

UPDATE ON BRAIN DISEASES IN DOGS & CATS

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The term encephalopathy refers to any disorder or disease affecting the brain. In its broadest interpretation, this includes disorders affecting the cerebrum (cerebral cortex and basal nuclei), brainstem (thalamus, hypothalamus, midbrain, pons and medulla), and cerebellum. This lecture will concentrate on disorders affecting the cerebrum.

Clinical Signs

The principal clinical signs associated with cerebral dysfunction are as follows;

- Altered mental status (obtundation, stupor (semi-coma) or coma)
- Change in behavior (loss of trained habits, failure to recognize owner, aggression, or hyperexcitability)
- Abnormal movements/postures such as pacing, wandering, circling, head pressing, twisted head and trunk (pleurothotonus)
- Postural reaction deficits in contralateral limbs
- Visual impairment (e.g. bumping into objects, menace deficit contralateral to side of lesion) with normal pupillary light reflexes
- Seizures

On the basis of signalment, history, and the results of a physical and neurologic examination, it may be possible to localize a lesion to the brain and occasionally to determine an approximate location. A similar neurologic syndrome will result from any one of a number of different diseases occurring at a given location. Many degenerative, metabolic, infectious, inflammatory, toxic, and vascular diseases may result in clinical signs of cerebral dysfunction. The cerebral cortex coordinates voluntary movements and reactions.

Clinical signs of cerebral cortex dysfunction include changes in behavior (lethargy, loss of trained habits, irritable, aggressive) or mental status (obtundation, semicoma, coma), and visual and postural reaction deficits. Behavioral changes usually result from a lesion of the limbic system or frontal lobe of the cerebral cortex. Since the frontal lobe has an inhibitory effect on some motor functions, a lesion here removes this inhibition and as a result the animal may continually pace. When an animal reaches a barrier pacing may be replaced with head pressing. Some animals circle, usually to the side of the lesion. Seizures may be partial or generalized.

Conscious visual perception requires intact visual pathways to the occipital lobes of the cerebral cortex. Unilateral lesions of the occipital cortex result in visual deficits in

the contralateral temporal visual field, with intact pupillary light reflexes. Bilateral lesions produce blindness.

Although the motor cortex is important for voluntary motor activity, it is not necessary for relatively normal gait and posture. Animals with lesions here may be able to stand, walk and run with minimal deficits, but control of finer movements is lost and they may have difficulty avoiding obstacles and contralateral postural reactions are usually deficient.

Although it is possible to localize a problem to the brain and sometimes to the approximate location within the brain, it must be remembered that clinical signs may be the same regardless of the underlying cause. Brain tumors, infections, congenital disorders, trauma, vascular disorders, degeneration, immunologic and metabolic disorders, toxicities, and idiopathic disorders may result in similar clinical signs. For this reason it is essential to follow a logical diagnostic plan for a cat or dog with signs of brain dysfunction.

Some Common Disorders Affecting the Cerebrum of Dogs and Cats

1. Degenerative -
 - a. Lysosomal storage diseases:
 - Fucosidosis - Springer spaniel
 - Gangliosidosis - cats, dogs
 - Ceroid lipofuscinosis - dogs
2. Anomalous/ Developmental -
 - a. Hydrocephalus
 - b. Lissencephaly - small smooth brain with absent gyri and abnormal arrangement of cells in cerebral cortex
 - c. Hydranencephaly - virtual absence of cerebral hemispheres and basal nuclei, with remnants of mesencephalic structures
 - d. Porencephaly - a circumscribed cerebral defect that communicates with the ventricular system
 - e. Meningoencephalocele - herniation of part of the brain and meninges through a defect in the skull
3. Metabolic
 - a. Hepatic encephalopathy
 - b. Miscellaneous
 - Hypoglycemia
4. Neoplastic
 - a. Primary brain tumor
 - b. Secondary brain tumor
 - Local extensions from skull, middle ear, pituitary, nasal cavity
 - Metastasis
5. Inflammatory/Infectious
 - a. Viral
 - Canine distemper
 - Old dog encephalitis
 - Feline infectious peritonitis
 - Parvovirus encephalitis
 - b. Unknown cause
 - Granulomatous meningoencephalomyelitis
 - Eosinophilic meningoencephalitis
 - c. Protozoal
 - Toxoplasmosis

- Neosporosis
 - d. Mycotic
 - Cryptococcus neoformans*
 - Others - *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Coccidioides immitis*, *Cladosporium trichoides*, *paecilomyces*, *Aspergillus* spp., etc
 - e. Bacterial
 - Abcessation
 - Sub-dural empyema
 - f. Miscellaneous
 - Verminous encephalitis
 - Foreign body migration
- 6. Traumatic
- 7. Vascular
 - a. Hemorrhage
 - b. Infarction
 - Feline ischemic encephalopathy

Diagnostic Plan

Patient signalment, history and physical and neurological examination findings will help to localize a lesion to the brain and possibly a particular area of the brain. Further diagnostic tests are required to localize the affected area within the brain, and to obtain an accurate diagnosis. These tests include CSF analysis, CT or MR imaging, and brain biopsy.

