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Topics in Feline Neurology

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Nervous system diseases of the cat are being recognized with increasing frequency owing to both advances in our understanding of cat diseases and the willingness of the public to pursue diagnostic examinations and procedures. Hopefully, in the future, many large case studies will help define the frequency, clinical presentation, and signalment for these diseases.

The following discussion will concern a few neurologic diseases that affect the cat. The specific disease, its pathogenesis, diagnosis, and treatment will be emphasized.

MENINGIOMAS

Pathologic features of spontaneous central nervous system tumors have been the subject of several reviews.[13, 21] These studies discussed the relative incidence and morphology of central nervous system tumors. Based on necropsy findings, the meningioma is the most common central nervous system tumor of the cat.[13, 21] One report indicated their incidence as 0.9 per cent of all nonhematopoietic neoplasms.[21] The meningioma is a benign tumor that arises from the arachnoid cells of the meninges, which are mesodermal in origin. Compared to the dog, neuroectodermal tumors in the central nervous system are relatively rare in the cat. The vast majority of meningiomas occur cranial to the foramen magnum; therefore, accompanying signs suggest brain, rather than spinal cord, disease.[13, 15] In one study, 25 of 30 solitary meningiomas arose from the supratentorial calvarium, compressing the cerebrum.[15] Although these tumors are benign, they cause devastating effects through compression and displacement of the surrounding nervous tissue, which is encased by the nonexpansive cranium. Edema of the nervous tissue is also a complication of the tumor, and often the signs observed are due to the edema rather than to the tumor mass itself.[6] The pathogenesis of this is unclear. In man, edema is not apparently due to increased vascularity, location, or histology of the meningioma but

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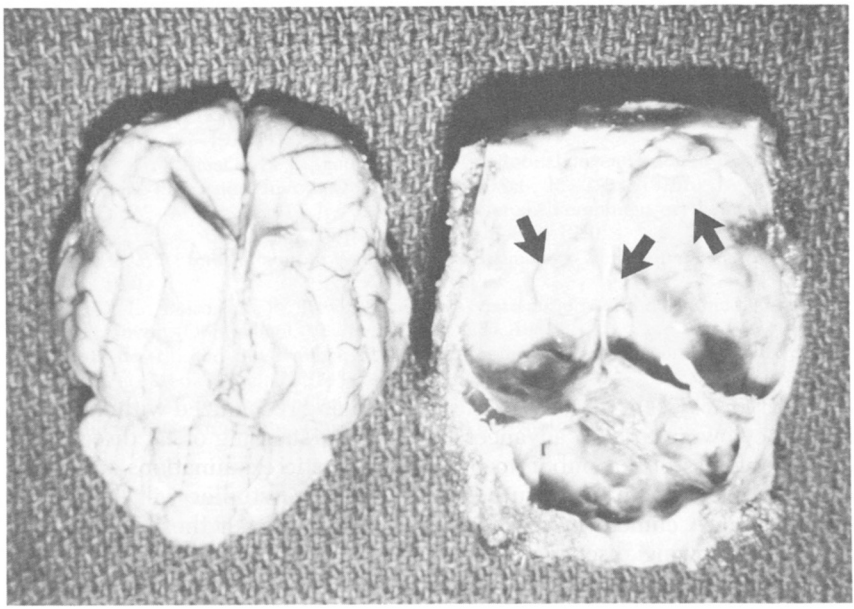

Figure 1. This 12-year-old cat presented with left cerebral deficits of 2-week duration. Postmortem examination revealed multiple meningiomas compressing the cerebrum.

rather is correlated to tumor size.[6] The edema occurs in white matter and appears to be vasogenic rather than cytotoxic. Two possible causes of the edema are humoral factors produced by the tumor and/or the ischemia produced by the compression of the tumor on underlying blood vessels.[15]

