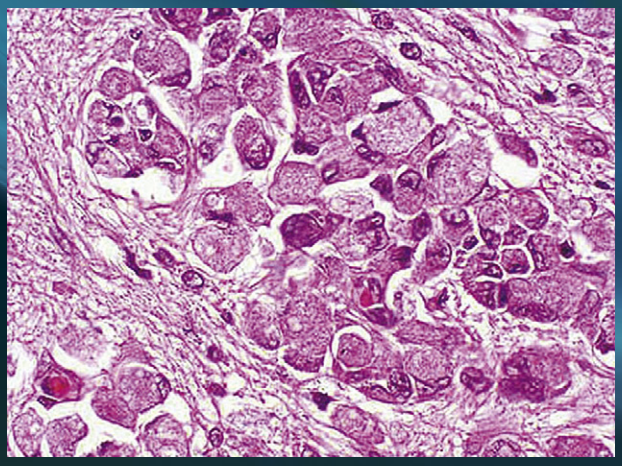
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



CHAPTER 15

Systemic or Multifocal Signs

There are many inflammatory, infectious, and degenerative diseases that produce multifocal central nervous system (CNS) signs and often simultaneous systemic disease. These disorders are categorized as multifocal, systemic, or diffuse diseases. Initially, some of these diseases may start with focal CNS signs, but they progress to affect other areas.

LESION LOCALIZATION

The key to recognition of these diseases is a neurologic examination that indicates the involvement of two or more parts of the nervous system that are not closely related anatomically. The most obvious example is an abnormality in both the brain and the spinal cord. All the possible combinations of signs of diffuse or multifocal diseases are too extensive to list, but Box 15-1 lists some of the more common ones.

Anytime abnormalities identified on the neurologic examination cannot be attributed to a single lesion, a multifocal neuroanatomic localization should be made. Etiologically, this group of diseases becomes more likely.

DISEASES

The major disease categories that produce systemic or multifocal signs are degenerative, metabolic, nutritional, inflammatory, toxic, and sometimes neoplastic and vascular disorders.

Diseases that are primarily skeletal in origin are mentioned but not discussed. Neoplastic and vascular disorders of the brain are further discussed in Chapter 12. Asymmetry often is associated with inflammatory, immune-mediated, neoplastic, and ischemic disorders. Diffuse and symmetric involvement is seen with degenerative, metabolic, and toxic disorders. The acute or chronic onset and the rate of progression may be of some help in establishing the diagnosis (Table 15-1).

Degenerative Diseases

Many degenerative diseases that are systemic or multifocal are either congenital and/or hereditary. However, the cause is still unknown for some of the spongiform and metabolic encephalopathies and dysautonomia. Congenital refers to a disease or malformation present at birth. It includes conditions that may be genetic or a result of exposure to toxins, malnutrition, or infection in utero. Not all congenital conditions are inherited and conversely, not all inherited conditions are congenital. The congenital malformations are discussed in Chapter 12 for the cerebrum and in Chapter 8 for the cerebellum.

Breed predilection and stereotypic clinical presentation for many of these disorders often suggest an inherited basis. Careful study of affected litters and pedigrees is required to determine the inheritance pattern. Selection processes used by breeders include inbreeding, linebreeding, and outcrossing. While selecting for a particular trait, inbreeding and linebreeding practices result in a reduction of genetic variability and an increase in homozygous and recessive traits. Simple inheritance (Mendelian) patterns have served as the basis for determining modes of inheritance of many genetic disorders. Many of these hereditary diseases have an autosomal recessive inheritance pattern. Dominant traits are more easily eliminated from the breeding pool of a breed by not breeding affected dogs. Determining inheritance pattern is more difficult for polygenetic and complex traits. Polygenetic inheritance refers to when proper development relies on sequential activation of genes or for traits of variable penetrance that result in a variety of phenotypes for a given genotype. Complex traits are determined by the interaction between environment and polygenetic predisposition. Having an understanding of the hereditary basis for these degenerative diseases is important because (1) they are genetic disorders and can be eliminated by selective breeding; (2) they may be confused with conditions of nongenetic origin, such as viral diseases; and (3) they can serve as excellent models of similar human diseases.

Differential Diagnosis

Many of these diseases have a similar clinical history and course. Clinical signs of conditions like the lysosomal storage diseases and some metabolic encephalopathies are delayed until the animal is older (usually within a few months after birth) because of the time required for build up of byproduct. Abiotrophies, disorders of premature neuronal degeneration, and other degenerative diseases affecting the axons and myelin

BOX 15-1

Examples of Systemic or Multifocal Signs

Lower motor neuron (LMN) signs (more than one location, may include cranial nerves): diffuse LMN diseases, polyneuropathy (see Chapter 7)
Brain and spinal cord signs: pelvic limb paresis and seizures
Systemic disease and CNS signs: fever, anorexia, ataxia, or seizures
Generalized pain: meningitis
Cerebral cortex and brainstem: cerebrum seizures and cranial nerve deficits, blindness, severe gait deficits, head tilt, circling
Forebrain: blindness with normal pupils (may be seen with brain swelling, hydrocephalus) (see Chapter 11)
Cerebellum and paresis: head tremor, ataxia, severe gait deficits, paresis
Ascending paralysis: pelvic limb paresis progressing to tetraparesis (focal cervical spinal cord lesion must be ruled out)

TABLE 15-1

Etiology of Systemic Diseases*

Classification	Acute Progressive	Chronic Progressive
Degenerative	Myelinolytic disorders	Storage disease, abiotrophy
Metabolic	Hepatic encephalopathy Hypoglycemia Endocrine disease Renal disease	Hepatic encephalopathy Endocrine disease
Neoplastic	Metastatic	Primary metastatic
Nutritional	Methionine deficiency	Hypovitaminosis Hypervitaminosis
Inflammatory	Infectious and noninfectious	Infectious (usually viral) and noninfectious
Toxic	Most toxins	Heavy metals Other toxins, chrome exposure

Modified with permission from Oliver JE, Hoerlein BF, Mayhew IG: Veterinary neurology, Philadelphia, 1987, WB Saunders.

can manifest signs within a few months or late in life. These disorders are often insidious and progressive. However, some diseases such as the storage and myelin disorders can have an acute onset once the neuron or myelin reaches a critical threshold of dysfunction.

The findings on neurologic examination may indicate a predominance of signs referable to the forebrain, cerebellum, spinal cord, or neuromuscular junction. These findings, and the age and breed of the animal, should suggest a small number of possibilities. Early in the disease course, neuronal cell body diseases often can be differentiated from demyelinating diseases. Proprioceptive positioning is commonly affected in demyelinating diseases but is rarely involved in the early stages of neuronal disease. Neuronal cell body, diseases (storage disease, abiotrophy) are more likely to have forebrain or cerebellar involvement. Axonal and myelin diseases of the sensory and motor tracts of the spinal cord are more likely to have general proprioceptive (GP) ataxia and paresis of an upper motor neuron (UMN) type. If the nerve or neuronal cell body is involved, signs of LMN weakness predominate. Weakness is not a predominant feature of pure demyelinating or cerebellar disorders. However, limb and whole body tremor is a feature of myelin and cerebellar diseases.

The degenerative diseases also must be differentiated from inflammatory (infectious and noninfectious), neoplastic, and toxic disorders. Specific diagnostic tests are available for most of these conditions and are discussed later in this chapter.

This section on degenerative diseases will focus on those that are multifocal (storage disorders) or have an unknown etiology. The metabolic encephalopathies that are of primary brain origin are discussed in Chapter 12. Other degenerative disorders involving the spinal cord and brain (myeloencephalopathies), which predominate as spinal cord diseases, are discussed in Chapters 6 and 7. Those that present primarily with LMN signs that involve the axon, myelin, and the neuronal cell body (motor neuron) are discussed also in Chapter 7. Diseases that are discussed in this chapter include (1) storage disorders, (2) abiotrophies, (3) multiple system degenerations, and (4) degenerative disorders that are of unknown cause.

Storage Disorders

Storage disorders are characterized pathologically by the accumulation of metabolic products in cells (Table 15-2 and Figure 15-1).

A genetically based deficiency of a key enzyme causes accumulation of the product in neurons, glia, or other cell types. The effects of the disease may be caused by the accumulation of the product or may be a direct result of the metabolic disturbance.[1] Because the clinical signs and the progression of the disease depend on the pathologic process, many of the conditions present in a similar fashion with multifocal CNS signs and sometimes also with peripheral neuropathy. Two groups are commonly recognized: neuronal storage diseases, in which the product accumulates in neurons, and leukodystrophies.[2] In general, leukodystrophy refers to inherited conditions of younger animals in which myelin synthesis or function is defective and cannot be maintained and may include storage disease pathogenesis. Globoid cell leukodystrophy is a storage disease caused by a deficiency of galactocerebroside activity, resulting in intracellular accumulation of a metabolite toxic to myelin-forming oligodendrocytes and Schwann cells (Figure 15-2).

The storage byproducts usually can be found in the lysosomes of neurons. Lysosomal storage diseases are characterized by accumulation of sphingolipids, glycolipids, oligosaccharides, or mucopolysaccharides within lysosomes.[3] The neuronal ceroid lipofuscinoses involve the accumulation of hydrophobic proteins but the pathogenesis remains unclear (see Figure 15-1).[3]

The storage diseases are rare, but several have been reported in domestic animals.[2] Most have been recognized in specific breeds of dogs or cats.[3,4] Animals are usually normal at birth, but they fail to grow normally. Signs typically occur within the first few months of life but may be delayed until adulthood with some conditions such as some of the neuronal ceroid lipofuscinoses.[5] Many of the storage disorders affect multiple organs and regions of the nervous system. Others affect only the myelin and only neurologic signs occur. Often neurologic

TABLE **15-2**

Lysosomal Storage Disorders in Domestic Animals

Disease Subgroup	Storage Disease (Human Disease)	Enzyme Deficiency	Species—Breed (age at onset)	Clinical Signs; Diagnosis	Inheritance	Reference
Glycoproteinoses						
	Fucosidosis	α-L-Fucosidase	C-*English springer spaniel* (6 mo-3 yr)	Cerebellar ataxia, behavioral change, dysphonia, dysphagia, seizures; DNA testing, enzyme assay	AR	215-219
	Mannosidosis (α-Mannosidosis)	α-D-mannosidase	F-DSH (7 mo), DLH, *Persian* (8 wk); B-Galloway, Murray gray, Aberdeen Angus (birth)	Cerebellar ataxia, tremor, corneal opacity, skeletal anomalies, neuropathy; B-cerebellar ataxia, aggressiveness; urine screening, enzyme assay, DNA testing	AR	220-226
	Mannosidosis (β-Mannosidosis)	β-D-Mannosidase	B-Salers; G-Anglo nubian (birth-1 yr)	Cerebellar ataxia, recumbency, skull and limb deformities; urine screening, enzyme assay	AR	227;228
	Lafora disease	α-Glucosidase	C-Beagle (5-9 mo), basset hound (3 yr), poodle (9-12 yr), wire-haired miniature *dachshund* (5-8 yr); F-DSH	Myoclonic seizures, dullness; muscle biopsy, DNA testing	AR	229-235
Oligosaccharidoses						
Glycogenoses						
	GSD type 1 (von Gierke disease)	Glucose-6-phosphatase	C-Silky terrier, *Maltese*, other toy breeds (weeks); F-DSH	Weakness, seizures, stupor; urine screening	AR?	236,237
	GSD type 2 (Pompe disease)	α-Glucosidase	C-Swedish Lapland dog (1.5 yr); F-DSH; B-beef shorthorn, Brahman (3-9 mo); O-Corriedale (6 mo)	Ataxia, muscle weakness, exercise intolerance, cardiac; muscle/liver biopsy, urine screening	AR	238-246
	GSD type 3 (Cori disease)	Amylo-1,6-glucosidase	C-German shepherd (2 mo), *curly-coated retriever (IIIA)* (1 yr)	Lethargy, exercise intolerance, organomegaly; muscle/liver biopsy, DNA testing	AR	247,248
	GSD type 4 (Andersen disease)	Branching enzyme	F-*Norwegian forest cat* (5 mo)	Cerebellar ataxia, muscle weakness, tremor, neuromuscular, organomegaly; muscle biopsy, enzyme assay, DNA testing	AR	249-251
	GSD type 5	Myophosphorylase	B-Charolais (weeks)	Exercise intolerance	AR	252
	GSD type7 (Tarui disease)	Phosphofructose kinase	C-*English springer spaniel* (8-12 mo)	Exercise intolerance	AR	253,254
Mucolipidosis						
	Mucolipidosis II (I-cell disease)	N-acetylglucosamine-1-phosphotransferase	F-*DSH*	Facial dysmorphism, dullness, retinal, ataxia; DNA testing	Unknown	255,256

Sphingolipidoses						
	GM1-gangliosidosis type 1 (Norman-Landing disease)	β-D-Galactosidase	C-Beagle cross (4-7 mo), Portuguese water dog (4-5 mo), English springer spaniel (4-5 mo), *Alaskan husky*, *Shiba dog*; F-*DSH* (2-3 mo); B-Friesian (birth); O-Coopworth Romney (1 mo), Suffolk (4 mo)	C, F-Cerebellar ataxia, corneal clouding, tremor, seizures, paralysis, skeletal, facial dysmorphism; B, O-ataxia, recumbency; enzyme assays, DNA testing	AR	257-264
	GM1-gangliosidosis type 2 (Derry disease)	β-D-Galactosidase	F-Siamese, Korat (7 mo), DSH; O-Suffolk (4-6 mo)	Same; O-rapid progression	AR	265-267
	GM2-gangliosidosis (Tay-Sachs disease) (Variant B)	β-N-acetyl hexosaminidase A (α-subunit)	C-German shorthair pointer (6-12 mo)	Cerebellar ataxia; urine screening; enzyme assay	Unknown	268,269
	GM2-gangliosidosis (Sandhoff disease) (Variant O)	β-N-acetyl hexosaminidase B (β-subunit)	C-Golden retriever; toy poodle, F-*DSH-Japan*, *Korat*, *Burmese-Europe* (2-3 mo); S-Yorkshire	Same; S-cerebellar ataxia, weakness	Unknown	270-274
	GM2AB-gangliosidosis (Bernheimer-Seitelberger disease) (Variant AB)	GM2 activator protein deficiency	C-Japanese spaniel (18 mo); F-*Korat* (18 mo)	Same	Unknown	275,276
	Galactosialidosis	Galactosialidosis with α-neuraminidase	C-Schipperke (5 yr)	Cerebellar ataxia	Unknown	278
	Glucocerebrosidosis (Gaucher disease)	β-D-Glucocerebrosidase	C-Sydney silky dog (6-8 mo); O-unknown; S-unknown	Cerebellar ataxia; enzyme assay; biopsy	AR(S)	279-281
	Globoid cell leukodystrophy (Krabbe disease)	β-D-galactosyl ceramidase (accumulation of psychosine)	C-*West Highland white terrier* (2-5 mo), *Cairn terrier* (2-5 mo), beagle (4 mo), poodle (2 yr), basset hound (1.5-2 yr), blue tick hound (4 mo), pomeranian (1.5 yr), *Irish setter* (6 mo); F-DSH, DLH (5-6 wk); O-Dorset (4-18 mo)	Cerebellar ataxia, tremor, paraparesis, neuropathy; muscle/nerve biopsy, enzyme assay; DNA testing	AR or unknown	282-292
	Metachromatic leukodystrophy	Arylsulfatase A	F-DSH (2 wk)	Progressive motor dysfunction, seizures, opisthotonus, neuropathy	Unknown	293
	Sphingomyelinosis (Niemann-Pick disease type A)	Sphingomyelinase	C-Miniature poodle (2-4 mo); F-Balinese, Siamese (2-3 mo); B-Hereford (5 mo)	Cerebellar ataxia, tremor, paraparesis, neuropathy; biopsy	Unknown, AR-Siamese	294-298

Continued

TABLE 15-2

Lysosomal Storage Disorders in Domestic Animals—cont'd

Disease Subgroup	Storage Disease (Human Disease)	Enzyme Deficiency	Species—Breed (age at onset)	Clinical Signs; Diagnosis	Inheritance	Reference
	(Niemann-Pick disease type C)	Cholesterol esterification deficiency	C-Boxer (9 mo); F-*DSH* (2-4 mo)	C-Cerebellar ataxia, hepatomegaly, neuropathy; F-cerebellar ataxia, hepatic; enzyme testing, DNA testing	Unknown	299,300
Mucopolysaccharidoses						
	MPS I (Hurler syndrome)	α-L-iduronidase	C-Plott hound (3-6 mo), *mixed-breed* (3-6 mo); F-*DSH* (10 mo)	Growth retardation, facial deformity, lameness, corneal opacity, cardiac; urine screening, enzyme testing, DNA testing	AR	301,302
	MPS II	Iduronate-2-sulfate sulfatase	C-Labrador retriever (5 yr)	Cerebellar ataxia, exercise intolerance, corneal opacity, facial dysmorphism; urine screening, enzyme assay	AR	303
	MPS III (A, B, D)	Sulfamidase A-heparin sulphamidase B-N-acetyl-alpha-D-glucosaminidase C-acetyl-CoA-alpha-glucosaminide N-acetyltransferase D-N-acetylglucosamine 6-sulphatase	C- *Huntaway dog* (IIIA) (18 mo), *Schipperke (IIIB)* (3 yr) wire-haired dachshund (IIIA) (3); B-*breed unknown-Australia (IIIB)* (2 yr); G-nubian (IIID) (birth)	Cerebellar ataxia, tremor, retinal degeneration, corneal opacity; G-weakness; urine screening, enzyme assay, DNA testing	AR	304-312
	MPS VI (Maroteaux-Lamy disease)	N-acetylgalactosamine 4-sulfase (arylsulfatase B)	C-Miniature pinscher (6 mo); F-*Siamese cat*, DSH (4-7 mo)	Growth retardation, facial deformity, corneal opacity, spinal fusion; urine screening, enzyme testing, DNA testing	AR	313-315
	MPS VII (Sly syndrome)	β–D-glucouronidase	C-Mixed breed; F-*DSH*	C-Paraparesis, cardiac; F-growth retardation, facial deformity, corneal opacity, spinal fusion, cardiac; urine screening, enzyme testing, DNA testing	AR	316,317

Proteinoses Ceroid Lipofuscinoses (Batten Disease)			All-Visual deficits, cerebellar ataxia, myoclonus, seizures of varying degree; tissue biopsy (autofluorescence)		
	CLN 1	Palmitoyl protein thioesterase I	C-Dachshund (mo)	AR(S)	Katz ML personal communication
	CLN 2	Tripeptidyl-peptidase	C-*Dachshund* (4-5 mo)	AR	318
	CLN 4 (not confirmed)	Unknown	C-*Tibetan terrier* (4-6 yr)	AR	319,320
	CLN 5	Soluble lysosomal membrane protein	C-*Border collie* (2 yr); O-*borderdale* (15 mo); B-Devon (12 mo)	AR	321-323
	CLN 6	Endoplasmic reticulum membrane protein	C-Australian shepherd (1-2 yr) O-*South Hampshire* (3 mo), *Merino* (7 mo)	Unknown or AR (O)	324-327
	CLN 8	Membrane protein of the endoplasmic reticulum	C-*English setter* (2 yr)	AR	328,329
	CSTD	Cathepsin D	C-*American bulldog* (2-4 yr); O-*White Swedish landrace*	AR	330-332
	CLN4 (Kuf's disease)	Arylsulfatase G	C-*American Staffordshire terrier* (>1 yr variable)	AR	335,334
	Unknown		C-Australian cattle dog (1-2 yr), Australian shepherd (more than one NCL), Chihuahua (2 yr), cocker spaniel (1.5-6 yr), collie, dachshund (4.5 yr), dalmatian (6 mo-1 yr), golden retriever (2 yr), Japanese retriever (3 yr), Labrador retriever, miniature schnauzer, poodle, Polish lowland sheepdog (0.5-4.5 yr), saluki (2 yr), spitz, Welsh corgi (6-8 yr); F- Siamese cat, Japanese DSH, European DSH (<1 yr); B-beefmaster (12 mo), Devon (12 mo), Holstein (adult); O-Rambouillet (4 mo); G-nubian (4 mo); E-Icelandic × Peruvian paso	Unknown	335-356

Modified from Oliver JE, Hoerlein BF, Mayhew IG: Veterinary neurology, Philadelphia, 1987, WB Saunders, Table 6-1; Mayhew IG: Large Animal Neurology, Ames, IA, 2009 Wiley-Blackwell, Table 30-2.
AR, Autosomal recessive; *AR(S)*, autosomal suspect; *CLN*, ceroid lipofuscinosis; *CTSD*, cathepsin D gene; *GSD*, glycogen storage disease; *GM*, gangliosidosis; *MPS*, mucopolysaccharidosis.
Breeds in italics signify mutation discovered; *C*, canine; *F*, feline; *B*, bovine; *O*, ovine; *S*, swine; *G*, goat; *E*, equine.

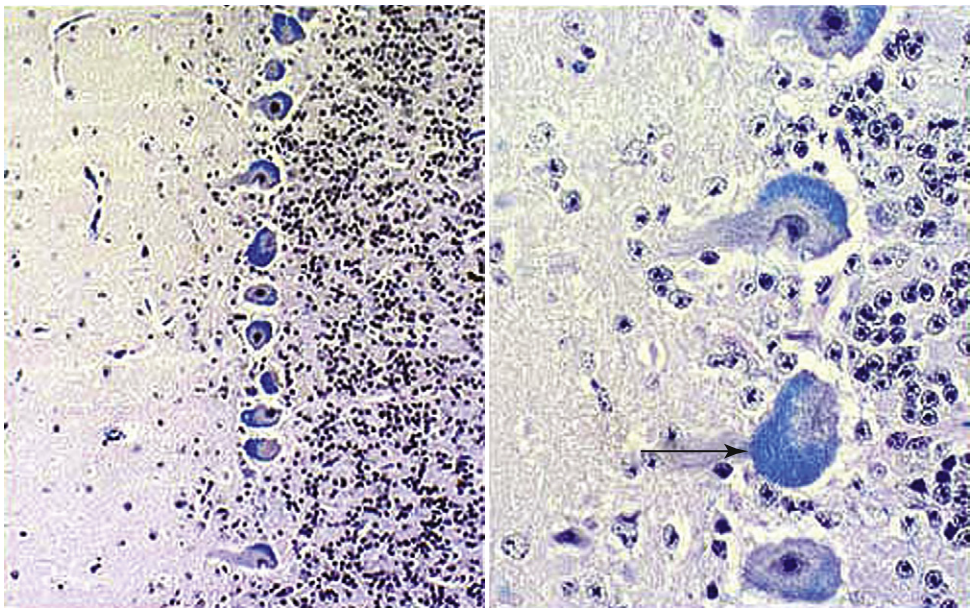


Figure 15-1 Bovine neuronal ceroid-lipofuscinosis. Luxol fast blue stain of the cerebellar cortex of a Devon cow with intense storage evident in Purkinje cells *(arrow)*. (Courtesy Cornell University College of Veterinary Medicine.)

