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Inflammatory Disease of the Central Nervous System

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"Encephalitis," "myelitis," and "meningitis" are terms applied to inflammatory conditions of the brain, spinal cord, and meninges, respectively. Because of the close anatomic proximity of these central nervous system (CNS) structures, inflammatory processes frequently involve more than one of them at a time. Thus, the terms "encephalomyelitis," "meningoencephalitis," and "meningoencephalomyelitis" may apply. One should approach any suspected CNS inflammatory problem as having the potential to become widespread (multifocal or diffuse) if it has not done so already.

In general, the majority of CNS inflammatory diseases present in an acute progressive manner; a more insidious onset is possible. Fungal diseases prove the most consistent exception, more commonly presenting with chronic progressive signs. Whenever rapidly developing and spreading dysfunction of the CNS is observed, inflammatory conditions must be considered at the top of the list of differential diagnoses.

CLINICAL SIGNS

The presenting complaints and clinical signs seen in inflammatory diseases of the CNS are highly variable, because all parts of the CNS are susceptible to inflammatory processes. Some etiologic agents have predispositions to particular areas of the CNS (such as canine distemper virus to the cerebellum) but cannot be relied upon to consistently involve those areas in each case. Neurologic dysfunction may be focal, multifocal, or diffuse in nature. Because of the rapidly progressive nature of many of these diseases, an initial focal localization may progress to multifocal or diffuse in a relatively short period of time.

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The predominant clinical signs in viral, protozoal, and parasitic diseases relate to parenchymal involvement of the brain and/or spinal cord. Rickettsial and fungal diseases may display parenchymal as well as meningeal signs. Bacterial diseases most commonly present with meningeal signs, which may spread to display parenchymal signs.

Encephalitis and Myelitis

Although clinical signs are highly variable in cases of encephalitis, some generalities can be made. Signs usually reflect diffuse brain parenchymal involvement that may be slightly asymmetric. Common clinical signs seen in encephalitis include altered states of consciousness (depression, stupor, and so forth), behavioral changes, visual impairment with intact pupillary light reflexes, incoordination, voluntary motor dysfunction, and cranial nerve dysfunction. Sometimes seizures may be a part of the history.

Myelitis occurs more frequently in association with encephalitis (encephalomyelitis). However, the spinal cord parenchyma may be involved in an inflammatory process without associated brain involvement. The clinical signs seen will depend on the location and extent of involvement. Spinal cord signs of sensory ataxia, depressed postural reactions, motor dysfunction, and possibly loss of pain sensation may occur in one or more limbs. Urinary and fecal incontinence may also be present.

Meningitis

Classically, two major clinical signs accompany meningitis: neck pain and fever. Afflicted animals are usually reluctant to be handled around the neck, displaying cervical hyperesthesia and muscle rigidity. Meningeal irritation may be sufficient to cause opisthotonus and forelimb hyperextension. Generalized hyperesthesia may also be present. Meningitis is usually accompanied by some degree of parenchymal involvement (encephalomyelitis) that may or may not be clinically evident.

Meningitis is not a common disease problem of companion animals. In bacterial meningitis, organisms gain access to the subarachnoid space through hematogenous spread, direct extension from the sinuses, ears, and eyes, penetrating trauma, and contaminated surgical instruments, including spinal needles. Once established, the inflammatory process usually spreads to involve parenchymal structures (meningoencephalomyelitis). Fungal organisms usually reach the CNS via hematogenous or lymphatic routes but may also arrive via direct extension from adjacent infections, as in fungal sinusitis. Rickettsial organisms infrequently involve the nervous system but may cause signs suggestive of meningitis (fever, hyperesthesia) along with signs of parenchymal involvement (depression, paresis, seizures, and so forth). Suspected immune-mediated meningitis[60] and meningitis/vasculitis[10] have also been reported. Viral, protozoal, and parasitic diseases primarily affect parenchymal tissues with associated meningeal reaction. Clinical signs in these conditions are more typical of encephalitis and/or myelitis than meningitis.

DIAGNOSTIC PROCEDURES

Minimum Database

In cases of suspected CNS inflammatory disease, the diagnostic plan should begin with a neurologic minimum database (MDB). This should include complete physical and neurologic examinations with special attention paid to the ophthalmic and otic examinations. In addition, an electrocardiogram should be included in preparation for the anesthesia necessary to collect cerebrospinal fluid (CSF). Laboratory tests should include a complete blood count (CBC), blood chemistry profile including electrolytes, urinalysis, and fecal analysis. Choice of additional laboratory tests will be based on the MDB results.