Clinical signs associated with the tumor may have an acute or chronic onset. This is due to a number of factors, including location of the tumor, rate of growth, amount of edema, and herniation of the brain. Over 66 per cent of affected cats are 10 years old or older, with 10 to 15 per cent of all cases having multiple meningiomas.[15] Due to the high incidence of solitary supratentorial tumors, signs related to unilateral cerebral disease would be expected. Ipsilateral circling, contralateral menace deficit, contralateral hemiparesis, and seizure disorders, are some of the signs associated with unilateral cerebral disease. The seizure disorder may be focal and contralateral to the tumor, or it may be generalized. The clinician should be alert for localizing signs at the initiation of the generalized seizure. In man, tumors with a parasagittal location have a significantly higher incidence of seizures, and although the incidence of seizures in cats with meningiomas appears to be less than in man, most were associated with a parasagittal location.[3, 15]

A tumor that arises from the falx cerebri may cause compression of both cerebral hemispheres, which causes signs suggestive of bilateral cerebral disease. Multiple meningiomas are present in 10 to 15 per cent of these cats and may be located in different areas of the brain, suggesting multifocal disease (Fig. 1). The cerebrum may herniate through the tentorium cerebelli, causing compression of the brainstem. The cingulate gyrus

is the most common area affected. In cats with meningiomas, the tentorial herniation is associated with tetraparesis and positional nystagmus, suggesting brainstem disease, which further confuses the diagnosis.[15] The cerebellum may herniate through the foramen magnum, resulting in coning of the cerebellum and compression of the medulla. Signs include tetraparesis, nystagmus, and decreased levels of consciousness. Cats with cerebellar herniation often have a "dry tap" when collection of cerebrospinal fluid is attempted from the cisterna magna. Mucopolysaccharidosis I has been associated with spinal cord compression, and recently has been correlated with meningiomas in young cats.[7]

Less commonly, the meningioma may arise in the posterior cranial vault or the spinal cord, and signs are referable to the area of the central nervous system affected. Spinal cord meningiomas are accessible to surgical excision.

The diagnosis of meningiomas in the cat may be confusing, particularly when the animal presents with central nervous system disease. Classically, the cat with a solitary cerebral meningioma should present with a progressive history of unilateral cerebral disease. However, the clinician must recognize the potential for multifocal and acute presentations. Cerebrospinal fluid is usually normal, with possibly a mild to moderate elevation in protein, in the absence of an increase in cells (albuminocytologic dissociation). Care must be exercised in collecting the cerebrospinal fluid if a meningioma is suspected, because of the potential for inducing brain herniation. Skull radiographs may be helpful by demonstrating speckled calcification within the tumor or hyperostosis of cranial bones adjacent to the mass (Fig. 2*A* and *B*). A meningioma should be suspected in an older cat when these radiographic changes are present in an area compatible with the neurologic localization of central nervous system disease. Computerized tomography of the brain is now available to veterinarians with increasing frequency. This procedure is very useful for evaluating mass lesions of the central nervous system and for making a definitive diagnosis prior to surgical intervention.[12]

Spinal cord meningiomas should be suspected when myelographic examination reveals an intradural, but extramedullary, mass. Spinal meningiomas may also calcify, aiding in the diagnosis of a focal spinal cord mass lesion.

Medical therapy for meningiomas is palliative, because there is no effective chemotherapy to reduce tumor mass. Steroid therapy may be indicated to reduce vasogenic edema produced by the tumor. Dexamethasone, starting at a dosage of 0.1 mg per kg given orally twice a day, may be attempted; results are variable, however. This may alleviate signs that are secondary to edema, but have no effect on the tumor itself. As mentioned previously, however, many of the clinical signs may be secondary to edema and a response to dexamethasone may be observed. In those cases in which seizures were present, phenobarbital therapy is initiated at 2.2 mg per kg given orally twice a day.

