Ne - Neurology
CANINE BRAIN TUMORS

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In dogs, meningiomas and gliomas appear to occur most frequently. Most primary brain tumors are solitary, but multiple primary brain tumors have been reported. Secondary or metastatic tumors appear to be less common and may result from local extension (e.g. nasal adenocarcinoma) or metastases from primary tumors elsewhere. Skull tumors may affect the brain by local extension. Although brain tumors occur in dogs of all breeds, either sex, and any age, the incidence increases over 5 years of age, and with certain breeds. Glial cell tumors and pituitary tumors occur commonly in brachycephalic breeds, whereas meningiomas occur most frequently in dolichocephalic breeds.

Pathology

Primary brain tumors originate from cells normally found within the brain and meninges. Secondary tumors are metastasis from a primary tumor located outside the nervous system, or occur by local invasion from adjacent non- neural tissues (e.g., bone). Pituitary gland neoplasms and tumors arising from cranial nerves are considered secondary brain tumors.

Brain tumors cause cerebral dysfunction through infiltration of normal brain tissue, compression of adjacent structures, disruption of cerebral circulation, and local necrosis. Secondary effects of brain tumors include hydrocephalus, increased intracranial pressure (ICP), cerebral edema, and brain herniation. Primary brain tumors often are slow growing and the brain adapts to the slow increase in ICP. During this period of compensation there may be a history of vague signs and subtle behavior changes. Even with a slowly progressive tumor, clinical signs may progress rapidly when compensatory mechanisms have been exhausted. Rapidly growing tumors do not permit the same degree of compensation and a sudden onset of severe neurological dysfunction may occur in the absence of premonitory signs.

History and Clinical Signs

Neurological signs resulting from a brain tumor depend primarily on the location, size, and rate of growth of the mass. Many dogs or cats will have a long history of "vague" signs, such as not wishing to be handled, hiding during the day, decreased frequency of purring, or diminished activity levels. Frequently focal or generalized seizures occur.

Focal neurological signs usually are indicative of a fairly well developed mass lesion. Neoplasms involving the brain stem may result in cranial nerve deficits. Weakness and sensory abnormalities often are seen with a lesion in the cerebral frontoparietal regions or their deeper pathways. Visual deficits may accompany masses that involve the visual pathways from the occipital lobe of the cerebrum to the optic nerve. Hearing loss involves the cerebellomedullary region, the brain stem, or temporal lobes of the cerebrum. Decreased ability to smell may be seen with lesions of the cribriform plate or olfactory bulbs, or other rhinencephalic connections. Difficulties with balance or gait suggest cerebellar or vestibular involvement.

Secondary effects of brain tumors include increased ICP and cerebral edema. Clinical signs include alterations in behavior (e.g., lethargy, irritability), circling, head pressing, compulsive walking, altered states of consciousness, or associated locomotor disturbances. The majority of cats or dogs with a brain tumor will be presented to a veterinarian with problems related to the secondary effects of a tumor.

Diagnostic Techniques

On the basis of signalment, history, and the results of complete physical and neurological examinations, it is possible to localize a problem to the brain and, in some cases, to determine the approximate location. Signs resulting from disease in a given location in the nervous system

will be similar regardless of the exact cause. In order to eliminate other categories of disease it is essential to follow a logical diagnostic plan. A minimum data base for these patients should include a hemogram, serum chemistry panel, urinalysis, survey radiographs of the thorax, and abdominal ultrasound. Although plain skull radiographs are of limited value in the diagnosis of a primary brain tumor, their use may facilitate detection of skull or nasal cavity neoplasms. Occasionally, lysis or hyperostosis of the skull may accompany a primary brain tumor (e.g., meningioma of cats), or there may be radiographically visible mineralization within a neoplasm. General anesthesia is necessary for precise positioning of the skull for radiographs.

Analysis of cerebrospinal fluid (CSF) is recommended as the results may help to rule out inflammatory diseases, and may support a diagnosis of a brain tumor. Care should be used in the collection of CSF, because frequently ICP is increased and pressure changes associated with CSF drainage may lead to brain herniation. Hyperventilation of the patient or administration of mannitol prior to CSF collection will help to decrease intracranial pressure. Increased CSF protein content and a normal to increased CSF white blood cell count are considered "typical" of a brain neoplasm although often CSF may be normal. Neoplastic cells may be present in CSF, particularly when sedimentation techniques are used for analysis.

Computed tomography (CT) and magnetic resonance (MR) imaging provide accurate information about the presence, location and size of intracranial neoplasms. MR images are superior to those of CT in certain brain regions (e.g., the brainstem). Meningiomas may be difficult to detect on MR images, without contrast administration. A meningioma may have a "mottled" appearance and an interface is often visible between the tumor and the surrounding brain on T1- and T2-weighted images. This hypointense signal may indicate a compressed arachnoid plane between the tumor and the brain, and also compression of the draining venous plexus. Hypointense areas within the meningioma may indicate intratumoral mineralization. The "dural tail" sign, while not necessarily specific for a meningioma, is often associated with either neoplastic infiltration of meninges beyond the margin of the meningioma or hypervascularity of the dura mater. Ideally, an intracranial lesion should be biopsied prior to the institution of therapy, however biopsy is not always attempted for practical reasons such as cost and morbidity.