Laboratory Tests. The MDB evaluates the general health of the animal, including the nervous system. Multisystemic involvement is often reflected in abnormal physical and laboratory findings. Knowing the organ system preferences of various etiologic agents helps the clinician formulate a reasonable differential list based on MDB abnormalities as well as identify additional tissues for possible culture.

In many animals, the inflammatory process will not extend outside the CNS. In these cases, it is not unusual for the MDB laboratory results to be totally normal. The nervous system is very effectively isolated from other organ systems by the blood-brain, blood-CSF, CSF-extracellular fluid, blood-eye, and blood-nerve barriers. Even though we normally assume these barriers are compromised in CNS inflammatory processes, that does not mean disease processes will be reflected in the MDB laboratory results. In my experience, animals with primary CNS inflammatory disease usually have normal MDB laboratory results (with the notable exception of feline infectious peritonitis [FIP]), requiring additional diagnostic tests to make the diagnosis.

Ophthalmic and Otic Examinations. The opthalmic and otic examinations are especially important in suspected cases of CNS inflammatory disease. Because the optic nerve extends directly from the brain, papilledema or optic neuritis may reflect a larger inflammatory process in the CNS. Many of the organisms that cause CNS inflammation also cause ocular lesions. Evidence of acute chorioretinitis, granulomatous chorioretinitis, vasculitis, retinal hemorrhage, retinal detachment, uveitis, corneal edema, keratitis, and conjunctivitis can assist greatly in ruling out possible etiologic agents.[95]

The ear is one of the most common sites of entry of organisms into the CNS. Otitis externa is extremely common in dogs and can extend to become otitis media/interna with subsequent invasion of the CNS. Oropharyngeal inflammation may also extend, causing otitis media/interna. Any signs of otitis should be investigated thoroughly in animals displaying CNS inflammatory disease.

Cerebrospinal Fluid

Cerebrospinal fluid analysis is the single most important diagnostic test that can be performed on animals suspected of having a CNS inflammatory disease. Even so, it is possible to have false-negative results or misleading

cellular populations. Great caution must be exercised in collecting fluid because of the potential dangers of anesthesia, tentorial herniation, and spread of infection.[60]

Risks of CSF Collection. Collection of CSF in companion animals requires general anesthetic restraint, which always entails some risks. When an animal has encephalitis, the risks are compounded by potential involvement of the respiratory centers of the brain stem and the reticular activating system. Encephalitic animals often present with already altered states of consciousness and are therefore much more susceptible to anesthetic accidents. Great care must be taken in administering and monitoring anesthesia in animals with encephalitis.

Encephalitis causes cerebral edema, which leads to increased intracranial pressure. When CSF is removed, the ventricular volume and, thus, intracranial pressure is reduced, allowing the parenchyma to swell further. If the intracranial pressure is sufficiently increased when CSF is removed, the cerebral hemispheres and cerebellum will move caudally under the tentorium cerebelli and through the foramen magnum, respectively, causing midbrain and medullary brain-stem compression. This is a life-threatening condition unless corrected immediately.

Clinical signs suggestive of increased intracranial pressure include altered mentation, altered pupillary size and responsiveness, poor to absent eye movements in response to alterations in head position (physiologic/vestibular nystagmus), motor dysfunction, and abnormal respiratory patterns. If increased intracranial pressure is suspected, CSF collection should be delayed while attempts are made to therapeutically reduce the pressure. Drugs that have proved helpful in reducing cerebral edema are osmotic diuretics, glucocorticoids (generally contraindicated in CNS inflammatory disease), dimethylsulfoxide, barbiturates, nonsteroidal analgesics, antifibrinolytic agents, antibiogenic amine compounds, endorphin antagonists, and blood flow stimulants.[73] These same drugs are advocated when tentorial herniation is suspected. Improvement in clinical signs indicates response to therapy, at which time a decision on CSF collection can be made. Fortunately, in most cases of inflammatory CNS disease, intracranial pressure is not elevated significantly enough to prevent collection and analysis of CSF.[72]

Collection of CSF may hasten the spread of an inflammatory process by altering CSF flow dynamics. During CSF collection, fluid is withdrawn at a rate faster than the normal flow rate of CSF through the ventricles, subarachnoid space, and central spinal canal. If the causative agent is present in the CSF, its movement through the CNS may be hastened. Also, the meninges may become contaminated secondary to the spinal tap.