Surgical therapy is the treatment of choice for solitary supratentorial tumors. Major problems with surgical management are firstly, the preoperative confirmation of the location of the mass, and secondly, confirmation

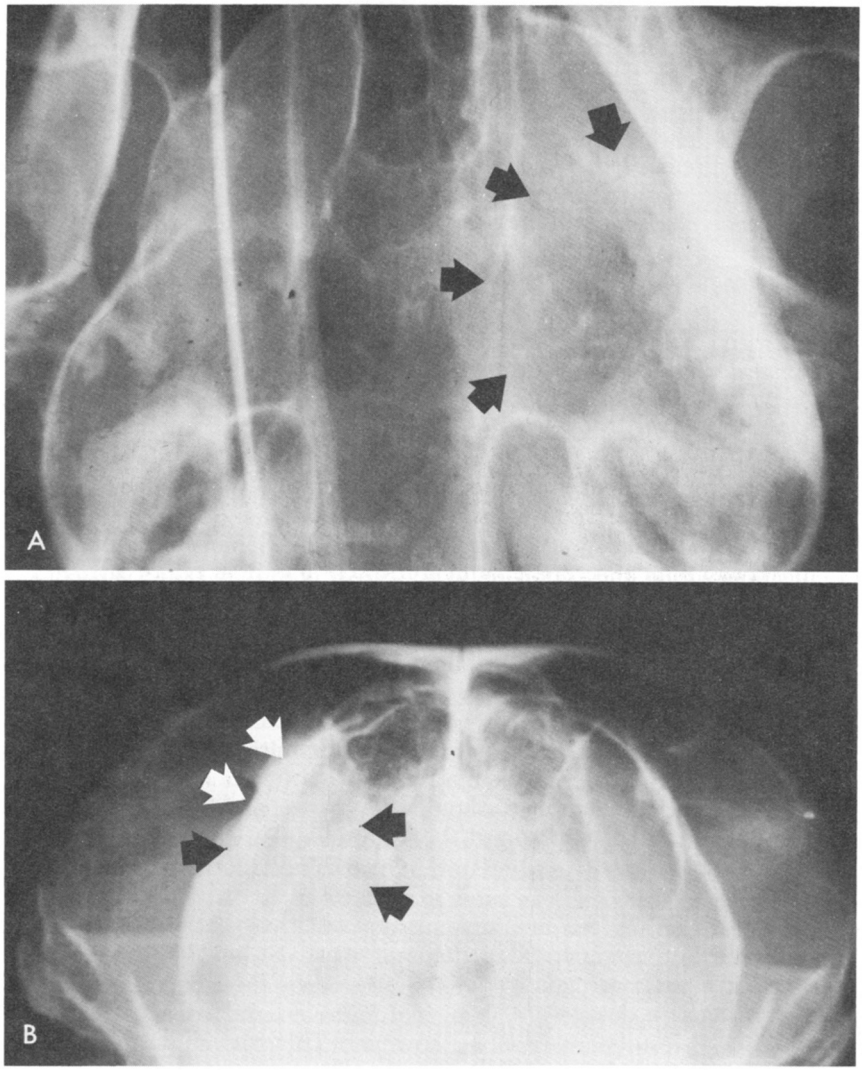

Figure 2. *A*, This ventrodorsal radiograph of the skull reveals increased water-tissue density and hyperostosis in the area noted *(arrows)*. The cat had a meningioma in this area. *B*, This radiograph of the skull of the cat in part *A* reveals the hyperostosis and increased water-tissue density caused by the meningioma.

that the tumor is benign. The most common complications of surgical removal of meningiomas in man are seizure disorders and hemiparesis.[3] In one study, 19 per cent of the patients developed seizure disorders after surgery. The potential causes for these seizures were excessive manipulation of brain tissue, cerebral edema, and cerebral venous occlusion.

The majority of meningiomas in cats are solitary and supratentorial, making surgical removal possible. An older cat presenting with unilateral cerebral disease should be considered a candidate for a cerebral meningioma, which may be amenable to surgical excision.