Non-neoplastic space-occupying lesions may mimic the CT or MR imaging appearance of a neoplasm and occasionally a metastasis may resemble a primary brain tumor. Currently, biopsy is the only method available for the definitive diagnosis of brain tumor type. Biopsy methods described include ultrasound-guided biopsy, and CT-guided biopsy. CT-guided stereotactic biopsy systems provide a relatively non-invasive, rapid, and extremely accurate means of tumor biopsy, with a low rate of complications.

Cytological evaluation of brain tumor biopsy specimens may be done within minutes of biopsy collection by means of crush preparations. Tissue samples are rapidly fixed in 95% alcohol and stained with hematoxylin and eosin. Accurate information using this rapid technique generally is available from both primary and metastatic nervous system tumors, and from non-neoplastic lesions. Air-dried slides of crush preparations also may be stained with Wright's stain and counter stained with Giemsa to provide additional information regarding cell types present in a mass.

Therapy

The aims of therapy for a brain tumor are to eliminate the tumor (or reduce its size) and to control secondary effects (e.g., increased ICP or cerebral edema). Palliative therapy for animals with a brain tumor consists of glucocorticoids for edema reduction and, in some cases (e.g., lymphoma), for retardation of tumor growth. Should seizure therapy be needed, phenobarbital is the drug best suited for the control of generalized seizures.

Surgery has become an essential consideration in the management of intracranial neoplasms of cats or dogs. The precise location, size, and type of a neoplasm, determine the extent of removal that is possible. Meningiomas, particularly those located over the frontal lobes of the cerebrum, often may be completely removed, especially in cats. In contrast, there is a significant morbidity and mortality associated with the surgical removal of caudal fossa and brainstem neoplasms. Partial removal of a brain neoplasm may relieve signs of cerebral dysfunction, provide a histological diagnosis, and may make an animal a better candidate for other therapy such as radiation. Surgical biopsy of a tumor must be approached with care to avoid seeding of tumor cells to normal tissue.

The use of radiation therapy for the treatment of primary brain tumors of dogs and cats is well established and it may be used either alone or in combination with other treatments. External beam, megavoltage irradiation currently is recommended for the therapy of brain tumors in dogs or cats. Although orthovoltage radiation

has been used it is not optimal because of poor beam penetration, profile, and limited field configuration. Careful treatment planning by a radiation therapist is essential. The selection of a radiation dose is based on considerations such as tumor type, location, and tolerance of the surrounding normal tissues.

Ne - Neurology

INFLAMMATORY CENTRAL NERVOUS SYSTEM DISEASE OF THE DOG

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The hallmark of CNS inflammation is infiltration of peripheral blood leukocytes into the neuroparenchyma and its coverings, resulting in various types of encephalitis and/or meningitis, and sometimes associated with altered vascular integrity that leads to oedema. The aetiologies of inflammatory disease of the CNS are very diverse. Simplistically, they can be classed as pathogenic and non-pathogenic, with the latter being potentially related to immune-system dysfunction. Infectious causes may be viral, protozoal, bacterial, rickettsial, or fungal.

Canine Distemper Encephalomyelitis

Canine distemper encephalomyelitis (CDE) is caused by a paramyxovirus (genus Moribillivirus) closely related to measles virus of man. Although the incidence is decreasing, CDE is still a common CNS disorder in the dog, primarily in unvaccinated dogs but also occasionally in those dogs with a vaccinal history. Young dogs are especially susceptible to infection, although older dogs are also at risk. While there are several different strains of the virus, there is only one serotype which means that exposure to one strain protects dogs against any subsequent challenge. The virus is most commonly spread by aerosol exposure, although rarely, the virus may be spread transplacentally. Dogs that are not immunized regularly may lose their protection and become infected following stress, immunosuppression, or contact with diseased animals. Fifty to 75% of susceptible dogs are subclinically infected but clear the virus from the body. Factors predisposing to development of clinical disease are multifactorial, including age, vaccination status, breed, and viral virulence.

Virus replication initially begins in lymphoid tissues. The initial systemic phase of infection by this virus is marked by immunosuppression. Virus reaches the CNS approximately 1 week after infection by virus-infected lymphocytes, monocytes, and platelets associated with immune complexes. Spread of virus through cerebrospinal fluid pathways may explain the frequent. A rapid and high-titered viral antibody response to CDV is crucial for recovery from viral infection with minimal or no clinical signs. Dogs unable to mount an adequate response develop a rapidly progressive disease and die. Dogs that mount a delayed or intermediate response tend to develop chronic neurological disease.