CSF Collection. CSF is most commonly collected from the cisterna magna (cerebellomedullary cistern), which provides the largest, most easily accessible reservoir of CSF in companion animals. Even so, care must be exercised during placement of the spinal needle or puncture of the medullary brain stem may occur, causing death subsequent to respiratory failure. If fluid is withdrawn too rapidly from the cisterna, tentorial herniation may occur. An advisable rate of removal is no faster than 1 ml per 30-second interval.[60] Lumbar subarachnoid puncture is extremely

difficult to perform and often does not yield adequate volumes for analysis. In addition, CSF collected from the lumbar subarachnoid space has been shown to differ in protein and cellular content from fluid collected from the cisterna magna, which could complicate interpretation.[2]

Collection of CSF should always be performed in an aseptic manner. Sternal or lateral positioning of the animal is determined by personal preference if the fluid is aspirated with a syringe. If drip collection is preferred, the animal will need to be plaed in lateral recumbency. Twenty-one- or 22-gauge 1.5-inch styleted spinal needles are adequate for use in all but the largest-sized dogs. Occasionally, a 2.5- to 3-inch needle will be necessary on giant breeds. For extremely small animals, 23- to 25-gauge "butterfly" needles with attached tubing can be very useful if an assistant is available to aspirate the fluid.

CSF Analysis and Interpretation. Routinely, CSF is analyzed for color and turbidity, protein content, total red (RBC) and white blood cell (WBC) counts, and the differential cell count. In addition, it is wise to try to culture the CSF if a bacterial or fungal etiology is suspected or if organisms are seen on cytologic examination.

In general, elevations in protein content and WBC count are seen in CNS inflammatory diseases. These increases will vary with the type of organism involved and the duration of the inflammatory process. Meningeal involvement seems to cause greater increases in both protein and cell count than pure parenchymal involvement.[72]

Protein Content. Viral diseases seem to cause the least amount of protein elevation, with the exception of the FIP virus, which can cause marked increases in protein.[51, 93] Bacterial, fungal, protozoal, and parasitic diseases cause moderate to marked elevations in protein.[72] Rickettsial diseases can have normal to minimal increases in CSF protein in Rocky Mountain spotted fever (RMSF)[11, 39, 40] compared with moderate to marked increases in ehrlichiosis.[10, 40] Cases of granulomatous meningoencephalomyelitis (GME) display mild to moderate (40 to 110 mg per dl) elevation of protein.[3, 10]

Cell Changes. Viral diseases generally cause slight to moderate pleocytosis (15 to 60 WBC per mm^3) that is primarily mononuclear (lymphocytes and macrophages) in nature.[73] If collected in the acute stages of viral disease, however, CSF may have neutrophilic pleocytosis and appear more like a bacterial meningitis.[50] Feline infectious peritonitis again proves to be the general exception, routinely displaying moderate to marked elevations of a mixed population of WBCs, including significant numbers of neutrophils.[72, 73]

Bacterial infections cause the most dramatic elevation in WBCs. A high percentage of WBCs are neutrophils early in the inflammatory process.[10, 73] As the disease progresses, a mixed population of neutrophils and mononuclear cells (primarily macrophages) may be seen.

Fungal diseases commonly present with moderate to marked elevations of a mixed population of mononuclear and polymorphonuclear cells.[10, 73] Protozoal diseases usually present with a moderate pleocytosis of mixed mononuclear and polymorphonuclear cells. Parasitic diseases display moderate to marked mixed mononuclear-polymorphonuclear pleocytosis, often with a significant percentage of eosinophils.

Rickettsial diseases have been reported to have normal to markedly increased cell counts.[10, 11, 40] The cells are reported to be mainly mononuclear in nature; however, in one report of RMSF, a great number of neutrophils (80 per cent) were present.[40] Eosinophilic pleocytosis has been reported in human RMSF.[21] Granulomatous meningoencephalitis usually has a moderate to marked number of mononuclear cells (lymphocytes, monocytes, macrophages) present in CSF.[3, 10, 73]

CSF Culture. Culture of CSF is difficult and often unrewarding, even when organisms can be seen on cytologic examination. Enriched media and special incubation techniques are usually required for successful culture of CSF.[39] Attempts to culture CSF should probably be reserved for those cases with increased protein content and neutrophilic pleocytosis (suspected bacterial involvement). Because of the frequency of false-negative CSF culture results and the rapidly progressive course of bacterial meningitis, antimicrobial therapy should not be delayed pending culture and sensitivity results.

Blood and Urine Cultures

Meningoencephalomyelitis can arise secondary to hematogenous spread of organisms from other organ system infections, such as bacterial endocarditis or urinary tract infection. Aseptically obtained blood, urine, and other tissue samples as indicated (tracheal wash, lung aspirate, and so on) can be cultured and often provide more definitive information about the cause of meningoencephalomyelitis than CSF cultures. It is advisable to collect these samples at the same time CSF is collected in the hopes of identifying the organism as rapidly as possible and, thus, expediating correct antimicrobial therapy.

