion of gadolinium tracers allows for real-time assessment of infusions to ensure appropriate delivery. Sequential T1 weighted transverse images **(a-c)** are shown for infusion of CPT-11 via a MRI-compatible catheter into an anaplastic (grade III) astrocytoma over ~1.5 hours. The catheter is apparent as a dark line (indicated by a white arrowhead in image **(a)**). Pre- and 6-week post-infusion transverse T2 weighted MR images **(d,e)** show marked reduction in tumor volume, with reduced mass effect and reappearance of the previously effaced lateral ventricle (V).



as susceptibility and oncogenic gene associations are elucidated. Continued molecular/genetic classification of canine tumors will be essential to allow appropriate development of targeted therapies, and whilst there will always be practical limitations linked to the diagnostic and therapeutic costs intrinsic to neuro-oncology, a concerted effort is necessary to promote a better understanding of the natural biology of these tumors and to develop histologically-based prospective therapeutic trials which are standard practice for other areas of veterinary oncology.

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HOW I APPROACH...

The circling cat

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KEY POINTS

- **Circling can be defined as a change in gait whereby the patient, incapable of moving in a straight line, follows a circular pathway.**
- **Circling is a very significant clinical sign for localizing a neurological lesion, as it specifically suggests the involvement of the anterior encephalon (forebrain).**
- **Neurolocalization is a basic but essential step in the approach to the neurological patient, as it allows the clinician to formulate a list of differential diagnoses based on the neuroanatomical area involved.**
- **In feline medicine, a neurological examination is often limited to a few hands-on tests; the patient's compliance can be affected by its temperament and other factors such as pain or stress.**

Introduction

The purpose of a neurological examination in veterinary medicine is to provide an answer to four specific questions:

- Does the patient have a neurological problem?
- Where is it?
- What are the differential diagnoses?
- What diagnostic tests must be performed to confirm my suspicions?

The first objective of the examination is to establish whether or not we are dealing with a disorder that is neurological in nature. Once this has been established, the second step is to identify the neuroanatomical area involved in the pathological process, based on the clinical signs present; this important assessment is referred to as neurolocalization (1).

Pathology

A neurological problem can result in pathology that involves the CNS (the central nervous system that consists of the brain and spinal cord), and/or the PNS (the peripheral nervous system which consists of the musculature and nerves). The CNS in turn may be subdivided into:

- The brain, which can be subdivided into anterior and posterior encephalon.
- The spinal cord, subdivided into segments; cervical (C1-C5), cervical-thoracic (C6-T2), thoraco-lumbar (T3-L3) and lumbo-sacral (L3-S3) (2).

Neurolocalization is a basic but important step in the approach to the neurological patient. It allows the clinician to formulate a series of differential diagnoses based on the relevant neuroanatomical area, the clinical signs and their progression (if any). Certain neurological pathologies can, however, affect two or more segments at the same time, and these are known as multifocal syndromes. To conduct neurolocalization correctly, we need to evaluate the clinical signs as a whole, and in particular assess the patient's sensory condition, gait, cranial nerves, postural reactions and spinal reflexes. Despite being carried out on a routine basis, some aspects of the clinical examination can be difficult to interpret, which may mask difficult or duplicitous diagnoses. Furthermore, and especially with feline medicine, animals are often not very cooperative, and the neurological examination can be limited by what the patient will allow; this in turn can be influenced by its temperament, as well as other factors such as pain or stress. Even so, neurolocalization represents a concept of such importance that it would require a more in-depth analysis beyond the scope of this paper; here we concentrate on the phenomenon of circling and the preferred approach to a cat that presents with this clinical sign, with a view to helping the clinician reach a diagnosis when presented with such a case.

Circling may be defined as a change in the gait, whereby an animal appears incapable of moving in a straight line but rather follows a circular trajectory, generally with a wide radius.This pathological condition may be accompanied by other neurological symptoms such as head pressing, seen typically when a patient, confronted by an obstacle, stops and presses its head against it (rather than going around it) until the obstacle is removed, leaving the way clear for it to continue. Note that this behavior is seen more frequently in dogs and is difficult to recognize in cats. Circling is a very significant clinical sign for neurolocalization of a lesion, as it specifically suggests the involvement of the anterior encephalon (forebrain), *i.e.*, anything located rostral to the tentorium: the cerebral hemispheres and the diencephalon. In particular, the caudate nucleus, which is involved in controlling voluntary movements, is often implicated in an animal that is circling. However, neurolocalization is not simply anatomical, but also functional; in fact, and especially with cats, if it is difficult to identify that a specific anatomical structure in the forebrain is involved, it is preferable to interpret the clinical signs from a neuro-functional perspective. Note that circling is a very useful sign for neurolocalization, as it is frequently ipsilateral to the lesion. Although if found to be associated with a contralateral lesion, the clinician must interpret the clinical presentation as a whole rather than focus on the individual signs.

In addition to the circling and head pressing already described, other clinical signs that are typically attributable to forebrain involvement include (in the most frequent order of occurence):

- Defects in the patient's vision; such defects can be difficult to recognize as they can vary from impaired sight to total blindness, but if a visual defect is noted, it is essential to firstly exclude the presence of any primary ocular pathology.

- Changes in mentation; unlike the situation in humans, these changes are often secondary to diffuse pathological changes within the forebrain. These changes may have an acute presentation, or can sometimes manifest in an insidious, gradual manner that is not easy to recognize. The most commonly described behaviors include apathy, sensory depression, and stupor through to a comatose state.

- Other signs that refer to the forebrain are epileptic seizures, tremors at rest, and alteration in postural reflexes, especially with the limbs contralateral to the lesion.

Unlike the situation in humans, it is obviously impossible to recognize functional alterations associated with changes in the cerebral cortex, such as difficulties with language, hearing, writing and thinking, which can assist a human physician with neurolocalization.

Diagnostic testing and differential diagnosis

When presented with a circling cat, it is essential to identify the underlying pathology by following the correct diagnostic process. The first step is to exclude secondary pathologies related to other organs by carrying out diagnostics such as hematology and biochemistry tests, thoracic radiography, and possibly abdominal ultrasound and cardiology assessment. It may then be necessary to undertake appropriate specific examinations under

general anesthetic such as magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) sampling and examination, and to perform an electroencephalogram (EEG).

For the neurological patient, the underlying etiologies may be divided into the following categories:
- **V**ascular
- **I**nfective-inflammatory
- **T**raumatic
- **A**nomalies
- **M**etabolic
- **I**diopathic
- **N**eoplastic
- **D**egenerative

The acronym VITAMIND can assist when considering possible differential diagnoses. The main pathologies that can involve the forebrain in cats are summarized below; where appropriate, reference is made to specific texts for further information.

Vascular pathologies

More advanced diagnostic methodologies, and especially MRI, have made it possible to diagnose cerebral vascular pathologies that were simply not recognized until just a few years ago (3). These pathologies may be secondary to ischemia, infarction or hemorrhage.

An ischemic event may be either focal or diffuse in nature. Focal cerebral ischemia is secondary to narrowing or obstruction of an artery and consequent hypoperfusion of the tissue that it supplies, and a focal ischemic event may be recognized by carrying out appropriate sequencing during MRI examination to identify the site of the lesion. A diffuse cerebral ischemia, on the other hand, can be secondary to generalized hypoperfusion, and may be more difficult to recognize; as there is no typical pathognomonic appearance on MRI, a more indirect clinical assessment may be required for diagnosis. Whilst outwith the scope of this paper, ischemic neuromyopathies in cats secondary to peripheral vascular obstruction (*e.g.*, with iliac vein thrombosis) should not be forgotten; the reader is directed to appropriate texts for more information on this subject.

Infective-inflammatory pathologies

CNS inflammation in cats, and in particular inflammation of the brain, can be secondary to various etiological agents of viral, protozoan, bacterial and prionic origin (4). Multifocal neurolocalization is often noted with these pathologies as there is involvement of multiple encephalic regions, and the clinical signs may relate to both anterior and posterior encephalon dysfunction. However, granulomatous-type focal lesions can result in more specific clinical signs.

The main infective viral agents in cats with CNS signs are infectious peritonitis virus (FIP or FeCoV), feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV). Various other viral agents may also cause neurological signs, but these are often not identified on diagnostic testing and may only become apparent on autopsy examination (5,6).

The main protozoal agent is *Toxoplasma gondii,* but note that this is often over-diagnosed, as the veterinarian often relies only on blood samples without conducting other diagnostic tests and in the absence of any clinical correlation.

Pathologies from a bacterial origin are, on the other hand, often underestimated and sometimes underdiagnosed; nevertheless, several reports have described clinical cases in which infections result in the formation of abscesses within the brain, for example due to direct post-traumatic contamination or from a bite (7). There are also reports of encephalitic meningitis from an otogenic origin, extending from bacterial infections affecting the middle and inner ear (8).

Trauma

Cranial trauma is not uncommon in pets, especially in cats with access to the outside environment. There are many possible causes including car accidents, falls, bites, penetrating kicks and wounds. A tentative diagnosis may be reached based on the medical history (and possibly by recognizing external wounds to the cranium) and confirmed with more in-depth testing. Note that in acute cases computerized tomography (CT) may be preferable to MRI, as CT allows for early recognition of fractures of the cranium and hemorrhage, and also requires a shorter time frame and anesthetic duration compared to MRI ***(Figures 1 and 2)***. Nonetheless, although diagnostic investigations have a fundamental role in cranial trauma, it is essential to remember the importance of managing the cranial trauma patient properly, so that any secondary damage is reduced to a minimum or avoided altogether; this is of course also pertinent to any spinal trauma that is present. Unless correctly treated at an early stage, secondary damage may lead to a cascade of events that can worsen clinical signs and result in a poor prognosis. Specifically, keeping intra-cranial pressure under control

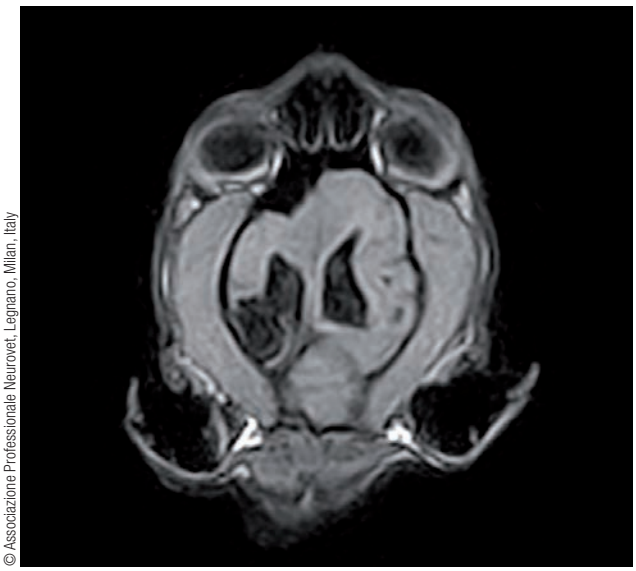


Figure 1. T3D T1 weighted image, dorsal plane of the forebrain of a 9-month old male cat with a history of cranial trauma. There were multiple fractures to the right aspect of the skull (frontal, temporal and parietal bones) and there is obvious loss of symmetry in the underlying structures. The trauma had caused a full thickness defect within the brain at the level of the right occipital-temporal lobe, allowing direct communication between the sub-arachnoid space and the lateral ventricle (so-called post-traumatic secondary porencephaly).

is of vital importance, as is guaranteeing adequate cerebral perfusion. Given the complexity of this subject, the reader is referred to specific texts for further information (9-11).

Anomalies

This large category includes pathologies relating to growth deformities or disorders with a congenital or hereditary basis. The main deformities affecting the encephalon (other than malformation of specific areas within the brain) relate to the ventricular system. Hydrocephalus (dilatation of the ventricles) can cause signs attributable to the forebrain, and the signs can be variable and fluctuating in nature depending on whether the hydrocephalus is primary in nature or results from an underlying secondary cause; this in turn determines the clinical approach and prognostic implications. In particular, occlusions in the ventricles due to inflammatory, neoplastic or deformative pathologies can form the basis of so-called hypertensive hydrocephalus, and (contrary to popular belief) this can be progressive in nature.

Metabolic disorders

Metabolic disorders in small animals, and especially in cats, are an important section of CNS pathologies, and include a multitude of conditions that can be secondary to electrolyte disorders, endocrine disorders or organ failure. These disorders may present with a wide variety of symptoms which can include circling. Here the pathologies of most interest (and those that are probably most common in clinical practice) are hepatic encephalopathy (HE) and uremic encephalopathy (UE). Hyperthyroidism should also be considered in a feline patient that circles. Hepatic dysfunction and changes in the urea cycle can cause HE because various endogenous toxins such as ammonia, amino acids (tyrosine, tryptophane), short-chain fatty acids, mercaptans and various biogenic amines can accumulate in the CNS and cause cerebral dysfunction, mainly by their effect on the glial astrocyte cells which have a specific pathogenic role (12). Metabolic disorders can also be associated with changes in the body's osmolarity, leading to a sudden secondary increase in intra-cranial pressure and rapid clinical deterioration.

A similar pathway exists in a uremic animal, whereby various factors – including increased levels of calcium in the cerebral parenchyma, increased levels of parathyroid hormone, cerebral hypoxia and changes in electrolytes, osmolarity and the acid-base balance – play a significant pathogenic role in the development of neurological signs. Hyperthyroidism in cats can manifest with different neurological signs, including anteropulsion (falling forwards when walking), circling and seizures (13).

A group of metabolic disorders, known as organic aciduria, that can cause encephalopathy has been recently described in cats (12). These disorders can be secondary to various pathological conditions, but the signs can be attributed specifically to changes in the metabolism of B group vitamins which have various important roles, especially in the Krebs cycle. Given that metabolic pathologies often present non-specific and unexpected symptoms, especially in feline medicine, we suggest that an extensive biochemical profile should be performed whenever presented with a circling cat to allow as much diagnostic information as possible to be obtained.

Idiopathic pathologies

Recent progress in diagnostic methods, and more especially MRI, has significantly reduced the percentage of pathologies with an unknown etiology, making it possible to improve the prognosis for patients. Despite this, in feline medicine – and specifically in the field of neurology – there are still various pathological conditions that have no adequate etiopathogenetic explanation.

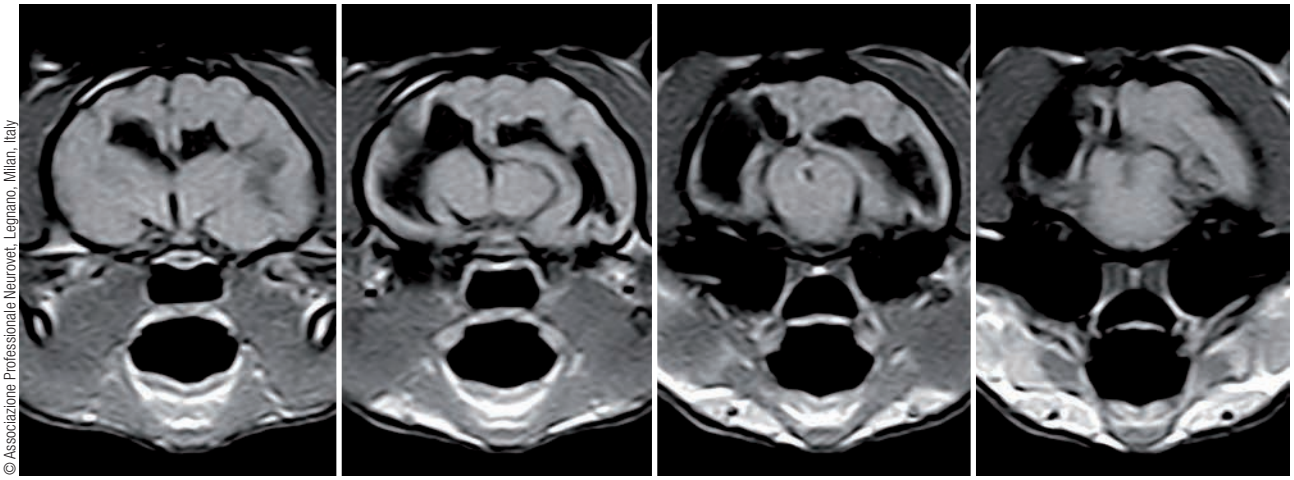


Figure 2. T3D T1 weighted image, transverse plane (4 consecutive slices) of the same patient in ***Figure 1***. There is loss of neural tissue, and the confluence between the ventricular space and sub-arachnoid space in the temporal-occipital region is obvious.

Included among these that involve the forebrain in the cat are primary epilepsy and necrosis of the hippocampus (14,15). Nonetheless, it would be unusual for these pathologies to cause clinical signs such as circling, and they are more likely to cause epileptic episodes (seizures). In our clinical practice, we have the option to perform an EEG ***(Figure 3)*** in patients that show neurological signs but have no obvious diagnosis. This technique has been employed for some time in human medicine but is still rarely employed in feline medicine, partly because it presents some difficulties in its execution and interpretation; it can however be used to supplement investigations to characterize disorders in the forebrain.