DIABETIC POLYNEUROPATHY

Polyneuropathies in cats are rarely described. Hopefully, in the near future, more studies and reports will be presented describing the various syndromes seen in the cat. The polyneuropathy associated with diabetes mellitus has been well described in man[3] and the dog.[4, 16] There have been reports of feline diabetic polyneuropathy;[4] however, only recently has it been well-documented.[10] Over 50 per cent of human diabetics receiving insulin have symptomatic neuropathy.[3] In man, there are three major neuropathic syndromes, with the most common being a symmetric distal polyneuropathy. The symmetric proximal motor neuropathy syndrome is characterized by weakness of the hip and thigh muscles. A syndrome of focal or multifocal neuropathies may occur, which often affects cranial nerves or may affect a single limb.

The pathogenesis of this neuropathy has been the subject of intense study in man and experimental animals.[3] The neuropathy probably results from an interaction of multiple metabolic factors. The most important cause is probably chronic hyperglycemia; however, the exact mechanism by which it disrupts nerve function is unknown. A decrease in myo-inositol concentration in diabetic rats, and reduction in axonal transport have been observed.[3, 19] The reduction in neuronal myo-inositol leads to sodium-potassium ATPase dysfunction. This results in increased resting intracellular sodium concentration, which leads to slowed nerve conduction and possibly to structural abnormalities in the affected nerves. Myo-inositol supplementation to diabetic rats may prevent or correct peripheral nerve dysfunction.[3] The reduction in axonal transport results in a lack of physiologic communication between the axon and cell body. This causes a lack of reparative changes, and may result in distal axonal degeneration.[19] Whatever the mechanism, there is no apparent difference between type I and type II diabetes in the development of polyneuropathy in man.[3] Euglycemia appears to be the most important factor in reversing the clinical neurologic abnormalities in man. Failure of neurologic deficits to improve after initiation of insulin therapy may be associated with an inability to achieve good control of hyperglycemia.[3]

The peripheral neuropathy may affect any nerve or group of nerves; however, the rear limbs seem to be particularly affected. This gives the cat the appearance of having dropped hocks (Fig. 3) and causes a peculiar gait that may prompt the owner to complain of a lameness or weakness in his

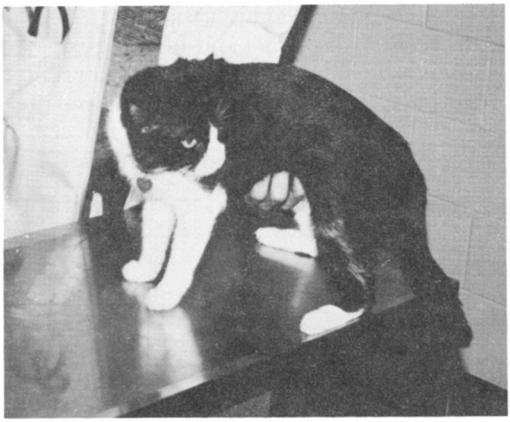

Figure 3. This 6-year-old cat with diabetes mellitus was presented for weakness in the rear limbs. Neurologic examination revealed hyporeflexia and postural reaction deficits but normal sensation in both rear limbs. Nerve conduction studies revealed slowed conduction velocities in the sciatic nerve and both ulnar nerves. No neurologic deficits were elicited from the forelimbs.

or her cat. If the weakness is mild, the owner may only note a problem when the cat jumps or tries to climb. Forelimb involvement may occur, but rear limb weakness generally predominates. Muscular atrophy may be generalized or focal, and most commonly involves the rear limbs. Historical signs suggestive of diabetes mellitus may be present for some months prior to the onset of weakness. Polyuria, polydipsia, polyphagia, and weight loss are usually observed, in addition to gait abnormalities. Although sensory abnormalities are frequent in man, affected cats appear to have normal sensation. Clinically, however, it is difficult to detect subtle sensory abnormalities during routine neurologic examinations of cats.