Serologic Tests

Serologic tests exist for *Brucella canis*, canine distemper virus (CDV), FIP, toxoplasmosis, rickettsial organisms, and fungal organisms. In my experience, FIP, toxoplasmosis, and fungal titers are extremely unreliable. To date, rickettsial titers out of the University of Illinois* and University of Georgia† laboratories have proved to be the most reliable.

The most helpful serologic tests are for *Brucella canis* and CDV. A number of tests are available for *Brucella canis*; some are more sensitive than others. False-positive and false-negative results are possible depending on the test used. For this reason, two or more of the tests are often performed before making a final determination. Test results should always be interpreted in light of the clinical findings.[39]

Canine distemper virus titers should be performed on serum and CSF simultaneously. Serum may have an increase in anti-CDV antibody from vaccination or natural infection. Because antibody is produced locally, an increase in CSF anti-CDV antibody (appearing 2 to 3 weeks after onset of disease) can occur only after CDV encephalitis and provides definite

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evidence that the virus has been present in the CNS. Increased CSF anti-CDV antibody has not been demonstrated in vaccinated dogs or in dogs with systemic disease without CNS involvement. Blood contamination may artificially increase the anti-CDV titer in the CSF but should be suspected at the time of collection or CSF analysis.[39, 73] The laboratory at Auburn University has provided the most reliable results in my experience.*

Skull Radiographs

If otitis interna/media is suspected as the cause of meningoencephalitis, skull films of the tympanic bullae may help in making the diagnosis. Sclerosis or lysis of an osseous bulla, increased density of a bulla cavity, or asymmetry of the bullae would all be suggestive of otitis interna/media. When meningoencephalitis is suspected secondary to cranial trauma, skull radiographs may help confirm the diagnosis.

Electroencephalography

Electroencephalography (EEG) is not an extremely helpful diagnostic test in CNS inflammatory disease. The findings may be abnormal but are nonspecific and do not assist in identification of the causative agent, selection of a therapeutic protocol, or prediction of the outcome.

Other Tests

Ear Cultures. If otitis interna/media is suspected as the source of the etiologic agent in meningoencephalitis, cultures of the middle ear may be helpful. These are extremely difficult to obtain without secondary contamination but may prove helpful in selecting correct antimicrobial therapy.

Fluorescent Antibody Testing for CDV. If performed during the time clinical infection is apparent, this test can be helpful in confirming the presence of CDV. Results are usually negative after the recovery stage begins and may even be negative during the infected stage. Consequently, negative results should not be used to rule out CDV.

THERAPY

Antimicrobial Agents

Antimicrobial agents are ideally selected based on specificity of action against the causative organism, bactericidal tendencies, accessibility to the site of infection, rapid action, and lack of undesirable side effects. When dealing with CNS inflammatory disease, accessibility becomes a critical problem owing to the natural barriers (primarily blood-brain and blood-CSF) against passage of drugs into the CNS. Drugs with a low degree of ionization, a low degree of plasma protein binding, and a high degree of lipid solubility in the un-ionized state are favored to enter the CNS because of increased membrane solubility. In addition, inflammatory damage may

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Table 1. *Effectiveness of Antimicrobials in CNS Inflammatory Conditions*

	ACTION	ROUTE	ORGANISMS
Good Penetration			
Chloramphenicol	Bacteriostatic	PO	+, −
Isoniazid	Bacteriostatic	PO	m
Metronidazole	Bactericidal	PO	a
Pyrimethamine	Bacteriostatic	PO	p
Rifampin	Bacteriostatic	PO	+, −, m, f
Sulfonamides	Bacteriostatic	PO	+, −, p
Trimethoprim	Bacteriostatic	PO	+, −
Trimethoprim-sulfamethoxazole	Bactericidal	PO	+, −, p
Intermediate Penetration (improved during inflammation)			
Amoxicillin	Bactericidal	PO	+, −, a
Ampicillin	Bactericidal	IV	+, −, a
Carbenicillin	Bactericidal	IV	+, −, a
Cephalosporins			
First-generation	Bactericidal	IV	+, −
Second-generation	Bactericidal	IV	−
Third-generation	Bactericidal	IV	−
Doxycycline	Bactericidal	PO, IV	+, −, a
Flucytosine	Bacteriostatic	PO	f
Methicillin	Bactericidal	IV	+
Minocycline	Bactericidal	PO, IV	+, −, a
Nafcillin	Bactericidal	IV	+
Oxacillin	Bactericidal	IV, PO	+
Penicillin G	Bactericidal	IV	+
Tetracyclines	Bacteriostatic	PO, IV	+, −, a
Vancomycin	Bactericidal	IV	+
Poor Penetration			
Aminoglycosides	Bactericidal	IV, IT	+, −, m
Amphotericin B	Bacteriostatic	IV, IT	f
Cephalosporins	Bactericidal	PO, IV	+, −
Erythromycin	Bacteriostatic	PO	+
Ketoconazole	Bacteriostatic	PO	f
Lincomycin	Bacteriostatic	IM	+, −, a