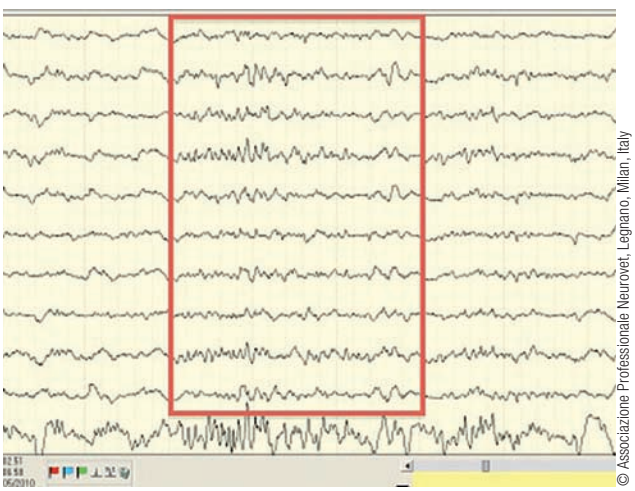
Neoplastic pathologies

Neoplasias affecting the CNS represent an important differential diagnosis in pathologies with cerebral involvement (16). Progress in diagnostics and the improved average life expectancy in our patients has increased the frequency of reports and papers published. Tumors may be classified as primary (originating directly within the CNS) or secondary (neoplasias that originate elsewhere and subsequently metastasize to the CNS). From a diagnostic perspective, they can also be classified as extra-axial (originating from the structures external to the cerebral parenchyma – ***Figures 4 and 5***) or intra-axial (originating inside the cerebral parenchyma) in their localization ***(Figure 6)***. Typical extra-axial tumors would include neoplasias that affect the cranium (*e.g.*, osteogenic sarcoma), tumors that arise within the nasal cavity (*e.g.*, carcinoma or neuro-blastoma), or tumors that originate from the meninges (*e.g.*, meningioma). The most frequent intra-axial neoplasia is lymphoma (which may be linked to FeLV); other intra-axial neoplasias include astrocytoma and oligodendroglioma (17). The classification can also help with the prognosis – for example, many meningiomas may be removed surgically and can carry a good prognosis.

Degenerative pathologies

The classification of degenerative pathologies is not always easy, and the same may be said about diagnosing degenerative pathologies. These often appear to be hereditary and relate to specific families and breeds. Given these characteristics, they often affect younger patients (possibly under one year of age), and the signs

Figure 3. An EEG trace from a patient who had developed seizures. Continual paroxysmal activity is seen as a series of spikes and spike-and-wave patterns spread over both cerebral hemispheres.



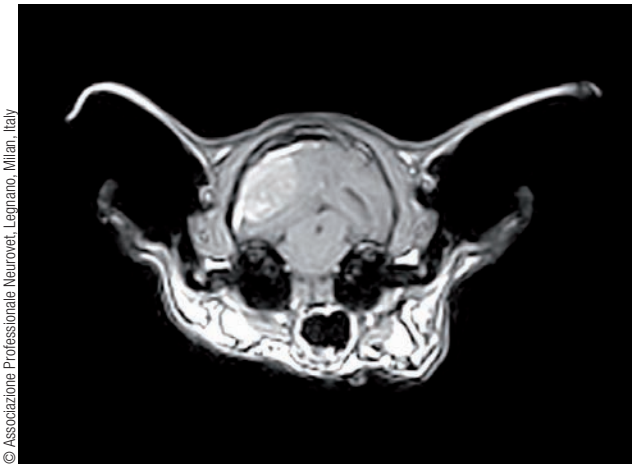


Figure 4. T3D T1 weighted image, transverse plane in a 13-year-old male cat. An extra-axial tumor can be seen in the right temporal-occipital region as an oval shaped lesion that contrasts markedly with the surrounding tissue; there is extensive involvement of the meninges (the so-called "dural tail" sign). Above the lesion there is marked thickening of the cranial bone; the falx cerebri is displaced to the left and the right lateral ventricle is compressed.

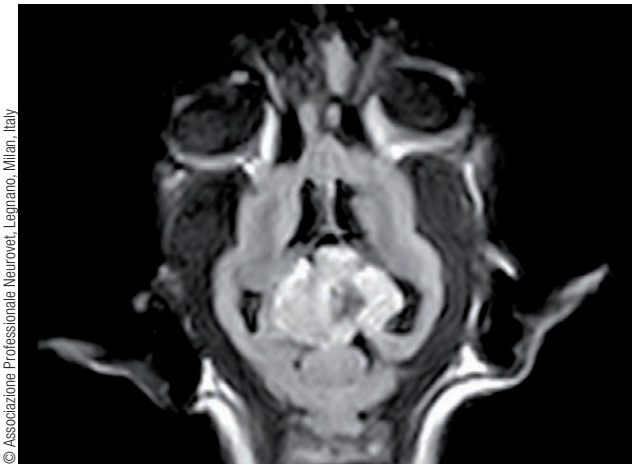
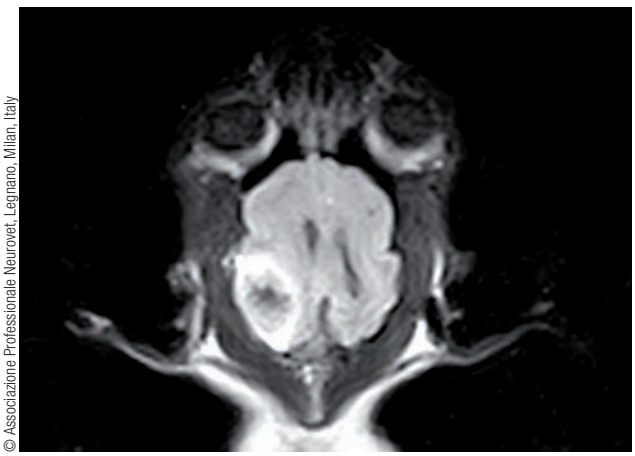


Figure 6. HR-FLAIR image, dorsal plane of the forebrain of a 5-year-old male cat. A tumor is evident at the level of the thalamic region, characterized by heterogeneous contrast capture, with invasion of the lateral ventricle. Note the accumulation of fluid in the left nasal cavity close to the ethmoid cribriform lamina.

rarely respond to any medical treatment. More recently, various pathologies have been described that are attributable to cumulative enzyme disorders (storage diseases); neurolocalization in these cases often suggests involvement of specific areas within the brain.

The main intra-cranial degenerative pathologies can be very selective and specifically affect the white or gray matter in the forebrain or the cerebellum. This however does not make it possible to identify specific clinical signs, but a thorough neurological examination can nonetheless assist in localizing the main neuroanatomic structures involved. Circling may be the only sign that can be found in these patients. The variability and sporadic nature of these pathologies mean that further information is outwith the scope of this paper, and the clinician is directed to more specific texts. A tentative diagnosis may be reached by taking into consideration all aspects, including the medical history, clinical examination, laboratory tests, MRI results, and CSF examination. To date, the prognosis for these patients is unfortunately usually poor, and because the diagnosis remains suspect for the great majority of these cases, except in rare situations, a necroscopic examination may be the only method that allows a definitive diagnosis.

Figure 5. T3D T1 weighted image, dorsal plane of the same patient. The tumor has a marked heterogeneous appearance, with mainly peripheral enhancement and a non-absorbent core. Histopathology examination after surgical excision demonstrated a transitional meningioma.



Conclusion

So, back to the original question: how should we approach circling in cats? As one would simply approach any pathology with cerebral involvement, circling is neither a specific or a pathognomic symptom, nor is it prognostic; it is merely indicative for localizing a disorder that involves the forebrain. It is therefore advisable, after careful clinical assessment, to offer an adequate diagnostic work-up that will firstly require conducting a series of basic evaluations (blood and urine analysis,

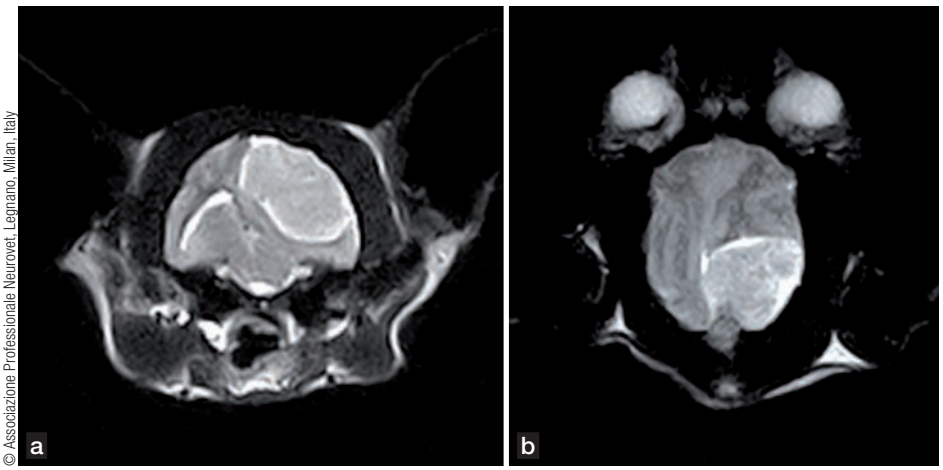


Figure 7. MRI is invaluable when dealing with a circling cat. It not only assists with diagnosis and prognosis, it allows consideration of the best treatment options. Here T2 weighted sequence transverse plane **(a)** and dorsal plane **(b)** images demonstrate an extra-axial hyperintensive tumor with well-defined margins; there is compression of the cerebral parenchyma with a marked mass effect (the secondary pathological effects caused by the tumor compressing or displacing surrounding tissues).

radiography of the chest and abdomen, and possible benchtop serological tests for the main and most probable infective pathologies, such as FIV and FeLV). At this point it is appropriate to propose a full clinical neurological examination, and possibly more in-depth diagnostics under general anesthetic, such as MRI and the CSF tests, in order to establish the best recommended treatment and assist with the prognosis ***(Figure 7)***.

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Vestibular syndrome in dogs

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Introduction

Failures of the vestibular system are among the more frequent neurological presentations in small animal practice. They can be regarded as clinically rewarding in that the neurological loss of function produces classical clinical signs, and initial recognition of most vestibular disorders usually poses no great difficulty. The next, perhaps more important, step is precise localization of the disease within the vestibular system; assessing the lesion as either peripheral (in the inner ear) or central (in the brain) may be a challenge. However, precise localization is essential, as this affects all subsequent decisions regarding diagnosis, prognosis and therapy, and the key question with "vestibular neurology" is therefore always: ear or brain? The answer is of fundamental importance for the patient, and this article aims to enable the reader to recognize vestibular disease, to distinguish between peripheral and central syndromes in a clinical setting, and to consider differential diagnoses for disorders of the peripheral vestibular system. Central vestibular disease will not be discussed in depth, as once this disorder has been recognized it is usually necessary to transfer the patient to a specialist center for MRI imaging and cerebrospinal fluid analysis.

KEY POINTS

- **Typical signs of a vestibular system disorder are generalized ataxia, nystagmus, head tilt and walking in circles.**
- **The clinician must determine if the peripheral (ear) or central (brain) section of the vestibular system is involved, as this is essential for all further diagnostic and therapeutic decisions.**
- **A combination of vestibular symptoms and unilateral facial nerve paralysis and/or Horner's syndrome without other neurological deficits invariably indicates middle or inner ear disease.**
- **Vertical nystagmus almost invariably indicates a central vestibular disorder.**
- **Peripheral vestibular disease may be diagnosed and treated by the general practitioner. Patients only require referral to a specialist for further diagnostic imaging when initial therapy fails.**

Structure and function

The vestibular system is made up of peripheral and central parts. The peripheral section consists of a receptor organ in the inner ear and the vestibular nerve. The central section, which processes information from the inner ear, is formed by the vestibular nuclei in the brainstem and certain regions within the cerebellum (the flocculonodular lobe and fastigial nucleus). Part of the cerebellum (the vestibulocerebellum) tends to have an inhibitory influence on the vestibular system, an important point when considering the pathological changes involved in vestibular disease.

These areas of the brain are linked through different pathways to their effector organs, the extraocular eye muscles and the musculature of the neck and limbs, allowing the vestibular system to fulfill the following functions:

- To respond to the effects of gravity
- To maintain balance during movement or weight transfer
- To co-ordinate head and eye movements

Two scenarios allow consideration of vestibular system physiology and facilitate understanding of the pathophysiological process:

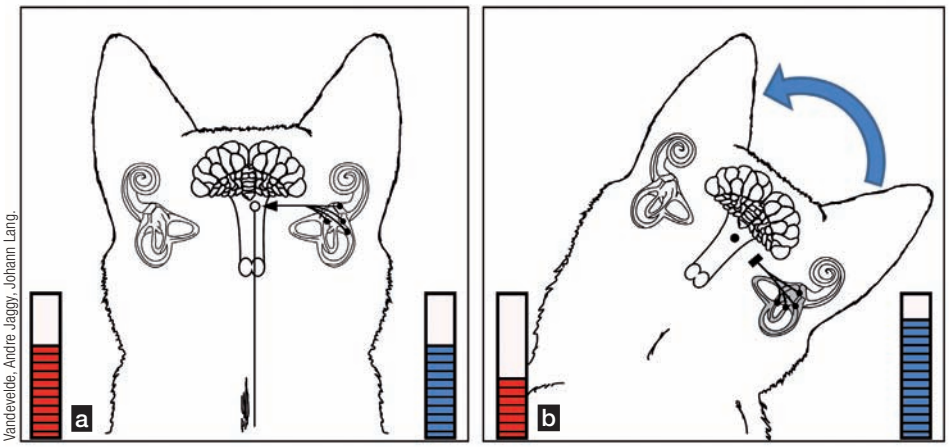

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Figure 1. Schematic diagram of the vestibular system's reaction to altered head position in a normal animal. **(a)** The vestibular system receives equal input from both inner ears when the head is upright. **(b)** When the animal tilts its head, the vestibular system receives relatively more input from the dependant side. The brain perceives this and responds by lifting the head accordingly.

- Maintenance of balance: the left and right vestibular systems continually send impulses to the brain. If the animal is in a level, upright position, then the impulse frequency from both sides is equal. However, if the head (or entire body) is tilted to one side, then the impulse frequency from the dependent side increases, so that the brain now receives more input from this side. Based on the difference in inputs, the brain recognizes the tilt and responds by straightening the body, *i.e.,* towards the side with less input ***(Figure 1)***.

- Co-ordination of head and eye movement: co-ordinated extraocular eye muscle movements are necessary to ensure that an animal perceives its surroundings in sharp detail during head movements. If the eyes were to follow every head movement, the brain would be incapable of processing the enormous number of images generated, and a blurred visual picture (similar to that seen from the window of a moving train) would result. The body's solution for this problem is as follows: if the head moves to one side, the eyes do not immediately move with the head but rather briefly fix on an image which is "recorded" and processed, before the eyes make a quick movement to "catch up" with the head. This is repeated as necessary – the eyes frequently stopping to take single "pictures" before moving to follow the head. In this way "single impressions" are formed which can be processed by the brain. These discrete, jerky eye movements are known as physiological nystagmus, and can be tested for by moving the patient's head while the animal is stationary; smaller animals can be picked up and turned rapidly left and right in front of the examiner in order to observe the response. The question is therefore; how does the brain know that the animal has moved its head to one side? The principle of input difference from left and right inner ears also applies here. If the animal shifts its head to the left, the left inner ear is stimulated and the impulse frequency increases in comparison to the right side. This allows the brain to recognize that the head is moving to the left, and it initiates the rhythmic eye movement in the direction of the head movement, with the fast-jerk phase towards the side with the higher input and away from the side with the lower input.

Failure of the vestibular system

Clinical symptoms of a lesion in the vestibular system, regardless of whether it is peripheral or central in origin, are as follows:

- Generalized ataxia
- Nystagmus
- Head tilt
- Circling
- Falling to one side +/- rolling

Vestibular ataxia is, in contrast to ataxia caused by spinal disease, characterized by a wide-based stance. This ataxia is often accentuated on one side, whereby the animal may lunge sideways in order to steady itself. Occasionally, the ataxia becomes so pronounced that the animal is incapable of walking and falls sideways when trying to take a step; in extreme cases it may even roll over onto the floor. As most vestibular losses of function are unilateral, the animal often walks in tight circles. In addition, the animal presents with a head tilt, with the affected side lower than the healthy one. The obvious symptoms of loss of function are merely physiological reactions from pathological input into the brain. As noted above, a reduced input from one side is interpreted by the brain as a shift in the body's weight to the side with more input and it corrects this shift, so that the head tilts to the side with less input in order to re-establish balance. In pathological cases this means the head is tilted

erroneously towards the diseased side, because this is delivering less input to the brain ***(Figure 2)***.

Another major sign of all vestibular disorders is pathological nystagmus; this can be observed with the patient stationary and the head immobile. Nystagmus by definition is an involuntary rhythmic movement of the eyeballs with slow and fast phases, and is classified by the direction of the fast phase. The slow phase is generally towards the "pathological" incident, while the fast phase represents the corrective re-compensation. Nystagmus is also classified according to the direction of eye movement (horizontal, rotatory or vertical), so if a dog demonstrates fast eye movement to the left, this is known as left horizontal nystagmus.

Horizontal nystagmus can be explained similarly to head tilting and is also the brain's "normal" reaction to faulty input. The lack of input from the vestibular system on one side leads to a relatively increased input from the healthy side; this is interpreted by the brain as a "head movement" to the higher input side, so that – although the head does not in fact move at all – a "physiological nystagmus" is initiated. Note that the fast phase of the horizontal nystagmus occurs away from the lesion and towards the direction of the supposed head movement (*i.e.*, towards the side with more input). An *aide memoire* is that a normal defense mechanism is to "quickly escape from a problem".

If an animal shows nystagmus which does not alter with changes in the head position, this is known as static pathological nystagmus. Positional nystagmus presents only with a change of posture (*e.g.*, when the animal is rolled onto its back) or if the type of nystagmus changes with an alteration in posture. A ventral or ventrolateral positional strabismus ***(Figure 3)*** may also be observed if the clinician extends the dog's neck. In cases of mild vestibular losses of function, this strabismus may be the only conspicuous finding on neurological examination (1).

It should be emphasized that vertical nystagmus invariably (and positional nystagmus frequently) indicates a central vestibular dysfunction.