Lesions may be found in gray and white matter. The earliest changes seen in the CNS are degenerative and appear to be the result of viral replication in glial cells, especially astrocytes, followed by viral-induced demyelination, while a non-suppurative inflammatory component occurs later, perhaps as viral immunosuppression is declining, and becomes superimposed on the

degenerative lesion, although both may be seen together.

Canine Distemper Encephalomyelitis in Immature Dogs: This is the most common form of distemper virus infection and is often initially characterized by systemic evidence of gastrointestinal and respiratory disturbances: vomiting, diarrhoea, coughing, and seromucopurulent oculonasal discharges. Hyperkeratosis of the footpad may be seen. Additionally, many animals have conjunctivitis and chorioretinitis. However, in one clinical report, only one third of the canine distemper cases had extraneural involvement. These systemic signs may precede, or occur simultaneously with, neurological signs. Neurological signs are quite varied, often asymmetrical, and usually suggest a multifocal distribution of lesions. Cortical and subcortical signs include generalized seizures and sometimes personality changes, such as depression and disorientation. Signs of localization in the brain stem include incoordination, hypermetria, falling, head tilt, and nystagmus. Occasionally, monoplegia and paraplegia are observed. A sign that is characteristic of distemper encephalitis is myoclonus (generalized or localized), or more correctly, flexor spasm. Appendicular flexor muscles, abdominal muscles, and the cervical musculature are most frequently involved. Sometimes the masseteric, temporalis, and periorbital muscles are affected. These rhythmic contractions are not necessarily associated with limb paresis or paralysis and usually persist during sleep. The movements are temporarily abolished by intravenous injection of local anesthetic agents. An abnormality in the motor neuron-interneuron pool in the spinal cord is thought to cause the muscle contractions. Contractions are not dependent on sensory nerves or descending pathways from the brain. Acute visual impairment (optic neuritis), typically accompanied by dilated, unresponsive pupils, may be the only clinical sign in some dogs. Canine distemper virus is a common cause of convulsions in dogs less than six months of age. Olfactory dysfunction has been reported in affected dogs. Neonatal infection prior to eruption of permanent dentition can cause enamel hypoplasia. Cell-mediated immunosuppression can occur with CDV, predisposing affected animals to other infectious agents, including *Toxoplasma gondii* and *Neospora caninum.*

Multifocal Distemper Encephalomyelitis in Mature Dogs: In mature dogs between the ages of 4 and 8 years, canine distemper virus can produce a type of multifocal encephalomyelitis (MDE) that is characterized by a chronic course. It is not unusual for an animal to be presented with a history of neurological signs that have been present for 12 months or more. The incidence of this disease is relatively low and does not appear to be related to breed or sex. Animals that have received vaccinations against distemper virus may be affected. This disease is not preceded by, nor is it coincident with, the systemic signs that are seen in younger dogs. Furthermore, it is not unusual for this slowly progressive disease to remain clinically and pathologically static. The initial neurological signs that are commonly seen in mature dogs with MDE include weakness of the pelvic limbs, generalized incoordination, and occasional falling. These signs frequently progress to tetraplegia. Generalized seizures or personality changes are not features of this disease and affected animals maintain a normal mental state. Many dogs will have unilateral or bilateral menace deficits, with normal or abnormal pupillary reflexes. Some animals will have signs of facial paralysis, head tilt, and nystagmus. Although head tremors may be seen, myoclonic movements or flexor spasms are usually not observed.

The diagnosis of canine distemper encephalomyelitis (in young dogs, especially) is usually based on history and clinical signs. The index of suspicion is higher in affected dogs that have not been vaccinated. Positive diagnosis may be made through use of immunofluorescent or immunocytochemical techniques to detect canine distemper viral antigen in brain sections and other tissues (e.g., mononuclear cells in blood smears, conjunctival or tracheal washes, or footpad biopsies).

Hematological and biochemical data are non-specific, although many affected dogs will be lymphopenic during the acute phase of illness. CSF analysis may reveal a moderate pleocytosis (15 to 60 WBCs/µl) of mononuclear cells (lymphocytes and macrophages), and elevated gamma globulins, although during the acute demyelinating stage of the disease, inflammatory reactions may be limited or lacking and CSF protein/cell count may be normal. Detection of CDV in urine using polymerase chain reaction (PCR) amplification has been recently reported as a useful routine screen for dogs with suspected distemper encephalomyelitis.

Prognosis is guarded. Seizures are an unfavorable prognostic sign. There is no treatment for CDE, except supportive, and dogs with progressive neurological signs leading to incapacitation need to be euthanized. The prognosis is better in dogs with non-progressive neurological complications, such as intermittent seizures, myoclonus, and visual impairment, although only seizures may respond to medication.

Post-vaccinal Canine Distemper Encephalitis: Post-vaccinal canine distemper encephalitis occurs in young animals, especially those less than six months of age. It has been recognized as a disease entity for a number of years and is believed to be associated with vaccination using live virus. The pathogenesis of this disease is unclear.