Key: + = gram-positive bacteria; − = gram-negative bacteria; a = anaerobic bacteria; m = mycobacteria; f = fungal organisms; p = protozoal organisms.

increase the CNS concentration of some drugs by increasing membrane permeability to the drugs or slowing their removal from the CSF (Table 1).[72]

    Bacterial Infections. Bacterial infections of the CNS are rapidly progressive and fatal if not treated aggressively. When bacterial infection is suspected, antibiotic therapy should be started immediately. Changes can be made later based on culture results or lack of response to therapy. High-dose intravenous bactericidal therapy is preferred to obtain the highest CSF concentrations of the most efficacious drug(s) as rapidly as possible. Bactericidal and bacteriostatic drugs should not be combined because of reduced efficacy.

    The most commonly reported organisms causing bacterial meningoencephalomyelitis in companion animals are *Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus albus, Pasteurella multocida, Pasteu-*

rella species, *Actinomyces* species, and *Nocardia* species.[10, 72, 73] Initial therapy should begin with the assumption that *Staphylococcus* is the most likely cause. High doses of intravenous (IV) penicillin G (10,000 to 20,000 U per kg every 4 to 6 hours), IV ampicillin (5 to 10 mg per kg every 6 hours), or oral (PO) amoxicillin (10 mg per kg every 8 hours) have been recommended.[39, 72] Ampicillin and amoxicillin are preferred to penicillin G by some because of their broader spectrum of activity.[39] If the causative organism proves to be a coagulase-positive *Staphylococcus*, medication can be changed to methicillin. Oxacillin can be used for penicillin-resistant staphylococci. Carbenicillin is the drug of choice for *Pseudomonas* infection.

It is tempting to begin therapy with chloramphenicol, believing the high concentrations achieved in CSF can overcome the disadvantage of being bacteriostatic. However, many strains of *Staphylococcus* have been shown to be resistant to this drug,[50] and it has demonstrated poor efficacy against gram-negative organisms.[39] It is probably best to use chloramphenicol when the organism has been determined to be sensitive or as a second-choice drug. Chloramphenicol and penicillin are antagonistic and should not be used simultaneously unless deemed absolutely necessary. When used together, penicillin administration should precede chloramphenicol by at least 24 hours.[72]

Trimethoprim-sulfonamide in combination is bactericidal. Both drugs penetrate the CNS barriers well. Together they have a relatively broad spectrum of activity. This combination should be kept in mind if initial treatment does not seem effective.

Metronidazole (10 to 15 mg per kg orally every 8 hours) penetrates the CNS well and is effective against anaerobic organisms. Penicillin and carbenicillin are probably more commonly used for CNS anaerobic infections, but metronidazole has proved effective.

Rifampin and isonizid are antituberculosis (*Mycobacterium tuberculosis*) drugs that reach significant levels in the CSF. Rifampin (10 to 20 mg per kg orally every 8 to 12 hours) has additional activity against *Staphylococcus* and some gram-negative bacteria and has been shown to enhance the antifungal effect of amphotericin B.

Aminoglycosides and penicillins are synergistic in combination. However, aminoglycoside penetration into the CNS is so poor that the only justification for its use in bacterial meningoencephalomyelitis is to treat a non-CNS source of infection.[72] Intrathecal (IT) administration of gentamicin every 6 hours has been advocated to overcome the CNS barriers. However, the disadvantages of this approach probably outweigh the advantages in the majority of cases.

In general, tetracyclines are not useful for treatment of CNS inflammation because they penetrate poorly, are bacteriostatic, and have a more limited spectrum. However, the newer lipid-soluble second-generation tetracyclines (minocycline and doxycycline) penetrate the CNS and have better activity against anaerobes and certain aerobic organisms. Minocycline in combination with streptomycin has proved very effective against *Brucella canis* infection.

In general, cephalosporins penetrate the CNS poorly.[28, 39, 50, 73] However, there are conflicting reports on the ability of some of the relatively

toxic first-generation cephalosporins (cephaloridine, cephalothin, cephalexin) to enter the CNS during times of inflammation.[31, 39, 50, 66] Cephalexin proved successful in *Staphylococcus aureus* meningitis in one report.[50] Some of the second- (cefamandole and cefoxitin) and third-generation (cefotaxime and moxalactam) cephalosporins have been shown to penetrate the CSF in sufficient levels to kill most organisms encountered. However, these drugs have demonstrated variable success in clinical settings.[39, 53, 67, 73]

To achieve the highest possible CSF levels as rapidly as possible, high-dose antibiotic therapy should be administered IV if possible for 1 to 2 weeks and then followed with oral medication. Antibiotic therapy should be continued for at least 4 weeks if treatment is to be successful. Very often, longer periods of administration will be required and relapses are possible.