The diagnosis of diabetes mellitus is confirmed by a finding of fasting hyperglycemia and glycosuria.[14] Neurologic examination reveals lower motor neuron disease of the affected segments. Signs include proprioceptive loss, muscle weakness, hyporeflexia, hypotonia of involved muscles, and muscle atrophy if the disease is sufficiently chronic. Many affected cats only have symptomatic involvement of the sciatic nerve, and signs would be expected solely within the sciatic distribution. Electromyography is helpful in confirming a peripheral neuropathy. Slowed motor nerve conduction velocities and spontaneous activity (positive sharp waves) are detected. Electrodiagnostic changes are often found in nerves that are considered normal on neurologic examination. Histopathologic examination of affected nerves reveals axonal degeneration and demyelination. These degenerative changes are not specific for diabetic polyneuropathy, however.

In man, control of hyperglycemia is the most effective treatment for diabetic polyneuropathy.[3] The diabetic cat is difficult to control accurately due in part to problems with urine collection. Therefore, the clinician must attempt to control the hyperglycemia as precisely as possible in order to attempt to reverse the polyneuropathy. Protamine zinc insulin may give adequate control when given once daily to cats, whereas neutral protamine Hagedorn (NPH) insulin may require twice daily administration.[14] The neurologic deficits may require months to resolve after euglycemia is restored; however, many cats will regain much of their neurologic function. Although clinical trials of myo-inositol and aldose reductase inhibitors have been carried out, their results are inconclusive.[3] The clinician should be

aware of diabetic polyneuropathy in cats and the fact that it is a potentially treatable disease, if the diabetes can be well-controlled.

FELINE INFECTIOUS PERITONITIS

Feline infectious peritonitis (FIP) was first reported in the early 1960s.[17] It is now known to be caused by a coronavirus, and it appears to be an immune complex disease. It is seen mainly in cats between 6 months and 5 years of age but may occur at any age.[17] Its incidence is difficult to evaluate, owing to the lack of specificity of serologic tests presently available. There are two major forms of the disease—the effusive and noneffusive forms. The effusive form is associated with involvement of the pleura and/or peritoneum and results in fluid accumulation in one or both cavities. Granulomatous involvement of the parenchymal organs, most commonly those in the peritoneal cavity, is present in the noneffusive form, but ocular and nervous tissues are also frequently involved.

The exact pathogenesis of FIP is unclear, but much has been learned recently. An immune complex pathogenesis of FIP is supported by the following evidence: circulating immune complexes, glomerular immune complex deposits, an aggravating effect of antibody on the course of the disease, and the observation that seronegative cats survive longer and have a longer incubation time than do seropositive cats.[8] The feline infectious peritonitis virus (FIPV) multiplies in macrophages, and antibodies are produced that form immune complexes and activate complement.[17] The virion-bound activated third component or complement (C3) then acts to promote and spread the infection by increasing the number of macrophages that are infected. As increased production of complement occurs, increased numbers of chemotaxins are produced at the site of complement activation. Polymorphonuclear cells are attracted to these areas, and FIP granulomas occur.[8] The lesion produced suggests an arthus-type reaction. Due to antibody excess, there is deposition of immune complexes in vessels where complement is fixed, which leads to chemotaxis for polymorphonuclear cells with associated tissue damage.[20] Because of the deleterious effect of humoral immunity, including both serum neutralizing and fluorescent antibody, the immunity to FIPV may be predominantly cell-mediated.[18] The noneffusive form of the disease may represent an intermediate stage between effusive FIP and immunity. This is postulated to be due to the presence of both humoral immunity and partial cell-mediated immunity in the noneffusive form (refer to the article "Feline Infectious Peritonitis: An Immune-Mediated Coronaviral Vasculitis" in the symposium *Advances in Feline Medicine I* for a discussion of the proposed pathogenesis of feline infectious peritonitis).[18] The majority of cases with nervous system signs are of the noneffusive form, but the effusive form of FIP may occasionally have central nervous system involvement.[9]

The clinical signs seen with central nervous system involvement are variable, depending on the site(s) of the nervous system involved.[4, 5, 16] It is important to remember that there may be multiorgan involvement, and clinical evidence of systemic disease (that is, weight loss, fever) may be

present. In the nervous system, FIP may present as a focal, multifocal, or diffuse disease, and may be acute or chronic. Cats may present with evidence of paraparesis secondary to spinal cord involvement. Because of meningeal inflammation, many of these cats have a focal area of hyperpathia. Some cats with focal spinal cord lesions have evidence of disease elsewhere in the nervous system.