If there is bilateral involvement of the vestibular system, one-sided functional abnormalities such as walking in circles and head tilt are not noted. Affected animals demonstrate searching, weaving head movements and physiological nystagmus is absent, *i.e.*, there is no rhythmic eye movement when the head moves; instead

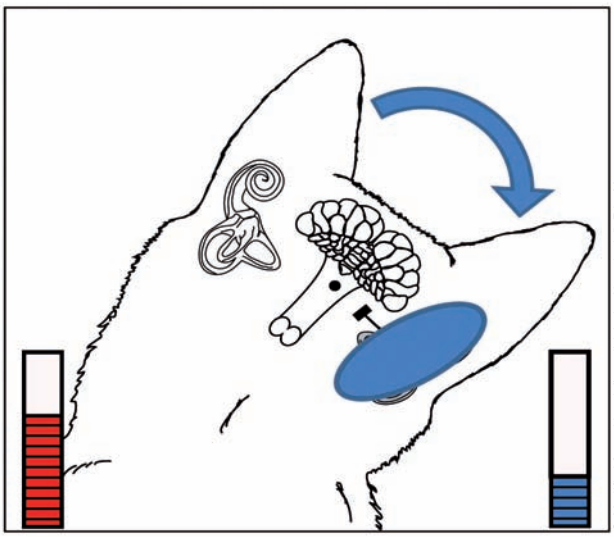

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Figure 2. Schematic diagram of the pathophysiology of head tilt. In diseases of the inner ear, the brain receives more input from the healthy side, which it falsely interprets as a head tilt towards the healthy side. The brain reacts to this apparent tilt by correcting the head so that the head is repositioned towards to the other, diseased side. Therefore the head tilt always occurs towards the diseased side.

the eyes move at the same time as the head. Bilateral vestibular syndrome in patients that retain normal levels of awareness and maintain the ability to walk are, as a general rule, peripheral in nature.

Central or peripheral – brain or ear?

In diseases of the peripheral vestibular system, the brain is not affected and so no additional neurological deficit is found on examination that would indicate involvement of the brain; patients show normal awareness, unimpaired vision, normal cranial nerve function, normal proprioceptive paw positioning and no limb paresis. There are two exceptions to this, as two nerves (the facial nerve and the sympathetic nerve) may be involved with a peripheral vestibular disorder. Parts of both nerves run through the middle ear or rest against the wall of the middle ear, and can be implicated in inner and middle ear disease. Involvement of the facial nerve, which runs through a channel in the wall of the middle ear (2) and which is only partially separated from the middle ear lumen by a thin membrane, causes paralysis of the facial musculature, visualized by drooping of the ear and lip ***(Figure 4)***, an enlarged palpebral fissure, a narrowed nostril, loss of the palpebral reflex and menace response. Involvement of the sympathetic fibers (which run through the middle ear to the eye) causes Horner's syndrome: ptosis (reduced eyelid opening), miosis (small pupil), nictitating membrane prolapse and enophthalmos. Other than signs related to

these two nerves, no other cranial nerve deficits should be observed with a peripheral vestibular syndrome. The inverse also applies: a vestibular syndrome with simultaneous facial paralysis and/or Horner's syndrome without other neurological deficits almost always indicates a peripheral lesion. If further cranial nerve signs develop, or there are other neurological deficits present which can be localized to the brain (limited awareness, limb paresis, diminished proprioceptive paw positioning, tremors, other cranial nerve deficits...), then this points to a central lesion.

As noted above, a vertical nystagmus invariably, and a positional nystagmus frequently, indicates a central lesion, whereas horizontal or rotatory nystagmus does not allow differentiation between a peripheral or central lesion. However, nystagmus frequency may assist with lesion localization; high frequencies (≥ 66 beats/minute) are more common with lesions of the peripheral vestibular system (3). Remember that (as noted above), an animal with bilateral peripheral vestibular disease can walk without circling and will show no physiological nystagmus or head tilt, only ataxia and searching head movements.

A paradoxical vestibular syndrome, which may occur with lesions of the central vestibular system, is also recognized. Here the classic symptoms of head tilt, circling and nystagmus do not correlate, in that an animal may circle, have a head tilt to the right, and show left horizontal nystagmus (which all suggest that the right side is affected), whilst diminished or absent proprioceptive paw positioning in both fore and hind left legs suggests a left-sided lesion. This paradox can be explained pathophysiologically as affected animals have a lesion in the angle between the caudal cerebellum and the brainstem, so that brainstem function (responsible for the proprioceptive paw positioning), the part of the cerebellum that influences the vestibular system (the flocculonodular lobe), and/or its connections to the brainstem (the caudal cerebellar peduncle) are affected. Remember that the cerebellum's output, which influences the vestibular system, is almost always inhibitory; if this inhibitory influence fails on the diseased side, this side now paradoxically gives a higher input into the brain, which is misinterpreted as the healthy side delivering less input. With a paradoxical vestibular disorder the head tilt and nystagmus are misleading, and it is the absent proprioceptive reflexes which accurately indicate the diseased side. The diagnostic importance of a paradoxical vestibular syndrome is that it is always caused by a lesion within the brain. The differential signs are summarized in ***Table 1***.

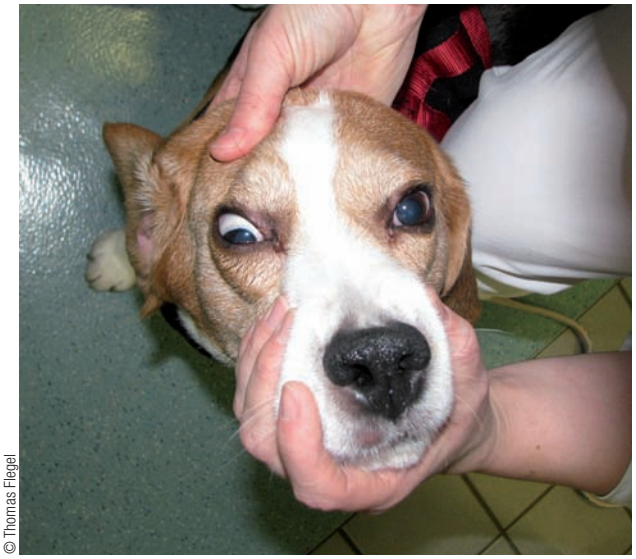
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Figure 3. A Beagle with a ventral strabismus of the right eye caused by vestibular syndrome; the strabismus is best seen by extending the neck.

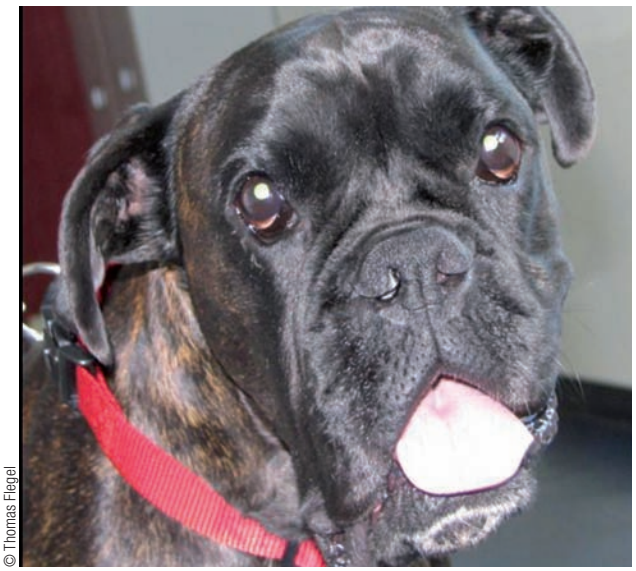
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Figure 4. A Boxer with right-sided peripheral vestibular syndrome. Note the head tilt to the right, signs of right-sided facial nerve paresis (drooping lip and ear), and an enlarged palpebral fissure.

Differential diagnoses of peripheral vestibular disease

The above section should enable the veterinarian to distinguish a peripheral lesion of the vestibular system from a central one. ***Table 2*** lists the most frequent differential diagnoses of peripheral and central causes of vestibular

Table 1. Differentiation of central (brainstem, cerebellum) or peripheral (inner ear) vestibular syndrome.

Sign	Peripheral	Central
Behavior	normal	abnormal
Awareness	normal	abnormal
Nystagmus	horizontal or rotatory	horizontal, rotatory or vertical
Nystagmus frequency	higher	lower
Cranial nerve deficits	facial nerve deficits Horner's syndrome	multiple cranial nerve deficits
Proprioceptive reflexes	normal	reduced
Motor function	normal	paresis, plegia
Paradoxical signs	not observed	possible
Ventral/ventrolateral strabismus	possible	possible

Table 2. Common etiologies of peripheral and central vestibular syndromes, in order of frequency.

Peripheral vestibular syndrome
• Otitis interna • Idiopathic vestibular syndrome • Hypothyroidism • Traumatic perforation of the eardrum with secondary otitis media/interna • Toxins: *e.g.*, - disinfectants: chlorhexidine - antibiotics: aminoglycosides, fluoroquinolones - heavy metals • Neoplasia • Head injury with fracture of the petrosal bone • Congenital vestibular syndrome (Akita Inu, Beagle, Cocker Spaniel, German Shepherd, Doberman, Tibetan Terrier) • Neuritis of the vestibulocochlear nerve
Central vestibular syndrome
• Encephalitis (non-infectious, infectious, expansion of otitis media/interna into the brain) • Infarction • Neoplasia • Intoxication (*e.g.*, metronidazole) • Skull-brain trauma (hemorrhage, contusion) • Enzyme storage disease

syndrome. All general practitioners should be able to diagnose peripheral vestibular disease, and a short discussion on the three most common etiologies of peripheral vestibular syndrome is worthwhile. It is the author's opinion that animals with a central lesion should always be referred to a specialist.

Otitis interna

Otitis media/interna is the underlying etiology in approximately 50% of patients with peripheral vestibular disease (4). Otitis media by itself does not cause loss of vestibular function, but the anatomical proximity of middle and inner ear means that otitis media is often associated with otitis interna. By comparison, it is rare to have otitis interna without involvement of the middle ear, so when otitis media occurs with simultaneous peripheral vestibular failure, this indicates that the inner ear is involved in the inflammatory process. Note that it is not inevitable that otitis externa will also be present, since infection can reach the middle and inner ear through hematogenous spread or by ascending from the pharynx through the Eustachian tube into the middle ear.

Aside from peripheral vestibular failures, otitis interna/media can, as noted above, involve two other nerves; the facial nerve, lying within the wall of the tympanic bulla, and fibers of the sympathetic nerve, running through the middle ear to the eye. Hence an otitis media/ interna can lead to a facial paralysis and Horner's syndrome; other cranial nerves should not be affected.

On the basis of the frequent causal relationship between middle and inner ear inflammation as well as otitis

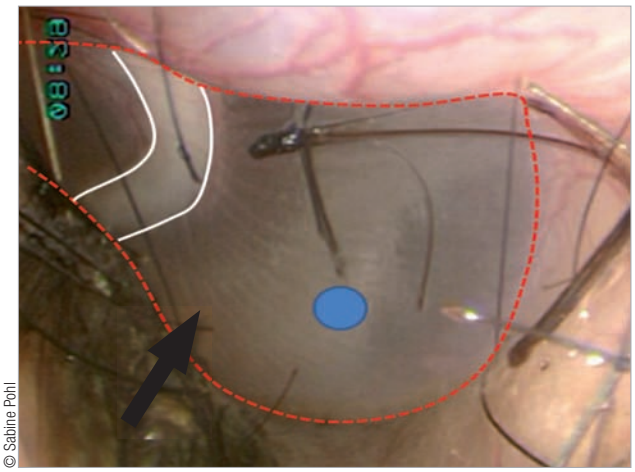

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Figure 5. View of the eardrum with the blue dot indicating the point for myringotomy. The puncture should always be made in the caudal aspect of the eardrum to avoid damage to the auditory ossicles; the malleus is arrowed.

externa, diagnosis of a peripheral vestibular syndrome should always prompt an otoscopic examination. This should allow the integrity of the eardrum and its color to be verified. If the eardrum is not visible due to secretions or cerumen, the ear should be flushed with a warm saline solution until the eardrum can be seen; a cleansing agent should not be used. If there is suspicion that the middle ear is infected, *e.g.*, the eardrum may appear yellowish due to pus behind it, a myringotomy (puncture of the eardrum) should be performed ***(Figure 5)*** using a spinal needle (0.7 x 75 mm) and syringe with otoscopic monitoring; the puncture should be made in the caudal aspect of the eardrum to avoid damage to the auditory ossicles. If no secretion can be extracted this way, the middle ear can be flushed with 0.5 mL of sterile saline and the liquid aspirated; any secretion and the aspirated fluid obtained should be subjected to cytology and bacterial culture.

Imaging is a useful diagnostic tool and otitis media/interna can frequently be identified with conventional radiography, although this requires careful positioning under general anesthesia ***(Figure 6)***. Inflammatory secretions may obscure the tympanic bulla and proliferative or destructive changes to the bulla wall (in the form of wall thickening or lysis) may be visualized ***(Figure 7)***. Mineralization of the external auditory canal may be noted as a result of chronic otitis externa. Normal radiological appearance does not exclude otitis media/interna, and in such cases cross-sectional imaging techniques (computed tomography, magnetic resonance imaging) may be necessary.

Therapy for otitis media/interna involves at least six weeks of antibiotics, ideally supported by bacteriological culture and sensitivity, although if this is not available either clindamycin, cephalosporin, potentiated sulfonamides or fluoroquinolones may be the drug of choice. Should the patient not respond to therapy, or if the animal exhibits severe signs at initial presentation, surgery, in the form of a bulla osteotomy or interventional otoendoscopy, is often required.

Idiopathic vestibular syndrome

This is an acute vestibular disorder arising in older dogs, typically at least 10 years of age. The clinical signs are related only to the peripheral vestibular system and are often marked compared to other causes of vestibular disease: extreme ataxia (sometimes with an inability to walk), head tilt and horizontal or rotatory nystagmus. Diagnosis is via signalment, careful clinical observation and exclusion of other causes. There is no specific therapy, but sometimes

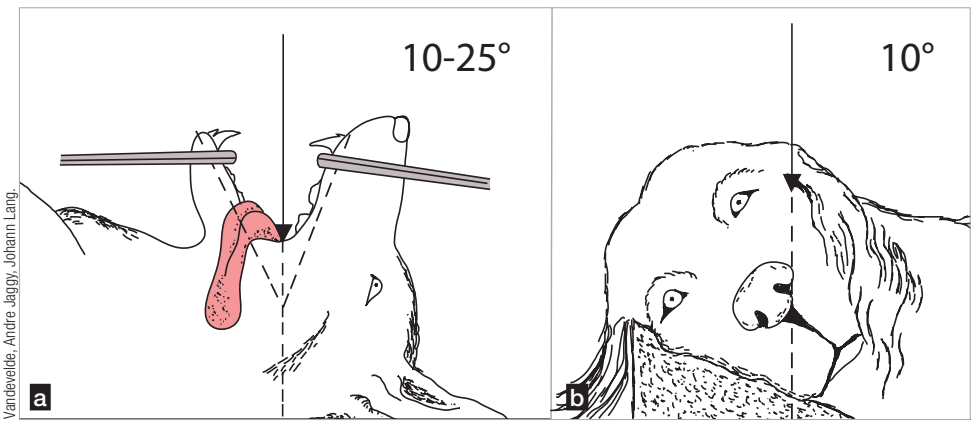

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Figure 6. Positioning of the head for radiography of the tympanic bulla; **(a)** open-mouth projection to image the tympanic bulla (the hard palate is angled at 10-25° to the vertical beam); **(b)** lateral oblique projection to image the tympanic bulla (the head is angled at 10° from the horizontal plane).

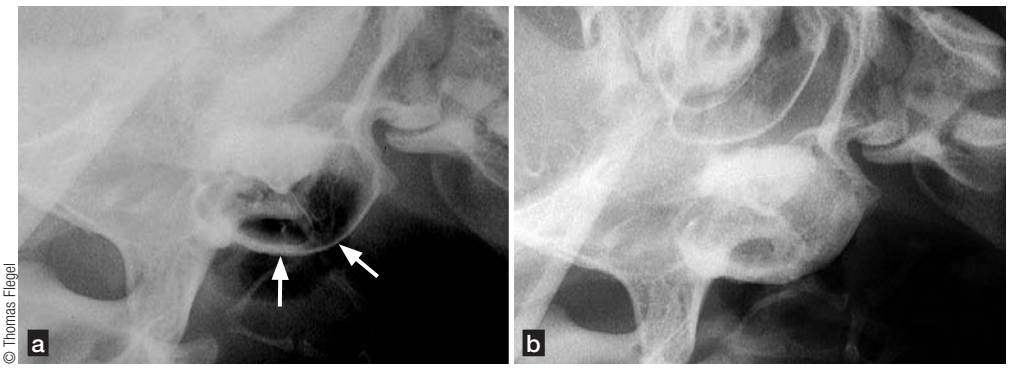

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Figure 7. Radiographs of the middle ear on lateral oblique projection.
(a) A normal tympanic bulla filled with air, with the bulla wall visible as a thin radiodense line (arrows).
(b) A diseased tympanic bulla due to otitis media; note the diffuse increased opacity of the bulla.

(based on comparison with the human situation) intravenous fluids and drugs such as propentofyllin (which have been shown to enhance blood flow) may be considered. Occasionally, centrally-acting anti-emetics (*e.g.*, maropitant, promethazin) may be necessary if the patient does not eat due to nausea. As a rule, signs improve within a few days, with reduced intensity of the nystagmus being the first indication of recovery, and although clinical signs generally disappear within 3-4 weeks the head tilt may remain permanently despite resolution of all other symptoms. However, even the head tilt can ameliorate over time as the brain seeks to compensate for the malposition caused by the vestibular damage.

Hypothyroidism

Hypothyroid-associated vestibular disorders exclusively affect older dogs, but general indicators of thyroid insufficiency (sluggishness, obesity, coat alterations, polydipsia) may not be present, and acute onset vestibular signs may be the sole manifestation of disease. Although there are various theories to explain the link between hypothyroidism and vestibular disease, there is currently no conclusive proof as to the exact etiology in this situation. This is generally a peripheral vestibular disorder, although occasionally a central syndrome may be seen (5). In some cases, the vestibular signs are combined with other failures of the peripheral nervous system such as limb paresis, facial paralysis and laryngeal paralysis.