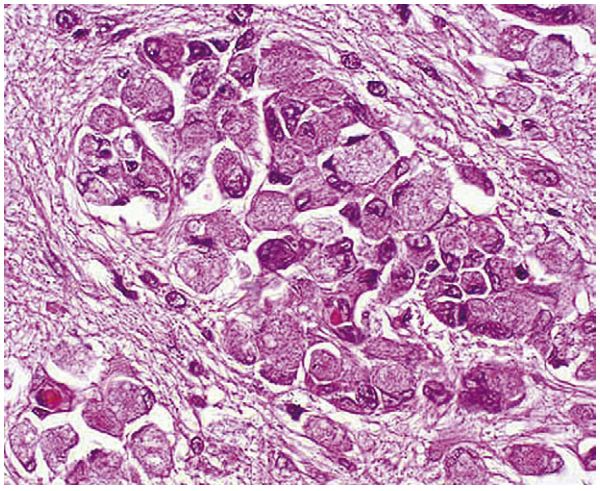


Figure 15-2 Canine globoid cell leukodystrophy. Note large globoid cells in white matter of cerebral cortex. The cells are filled with myelin breakdown products. (Courtesy Cornell University College of Veterinary Medicine.)

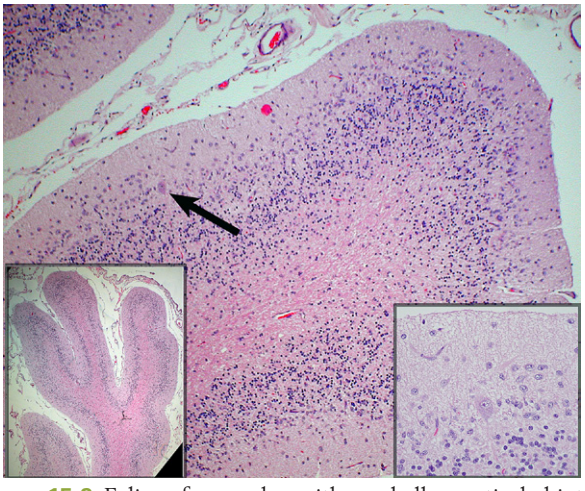


Figure 15-3 Folium from a dog with cerebellar cortical abiotrophy. The cerebellar cortex is almost devoid of Purkinje neurons. A single purkinje neuron is visible *(arrow)*. Subjectively there are few granule cell neurons than normal. Gliosis is also pressent (10× mag). *Right inset*, Higher magnification of a purkinje neuron. *Left inset*, Folia are smaller than normal.

signs include cerebellar ataxia, myelopathy, and encephalopathy. Cerebellar signs are often the first sign of storage diseases because of the complex integration of the fast conducting sensory and motor pathways (see Chapter 8).[4] The cerebellum also is particularly sensitive to disorders affecting myelin. Seizure events that occur with some storage disorders usually manifest at the end stage of the disease process. Storage disorders for which seizure activity is a predominant clinical feature include ceroid lipofuscinosis, glycoproteinoses, and leukodystrophies.[4]

Most of the diseases that have been studied have a recessive mode of inheritance, and so only a portion of the litter is affected (see Table 15-2). Lysosomal storage diseases will have signs in other organs including the retina. Skeletal and facial malformations are prominent in the mucopolysaccharidoses. In general, lysosomal storage disorders tend to be slowly progressive and lead to the animal's death.[4] Enzyme replacement, small molecule, gene, and cell-based therapies may have value in some conditions and have only been used experimentally in affected animals.[3,6] Genetic testing may be available for some of these disorders. Colonies of animals for some of these diseases have been established at research institutions.

Abiotrophies and Other Degenerative Diseases

The normal neuron is not capable of dividing and reproducing itself but has the capacity to survive for the life of the animal. Abiotrophy is a process by which cells develop normally but later degenerate due to an intrinsic cellular defect.[7] The degeneration of the neuronal cell body can primarily involve the neurons of the cerebellum, cerebrum, nerve, or multiple systems (Figure 15-3; see Chapters 7 and 8).

The multisystem disorders are further characterized as to the primary site of the degenerative process—cell body, axon, myelin, and so forth that also involve other anatomic regions of the CNS or the peripheral nervous system (PNS). Clinical signs relate to the predominant region of the nervous system affected. The motor neuron degenerations are rare and usually occur in young growing animals with an insidious and progressive clinical disease course of neuromuscular weakness and generalized LMN signs (see Chapter 7). Myelin disorders cause ataxia and tremor that progresses to paresis. Diffuse myelinopathies occur with inherited, metabolic, and toxic disorders. Primary cerebellar cortical degeneration refers to degeneration and loss of Purkinje cells and/or granule cells. Pathologic processes of cerebellar degeneration are classified microscopically as atrophy, abiotrophy, and transsynaptic neuronal degeneration. *Atrophy*, a term that lacks specificity, refers to loss of cerebellar mass often as a result of a degenerative process (Figure 15-4).[2,8]

Cerebellar degenerative disorders cause clinical signs of cerebellar ataxia and intention tremor (see Chapter 8). The progression of these abiotrophies and degenerative processes is generally slow (over months) but unrelenting. Like the storage diseases, they are rare, usually inherited, and in most instances eventually fatal. The course of disease is usually insidious but can be rapid.

Multisystem Neuronal Degenerations. These disorders often first cause cerebellar cortical degeneration and later involve other neuronal populations. A multisystem degeneration in rottweilers characterized by neuronal vacuolation has been recognized in young rottweiler dogs.[9] Affected dogs develop progressive GP ataxia, tetraparesis, cerebellar dysfunction, and laryngeal paralysis. Intracytoplasmic vacuoles are prominent in the cerebellar nuclei and other brainstem nuclei and ganglia. There is bilaterally symmetric degeneration in the spinal cord. Young Cairn terriers show a progressive GP ataxia, tetraparesis, and cerebellar signs.[10] Histopathology reveals neuron degeneration in the spinal cord, brainstem, and thalamus, and degenerative changes in the tracts of the spinal cord and brainstem. A multisystem degeneration recognized in young cocker spaniels manifests cerebellovestibular and forebrain signs.[11] Histopathology shows widespread neuronal degeneration in the cerebellum and brain with presence of swollen axons. Recently, a multisystem degeneration has been described in golden retrievers that show tremor, progressive tetraparesis, and generalized LMN signs.[12] The spinal cord had changes consistent with axonopathy; there was loss of cranial nerve motor nuclei; and nerves had evidence of Wallerian degeneration.

Multisystem degenerations also involve the basal ganglia, such as the caudate nucleus and substantia nigra, that cause movement disorders similar to Huntington and Parkinson disease in humans. These disorders have been recognized in Kerry blue terriers and Chinese crested dogs.[13,14] In these breeds, cerebellar ataxia begins between 3 and 6 months of age. As the basal nuclei degenerate, affected dogs have increasing difficulty initiating movements and maintaining balance. These disorders are autosomal recessive and have been linked to a locus on chromosome 1.[14]

Dysautonomia. In veterinary medicine, the term *dysautonomia* refers to acute or subacute idiopathic panautonomic failure involving both the parasympathetic and sympathetic systems. Dysautonomia is also described in Chapters 3, 9, and 11. It is a progressive degenerative disease of the ganglia of the autonomic nervous system. The general somatic efferent system is not affected except for involvement of the anal sphincter. Dysautonomia was first recognized in horses in Scotland (grass sickness) and then described in cats in the United Kingdom and Europe in the early 1980s.[15,16] Dysautonomia was first described in dogs from southwest Missouri and Wyoming in 1988 and continues to be reported in Missouri and surrounding states.[17-19] The etiology is still unknown but a toxico-infectious etiology resulting from *Clostridium botulinum* type CD has been proposed in horses. Acute or subacute autonomic neuropathy of people is similar to the animal forms and studies suggest an immune-mediated basis for this disease.

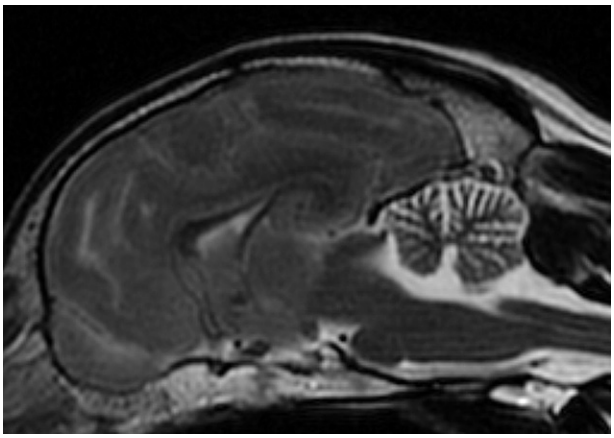


Figure 15-4 Sagittal T2W MRI from the dog in Figure 15-3. The cerebellum is small. There is atrophy of the folia as evidenced by increase amount of cerebrospinal fluid overlying the folia as well as within the fourth ventricle.

In dogs, dysfunction of the parasympathetic nervous system predominates, although signs related to the sympathetic nervous system may be present as well.[20] The disease is most common in young adult free-roaming dogs (median age of 18 months) and tends to affect medium- to large-breed dogs. Many affected dogs are from rural environments but the disease has been documented in dogs maintained strictly in kennel environments. The peak incidence in Missouri is from late winter to early spring. The following clinical signs develop and are progressive over 2 to 3 weeks. All signs may not be present in all dogs.

- Dysuria, distended urinary bladder: The pelvic nerve is a parasympathetic nerve that innervates the detrusor muscle. Detrusor muscle dysfunction is a common finding.
- Mydriasis and absent pupillary light reflexes: Pupillary constriction is a function of the parasympathetic fibers contained in the oculomotor nerves.
- Elevated third eyelid: This sign is present in about 50% of cases, suggesting some dysfunction of the sympathetic nervous system.
- Dry mucous membranes, decreased tear production: Dry mouth, nose, and eyes are common findings. Secretions are largely the function of the parasympathetic nervous system.
- Vomiting, regurgitation: Megaesophagus is a common finding. The vagus nerve (parasympathetic) innervates the esophagus and stomach and plays a major role in esophageal and gastric motility.
- Decreased anal (perineal) reflex: The external anal sphincter is innervated by the pudendal nerve, a general somatic efferent nerve. This is the only sign of somatic dysfunction.
- Intestinal ileus: Distention of the intestinal tract is a less common finding. Constipation and diarrhea may be seen in some dogs.
- Weight loss, muscle wasting, and decreased appetite
- Gait, postural reactions, and spinal reflexes are not affected

Dysautonomia also has been reported in cats but no clear risk factors have been identified.[21] Cats have clinical signs similar to dogs.

Dysautonomia should be suspected from the cluster of clinical signs. Although myasthenia gravis and botulism cause some of these signs, the presence of weakness in the skeletal muscles is not observed in dysautonomia. One of the best clinical procedures for confirming dysautonomia is to demonstrate denervation hypersensitivity to the pupils. Pilocarpine ophthalmic solution (1%) is diluted to a concentration of 0.05% with normal saline. One to two drops are placed in one eye and the pupils are observed every 15 minutes. Dogs with dysautonomia have rapid pupillary constriction compared with normal dogs who either do not respond at all or show delayed responses. If no response is seen in 90 minutes, the test is repeated with 1% pilocarpine. Unless parasympatholytic drugs (atropine) or toxins are present, rapid pupillary constriction should occur. Lack of innervation causes an upregulation of the postsynaptic receptors with denervation supersensitivity in neurotransmission.

Thoracic radiographs frequently show megaesophagus and abdominal radiographs reveal distention of the urinary bladder and sometimes intestinal ileus. Unless detrusor atony is present from prolonged detrusor paralysis, dogs may void urine in response to low doses of bethanechol.

No definitive treatment is available. Symptomatic therapy includes bethanechol, pilocarpine to increase tear production and to reduce photophobia from dilated pupils, metoclopramide to stimulate gastrointestinal motility, and frequent evacuation of the bladder. The mortality rate in canine dysautonomia is approximately 90%. There are isolated reports of dogs developing partial recovery.

Metabolic Disorders

Normal nervous system function depends on a closely regulated environment. Conversely, homeostasis is coordinated by the nervous system through the neuroendocrine, autonomic, and somatic systems. Systemic disorders altering homeostasis often have profound effects on the nervous system.

Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a complex metabolic disorder resulting from abnormal liver function.

Pathophysiology. HE has been reported in four types of liver disease: (1) severe parenchymal liver damage, either acute or chronic (cirrhosis, neoplasia, toxicosis); (2) anomalous portal venous circulation (rare in large animals); (3) microvascular dysplasia, and (4) congenital urea-cycle enzyme deficiencies (rare).[22] Parenchymal liver diseases other than cirrhosis (fatty infiltration, chronic active hepatitis, and so forth) usually do not cause hepatic encephalopathy except in the terminal stages of the disease. Pyrrolizidine alkaloids in certain plants such as *Senecio* spp. and *Crotalaria* spp. cause parenchymal liver damage and hepatic encephalopathy in herbivores. Parenchymal disease severely reduces the capacity of the liver to perform its normal metabolic functions. Portosystemic venous shunts divert a significant portion of the portal blood past the liver into the vena cava. Potentially toxic substances that normally are absorbed from the gastrointestinal (GI) tract and detoxified in the liver enter the systemic circulation. Similar to portosystemic venous shunting, the pathophysiology in microvascular dysplasia involves shunting of portal blood into the systemic circulation but occurs within the liver vasculature on a microscopic level. Urea-cycle enzyme deficiencies prevent the metabolism of ammonia to urea.

The metabolic changes that cause the clinical syndrome of hepatic encephalopathy result from failure of the liver to (1) remove toxic products of gut metabolism and (2) synthesize factors necessary for normal brain function.[22] The exact cause of hepatic encephalopathy is unknown, but current theories of the pathogenesis include (1) ammonia as the primary putative neurotoxin, although other synergistic toxins may be involved; (2) disorders of aromatic amino acid metabolism resulting from alterations in monoamine neurotransmitters; (3) disorders of gamma-aminobutyric acid (GABA) or glutamate; and (4) increased cerebral concentrations of an endogenous benzodiazepine-like substance.[23] Ammonia is probably the most important toxic substance, although the level of ammonia in the blood does not necessarily correlate with the severity of the CNS disturbance.[24]

Clinical Signs. Most animals with liver disease severe enough to produce HE have other clinical signs indicative of hepatic failure, such as vomiting, anorexia, weight loss, retarded growth, ascites, polyuria-polydipsia, and sometimes icterus. The neurologic signs are frequently worse after feeding, especially if high-protein food is given. The release of nitrogenous materials into the portal circulation exacerbates the signs. Obtundation that may progress to stupor and coma is the most common neurologic sign. Other signs of forebrain involvement such as behavior change, continuous pacing and head pressing, blindness, and seizures also are common. Frequently, the clinical picture is that of a waxing and waning diffuse encephalopathy. The postural reactions and reflexes are only minimally involved except when the animal is nearly comatose. The cranial nerves are not markedly affected except that vision may be impaired (decreased menace response with normal pupillary light reflexes [PLRs]). Ptyalism is common, especially in cats.

A variety of factors can precipitate the neurologic signs of HE in an animal with marginal liver function (Table 15-3).

Any source of protein in the digestive tract is a common cause. Hemorrhage in the gastrointestinal (GI) tract, constipation, or increased fatty acids also may precipitate a crisis. Alterations in fluids, electrolytes, or pH may increase

TABLE 15-3

Management of Hepatic Encephalopathy (HE)

Factors That Exacerbate HE	Management of HE
Increased dietary protein and fatty acids	Low-protein, low-fat diet
Bacterial production of ammonia in large bowel	Diet, antibiotics
Constipation leading to bacterial production of ammonia in large bowel	Diet, laxatives, enemas in acute lactulose
Gastrointestinal hemorrhage	Monitoring and treatment of ulcers, bleeding disorders, hookworms, whipworms
Hypokalemia, hypovolemia, alkalosis—aggravated by diuretics	Monitoring and correction of fluid and electrolyte imbalance, use of potassium-sparing diuretics with caution or not at all
Transfusion of stored blood	Use fresh blood
Sedatives, narcotics, anesthetics	Use depressant drugs with extreme caution (in lowest possible dosages), and monitor carefully
Infections, fever	Monitoring and supportive treatment

the blood and tissue ammonia levels. Decreased renal function reduces elimination of ammonia and other metabolites. Fever and infection cause increased tissue catabolism and increased nitrogen release. Stored blood for transfusions may have an excess of ammonia. Depressant drugs directly affect the brain and frequently are metabolized in the liver. The first evidence of hepatic dysfunction often is slow recovery from anesthesia. Diuretics used to treat ascites may cause HE through their effect on potassium, renal output of ammonia, and alkalosis.

A range of clinicopathologic abnormalities may be present, depending on the cause. Microcytosis with normochromic erythrocytes, ammonium biurate crystals in the urine, and lowered cholesterol, blood glucose, and vitamin K dependent clotting factor levels may be seen with liver failure. Frequently, serum albumin and serum urea nitrogen levels are low. Parenchymal disease often causes elevations in liver enzymes, such as serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). These enzymes usually are not elevated significantly in portacaval shunts.[25] Hepatic dysfunction may be confirmed with tests such as the ammonia tolerance test or preprandial and postprandial serum bile acids measured after a 12-hour fast.[26,27] Hepatic ultrasonography (US) is a sensitive indicator of liver size, but the definitive diagnosis of anomalous portal vein circulation requires US, contrast-enhanced radiography or computed tomography (CT), or nuclear medicine. Depending on the experience of the operator, abdominal US has a sensitivity of about 80% and a specificity of about 65% for the detection of extrahepatic portosystemic shunts (PSS). The sensitivity for detection of intrahepatic shunts is nearly 100%.[28] Radiocolloid scintigraphy using technetium-99m sulfur colloid (TcSC) is used to evaluate liver size and shape. Transcolonic TcSC procedures have been described for the diagnosis of macrovascular shunts in dogs, cats, and potbellied pigs.[29,30] Biopsy is required for confirmation of parenchymal disease.

The successful medical management of HE depends on the cause of the liver disorder and the degree of liver malfunction. Animals with marginal liver function may be managed by reducing the sources of nitrogenous products in the GI tract (see Table 15-3). A high-carbohydrate, low-fat, low-protein diet with high biologic value is indicated. If dietary management alone is inadequate, then oral, nonabsorbable antibiotics (such as neomycin) may be given to reduce the bacterial flora that split urea. Mild laxatives or lactulose (a nonabsorbable disaccharide) may be helpful.[31,32] In addition to its laxative effects, lactulose creates an acid environment in the colon that allows NH_3 to be trapped as NH_4^+ in the gut lumen.

Acute crises of hepatic encephalopathy require more vigorous treatment. Protein sources must be removed completely. Enemas and laxatives are used to remove all nitrogenous material from the GI tract. Sedative drugs, methionine, and diuretics are discontinued. Sources of GI hemorrhage are corrected if they are present. Administration of antibiotic aimed at altering the GI bacterial flora in an attempt to reduce ammonia production should be considered. Antibiotics can be given parenterally or as a retention enema in animals unable to receive oral medications. Dehydration, hypokalemia, and alkalosis are managed with intravenous (IV) fluid therapy. Renal output must be maintained to eliminate nitrogenous products. Oxygen therapy may be necessary, especially in cases of coma. The prognosis for herbivores with hepatic encephalopathy from pyrrolizidine toxicity is poor.

Specific treatment of the cause is instituted, if possible. Unfortunately, most chronic liver diseases and the urea-cycle enzyme deficiencies cannot be treated specifically. Portosystemic shunts may be corrected surgically if portal circulation to the liver is adequate. Partial occlusion of the shunt may be effective. Seizures and neurologic complications following PSS attenuation have been well documented.[33,34] Potential risk factors for neurologic complications include older dogs and dogs with single extrahepatic and portoazygos shunts.[35] For details of the management of hepatic encephalopathy, the reader should consult the references.[23,24,32,35,36-39]

Ketonemic Syndromes

Ketosis. These diseases occur primarily in ruminants and are characterized by hypoglycemia and the accumulation of ketones in body fluids. Conditions that have been recognized include bovine ketosis (acetonemia) and pregnancy toxemia of cattle, sheep, and goats. Unlike most monogastric animals, ruminants produce most of their glucose supplies from the gluconeogenesis of volatile fatty acids (acetic, propionic, and butyric acids). Nearly 50% of the glucose in a cow is normally derived from dietary propionic acid that is converted to glucose in the gluconeogenic pathway. Reduction of propionic acid production in the rumen can result in hypoglycemia and the subsequent mobilization of free fatty acids and glycerol from fat stores. The liver has a limited ability to use these fatty acids because the levels of oxaloacetate are low. Acetyl coenzyme A therefore is not incorporated into the tricarboxylic acid cycle and is converted into the ketone bodies acetoacetate and ß-hydroxybutyrate. When the production of ketones by the liver exceeds peripheral use, pathologic ketosis results.

Both ketosis and primary hypoglycemia are involved in the development of the clinical signs. The most common signs include depression, partial to complete anorexia, weight loss, and decreased milk production. The neurologic signs present in some cows include ataxia, apparent blindness, salivation, tooth grinding, excessive licking, muscle twitching, head pressing, and hyperesthesia. Cows may charge blindly if they are disturbed.

The diagnosis of bovine ketosis is based on the presence of elevated ketone levels in blood and milk with concomitant hypoglycemia. The odor of ketones may be perceived on the breath and in the urine. The immediate therapy is an IV injection of glucose, followed by oral administration of 125 to 250 g of propylene glycol twice a day. Corticosteroids are also beneficial in cows that are not septic. Cows with severe neurologic signs can be treated with 2 to 8 g of chloral hydrate orally twice a day for 3 to 5 days.

Pregnancy/Toxemia. Pregnancy toxemia is a condition that is closely related pathophysiologically to bovine ketosis. It occurs in ewes during the last 6 weeks of pregnancy, when the demand for glucose by developing fetuses is large. Pregnancy toxemia occurs in pastured or housed beef cows during the last 2 months of pregnancy. Overweight cows or those bearing twin calves are especially susceptible. In ewes and cows, the basic cause is nutrition insufficient to maintain normal blood glucose concentrations when fetal glucose demands are high. Hypoglycemia precipitates the ketosis, as has been described earlier in this section.

In sheep, clinical signs may develop in a flock and may extend for several weeks. Ewes become depressed and develop weakness, ataxia, and loss of muscle tone. Terminally, recumbency and coma develop. Neuromuscular disturbances include fine muscle tremors of the ears and the lips. In some cases, seizures develop. "Stargazing" postures and grinding of the teeth are common. The neurologic signs in cattle include depression, excitability, and ataxia. The diagnosis of pregnancy toxemia is based on the history, clinical signs, and presence of ketosis and hypoglycemia.