Granulomatous Meningoencephalomyelitis

Granulomatous meningoencephalomyelitis (GME) is a sporadic, idiopathic, inflammatory disease of the CNS of dogs. This disease appears to have a worldwide distribution, with recent reports coming from the USA, Australia, New Zealand, and Europe. The cause of GME is unknown.

Most cases of GME occur in small breed dogs, and commonly in terrier and toy breeds and Poodles, although any breed may be affected. The majority of confirmed cases occur in young to middle-aged dogs, with a mean age around 5 years (ranging from 6 months to 12 years). GME occurs in both sexes; however, there appears to be a higher prevalence in females. A lack of obvious correlation between clinical signs and the course of the disease has been reported. Clinical signs usually reflect several (i.e. multifocal) syndromes, e.g., cerebral, brain stem, and spinal cord syndromes, as a result of the scattered distribution of lesions. However, focal signs have been reported in up to 50% of cases. Common signs include incoordination, ataxia and falling, cervical hyperesthesia, head tilt, nystagmus, facial and/or trigeminal nerve paralysis, circling, visual deficits, seizures, depression, and tetanic spasms. Occasionally, fever, peripheral neutrophilia, and excess non-segmented neutrophils will accompany the clinical neurological signs. An infrequently reported ocular form of GME appears to be related to lesions localized in optic nerves and optic chiasm resulting in visual impairment and abnormal pupillary reflexes.

A tentative diagnosis of GME may be suggested by signalment data, the clinical course of the disease, and clinical signs. Haematology, serum chemistry, and urinalysis studies are usually normal and electroencephalographic recordings are frequently non-specific. Rarely, an intrathecal filling-defect may be detected myelographically in dogs possibly due to focal cord swelling or subarachnoid granulomas. The most useful diagnostic aid is CSF analysis. In most dogs, CSF is abnormal with mild to pronounced pleocytosis, ranging from 50 to 900 WBCs/µl. Cells are predominantly mononuclear, including lymphocytes (60 - 90%), monocytes (10 - 20%), and variable numbers of large anaplastic mononuclear cells with abundant lacy cytoplasm. While neutrophils typically comprise from 1 - 20% of the cell type differential, they may be the predominant cell type on rare occasions. Occasionally, protein is elevated without pleocytosis. In one retrospective study of dogs with GME, lumbar-derived CSF contained fewer cells and less protein than CSF derived from cisternal puncture. CSF protein and cellularity is not necessarily influenced by the degree of meningeal involvement or the extent of necrosis within the granulomatous lesions. A combination of CSF and MRI findings may also be useful, the latter being characterized by isointense lesions on T1-weighted images. Pial/dural meningeal enhancement may be found with MRI. Although infrequently performed, brain biopsy can be a very useful diagnostic test in animals with focal lesions.

Prognosis for permanent recovery is poor. Some dogs die from inhalation pneumonia secondary to megaesophagus. Shortest survival periods, ranging from several days to weeks, are seen with the disseminated and ocular forms. Longer survival periods of from 3 to 6 months, or longer, are more suggestive of a focal lesion. In one retrospective study of 42 dogs with GME , median survival time for dogs with focal versus disseminated disease was 114 and 14 days, respectively, and dogs with focal forebrain signs (e.g., seizures) had significantly longer survival times (>395 days) than did dogs with focal signs in other areas of the CNS (59 days). Long-term therapy is generally unsatisfactory, although temporary remission of signs is often achieved with corticosteroid administration, such as oral prednisone, 1 to 2 mg/kg/day initially for several days, then reducing the dosage to 2.5 - 5 mg on alternate days. Most dogs will require continued therapy to prevent recurrences of signs. Improvement may last for several days, weeks or months, although most will eventually succumb to the disease. Part of the temporary improvement may be related to a reduction of mast cell function in dogs receiving glucocorticoid medication. Cessation of glucocorticoid therapy is invariably associated with rapid and dramatic clinical deterioration. Results of a recent retrospective study suggested that radiation therapy (e.g., total doses ranging from 40 to 49.5 Gy, divided in 2.4- to 4.0-Gy fractions) may be an effective treatment for dogs with GME, particularly those with clinical signs suggesting focal involvement. Promising clinical, CT, and CSF results following use of cytosine arabinoside (at 50 mg/m2, SQ, bid x 2 days, repeat q 3 weeks) in an 8 year old Shih Tzu, suggests that this potent anti-inflammatory drug may be an effective sole therapy for the long-term treatment of GME in dogs.