The diagnosis is made on determination of decreased fT_4 and increased TSH levels. The TSH stimulation test, using genetically produced human TSH, is often not performed in veterinary practice due to cost, but is generally regarded as the gold standard for diagnosis and should be performed in cases of doubt. Clinical signs frequently improve with thyroid supplementation (levothyroxine at 20 µg/kg q12H; maximum 0.8 mg q12H), and recovery often occurs within a few days of commencing treatment, although it can take weeks or even months on therapy for improvement to be noted.

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Descriptive epidemiology of idiopathic seizures in dogs

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Introduction

Epilepsy is thought to be the most common neurologic condition in dogs (1), and many breeds appear to be genetically predisposed (2). The impact of idiopathic (primary) epilepsy can be severe, as affected dogs are reportedly at increased risk for premature death and owners describe difficulty in caring for them (3). The purpose of the present study was to characterize a general population of dogs with idiopathic seizures with the aim of better understanding this condition.

Method of analysis

The medical records of all canine patients seen at 818 Banfield hospitals in 2012 were examined to identify dogs with a diagnostic code indicative of seizures (acquired, active, idiopathic or not further classified) or epilepsy during that period. For the analysis, only dogs diagnosed with idiopathic (primary) seizures were included, to ensure exclusion of animals with seizures attributable to an identifiable (secondary) abnormality. A random sample of 50 records of dogs with idiopathic seizures was then reviewed to verify that they had no identified disease (*e.g.*, intracranial abnormality or metabolic disorder) or lab test results (*e.g.*, hypocalcemia or hypoglycemia) that might explain the seizures. Data extracted included age at first diagnosis at Banfield, current reproductive status, breed size, breed and whether or not the dog was overweight. Breed size was classified according to the mean adult weight for each breed, as follows: small < 9.1 kg; medium 9.1-22.6 kg; large 22.7-40.9 kg; giant > 40.9 kg. Both prevalent (existing) and incident (new) cases were included in the analysis, so that individuals may have been first diagnosed in 2012 or earlier, but all dogs identified had had idiopathic seizures at some point during this year.

Summary statistics were calculated as appropriate for the data distribution, including 95% confidence intervals (CIs). The Chi square test was used to test the hypothesis that the distribution of assessed factors among dogs with idiopathic seizures differed significantly from that in the general canine patient population. Because of the multiple hypotheses tested, values of $P < 0.01$ were considered significant.

Results

During 2012, 23,278 (1.1%) of the 2,190,019 dogs seen at Banfield had a diagnosis of seizures or epilepsy. Of these, only 1,991 (8.6%, or 0.1% of the total number of dogs) were indicated as having idiopathic seizures and were included in the analysis. The mean ± SD age at first diagnosis was 8.3 ± 2.9 years.

The proportion of neutered males (but not spayed females) was higher among dogs with idiopathic seizures than in the general population ***(Table 1)***. On the other hand, sexually intact dogs of both sexes were under-represented. Dogs were significantly more likely

Table 1. Distribution of various characteristics in dogs with idiopathic seizures.

Characteristic	% of seizure patients (95% CI)	% of general population	*P* value
Overweight	33.8 (31.7-35.9)	21.3	< 0.001
Reproductive status			
Intact female	3.7 (2.9-4.5)	11.5	< 0.001
Intact male	9.6 (8.3-10.9)	15.3	< 0.001
Spayed female	37.8 (35.7-39.9)	36.5	0.2319
Neutered male	48.9 (46.7-51.1)	36.6	< 0.001
Breed size*			
Giant	0.7 (0.3-1.1)	1.9	< 0.001
Large	20.6 (18.8-22.4)	20.7	0.912
Medium	27.6 (25.6-30.0)	26.7	0.369
Small	51.1 (48.9-53.3)	50.7	0.689

*Small [mean adult weight for breed, < 9.1 kg], medium [9.1-22.6 kg], large [22.7-40.9 kg] and giant [> 40.9 kg]

Table 2. Distribution of breed (size classification indicated) in dogs with idiopathic seizures.

Breed	% of seizure patients (95% CI)	% of general population	*P* value
Beagle (medium)	6.4 (5.3-7.5)	2.5	< 0.001
American Cocker Spaniel (medium)	4.8 (3.9-5.7)	1.7	< 0.001
Dachshund (small)	4.6 (3.7-5.5)	3.2	0.004
Golden Retriever (large)	3.9 (3.1-4.8)	2.5	0.001
Yorkshire Terrier (small)	3.7 (2.9-4.5)	5.8	< 0.001
Pomeranian (small)	3.5 (2.7-4.3)	2.3	0.004
German Shepherd Dog (large)	2.3 (1.6-3.0)	3.6	< 0.001
Shih Tzu (small)	2.3 (1.6-3.0)	5.9	< 0.001
Toy Poodle (small)	2.1 (1.5-2.7)	0.8	< 0.001
Boxer (medium)	1.5 (1.0-2.0)	2.9	< 0.001
Border Collie (medium)	1.4 (0.9-1.9)	2.9	< 0.001
Italian Greyhound (small)	1.4 (0.9-1.9)	0.2	< 0.001
Miniature Poodle (small)	1.4 (0.9-1.9)	0.6	0.005
Maltese (small)	1.2 (0.7-1.7)	3.4	< 0.001
Pit Bull (medium)	1.1 (0.6-1.6)	5.2	< 0.001
English Bulldog (medium)	0.5 (0.2-0.8)	1.2	< 0.001
Rottweiler (large)	0.4 (0.1-0.7)	1.1	< 0.001
West Highland White Terrier (small)	0.3 (0.1-0.5)	0.6	0.007
American Bulldog (large)	0.2 (0-0.4)	0.5	< 0.001
Cavalier King Charles Spaniel (small)	0.2 (0-0.4)	0.5	0.001
Havanese (small)	0.1 (0-0.2)	0.3	0.003
Mastiff (giant)	0.1 (0.1-0.2)	0.4	< 0.001

to be overweight than dogs in the general population, whilst giant-sized breeds were significantly under-represented. Some specific breeds were identified as either over- or under-represented ***(Table 2)***. Note that more than 200 breeds were seen during the year, so the table only includes breeds that were identified as being at significantly ($P < 0.01$) higher or lower risk of idiopathic seizures than mixed breed dogs.

Discussion

The mean age at first diagnosis of idiopathic seizures was higher (8.3 ± 2.9 years) than previously reported (3,4), but some dogs may have been originally diagnosed at other hospitals prior to visiting Banfield. With respect to the size distribution, no difference was evident between dogs with epilepsy and dogs in the general hospital population (*i.e.*, the 2.19 million dogs seen at Banfield in 2012), with the exception of giant breeds, which were under-represented and may be less predisposed to epilepsy. Another study (1) found that the odds of epilepsy increased with increasing body weight (with dogs > 40 kg at highest risk) but did not control for breed size, and the difference between the two studies may be attributable to overweight body condition. In our study, overweight dogs were over-represented among epileptics *versus* the general population, but it was not established if the overweight condition preceded or followed the development of epilepsy.

Four breeds were over-represented in our review; of these, Beagles are reportedly at higher risk for idiopathic epilepsy (4,5), but the other three breeds (American Cocker Spaniel, Toy Poodle, and Italian Greyhound) have not been previously reported to be at increased risk. Neutered males were over-represented in the study, and this finding corresponds with a previous report (2).

The prevalence of idiopathic seizures in our study (0.1%) was considerably lower than the prevalence of 0.62% reported previously (1). This value should not be used as an estimate of idiopathic epilepsy in the general US pet dog population because, for logistical purposes, only the diagnostic code of "idiopathic seizures" (rather than detailed information from the medical notes) was used to identify affected dogs. It is also worth noting that the study which reported a seizure prevalence of 0.62% was conducted on dogs in the UK, and geographical factors may therefore play a part in the different value obtained in our study.

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Acquired canine metabolic encephalopathies

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Introduction

Numerous metabolic diseases can cause neurological signs in dogs, and metabolic neurological disorders are classified into two categories: 1) diseases resulting from inborn errors of metabolism, including lysosomal storage diseases, organic acidurias, mitochondropathies, and peroxisomal disorders, and 2) acquired diseases arising from peripheral organ dysfunction or failure that secondarily affect the nervous system. In this review, the term "acquired metabolic encephalopathy" (AME) will refer to clinical evidence of brain dysfunction arising from disease of systemic organs. Inborn errors of metabolism are reviewed elsewhere (1,2).

KEY POINTS

- **Acquired metabolic encephalopathies (AME) are a diverse group of neurological disorders characterized by aberrations in brain function resulting from disease in systemic organs.**
- **The clinical signs of AME typically reflect diffuse forebrain dysfunction.**
- **Hypoglycemia and hepatic encephalopathy are the most common etiologies of AME in dogs.**
- **Cerebrovascular complications of canine endocrine and metabolic disorders, such as stroke, are common in small animal practice.**
- **Polysystemic clinical signs and evidence of organ dysfunction are often observed on physical examination and laboratory investigations in dogs with AME.**
- **Prompt recognition of AME-related neurological dysfunction may allow reversion of signs with supportive care and appropriate treatment of the underlying cause.**

Etiologies and clinical signs of canine AME

AME etiologies are shown in ***Table 1***, with the two most common causes being hypoglycemia and hepatic encephalopathy (HE). Among the etiologies of hypoglycemia ***(Table 2)***, paraneoplastic, transient juvenile, and insulin overdosage are most frequently implicated (3). Congenital portosystemic vascular anomalies (PSVA) and cirrhosis, usually secondary to chronic hepatitis, resulting in portal hypertension and the development of multiple acquired portosystemic collaterals ***(Figure 1)*** are the most common causes of canine HE (4).

The neurological manifestations of hypoglycemia and HE reflect diffuse forebrain dysfunction (5). Early clinical signs of neuroglycopenia, observed with plasma glucose concentrations < 3.5 mmol/L (63 mg/dL) include hyperexcitability and tremors, and are due to increased sympathetic tone and release of catecholamines, glucagon, and cortisol in an attempt to increase plasma glucose. The most common signs of hypoglycemia and HE include depressed levels of consciousness, thalamocortical visual deficits, and generalized seizures (3,5). Bizarre behaviors such as aimless wandering and head pressing are also frequently noted in dogs with HE; bilateral miosis, anisocoria, and myoclonus may be occasionally observed. Glucose concentrations < 1.5 mmol/L (27 mg/dL) are associated with severe signs such as coma and death. Clinical signs of hypoglycemia and HE can be episodic, and HE signs may be exacerbated post-prandially (4,5).

Table 1. Mechanisms and etiologies of metabolic brain dysfunction (ICON).

Mechanism of disease	Examples	Specific etiologies
Ionic/electrolyte imbalance	Hypocalcemia	• Primary hypoparathyroidism • Pregnancy/lactation
	Hypernatremia	• Central diabetes insipidus • Polyuric kidney disease
	Hyponatremia	• Hypoadrenocorticism • Hypothyroid myxedema coma
Cerebrovascular disease	Stroke* Hypertensive encephalopathy	• Chronic kidney disease • Diabetes mellitus • Hyperadrenocorticism • Hypothyroidism • Primary or secondary hypertension • Pheochromocytoma
Organ dysfunction	Hepatic encephalopathy*	• Congenital portovascular anomalies • Cirrhosis
	Uremic encephalopathy	• Acute kidney disease • Chronic kidney disease
Neuroglycopenia	Hypoglycemia*	See ***Table 2***

*Common etiologies

Table 2. General mechanisms and etiologies of hypoglycemia.

Glucose deficiency	Glucose overutilization	Multifactorial
Starvation	Insulinoma*	Sepsis
Malabsorption	Hypoglycemic drug ingestion	
Hypoadrenocorticism	Cachexia with fat depletion	
Neonatal hypoglycemia	Hunting dog hypoglycemia	
Transient juvenile hypoglycemia*	Iatrogenic insulin overdose*	
Hepatic disease*	Extrapancreatic neoplasia*	
Congenital metabolic disorders (*e.g.*, glycogen storage disease)		

*Common etiologies

The use of magnetic resonance imaging (MRI) has resulted in increased recognition of cerebrovascular disease (CVD) in veterinary practice. CVD is any abnormality of the brain caused by a pathologic process affecting its blood supply. Endocrine and metabolic disorders identified as risk factors for the development of CVD in dogs include chronic kidney disease (CKD), diabetes mellitus, hyperadrenocorticism (HAC), hypothyroidism, and pheochromocytoma ***(Table 1)*** (6,7), and the most common clinical manifestation of CVD is a cerebrovascular accident (CVA) or stroke (7). In contrast to other causes of AME, the clinical hallmark of CVA is an acute onset of focal brain dysfunction that is non-progressive after 72 hours (7); specific neurologic deficits associated with a stroke relate to the size and topographic location of the CVA within the brain (6,7). Hypertensive encephalopathy is another vascular complication of metabolic disorders, and is clinically characterized by diffuse forebrain signs such as obtundation, seizures, and thalamocortical blindness. Hypertensive encephalopathy occurs in dogs with severe hypertension (blood pressure [BP] > 200 mmHg systolic), acute abrupt rises in blood pressure, or both (8).

Historical or physical evidence of disease affecting multiple organs in addition to the brain will often be present in dogs with AME. Abnormalities in appetite and body condition are common and can range from anorexia to polyphagia and cachexia to weight gain, respectively. Dogs with HE usually have concurrent signs of hepatic dysfunction including vomiting, diarrhea, weight loss, polyuria, and polydipsia. Palpation of hepatic or intestinal masses or lymphadenopathy may be possible in dogs

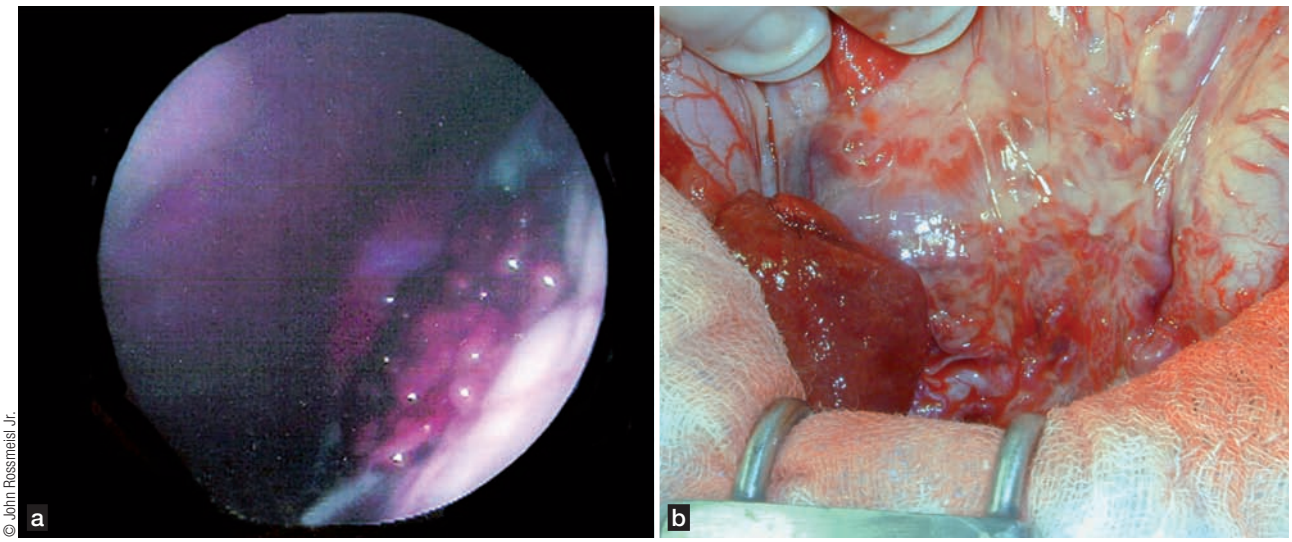


Figure 1. Acquired, end-stage hepatopathies associated with canine hepatic encephalopathy. **(a)** Laparoscopic image demonstrating microhepatica and macronodular cirrhosis of the liver in an 8-year-old, castrated male Siberian Husky with hepatic encephalopathy secondary to idiopathic chronic hepatitis. **(b)** Intraoperative view of multiple, acquired portosystemic shunts in a 7-year-old, spayed female mixed breed dog with hepatic encephalopathy from copper-associated hepatitis.

with paraneoplastic hypoglycemia. Ocular lesions may be observed in hypertensive dogs with CVA or hypertensive encephalopathy; clinical features of hypertensive retinopathy include anterior and posterior segment hemorrhage, retinal detachment, secondary anterior uveitis, and (in severe cases) papilledema ***(Figure 2)***.

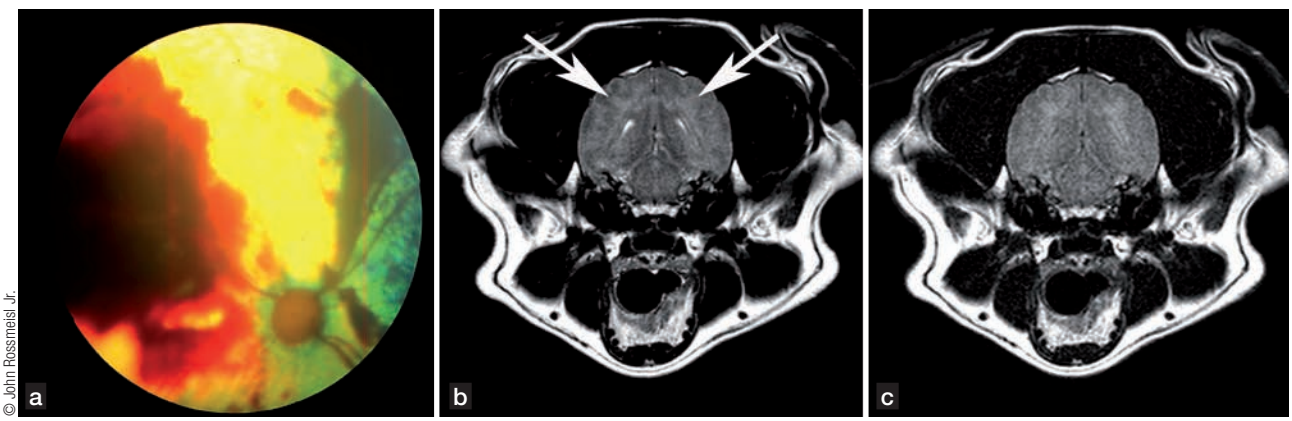
Pathophysiology of AME

AME result from abnormalities in the brain's physiochemistry induced by disturbances of homeostatic mechanisms. The pathophysiologic hallmark of AME is a general depression in brain function that is usually reversible with correction of the underlying metabolic defect. However, if left untreated, AME can lead to permanent secondary structural damage to the brain.