In sheep, flock treatment consists of increasing the availability of glucose precursors in the diet or drenching affected ewes twice daily with 200 mL of a warm 50% glycerol solution. The

anabolic steroid trenbolone acetate also is beneficial given in 30-mg doses administered intramuscularly (IM). Induction of parturition or fetal removal by cesarean section also may be needed to reduce the metabolic drain on the ewe. Cattle are treated by the method described for bovine ketosis. Pregnancy toxemia can be prevented by ensuring adequate nutrition during pregnancy.

Renal Failure

The terminal stages of renal failure may cause tetany or seizures. Chronic renal disease may be associated with vomiting, diarrhea, anorexia, muscle wasting, and weakness. Encephalopathy, polyneuropathy, and polymyopathy have been seen in humans with chronic renal disease, especially those receiving hemodialysis. Renal encephalopathy has been reported in cows and dogs.[40-42] Alterations in parathyroid hormone levels and electrolyte metabolism, especially calcium and potassium, may cause signs that are related to the nervous system (discussed later in this chapter). Parathyroid hormone can have a primary neurotoxic effect and secondarily cause hypercalcemia.

Endocrine Disorders

Endocrine disorders that affect electrolyte and glucose homeostasis may produce neurologic signs in affected animals. Hormonal excess or deficiency may affect the function of nerves or muscles directly. Pituitary lesions may cause signs of hormonal and forebrain dysfunction if the disease extends into the hypothalamus (Figure 15-5).

In this section, specific endocrine and metabolic diseases that produce prominent neurologic signs of weakness are discussed. Those that cause involuntary movements such as tetany or constant, repetitive myoclonus (tremor) are discussed in Chapter 10. Readers should seek other textbooks for in-depth descriptions of each disorder.

Many endocrine and metabolic diseases cause electrolyte disorders that result in weakness because they affect neuromuscular functions. With certain conditions, clinical signs improve with rest and are exacerbated by exercise. The term *episodic weakness* has been applied to this condition (see Chapter 7).

Hypocalcemia

Parturient Paresis. Parturient paresis, or milk fever, is a hypocalcemic metabolic disorder that occurs in mature dairy cows, sows, sheep, and, rarely, horses, usually within 48 hours of parturition. The affected cows are usually older than 5 years of age, and incidence is increased in the heavy milk producers and Jersey breed. Many dairy cows are marginally hypocalcemic at parturition, and any factor that decreases the metabolic adjustment to this hypocalcemia may cause paresis. Such factors include milk yield versus calcium mobilization from

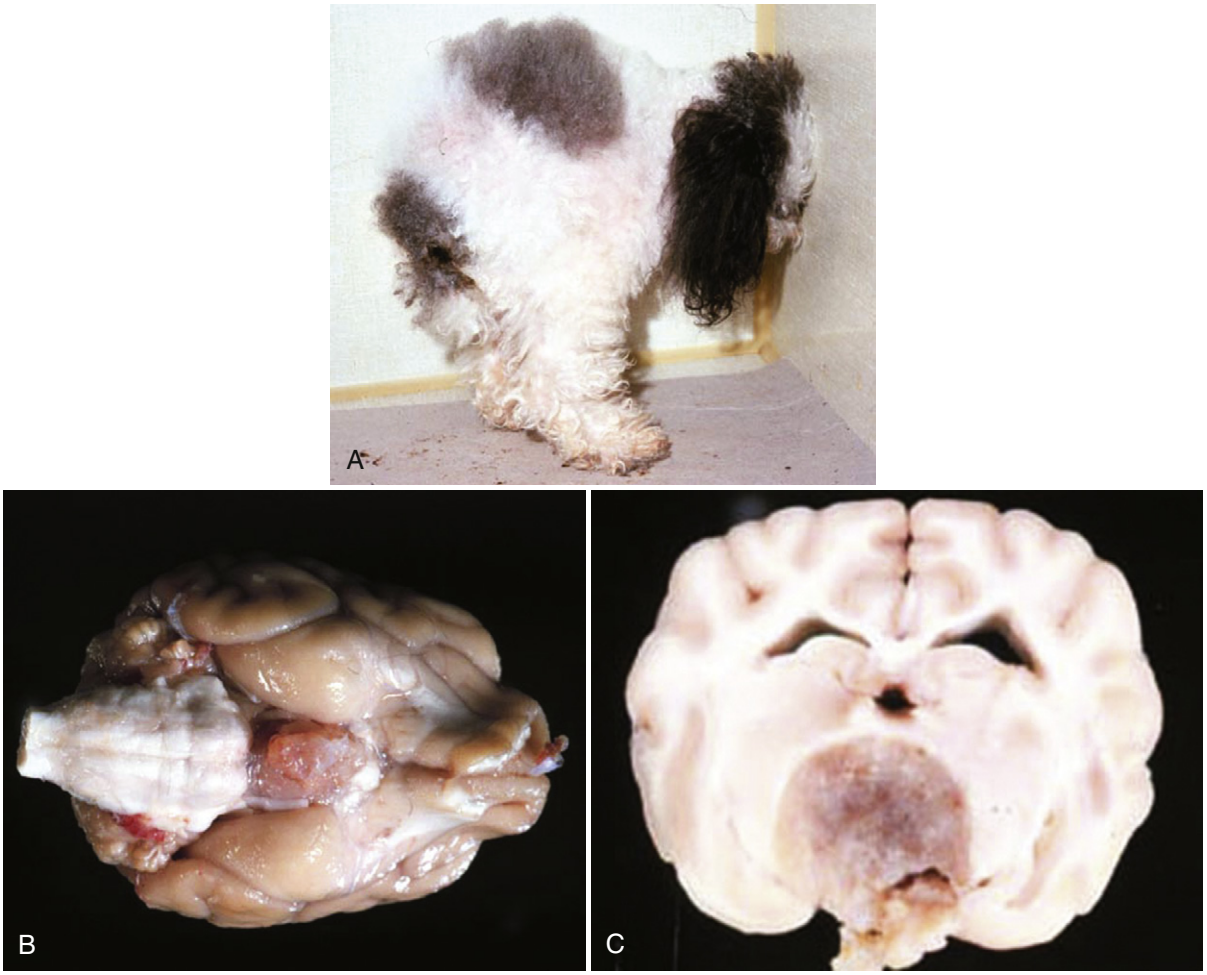


Figure 15-5 **A,** Older toy poodle showing head pressing behavior from pituitary macroadenoma. **B,** Brain from dog in **A.** Note mass at the base of the hypothalamus arising from the pituitary gland. **C,** Cross section of brain from **B.** Note the large mass invading the hypothalamus.

bone and gut, the ratios of calcium to phosphorus in the diet, anorexia and decreased intestinal motility, and dietary pH.

The onset of parturient paresis (stage 1) is often missed and is characterized by apprehension, anorexia, ataxia, and limb stiffness. Stage 2 is marked by progressive muscular weakness, recumbency, and depression. The head is usually turned to the flank, and an S-shaped curvature of the neck may be present. Other signs include dilated pupils, decreased pupillary light reflexes, reduced anal reflex, decreased defecation and urination, no ruminal motility, protrusion of the tongue, and frequent straining.

Stage 3 occurs in about 20% of cases and is characterized by lateral recumbency; severe depression or coma; subnormal temperature; a weak, irregular heart rate; and slow, irregular, shallow respirations. The pupils are dilated and unresponsive to light. Bloating may occur. Changes in serum ions include hypocalcemia, hypophosphatemia, and hypomagnesemia. With prolonged anorexia, serum sodium and potassium levels may decrease.

Intravenous calcium salts (Ca, 1 g per 45 kg of body weight) are usually effective. Calcium borogluconate is commonly used; a 25% solution contains 10.4 g of calcium per 500 mL. Milk fever can be prevented in susceptible cows or herds by the administration of vitamin D or its analogs or by the manipulation of the prepartum dietary calcium and phosphorus levels.

Dogs and Cats. Hypocalcemic syndromes are well documented in dogs and cats (also see Chapter 10).[43] In both species, primary hypoparathyroidism is a documented cause of chronic hypocalcemia. In cats, hypoparathyroidism is sometimes caused by inadvertent surgical resection of the parathyroid glands during thyroidectomy for the treatment of hyperthyroidism. Hypocalcemia may be associated with chronic renal disease in dogs and cats. It is the major biochemical abnormality in dogs with eclampsia and may be observed in animals receiving blood transfusions containing calcium-chelating anticoagulants. Enema solutions that contain phosphate may cause hypocalcemia in cats. Ionized hypocalcemia occurs in critically ill dogs; especially dogs with sepsis.[44]

When the total serum calcium concentration falls below 6 to 7 mg/dL (ionized <0.6 to 0.7 mmol/L), the clinical signs of hypocalcemia are likely to occur.[45] Hypocalcemia increases membrane hyperexcitability by decreasing the membrane threshold to more easily elicit an action potential. Tetanic muscle contractions are the most common clinical signs, but some dogs develop muscle weakness early in the disease. Hypocalcemia should be investigated when the total serum calcium concentration is less than 7.0 mg/dL and the serum albumin concentration is normal. Serum ionized calcium concentrations help to confirm the diagnosis. Once the diagnosis of hypocalcemia is confirmed, the underlying cause should be identified. The diagnosis of both eclampsia and iatrogenic hypoparathyroidism is usually obvious from the history and physical findings. Primary hypoparathyroidism may be confirmed through parathormone (PTH) assays conducted at specialized laboratories.

Animals experiencing seizures should be given 10% calcium gluconate solution IV at a dose of 0.5 to 1.5 mL/kg. The dosage should be slowly infused over a 10- to 20-minute period, and the heart rate and Q–T interval should be closely monitored with an electrocardiogram (ECG) recording. The calcium dose can be repeated every 6 to 8 hours as a bolus injection.

Oral maintenance therapy is instituted when the total serum calcium concentration is consistently less than 7.0 mg/dL. Calcium gluconate or calcium lactate is administered orally in doses of 1 to 4 g for dogs and 0.5 to 1.0 g for cats. In parathyroid deficiency, vitamin D therapy is required. Dihydrotachysterol (DHT) is a synthetic vitamin D that is active in the absence of PTH. The loading dose is 0.03 mg/kg daily administered orally for 3 to 4 days.[46] The maintenance dose is 0.01 to 0.02 mg/kg per day. Calcitriol is a vitamin D analog that is used to treat subacute and chronic hypocalcemia in dogs. The initial dose is 10 to 15 ng/kg twice a day for 3 to 4 days. Then the dose is reduced to 2.5 to 7.5 ng/mg twice a day. Animals should be closely monitored because hypercalcemia may be a complication of vitamin D therapy, especially when supplemental calcium salts are administered.[46]

Diabetes Mellitus

Diabetes mellitus may result in a variety of neurologic signs. Insulin deficiency results in failure of glucose transport into muscle and adipose tissue. An early sign of diabetes mellitus may be exercise intolerance and weakness. As insulin deficiency progresses, ketonemia develops from a marked increase in lipolysis and serum fatty acids. The ensuing metabolic acidosis results in depressed cerebral function that culminates in coma and death. In the untreated ketoacidotic dog or cat, hyperkalemia can cause flaccid muscles by depressing neuromuscular and cardiovascular functions. With therapy and correction of the acidosis, potassium ions reenter cells, and hypokalemia may be a complication that fosters muscle weakness and depression. In some animals, the hyperglycemia may be severe, even though acidosis is absent. This syndrome is called hyperosmolar nonketotic coma. Clinical signs result from the hyperosmolar effects of glucose on the cerebral cortex. Diabetic animals, especially cats, may also develop neuropathy with associated LMN signs (see Chapter 7).

The comatose diabetic animal is a difficult therapeutic challenge. The clinician must exercise great care in performing insulin, acid-base, electrolyte, and fluid therapy. Interested readers should consult other texts for an in-depth discussion of the diagnosis and management of the diabetic patient.

Hypothyroidism

Deficiencies of thyroxine result in a marked decrease in forebrain function and basal metabolic rate. Severely hypothyroid dogs may become obtunded or may appear dull and unresponsive. Coma also known as myxedema coma may occur in severe cases.[47-49] A very low voltage electroencephalogram (EEG) usually is seen. The forebrain signs improve dramatically after replacement thyroid medication. Polyneuropathy and myopathy have been recognized in dogs without the usual signs of hypothyroidism.[50,51] Clinical signs of polyneuropathy include laryngeal paralysis, vestibular dysfunction, and paresis involving various peripheral and cranial nerves (Figure 15-6).[50,52] Hypothyroidism may cause hyperlipidemia and atherosclerosis, conditions that are risk factors for CNS infarction.[50]

The fact that the animal has a polyneuropathy rather than a single problem may be defined by electromyography (EMG) or other electrodiagnostic tests. Measurement of free thyroxine and thyroid-stimulating hormone (TSH) concentrations or TSH response testing are necessary to confirm a diagnosis.[53,54] Many of these animals respond well to thyroid hormone supplementation, but weeks to months may be required for nerve function to recover.[55]

Hyperadrenocorticism

Hyperadrenocorticism (Cushing disease/syndrome) occurs in dogs, horses, and cats. In dogs and horses, pituitary adenomas that hypersecrete adrenocorticotropic hormone (ACTH) are the most common cause, but functional cortisol-secreting adrenal tumors also produce this syndrome in dogs and

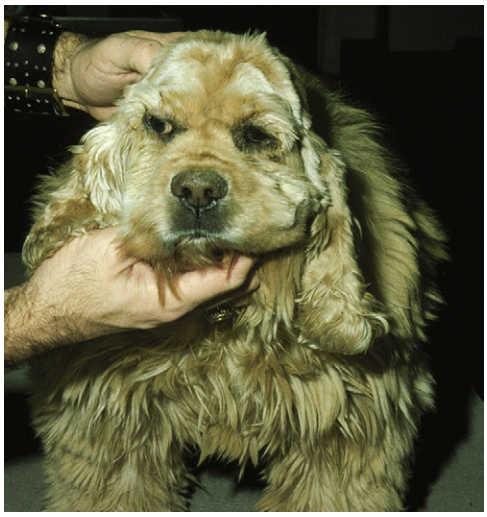


Figure 15-6 Older cocker spaniel dog with myxedematous hypothyroidism and facial nerve paralysis.

cats. The clinical signs are caused by the metabolic effects of hypercortisolemia. Generalized muscle weakness resulting from the catabolic effects of glucocorticoids is a common finding. Some dogs develop muscle degeneration, known as steroid-induced myopathy (see Chapters 7 and 10). This condition produces spontaneous muscle contractions (pseudomyotonia) and a stiff gait.

Pituitary adenomas (macroadenomas) may create neurologic signs by growth and expansion into the hypothalamus (see Figure 15-5, *A* through *C*).[56] Signs of pituitary macroadenomas are usually vague and include depression, confusion, circling, ataxia, and seizures.[57] Macroadenomas are more common in older, large-breed dogs. Pituitary tumors causing hyperadrenocorticisms may be present without causing neurologic signs.[57]

In dogs and cats, hyperadrenocorticism is confirmed with screening tests such as the low-dose dexamethasone suppression test, the ACTH stimulation test, or the urine cortisol:creatinine ratio. Pituitary-dependent hyperadrenocorticism is differentiated from functional adrenocortical tumors with the high-dose dexamethasone suppression test or ACTH assay or both. Similar tests and measurement of increased plasma ACTH concentrations are useful in the diagnosis of equine Cushing disease.[58] Abdominal US may also be helpful in the diagnosis of adrenal gland disease. Macroadenomas can be accurately diagnosed with MRI or CT.[59] In dogs, pituitary-dependent hyperadrenocorticism is usually treated medically with mitotane or trilostane.[60] Mitotane causes necrosis of the adrenal cortex, primarily the zona fasciculata and reticularis, and results in markedly decreased cortisol production. If the dosage is carefully monitored, aldosterone secretion is much less affected. Side effects include vomiting, diarrhea, anorexia, weight loss, and depression. Trilostane reduces synthesis of cortisol, aldosterone, and adrenal androgens. It also can be used in dogs, cats, and horses for pituitary and adrenal-dependent hyperadrenocorticism. It is well tolerated and has fewer side effects than mitotane. However, it may not produce long-term control of clinical signs. Readers are encouraged to consult internal medicine textbooks or veterinary drug handbooks for dosages and correct regimens for each drug. In dogs and cats with pituitary macrotumors, treatment also is directed at control of the pituitary mass (see Chapter 12). Adrenalectomy is recommended for adrenocortical neoplasia.

Hypercalcemic Syndromes

An increased concentration of serum calcium may result in neuromuscular, cardiovascular, and renal dysfunction. Hypercalcemia (>14 mg/dL) increases membrane threshold (making it more difficult to depolarize the membrane) resulting in hypoexcitability of the muscle membrane. CNS reflex and response activities and muscles become sluggish and weak. Hypercalcemia decreases the Q–T interval of the ECG and decreases myocardial function. Hypercalcemia impairs renal concentrating ability. In prolonged hypercalcemia, mineralization of soft tissue may occur. The syndrome of hypercalcemic nephropathy is well documented in animals and culminates in chronic renal failure. In dogs calcium levels above 12.5 mg/dL may result in hypercalcemic signs. Ionized calcium concentrations should be measured to confirm hypercalcemia. In some cases, muscle weakness may be worse during exercise.

Several causes of hypercalcemia exist, including primary hyperparathyroidism, paraneoplastic syndromes, vitamin D rodenticide intoxication, hypoadrenocorticism, and iatrogenic calcium therapy.[61] Primary hyperparathyroidism results from autonomously functioning parathyroid adenomas. These tumors secrete PTH in the presence of increasing serum calcium concentrations. Certain nonendocrine tumors such as lymphosarcoma, anal sac adenocarcinoma, squamous cell carcinoma, and thymoma secrete substances with PTH-like activity that results in hypercalcemia.[62-64] This syndrome is called the hypercalcemia of malignancy and is the most common cause for hypercalcemia in dogs and cats.[64] Rodenticides that contain analogues of vitamin D promote increased absorption of calcium and may produce hypercalcemia.[65]

The symptomatic therapy of hypercalcemia includes IV diuresis with 0.9% saline and furosemide. Corticosteroids also are beneficial because they promote the renal excretion of calcium. Clinicopathologic data for the diagnosis of lymphoma should be obtained before administration of corticosteroids as these drugs can induce remission confounding the diagnosis of lymphosarcoma. Salmon calcitonin may also be given to decrease serum calcium concentrations.[66]

Hyperkalemia

Increased serum concentrations of potassium (>6.5 mEq/L) decrease the resting membrane potential causing an increase in membrane excitability. Eventually, the muscle is unable to repolarize and the muscle fatigues. Excessive extracellular potassium causes cardiac flaccidity and decreases the conduction of impulses through the atrioventricular (AV) node. Thus, heart rate and cardiac output may be severely depressed. Hyperkalemia therefore manifests as generalized weakness that may worsen with exercise.

Adrenal Insufficiency. Hyperkalemia may occur secondary to severe acidosis; however, the usual cause is adrenal insufficiency. Adrenal insufficiency, a chronic immune-mediated adrenalitis, may result in aldosterone deficiency secondary to atrophy of the zona glomerulosa. Hyperkalemia and hyponatremia contribute to the typical signs of depression, anorexia, vomiting, diarrhea, weakness, bradycardia, and hypotension secondary to decreased cardiac output. The disease responds well to fluid therapy and replacement adrenocortical hormone therapy.

Hyperkalemic periodic paralysis. Hyperkalemic periodic paralysis (HPP), an episodic syndrome of muscular weakness and fasciculations, occurs in young, adult quarter horses (see Chapter 7).[67] This is an autosomal dominant inherited disease caused by a genetic mutation in the α-subunit of the equine adult sodium-channel gene.[68] It is associated with marked hyperkalemia without major acid-base imbalance or high serum activity of enzymes derived from muscle. The episodes occur spontaneously or can be induced by administration of potassium chloride orally. Electromyographic changes include

fibrillation potentials, positive sharp waves, and complex repetitive discharges. Histologic changes in muscle are minimal but may include vacuolation of type-2b fibers or mild degenerative changes. Hyperkalemia or normokalemia may occur during episodes. Intravenous administration of calcium, glucose, or bicarbonate results in recovery. Administration of acetazolamide, 2.2 mg/kg orally every 8 to 12 hours, prevents the episodes. Decreasing the potassium content of the feed may also be effective. This can be done by feeding oat hay, feeding grain two to three times daily, and providing free access to salt.[67]

Hypokalemia

Decreased serum concentrations of potassium decrease the activity of skeletal muscle because the membranes are hyperpolarized. In other words, decreased extracellular potassium causes a decrease in membrane sensitivity by increasing the resting membrane potential. Muscle weakness and even paralysis may occur. The primary causes of hypokalemia include diuretic therapy, vomiting, diarrhea, alkalosis, excessive mineralocorticoid therapy for adrenal insufficiency, renal failure, and diabetic ketoacidosis. Hypokalemic myopathy is well documented in cats with renal failure, in cats with chronic anorexia, and in cats receiving low-potassium diets. Most patients respond well to potassium supplementation (see Chapter 7).

Hypoglycemia

Hypoglycemia causes altered CNS function similar to that associated with hypoxia. The blood glucose concentration is of prime importance for normal neuronal metabolism because glucose oxidation is the primary energy source. No glycogen stores are present in the CNS. Glucose enters nervous tissue by noninsulin dependent transport mechanisms. Hypoglycemia at glucose concentrations less than 40 mg/dL can precipitate signs of hypoglycemia. Neurologic signs of hypoglycemia are manifested by dullness, hypothermia, weakness, seizures, and coma. Factors responsible for clinical signs include rate of decrease, level, and duration of hypoglycemia. The severity of the CNS signs may be related more to the rate of decrease than to the actual concentration of glucose. Sudden drops in glucose levels are more likely to cause seizures, whereas slowly developing hypoglycemia may cause weakness, paresis, behavioral changes, or stupor.

Neonatal Hypoglycemia. Studies in puppies have shown that during hypoglycemia, lactic acid is not only incorporated into the perinatal brain but also consumed to the extent that the metabolite can support up to 60% total cerebral energy required for metabolic processes.[69] Although the neonatal brain can readily metabolize ketone bodies, lack of body fat and prolonged time necessary to produce ketones prevent this mechanism from protecting neonates from acute hypoglycemia. Hypoglycemia in young animals may be secondary to malnutrition, parasitism, stress, or some GI abnormality. Puppies are frequently extremely depressed or comatose. Serum glucose should be determined, and IV glucose is administered immediately (2 to 4 mL of 20% glucose per kilogram of body weight). Diazepam often will have no effect on halting hypoglycemic seizures. Continued signs of stupor or coma indicate brain swelling and are treated with hypertonic solutions (see Chapter 12). Dietary regulation, including tube feeding if necessary, must be established to maintain normoglycemia.