Glucocorticoids, in combination with antibiotics, have been recommended to reduce tissue inflammatory response in cases of meningoencephalitis.[13, 90] Because of the difficulty of getting microcidal levels of antimicrobials into the CNS, successful treatment of bacterial and fungal meningoencephalitis depends a great deal on the body's ability to mobilize its natural defense mechanisms to assist in removal of the causative agents. Doses of glucocorticoids sufficient to reduce cerebral edema are immunosuppressive and have been associated with increased morbidity, mortality, and relapses.[39] Most authors agree that osmotic diuretics should be used instead of glucocorticoids if cerebral edema is deemed significant enough to require treatment.[39, 72, 73]

Fungal Infections. Central nervous system fungal infections are difficult and usually unrewarding to treat. The disease is often multisystemic and seldom recognized in the early stages of CNS involvement.[7, 19, 25, 26, 32, 37, 38, 44, 45, 55, 61, 68, 70, 71, 74, 77, 79, 85, 94, 97, 100, 105, 108] Combinations of antimicrobial agents seem to be more efficacious than individual drug therapy. Amphotericin B, flucytosine, and ketoconazole are the main agents used, none of which penetrate the CNS well. Rifampin, which does penetrate the CNS, has been shown to enhance amphotericin B activity. Most therapeutic regimens begin with amphotericin B (0.15 to 0.50 mg per kg IV every 2 days;[72] 0.22 mg per kg gradually increased to 0.75 mg per kg 3 times weekly to a total dose of 7 to 20 mg per kg[28]) and add flucytosine or ketoconazole. Intrathecal amphotericin B (0.1 to 0.5 mg IT every 2 to 3 days to a total of 10 to 15 mg[72]) has been advocated to increase the concentration of the drug in CSF.

Flucytosine and amphotericin B act synergistically in vitro against *Cryptococcus neoformans*. This combination does not seem to have as good an effect in cases of coccidioidomycosis, probably because IV amphotericin B does not reach high enough levels to be effective. Therefore, IT amphotericin B is recommended for *Coccidioides immitis* infections. Ketoconazole may be effective against *Candida* species, *Coccidioides immitis*, *Histoplamsa capsulatum*, and *Cryptococcus neoformans*, but it penetrates the CNS poorly. Its use is probably more beneficial for systemic rather than CNS fungal involvement. Rifampin in combination with amphotericin B seems to be most helpful against *Histoplasma capsulatum*. None of these drugs work well against *Aspergillus* species, but amphotericin B combined with flucytosine or rifampin should be tried.

Newer-generation imidazoles are currently under investigation that appear to reach significant levels in the CSF during inflammation. When approved, these drugs may offer new hope in the treatment of fungal meningoencephalomyelitis.

Viral Infections. No effective treatments are known for the viral nervous system diseases. At best we can offer good nursing care and support against secondary bacterial invaders. Glucocorticosteroids may lessen some of the clinical signs but also suppress the natural defense mechanisms that are the body's only mechanism of overcoming viral infection.

Antiviral drugs are of great interest but, to date, have proved quite toxic when given systemically. Viruses seem to be susceptible only during replication, which has usually occurred by the time the diagnosis is made.[28, 39] In general, these drugs are not currently of practical usefulness in viral diseases of companion animals.

No treatment should be attempted in cases of rabies and pseudorabies because of the risk to public health.[87, 88, 92, 107] Megadoses of vitamins and intravenous modified live vaccine have not proved beneficial in cases of canine distemper.[28] Immunosuppressive drugs (glucocorticoids, melphan, cytoxan) have been used in cats with FIP with poor long-term results.[28, 39, 51, 54] Increasing the environmental temperature of puppies afflicted with neonatal canine herpesvirus may lower mortality.[76, 110]

Meningoencephalitis caused by canine parainfluenza virus has been reported clinically and experimentally.[5, 6, 27] The importance of canine parainfluenza virus in naturally occurring neurologic disorders remains to be determined. No treatment is currently known.