Cerebral energy metabolism and blood flow

The brain is a metabolically active organ that is exquisitely sensitive to alterations in blood flow or energy supply (7,9). Brain function depends on continuous delivery of oxygen and glucose for production of ATP sufficient to maintain ionic pump functions, synthesis, release, and recycling of neurotransmitters, and other intracellular metabolic functions. Despite comprising 2% of total

Figure 2. Hypertensive retinopathy and encephalopathy in a 9-year-old, spayed female mixed breed dog with pheochromocytoma. Fundoscopic image demonstrating retinal hemorrhages and detachment **(a)**. Transverse T2-weighted **(b)** and fluid attenuated inversion recovery **(c)** MRI images at the level of mesencephalic aqueduct; the bilaterally symmetric hyperintensities in the subcortical white matter (arrowed) indicate edema.



body mass, blood flow to the brain accounts for 15-18% of resting cardiac output, and brain metabolism consumes 20% of the body's oxygen and 25% of the glucose.

The final common denominator of ischemic/hypoxic or hypoglycemic brain injury is a reduction of energy substrates (hypoxemia or hypoglycemia) within the blood, or a decrease in cerebral blood flow (ischemia) that falls below the minimum threshold required to maintain normal brain function (9). Brain ischemia consists of reduced perfusion, neuroglycopenia, and an increase in carbon dioxide concentration. Glucose delivery to the brain occurs by concentration gradient-mediated facilitated transport, which is insulin-independent. The brain has a limited supply of glycogen that can be mobilized to lactate for provision of energy in the face of hypoglycemia (9), but severe and sustained ischemia/hypoxia or hypoglycemia will eventually exhaust ATP stores.

Once ATP is depleted, Na^+-K^+ ATP-ase pumps fail and transmembrane ionic gradients are disrupted. This liberates excitotoxic neurotransmitters, which initiate and potentiate a cascade of biochemical events ultimately culminating in brain necrosis. Complete ischemia to the brain will result in consumption of available oxygen within seconds, and total ATP depletion within minutes. Neuronal necrosis from hypoglycemia requires blood glucose concentrations to fall below ~ 1-1.5 mmol/L (18-27 mg/dL) for 30 minutes or more (9).

Cells with higher metabolic rates are preferentially susceptible to hypoglycemic or ischemic/hypoxic injury. Neurons in the cerebral cortex, hippocampus, cerebellum, and thalamic nuclei are the most vulnerable cellular populations within the brain, followed by oligodendroglia, astrocytes, and microglia (7,9).

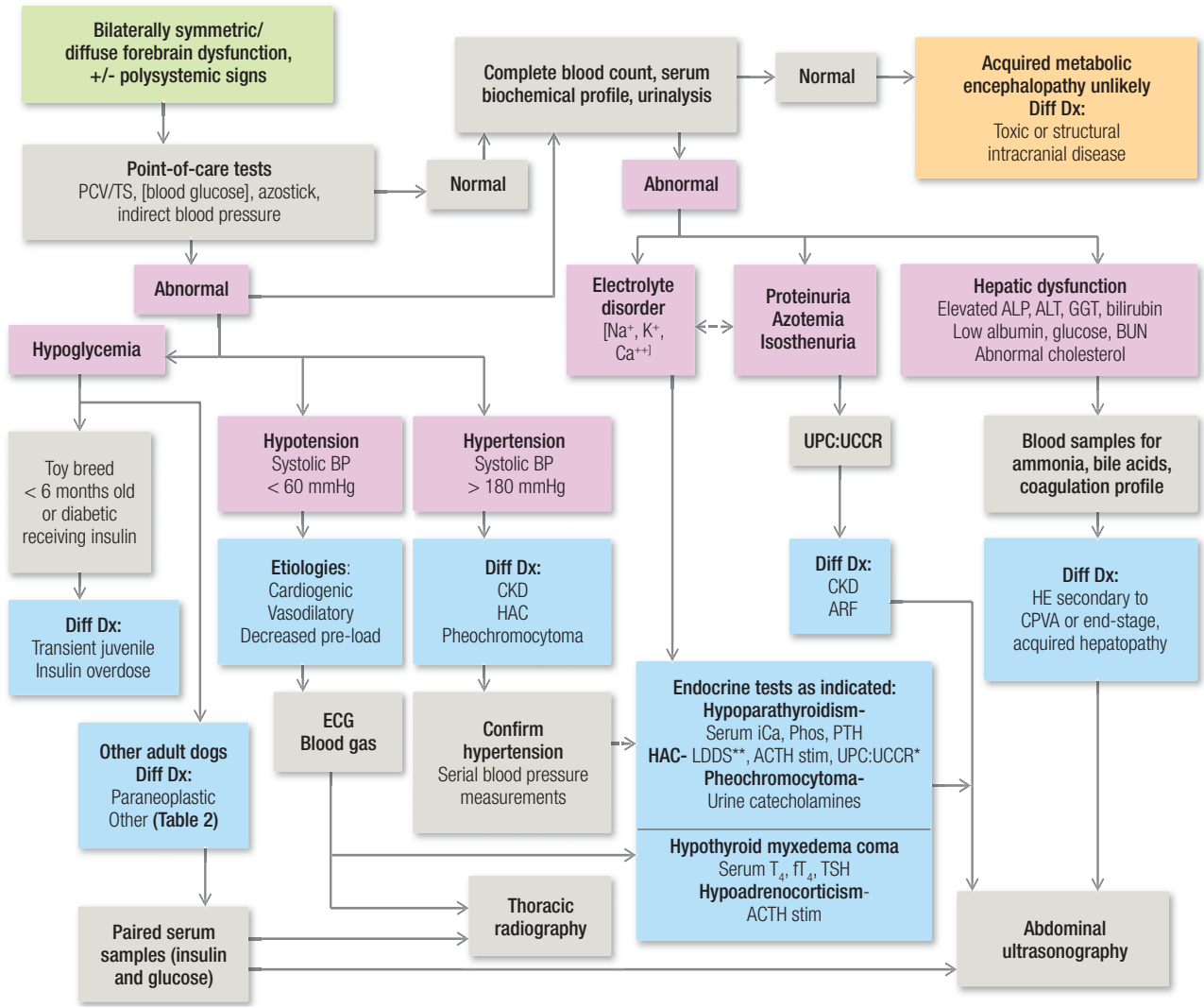
Global brain ischemia or hypoxia can result from cardiac arrest or anesthetic accidents. There are numerous causes of CVD, all of which can cause focal ischemia. CVA are characterized by ischemia with or without infarction as a result of vascular occlusion (ischemic stroke), and hemorrhage caused by compromised integrity of the vascular wall (hemorrhagic stroke). The potential reversibility of an ischemic insult is dependent on the severity of the reduction in blood flow and its temporal duration. The final result of irreversible ischemia is brain necrosis (infarct) of the affected area, but this is a dynamic process; an infarct has a central core of severely hypoperfused tissue that rapidly dies, and a surrounding penumbra of tissue with a more moderate decrease in blood flow – the penumbra maintains the potential to recover and is the target for most therapeutic interventions (7).

Systemic hypertension may accompany various canine endocrine and metabolic disorders associated with CVA, including CKD, diabetes mellitus, hyperadrenocorticism, and pheochromocytoma. Although the pathophysiology of hypertensive encephalopathy is incompletely understood, it is believed to result from dysfunctional myogenic cerebral autoregulatory mechanisms leading to hyperperfusion and vasogenic and interstitial brain edema formation ***(Figure 2)*** (8).

Hepatic encephalopathy

The pathogenesis of HE is multifactorial and has been extensively reviewed (4,5,10,11). It results from the decreased metabolism of endogenously generated toxins due to intrinsic liver dysfunction or the presence of abnormal portosystemic collateral vasculature which allows toxins to bypass the liver (5). Toxin accumulation leads to disturbances in brain function including disrupted neurotransmission, a compromised blood-brain barrier (BBB), and alterations in cerebral blood flow (5,10). A singular toxin has not been identified that accounts for all of the derangements seen in the brain with HE, and numerous neurotoxins, such as aromatic amino acids, serotonin, endogenous benzodiazepines, and manganese have been implicated in the pathogenesis; however, the ammonia hypothesis remains a central paradigm (11). This states that hyperammonemia resulting from decreased hepatic function and portosystemic shunting is the putative cause of HE. With impaired hepatic urea synthetic ability, the major method of ammonia detoxification will occur via metabolism to glutamine in astrocytes (5,11). Thus, in the presence of hyperammonemia, glutamine, a potent osmolyte, accumulates within astrocytes: this results in intracellular edema and impairs astrocyte function in neurotransmission and maintenance of BBB integrity (5). Hyperammonemia also generates reactive oxygen species which alter cellular membrane and mitochondrial permeability, contributing to cerebral edema formation.

Recently, the synergistic role of inflammation and infection in modulating the effects of ammonia in HE have been identified. The hyperammonemic brain is sensitized to the systemically generated pro-inflammatory milieu of cytokines that accompany many liver diseases associated with HE, which can initiate or perpetuate brain inflammation or neurotransmitter dysfunction. Hyperammonemia induces neutrophil dysfunction through the



*UPC:UCCR - urine cortisol: urine creatinine and UPC;UCCR – urine protein; urine creatinine ratio

** LDDS – Low-dose dexamethasone suppression test

Figure 3. Diagnostic algorithm for canine AME. The tests necessary for diagnosis of most AME are routinely used and widely available in veterinary practice.

release of reactive oxygen species, which contribute to oxidative stress, systemic inflammation, and abrogates the immune response to infection (10,11).

Diagnostic approach to AME

Identification of bilaterally symmetric or diffuse forebrain neurologic dysfunction should prompt laboratory investigations ***(Figure 3)*** with the primary goal of identifying the etiology of the AME. Point-of-care testing will rapidly identify dogs that require immediate therapy for anemia, hypoproteinemia, hypoglycemia, or hypotension, while awaiting results of more comprehensive clinicopathologic tests. Although there are numerous causes of AME, physical and laboratory examinations will usually provide sufficiently complimentary and fundamental information to allow refinement of subsequent diagnostics and identification of the underlying cause.

With the exception of CVA, advanced neuroimaging of the brain is usually not required for diagnosis of AME, but the MRI features of canine AME have been reported (8,12). In dogs with HE, MRI abnormalities may include cerebrocortical atrophy and bilaterally symmetric T1-hyperintensities within the lentiform nuclei, presumably due to manganese accumulation ***(Figure 4)*** (12). Brain imaging in CVA will not only confirm the diagnosis, but will also exclude other differential diagnoses for acute onset and focal brain dysfunction, such as encephalitis,

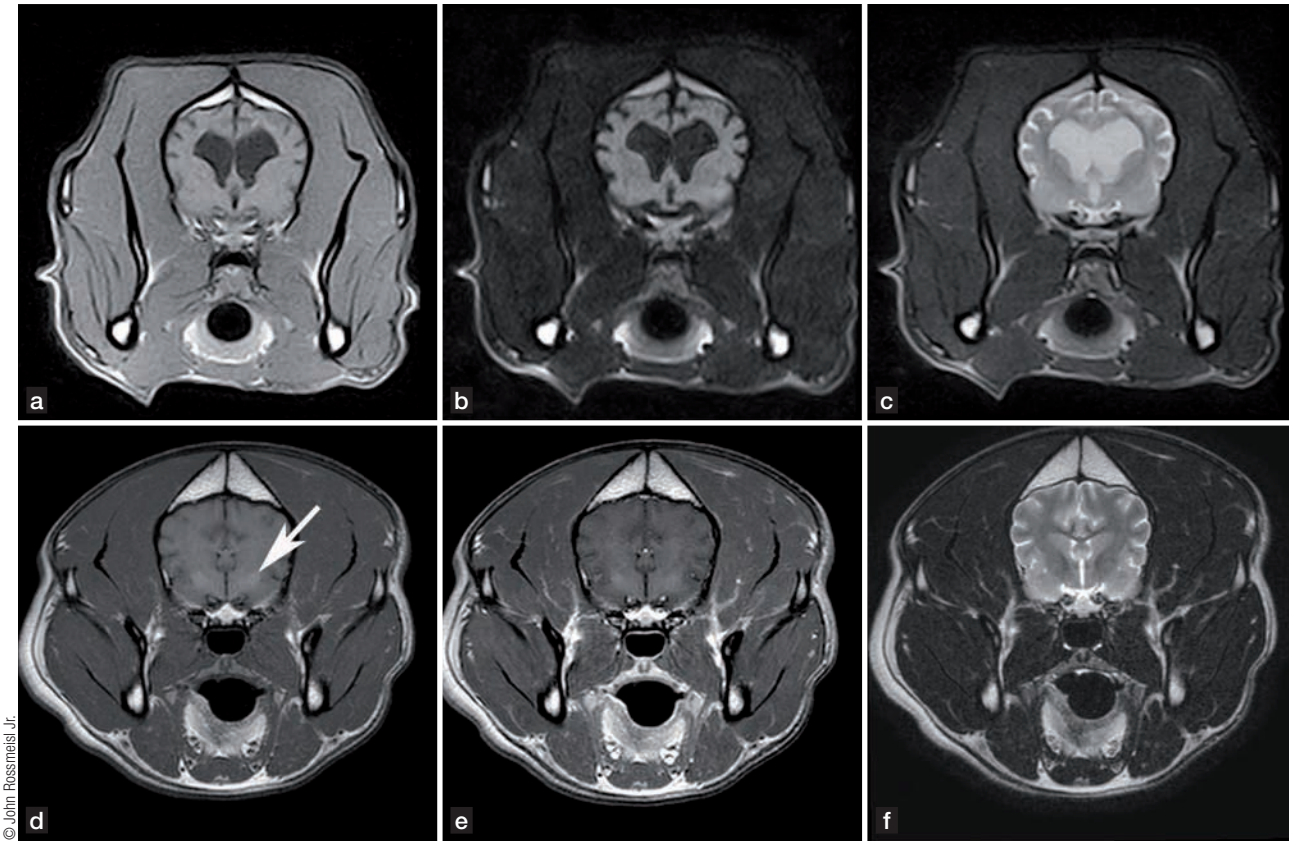


Figure 4. MRI features of hepatic encephalopathy associated with congenital portosystemic shunts. Top panels **(a-c)** obtained from a 2-year-old, female Cocker Spaniel with chronic behavioral changes show diffuse cerebrocortical atrophy as demonstrated by the excessively deep and widened sulci and lateral ventriculomegaly. Bottom panels **(d-f)** obtained from a 1-year-old Bulldog with congenital, intrahepatic PSVA show bilaterally symmetric T1-hyperintense, non-contrast-enhancing lesions within the lentifom nuclei (arrowed in image **d**). In both rows of images, the left panels are T1-weighted images and the right panels T2-weighted images. The top middle panel is a FLAIR image, and the bottom middle panel is a T1-weighted post-contrast image.

trauma, and neoplasia. The imaging features of CVA have been well documented ***(Figure 5)*** (6,7).

Laboratory investigations are rarely normal in dogs with AME, thus an unremarkable CBC, serum biochemical profile, and urinalysis in a dog with clinical signs of diffuse or bilaterally symmetric forebrain dysfunction greatly increase the probability that a toxic encephalopathy or structural brain disorder is present.

Treatment of AME

There are three components to therapy: 1) restoration and maintenance of vital homeostatic functions, 2) initiation of appropriate therapy for the specific etiology, and 3) symptomatic treatment of any associated complications. Restoration of vital parameters for dogs with AME follows the unifying principles of emergency medicine: maintenance of peripheral tissue oxygenation, perfusion and arterial blood pressure. Clinicians should make every attempt to achieve normal ventilation, normovolemia, and normotension. Any electrolyte or acid-base disturbances identified should be judiciously corrected.

Cerebral edema, which is a fundamental event in hypertensive encephalopathy and a complication of hypoglycemia and HE, can be treated with mannitol (0.5-1.0 g/kg IV over 15-30 minutes) and furosemide (0.75-2 mg/kg IV) (5,8). Dogs should be well hydrated and normotensive prior to diuretic treatment.