Hypoglycemia in puppies also occurs because of immature hepatic enzyme systems, deficiency of glucagon, and deficiency of gluconeogenic substrates. Fatty liver syndrome causes hypoglycemia in toy breed puppies at 4 to 16 weeks of age.[70] Persistent and recurrent hypoglycemia, hepatomegaly, acidosis, and ketosis suggest a glycogen storage disorder.[71] Liver and muscle biopsies are required to make a definitive diagnosis. The management of these cases is frequently unsuccessful.

Insulinoma. Adult-onset hypoglycemia usually is caused by a functional tumor of the pancreatic β-islet cells commonly called insulinomas.[72-74] Excessive insulin produces an increased transfer of blood glucose into the nonneuronal cellular compartments, resulting in hypoglycemia and abnormal CNS metabolism. Although insulinomas are relatively rare, increasing awareness has resulted in more frequent diagnosis. Most insulinomas in dogs have metastasized to the local lymph node (stage II) or liver (stage III) and other sites by the time a definitive diagnosis is made. In addition to hypoglycemia, insulinomas may also induce peripheral neuropathies (see Chapter 7). Other neoplasms (e.g., leiomyosarcoma) also may induce hypoglycemia.[75]

Seizures associated with insulinomas are more frequently related to exercise, fasting (or, conversely, eating), and excitement. Other signs such as weakness, facial and muscle tremors, disorientation, and behavioral changes are also common. The signs are episodic until irreversible neuronal damage occurs. LMN paresis can be detected in dogs with peripheral neuropathies.

Blood glucose concentrations after a 12-hour fast are usually below normal (<60 mg/dL). Longer fasts (24 to 48 hours) may be necessary in some cases, but animals should be monitored closely during this time. serum insulin levels are more specific for making a diagnosis.[76] Serum insulin concentrations are near zero when serum glucose concentrations are less than or equal to 30 mg/dL. Serum insulin levels should be measured when the blood glucose concentrations are below 60 mg/dL. Normal or increased serum insulin concentrations in hypoglycemic dogs are strongly suggestive of insulinoma. An amended insulin:glucose ratio greater than 30 is supportive of an insulinoma. The glucagon tolerance test may be used as an alternative procedure, but it carries a greater risk of profound hypoglycemia during the test. Abdominal ultrasonography, CT, or MRI may detect pancreatic masses in some cases and help localize the lesion for surgical resection.

The management of patients in coma and status epilepticus is discussed in Chapters 12 and 13, respectively. Surgical removal of the tumor is indicated when the patient's condition has stabilized. The reported incidence of malignancy ranges from 56% to 82%; therefore the prognosis is poor even with successful removal of the pancreatic focus.[72,73] Animals with insulinoma should be fed several small meals each day. Diets high in simple sugars should be avoided. Symptomatic treatment with glucocorticoids such as prednisolone, given at a dosage of 0.25 to 0.50 mg/kg per day, help to normalize the blood glucose concentration because of their antiinsulin effects. Streptozotocin is effective in dogs with even metastatic disease. Concurrent saline diuresis should be given to prevent renal toxicity. Seizures may persist because of prior neuronal injury even though serum glucose levels have been normalized.[76]

Nutritional Disorders

Nervous system disorders caused by nutritional deficiencies or excesses are uncommon in companion animals, but they are more common in food animals. Severe malnutrition can cause a variety of abnormalities that are related to multiple deficiencies.

Vitamin A Deficiency

Deficiencies in vitamin A can produce night blindness. Hypovitaminosis A in young animals may cause excessive thickening of the skull and the vertebrae with secondary compression of nervous tissue (especially of the cranial nerves as they pass through the foramina). Decreased absorption of CSF may result in communicating hydrocephalus.[77] Skull malformation and cerebellar herniation have been reported in exotic

cats fed a vitamin A–deficient diet.[78] Hypovitaminosis A is rare or rarely recognized in companion animals but has been reported in food animals.[77-80] Blindness in cattle with vitamin A deficiency is caused by several pathologic mechanisms.[81] Papilledema occurs in adult animals secondary to increased CSF pressure, which is secondary to decreased absorption. Photoreceptor abnormalities, especially affecting the rods, lead to night blindness. Similar changes occur in growing calves, but, in addition, the optic nerves are compressed by narrowing of the optic canals, resulting in ischemia and direct interference with the nerve.

Vitamin E Deficiency

A noninflammatory myopathy may be produced by vitamin E deficiency; however, vitamin E deficiency is rare in companion animals. Calves and sheep have a myopathy associated with a deficiency in vitamin E and selenium. Swine may die suddenly because of degeneration of cardiac muscle. Retinal degeneration may occur secondary to vitamin E deficiency (see Chapter 11). Low vitamin E blood levels have been associated with degenerative myeloencephalopathy and motor neuron disease in horses (see Chapter 7).[82,83]

Vitamin B Complex–Thiamine Deficiency (Polioencephalomalacia)

Deficiencies in B vitamins can cause pathologic changes in both the CNS and PNS. Thiamine deficiency has been reported in dogs, cats, and ruminants.[79,84-87] The syndrome in dogs progresses from anorexia to paraparesis, tetraparesis, seizures, and coma in approximately 1 week.[87] Malacia and hemorrhage were found in multiple sites in the brain and the spinal cord, with the most severe lesions in the brainstem. Animals treated with thiamine recovered. A peripheral neuropathy with LMN paralysis can occur.[84]

Cats with thiamine deficiency often have characteristic ventral flexion of the head and the neck, sometimes causing the mandible to touch the sternum. Vestibular ataxia and seizures may be present. The pathologic lesions are similar to those that occur in dogs.[79] The deficiency in dogs was produced by a diet consisting entirely of cooked meat or a specific thiamine-deficient diet.[87] Cat foods with fish as the primary ingredient contain thiaminase, which destroys thiamine in the diet.[79]

Treatment should be instituted immediately for any animal suspected of having thiamine deficiency. In dogs and cats, 50 to 100 mg of thiamine should be given IV and then repeated IM daily until a response is obtained or another diagnosis is established.

Polioencephalomalacia (symmetric necrosis of the cerebral cortex) is caused by thiamine deficiency in young ruminants (feedlot calves and lambs). The deficiency results from increased breakdown of thiamine in the rumen by thiaminase-secreting bacteria or from sulfur toxicity. Animals have usually been moved from a marginal pasture to a lush pasture, are in a feedlot, or have had some similar change in feeding patterns. Feedlot diets high in sulfates decrease thiamine production in the rumen and may inhibit the production of ATP. Animals younger than 2 years of age are most commonly affected.[86]

Clinical signs are primarily forebrain in origin and include depression, pacing, head pressing, blindness, ataxia, teeth grinding, opisthotonos, and seizures. Dorsomedial strabismus has been attributed to trochlear nerve (cranial nerve [CN] IV) paralysis. Increased intracranial pressure is common and may lead to transtentorial herniation. Symmetric laminar cortical necrosis is the most prominent pathologic finding (Figure 15-7).

Edema of the brain with flattening of the gyri may be present. Measurement of transketolase, the thiamine-dependent coenzyme, is helpful for making a diagnosis. Autofluorescence of the cut surface of the cerebral cortex under ultraviolet light may assist diagnosis (see Figure 15-7).

The condition should be treated with thiamine, 250 to 1000 mg administered IV or IM for 3 to 5 days. Corticosteroids should be given if CNS signs are severe. Severely affected animals may have permanent cortical damage.[88]

Niacin and riboflavin deficiencies are less common, but because animals with thiamine deficiency also may have deficiencies in these vitamins, multiple B-complex preparations are indicated. The diet should be corrected to prevent recurrences.

Vitamin A Toxicity

Increased levels of vitamin A have been reported in cats fed predominantly liver diets. Hypertrophic vertebral bone formation causes ankylosing spondylosis, usually of the cervical vertebrae but in some cases extending to the lumbar region. The clinical signs relate primarily to the rigidity of the vertebral column. A compressive neuropathy occurs in severely affected cats. Dietary correction stops the progression of the spondylosis but does not significantly reduce the existing spondylosis that is present. Antiinflammatory and analgesic drugs have been recommended but must be used with caution, especially in cats.[79]

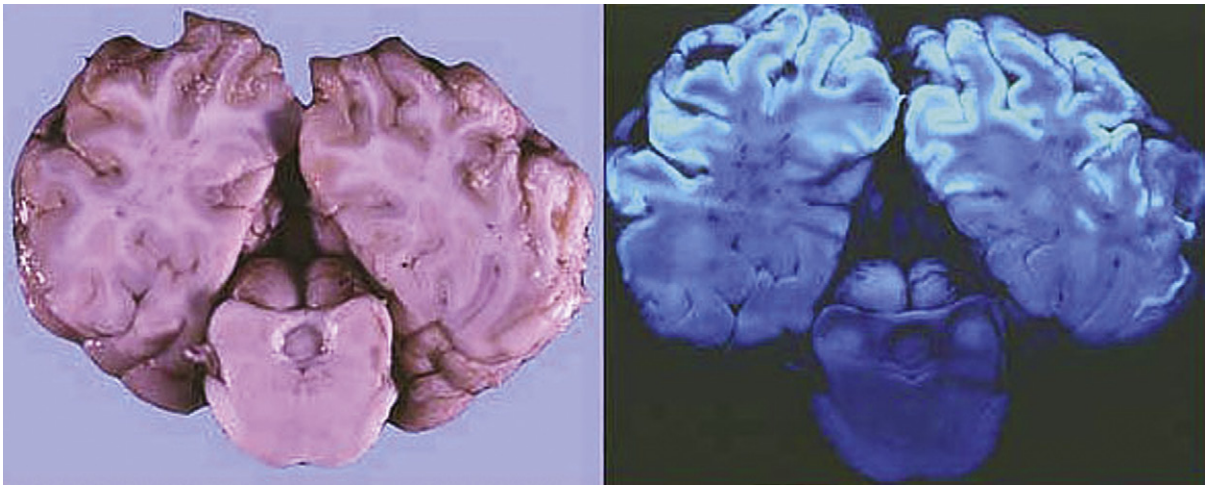


Figure 15-7 Polioencephalomalacia in a calf. There is acute cortical necrosis evidenced by locally extensive softening and discoloration *(left image)* and highlighted by fluorescence under ultraviolet light. (Courtesy Cornell University College of Veterinary Medicine.)

Toxic Disorders

Toxicities causing CNS dysfunction are common in both small and large animals. Many cause biochemical changes and are potentially reversible, whereas others produce structural damage. The more common toxicants are listed in Table 15-4.

Toxicologic disorders, including those caused by poisonous plants, are discussed in detail in several texts.[79,89,90] A helpful information resource about toxic agents and treatment protocols is the ASPCA's National Animal Poison Control Center (*http://www.napcc.aspca.org*).

Diagnosis

A history of exposure to a toxin is the most important factor in establishing the diagnosis in cases of poisoning. Neurologic signs of intoxication include (1) seizures; (2) depression or coma; (3) tremors, ataxia, and paresis; and (4) LMN signs. Animals that show any of these four signs must be considered as possible poisoning victims until proved otherwise. Metabolic and inflammatory disorders are most commonly confused with toxicosis.

Toxins can cause imbalances of neurotransmitter in the CNS to cause tremor. In particular neurotoxic agents that stimulate the CNS will manifest signs of hyperactivity, hyperesthesia, muscle tremor and fasciculation, and behavior changes. Toxicants affecting the autonomic nervous system induce clinical signs by interference with cholinergic neurotransmission. Stimulation of the cholinergic neurotransmission will result in bronchoconstriction, muscle tremors, exocrine gland stimulation, bradycardia, and other CNS effects. Toxins may exert effects at the neuromuscular junction through increased release of acetylcholine and increased receptor stimulation and subsequent muscular fatigue. Blockade of cholinergic neurotransmission depends upon the type of cholinergic receptor involved. Muscarinic receptor blockade causes CNS depression. Nicotinic receptor blockade results in skeletal muscle paralysis and often tremor. Toxins such as bromethalin and

TABLE 15-4

Common Toxicants

Use	Toxicant	Primary Effect
Pesticides	Chlorinated hydrocarbons	CNS stimulation
	Organophosphates	Binding of acetylcholinesterase
	Carbamates	Binding of acetylcholinesterase
	Pyrethrins	Blocking of nerve conduction and GABA inhibition
	Metaldehyde	CNS stimulation
	Arsenic	GI irritation
Rodenticides	Strychnine	Blocking of inhibitory interneurons (glycine)
	Thallium	GI irritation, CNS stimulation, peripheral neuropathy, skin lesions
	α-Naphthylthiourea (ANTU)	GI irritation, pulmonary edema, depression,coma
	Sodium fluoroacetate (1080)	CNS stimulation
	Warfarin	Anticoagulation
	Zinc phosphide	GI irritation, depression
	Phosphorus	GI irritation, CNS stimulation, coma
	Cholecalciferol	CNS depression, cardiac depression
	Bromethalin	Acute—CNS stimulation; chronic—CNS depression
Herbicides and fungicides	Numerous	GI irritation, CNS depression, some are stimulants
Heavy metals	Lead (see arsenic and thallium)	GI irritation, CNS stimulation or depression (see above)
Drugs	Narcotics	CNS depression
	Amphetamines	CNS stimulation
	Barbiturates	CNS depression
	Tranquilizers	CNS depression
	Aspirin	GI irritation, coma
	Marijuana	Abnormal behavior, depression
	Anthelmintics	GI irritation, CNS stimulation
	Ivermectin	Depression, tremors, ataxia, coma
Garbage	Staphylococcal toxin	GI irritation, CNS stimulation
	Botulinum toxin	LMN paralysis
Poisonous plants	Various	Various
Antifreeze	Ethylene glycol	GI irritation, CNS stimulation, renal failure
Detergents and disinfectants	Hexachlorophene	CNS stimulation or depression, tremors
	Phenols	GI irritation, CNS degeneration
Animal origin	Snake bite	Necrotizing wound, shock, CNS depression
	Toad (*Bufo* spp.)	Digitoxin-like action, CNS stimulation
	Black widow spider	Initial signs—spasms, pain tremor initally; later signs—LMN paralysis
	Lizards	GI irritation, CNS stimulation or depression
	Tick paralysis (*Dermacentor* spp. *Ixodes* in Australia)	LMN paralysis

hexachlorophene affect myelin causing intramyelinic edema and alter conduction of the action potential.

When an animal shows signs suggestive of poisoning, the owner must be questioned carefully to find a possible source. Animals in status epilepticus must be treated immediately, and the history must be obtained later (see Chapter 13). Direct questions regarding agents that are capable of producing the signs must be asked. Owners usually are aware of common agents such as insecticides and rodenticides, but they may have difficulty identifying a source of lead poisoning and may be reluctant to admit a source of illicit drug intoxication.

The clinical signs may be sufficient for the clinician to establish a presumptive diagnosis (e.g., intoxication from strychnine and organophosphates). Other agents, such as lead and drugs, may require laboratory confirmation (Tables 15-5 through 15-8) or tissue analysis.

Toxicants Causing Seizures

The most common sign of poisoning in small animals is seizures (see Table 15-5). The CNS is primarily or secondarily involved with a variety of toxic substances. Dorman reported that seizures occurred in 8.2% of all cases of suspected

TABLE 15-5

Common Toxicants Causing Seizures

Toxicants	Diagnosis	Management	Prognosis
Organochlorines	Exposure; muscle fasciculations common; laboratory confirmation difficult	Removal of toxicant—washing, gastric lavage; sedation or anesthesia with barbiturates	Poor with seizures
Organophosphates and carbamates	Exposure; salivation, diarrhea, constricted pupils, muscle weakness; blood cholinesterase level decreased; tissue analysis poor	Removal of toxicant; atropine; pralidoxime chloride (2-PAM) (not for carbamates)	Good if treated early
Pyrethrins	Exposure; tremor, salivation, ataxia, seizures; analysis of tissues	Removal of toxicant; sedation	Good if treated early
Strychnine	Exposure; tetany without loss of consciousness, increased by stimulation or noise; laboratory analysis of stomach contents, urine, tissues	Removal of toxicant—gastric lavage or emesis; sedation—barbiturates; respiratory support if needed	Good if treated early
Bromethalin	Exposure; high dose—excitement, tremor, seizures; low dose—tremor, depression, ataxia	Removal of toxicant—activated charcoal; corticosteroids, mannitol	Fair if treated vigorously for several days
Sodium fluoroacetate (1080)	Exposure; seizures are clonic and severe; laboratory confirmation difficult	Removal of toxicant; sedation—barbiturates	Poor with seizures
Thallium	Exposure; GI signs, seizures only in severe poisonings; laboratory analysis of urine and tissues	Removal of toxicant; diphenylthiocarbazone (Dithion) early, ferric ferrocyanide (Prussian blue) late late	Poor with seizures, fair with other signs, good with treatment
Lead	Exposure (may be difficult to document); chronic intoxication may cause intermittent seizures, behavioral change, tremor, GI signs; blood lead level >0.4 ppm; basophilic stippling, nucleated red blood cells (RBCs) with no anemia	Removal of toxicant; calcium ethylenediaminetetraacetic acid, 2,3-dimercaptosuccinic acid	Good with treatment
Staphylococcal toxin	Exposure to garbage; severe GI signs; isolation of toxins and testing in laboratory animals laboratory animals	Removal of toxicant; sedation	Poor with seizures; animals usually die rapidly
Toad (*Bufo* spp.—reported only in southern Florida)	Exposure; severe buccal irritation	Wash mouth; sedation—anesthesia	Fair if treated within 15-30 min, otherwise poor
Amphetamines	Exposure to prescription or "street" drugs; hyperactivity, dilated pupils; analysis of urine	Removal of toxicant; sedation or anesthesia—barbiturates	Good if treated early
Metaldehyde	Exposure to snail bait; tremor, ataxia, salivation; seizures are tonic, similar to strychnine, but not changing with stimuli; laboratory analysis of stomach contents	Removal of toxicant; sedation or anesthesia; support respiration	Fair if treated early
Caffeine and other methylxanthines	Ataxia, tachycardia, seizures, coma; laboratory analysis of stomach contents and tissues	Removal of toxicant; sedation, fluids	Fair with treatment
Zinc phosphide	Exposure to rodenticide; behavioral changes, hysteria followed by seizures; GI irritation; analysis of stomach contents and tissues	Removal of toxicant; oral and intravenous bicarbonate; sedation—barbiturates	Poor

TABLE 15-6

Common Toxicants Causing Behavioral Changes, CNS Depression, or Coma

Toxicants	Diagnosis	Management	Prognosis
Drugs—narcotics, barbiturates, tranquilizers, marijuana	Degree of depression depends on dose; source of pharmaceuticals or "street" drugs; laboratory analysis of blood or urine	Removal of toxicant, narcotic antagonists, diuresis, support respiration	Good with treatment
α-Naphthylthiourea (ANTU)	Exposure; pulmonary edema; depression and coma terminal; laboratory analysis of stomach contents and tissues	Removal of toxicant, treatment of pulmonary edema	Poor
Ethylene glycol	Exposure; GI irritation, renal failure; oxalate crystals in urine	IV ethanol (30%) with sodium bicarbonate; alternative for dogs—4-methylpyrazole	Poor with coma, fair to good if treated early
Cholecalciferol	Exposure; depression, weakness, cardiac depression, renal failure	Removal of intoxicant; IV saline diuresis, furosemide, corticosteroids	Fair with treatment
Many poisons produce coma terminally			

TABLE 15-7

Common Toxicants Causing Tremor, Ataxia, or Paresis

Toxicants	Diagnosis	Management	Prognosis
Hexachlorophene	Exposure; usually young, nursing animal; large dose causes GI irritation, severe depression; chronic exposure causes cerebellar signs and CNS edema	Removal of toxicant, supportive care; treatment for cerebral edema	Fair; may be residual effects
Lead	Chronic lead poisoning may produce cerebellar signs and dementia (see Table 15-5)	See Table 15-5	Good
Organophosphates	Chronic low doses (flea collars, dips) may produce tremor and weakness (see Table 15-5)	See Table 15-5	Good
Organochlorines	Low-dose exposure may produce weakness and muscle fasciculation (see Table 15-5)	See Table 15-5	Fair to good
Tranquilizers	Ataxia common with tranquilizers (see Table 15-5)	None needed	Good
Marijuana	Behavioral changes and ataxia common	Removal of toxicant	Good
Ergot alkaloids	Cattle and other herbivores grazing on Dallis grass or ryegrass; ataxia, uncoordinated gait	Removal from pasture	Good
Nitro-bearing plants (e.g., *Astragalus* spp., locoweed)	Cattle, sheep, horses; ataxia, weakness or hyperexcitability, death	Removal from pasture	Fair in ruminants; may be permanent CNS damage
Yellow star thistle	Horses have an acute onset of rigidity of muscles of mastication and involuntary movement of the lips; ataxia, circling, and pacing may occur; lesions are necrosis of the globus pallidus and substantia nigra	No treatment known	Poor

toxicosis.[91] Toxins induce seizures through a number of different mechanisms: increased excitation, decreased inhibition, and interference with energy metabolism.[92] The animal may show (status epilepticus) or cluster seizures (e.g., from organophosphates, strychnine) or may have a history of intermittent seizures (e.g., from lead). Animals in status epilepticus must be treated immediately (see Chapter 13).

Tetany. The tetany produced by strychnine is differentiated from the seizures produced by other agents in this group. Tetany is a period of sustained muscular contraction with intermittent periods of relaxation. Despite the severe muscle contractions, the animal is conscious. Tetany caused by strychnine may be confused with hypocalcemic tetany seen in lactating animals of all species or in tetanus. Intravenous calcium provides immediate relief in cases of hypocalcemia. The term *tetanus* is associated with the toxic effects of *Clostridium tetani*. Tetanus is much slower in onset than is strychnine poisoning and generally causes more continuous contraction of the muscles. Seizures from other agents produce clonus (alternating flexion and extension).