Steroid Responsive Meningitis-Arteritis

A severe form of steroid responsive meningitis-arteritis (SRMA) has been reported in Beagles, Bernese Mountain Dogs, Boxers, German Short-Haired Pointers, and sporadically in other breeds. This condition has a worldwide distribution and represents one of the most important inflammatory diseases of the canine CNS. Beagles, especially but not exclusively those in laboratory-bred colonies, appear at risk. In the Beagles, the condition has been termed Beagle pain syndrome, necrotizing vasculitis, polyarteritis, panarteritis, juvenile polyarteritis syndrome, and primary periarteritis. In other breeds, this condition previously appears under the terms necrotizing vasculitis, corticosteroid-responsive meningitis, aseptic suppurative meningitis, and corticosteroid-responsive meningomyelitis. This plethora of terminology reflects not only the dearth of knowledge about this condition but also highlights important clinical signs such as pain, improvement following corticosteroid medication, and histologic involvement of the meninges and blood vessels.

Affected animals usually are most commonly young adults between 8 and 18 months of age, although the age range may extend from 4 months to 7 years. The clinical course is typically acute with recurrences. A more protracted form of the disease may be seen following relapses and inadequate treatment. Signs include recurring fever, hyperesthesia, cervical rigidity, and anorexia. There may be a creeping gait, arching of the back with head held down, and crouched posture. Some dogs with protracted disease may show clinical signs of parenchymal involvement such as ataxia, paresis, tetraparesis or paraplegia. Hematological studies often reveal a peripheral neutrophilia with a left shift, increased erythrocyte sedimentation rate, and in some cases, an elevated α2-globulin fraction. CSF studies indicate increased protein and neutrophilic pleocytosis (in some dogs as high as 12,600 WBCs/μm). Dogs with chronic disease may have a normal or mildly increased CSF protein content and a mild to moderate, mixed cell pleocytosis. In acute and chronic forms of the disease, the majority of affected dogs show elevated IgA levels in CSF and serum, presumably as a result of dysregulation of the immune system. CT imaging may help localize changes in the CNS (meninges, spinal cord, and brain) and assist in the efficacy of therapy.

The cause of SRMA remains unknown. To date, no bacterial or viral infectious agents have been identified, although activated T cells have been found in some dogs indicating these cells have had contact with some unidentified antigen.

The prognosis is guarded to favorable, especially in dogs with acute disease that are treated promptly using immunosuppressive doses of corticosteroids. Untreated dogs tend to have a remitting and relapsing course. Tipold recommends the following long-term therapy (e.g., for at least 6 months), especially in any dog that has had a relapse: prednisolone at 4 mg/kg/day, PO or IV initially. After 2 days, the dose is reduced to 2 mg/kg daily for 1 to 2 weeks, followed by 1 mg/kg daily. Dogs are re-examined, including CSF analysis and hematology, every 4 to 6 weeks. When signs and CSF are normal, the dose can be reduced to half of the previous dosage until a dosage of 0.5 mg/kg every 48 to 72 hours is attained. Treatment is stopped 6 months after clinical examination, CSF, and blood profiles are normal. In refractory cases, other immunosuppressive drugs such as azathioprine (at 1.5 mg/kg PO every 48 hours) may be used in combination with steroids (e.g., alternating each drug every other day). Antibiotics are ineffective. Results of a long-term treatment protocol (up to 20 months) involving 10 dogs with SRMA have been recently published. Eight of the 10 dogs were without clinical signs up to 29 months after the treatment was terminated. Long-term glucocorticosteroid treatment resulted only in mild clinical side effects, such as polyuria/polydipsia, polyphagia and weight gain, which were reversible after the therapy was discontinued. It was noted that elevated serum and CSF IgA levels did not decrease to normal values during prednisolone treatment and were still slightly increased after the therapy was discontinued. Monitoring of CSF cell count in dogs with this condition was a sensitive indicator of success of treatment. In addition, older dogs with high IgA levels in the CSF and frequent relapses seemed to require a longer duration of therapy and had a less favorable prognosis long term.

Note that Akitas, Bernese Mountain dogs, and other breeds with immune-mediated polyarthritis may show similar clinical signs as animals with SRMA and have concurrent meningitis.

Bacterial Meningitis

Bacterial meningitis is a rarely reported condition in dogs and cats. Animals of any age may be affected, although most affected dogs are adult, with a mean age around 5 years. Bacterial infections of the CNS most often occur via haematogenous spread from distant foci within the body (e.g., lung or splenic abscess, vegetative endocarditis, pleuritis, and urinary tract infections), by direct extension from sinuses, ears and eyes, as a result of trauma (e.g., bite wound), meningeal spread with entry along nerve roots,

or from contaminated surgical instruments (e.g., spinal needle). Organisms usually disseminate via CSF pathways and produce cerebrospinal meningitis, often associated with microabscess formation of brain and spinal cord. A plethora of organisms have been cultured from dogs with bacterial meningitis including *Pasteurella* sp (e.g., *P. multocida*), *Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus albus, Actinomyces* sp*, Nocardia* sp*, Escherichia coli, Streptococcus* sp *(e.g., S. pneumoniae)* and *Klebsiella* sp.