Hypoglycemia

Acute hypoglycemic crises are treated with 50% dextrose (0.5-1.0 g/kg diluted 1:4 with 0.9% NaCl IV over 1-5 minutes), followed by IV infusions of 2.5-5.0% dextrose solution to maintain euglycemia. Intravenous glucagon (5-15 ng/kg/min as a constant rate infusion) has been shown to be efficacious in maintaining euglycemia in dogs with insulinomas or other causes of refractory

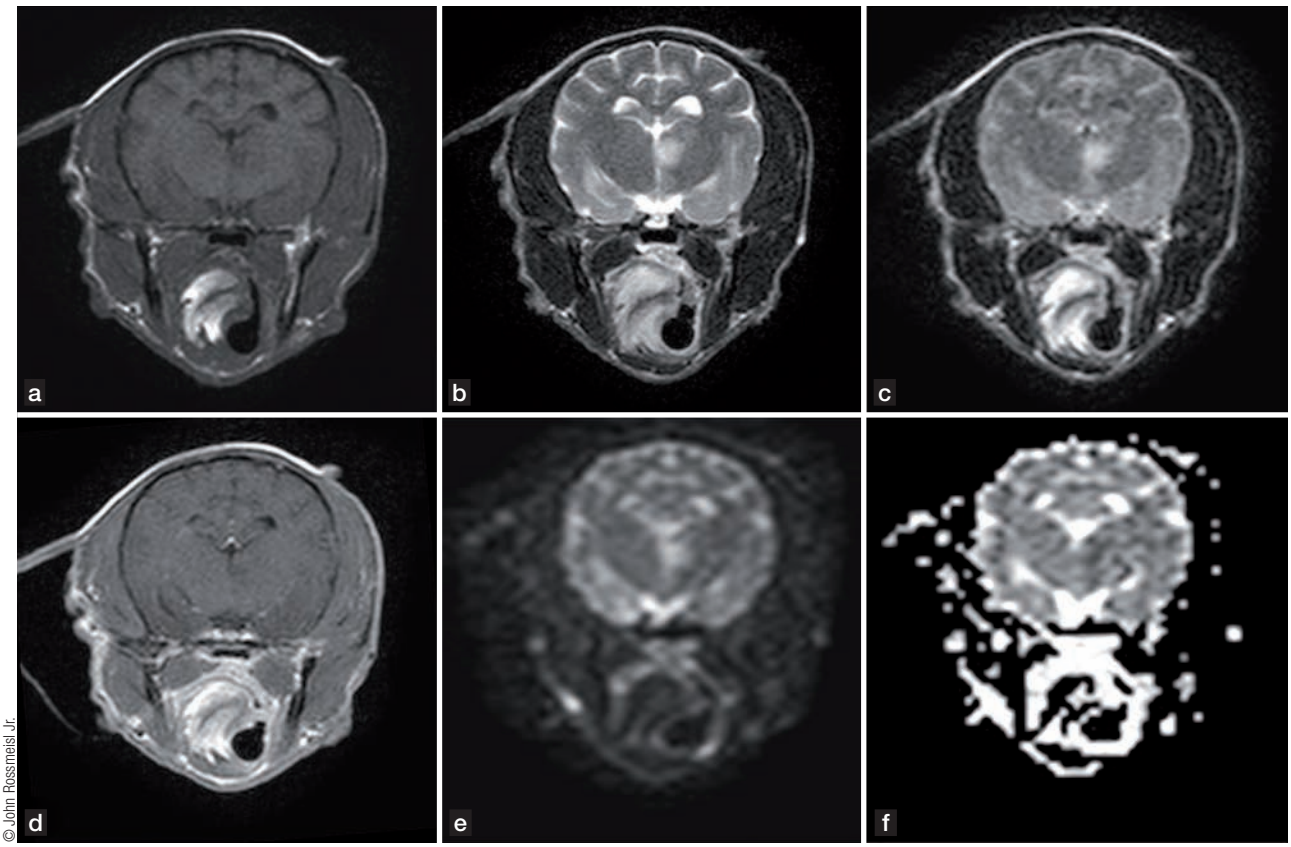


Figure 5. MRI appearance of thalamic ischemic stroke. A focal lesion is present in the left diencephalon that is T1-hypointense **(a)**, T2 **(b)** and FLAIR **(c)** hyperintense, and non contrast-enhancing **(d)**. The irreversibly damaged infarcted region appears hyperintense on the diffusion weighted image **(e)** and as an area of diminished signal in the corresponding apparent diffusion coefficient map **(f)**.

hypoglycemia (13). Dogs with transient juvenile or recurrent substrate-limited hypoglycemia benefit from frequent feeding of energy dense diets, such as those formulated for puppy growth or illness recovery.

Hepatic encephalopathy

Surgical correction of congenital PSVA is potentially curative, whilst treatment of HE secondary to acquired, end-stage hepatic disease is primarily palliative. Correction or avoidance of any factors known to precipitate HE, such as dehydration, gastrointestinal hemorrhage, constipation, hypokalemia, infection, and hepatically metabolized drugs is crucial (4,5). The fundamental role of ammonia in the pathophysiology of HE is evident in the fact that most therapies of value reduce ammonia production or absorption.

Dietary modification is paramount in the management of HE (14) as intestinal ammonia production can be greatly reduced through a nutritionally balanced, yet protein-restricted diet, such as prescription low-protein liver diets, divided into several daily meals.

Endogenous and dietary ammoniagenic substances can be reduced by administration of cleansing enemas or non-absorbable disaccharides, such as lactulose (0.5-1.0 mL/kg PO q8H). Lactulose is a purgative and lowers the colonic pH, resulting in a microenvironment unfavorable to urease-producing bacteria. Colon acidification reduces ammonia absorption by trapping ammonium ions in the bowel lumen. Administration of antibiotics with a spectrum that includes urease-producing bacterial flora, such as neomycin (10-20 mg/kg PO q8-12H), amoxicillin (22 mg/kg PO q8H), or metronidazole (7.5-15 mg/kg PO q12H), is also recommended.

Seizures associated with HE can be treated with levetiracetam (20-40 mg/kg PO, SC, or IV q8H) or potassium

bromide (30-40 mg/kg PO q24H). Pretreatment with levetiracetam for at least one day prior to surgical attenuation has been reported to decrease the risk of postoperative seizures and death in one study of dogs with extrahepatic PSVA (15).

CVA and hypertensive encephalopathy

Dogs with clinical or diagnostic imaging evidence of CVD should be screened for hypertension, and evaluated for predisposing medical conditions (6). The therapeutic goals for dogs with CVA are maintaining cerebral blood flow and normal ventilation to preserve tissue in the ischemic penumbra (7). There is currently no evidence to support thrombolytic therapy in veterinary patients with CVA, unless indicated for treatment of a predisposing condition; most dogs with CVA will improve clinically within 2-4 weeks with supportive care.

Antihypertensive treatment is indicated in hypertensive (systolic BP >160 mmHg or diastolic BP > 95 mmHg) dogs with encephalopathic signs. Enalapril (0.5 mg/kg PO q12-24H) or amlodipine (0.1-0.2 mg/kg PO q24H) may be beneficial alone or in combination (8). The acute and often severe (≥ 200 mmHg systolic) elevations in blood pressure that accompany hypertensive encephalopathy warrant usage of antihypertensive drugs with a rapid onset of action; hydralazine (0.1-0.2 mg/kg IV or IM q2-4H as needed), or esmolol (50-75 µg/kg/min IV constant rate infusion) in combination with furosemide (0.75-2 mg/kg IV q8-24H), for both its antihypertensive and anti-edema effects, may be used. Dogs treated with these agents should be closely monitored for the development of hypotension during therapy. Phenoxybenzamine (0.25 mg/kg PO q8-12H) is the treatment of choice for hypertensive dogs with pheochromocytoma (16). Neurological deficits associated with hypertensive encephalopathy should improve within 24-72 hours of blood pressure normalization (8).

Conclusions

Identification of clinical signs of diffuse forebrain dysfunction in dogs with or without signs of systemic organ dysfunction should raise the clinician's index of suspicion for AME, and is an indication for performance of a complete blood count, serum biochemical profile, and urinalysis. Integration of historical, physical, and laboratory abnormalities will typically allow definitive diagnosis of the etiology, and with prompt therapy directed at the etiology and supportive measures focused on restoration of cerebral blood flow, energy substrate delivery, and ionic homeostasis, the neurological dysfunction is often reversible.

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Canine lysosomal storage diseases

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Introduction

Degenerative heritable diseases involving the brain can often seem intimidating due to the large number of different disorders and the fact that many breeds are predisposed to certain specific diseases. However, if the various disorders are grouped according to their identifiable characteristics (*i.e.*, what makes each stand out from the rest), they can become more manageable. This article considers the clinical characteristics of lysosomal storage diseases, focusing on clues that help to identify these disorders in a particular patient, and discusses testing that can aid in diagnosis. However comparison tables are included ***(Tables 1 and 2)*** to highlight various degenerative canine encephalopathies with clinical signs that can overlap with that of lysosomal storage disorders, particularly those seen in young animals and in breeds predisposed to multiple degenerative disorders.

KEY POINTS

- **Animals diagnosed with lysosomal storage diseases are typically less than 1 year of age. Exceptions can include neuronal ceroid lipofuscinosis and globoid cell leukodystrophy.**
- **Simple physical examination and routine diagnostic testing (*i.e.*, blood work, radiography, ultrasound exam) can yield important diagnostic clues in animals with lysosomal storage diseases.**
- **Genetic testing is available in some cases for specific breed-related problems.**
- **A negative (*i.e.*, "normal") metabolic disease panel does not guarantee the absence of a lysosomal storage disorder.**

Etiology of lysosomal storage disorders

Most degenerative encephalopathies, including lysosomal storage disorders, are suspected to result from inborn metabolic derangements occurring at the cellular level. Other proposed causes include abnormally programed cell death and a genetic predisposition for autoimmune destruction of neurons and/or glial cells. As the name implies, lysosomal storage diseases more specifically occur as a result of the absence or dysfunction of a lysosomal enzyme. In normal circumstances, intracellular materials such as cell membrane components are broken down within lysosomes, in a predictable step-by-step fashion, by a series of lysosomal enzymes, allowing end products to be recycled into new cellular materials. If a step within this chain of events cannot be performed because the necessary enzyme is either deficient or absent, the material resulting from the previous step inappropriately remains and accumulates (*i.e.*, "stored"), typically in the form of spheroids. This accumulation of residual substrate causes neuronal swelling and toxicity, affecting both the neurons and the surrounding glial cells. In most lysosomal storage diseases the dysfunctional step involves an acid hydrolase, particularly exoglycosidases; in the case of neuronal ceroid lipofuscinosis a proteinase is instead deficient (1-5).

Lysosomal storage disorders involving the central nervous system may be grouped by the storage product that accumulates, as shown in ***Table 3***. An autosomal recessive mode of inheritance is suspected for most lysosomal storage diseases, although the specific causative mutation remains to be elucidated in many subtypes (1-4).

Table 1. Manifestations of breed-related subacute hereditary necrotizing encephalitis that clinically resemble lysosomal storage diseases.

Disease name	Typical age at onset	Clinical manifestations	Progression	Diagnostic tests
L-2 hydroxyglutaric aciduria*(20)	4-5 years (4 months-7 years)	Seizures, behavior/mentation changes, cerebellar ataxia, head tremors	Insidious onset, slow progression	Elevated L-2-hydroxyglutaric acid levels in plasma/urine
Cerebellar cortical degeneration* (21)	4-6 years (18 months-9 years)	Cerebellovestibular	Slow progression	MRI, brainstem auditory evoked response testing
Neuronal ceroid lipofuscinosis (adult-onset thalamocerebellar degeneration)*(22)	2-5 years	Cerebellovestibular ataxia	Slow progression	Canine ceroid lipofuscinosis (CCL) test
Subacute necrotizing encephalopathy of Staffordshire Bull Terriers (Leigh-like syndrome)*(23)	6-8 weeks	Cerebellovestibular, strabismus	Rapidly progressive	Elevated lactate level, abnormal lactate:pyruvate ratio
Subacute necrotizing encephalopathy of Alaskan Huskies (23,24)	7 months-2.5 years	Cerebellovestibular ataxia, seizures, visual deficits, behavioral changes	Acute onset, then static or improved; frequent recurrences	None
Subacute necrotizing encephalopathy of Yorkshire Terriers (23)	4 months-5 years	Mentation changes, visual deficits, seizures, ataxia	Rapidly progressive	None

*Affected breed - Staffordshire Bull Terrier

Table 2. Canine degenerative cerebellar disorders with clinical signs similar to lysosomal storage diseases.

Cerebellar disease	Primary affected breed(s)	Other reported breeds	Age of onset	Associated signs
Cerebellar cortical degeneration/ abiotrophy (1,2,21)	Kerry Blue, Staffordshire* & Staffordshire Bull Terriers; Gordon Setter*, Border and Rough-coated Collies, Brittany Spaniel*, Bullmastiff, and Old English Sheepdog*	Scottish Terrier*, Samoyed, Airedale, Labrador and Golden Retrievers, Finnish Harrier, Beagle, Cocker Spaniel, Great Dane, Cairn Terriers	3-12 months	Cerebello-vestibular; progressive
Neonatal ataxia (1,2)	Coton de Tulear	N/A	~2 weeks	Cerebello-vestibular, “swimmers”; non-progressive
Neuroaxonal dystrophy (1,2)	Rottweiler	Collie, Boxer, German Shepherd, Chihuahua	1-2 years	Cerebello-vestibular; progressive
Hepatocellular degeneration syndrome (25)	Bernese Mountain Dog	N/A	4-6 weeks	Cerebellar & hepatocellular degeneration; progressive
Neonatal granuloprival ataxia (1,2)	Jack Russell and Parson Russell Terriers	N/A	1-2 months	Cerebellar ataxia
Late-onset ataxia (1,2)	Jack Russell and Parson Russell Terriers	N/A	6-9 months	Cerebellar dysfunction; progressive

*Adult onset, 2-8 years old

Clinical signs

Affected dogs are born asymptomatic, but as storage materials accumulate they gradually develop neurological signs, which tend to appear insidiously but worsen over weeks to months; occasionally, dogs may experience an acute aggravation of clinical signs, which can mimic a sudden onset of disease if previous subtle abnormalities were unnoticed (1).

The clinical signs appear within the first year or two after birth (*i.e.*, first weeks to months) with most lysosomal storage diseases. Dogs with neuronal ceroid lipofuscinosis also typically develop signs as young adults (*i.e.*, 1-2 years of age), although they can infrequently remain symptom-free until well into adulthood; onset as late as 9 years of age has been described. Similarly, depending on the breed, manifestation of canine globoid cell leukodystrophy can range from as young as 6 weeks up to 4 years of age (1-3,6-8), and one report has described a 14-year-old Pomeranian with this condition (6)

Neurologically, cerebellar dysfunction is initially noted, with or without a vestibular component. Cerebellar signs commonly include intention tremors, cerebellar (*i.e.*, hypermetric, spastic) ataxia, and a wide-based stance. There may also be a menace deficit (without changes in vision or facial nerve dysfunction) and anisocoria. This is followed by increasingly diffuse involvement of the central nervous system, ending in global/multifocal encephalopathic signs. The early presentation differs in canine neuronal ceroid lipofuscinosis, fucosidosis, and neuronal glycoproteinosis (Lafora's disease), which may initially present as forebrain dysfunction, with seizures, visual deficits and behavioral and mentation changes; cerebellar dysfunction develops later in the disease course in these cases (1-4,6-10).

Extracranial manifestations often develop in addition to neurologic dysfunction. This can include peripheral nerve dysfunction in dogs with fucosidosis, globoid cell leukodystrophy, glycogenoses, and sphingomyelinosis. Palpable enlargement of the ulnar nerve is detectable in dogs with fucosidosis, which serves as an excellent beacon for the disease ***(Figure 1)*** (1,2). Skeletal abnormalities, such as dwarfism, craniofacial malformations, and joint laxity and effusion develop in dogs affected by gangliosidosis, mannosidosis, mucopolysaccharidosis, and mucolipidosis II. In the latter two diseases, continuous vertebral growth can result in nerve root compression and bony intrusion into the spinal cord, causing a compressive myelopathy and spinal pain. Gangliosidosis manifests instead as abnormally enlarged intervertebral disc spaces, along with dwarfism and facial abnormalities (11).

Lysosomal storage diseases can also have more global systemic manifestations. In particular, organomegaly of the liver and spleen can develop in cases of sphingomyelinosis, mannosidosis, glycogenosis, glucocerebrosidosis, gangliosidosis, and mucopolysaccharidosis. In addition, cardiac disease (in glycogenosis), retinal degeneration (in ceroid lipofuscinosis, mucolipidosis II), and corneal opacity (in mucopolysaccharidosis I, VI, VII, gangliosidosis, mannosidosis) may be seen (1,9).

Diagnosis

Initial clinical suspicion is based upon a compatible signalment and clinical history; *i.e.*, young age, reported breed, and slowly progressive clinical signs, particularly with initial manifestations suggesting cerebellar dysfunction. Extracranial manifestations, such as ulnar nerve enlargement or craniofacial malformations, raise the index of suspicion.

Where available, genetic testing (*i.e.*, genotyping assays) provides the most rapid and least invasive method of diagnosis in an animal with a compatible clinical presentation. In most cases samples (cheek swabs)

Table 3. Classification of lysosomal storage diseases.