Insecticides. Organophosphates may be distinguished from organochlorines by their profound effect on the autonomic nervous system, producing profuse salivation, constricted pupils, and diarrhea. Organochlorines frequently

TABLE 15-8

Common Toxicants Causing LMN Signs

Toxicants	Diagnosis	Management	Prognosis
Botulinum toxin	Exposure to contaminated food, carrion, and so forth; ascending LMN paralysis (see Chapter 7)	See Chapter 7	Good
Tick paralysis (*Dermacentor* spp., *Ixodes* species in Australia)	Presence of ticks; ascending LMN paralysis (see Chapter 7)	Removal of ticks (see Chapter 7)	Good in the United States of America; poor in Australia
Drug reaction (nitrofurantoins, doxorubicin, vincristine)	Exposure; rare in animals	Removal of source	Fair
Cyanide (from *Sorghum* spp. grass)	Cauda equina syndrome with dysuria, flaccid anus and tail, prolapsed penis; may progress to paraplegia; usually occurs in horses	Removal from pasture; no treatment available	May improve after removal from source; residual deficits common
Organophosphates	Chronic exposure may cause LMN signs; axonopathy affecting pelvic limbs first	Removal of source; atropine and pralidoxime if acute signs present; no treatment for peripheral neuropathy	Fair to poor
Heavy metals (lead, arsenic, mercury, thallium)	Chronic exposure, rare in animals (see Table 15-5)	See Table 15-5	See Table 15-5
Industrial chemicals (acrylamide, carbon disulfide, polychlorinated biphenyls)	Not reported in animals; presumably could cause distal axonopathy	Removal from source	Unknown

produce fine-muscle fasciculations, even between seizures. Pyrethrins and pyrethroid insecticides alter both sodium and chloride conductance causing tremor and seizures. The seizure may be preceded by tremors, ataxia, salivation, and other signs. Class I and II pyrethrins and pyrethroid compounds act on voltage-gated sodium channels in nerve and muscle, causing persistent depolarization and failure of membrane repolarization. Class II pyrethroids also inhibit binding of GABA to the $GABA_A$ receptor, which prevents influx of chloride.

Miscellaneous Stimulants. Ingestion of products containing caffeine and other methylxanthines, including chocolate, may also cause seizures. Metaldehyde, a common snail bait, can cause continuous seizures.[91] Both bromethalin and hexachlorophene are toxins that result in intramyelinic edema and demyelination. Bromethalin is a rodenticide that uncouples oxidative phosphorylation depleting cellular ATP.[93,94] Clinical signs include ataxia; conscious proprioceptive deficits; paresis/paralysis; depression, which can progress to stupor; focal or generalized seizures; decerebrate posture; and vocalization.

Metronidazole. Central nervous system signs of lead intoxication are seen most often in cases of chronic exposure.[95-99] The seizures are intermittent. The differential diagnosis of seizure disorders is discussed in Chapter 13. Laboratory analysis of the blood for evidence of lead is diagnostic. If the blood lead values are in the high normal range and lead poisoning is suspected, treatment followed by measurement of urine lead levels is diagnostic. Other toxicants causing seizures are seen infrequently.

Metronidazole is an antimicrobial, antiprotozoal agent that is lipophilic readily penetrating the blood-brain barrier and causes neurotoxicity in dogs and cats.[100-102] The drug is also used in the chronic treatment of inflammatory bowel disease. Neurologic signs include seizures, tremors, ataxia, blindness, hyperactivity, and vestibular dysfunction. Doses of metronidazole reported to be toxic in cats ranged from 111 mg/kg of body weight per day for 9 weeks to 58 mg/kg of body weight per day for 6 months.[101] The neurologic signs resolved within days of drug withdrawal and supportive treatment. In dogs, doses as low as 67.3 mg/kg of body weight per day for 3 to 14 days caused neurotoxicity.[100] In a report of five dogs, two were euthanized because of severe CNS disease, and three recovered after several months.[100] Most dogs recover within 7 to 14 days. Diazepam may be effective in treatment of the neurologic signs because it facilitates the effects of GABA, a potent inhibitory neurotransmitter.[102] Diazepam, 0.43 mg/kg PO every 8 hours for 3 days, decreased response time from 4.25 days for untreated dogs to 13.4 hours for treated dogs. In addition, the time to recovery was reduced from 11 days to 38.8 hours.[102]

Ivermectin. Ivermectin is widely used as an antiparasitic agent and heartworm preventative. It is also used in higher doses for the treatment of sarcoptic and demodectic mange in dogs. In most breeds of dogs, ivermectin has a wide margin of safety. Collies, Australian shepherds, Shetland sheepdogs, and Old English sheepdogs have an increased sensitivity to ivermectin and related compounds. These breeds have a genetic mutation that results in a nonfunctional P-glycoprotein.[103,104] P-glycoprotein plays an important neuroprotective role in the blood-brain barrier in that it enhances the transport of drugs from the CSF back into circulation. Ivermectin is a GABA agonist that inhibits activity at presynaptic and postsynaptic neurons in the CNS. Clinical signs of ivermectin neurotoxicity include depression, disorientation, tremors, ataxia, blindness, mydriasis, retinopathy, seizures, and coma.[104-107] Clinical signs are dose dependent in that susceptible breeds rarely develop clinical signs at 6 μg/kg once a month, which is the standard dose for heartworm prevention. Doses exceeding 200 μg/kg may cause clinical signs in susceptible breeds and doses above 400 μg/kg may cause death.[105] The recovery period may take more than 3 weeks. There is no specific anecdote for ivermectin toxicity. Three adult horses developed neurologic signs 18 hours after oral administration of ivermectin paste.[108] Signs included depression, ataxia, drooping

of the lips, mydriasis, decreased pupillary light reflexes, absent menace responses and muscle fasciculations. Two horses recovered following symptomatic therapy.

Toxicants Causing Behavioral Change, Stupor, or Coma

Stupor or coma may be seen with almost any poison in the terminal stages. Drugs such as narcotics, barbiturates, and tranquilizers most frequently cause stupor or coma and also may cause behavioral changes in smaller doses (see Table 15-6). Some other agents such as chlorpyrifos and lead also can produce behavioral changes with chronic intoxication.[99,109] The diagnosis may be obvious if the source is known (e.g., with accidental overdosing with an antiepileptic drugs or ingestion by an animal of its owner's tranquilizers). Reports of animals that have ingested illicit drugs are not uncommon, and the owner is usually reluctant to admit the source of the intoxication in these cases. Laboratory analysis of blood or urine may be necessary to confirm the diagnosis.

Leukoencephalomalacia (Moldy Corn Toxicity). Leukoencephalomalacia is caused by the mycotoxin fumonisin B1 found in contaminated corn. The toxin creates a severe liquefactive necrosis and degeneration of the cerebrum, brainstem, and spinal cord. The disease has a worldwide distribution and typically occurs in the late fall through early spring. Neurologic (most common) and hepatoxic syndromes are recognized. Clinical signs develop 3 to 4 weeks after daily ingestion of contaminated corn. The onset of clinical signs is rapid with death occurring in 2 to 3 days. The CNS signs are similar to other equine encephalopathies. The hepatotoxic syndrome is associated with swelling of the lips and nose, somnolence, severe icterus, petechia of mucous membranes, abnormal breathing, and cyanosis. Diagnosis is based on histopathology. Analysis for the toxin in feed is recommended. There is no treatment and mortality is high.

Toxicants Causing Tremors, Ataxia, and Paresis

Chronic organophosphate poisoning from flea collars and topical or systemic insecticides frequently causes signs that are suggestive of cerebellar disease or muscle weakness (see Table 15-8). The finding of weakness is not consistent with pure cerebellar disease, so when both are present, poisoning must be considered.[110] Organophosphates bind acetylcholinesterase to cause muscle weakness through effects on the neuromuscular junction (see Chapter 7) and have direct CNS effects causing seizure. Tremor and fasciculation associated with muscle weakness occur as a depolarizing neuromuscular junction blockade effect take place. Atropine is used to counteract the muscarinic effects of the organophosphate. Pralidoxime chloride (2-PAM) is a drug that acts specifically on the organophosphate-enzyme complex and freeing the enzyme. Hexachlorophene toxicity has been seen in puppies with signs of tremor and ataxia.[111-113] Severe depression may follow. The usual source has been repeated washing of the bitch's mammary glands with a soap containing hexachlorophene. Bathing young dogs or cats of any age in hexachlorophene soap also has produced the syndrome. Hexachlorophene is rarely available now.

Metaldehyde poisoning, which produces tremor and ataxia progressing to depression and coma, is seen frequently in areas where the substance is used for snail bait. Chronic lead poisoning (see Chapter 10) and numerous plant toxicities cause tremor and ataxia (Table 15-7). Mycotoxins also can cause severe tremors and seizures in dogs (see Chapter 10).

Toxicants Causing LMN Signs

Botulism and tick paralysis cause generalized LMN paralysis by blockade of the neuromuscular junction (see Table 15-8). These conditions are discussed in Chapter 7. Some drugs (e.g., nitrofurans and chemotherapeutic drugs and some chronic toxicities (such as lead, organophosphate, and arsenic poisoning) can produce peripheral neuropathies. Other signs usually predominate, however.

Toxic Plants

Toxic plants causing neurologic syndromes of herbivores are summarized in Table 15-9.

Treatment

Removal of the toxic substance is the most important part of the treatment for many toxicities. Agents that have entered the animal through the skin, such as insecticides, should be removed by thorough washing and rinsing. Ingested agents may be removed by inducing emesis, performing gastric lavage, or administering laxatives or enemas. Diuresis may promote excretion when absorption has occurred. Activated charcoal is an effective adsorbing agent.[114] Electrolyte imbalances and other secondary metabolic disorders are treated symptomatically and by managing the underlying disease process. Status epilepticus is a life-threatening emergency and must be treated accordingly (see Chapter 13).

Specific treatments for the various toxicities are outlined in Tables 15-5 through 15-9. The reader should consult the references for details.[79,89,90,115] Toxins causing spasticity can be counterbalanced with use of muscle relaxants. Diazepam (0.25 to 1.0 mg/kg IV or per rectum) is a centrally acting muscle relaxant and can relieve acute-onset tremor disorders. However, diazepam should be avoided in cats with organophosphate toxicity as it may potentiate muscle tremor, and other muscarinic signs. Methocarbamol also a centrally acting muscle relaxant can be administered. Often a dark, quiet room is necessary to remove external stimuli associated with CNS stimulants (strychnine, bromethalin, etc.). Frequent patient monitoring and other measures of supportive care are important. Fluid therapy maintains electrolyte concentration and normovolemia. Oxygenation, blood pressure, electrolytes, and glucose should be monitored. In severe cases of respiratory muscle weakness, assisted ventilation may be necessary.

Inflammatory Diseases

The inflammatory diseases of the nervous system are caused by infectious and parasitic organisms or are immune mediated. Canine distemper, feline infectious peritonitis, equine protozoal myeloencephalitis, West Nile encephalomyelitis, alphaviral encephalomyelitis, and bacterial infections, including thromboembolic meningoencephalitis and listeriosis, are common infectious causes of CNS inflammatory disease. Some fungal diseases are common in endemic areas. Most of the other diseases are relatively uncommon. Infectious diseases are discussed in many textbooks.[116-121] Granulomatous meningoencephalomyelitis, steroid-responsive meningoencephalitis, and other breed-specific meningoencephalitides are common noninfectious or immune causes of CNS inflammatory disease. The differential diagnosis is discussed in the next section. The more common inflammatory diseases are outlined in Tables 15-10 to 15-17.

Principles of Diagnosis

Most of the inflammatory diseases are characterized by an acute onset. All are progressive, and some are chronic-progressive. Diffuse or multifocal involvement is characteristic of most of the diseases in this group, but localized signs also occur. The minimum database (see Chapters 1 and 4) may provide evidence of systemic infection (e.g., alterations in white blood cell [WBC] count), although many primary CNS inflammatory diseases do not produce a systemic response.

Text continued on p. 462.

TABLE 15-9

Examples of Several Plant (and Fungal) Toxicoses of Domestic Herbivores That Can Result in Syndromes Characterized by Neurologic Signs

Plant	Species Affected	Neurologic Signs	Pathophysiology	Neural Legions	Treatment	Prognosis
Ryegrass	Sheep, cattle, horses	Ataxia, tremor, tetany	Penitrem and fumi tremorgenic mycotoxins from *Penicillium* spp.	Secondary Purkinje cell degeneration	Diazepam	Good
Phalaris spp.	Sheep, cattle	Ataxia, tremor, weakness, seizures	Dimethyltryptamine alkaloids act as monoamine oxidase inhibitors	Neuronal pigmentation (indole melanins)	?Diazepam	Poor
Paspalum, Dallis grass	Cattle, sheep	Ataxia, tremor	*Claviceps paspali* ergot alkaloids probably neurotoxic	None	—	Good
Swainsona spp. and locoweeds	Sheep, cattle, horses	Weight loss, ataxia, aggressiveness	Indolizidine alkaloid (swainsonine) induces α-mannosidosis	Neuroaxonal dystrophy, neurovisceral storage products	Reserpine (locoweed)	Fair to very good
Sorghum spp.	Horses, cattle, sheep	Ataxia, bladder paralysis	Possibly HCN or lathyrogenic toxins	Spinal cord degeneration	—	Poor to fair
Solanum esuriale	Sheep	Exercise intolerance, weakness, arched back (humpyback)	Unknown (suspected toxin in *S. esuriale*)	Spinal cord fiber degeneration; myopathy	—	Poor
Solanum fastigiatum, S. dimidiatum, S. kwebense	Cattle	Cerebellar ataxia, "cerebellar seizures"	Suspected induction of gangliosidosis	Purkinje cell vacuolation and degeneration	—	Poor
Cycad palms	Cattle, goats, horses	Ataxia, recumbency	Possibly toxic glycosides, cycasin and macrozamin	Spinal cord degeneration	—	Poor
Melochia pyramidata	Cattle	Ataxia, recumbency	Unknown	Spinal cord and nerve degeneration	—	Poor
Tribulus terrestris	Sheep	Asymmetric pelvic limb weakness	Possibly neuromuscular process	None	—	Poor
Karwinskia humboldtiana	Goats	Hypermetria, weakness	Unknown	Peripheral neuropathy, central neuroaxonal dystrophy, myopathy	—	Poor

Nardoo fern, *Marsilea drummondii*	Sheep	Depression, blindness, convulsions	Probably a thiaminase	Polioencephalomalacia	Thiamine	Good if early
Birdsville indigo, *Indigofera linnaei*	Horses	Weight loss, ataxia, weakness	Arginine antagonist alkaloids; indospicine, canavine	None	Arginine-rich feeds (gelatin, Lucerne)	Good
Mexican fireweed, *Kochia scoparia*	Cattle	Blindness (nephrosis, hepatitis)	Saponins, alkaloids, oxalates; possibly thiaminase	Polioencephalomalacia	—	Poor
Buckeye, *Aesculus* spp.	Cattle	Staggering, convulsions	Glycosides and alkaloids described	Unknown	—	Fair
Helichrysum argyrosphaerum	Sheep, cattle	Peripheral blindness, nystagmus, weakness	Unknown	Patchy status spongiosus, white matter	—	Fair for life, poor for vision
Yellow star thistle, Centaurea solstitialis	Horses	Depression, pacing, dystonia of muscles of prehension, mastication, and deglutition	Uknown	Nigropallidal encephalomalacia	Tube feed	Poor, starve

Modified from Kornegay JN, Mayhew IG: Metabolic, toxic, and nutritional diseases of the nervous system. In Oliver JE, Hoerlein BF, Mayhew IG, editors: Veterinary neurology, Philadelphia, 1987, WB Saunders.

TABLE 15-10

Bacterial Diseases of the Nervous System

Disease	Cause	Incidence	Clinical Signs and Pathology	Course and Prognosis	Diagnostic Tests	Treatment
Meningitis	*Staphylococcus, Pasteurella,* others	Variable, but generally uncommon	Generalized or localized (especially cervical) hyperesthesia; degree of illness variable; temperature and white blood cell (WBC) count may be normal count may be normal	Usually acute onset, but may be chronic; prognosis good with early treatment	CSF (protein often >200 mg/dL, increased cells, primarily neutrophils), culture and sensitivity testing	Antibiotics according to sensitivity: ampicillin, trimethoprim, chloramphenicol
Meningoencephalomyelitis	As in meningitis	Uncommon	As in meningitis, plus signs of brain or spinal cord disease; often includes blindness, seizures, ataxia, cranial nerve deficits	Usually acute: prognosis good with early treatment, but neurologic deficits are common	Same as meningitis; EEG may indicate encephalitis; cross-sectional imaging	Same as for meningitis; seizures—diazepam, phenobarbital; acute cerebral edema—mannitol, hypertonic saline
Abscess	As in meningitis	Rare	May have focal signs or focal signs plus signs of meningitis or meningoencephalitis	May be chronic; progression may be rapid once signs are obvious	Same as in meningoencephalitis	Same as for meningoencephalitis
Vertebral osteomyelitis, discospondylitis (see Chapter 6)	*Staphylococcus, Brucella canis,* others	Moderately frequent in dogs	Pain, usually focal; may have spinal cord compression; usually clinically ill, often over weeks to months	Chronic, may become acute when spinal cord is compressed	Radiography, cross-sectional imaging, *Brucella* serology; blood and urine culture and sensitivity	Antibiotics, preferably bactericidal; curettage, decompression if spinal cord is compressed
Tetanus	*Clostridium tetani*	Rare except in horses	Extensor rigidity of all limbs, often with opisthotonos; contraction of facial muscles, prolapsed nictitating membrane; usually infected wound; toxin blocks glycine release	Acute onset, often lasts 1-2 wk, animals may die; prognosis fair if treated	Signs, history, isolation of organism from wound	Penicillin, metronidazole, tetanus antitoxin, tranquilizers or muscle relaxants; quiet environment; treat wound, nursing
Botulism	*Clostridium botulinum*	Sporadic	LMN-type paralysis. often beginning with pelvic limbs, progressing to tetra- paresis in less than 24 hr; caused by toxin blocking neuromuscular transmission	Acute onset, lasts about 2 wk; good prognosis unless respiratory paralysis is present early	Serum, fecal analysis, history, EMG, and nerve conduction velocity	Enemas and laxatives early, supportive care, antitoxin usually not effective
Thromboembolic meningoencephalitis	*Histophilus somni*	Cattle, primarily young in feedlot	Fever, depression, blindness, lack of coordination, cranial nerve signs, seizures	Acute progressive; fair prognosis with early treatment	History, CSF (increased protein, increased neutrophils), culture	Antibiotics, vaccine available
Listeriosis	*Listeria monocytogenes*	Sporadic in ruminants	Depression, asymmetric ataxia and paresis, cranial nerve signs, central vestibular signs	Acute progressive in sheep and goats, more chronic in cattle; poor prognosis if CNS signs are present	History, signs, CSF (increased protein, increased mononuclear cells), histopathology, fluorescent antibody, isolation of organism	Antibiotics (penicillin, sulfonamides, tetracyclines) for 2-4 wk

TABLE 15-11

Mycotic and Actinomycetes Infections of the Nervous System

Disease	Cause	Incidence	Clinical Signs and Pathology	Course and Prognosis	Diagnostic Tests	Treatment
Cryptococcosis	*Cryptococcus neoformans*	Low; primarily in eastern and midwestern United States but not reported throughout United States	Nose and sinuses usually are infected, with extension to brain; ocular lesions and blindness common; CNS involvement common	Chronic; guarded prognosis	Cytology and culture of exudates, serology, antigen test, CSF (increased protein, increased cells, neutrophils and mononuclear cells, possibly organisms)	Itraconazole, fluconazole*
Blastomycosis	*Blastomyces dermatitidis*	Low; primarily in eastern and midwestern United States	Rarely involves CNS; pyogranulomatous encephalitis or single or multifocal granulomas; frequently involves lungs, skin, and eyes	Chronic; poor prognosis	PCR, serology, cytology	Amphotericin B,* 5-fluorocytosine, ketoconazole, itraconazole, fluconazole
Histoplasmosis	*Histoplasma capsulatum*	Low, primarily in central United States	CNS involvement uncommon; involves reticuloendothelial cells of most viscera	Chronic; guarded prognosis	PCR, serology, cytology	Amphotericin B,* 5-fluorocytosine, ketoconazole, itraconazole, fluconazole
Coccidioidomycosis	*Coccidioides immitis*	Can be relatively common in endemic areas of southwestern United States	CNS involvement uncommon; pulmonary infection common	Chronic; poor prognosis	PCR, serology, cytology	Amphotericin B,* 5-fluorocytosine, ketoconazole, itraconazole, fluconazole
Nocardiosis	*Nocardia* sp.	Low throughout United States	Systemic disease, signs similar to canine distemper, respiratory or cutaneous forms; CNS abscesses and vertebral osteomyelitis reported	Chronic; poor prognosis	Smears, cultures, CSF (increased protein, increased cells, neutrophils)	Penicillin, sulfonamides, trimethoprim
Actinomycosis	*Actinomyces* sp.	Low throughout United States	Similar to nocardiosis	Chronic; poor prognosis	Similar to nocardiosis	Penicillin, clindamycin, erythromycin, lincomycin
Paecilomycosis	*Paecilomyces* sp.	Rare	Disseminated form of discospondylitis	Chronic; poor prognosis	Culture, biopsy	None
Aspergillosis	*Aspergillus* sp.	Primarily in large animals	Encephalitis can develop after immunosuppression or guttural pouch infection	Chronic; poor prognosis	Culture, CSF, cytology	Amphotericin B,* 5-fluorocytosine, ketoconazole, itraconazole, fluconazole
Phaeohyphomycosis	*Cladosporium* sp.	Rare	Encephalitis with granulomas has been reported in dogs and cats	Chronic; poor prognosis	Culture, biopsy	Amphotericin B,* 5-fluorocytosine, ketoconazole, itraconazole, fluconazole

*Itraconazole and fluconazole have been used effectively in some cats with cryptococcal encephalitis and are the preferred treatment. Data for other fungal CNS infections are largely lacking.