Irrespective of the etiologic agent, bacterial meningitis usually is acute in onset and tends to be characterized by a group of clinical signs that include hyperesthesia, fever, cervical pain, and frequently, cervical rigidity. In addition, vomiting, bradycardia, anorexia, occasional cranial nerve deficits, and seizures may be observed. Seizures may be caused by high fever, hypoglycemia, brain edema, or inflammation, while vomiting may result from increased intracranial pressure or from direct effects on the vomiting center. In some animals, clinical signs may develop that suggest parenchymal involvement. The clinical diagnosis of bacterial meningitis is supported by the finding of highly pleocytic CSF (500 to 1000+ WBCs/µl) with a high proportion of neutrophil cells. The protein content of the CSF is usually increased as well (100 to 1000+ mg/dl). Low CSF glucose, relative to plasma glucose values, are typical. Organisms may be seen on CSF cytology. Neutrophilia may be present in blood samples and there may be evidence of shock, hypotension, and disseminated intravascular coagulation Thrombocytopenia, abnormal liver enzymes, electrolyte imbalance, abnormal anion gap, and uremia have been reported in some cases [278]. Electroencephalographic traces may demonstrate high voltage (30 - 70µv), fast (20 - 35 Hz) or slow (5 - 10 Hz) wave activity. Definitive diagnosis is made by bacterial culture of CSF (both aerobic and anaerobic). Blood and urine cultures may incriminate a pathogenic organism when CSF cultures are negative (which is usually the case in our experience). Meningeal inflammation, ventriculitis, and possibly brain edema can be detected using MRI or CT scans.

Pathological findings that are characteristic of bacterial meningitis include diffuse infiltration of inflammatory cells (by both polymorphonuclear and mononuclear cells) into the leptomeninges. Frequently, inflammation is found throughout the entire subarachnoid space of the brain and spinal cord. Vasculitis is often pronounced. Bacterial invasion of CNS parenchyma is characterized by mononuclear and polymorphonuclear inflammatory infiltration and extensive perivascular cuffing. Necrosis of gray and white matter, sometimes associated with vascular thrombosis, may be observed with infiltration of macrophages, neutrophils and plasma cells.

Prognosis is guarded since death is common even if appropriate therapy is administered, and relapses are frequently encountered. Appropriate use of antibiotics, according to the culture results, is basic to successful therapy of bacterial meningitis (encephalomyelitis). Antibiotic therapy should be maintained for several weeks after clinical signs have resolved. Chloramphenicol (up to 50 mg/kg, IV, IM, or SC, bid), metronidazole (10 - 15 mg/kg, PO, tid), trimethoprim-sulfonamide (from 30 to 60 mg/kg, PO, daily; note that complications may include sulfonamide urolithiasis in dogs and nephrotoxicity in cats) penetrate the CNS in therapeutic concentration. Ampicillin and penicillin enter the CNS only with meningeal irritation. Aminoglycosides and cephalosporins reportedly do not adequately penetrate the CNS, even when inflammation exists. Intrathecal administration of antibiotics should only be considered in refractory cases. Corticosteroids, in general, are contraindicated in the treatment of bacterial meningitis . It has been suggested that *Staphylococcus* sp. should be assumed when the organism involved is not known [277]. Ampicillin, 5 - 10 mg/kg, IV, every 6 hours is recommended. Diazepam or other anticonvulsants can be used for seizures if they occur. Osmotic diuretics may be useful for treating increased intracranial pressure secondary to brain oedema.

Note that it may be very difficult to differentiate between bacterial meningitis and steroid responsive meningitis-arteritis (SRMA). The latter is more common and probably should be at the top of the differential list. Analysis of CSF for elevated levels of IgA should be diagnostic for SRMA.

Mycotic Diseases of the CNS

Mycotic agents sporadically produce a granulomatous meningoencephalomyelitis in dogs and cats. The more common mycotic infections of the CNS are caused by *Cryptococcus neoformans, Blastomyces dermatitidis, Histoplasma capsulatum* and *Coccidioides immitis.* Each agent has a particular geographic distribution in the USA. The pathogenesis is similar for blastomycosis, histoplasmosis and coccidioidomycosis. The organism is present in the soil, producing mycelia and airborne spores. The coccidia of spores are probably inhaled, deposited in the alveoli, phagocytosed and converted into the spherical parasitic, yeast form. This form is disseminated via lymphatics producing local hilar lymphadenopathy and there

is hematogenous spread to other organs. The fate of the infected host is believed to be dependent upon time and ability to develop cellular immunity to fungal antigens. Unlike other mycotic diseases, *C. neoformans* exists only in the yeast form and has a worldwide distribution. Endemic areas have not been identified. Infection is probably acquired from the environment rather than from animals. Cryptococcosis infection often occurs in mature dogs and cats that are immunodepressed (e.g., cats with feline leukemia virus or feline immunodeficiency virus, or dogs with ehrlichiosis), and infection may be accelerated or worsened by glucocorticoid therapy. Cats contract the disease more frequently than dogs. The natural route of infection is generally believed to be the respiratory tract, with subsequent hematogenous and lymphogenous dissemination to other areas of the body. As with bacteria, mycotic infections also may reach brain and spinal cord by direct spread from an adjacent infection, e.g., from the nasal chambers, tooth alveolus and sinuses, outer ear, eustachian tube, middle/inner ear, petrous temporal bone, and basilar bone.