Parvovirus and coronavirus/parvovirus vaccines have been incriminated as the causes of neurologic dysfunction in puppies. Signs of meningoencephalitis were seen in four puppies shortly after diagnosis of parvovirus enteritis.[14] Parvovirus was isolated from the brain of a puppy that died of a severe necrotizing vasculitis and encephalomalacia without clinical signs of enteritis.[46] Eight puppies were reported to have neurologic signs following vaccination with a canine coronavirus-parvovirus vaccine.[109] In these reports, treatments were not described and all puppies died.

Rickettsial Infections. Ehrlichiosis *(Ehrlichia canis)*, Rocky Mountain spotted fever *(Rickettsia rickettsii)*, and salmon poisoning disease *(Neorickettsia helminthoeca)* have been reported to cause encephalitis in companion animals.[10, 11, 39, 52] However, these diseases are more commonly associated with other clinical signs (pyrexia, petechiation, anemia, lymphadenopathy, splenomegaly, and so on). Lyme disease *(Borrelia burgdorferi)* has been identified in animals.[49, 57] Limb and joint disorders are the main clinical signs reported in dogs, but neurologic involvement has been reported in human beings and should be watched for in animals.[4, 12, 75, 106]

Tetracyclines and chloramphenicol have been shown to be effective against rickettsial organisms but are bacteriostatic. Elimination of the organisms from the body depends on the immunocompetence of the animal. The use of chloramphenicol is not advised in anemic animals but can be preferable in young dogs to avoid tetracycline staining of the teeth. Supportive therapy will vary among individual cases but may include fresh blood or platelet-rich plasma transfusions, bone marrow stimulants, fluid

therapy, and appetite stimulants. Doxycycline has proved more effective than oxytetracycline in the treatment of ehrlichiosis. Being a lipid-soluble tetracycline, doxycycline has better penetration into the CNS and should be preferred in cases with CNS involvement.

Protozoal Infections. Protozoal infections of the CNS are rare in companion animals. Toxoplasmosis, babesiosis, encephalitozoonosis, trypanosomiasis, and an amebic meningoencephalitis have been reported. Treatment of these conditions has variable results with a generally guarded to poor prognosis.

Pyrimethamine and sulfadiazine in combination are more effective against CNS toxoplasmosis than trimethoprim-sulfonamide. Folinic acid should be simultaneously administered to combat pyrimethamine-induced bone marrow suppression.[28, 39] Medications used to treat systemic toxoplasmosis have limited effectiveness (chloramphenicol) or do not penetrate into the CNS well (tetracycline, clindamycin).[39]

Imidocarb dipropionate, diminazene aceturate, and phenamidine isethionate (aromatic diamidines) are suggested for canine babesiosis. Imidocarb dipropionate is also effective against *Ehrlichia canis.* Two intramuscular injections of 5 mg per kg of imidocarb dipropionate given 14 days apart seem effective against *Babesia canis* and *Ehrlichia canis.* No drug has been completely successful in clearing *Babesia gibsoni.* A single dose of primaquine phosphate intramuscularly (0.5 mg per kg) is recommended for feline babesiosis *(Babesia felis).*[39]

Lithium antimony thiomalate[73] and nifurtimox (8 to 30 mg per kg per day orally for 3 to 5 months)[39] have been recommended for treatment of trypanosomiasis. No treatment exists for encephalitozoonosis.[91, 98]

Acanthamoeba castellani was diagnosed histopathologically in an immunosuppressed puppy with rapidly fulminating meningoencephalitis.[75] *Acanthamoeba* species have also been reported to cause meningoencephalitis in human beings.[104]

Parasitic Infections. Parasites rarely cause CNS damage in companion animals. *Dirofilaria immitis*[18, 24, 34, 56, 58, 89] and *Cuterebra* species[17, 62, 84] larvae are the most frequently reported. Parasitic involvement should be suspected if a pleocytic CSF is present with a high percentage of eosinophils. *Dirofilaria immitis* may be suspected if blood tests are positive.[18, 24, 34, 58, 89] There are no definitive tests for the presence of *Cuterebra* larvae.[17, 62, 84] These conditions are usually diagnosed on postmortem examination; therefore, successful treatments are rarely described. Successful surgical removal of extramedullary larvae is possible.[56]

Other suspected and confirmed parasitic infections of the CNS have been reported. A cat with acute neurologic signs and CSF eosinophilic pleocytosis was reported to recover following therapy with levamisole.[17] A confirmatory diagnosis of the etiology could not be made. Granulomatous encephalomyelitis caused by *Angiostrongylus cantonensis* has been reported in puppies.[59] *Trypanosoma evansi* was confirmed as the cause of meningoencephalitis in dogs.[15]

Protothecal Infections. Prototothecosis is an extremely rare cause of CNS inflammation in companion animals. No successful treatments have been reported.[39]

UNDETERMINED ETIOLOGY

Steroid-Responsive Meningitis

Multisystemic polyarteritis (necrotizing vasculitis) involving the meninges has been reported. All dogs displayed clinical signs characteristic of meningitis (pyrexia, pain, and cervical rigidity); the majority of these dogs were relatively young animals.[41, 43, 47, 65] In two of the reports in which related dogs were involved, CSF revealed a neutrophilic pleocytosis and elevated protein content; a peripheral neutrophilia was present.[41, 65] Steroids were used in these dogs and caused transient to long-lasting improvement. No organisms were identified, and all authors suspected an immune-mediated cause of the vasculitis.