TABLE 15-12

Protozoal Diseases of the CNS

Disease	Cause	Incidence	Clinical Signs and Pathology	Course and Prognosis	Diagnostic Tests	Treatment
Toxoplasmosis	*Toxoplasma gondii*	Common infection but infrequent clinical problem	Clinical manifestations usually associated with another disease or immunosuppression; CNS, eyes, lungs, gastrointestinal tract and skeletal muscles often affected	Chronic; fair to poor prognosis	Serology, oocysts in stool (cats), biopsy, CSF (increased protein, mononuclear cells and neutrophils)	Sulfonamides, pyrimethamine, clindamycin
Neosporosis	*Neospora caninum*	Uknown frequency, cases of toxoplasmosis reported in past were sometimes *Neospora;* reported in dogs and rarely in cats, cattle, and horses	Similar to toxoplasmosis; ascending paralysis of limbs with extension of the pelvic limbs is frequent in young pups	Chronic progressive; fair to poor prognosis	CSF, biopsy, isolation of organism, serology	Sulfonamides, pyrimethamine, clindamycin are probably effective if given early
Babesiosis	*Babesia* spp.	Rare in United States	Parasite of red blood cells; rarely causes CNS disease, hemorrhage; more severe with other infections, such as *Ehrlichia*	Acute to chronic; poor prognosis	Peripheral blood smears, serology	Diminazene, phenamidine, or imidocarb
Encephalitozoonosis	*Encephalitozoon cuniculi*	Rare; primarily affects dogs <2 mo old	Acute encephalitis, ataxia, tremors, behavioral changes	Acute; poor prognosis	Serology, culture, histopathology	None
Trypanosomiasis	*Trypanosoma cruzi*	Rare in United States	Parasite of red blood cells; rarely causes CNS disease	Chronic, fair prognosis with treatment	Peripheral blood smears	Nifurtimox
Equine protozoal myeloencephalitis	*Sarcocystis neurona (Sarcocystis falcatula)*	Fairly common in horses	Systemic, multifocal, involving almost any part of the nervous system: commonly spinal cord, cauda equina, and cranial nerve signs	Chronic, progressive; guarded prognosis; treatment may be effective	CSF: Western blot, ELISA, IFA, and PCR	Pyrimethamine, trimethoprim-sulfonamide, diclazuril, ponazuril, nitazoxanide
Coccidiosis	Several species	Common enteric, rare CNS, several species of animals affected	Enteric coccidiosis is reported to cause CNS signs in some cases; *Sarcocystis* spp. may cause myopathy	Variable	Fecal identification, organism in muscle biopsy or necropsy	Sulfonamides, amprolium
Hepatozoonosis	*Hepatozoon canis*	Rare; dogs	Muscle pain and gait abnormalities may be seen	Chronic; guarded prognosis	Biopsy, PCR	Possibly sulfonamides, pyrimethamine (efficacy not known)

TABLE 15-13

Viral Diseases of the CNS

Disease	Cause	Incidence	Clinical Signs and Pathology	Course and Prognosis	Diagnostic Tests	Treatment	Prevention
Multiple Species							
Rabies	Rhabdovirus	Variable; all mammals Rare; more common in cats	Initially behavioral changes; rapid progression to either furious or dumb form; atypical variants are common in large animals (colic in horses and tenesmus in cattle) *Furious:* restlessness, wandering, biting, aggression, seizures *Dumb:* severe depression, pharyngeal and hypoglossal paralysis, progressive paralysis *Paralytic:* Ascending paralysis; progresses to include other brain signs	Acute, progresses to death in 3-10 days from onset	Necropsy: FA of brain	None	Vaccine
			Postvaccinal: Inadequate attenuated virus; rare; progressive ascending paralysis to diffuse CNS signs	Acute, progressive, poor prognosis	Necropsy: FA	None	Use proper vaccine
Pseudorabies	Herpesvirus	Rare; eradicated in domestic swine in United States	Swine: subclinical in adults; neonates: seizures, tremors, ataxia, death Other animals: excitement, intense pruritus and self-mutilation at site of viral entry; rapid progression to coma and death; contact with swine	Acute; progression to death in 1-2 days	Necropsy: FA on brain and spinal cord	None	Avoid contact with infected swine
Dogs							
Canine distemper	Morbillivirus	Common; dogs. Also large cats, raccoons, ferrets, marine mammals	*Acute:* young dogs; systemic illness; respiratory and gastrointestinal signs; CNS: acute seizures *Chronic:* Young or mature dogs. Demyelination of cerebellum, cerebral peduncles, optic nerves and tracts, and spinal cord. May begin with focal signs and progress to multifocal lesions. CNS signs occur weeks to months after systemic illness or without systemic signs. *Old dog encephalitis:* Mature or older dogs. Necrosis of cerebral gray matter. Forebrain signs predominate.	Acute to chronic; poor prognosis	CSF, FA on CSF, serology. Histopathology	Supportive; anticonvulsants	Vaccine
			Postvaccinal: see chronic distemper	1-2 wk postvaccination; acute and progressive	See distemper		None

Continued

TABLE 15-13

Viral Diseases of the CNS—cont'd

Prevention	Cause	Incidence	Clinical Signs and Pathology	Course and Prognosis	Diagnostic Tests	Treatment	Prevention
Infectious canine hepatitis	Canine adenovirus type I	Rare	Affects vascular endothelium, which may cause CNS signs; primarily affects liver, kidney, and lung. Can cause hepatoencephalopathy	Acute to chronic	Clinical pathology profile (liver)	Supportive	Vaccine
Canine herpesvirus	Canine herpesvirus	Sporadic; neonates and young puppies	In utero or early postwhelping exposure; polysystemic signs: depression, diarrhea, rhinitis, coma, opisthotonus, seizures	Acute progressive to death	Virus isolation; histopathology	Supportive	Colostrum; hyperimmune serum
Cats							
Feline infectious peritonitis	Coronavirus	Relatively common in cats	*Effusive form (wet):* diffuse, fibrinous peritonitis *Noneffusive (dry) form:* disseminated pyogranulomatous lesions in viscera, CNS, and eye. CNS signs can be focal or disseminated. Meningeal involvement and secondary hydrocephalus are common.	Slowly progressive; eventually fatal	Neutrophilic leukocytosis; increased serum globulins; CSF; mixed pleocytosis and increased protein	Supportive	Vaccine; marginally effective. Isolate infected cats
Feline panleukopenia	Parvovirus	Sporadic; neonatal cats	In utero or early postnatal CNS infection causing cerebellar hypoplasia (see Chapter 8)	Present at birth; nonprogressive	Necropsy	None	Vaccine
Feline leukemia virus (FLV)	Retrovirus	Common; cats	Epidural lymphoma causes spinal cord signs; diffuse brain disease may be present; systemic involvement and immunosuppression are common	Chronic progressive	Imaging, CSF, ELISA, FA, PCR	Combination chemotherapy	Vaccine
Feline immunodeficiency virus (FIV)	Lentivirus	Rare for neurologic signs	Behavioral signs	Chronic	ELISA, histopathology	None	Vaccine
Feline paramyxovirus	Paramyxovirus	Rare	Similar to canine distemper; demyelination; myoclonus reported	Chronic progressive	Virus isolation	None	None
Horses							
Encephalomyelitis (Western, Eastern, Venezuelan)	Togavirus (alphaviruses)	Variable; sporadic outbreaks in United States	Depression, fever, anorexia, ataxia, pacing, and circling; cranial nerve involvement in some cases	Acute progressive; guarded prognosis	CSF; serology; virus isolation; histopathology	Supportive	Vaccine mosquito control

West Nile virus	Togavirus (flavivirus)	Variable outbreaks; horses, birds and humans; sometimes other species including dogs and cats	Fever, paresis, ataxia, and muscle fasciculations. Lesions most severe in spinal cord; usually asymmetric and multifocal. Abnormal mentation and cranial nerve abnormalities occur in 44% to 67% of affected horses.	Acute progressive; guarded prognosis	CSF; plaque reduction neutralization tests (PRNTs); IgM capture ELISA test	Supportive	Vaccine
Equine herpesvirus	Equine herpesvirus 1 (EHV 1)	Variable	Upper respiratory infection, abortion, ataxia, urinary incontinence, paresis, signs more severe in pelvic limbs, sometimes cranial nerve signs	Acute progressive; fair to good prognosis	CSF, serology	Supportive Acyclovir	Vaccine ± isolation
Equine infectious anemia (EIA)	Retrovirus	Rare CNS signs	Behavioral changes, blindness, ataxia, weakness	Chronic progressive	Coggin test	Supportive	None
Cattle							
Infectious bovine rhinotracheitis (IBR) 1 and 5	Bovine herpesvirus types 1 and 5	Rare form of IBR	Calves <6 wk of age most susceptible. Fever, depression, respiratory signs, salivation, ataxia, circling, nystagmus, blindness, coma	Acute progressive; fatal	CSF; virus isolation; FA; immunoperoxidase; histopathology	Supportive	Vaccine
Malignant catarrhal fever	Herpesvirus	Sporadic	Adult cattle: depression, blindness, pacing, seizures, death; nasal and ocular discharge	Acute progressive to death	Histopathology	Supportive	None
Swine							
Enteroviral encephalomyelitis	Enterovirus	Variable	Pelvic limb paresis and ataxia, paralysis, seizures	Acute progressive; recovery or death in 1-3 wk	Virus isolation, serology	Supportive	Vaccine
Hemagglutinating encephalomyelitis virus	Coronavirus	Sporadic	Young swine: depression, ataxia, seizures, hyperesthesia	CNS form is acute	Serology; virus isolation	None	None
Porcine paramyxovirus	Paramyxovirus	Rare	Nursing piglets: depression, ataxia, seizures, weakness, tremor, blindness, and panophthalmitis	Acute progressive; fatal	Viral isolation; histopathology	None	None

Continued

TABLE 15-13

Viral Diseases of the CNS—cont'd

Prevention	Cause	Incidence	Clinical Signs and Pathology	Course and Prognosis	Diagnostic Tests	Treatment	Prevention
Sheep and Goats							
Visna, maedi	Lentivirus	Variable; sheep >2 yr old; horizontal transmission	Visna: ataxia, pelvic limb paresis; progressive to tetraparesis; facial tremors, blindness Maedi: progressive pneumonia	Chronic progressive; fatal in 1-2 yr	CSF, virus isolation, serology, histopathology	None	Culling carriers, chronically infected sheep
Louping ill (ovine encephalomyelitis)	Togavirus	Ireland; tick vector (Ixodes). Young sheep; sometimes horses, wildlife and other ruminants	Ataxia of head, trunk, and limbs. Rabbit hopping gait, blindness, seizures	Acute progressive; 50% fatal	Serology, virus isolation, presence of ticks	Supportive	Vaccine
Caprine arthritis-encephalitis virus (CAE virus)	Retrovirus (lentivirus)	Kids 2-6 mo old (virus shed in colostrum)	Persistent asymptomatic infection in adults. Progressive ataxia and paresis worse in pelvic limbs, tremors, opisthotonus. Evidence of arthritis, pneumonia, and mastitis (hard bag) in herd.	Acute to chronic progressive; fatal in kids	Agar gel immunodiffusion (AGID) blood	None	Culling chronically infected adults; heat treat colostrum
Border disease (hairy shaker lamb)	Pestivirus (similar to BVD of cattle)	Lambs (transmission is vertical and horizontal). Can affect goats and cattle	In utero infection before 50 days of gestation. Hairy wool, tremors of head and neck, ataxia. Flock history of abortion, infertility, deformed lambs. Goats: abortion and muffied fetus. Cattle: early abortion	Chronic; persistent infections	PCR, serology	None	Remove persistently infected animals

TABLE 15-14

Rickettsial and Chlamydial Diseases of the CNS

Disease	Cause	Incidence	Clinical Signs and Pathology	Course and Prognosis	Diagnostic Tests	Treatment
Rocky Mountain spotted fever	*Rickettsia rickettsii*	Fairly common in endemic areas of United States; dogs	Meningitis, ataxia, other CNS signs, can look like canine distemper	Acute; good prognosis with treatment	History of ticks, signs; thrombocytopenia, serology	Doxycycline, chloramphenicol
Ehrlichiosis	*Ehrlichia canis*	Rarely CNS signs in dogs	Meningitis, encephalitis	Acute to chronic; good prognosis if treated early	Pancytopenia, thrombocytopenia, serology	Doxycycline, chloramphenicol
Salmon poisoning	*Neorickettsia helminthoeca*	Rare, Pacific Northwest United States	Depression and convulsions terminally; paresis of pelvic limbs less common; nonsuppurative meningoencephalitis	Acute; fair to good prognosis if treated early	History of eating salmon, fluke eggs in feces	Doxycycline, chloramphenicol
Sporadic bovine encephalomyelitis (Buss disease)	*Chlamydia psittaci*	Sporadic, young cattle	Respiratory disease, polyarthritis, diffuse cerebral signs	Acute progressive; mortality approximately 50%	History, signs, CSF (increased protein, increased mononuclear cells), serology	Tetracycline, tylosin
Neuroborreliosis (Lyme disease)	*Borrelia burgdorferi*	Rare, except in endemic areas	Depression, meningitis	Acute to chronic (poorly characterized)	Antibodies to *B. burgdorferi* (especially in CSF)	Third-generation cephalosporins, tetracyclines

TABLE 15-15

Parasitic Diseases of the CNS

Disease	Cause	Incidence	Clinical Signs and Pathology	Course and Prognosis	Diagnostic Tests	Treatment
Dirofilariasis	*Dirofilaria immitis,* microfilaria or aberrant adult	Rare, areas with heartworm disease	CNS signs rare; microfilaria or migrating adult heartworms may cause infarction; seizures and other cerebral signs	Acute onset; prognosis guarded	Blood smear or serology to confirm heartworm disease, CSF (increased eosinophils suggestive), difficult to prove antemortem	None proven
Larva migrans	*Toxocara canis* and other species	Rare	Granulomas in brain or spinal cord from migrating larvae; signs related to location of lesion	Acute or chronic; prognosis depends on severity of signs	None, necropsy	None
Cuterebrosis	*Cuterebra* spp.	Rare	CNS signs depend on location of lesion	Acute to chronic; guarded prognosis	None, necropsy	None
Coenurosis	*Coenurus* spp.	Rare; most often reported in sheep	CNS signs depend on location of lesion	Acute to chronic; poor prognosis	None, sheep have softening of skull that can be palpated or seen on radiographs	Surgical removal in sheep

TABLE 15-16

Immune-Mediated Diseases of the CNS

Disease	Cause	Incidence	Clinical Signs and Pathology	Course and Prognosis	Diagnostic Tests	Treatment
Coonhound paralysis	Probable immune reaction to transmissible agent in raccoon saliva or environment	Fairly high in some areas; dogs	Ascending LMN paralysis; may last approximately 6 wk; ventral roots and peripheral nerves have segmental demyelination and some axon loss	Acute onset, lasts approximately 6 wk; good prognosis with good nursing	History, EMG, nerve conduction studies	Supportive
Postvaccinal rabies	CNS tissues in vaccine	Rare—these vaccines are no longer used	Ascending paralysis; demyelination from immune reaction to myelin in brain-origin vaccines	Acute onset, progressive; poor prognosis	None	None

Therefore, positive findings in laboratory data are useful, but negative findings do not rule out infectious disease. Focal deficits should be investigated according to the location of the lesion (see Chapters 5 through 15).

Analysis of CSF is a useful test for establishing the diagnosis of inflammatory disease (see Chapter 4). Increases in CSF protein concentrations range from low (50 to 100 mg/dL) in chronic viral diseases to very high (>300 mg/dL) in bacterial and fungal infections. Characteristic cell changes are increased mononuclear cells in viral diseases; increased neutrophils in bacterial diseases; increased numbers of both mononuclear cells and neutrophils in mycotic and protozoal diseases and feline infectious peritonitis; and increased numbers of mononuclear cells, neutrophils, and some eosinophils in parasitic, fungal, and immune-mediated diseases. *Exceptions are common*. For example, chronic bacterial infections may cause a

TABLE 15-17

Unclassified (noninfectious) Inflammatory Diseases of the CNS in Dogs and Cats

Disease	Cause	Incidence	Clinical Signs and Pathology	Course and Prognosis	Diagnostic Tests	Treatment
Steroid-responsive Meningitis-Arteritis (SRMA)	Unknown	Uncommon. Dogs less than 2 yr of age. Large-breed dogs: boxers, Bernese mountain dogs	Severe cervical hyperesthesia from inflammation of meninges and arteries. Sometimes associated with immune-mediated polyarthritis.	Acute and progressive; fair to good prognosis	CSF: neutrophilic pleocytosis and increased protein; increase IgA in serum and CSF	Immunosuppressive doses of prednisone
Necrotizing vasculitis	Unknown	Likely a severe form of SRMA. Seen in young beagles, Bernese mountain dogs and German short-haired pointers	Severe necrotizing vasculitis of the meninges, especially in cervical region. Signs similar to SRMA but more likely to have paresis. Spinal cord infarction reported in Bernese mountain dogs	Acute progressive; guarded prognosis	CSF: see SRMA	See SRMA
Pyogranulomatosis meningoencephalomyelitis	Unknown	Rare; reported in pointers	Mixed mononuclear-neutrophil infiltration of meninges and parenchyma of brain and spinal cord. Severe cervical pain, atrophy of cervical muscles, mild ataxia	Acute progressive; guarded to poor prognosis	CSF: neutrophilic pleocytosis; histopathology	See SRMA; some dogs respond to antibiotics
Granulomatous meningoencephalomyelitis (GME)	Unknown; probably type IV hypersensitivity	Relatively common in small-breed dogs	Granulomatous infiltrates in meninges, perivascular spaces, and brain parenchyma. Lesions may be disseminated, focal, or multifocal. Signs depend on lesion distribution. Cervical pain is common.	Chronic progressive; guarded prognosis, relapses are common	CSF: presence of macrophages is useful; histopathology, MRI	Prednisone, cytosine arabinoside, cyclosporine, other immunosuppressants
Necrotizing meningoencephalitis (NME); necrotizing leukoencephalitis (NLE)	Unknown; possibly immune mediated	Rare disease reported in young pugs, Maltese, Pekingese, Chihuahua, Yorkshire terrier, shih-tzu, French bulldog; West Highland white terrier, Boston terrier, Japanese Chin, miniature pinscher	Lymphoplasmacytic perivascular infiltrates in cerebrum and meninges. Multifocal necrosis in cerebrum. Seizures and other forebrain signs. Brainstem signs occur more with NLE.	Chronic progressive; poor prognosis	CSF (lymphocytic pleocytosis, increased protein); MRI	See GME; responds poorly to immunosuppressants
Feline polioencephalomyelitis	Unknown	Rare	Pelvic limb paresis, tremors, hyperesthesia. Spinal cord neurons and white matter primarily affected; brain lesions are scattered	Chronic progressive; poor prognosis	Histopathology; some cats have leukopenia and nonregenerative anemia	None

mononuclear cell response, especially increases in macrophages, whereas some viral diseases cause increased neutrophils in the CSF. The presence of a few neutrophils in the CSF is not necessarily abnormal. The only cell whose presence in the CSF seems consistently abnormal is the macrophage. The CSF can be normal in CNS inflammation.

Clinical suspicion of an infection is an adequate indication for bacterial and fungal cultures and bacterial sensitivity tests. The presence of antibodies in the CSF to specific viruses or to other infectious agents provides evidence of infection because they are not present in normal, vaccinated animals or those with systemic infection but without CNS disease (also see Chapter 4).[92] In CSF samples contaminated by blood (hemorrhage), serum albumin and antibody concentrations should be compared with concentrations in the CSF. When the level of CSF antibodies exceeds that of serum, CNS infection is more likely. Inflammation may increase the permeability of the blood-brain barrier, allowing serum antibodies to leak into the CSF.

Principles of Medical Treatment

Medical treatment is most commonly indicated for infections involving the nervous system. Physical therapy also is necessary for rehabilitation (see Chapter 14). Seizures (see Chapter 13) and other diseases requiring specific treatment are covered in the descriptions of the diseases. The management of CNS edema resulting in increased intracranial pressure is discussed in Chapter 12 in the section on brain trauma. Management of pain is reviewed in Chapter 14.

Effective therapy for CNS infections depends on the identification of the cause and selection of the appropriate antimicrobial agent. Identification is based on CSF analysis in which the organism may be observed (albeit rarely), culture and when available, polymerase chain reaction (PCR) testing, and measurement of antibody or antigen titers. Selection of the appropriate antimicrobial agent depends on two principles: (1) the agent must be effective against the microbial target without severely injuring the patient; and (2) it must be delivered to, and must penetrate, the CNS. Unfortunately, anatomic and physiologic barriers to successful therapy for CNS infections exist, especially when certain drugs are used. The combined effects of these obstacles create a functional blood-brain barrier.

The combined functions of the CNS capillaries and the choroid plexus create a barrier to the movement of drugs from the capillary or pericapillary fluid into nervous tissue or CSF. Discrepancies between serum and CNS drug concentrations occur because of two factors: those promoting drug accumulation in the CNS (the secretory selectivity of the choroid plexus) balanced against those preventing drug accumulation (the special anatomy of CNS capillaries and drug efflux pumps such as P-glycoprotein). In capillaries outside the CNS, drugs and other agents pass from the blood through clefts between endothelial cells and through fenestrations in the capillary basement membrane. In the CNS, capillary endothelial cells are joined by tight junctions that seal the intercellular clefts. The capillary basement membrane has no fenestrations and glial cell foot processes surround the capillaries helping create a barrier to diffusion.

In the CNS, a drug must penetrate an inner bimolecular lipid membrane, the endothelial cell cytoplasm, an outer lipid membrane, and a basement membrane and then traverse the glial foot processes.[122] Penetration of a drug is largely a function of its endothelial membrane solubility. Membrane solubility is favored by (1) a low degree of ionization at physiologic pH, (2) a low degree of plasma protein binding, and (3) a high degree of lipid solubility of the unionized drug.[123,124] Certain highly lipid-soluble drugs bind strongly to tissue sites in the brain, permitting high concentrations to be achieved within nervous tissue.

Regulation of CSF solutes occurs at the choroid plexus. Plasma dialysate that filters through fenestrated capillaries is selectively secreted by choroid epithelial cells. Certain CSF constituents also are actively reabsorbed by the choroidal epithelial cell, which tends to clear these substances from the CSF and from nervous tissue. This active transport system for weak organic acids removes drugs such as penicillin and gentamicin. Inflammation may block this system, allowing drug concentrations in the nervous tissue to increase. In addition, inflammation may increase the permeability of endothelial membranes to certain antibiotics, allowing these drugs to penetrate nervous tissue in cases of disease. In the normal animal, these antibiotics penetrate poorly. As the inflammation decreases, penetration of the antibiotic also decreases.

Antimicrobial Agents in Treating Infections

Antimicrobiocidal agents are grouped by their capacity to achieve concentrations in CSF sufficient to inhibit microorganisms throughout the period of therapy.[124] Table 15-18 lists these drugs relative to achievable concentrations in CSF.

Microbicidal drugs are preferred to microbiostatic drugs whenever possible. Antibiotics such as the aminoglycosides diffuse poorly, even in the presence of inflammation. Intrathecal administration may be required for adequate CSF concentrations to be achieved, but this route is rarely used in animals because of the necessity for anesthesia with each injection. Placement of intraventricular catheters can facilitate the injection of drugs into the CSF.