Vestibular signs are common in cats with FIP meningoencephalitis. Clinical signs include ataxia, nystagmus, head tilt, and intention tremors.[4, 5, 16] Seizures may also be present and occasionally may be the only presenting sign of FIP. Cats with convulsions due to FIP pose a diagnostic challenge, because (as will be discussed later), serologic diagnosis is often inconclusive. Cats that present with a seizure disorder will progress to develop other neurologic signs.[9] Cats with encephalitis due to FIP may have fluctuating neurologic signs, as a result of a number of factors. One is development of new lesion(s) in the central nervous system whereas another is the development of hydrocephalus.[11] The hydrocephalus is due to stenosis or obstruction of the normal circulatory pathways of cerebrospinal fluid, which is secondary to the inflammatory process. Another potential cause for a fluctuating course is the possibility of an ischemic encephalopathy secondary to the vasculitis.[22] Occasionally, the clinician may be presented with a cat with a focal mass lesion, which is slowly progressive and mimics a tumor. Therefore, FIP should be considered in *any* cat with neurologic disease.

Central nervous system FIP is a diagnostic dilemma for the clinician, as there are no clinical signs that allow clear differentiation from other diseases. The effusive form of FIP is easily identified on clinical examination and is rarely difficult to confirm. The central nervous system form may present with any group of neurologic signs, and historically may be acute or chronic. Systemic involvement may be helpful in confirming FIP. As mentioned, however, most of the central nervous system FIP is associated with the noneffusive form and may not have signs referable to other systems.

Several techniques for quantitating the humoral response to coronavirus have been developed, including indirect immunofluorescence (IFA), virus neutralization, ELISA, and passive hemagglutination.[2] It must be remembered that, at this time, there is no serologic test that will differentiate antibodies to FIPV from those directed against non–FIP-causing coronaviruses.[1, 2, 17] (Refer to the article "Diagnostic Testing for Feline Viral Diseases" in the symposium *Advances in Feline Medicine I* for a discussion of the limitations of coronaviral serology.)

Elevation of plasma proteins are seen in about 50 per cent of cats with effusive disease, and 75 per cent of cats with the noneffusive form of FIP.[17] This elevation is due to increases in alpha-2, beta and gamma globulins.[17] Unfortunately, this is a nonspecific elevation, which suggests chronic inflammation from any source.

Variable changes in cerebrospinal fluid only occurs in cats with noneffusive FIP. If the area involved is adjacent to the cerebrospinal fluid or ependyma, a marked pleocytosis and protein elevation may be found. In some cases, this pleocytosis is predominantly due to polymorphonuclear

cells, and the protein elevation is greater than 300 mg per cent. However, the pleocytosis may be entirely due to mononuclear cells, and albuminocytologic dissociation may occur. When the area affected is subependymal and localized, the cerebrospinal fluid may be normal. As with other tests, the cerebrospinal fluid must be interpreted in light of other clinical findings. However, a neutrophilic pleocytosis with marked protein elevation is highly suggestive of the central nervous system form of FIP.

There is no effective therapy for the central nervous system form of FIP at this time. Immunosuppressive drugs may have some potential in selected cases.[17] Prednisone and other more potent immunosuppressive agents have been used. The clinician must remember that many of the more potent immunosuppressive agents do not cross the blood brain barrier and would not be effective in central nervous system disease. The author initially uses 1.1 mg per kg per day of prednisone given orally, twice a day. This is tapered slowly over 3 to 4 weeks following clinical remission. If seizures are present, the cat should be treated with 1.1 mg per kg per day of phenobarbital, given orally twice a day. The anticonvulsant therapy is continued when clinical remission is achieved. The prognosis is poor, for the conditions of most cats will eventually worsen.

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