Following a complete history and physical and neurologic examination, a minimum data base for an animal with signs of brain dysfunction should be obtained. This should include a hemogram, serum chemistry panel, and urinalysis. Survey thoracic radiographs and abdominal ultrasound help to rule out problems elsewhere. The major objective in doing these tests is to exclude disease outside the brain as a cause of the signs of cerebral dysfunction.

Plain skull radiographs are useful for detecting problems of the skull or nasal cavity that may have extended to the brain. Occasionally, lysis or hyperostosis of the skull may accompany a primary brain tumor (e.g., meningioma of cats) or there may be mineralization of a neoplasm. Skull radiographs are of little value in detecting dysfunction within the brain.

Cerebrospinal Fluid

Analysis of cerebrospinal fluid (CSF) is recommended as an aid in the diagnosis of a brain disorders. The results of CSF analysis may help to identify inflammatory causes of cerebral dysfunction, and in some cases may support diagnosis of a brain tumor. CSF bathes the entire CNS, both internally (the ventricles and central canal) and externally (the subarachnoid space). CSF composition may be affected by many nervous system diseases and the ease with which this fluid may be collected has made it a useful diagnostic tool in the diagnosis of CNS disease. Unfortunately, for cells to be shed into the CSF a disease must involve the ventricular system or the subarachnoid space. Disorders involving deeper brain structures (e.g. neoplasms) may not shed cells into the CSF. Frequently these diseases disrupt the blood-brain barrier allowing protein to leak into the CSF and resulting in an increased protein level. CSF must be evaluated keeping in mind history and clinical signs. Neoplasms and some other non-inflammatory diseases may result in inflammatory changes in CSF composition. CSF composition may also change as a disease becomes more chronic. Also, following various therapies CSF may no longer accurately reflect an etiology Care should be used in the collection of CSF, because frequently an increased intracranial pressure (ICP) may be present in association with a brain tumor, and

pressure alterations associated with CSF removal may cause brain herniation. Because CSF pressure measurements are of limited usefulness, it is often desirable to utilize techniques such as hyperventilation to decrease intracranial pressure prior to CSF collection.

CSF may be collected at either the cerebellomedullary cistern or by lumbar puncture. In general the cerebellomedullary cistern is easier to perform, allows collection of a larger volume and generally collection from this area results in less blood contamination. All patients undergoing CSF collection should be anesthetized appropriately. If it is suspected that intracranial pressure is elevated the patient should be hyperventilated for several minutes prior to collection as well as during and after collection in order to decrease arterial CO₂ and intracranial pressure. Complications of CSF collection include needle injury to the brain and herniation of the brain, usually due to high intracranial pressure. Both these complications may be fatal if appropriate steps to reduce intracranial pressure (hyperventilation and mannitol administration) are not instituted immediately.

CT and MRI

CT and MRI allow imaging of brain tissue rather than just the surrounding bony skull. Both can distinguish lesions which have only slightly different densities than the surrounding tissues and this can be further enhanced by contrast agents allowing the identification of masses and other abnormal tissues within the brain. Images obtained by means of MRI may be superior to those of CT especially in certain areas such as the brain stem, although CT is usually better for bony lesions (e.g. middle ear studies). While the major tumor types are reported to have characteristic CT or MRI appearances, non neoplastic lesions may mimic the CT or MRI appearance of a neoplasm, and occasionally a metastasis may resemble a primary brain tumor on CT or MRI images. Patients for either CT or MRI must be anesthetized, intubated, and hyperventilated whenever an increase in ICP is even suspected. Proper patient positioning is extremely important. The animals should be placed in sternal recumbency with the head extended. The entire calvaria should be examined in the non contrast series of images. This should be followed by a post contrast series of images.

Cerebrovascular Disease of Dogs & Cats

Cerebrovascular disease is defined as any abnormality of the brain resulting from a pathologic process affecting its blood supply.