Category	Examples of storage disease
Glycoproteinosis	Fucosidosis; mannosidosis; neuronal glycoproteinosis (Lafora's disease)
Oligosaccharidoses	Glycogenosis types I A, II, III A and IV
Sphingolipidoses	Gangliosidosis GM1 types I and II; glucocerebrosidosis; globoid cell leukodystrophy
Mucopolysaccharidoses	Mucolipidosis type II; mucopolysaccharidoses type I, II, III A and B, VI, VII
Proteinosis	Ceroid lipofuscinosis

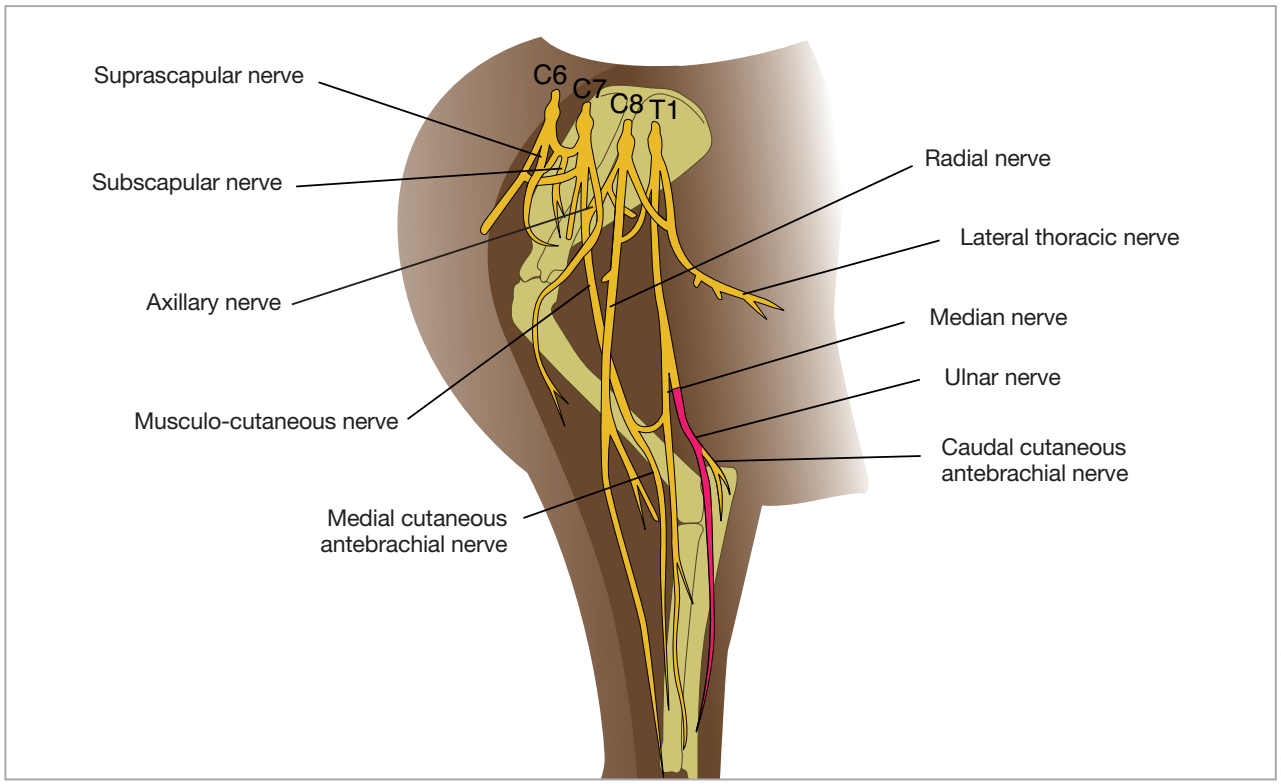

Figure 1. The clinician should carefully assess the forelimbs during physical examination; an enlarged ulnar nerve may be detected in dogs with fucosidosis.

can be obtained and submitted by owners directly. Unfortunately, these tests are only available for a subset of lysosomal storage diseases and in specific breeds where the underlying mutation has been identified. Specifically, of the glycoproteinoses, only fucosidosis has an available genetic test for English Springer Spaniels. Of the sphingolipidoses, gangliosidosis GM1 (Portuguese Water dogs), gangliosidosis GM2 (Japanese Chins), and globoid cell leukodystrophy (Cairn and West Highland White Terriers) have tests commercially available in some countries. The genetic mutation responsible for glycogenosis type IIIa (an oligosaccharidosis) can be detected in the Curly Coated Retriever, whereas that of neuronal ceroid lipofuscinosis can be found in the Border Collie, Tibetan Terrier, Dachshund, American Bulldog, and English Setter breeds. Lastly, genetic testing is available for mucopolysaccharidosis types IIIB (Schipperke), VI (Miniature Pinscher), and VII (German Shepherd dog) (3,9,11-13).

In cases where a lysosomal storage disease is suspected but genetic testing is either unavailable for the affected breed or negative test results are obtained, definitive diagnosis necessitates identification of the specific accumulated storage product or demonstration of a particular enzyme deficiency. In these cases routine tests can often provide important clues.

Physical examination can reveal classic suggestive abnormalities such as ulnar nerve enlargement, craniofacial malformations, and joint laxity. Abdominal palpation and ultrasonography may reveal organomegaly and, if followed by ultrasound-guided biopsy of affected organs, can allow identification of storage material. Simple blood smear evaluations reveal abnormal storage material within leukocytes in some cases. Finally, an ophthalmologic examination is important to determine if retinal degeneration or corneal abnormalities are present (1,5,11-15).

If clinical evidence of a myelopathy is found on neurologic examination, spinal radiographs serve as a useful screening test to determine whether vertebral bony proliferation is present (as seen in mucopolysaccharidosis and mucolipidosis II). In these cases the presence and extent of spinal cord compression may be confirmed

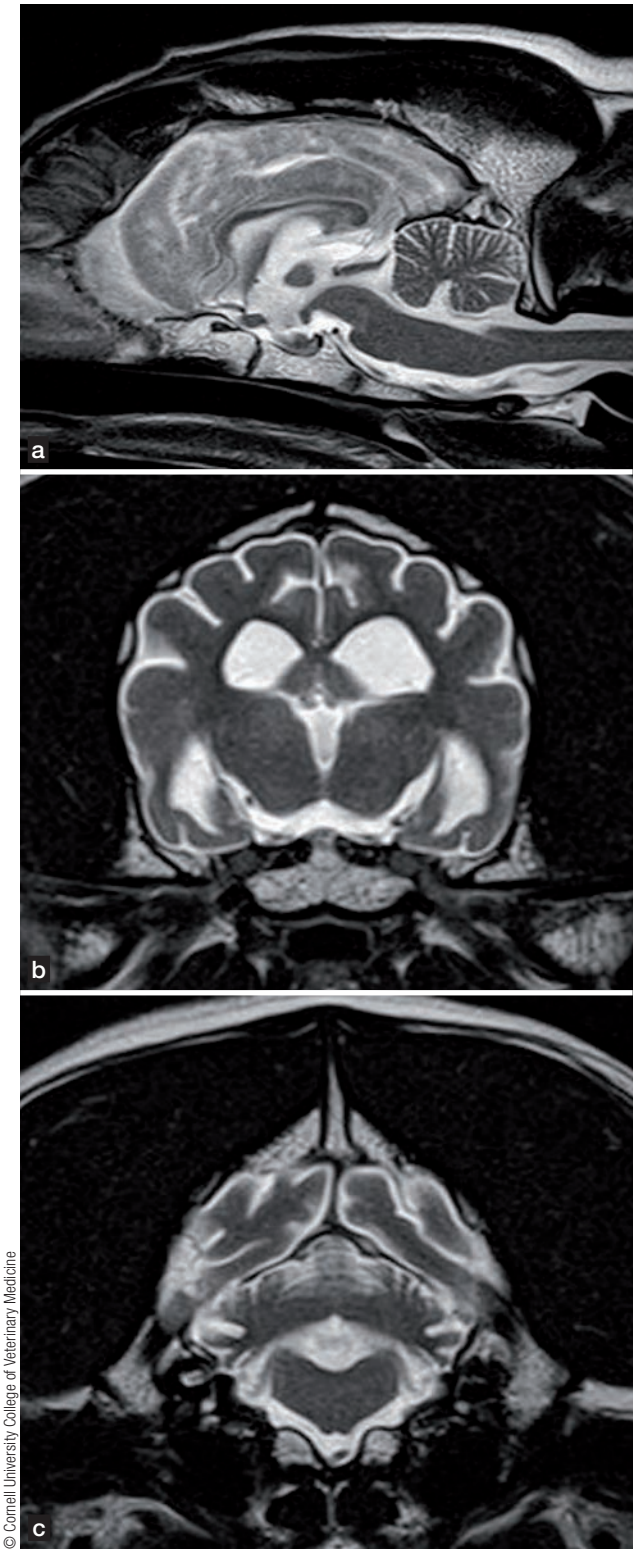

Figure 2. Sagittal **(a)** and transverse **(b-c)** T2-weighted MRI images of the brain demonstrating atrophy of the cerebral cortex, interthalamic adhesion, and cerebellum in a 1-year-old mixed-breed dog with a history of seizures.

using magnetic resonance imaging (MRI). Imaging of the brain with computed tomography or MRI may also prove useful towards attaining a presumptive diagnosis, as certain storage diseases can have classic findings. For example, dogs with neuronal ceroid lipofuscinosis and mucopolysaccharidosis I demonstrate cerebrocortical atrophy and secondary ventriculomegaly; these changes are also seen with canine cognitive dysfunction, but if demonstrated in an animal too young to have cognitive dysfunction this would raise suspicion of storage disease ***(Figure 2)*** (1,5,14). Meningeal thickening is reported in addition to cerebrocortical atrophy in Chihuahuas with neuronal ceroid-lipofuscinosis (7). In contrast, MRI in dogs with globoid cell leukodystrophy and gangliosidosis (GM1) may show diffuse symmetric white matter involvement; brain atrophy develops later in these cases (1,4,10).

Cerebrospinal fluid analysis typically yields normal results or demonstrates a non-specific, mild elevation in protein levels, but can be helpful in excluding other differential diagnoses such as infectious or presumed autoimmune encephalitides. Skin and brain biopsies may prove useful in identifying accumulated storage products. Finally, specific "metabolic disease panels" that evaluate blood and urine samples for the presence of an inborn error of metabolism, including lysosomal storage disorders, can yield a definitive diagnosis. Unfortunately, however, not all errors of metabolism can be identified; for example, of the lysosomal storage diseases, only mannosidosis, mucopolysaccharidosis and gangliosidosis can be detected in urine samples. For this reason, a "normal" metabolic panel does not exclude the presence of an inborn error of metabolism (1,2,12,13).

Treatment

In general, these conditions are associated with a poor prognosis, as clinical signs progress despite attempts to slow their course. Gene therapy (*i.e.*, delivering a normal, functional, copy of the mutated gene) is at an early stage but has had promising results, particularly in the case of feline α-mannosidosis. The fact that dogs can mimic multiple human lysosomal storage diseases has facilitated advances in the treatment of canine storage diseases. For example, cerebrospinal fluid-mediated gene transfer in Beagles with mucopolysaccharidosis IIIA and VII has had preliminarily positive results (16,17). Intrathecal administration has also allowed effective recombinant protein delivery and resulted in reduced severity of disease in dogs with mucopolysaccharidosis I.

However, the blood-brain barrier serves as a major barrier to systemic drug delivery, hence the requirement for invasive treatment methods such as intrathecal drug delivery. In addition, methods of controlling the humoral immune response to protein administration, the dosages and frequency of administration remain to be fully elucidated in most cases. For this reason, to the author's knowledge there are no commercially available treatments for canine lysosomal storage diseases at this time (18,19).

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Feline cognitive dysfunction syndrome

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Introduction

Cognitive dysfunction is a condition of the older cat, and so of growing importance to the practitioner as the feline population demographic ages. In the USA, there has been a 15% increase in the number of cats over 10 years old within the last 20 years, and more than 18 million cats in the USA are now 12 years or older (1), whereas in the UK there are an estimated 2.5 million senior cats, about 30% of the owned population; across Europe, the total is around 20 million (30% of the pet cat population) (2). Accordingly, there is a need for the veterinary profession to focus more attention on quality of life issues and not simply accept certain changes as inevitable. Unfortunately, there is no consensus at which a cat becomes physiologically senior, since individuals may age at different rates. A pragmatic way to classify older cats is to consider those between 7-10 years old as "middle-aged", those between 11-14 years old as "senior", and those over 15 years old as "geriatric". When it comes to brain deterioration, 50% of cats have signs of dementia at 15 years of age; in humans, approximately 50% of 85 years old have such signs (3-5). In this article, for the sake of simplicity, the term "senior" refers to all older cats.

KEY POINTS

- **Cognitive dysfunction syndrome (CDS) is a condition of the older cat and is of growing importance to the practitioner as the feline population demographic ages.**
- **CDS must be distinguished from other age-related changes which may cause superficially similar signs.**
- **CDS cannot be cured, but its progress can be slowed, and clinical signs may be improved with medical and behavioral intervention.**
- **There is a need for the veterinary profession to focus more attention on quality of life issues and not simply accept certain changes as inevitable.**

Cognitive dysfunction syndrome (CDS) is a specific disorder affecting both older dogs (in whom it is well studied as a model of human Alzheimer's dementia) and cats. CDS needs to be distinguished from other age-related changes (which can cause superficially similar signs) as its neurological features indicate specific interventions which can be unhelpful or even contra-indicated in the management of some of its differentials. Although behavior is controlled by the brain, it is important to appreciate that not all age-related behavior problems are due to poor brain function; behavioral problems in senior individuals can reflect age-related deterioration in a wide range of

tissues. For example, house-soiling may start because of the pain associated with arthritis when trying to access a litter tray. Irritability manifested as aggressive behavior may result from general discomfort (*e.g.*, dental pain), or metabolic diseases such as hyperthyroidism, and increased anxiety may be a sign of chronic kidney disease. These changes may be the first overt sign of the more remote problem and are therefore important in enabling an early diagnosis. To accept such alterations in the senior cat as "inevitable effects of aging" is to disregard the care of patients, and this article aims to provide an overview of brain aging, and especially feline CDS, whilst offering guidance to the practitioner on diagnosis and potential treatment options.

Aging and CDS

Neuropathology of age-related brain changes

The association between neuropathology and age-related behavioral disorders in cats is not well defined. However, as with humans and dogs, there are changes in cat brain anatomy and physiology, such as cerebral atrophy, resulting in increased ventricular size, widening of sulci ***(Figure 1)*** and atrophy of the cholinergic system in the locus ceruleus which may explain disruption of the sleep-wake cycle (6). Abnormal mitochondria, large vacuoles and accumulation of lipofuscin have been observed ultrastructurally, with fewer microfilaments on dendrites in this area (7).

Brain aging and CDS are not the same, and the former does not necessarily result in the latter; CDS has specific pathological features. Aβ plaque formation, which is thought to be involved in brain aging and Alzheimer's disease in humans, has been found in the brain of cats as well (3), but the distribution is different and the association between Aβ deposition and CDS in senior cats (unlike Alzheimer's in humans or CDS in dogs) has not been confirmed. One study of three aged cats with abnormal behavior demonstrated senile plaques in the brain (8), and whilst one paper reported that these plaques were more common in cats with behavioral disorders (9), another study of cats with well documented CDS failed to demonstrate a correlation between behavioral changes and Aβ formation (3). Hyperphosphorylated tau fibrils, another feature of human Alzheimer's, can also be found in cats with senile plaque formation, but the association between it and CDS has yet to be established (3,9).

Behavioral changes during aging

As a cat ages, many behavioral alterations may occur that are often overlooked or viewed as inevitable age-related changes. Owners appear to seek help largely for those changes that impact on their own quality of life, *e.g.*, when a cat soils in the house or is aggressive, but other changes may occur more frequently ***(Table 1)***, and many common changes may therefore go unreported by owners unless they are specifically raised by the veterinarian. One survey suggested 75% of owners will report signs of CDS when specifically asked about them, but only 12% volunteer this information (10), and many cases go undiagnosed; one study found 14% of animals aged 8-19.75 years had CDS but the diagnostic prevalence was only 1.9% (11). In cats aged 11-21 years, it has been found that 36% exhibited behavioral signs that could not be attributed to any underlying medical disease (12); between 11-14 years of age the most common alteration was in social alteration, while in those > 15 years old the most frequent change was excessive vocalization and altered activity levels.

Diagnosis of behavioral problems

General approach

The diagnosis of feline CDS is often a diagnosis of exclusion, inferred *ante-mortem* in older cats when there has been a decline in a particular cluster of behaviors

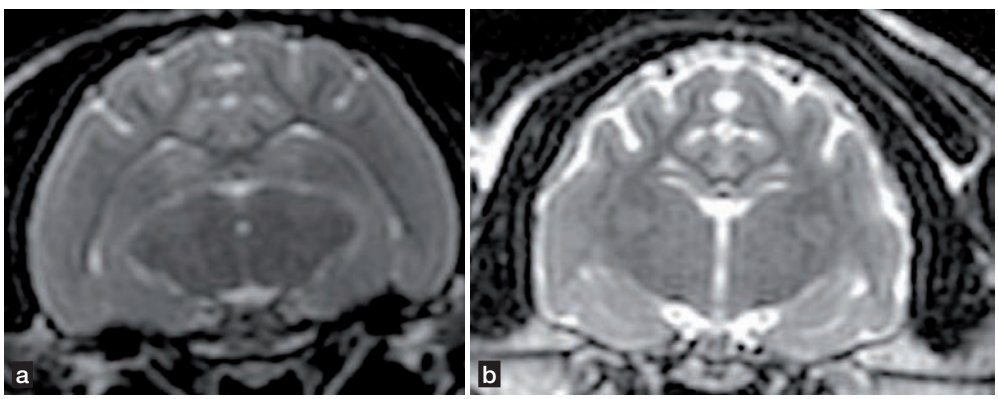

Figure 1. Transverse MRI sections from 1-year-old **(a)** and 13-year-old **(b)** cats. The CSF appears white. In the older cat, the ventricles are enlarged, but cortical atrophy has caused the sulci to increase in size, and are therefore more prominent as a result.

Table 1. Comparisons of behavioral problems as reported by owners of senior cats to three referral practices and more generally (VIN - Veterinary Information Network - data) (13).