While the overall incidence of CNS involvement by mycotic diseases is low, *C. neoformans* may be more likely to be incriminated than the other organisms in dogs. Neurological signs will vary according to lesion location and severity. The signs may reflect either a focal mass lesion or a diffuse multifocal disease process. Neurological signs may include seizures, depression, disorientation, circling, ataxia, falling, pelvic limb paresis, paraplegia, anisocoria, pupillary dilatation and blindness. Deficits of one or several of cranial nerves 5 to 12 are often present. Note that these signs may be seen with any of the mycotic infections. Radiographic evidence of diffuse miliary to nodular interstitial pulmonary infiltrates may be seen with blastomycosis, histoplasmosis, and coccidioidomycosis. Gross lesions may include thickening of the meninges, which sometimes have a gelatinous, cloudy appearance. On sectioning of the brain, cystic spaces may be seen within the parenchyma. These spaces reflect expanded perivascular spaces and are frequently filled with crytococcal organisms having a round/ovoid cell body and surrounded by a halo-like capsule that stains strongly with PAS or Mayer's mucicarmine. In cats, only a minimal or mild nonsuppurative inflammatory response may be present. In affected dogs, the cellular response is more granulomatous with epithelioid macrophages, lymphocytes, and plasma cells. The organism may be found as free hyphae or yeast form some of which may be budding. The yeast form is often present within macrophages. Ocular lesions associated with a cell-mediated chorioretinitis may also be observed.

Pyogranulomatous encephalitis has been reported occasionally in dogs and cats in association with blastomycosis. Neurological disease associated with histoplasmosis and coccidioidomycosis is rare or quite uncommon, although granulomatous meningitis attributable to *C. immitis* was diagnosed on postmortem examination in a 4 year old Border Collie by demonstration of coccidioides endospores in brain tissue. There are a few reports of CNS infection in dogs and cats associated with uncommon opportunistic fungi, such as phaeohyphomycoses, in which the agents involved are almost always Cladosporidium species, and usually *C. bantianum*. CNS disease is usually due to localized brain abscess or to multiple large pyogranulomatous lesions in the cerebrum and meninges, sometimes with multifocal malacic foci, and is invariably fatal.

Diagnosis of mycotic infection is based on demonstration of the organisms in tissue sections using immunofluorescent procedures or in material taken from aspirates or impression smears, culture, and serology. A commercial latex agglutination test is available for detecting cryptococcal capsular antigen in serum, urine, or cerebrospinal fluid. Inflammatory mycotic lesions may be detected using MRI.

Prognosis of mycotic infection is always guarded, especially in the disseminated form and with CNS involvement. Most of the organisms are sensitive to treatment with amphotericin B (AMB), e.g., using a dosage of 0.1 to 0.5 mg/kg body weight, IV, three times weekly, in dogs and cats. The treatment of choice for cryptococcosis still appears to be AMB and flucytosine (FCY), although toxic epidermal necrolysis may sometimes be seen as a side-effect. A recommended dosage for FCY is 120 mg/kg body weight, divided into 4 equal doses daily. Due to the inability of AMB and FCY to cross the blood-CNS barrier, it is recommended that these drugs be used in combination with other antifungal agents such as itraconazole (ITZ, at 5 - 10 mg/kg, PO, bid) or fluconazole (FCZ, at 5 - 15 mg/kg, PO, bid) in animals with CNS disease. It would seem that the same recommendation would apply to other fungal diseases having CNS involvement, e.g., itraconazole at 10 mg/kg, PO, daily is suggested for dogs with blastomycosis/brain involvement. In a recent report of cryptococcosis in 19 cats, treatment with ketoconazole (KTZ), was unrewarding in cases with CNS involvement, although KTZ and ITZ (both at 10 mg/kg, PO, daily) successfully treated a small number of experimentally-infected cats, including some with CNS disease.

Protozoan Encephalitis-encephalomyelitis

Toxoplasma, Neospora, and *Sarcocystis* are three genera of the phylum Apicomplexa that cause encephalomyelitis in dogs and cats.