Stroke or cerebrovascular accident (CVA) is the most common clinical manifestation of cerebrovascular disease, and may be broadly divided into (1) ischemic stroke and (2) hemorrhagic stroke. Ischemic stroke results from occlusion of a cerebral blood vessel by a thrombus or embolism, depriving the brain of oxygen and glucose, whereas hemorrhagic stroke results from rupture of a blood vessel wall within the brain parenchyma or subarachnoid space. Ischemic strokes are more common, and an underlying cause is found in about 50% of cases. The most common concurrent medical conditions found in dogs are hyperadrenocorticism, chronic kidney disease, hypothyroidism and hypertension. Hemorrhagic strokes are rare and have been reported secondary to rupture of congenital vascular abnormalities, brain tumors, intravascular lymphoma, cerebral amyloid angiopathy and impaired coagulation. Signs are typically peracute in onset, and then they plateau. Worsening edema can sometimes lead to progression of neurologic signs

MRI is the imaging modality of choice. CT can detect hemorrhage and is useful for ruling out mimics of stroke, but it is not very sensitive in detecting ischemic changes. Ancillary diagnostic tests for ischemic strokes include CBC, chemistry, UA, serial blood pressure measurements, urine protein/creatinine ratio, d-dimers, endocrine testing, thoracic radiographs, abdominal ultrasound and echocardiography.

Ancillary diagnostic tests for hemorrhagic stroke include serial blood pressure measurement, CBC, chemistry, BMBT, PT/PTT, thoracic radiographs and abdominal ultrasound.

Treatment, regardless of type, includes supportive care and management of neurologic and non-neurologic complications, as well as treating any underlying causes.

Most cases of ischemic stroke recover within a few weeks with just supportive care. Hemorrhagic stroke is far less common, but associated with higher mortality. The risk of neurologic deterioration is highest in the first 24 hours. Dogs with concurrent medical conditions have significantly shorter survival times and are more likely to suffer from subsequent infarcts.

Previously considered uncommon, CVA is being recognized with greater frequency in veterinary medicine since magnetic resonance imaging (MRI) has become more readily available. Once the diagnosis of ischemic or hemorrhagic stroke is confirmed, potential underlying causes should be investigated and treated accordingly.

Hippocampal Necrosis of Cats

A profound encephalopathy of cats, caused by necrosis of the hippocampus, has been described. The syndrome is characterized by progressive, partial or generalized seizures, behavior changes (particularly *aggression*), and pathological features confined to the limbic system (including hippocampus and piriform lobe of the cerebrum).

In one study, the clinical records of 38 cats (1985-1995) with a neuropathologically confirmed diagnosis of necrosis of the hippocampus and occasionally the piriform lobe of the cerebrum were evaluated retrospectively. There was no sex or breed predisposition. Most cats were between 1 and 6 years of age (mean age 35 months) and had either generalized or complex-partial seizures of acute onset and rapid progression. The seizures had a tendency to become recurrent and to present as clusters or even status epilepticus later in the course of the disease. Fourteen cats died spontaneously, and 24 were euthanized. Histopathologic examination revealed bilateral lesions restricted to the hippocampus and occasionally the piriform lobe of the cerebrum. The lesions seemed to reflect different stages of the disease and consisted of acute neuronal degeneration to complete malacia, affecting mainly the layer of the large pyramidal cells but sometimes also the neurons of the dentate gyrus and the piriform lobe. The clinical, neuropathologic, and epidemiologic findings suggest that the seizures in these cats were triggered by primary structural brain damage, perhaps resulting from excito-toxicity. The cause remains unknown, but epidemiologic analysis suggests an environmental factor, probably a toxin.

Brain Tumors of Dogs & Cats

The Past: Surgery, Irradiation and Chemotherapy

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

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

Surgery

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

Radiation Therapy

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

Chemotherapy

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

The Present: Therapeutic Delivery Strategies for Canine Brain Tumors

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

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

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

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

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

In addition to barriers preventing movement of therapeutic agents from the blood into the brain parenchyma, mechanisms are also present to limit movement into the cerebrospinal fluid (CSF). Passage of substances through the arachnoid membrane is