Two reports of 13 young dogs with corticosteroid-response meningitis parallel the clinical and laboratory findings reported in the cases with confirmed polyarteritis.[64, 80] Only one of these dogs underwent pathological examination after 6 months of intermittent steroid administration. Chronic active suppurative leptomeningitis and leptomeningeal fibrosis were reported, but nothing specific was said about the meningeal vessels. An immune mechanism was suspected in all these dogs.

Granulomatous Meningoencephalitis/Reticulosis

Numerous cases of a nonsuppurative inflammatory disease with focal or diffuse CNS lesions have been reported in dogs[1, 3, 8–10, 20, 22, 48, 69, 72, 73, 81, 101] but only rarely in cats.[111] Ocular involvement has also been reported.[29, 30, 35, 96] The term "reticulosis" was formerly used to describe what is now called disseminated GME (inflammatory reticulosis), focal GME (neoplastic reticulosis) and ocular GME (ocular reticulosis). Clinical signs reflect the focal, multifocal, or diffuse nature of CNS involvement. Focal GME most commonly involves the brain stem, whereas disseminated GME is usually widespread, especially in the cerebrum, lower brain stem, cerebellum, and cervical cord. The cause is unknown, but an immunologic basis is suspected.

Signalment is nonspecific and clinical signs can be acute or chronic progressive, varying with the sites of CNS involvement. CSF has a mild to moderate (40 to 110 mg per dl) elevation in protein and a moderate to marked (50 to 660 WBC per mm^3) mononuclear pleocytosis (lymphocytes, monocytes, macrophages). Temporary clinical improvement may be seen with glucocorticoid therapy, but no effective treatment is known.

Polioencephalomyelitis in Cats

A chronic progressive syndrome of ataxia, paresis, tremors, pupillary abnormalities, and seizures has been reported in cats of varying breeds and ages.[42, 102] The pathology was suggestive of a viral cause, but organisms could not be demonstrated. The lesions were very similar to lesions reported in lions and tigers in which a viral cause was also suspected but never confirmed.[33] Other similar cases have been reported.[52, 63]

Chronic Encephalitis of Pug Dogs

A chronic progressive granulomatous meningoencephalitis causing diffuse degeneration of white matter and less often gray matter has been

reported in Pug dogs 9 months to 4 years of age.[23] The clinical signs predominantly relate to cerebral lesions (generalized seizures, ataxia, paresis, circling, depression, partial motor seizures, visual deficits with intact pupillary reflexes). Central vestibular, cerebellar, and spinal cord signs have also been reported. Death is usually preceded by status epilepticus. Cerebrospinal fluid shows elevated protein content and a moderate elevation of lymphocytes and other mononuclear cells. Viral isolation has been unsuccessful, leaving the etiology unknown. A familial predisposition warrants investigation. There is no specific treatment known. Seizures are often refractory to anticonvulsants, and corticosteroids have not proved helpful.

Eosinophilic Meningoencephalitis in a Cat

A cat with neurologic signs including disorientation, inability to stand, visual and hearing losses, and seizures displayed mild CSF pleocytosis (17 WBC per mm^3) with 81 per cent eosinophils and a mild elevation in CSF protein (24 mg per dl). The cause was suspected to be a type I hypersensitivity reaction. The cat was successfully treated wtih dexamethasone.[86]

PROGNOSIS

Diagnostic findings in CNS inflammatory disease may vary widely between different animals affected with the same etiologic agent, often making diagnosis and choice of therapy extremely difficult. Many of these diseases can only be positively confirmed through pathologic examination. The prognosis in any CNS inflammatory disease must be considered guarded to poor, even when there seems to be response to therapy. Temporary remissions and relapses are common.

SUMMARY

Inflammatory diseases involving the central nervous system can be difficult to diagnose and frustrating to treat. The clinician can maximize successful treatment of these patients by recognizing the clinical signs in the early stages of disease, following a logical diagnostic plan to identify the specific etiologic agent involved, and formulating an appropriate and aggressive therapeutic plan. Treatment will not always be successful owing to lack of effective treatments and irreversible neurologic damage.

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