Infectious Inflammatory Disease

Bacterial Infections (See Table 15-10)

Bacterial Meningoencephalomyelitis. The pathogenesis, pathophysiology, and implications of treatment of bacterial meningitis in humans and experimental animals have been reviewed.[100] Bacteria must be able to survive in the intravascular space, penetrate the blood-brain barrier, and colonize in the meninges or CSF. Breakdown of the blood-brain barrier causes exudation of albumin into the CSF and facilitates the development of brain or spinal cord edema. Experiments in rats suggest that bacteria in the CSF elicit the release of endogenous inflammatory mediators that are important in the development and progression of clinical signs.[125] Experimental studies in rabbits reveal that the inflammatory process causes brain edema, probably secondary to loss of cerebrovascular autoregulation, direct cytotoxicity, and increased CSF outflow resistance.[101]

These findings may have important therapeutic implications. Rapidly acting bactericidal therapy delivered into the CSF is mandatory because only bactericidal therapy is associated with a cure in humans and experimental animal models. Rapid destruction of bacteria could release high concentrations of inflammatory bacterial toxins (lipopolysaccharides), which might exacerbate the inflammatory process.[126-128]

These studies also suggest that adjunctive therapy with antiinflammatory agents may be beneficial in bacterial meningitis.[101] In animals with experimental *Streptococcus pneumoniae* meningitis, methylprednisolone reduced CSF outflow resistance and both methylprednisolone and dexamethasone reduced brain edema.[101] Pretreatment with dexamethasone followed in 15 to 20 minutes with third-generation cephalosporins resulted in decreased inflammatory mediator release in laboratory animals with *Haemophilus influenzae* CNS infections.[127] Several controlled studies in children with bacterial meningitis demonstrated the benefits of adjunctive corticosteroid therapy, especially when corticosteroids were administered 15 to 20 minutes before bactericidal antibiotic therapy.[128] In these studies, dexamethasone was given

TABLE 15-18

*Antimicrobial Drugs: Ability to Penetrate the Blood-Brain Barrier**

	Good	Intermediate	Poor
Microbicidal	Trimethoprim	Penicillin G†	Penicillin G Benzathine
	Moxalactam	Ampicillin†	
	Cefotaxime	Methicillin†	Cephalosporins§
	Ceftazidime	Nafcillin†	Aminoglycosides
	Metronidazole	Carbenicillin†	
	Enrofloxacin	Oxacillin	
	Vancomycin		
Microbistatic	Chloramphenicol	Tetracycline	Amphotericin B
	Sulfonamides	Flucytosine	Erythromycin ‖
	Isoniazid	Clindamycin	
	Minocycline‡		
	Doxycycline‡		
	Rifampin		

*Drugs prohibited for use in all food-producing animals: Chloramphenicol, clenbuterol, diethylstibestrol (DES), dimetridazole, ipronidazole and other nitroimidazoles, furazolidone, nitrofurazone, and other nitrofuans, sulfonamide drugs in lactating dairy cattle (except approved use of sulfadimethoxine, sulfabromomethazine, sulfaethoxypyridazine), fluoroquinolones, glycopeptides (http://www.fda.gov).
†High intravenous doses are needed to achieve the maximal effect.
‡Lipid-soluble tetracyclines that achieve higher concentrations in CSF than do other tetracyclines.
§First and second generation, may be effective early in bacterial meningitis; concentrations dramatically decrease with repair of the blood-brain barrier.
‖ Penetration in the face of inflammation is unpredictable.

15 to 20 minutes before cefotaxime therapy and was continued every 6 hours for 4 days.

Other antiinflammatory agents that might be useful include indomethacin, pentoxifylline, and superoxide dismutase. Specific monoclonal antibodies have shown promise in experimental models of bacterial meningitis, especially when dexamethasone is also administered.[129]

Although these studies may have therapeutic implications for bacterial meningitis in domestic animals, controlled studies regarding these species have not been published. Furthermore, these studies involve specific neurotrophic bacteria in humans that may behave differently than the agents producing meningitis in animals. Ultimately, the use of corticosteroids in animals with confirmed or suspected CNS infection should be done judiciously and with caution. Despite the obvious counterintuitive rationale for their use, corticosteroids may be beneficial to reduce edema and alleviate clinical signs. When used, the dosage of corticosteroids should be tailored to the least amount necessary to control clinical signs. When possible, rapid tapering of the dosage should be prescribed based on continued response to therapy in an effort to restrict the administration of corticosteroids to short-term usage.

Bacterial Meningoencephalomyelitis in Dogs and Cats. Bacterial meningoencephalomyelitis is not common in dogs and cats. It usually occurs in association with bacteremia secondary to endocarditis, urinary tract infections, and pulmonary infections. Critically ill patients may have added risk of CNS infection. Meningitis may also occur from extension of infection in structures adjacent to the nervous system, such as the nasal passages, sinuses, and internal ears as well as direct penetration into the CNS such as occurs with bite wounds. Aerobic bacteria associated with bacterial meningitis in dogs and cats include *Pasteurella multocida, Staphylococcus Pseudintermedius, Streptococcus* spp., *and Escherichia coli*.[124,130,131] Uncommonly, *Proteus, Pseudomonas, Salmonella*, and *Klebsiella* organisms may be the causative agents. These gram-negative organisms are more common in nosocomial infections of critically ill patients. *Bartonella* sp. may also cause CNS disease in dogs.[132] Anaerobic bacteria isolated from dogs and cats with CNS infection include *Bacteroides, Fusobacterium*, *Peptostreptococcus,* and *Eubacterium*.[133]

Definitive treatment of bacterial meningitis is based on isolation of the organism from the CSF and determination of its antibiotic sensitivity. Other diagnostic tests include serology and PCR testing. The identification and elimination of the source of infection are imperative to successful treatment. Blood and urine cultures may be useful to identify the causative agent. Pending the outcome of CSF cultures, the initial antibiotic therapy in small animals is based on clinical findings of concomitant infection and the most likely causative agent present. Broad-spectrum bacteriocidal antibiotics that penetrate the CSF are chosen.

Trimethoprim-sulfonamide combinations and enrofloxacin are good initial choices. Both are available to veterinarians, penetrate the CSF in good concentrations, cover a broad spectrum of bacterial agents, and are not expensive compared with third-generation cephalosporins. Enrofloxacin has greater activity against gram-negative bacteria and very little activity against anaerobes.[134] Clindamycin hydrochloride may be used concurrently to provide anaerobic and gram-positive coverage. For animals unable to receive oral medications, parenteral formulations of enrofloxacin and clindamycin hydrochloride are available. The dose for enrofloxacin in dogs is 2.5-5.0 mg/kg PO, IM, SC, IV every 12 hours. Enrofloxacin should be used with care in dogs 2 to 12 months of age to avoid cartilage damage. The dose of enrofloxacin in cats is 5 mg/kg once a day PO or 2.5 mg/kg IM every 12 hours. Rare incidence of retinal toxicity in cats have been reported at doses >15 mg.kg/day. The dose for clindamycin in dogs and cats is 3-11 mg/kg PO, IV, IM SC every 8 hours. Gastroenteritis is the most common side effect of clindamycin therapy in dogs and cats. The initial dose for trimethoprim-sulfonamides is 30 mg/kg every 12 hours for 5 to 7 days and then 15 mg/kg every 12 hours for 10 to 14 days.

Third-generation cephalosporins such as cefotaxime and ceftazidime penetrate the CSF in good concentrations and are effective against many resistant gram-negative bacteria.[135] They are usually effective against anaerobes but have reduced activity against gram-positive cocci. Ceftiofur, approved for use in animals, does not cross the blood-brain barrier unless inflammation is present, and, in this regard, is similar to the aminopenicillins. When gram-negative sepsis is suspected as the cause of the meningitis, the third-generation cephalosporins are the drugs of choice.

Meningitis caused by gram-positive bacteria may respond to high doses of aminopenicillins.[131] Many isolates of *S. Pseudintermedius* and *S. aureus* secrete beta lactamase, which inactivates most aminopenicillins. Aminopenicillins combined with clavulanic acid and lactamase-resistant penicillins such as methicillin or oxacillin are better choices for staphylococcal infections. Rifampin is bactericidal, readily penetrates the CSF, and has very good activity against staphylococci.[136] It is also effective against many gram-negative bacteria. Bacterial resistance to rifampin develops readily, especially when it is given as a single agent. For staphylococcal infections, rifampin is best combined with β-lactam antibiotics. The human dose of 10 mg/kg daily produces a concentration in canine serum four times that required in people to inhibit bacteria but also causes adverse side effects in dogs. A dose less than 10 mg/kg daily is recommended, but definitive pharmacologic studies have not been published.[136] Rifampin also may be useful in treating chronic abscesses and pyogranulomatous infections. Imipenem is a β-lactam compound that belongs to the carbapenem family of antibiotics. It has broad-spectrum activity against most gram-positive and gram-negative aerobes and anaerobes. Imipenem is useful in the treatment of nosocomial gram-negative infections that do not respond to other antibiotic regimens.[135,137] After intravenous administration, imipenem penetrates the CSF in good concentrations.

Occasionally, systemic infection with *Brucella canis* extends to the nervous system. While most animals are euthanized due to zoonotic issues, brucellosis can be treated with combination of streptomycin and minocycline. Streptomycin should be administered for 2 weeks by parenteral injection. Minocycline should be given orally for 4 weeks in combination with the 2-week course for streptomycin.[138,139] It is difficult to eradicate brucella infections in animals.

Bacterial Meningoencephalomyelitis in Horses. Bacterial meningitis occurs most commonly in septicemic foals that do not acquire passive transfer of immunity.[140-142] Common primary sites of infection include the GI tract, lung, and umbilicus. Pneumonia, peritonitis, hypopyon, septic arthritis, and omphalophlebitis are common. Extension to the brain and spinal cord frequently occurs if treatment is not aggressive.

The diagnosis of meningitis in foals is confirmed by cytologic evaluation and bacterial culture of the CSF. A neutrophilic pleocytosis is typical, and cell counts may exceed 1000 cells/uL (normal <5 cells/uL).[142,143] The total CSF protein level is usually more than 100 mg/dL. *E. coli* and *Klebsiella* spp. are the most frequently isolated organisms.[142,143]

Although definitive antibiotic therapy is based on bacterial culture and antimicrobial sensitivity testing, initial empiric therapy is based on the assumption that gram-negative enteric bacteria are the most likely cause. Third-generation cephalosporins are the antimicrobials recommended in foals. These include cefotaxime sodium (40 mg/kg IV q8h) and ceftazidime (50 mg/kg IV q12h). Ceftiofur (2 to 4 mg/kg IV q12h) is available to veterinarians but does not penetrate the CSF in normal horses. Although very expensive, these antibiotics can rapidly sterilize the CSF and may shorten the total treatment time and thus reduce overall costs of therapy.[140] Trimethoprim-sulfonamide combinations may be effective but are less so than the third-generation cephalosporins previously described.

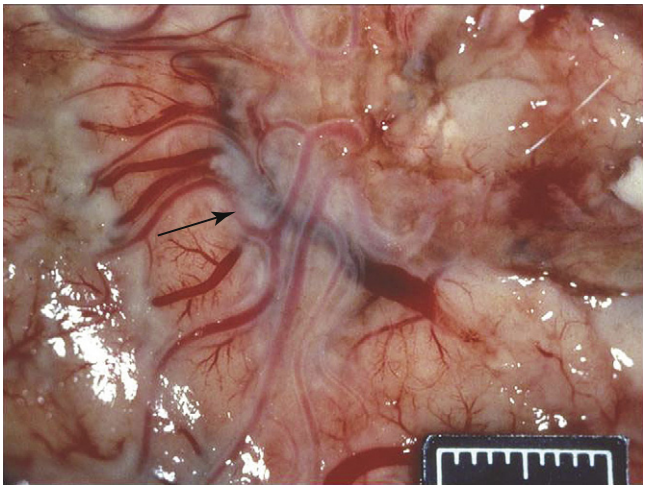


Figure 15-8 Suppurative meningitis in a calf. Note the cloudy and thickened meninges that tend to obscure engorged (inflamed) blood vessels *(arrow)*. (Courtesy Dr. Roger Panciera, Oklahoma State University College of Veterinary Medicine.)

Adjunctive antiinflammatory therapy and other supportive care are used in foals with progressive neurologic dysfunction. Corticosteroids (dexamethasone, 0.15 mg/kg q6h IV) are used with caution in septic foals because corticosteroid therapy can cause rapid bacterial dissemination.[140] Dimethyl sulfoxide (1 g/kg IV q24h) may help to reduce CNS inflammation and edema and protect against reperfusion injury when cerebral ischemia is present. Mannitol (0.25 to 1.0 g/kg IV q24h) helps reduce CNS edema. Plasma transfusions (1 to 2 L IV) and enteral hyperalimentation may be indicated. Diazepam (0.2 to 0.5 mg/kg every 15 minutes) or phenobarbital (10 to 20 mg/kg IV q8h) or both can be given to control seizures.[115]

Bacterial Meningoencephalomyelitis in Cattle. Bacterial meningitis is the most common CNS disease in neonatal calves.[119] It develops secondary to septicemia and bacteremia associated with failure of passive transfer of colostral antibodies. A presumptive diagnosis of bacterial meningitis with failure of passive transfer is based on presence of omphalophlebitis or septic arthritis, fever and signs suggestive for meningoencephalomyelitis (obtundation, tetraparesis, hyperesthesia, and multiple cranial nerve deficits) (Figure 15-8).

Neutrophilic pleocytosis and increased protein are present in the CSF of 60% to 70% of affected calves. Mononuclear pleocytosis may be present in chronic disease. The identification of bacteria in the CSF is less than 50% of cases examined. *E. coli* is the organism most frequently responsible in clinical cases.[119] Isolates may be resistant to trimethoprim-sulfonamides, and many, if not most, are now resistant to triple sulfonamide drugs. Other bacterial agents include *Salmonella* sp. and *Arcanobacterium pyogenes*. Most affected calves die or are euthanized, usually within 2 to 3 days after diagnosis and initiation of therapy.

Treatment of bacterial meningitis in calves is difficult and the mortality rate is high.[144] Selection of antimicrobial drugs is based on culture and sensitivity of bacteria from the CSF; however, their use is often empirical. The antimicrobial regimen should be broad spectrum against gram-negative and gram-positive bacteria. Although trimethoprim-sulfonamides and triple sulfonamide drugs are frequently chosen to treat bacterial meningitis in calves, studies indicate an emerging resistance of gram-negative bacteria to these drugs. Ampicillin

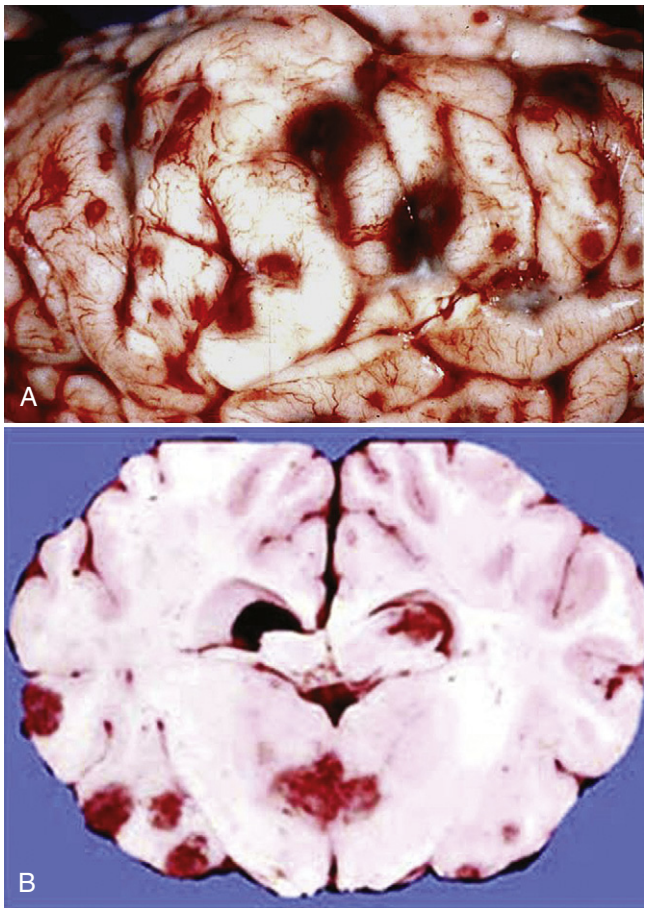


Figure 15-9 **A,** Extensive hemorrhages in the cerebral cortex are typical gross lesions of thromboembolic meningoencephalomyelitis. **B,** Note the multiple hemorrhagic lesions seen in cross section of the brain in **A.** (**A** and **B,** Courtesy Dr. Roger Panciera, Oklahoma State University College of Veterinary Medicine.)

(10 to 20 mg/kg IV q8h) has been used in combination with other antimicrobials. Although expensive, the third-generation cephalosporins (such as ceftiofur, 5 to 10 mg/kg IV or IM q12h) are rational empiric drugs for treatment. Because of their cost, the use of these drugs may not be economically feasible in many cases. Adequate amounts of colostrum and early recognition and treatment of bacterial infections is essential for prevention of bacterial meningitis in calves.

Thromboembolic Meningoencephalitis (TEME). *Histophilus somni* (formerly *Haemophilus somnus*) is the major cause of TEME in cattle.[145] Exposure to this organism is widespread, and up to 25% of cattle may harbor serum antibodies to the organism. *H. somni* persists in the urinary and reproductive tracts of cattle and is shed in urine and reproductive secretions. The disease is most common in weaned calves, and outbreaks of TEME occur 1 to 2 weeks after cattle arrive at the feedyard.[146] Bronchopneumonia is the most common form of hemophilosis, but arthritis, myelitis, retinitis, myocarditis, laryngitis, otitis media or otitis interna, and conjunctivitis also occur. TEME usually follows the occurrence of pneumonia by 1 to 2 weeks. Morbidity is low, and mortality is high. Diagnosis is based on history and physical examination. Changes in CSF reflect a bacterial infection that often is hemorrhagic. Necropsy findings provide a definitive diagnosis with presence of hemorrhagic infarcts in the brain and spinal cord. Histology reveals vasculitis, thrombosis, and neutrophilic infiltrates (Figure 15-9).

As with the neurotrophic bacteria that infect people, *H. somni* possesses several virulent factors (mucopolysaccharide capsule, outer membrane proteins, and endotoxin concentrated in the cell wall) that enhance its penetration into, and subsequent injury to, the CNS. *H. somni* colonizes the small vessels of the meninges, brain, and spinal cord. Fibrin thrombi and brain infarction cause the neurologic signs. The most effective antibiotics for TEME include the aminopenicillins, ceftiofur, oxytetracycline, and florfenicol. All are approved for use in food animals and penetrate the CSF when active inflammation is present. Parenteral oxytetracycline is used for non-CNS infections. Treatment of animals that progress to recumbency is often not effective. When a case is suspected, the other animals in contact should be closely monitored to detect and treat at the early disease stage.

Listeriosis (Circling Disease). *Listeria monocytogenes* is a resistant and ubiquitous bacterium that causes CNS disease in people and domestic animals (listeriosis, circling disease, silage disease).[147] Ruminants appear more susceptible to infection than do other domestic animals. The organism can be transmitted in silage and other feed. Food-borne infection is common in humans. Outbreaks usually occur in the winter. In cattle and sheep, the organism penetrates the oral mucosa via wounds and is transmitted to the brain in a retrograde fashion via the trigeminal nerve. Signs related to infection of the rostral medulla (trigeminal, facial, and vestibulocochlear nerve dysfunction) are common. Although meningitis and encephalitis are the classic manifestations of listeriosis in ruminants, spinal cord disease, abortion, and mastitis also occur. Clinical signs of encephalitis are often more severe in small ruminants. The most useful antemortem diagnostic test is CSF analysis. Characteristic findings include increased protein concentration and nucleated cell count with mononuclear cells predominating. Definitive diagnosis is made by histopathology. Gross necropsy findings are not very remarkable. Histopathology reveals multifocal areas of necrosis with infiltrations of macrophages and neutrophils. Diagnosis is confirmed by isolation of the organism from body fluids or tissues. Warm or cold enrichment methods are used to isolate the organism but immunohistochemistry is more successful than bacteriologic culture for detecting *L. monocytogenes* in brain tissue. Treatment is initiated early and involves long-term parenteral antibiotic therapy (penicillin, ampicillin, amoxicillin, or oxytetracycline). Prevention is aimed a limiting fecal contamination of the feed from ruminants and wildlife.

Bacterial Brain Abscess. Brain abscesses are more common in large animals than in dogs and cats. Neurologic signs relate to the specific location of the abscess and compression or necrosis of surrounding neurologic structures. Large abscesses may create signs similar to any other intracranial mass. Increased intracranial pressure, cerebral edema, and brain herniation may occur (Figure 15-10).

The pituitary abscess syndrome has been described in cattle, goats, sheep, and swine (Figure 15-11).[148]

The anatomy of the rete mirabilis and its close association to the pituitary gland may explain the predilection for pituitary abscesses in cattle. The primary clinical signs include depression, ataxia, blindness, absence of the pupillary light reflex, dysphagia, dropped jaw, head pressing, bradycardia, nystagmus, and strabismus. The CSF may contain increased total protein concentrations and pleocytosis. Bacterial cultures of CSF are usually negative. *Arcanobacterium pyogenes* and *Pasteurella multocida* are most commonly isolated from abscesses at necropsy.[148] Infection at other sites with the same organisms occurs in about 50% of cases. The mortality rate is nearly 100%, and successful therapy is rare.

In horses, brain abscesses are usually caused by *Streptococcus equi*, but other streptococci are occasionally isolated.[149]

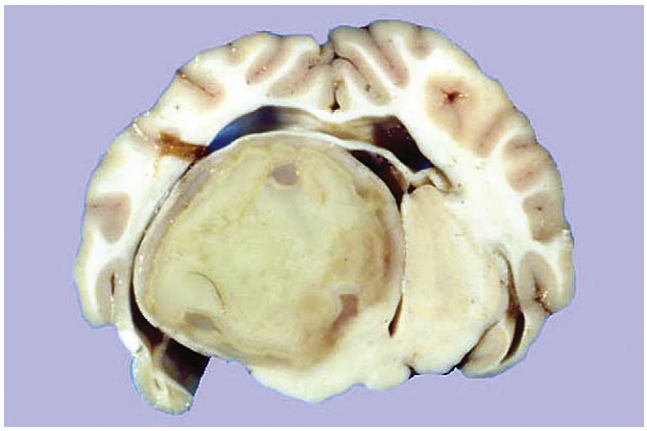


Figure 15-10 Large brain abscess in a sheep. (Courtesy Cornell University College of Veterinary Medicine.)

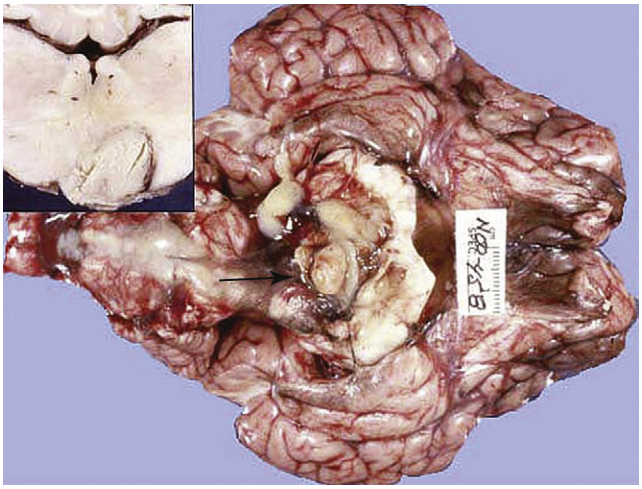


Figure 15-11 A large and destructive pituitary abscess in a cow *(black arrow)*. Inset figure shows abscess extending into the hypothalamus. (Courtesy Cornell University College of Veterinary Medicine.)