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

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

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

- Improve entry through the BBB by modification of therapeutic drugs.
 - a. Increase influx.
 - b. Decrease efflux.
 - c. Utilization of carriers/receptors.
- Disruption of the BBB.
 - a. A variety of approaches have been used to disrupt BBB integrity including:
 - i. Chemical (often toxic), DMSO, ethanol, aluminium, irradiation, hypertension, hypercapnia, hypoxia.
 - ii. Osmotic agents such as mannitol and arabinose.
 - iii. Biochemical agents such as leukotriene C4, bradykinin, histamine etc.
- Circumventing the BBB.
 - a. Using non-vascular delivery of therapeutic agents directly into the CNS is appealing in many ways. Apart from removing the BBB as a restriction to delivery of many potent anticancer therapies, targeting the drugs directly potentially reduces systemic toxicity, degradation and immunological stimulation (particularly with protein and virally based therapies). However strategies are generally more invasive requiring craniotomy or insertion of catheters.
 - i. Intraventricular/intrathecal infusion.
 - ii. Wafers/microspheres/microchips.
 - iii. Delivery from biological tissues
 - b. Delivery of therapies directly from living cells within the brain or tumor itself can provide sustained levels of drugs in specific targeted regions. The two main strategies examined to date are:
 - i. Implantation of transfected cell lines.
 - ii. Transduction of resident CNS cells or brain tumor cells with gene therapy constructs.
- Interstitial delivery.
 - a. Both gene therapies and direct acting drugs, such as chemotherapeutics, can be delivered directly into tumor or brain parenchyma. AAV vectors carrying thymidine kinase suicide constructs and antiangiogenic agents have been shown to be efficacious in both *in vitro* and *in vivo* models, and direct injection into canine primary brain tumors has been done. Results in clinical tumors however have been disappointing

mainly due to limited distribution of the therapy beyond the local region of the injection site.

The Future: Biopsy and Convection Enhanced Delivery

Brain Biopsy

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

Convection enhanced delivery (CED)

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

Thiamine Deficiency of Cats

Cats are susceptible to thiamine deficiency because of their high-dietary requirement for thiamine, and because fish-based diets that contain thiaminases before processing are often fed to cats. In people, thiamine requirement is directly related to both total caloric intake and the proportion of calories provided as carbohydrates.

All of the published reports to date of thiamine deficiency in cats eating commercially available diets have involved canned foods. Canned foods are more susceptible to thiamine loss because of the high temperature involved in the processing of these diets, in particular when the pH is above 5.

The primary sources of thiamine supplementation in commercially available pet foods are synthetic (thiamine mononitrate and thiamine hydrochloride), and these sources are more susceptible to destruction than the thiamine present in plant and animal tissues. Thiamine can be destroyed by sulfate trace minerals and sulfite preserved meats which cleave the thiamine at the methylene bridge. In addition, thiamine is oxidized by ultraviolet and gamma irradiation and degraded by thiaminase enzyme activity found predominantly in shellfish, fish viscera, and some bacteria. Thiaminase is destroyed by heat processing; however, if raw ingredients are not promptly or properly cooked, destruction could result in lower than expected concentrations of thiamine. Given there are no real safety concerns regarding increased dosages of thiamine in either the cat or dog, and processing losses can exceed 90%, fortification in diet premixes warrants careful consideration to ensure appropriate thiamine concentrations in the final product.

Thiamine deficiency is a readily reversible neurological disorder that warrants consideration in any cat manifesting compatible clinical and neurological signs. The differential diagnoses for the multifocal intracranial disease suspected in all cats based on their neurological examinations included toxic and metabolic disease. Foods should also be evaluated for their adequacy as the sole or primary diet, as many unbalanced canned products are widely available and are marketed and labeled similarly to complete diets. Further studies assessing thiamine content of canned feline diets are warranted.

Abscessation of the Central Nervous System in Cats

Infection of the CNS may result in an *abscess* formation (a circumscribed collection of purulent material within the CNS, its surrounding membranes, or in the epidural space) and/or much less frequently, *empyema* (collection of pus in subdural or epidural locations). The term "pyocephalus" refers to a purulent effusion within the cranium and is synonymous with "pyencephalus". In animals, the empyema tends to be in cranial subdural sites and in spinal epidural locations.

Abscesses within the CNS are uncommon in cats but may arise as a result of either metastasis from distant foci of infection (e.g., lung abscesses and bacterial endocarditis), by direct extension from sinuses, ears, and eyes, as a result of trauma (e.g., bite wound), or from contaminated surgical instruments (e.g., spinal needle). Brain abscess may also result from penetration of the cranial cavity and brain substances by an exopharyngeal foreign body (e.g., sewing needle). Several instances of spinal epidural infection in the cat have followed tail fracture or a purulent granulomatous dermatitis involving the tail. The common sites for direct extension are the cribriform plate and the inner ear, resulting in abscess formation in the frontal lobe and the cerebellopontine angle, respectively. Spinal epidural infections also may result from vertebral osteomyelitis or paraspinal abscess. Abscesses of hematogenous origin, such as those that spread from pulmonary infection, bacterial endocarditis, or congenital heart disease with right to left shunting, appear to have a predilection for the CNS parenchyma, especially in the hypothalamus and cerebral cortex, and particularly in less vascularized areas such as white matter and junctions of gray and white matter. It is thought that neuraxial abscessation occurs preferentially in areas of

focal ischemia or necrosis. Typically, CNS abscesses are associated with bacteria, but are occasionally caused by fungi.