Behavioral referral practices (83 cats, aged > 10 years)	VIN boards (100 cats, aged 12-22 years)
House soiling (elimination and marking) 73%	Excessive vocalization 61% (night vocal 31%)
Intercat aggression 10%	House soiling (elimination and marking) 27%
Aggression to humans 6%	Disorientation 22%
Excessive vocalization 6%	Aimless wandering 19%
Restlessness 6%	Restlessness 18%
Overgrooming 4%	Irritability/aggression 6%
	Fear/hiding 4%
	Clinging attachment 3%

associated with cognitive ability that cannot be attributed to any related medical conditions. These signs typically include disorientation or confusion, alterations in social relationships (following the owner more or social withdrawal), a change in activity, alterations in the sleep-wake cycle, inappropriate vocalization, a decline in learning and memory, a change in interest in food, and decreased grooming activity (14). When a senior cat is presented with behavioral problems, two main differential categories must be excluded: firstly, environmental changes that affect the cat's behavior, *e.g.* a new baby or pet, a house move etc.; and secondly (and more difficult to exclude), other medical problems. During aging, cats are likely to develop an increasing number of both intra- and extra-cranial health problems, but it can be particularly difficult sometimes to diagnose what role, if any, they play in the cat's behavior. Intra-cranial differentials include pathologies such as forebrain meningiomas and vascular accidents which can cause either sensory deficits or motor control problems. Extra-cranial differentials include a range of metabolic disorders, especially those affecting liver or kidney function, endocrine problems such as hyperthyroidism, and various conditions which compromise cardiorespiratory and circulatory function. Perhaps most important are causes of pain such as arthritis or periodontal disease. Periodontal disease may occur in over 60% of cats older than 3 years (15) and osteoarthritis may be present in 70-90% of cats over 10 years of age (14). The latter may not present as an obvious lameness, but instead as abnormal elimination habits, poor grooming and/or aggressive behavior (16). It is also important to realize that other behavioral problems, such as anxiety, may coexist alongside CDS and any concurrent medication for other conditions may also impact on behavior.

Approach to feline CDS

It is suggested that the acronym DISHA, which is used to describe the cardinal signs of CDS in dogs, can also be applied to cats. DISHA refers to:

- **D**isorientation
- **I**nteraction alterations with owners and other pets
- **S**leep-wake cycle changes
- **H**ousesoiling
- **A**ctivity level alterations (decreased or increased)

However, other signs such as excessive vocalization, altered response to stimuli, reduced self-hygiene and alteration in appetite may also be important to the diagnosis of feline CDS (13), but these changes are reported quite frequently in senior cats with other conditions and so the diagnosis is based on careful evaluation of these signs in the context of the individual. It is unreasonable to expect exclusion of all other medical options before suggesting a diagnosis of CDS.

When spatial disorientation is reported (*e.g.*, where the cat is trapped in a corner or stares at a wall), neurologic disorders such as sensory deficits, pain and disrupted motor functions must be ruled out. Disorientation was reported in 22% of senior cats in general practice (13) and is often taken as a strong indicator of potential CDS, as few common medical conditions will result in similar behavior, especially if other neurological deficits are absent.

A cat may show altered social interactions such as irritability or wanting to be near people or other cats, with aggressive behavior occurring in ~6-10% of senior cats (13), but before suggesting these signs are associated with CDS, medical conditions relating to pain and sensory deficits should be ruled out, alongside specific behavioral conditions such as attention seeking or social conflict in the home.

An abnormal sleep-wake cycle, with the cat waking up, vocalizing and disturbing the owner during the night, may also be the result of pain, sensory deficit and hypertension and is the most common owner-reported problem (61% of cases (13)). A cat with painful joints due to osteoarthritis may avoid resting in the same position for a long period of time and will no longer sleep through the night. This is an obvious welfare concern, and so the evaluation of painful medical conditions (*e.g.*, with radiographs or a trial with a short analgesia course) should be a priority if alterations in the sleep-wake cycle are thought to be a sign of CDS.

House soiling (*i.e.*, urine or feces outside the litter tray) is a major reason for owners seeking help from their veterinarian; 27% of senior cats presented with behavioral problems show this sign (13). Whilst house soiling by senior cats may be caused by many of the same conditions that affect younger cats (*e.g.*, cystitis, colitis, litter tray aversion, scent marking etc.), the likelihood that painful conditions can alter use of a litter box is greater in older animals; *e.g.*, osteoarthritis may limit the potential to climb a staircase to access a tray sited in an upper room. For this reason, investigation of litter tray and changes to the environment are essential when considering the potential significance of house-soiling to CDS, and while CDS may well cause house soiling it does not exclude concurrent medical or behavioral issues.

Senior cats can be expected to decrease their activity level due to chronic pain and musculoskeletal weakening, and it is important to appreciate that a CDS related change in activity will often coexist alongside decreased activity due to other conditions, and in these cases both must be recognized and addressed accordingly. Senior cats may also increase their activity level, in the form of repetitive activity, aimless wandering or restlessness for many reasons. These behaviors can be elicited by painful, metabolic or behavioral conditions such as anxiety as well as being specifically evoked by CDS. Increased or decreased activity level is present in 20% of senior cats in first opinion practice (13), and decreased activity in itself as an aid to diagnosing CDS is generally low as it has so many other explanations; on the other hand, increased activity levels are perhaps more indicative of potential CDS, especially when the form of increased activity is carefully examined, any pain has been controlled and hyperthyroidism ruled out.

Other behaviors that are described in senior cats include excessive vocalization, altered response to stimuli, decreased self-hygiene and altered appetite and may be linked to both age-related extra-cranial medical changes and CDS. Pain, sensory deficits and hypertension are particularly important to evaluate alongside CDS. Excessive vocalization is one of the most common owner complaints, with 61% of elderly cats showing this sign in first opinion practices (13), and if painful conditions can be excluded it is one of the more useful signs in the diagnosis of CDS. CDS-related changes may also result in specific anxiety problems as well as temperament alterations.

Often, CDS is characterized by a steady progression, and so evaluating any recent change can be useful. A simple standard questionnaire that covers the points raised above may be useful in this regard.

Treatment options

CDS cannot be cured, but its progress can be slowed and clinical signs may be improved with medical and behavioral intervention. Early diagnosis and treatment are important not only for the improvement of the cat's quality of life, but for the owners' too. Options include behavioral measures, pharmacotherapy, and nutritional supplements, and along with other general measures for aging may work synergistically to improve a senior cat's welfare. Where CDS is accompanied by anxiety, appropriate psychoactive medication should be considered and/or pheromonatherapy; the latter may be particularly useful when there are medical contra-indications to the use of drugs and when the primary signs relate to disorientation.

Pharmacotherapy

Selegiline and propentofylline are licensed in some countries for CDS and age-related changes in dogs, and can be used in cats, but the potential benefits (which can be very large) need to be weighed against the risks. Selegiline, a monoamine oxidase B inhibitor, is said to help ameliorate signs such as disorientation, excessive vocalization, decreased affection and repetitive activity, with a recommended dose of 0.5-1.0 mg/kg q24H (17). The most common adverse effects are gastrointestinal signs,

but are rarely significant in otherwise healthy animals, and in the authors' opinion it is the drug of first choice in cats with clear signs of CDS. Propentofylline, a xanthine derivative which increases cerebral blood flow, has been used to treat older dogs suffering from dullness and lethargy, and anecdotally has been reported to be effective in aged cats as well at 12.5 mg (quarter of a 50 mg tablet) per cat q24H (18).

Products that enhance cholinergic activity or which increase acetylcholine secretion may also have beneficial effects in cats with CDS, but their efficacy, pharmacokinetics and toxicity have yet to be established (7), and so their use is perhaps best left to specialists. Given the evidence for reduced cholinergic activity in the brains of cats with CDS, it is better to avoid anticholinergic drugs (*e.g.*, atropine, scopolamine, trihexyphenidyl and propantheline).

Nutritional and dietary therapy

There are few scientific studies on dietary treatment options for cats with CDS, and so many decisions are based on an adaptation of interventions used in other species. Dietary management with vegetables, nuts, whole grains and vitamins E and C can reduce the risk of cognitive decline and dementia in humans, and various dietary products containing antioxidants, fish oils and other nutritional supplements are promoted for use in cats with age-related problems. There is no peer-reviewed literature to support their value, but they may be useful adjuncts in certain situations. A preliminary study involving 46 cats on a diet supplemented with tocopherols, carnitine, vitamin C, beta-carotene, docosahexaenoic acid, methionine and cysteine reported that owners perceived improved behavior compared to subjects on a control diet (19), but it remains uncertain which of the many ingredients may actually be effective. Another supplement containing choline, phosphatidylcholine, methionine, inositol, vitamin E, zinc, selenium, taurine and other B vitamins was reported to improve confusion and appetite in 9 out of 21 cats (20). Theoretically, diets supplemented with medium-chain triglycerides may benefit aged cats but have not been evaluated in feline CDS (21). Peer-reviewed efficacy studies on even the commercially available supplements for senior cats are sadly lacking, with claims based on purely theoretical grounds and anecdote. These include herbal and nutritional supplements (such as those based on ginkgo biloba, pyridoxin, vitamin E and resveratrol), and a specific feline supplement containing phosphatidylserine, omega-3 fatty acids, vitamins E and C, L-carnitine, coenzyme Q and selenium. Note that some canine products containing alpha-lipoic acid should be avoided, because the ingredients used may be toxic to cats. However, at least one product for cats, based on S-adenosylmethionine, has been shown in a placebo-controlled laboratory test to be associated with better performance in a learning task in aged subjects (22).

Environmental modification

Environmental enrichment plays a specific role in maintaining the cognitive functioning of cats, but it is important to ensure that the animal maintains control over its environment. Excessive psychological demand will antagonize the improvement sought from enrichment, so the introduction of any new potential stressors such as environmental changes must be managed with care. The aim should be to maintain the general environmental context of the cat, while introducing new, low intensity, interesting stimuli. A young kitten to "brighten up the old cat" is not recommended. Some cats with CDS may have difficulty in coping with environmental changes or learning new routines, and so alterations may need to be quite limited and focused, with essential changes made very gradually. Some cats, especially those who get easily disoriented, can benefit from a restructuring of their environment to simplify their core area by providing everything that the cat needs (food, litter box, resting area, etc.) in a single room (14). It is also important to maintain a structured daily routine to assist temporal orientation.

Cats should have sufficient outlets and scope for maintaining their normal behavioral patterns. Plans may be required to ensure sufficient play for the cat, *e.g.*, using toys rather than social "rough-and-tumble" games. Alternative activities like hide-and-seek activities or reward-based training, and new forms of object play (*e.g.*, food manipulating toys and hanging food toys) can provide useful mental stimulation if they are not frustrating. For this reason, electronic games like laser mice and hunting on a computer screen are not recommended, as there is often no physically satisfying outlet for the cat at the end.

General adaptations

Medical conditions, and especially painful degenerative conditions, become more frequent as a result of aging, and owners should facilitate the compensations required as a result to protect their cat's welfare by modifying the domestic environment accordingly. Senior cats may be less comfortable about going outside or upstairs, and there may be an increased risk of elimination in the house

if a downstairs litter tray is not provided in an appropriate, easily accessible location. Low-sided trays on every floor accessed by the cat are recommended and should be in suitably private areas. Providing a ramp up to any cat-flap or favored area may help an animal access it more easily ***(Figure 2)***. Readily accessible food and water are also essential, and improved access may be preferred rather than relocating the feeding station. If a new location is to be used, it is worth providing several bowls initially in more easily accessible areas to see which are preferred by the cat to minimize the stress of the change.

Prognosis and long-term outlook

Early diagnosis is most important to slowing the rate of change due to CDS (which cannot be cured), and routine screening of older cats for potential signs should be the norm, with the veterinarian taking a proactive role in this regard and raising client awareness about the substantial potential to maintain a good quality of life as the cat ages. Expensive diagnostic procedures (*e.g.*, MRI) are rarely justifiable when a rational methodological approach is used in a way that focuses on welfare and risk management to identify and support cats with possible CDS.

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Figure 2. Steps and other innovations can help older cats to continue to access preferred places, such as raised areas, as they age.

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CUT-OUT AND KEEP GUIDE...

Nerve injury and pain

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Pain resulting from direct damage to the peripheral or central nervous system is a different creature than from any other process. Nerve injury can arise from many causes ***(Table 1)*** and results in a rapid and specific cascade of events leading to unique cellular, molecular, and microanatomic changes. In brief, nerve injury causes ectopic signaling from both the site of the injury (neuroma) and the dorsal root ganglion (DRG). This results in altered connectivity in the DRG and the dorsal horn of the spinal cord (via sprouting of afferents and post-ganglionic sympathetics), altered spinal excitability via loss of inhibitory control, and activation of non-neuronal (immunomodulating, glial) cells. Gene expression changes to neurons can make this condition permanent. As a result of these changes, patients can experience "maladaptive pain", which may take various facets including protracted pain, hyperalgesia (exaggerated response to a noxious stimulus), allodynia (pain evoked from a non-noxious stimulus), spontaneous pain, dysesthesias (pain in conjunction with other sensations such as tingling or itch), pain distant from the original site of injury, and pain associated with sympathetic signs (Complex Regional Pain Syndrome).

Table 1. Classification of nerve injury by etiology.

Type of nerve injury	Examples
Trauma	Blunt, surgical (transection/ amputation)
Compression	Intervertebral disc disease, neoplasia, constriction/ligation
Chemical	Neurotoxins, chemotherapeutic agents *e.g.*, vinca alkaloids (vincristine), platinum-based (cisplatin, carboplatin)
Radiation	
Metabolic	Diabetes mellitus
Infectious	Herpes virus (Shingles in humans)
Immune-mediated	Polyradiculoneuritis (a syndrome similar to Guillain-Barré in humans)

Treatment of nerve injury-related pain

When considering neurogenic, neuropathic pain in dogs and cats, it is important to remember that there are no data, other than anecdotal reports, upon which to suggest treatment strategies. The clinician should consider that customary analgesia methods for common inflammatory conditions may not apply to pain emanating from direct nerve injury (although chronic inflammation can and will eventually begin to share some of the maladaptive characteristics previously described). For example, since gross inflammation is not the most prominent feature of nerve injury-related pain, NSAIDs are unlikely to be highly effective in such circumstances, at least as a single agent. The principles of neuropathophysiology and neuropharmacology lend themselves to a rationale for certain drug types and classes, and a pharmacologic approach that emphasizes enhancing inhibitory neurotransmitters (serotonin, norepinephrine, gamma amino-butyric acid), blocking and down-regulating ion channels, dampening glial activity, and even neurotoxic strategies may be effective ***(Table 2)***. Whilst the human experience is far more robust, remember that what works for one patient may not have a reproducible effect in others. The variability in neuropathophysiology and individual expression makes it nearly impossible to predict the most effective strategy for a given patient, creating serious limitations in terms of making specific recommendations for animals – whether with regards to drug choice, dose, schedule, and even route. Customary doses can however be found in various formularies.

Treatment of nerve injury-related pain remains an active area of research in humans, with some novel modalities (*e.g.*, neurotoxins and drugs with anti-glial activity) and strategies already in clinical use or in development. Novel targets (*e.g.*, application of compounds intrathecally to directly affect the dorsal horn spinal processing) to diminish the maladaptive pain from nerve injury are also under active investigation, and whilst their use in animals is currently limited to experimental models, they may have clinical applications in the future.

Table 2. Medications used in the treatment of neurogenic and neuropathic pain.

Drug class	Primary pain-modifying mechanism	Examples	Comments
Anti-convulsants	Down-regulation of voltage-dependent calcium channels	Gabapentin, pregabalin	• Very popular in humans due to favorable AE profile.
Tricyclic anti-depressants (TCA)	Enhancement of inhibitory neurotransmitters serotonin, norepinephrine	Amitriptyline	• Most effective drug for post-herpetic neuropathy in humans, but AE can be problematic.
Selective Serotonin - Norepinephrine Reuptake Inhibitors (SNRI's)	Enhancement of inhibitory neurotransmitters serotonin, norepinephrine	Duloxetine, venlafaxine	• Duloxetine has unfavorable PK when given PO in dogs. • Venlafaxine has ~ 50% oral bioavailability. • SSRI's (*e.g.*, fluoxetine) have not shown promising pain-modifying effects.
Tramadol	Enhancement of inhibitory neurotransmitters serotonin, norepinephrine; in cats, also produces an opioid metabolite	Tapentadol (the parent drug) has opioid as well as serotoninergic, noradrenergic activity but has very low PO bioavailability in dog	• A unique drug which does not appear to produce an opioid metabolite in dogs as in humans. • Pain-modifying effects in dogs and cats post-surgery when given parenterally. • Unfavorable oral PK in dogs (diminished plasma levels after sequential PO administration). • Oral PK in cats is more favorable.
Opioids	Closes dorsal horn pre-synaptic calcium channels which diminishes release of excitatory neurotransmitters; opens post-synaptic potassium channels which hyperpolarizes second order neuron	Pure *mu* agonists: morphine, hydro-morphine, methadone (IV/SC/IM), fentanyl (IV/SC/IM; transdermal solution or patch), codeine and hydrocodone (PO) *Kappa* agonists: butorphanol, nalbuphine	• Effective in humans PO for nerve injury-related pain. • Long-term use can cause tolerance (requiring dose escalation), dependence, and unpleasant AE's such as constipation and urinary retention. • Oral opioids in dogs have a robust first-pass effect, and no data exist for their pain-modifying effect, but studies suggest a role for codeine and hydrocodone in this species. • Reports in humans note sequential parenteral nalbuphine for chronic maladaptive pain with a lower AE profile.
NMDA receptor antagonist	Diminishes post-synaptic sodium and calcium influx	Ketamine (IV infusion or topical cream), amantadine	• Ketamine used for Complex Regional Pain Syndrome in humans.
Na-channel blocker	Neuronal cell membrane- and DRG-stabilizing properties	Local anesthetics (*e.g.*, lidocaine, bupivacaine, mepivacaine) Mexitiline (PO)	• Given locoregionally and/or applied perineurally prior to nerve transection as a preventative measure to limit subsequent pathophysiology of nerve damage. • Lidocaine (IV infusion or topical patch) has been used clinically for active neurogenic/neuropathic situations.
NSAID	Decreases pro-inflammatory prostaglandin synthesis, also has independent central analgesic effects	Carprofen, deracoxib, firocoxib, meloxicam, robenacoxib, mavacoxib	• May be especially beneficial in disc rupture, where production of prostanoids plays a pathophysiological role.
Cannabinoids	May act in a way similar to opioids; other probable mechanisms as well including serotoninergic, immune-modulating, and central effects	Cannabidiol, dronabinol	• The abuse potential of this class of drugs means that sourcing can be problematic.

Abbreviations; AE = adverse effects; PK = pharmacokinetics; IV = intravenous; PO = *per os*

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