Toxoplasmosis and Neosporosis: Toxoplasmosis is an infectious condition caused by the protozoal parasite *Toxoplasma gondii* and occurs in acquired and congenital forms in man and animals. Cats are the definitive host for this parasite. The three known infective stages of *Toxoplasma gondii* are bradyzoites, tachyzoites and sporozoites. The three modes of transmission are carnivorism (ingestion of encysted bradyzoites), fecal contamination, and in utero infection. These modes of transmission involve the different infective stages as follows: carnivorous ingestion of encysted bradyzoites, tachyzoites or both; contamination with feline feces containing sporozoites of sporulated oocysts; transplacental infection of the fetus with tachyzoites after ingestion of encysted bradyzoites or sporulated oocysts by the mother. Humans, sheep, pigs, dogs and (rarely) cats are known to transmit *T. gondii* transplacentally. In humans, congenital infection occurs when a woman becomes infected during pregnancy. *Toxoplasma* oocysts are shed in feline feces unsporulated and are not infective until sporulated (1 - 5 days). Sporulated oocysts can survive in soil for several months. Land snails, earthworms, flies and cockroaches may serve as transport hosts for oocysts. Most mammals become intermediate hosts through ingestion of oocysts. Following the acute systemic infection in intermediate hosts in which the organism can be disseminated to many body organs (this phase may be subclinical), tissue cysts form, most commonly in the CNS, skeletal muscle, and heart muscle. This conversion is related to development of the host humoral and cellular immune response. The parasites are mainly intracellular and subclinical infection may persist for the life of the host. Activation of toxoplasmosis may occur in association with severe immunosuppressive disorders. The condition is often associated with canine distemper or other infections such, as ehrlichiosis, or with glucocorticoid therapy. Clinical toxoplasmosis is most commonly seen in young dogs less than 1 year of age or in immunocompromised older dogs. Note that many disorders previously ascribed to toxoplasmosis in dogs have now been found to be cases of neosporosis caused by *Neospora caninum*, an apicomplexan protozoan parasite that can infect puppies in the neonatal period. Dogs are the only proven definitive host for *N. caninum*. Its life cycle is unknown, although transplacental transmission has been shown in dogs. It has a wide host range, but its zoonotic potential is unknown. Older dogs may also be affected. Fatal neosporosis has been documented throughout the world and *Neospora caninum* has been isolated in the USA and in several European countries. These isolates may have significant biological and genetic differences. Because many cases of neurological disease previously diagnosed as toxoplasmosis are now turning out to be examples of neosporosis, the acronym TX-NS will be used in the following discussion to encompass both protozoa.

TX-NS in dogs resulting in a systemic infection will typically affect most organs, and the CNS, in particular. Neurological signs associated with TX-NS encephalomyelitis are variable and may reflect a focal or multifocal disease process. In dogs, signs include hyperexcitability, depression, intention tremor, paresis, paralysis, head tilt, and seizures.

In the diagnosis of TX-NS neurological disease, abnormal hematological parameters may include non-regenerative anemia, neutrophilic leukocytosis, lymphocyosis, and eosinophilia. Serum alanine aminotransferase and aspartate aminotransferase levels may be increased, especially in dogs with acute hepatic and muscle necrosis. Results of CSF may be abnormal, with elevated protein content and a mixed monocytic-polymorphonuclear pleocytosis. An eosinophilic pleocytosis was found in 2 dogs with a granulomatous encephalomyelitis due to protozoan infection. Xanthochromia will be present if hemorrhage has occurred. Electromyographic testing may reveal fibrillation potentials, positive sharp waves, bizarre high-frequency potentials, and myotonic-like discharges. Nerve conduction velocities may be decreased. Serum creatine kinase levels are often increased. Protozoan meningoencephalitis has been detected using MRI scans. The close resemblance between *T. gondii* and *N. caninum* tachyzoites and tissue cysts prevents definitive diagnosis by histopathology, and the clinical syndromes appear to be identical. Differentiation between the two protozoan organisms can be made using assays for circulating antibodies, by tissue immunocytochemistry, and ultrastructural studies. Sensitive polymerase chain reaction assays have been reported for the detection of both *Neospora caninum* DNA and *Toxoplasma gondii* DNA in biological samples. Muscle biopsy of appropriate muscles (as suggested by the clinical signs) may also provide the possibility of a definitive premortem diagnosis using the aforementioned techniques. Prognosis is poor when signs of pelvic limb spasticity are observed and is guarded in any animal with signs of CNS disease. In one study involving 27 cases of neosporosis,

recovery was less likely in peracute cases with severe clinical signs, and when treatment was delayed [535]. Many animals with myositis-polyradiculoneuritis have concomitant lesions in the CNS. A 4 to 8 week regimen of trimethoprim-sulfonamide (at 15 - 20 mg/kg combined dose, PO, bid) and pyrimethamine (at 1 mg/kg, PO, daily) has successfully treated animals with TX-NS-induced encephalomyelitis and myositis-polyradiculoneuritis [378,411]. Clindamycin is considered to be the drug of choice for treating canine and feline toxoplasmosis, at a dose of 10 to 40 mg/kg/day, PO or IM, divided bid to tid. This dose can also be used for treating dogs with neosporosis. Clindamycin crosses the blood-brain barrier. Oral and parenteral dosages are similar because of the good intestinal absorption of clindamycin. Oral clindamycin can cause anorexia, vomiting, or diarrhoea in dogs and cats.