Aerobic bacteria such as *Streptococcus*, *Staphylococcus*, *Pasteurella*, and *Nocardia* may be more common than anaerobic bacteria as causes of CNS infection in dogs and cats. Nevertheless, anaerobic bacteria such as *Bacteroides*, *Fusobacterium*, *Peptostreptococcus*, *Actinomyces*, and *Eubacterium* are reported to be important pathogens in cats, causing either brain abscesses or subdural empyema. *Actinomyces* typically spreads by direct extension, although brain and possibly vertebral abscesses may result from hematogenous dissemination.

Otogenic Intracranial Infection

Extension of otitis media/interna into the central nervous system is a serious complication that may occur in cats of any age, breed or gender. Most intracranial complications originate from sub-acute to chronic ear infections, resulting in abscess formation in the brain.

Cerebral Phaeohyphomycosis

Phaeohyphomycosis refers to invasive disease caused by several species of dematiaceous fungi.

Cognitive Dysfunction Syndrome

Cognitive dysfunction syndrome (CDS) is an age-related neurodegenerative disease that impairs memory and learning. CDS may manifest itself in multiple nonspecific clinical signs that increase in frequency and severity over time in affected cats.

- Cognitive dysfunction is an age-related neurodegenerative disease that impairs memory and learning.
- Cognitive dysfunction can cause various behavioral changes. Make sure to rule out diseases that can mimic these signs.
- There are many forms of cognitive dysfunction and often they involve the depletion of neurotransmitters or disruption of neural pathways.
- The common denominator in all cases of neurodegeneration and cognitive decline is oxidative stress and mitochondrial dysfunction.

Alterations in cell function and neurotransmission in the brain of the CDS patients lead to malfunctions of short-term memory, loss of learned behavior, impairment of the processing of sensory information, reduction in cognitive capacity, and alterations of mood. The progression of CDS is related to the general rate of aging of cats and dogs. Quite significant changes may occur in the space of weeks or months. Worsening of the condition may be precipitated by stressful events such as hospitalization, kenneling, surgery or a house move. Ideally, cats should be behaviorally assessed before these events.

- **Emotional changes:** mild emotional changes may be the first signs of the onset of dementia. Signs include depression (reduction in activity, play and interest in activities the cat formerly enjoyed). Increases in anxiety and fear leading to irritability and aggressiveness.
- **Defects of short-term memory:** the animal repeatedly performs certain actions such as asking for attention, food and other rewards. Malfunction of short-term memory is at the root of many of the problems seen in CDS.
- **Disorientation:** the animal has trouble recognizing people, locations, or objects. This may lead to secondary problems, such as house soiling and difficulty finding locations in the home (e.g., door to outside, cat flap, water and food dish).

- **Changes in sleep-wake cycle:** the animal tends to sleep mostly during the day and appears restless at night, often waking up and crying out loudly. Pain and illness are also significant factors in night-time restlessness (e.g., chronic arthritic pain may make rest uncomfortable, and deafness can result in the cry becoming louder than previously).
- **Loss of learned behaviors:** failure to respond to commands and social signals that inhibit unwanted behavior. This contributes to loss of social inhibition and alterations in relationships with people and other animals in the home.
- **Loss of house training** (example of a learned behavior): a previously house trained animal will suddenly urinate and/or defecate inside the house and/or outside its litter box. This clinical sign can be caused by numerous medical and behavioral problems that have to be ruled out, especially osteoarthritis, hyperthyroidism and hypertension.
- **Changes in interaction with the environment:** reduced greeting of the owner, familiar persons or pets, decreased response to commands. A depressed mood and lack of interaction tends to isolate animal from their owners, who may not instigate play or give attention. Through a loss of stimulation and reward of normal activity the degradation of the human-animal bond leads to social isolation that contributes to worsening signs of CDS.
- **Neurological** : in the latter stages of CDS, neurological impairment may be seen. These include ataxia, apparent sensory loss (loss of vision/hearing) and changes in locomotion. Any neurological signs must be investigated thoroughly as there are numerous other potential medical causes.

Treatment

The drug Anipryl (selegiline), used by humans to treat Parkinson's disease, has been reported to dramatically improve clinical signs and the quality of life for many dogs with cognitive dysfunction syndrome.

An additional benefit may come from feeding the therapeutic diet Hill's b/d. This diet is specifically formulated with extra antioxidants for older dogs.

Older dogs may also benefit from treatment with acupuncture and Chinese herbs.

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