The prognosis is generally poor. If diagnosed by CT, successful surgical drainage is possible.[150] Brain abscesses are rare in dogs and cats but may result from extension of purulent otitis media/interna, rhinitis, sinusitis, open skull fractures, and foreign-body penetration of the brain. The causative agents are usually *Staphylococcus* spp., *Streptococcus* spp., and *Pasteurella* spp. Anaerobes may also be isolated in some cases. Localization of the abscess with CT or MRI may allow surgical drainage or excision. Methicillin, oxacillin, and rifampin may be useful for gram-positive infections. Clindamycin and metronidazole may be given in anaerobic infections. A guarded prognosis should be made.

Cats may have meningitis secondary to abscesses that are caused by anaerobic bacteria. Penicillin or amoxicillin is effective and reasonable in cost. Clindamycin or metronidazole is a good alternative for resistant infections.[151] If accessible, surgical drainage of intracranial infections should be considered.

Discospondylitis (also see Chapter 6)

The most common cause of bacterial discospondylitis in dogs is *Staphylococcus pseudintermedius*; occasionally *Brucella canis* organisms are the source.[152] The disease may be associated with urinary tract infection and bacteremia. In staphylococcal discospondylitis, penicillinase-resistant antibiotics should be chosen. Cephalosporin, methicillin, or oxacillin is usually effective. Antibiotic therapy should be continued for 4 to 6 weeks. If medical treatment is not successful, surgery is recommended to obtain a biopsy and culture. Animals with severe paresis may require decompression. In *B. canis* discospondylitis, therapy is expensive and may not eradicate the infection effectively. Streptomycin-minocycline combinations are used as described for meningitis.[114] Affected dogs should be neutered and isolated from other dogs.

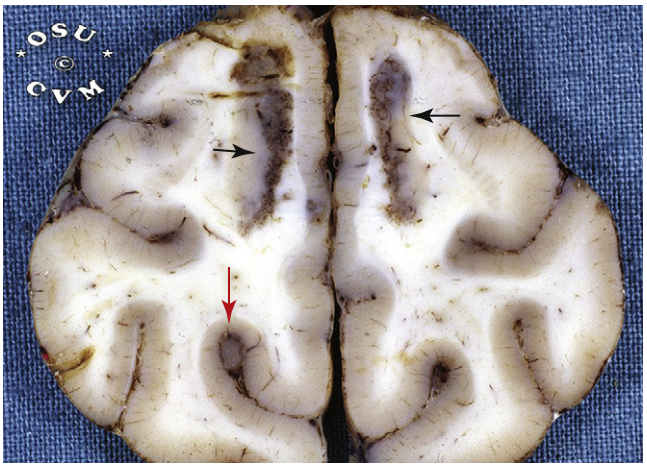


Figure 15-12 Multifocal cryptococcosis in a dog. Note the thickened meninges *(black arrows)* and extension of the infection into the brain surface *(red arrow)*.

Mycotic Infections (see Table 15-11)

The more common mycotic infections of the CNS are caused by *Cryptococcus neoformans*, *Blastomyces dermatitidis*, and *Coccidioides immitis*. They produce polysystemic disease, including granulomatous meningoencephalomyelitis or neuritis (Figure 15-12).

A definitive diagnosis is made by isolation or identification of the organism in the CSF or other body secretions. Treatment regimens are similar for the various deep mycotic agents, as discussed below.

Therapy

Cryptococcal Meningitis. For many years the mainstay of therapy for the deep mycotic pathogens has been amphotericin B. This drug is poorly absorbed from the GI tract and must be given IV for a full therapeutic effect. Amphotericin B diffuses poorly into the CSF. For this reason, although amphotericin B has value in fulminating systemic infections, agents such as itraconazole and fluconazole are preferred for cryptococcal meningitis. Several therapeutic regimens of amphotericin B have been described.

Flucytosine, when combined with amphotericin B, acts synergistically in vitro against *C. neoformans*. It achieves satisfactory concentrations in the CSF. The oral dose of flucytosine is 50 to 75 mg/kg every 8 hours.[153,154] The rate of relapse is considerably lower with the combined therapy. Side effects include leukopenia, thrombocytopenia, vomiting, and diarrhea.

Successful management of cryptococcal meningitis has been reported with the azole and triazole antifungal compounds.[130,131] At usual concentrations achieved in the plasma these compounds are considered fungistatic, but at higher concentrations they may be fungicidal.[155] The azoles and triazoles inhibit synthesis of ergosterol in the fungal cell membrane. Ketoconazole, itraconazole, and fluconazole have been studied in dogs and cats. All are well absorbed from the GI tract. Absorption of itraconazole is enhanced by food in the intestinal tract.

Ketoconazole does not penetrate the CSF in adequate concentrations to be effective, and yet reports exist of success with this agent in the treatment of cryptococcal meningitis, especially when combined with flucytosine.[157] Ketoconazole therapy is associated with hepatic dysfunction, elevated liver enzymes, and suppression of endogenous steroid synthesis. It has a slow onset of action, and in life-threatening conditions ketoconazole is often combined with amphotericin B to provide immediate fungicidal activity in all tissues except the eye and the CNS. The dose of ketoconazole for dogs and cats is 10 to 15 mg/kg daily.

Itraconazole has a broad spectrum of activity against many fungal organisms and has been effective in the treatment of cryptococcal meningitis in cats.[158] In systemic blastomycosis, itraconazole produces a cure rate equal to or greater than that of combined therapy with ketoconazole and amphotericin B. Itraconazole is less toxic than ketoconazole but is more expensive. Fluconazole is a bistriazole compound with broad-spectrum antifungal activity. It is well absorbed from the GI tract and has a bioavailability greater than 90%.[156] It penetrates into the meninges and CSF with or without inflammation. Fluconazole is the drug of choice in the treatment of cryptococcal meningitis in humans and is used in dogs and cats with mycotic infections of the CNS. Serious side effects are uncommon. The recommended dose in dogs and cats for both itraconazole and fluconazole is 10 mg/kg daily divided twice daily for 2 to 3 months beyond the resolution of all signs.[159] The successful resolution of cryptococcal meningitis and optic neuritis with fluconazole has been reported in the horse. The dose was 5 mg/kg per day and the horse was treated for 197 days.[160]

Coccidioidal Meningitis. *Coccidioides immitis* is not susceptible to the synergistic activity of combined amphotericin B and flucytosine therapy but may respond to ketoconazole administered at 10 mg/kg every 24 hours for 9 to 12 months.[136] Although in some cases treatment resolved the clinical signs, recurrences were common when treatment was discontinued. Similar results were found in a few cases treated with itraconazole and fluconazole.[161]

Other Systemic Fungal Infections. *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Aspergillus* spp., *Candida* spp., and *Sporothrix schenckii* occasionally are involved in meningitis. Treatment is the same as for cryptococcosis and coccidioidomycosis.[162-165]

Actinomycetes Infections (see Table 15-1)

Tuberculous Meningitis. Although it is nearly nonexistent in dogs and cats, tuberculous meningitis occurs occasionally in primates. Most of the antituberculous drugs readily penetrate the CNS. A combination of isoniazid and ethambutol is suggested. Other effective drugs include rifampin, ethionamide, pyrazinamide, and cycloserine.

Nocardiosis. The drugs of choice have been triple sulfonamides or trimethoprim-sulfa combinations. Their in vitro effect, however, has not been duplicated in vivo. The drugs should be given in high doses, and precautions should be taken to prevent nephrotoxicity. Alternative drugs include minocycline, amikacin, and erythromycin combined with ampicillin.[166]

Actinomycosis. The drug of choice is ampicillin given IV at 10 to 20 mg/kg every 6 hours.[166] Therapy is continued with clindamycin, chloramphenicol, or minocycline.

Protozoan Infections (see Table 15-12)

Toxoplasmosis. *Toxoplasma gondii* is an intracellular coccidian parasite that produces systemic infection in dogs and cats and occasionally in other domestic animals. Cats are the definitive host and pass oocysts in the feces. In cats infection may occur through ingestion of any of the three life stages of the organism or transplacentally.[167] The organism may infect the muscle, CNS, liver, lung, and eye. A variety of clinical signs may occur, including uveitis, retinitis, myositis, pneumonia, and encephalitis. The diagnosis of clinically active toxoplasma infection is based on suggestive clinical signs, demonstration of *T. gondii* tachyzoites or bradyzoites in tissue biopsy sections, or immune testing for antibodies or antigen in serum, ocular fluid, or CSF. Although several immunologic tests are commercially available, the *T. gondii*-specific immunoglobulin M (IgM) and IgG enzyme-linked immunosorbent assay (ELISA) are most often used in dogs and cats. IgM levels tend to increase within 2 to 4 weeks of infection but are negative by 16 weeks.[168] IgM titers more than 1:256 indicate recent or active infection. A fourfold increase in IgG titers also indicates recent or active disease. Both IgG and IgM titers can be assessed in samples of CSF and compared with serum concentrations of albumin, IgG, and IgM. When the levels in CSF exceed those in serum, active or recent CNS infection should be suspected.

Clindamycin hydrochloride is the primary antimicrobial selected to treat clinical toxoplasmosis in dogs and cats. The dose in cats is 12.5 to 25 mg/kg orally or IM every 12 hours. The dose in dogs is 10 to 20 mg/kg orally or IM every 12 hours. Although clindamycin does not adequately penetrate the CSF of humans, the drug may penetrate the CSF of cats in sufficient levels to be effective for neurologic disease.[169] Transient vomiting is a common side effect in some cats. Cats should be treated for at least 4 to 5 weeks.

Neosporosis. Neosporosis is caused by the protozoan *Neospora caninum*. Natural infections have been reported in dogs and calves. The muscles and the CNS are the most common sites of infection. Affected animals typically develop nonsuppurative encephalomyelitis, polyradiculoneuritis, and myositis. A positive diagnosis is based on demonstration of the organism in blood, CSF, or tissues. A fluorescent antibody test can detect *N. caninum*–specific antibodies. Clinical experience with treatment is limited, but treatment with clindamycin should be tried early in the course of illness. Sulfadiazine may also be effective (see also Chapter 7).[167]

Equine Protozoal Myeloencephalitis (EPM). EPM is described in Chapter 6 because clinical signs commonly manifest as spinal cord dysfunction. It is the most common neurologic disease in horses with multifocal or asymmetric neurologic deficits. Infection of the CNS may occur anywhere, but the spinal cord is most commonly affected.[170-173] EPM is most commonly caused *Sarcocystis neurona*. A small number of EPM cases have been attributed to infection by *Neospora hughesi*. The opossum is the definitive host for *S. neurona* and harbors the sexual stages of the protozoa within its gastrointestinal tract. Natural intermediate hosts for *S. neurona* that have been identified include the skunk, raccoon, cat, Pacific harbor seal, and nine-banded armadillo. The horse is an aberrant dead-end host. Horses are most likely infected by fecal-oral transmission. The diagnosis and treatment of EPM are discussed in Chapter 6.

Viral Infections

The viral diseases causing encephalomyelitis are summarized in Table 15-13. Viral infection of the CNS may fit into one of three categories: (1) viral invasions resulting in inflammation (viral meningitis, encephalitis, encephalomyelitis, or poliomyelitis); (2) postinfectious, noninflammatory encephalopathic states; and (3) postinfectious and postvaccinal inflammatory states ("old dog" encephalitis, perhaps polyradiculoneuritis, brachial plexus neuropathy).

Rabies. Rabies is caused by a rhabdovirus that results in a fatal encephalomyelitis in mammals. Common sources of infection include bites from skunks, bats, raccoons, foxes, and coyotes.

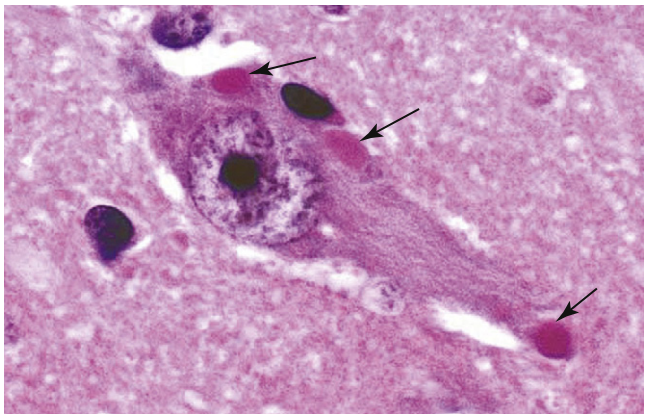


Figure 15-13 Brain from a horse with rabies. Note the prominent Negri bodies *(arrows)* in a neuron. (Courtesy Cornell University College of Veterinary Medicine.)

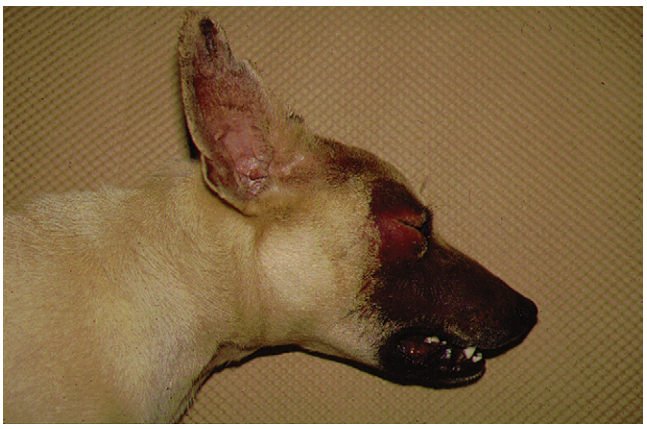


Figure 15-14 Dog with pseudorabies. Note the extensive self-mutilation of the head secondary to severe pruritus. (Courtesy Dr. Joan Coates.)

The virus is transmitted via infected saliva (animal bites, contamination of wounds) and is transmitted by retrograde axonal transport to the brain and spinal cord. Lesions in the nervous system are most severe in the midbrain, cervical spinal cord, and cranial nerve ganglia and include perivascular cuffs of plasma cells and lymphocytes. The Negri body, found in neurons, is the classical inclusion body of rabies virus (Figure 15-13).

Three forms of rabies have been described in domestic animals: furious, dumb, and paralytic. Initially, infected animals often develop behavioral changes with rapid progression to one of the three forms. The furious form is characterized by restlessness, wandering, aggression, and seizures. The dumb form is characterized by progressive paralysis, pharyngeal and hypoglossal paralysis, depression, and head pressing. The paralytic form occurs more commonly in large animals than in dogs and cats. It is a progressive ascending paralysis that may begin as a shifting leg lameness. In cattle, the most common clinical signs are salivation, bellowing, aggressiveness, paresis/paralysis, and straining. Colic, aggressiveness, hyperesthesia, and ataxia are common clinical signs in horses. Sheep will commonly manifest hyperesthesia, tremors, and salivation. Goats and pigs also manifest mainly aggressiveness, hyperexcitability, and squealing. It is important to keep in mind that rabies can clinically present with any neurologic sign.

Definitive diagnosis is a positive fluorescent antibody test performed on brain tissue. There is no effective treatment. Infected animals and those suspected to be infected should be euthanized and brain submitted for fluorescent antibody (FA) examination. Given the human health hazard, FA examination of the brain should be pursued in every suspected case in which there has been significant risk of exposure to humans. If uncertainty exists, a state health official should be contacted for advice. Vaccines are available and very effective in domestic animals. Despite their efficacy, rabies infection can occur in vaccinated animals.[172]

Pseudorabies. Pseudorabies (Aujeszky disease, mad itch) is caused by a neurotrophic α-herpesvirus. The virus can be latent or subclinical in adult swine and pigs are thought to be the source of infection in other animal species. After a pig bite, the virus enters the skin and travels to the brain or spinal cord by retrograde axonal transport. The incubation period is 90 to 156 days. Piglets show seizures, tremors, ataxia, and death. In other species, severe pruritus, dermal abrasions, swelling, and alopecia develop at the site of virus inoculation (Figure 15-14).

Other signs include ataxia, paresis, circling, aggression, depression, and seizures.

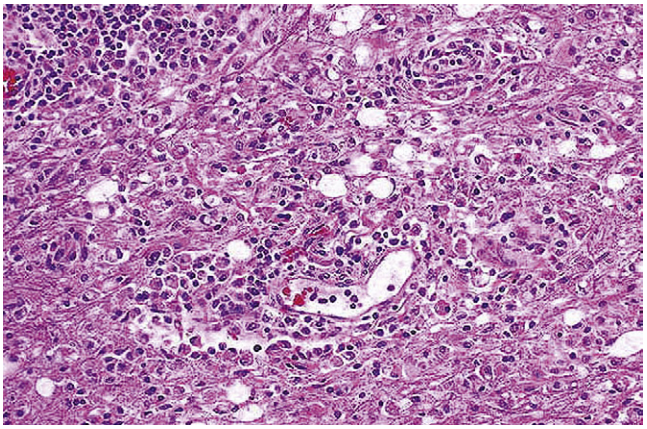


Figure 15-15 Canine distemper encephalomyelitis. Cerebellar folial white matter with perivascular lymphocytes and plasma cells, numerous macrophages and vacuolated neuroparenchyma. (Courtesy Cornell University College of Veterinary Medicine.)

Diagnosis is based on viral isolation and histopathology. There is no effective treatment. Pseudorabies has been eradicated from domestic swine in the United States.

Canine Distemper Virus. Canine distemper is a common polysystemic disease of dogs that may infect the CNS. The virus is also pathogenic in ferrets, raccoons, big cats, and other animal species. There are three neurologic syndromes. Acute distemper occurs in susceptible young dogs and respiratory and digestive signs predominate. Neurologic signs may occur later in the clinical course but many dogs die before these signs develop. Seizures are the most common neurologic manifestation. Lesions most commonly represent a polioencephalomyelitis.

Chronic distemper encephalomyelitis occurs in young dogs that survive the acute stages of the disease and in mature dogs without signs of system disease. Chronic distemper is a multifocal severe demyelinating meningoencephalomyelitis. Lesions are most common in the cerebellum, cerebellar peduncles, cervical spinal cord, optic tracts, and periventricular white matter (Figure 15-15).

Clinical signs include progressive and severe ataxia, paresis, depression, and generalized or "chewing gum" seizures (focal seizures involving biting movements of the mandible). Constant repetitive myoclonus, twitching of temporal or

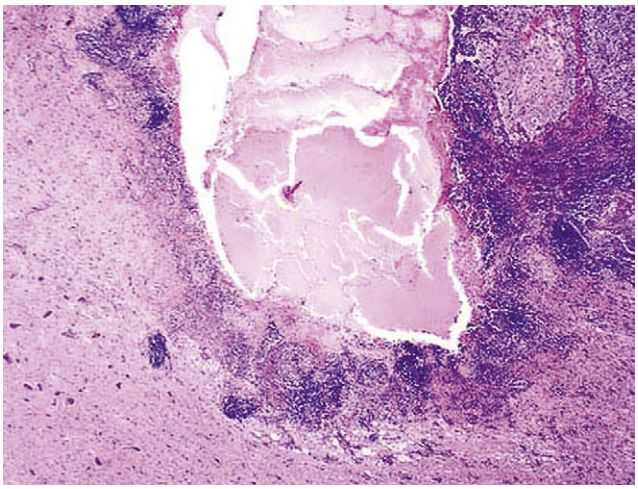


Figure 15-16 Neurologic feline infectious peritonitis with extensive periventricular inflammation and protein effusion into the ventricular lumen. (Courtesy Cornell University College of Veterinary Medicine.)

appendicular muscles, occurs in some dogs and is supportive of the diagnosis. Distemper virus may cause chorioretinitis and optic neuritis and visual deficits may develop.

Old dog encephalitis is a rare form of canine distemper that appears to be a manifestation of chronic viral infection after years of latent brain infection. The clinical signs result from necrosis of cerebral gray matter and are typical of other forebrain disorders.

The diagnosis of canine distemper is based on positive FA tests on neural tissue, cerebrospinal fluid cells (infected lymphocytes), or other lymphoid tissues. Other supporting findings include ophthalmologic evidence of chorioretinitis, increased lymphocytes and protein in CSF, and distemper myoclonus.

There is no definitive treatment. Seizures can be managed with anticonvulsants drugs such as phenobarbital but control is difficult. Vaccines are highly protective against both system and neurologic signs.

Feline Infectious Peritonitis Virus (FIP). The noneffusive (dry) form of FIP virus includes neurologic signs in some cats. The FIP virus induces a vasculitis involving the meninges, ependymal lining, and choroid plexus (Figure 15-16).

Characteristic histopathologic lesions are a pyogranulomatous meningoencephalitis and lymphoplasmacytic periventriculitis. The lesions are most severe around the third ventricle of the brain resulting in an obstructive hydrocephalus. Ataxia related to vestibular dysfunction is the most common neurologic sign. Intention tremor and fine head tremor have been associated with cerebellar and meningeal disease. Forebrain, cerebellar, and thoracolumbar spinal cord signs are also common. Signs are slowly progressive and eventually fatal. Affected cats frequently have an anterior uveitis.

Diagnosis is based on clinical signs, presence of ocular lesions, cytology of abdominal effusion if present, and CSF analysis (neutrophilic-lymphocytic pleocytosis and increased protein). There is no effective treatment.

Equine Herpesvirus-1 (EHV-1). Equine herpesvirus type 1 causes a diffuse multifocal myeloencephalopathy and is discussed in detail in Chapter 6.

West Nile Virus. West Nile virus is a flavivirus that causes acute polioencephalomyelitis in birds, horses, and humans and rarely in other animal species.[173-175] In horses the most common clinical signs are fever, paresis, ataxia, and muscle fasciculations.[173] The lesions are most severe in the spinal cord and are usually asymmetric and multifocal. Abnormal mentation and cranial nerve abnormalities occur in 44% to 67% of affected horses.[173] See Chapter 6 for discussion of diagnosis and treatment.

Western, Eastern, and Venezuelan Equine Encephalomyelitis (WEE, EEE, VEE). A group of mosquito-transmitted alphaviruses cause encephalomyelitis in horses (Eastern, Western, and Venezuelan equine encephalomyelitis). Descriptions have been mainly reported in humans, horses, and in a number of other mammalians, including dogs, cats, cattle, camelids, rodents, and pigs.[176-178] The causative agents are single-stranded enveloped RNA viruses, *Alphavirus* genus of the family Togaviridae. Birds are involved in application of the disease. Susceptible horses, usually younger, show clinical signs 2 to 3 weeks after viral infection of birds. Times for peak infection are June to August in the southern states and September in the northern states. The clinical signs include mild to severe pyrexia, anorexia, stiffness, propulsive walking, depression, hyperesthesia, aggression, and excitability.[179] Obtundation is the most common clinical sign and seizures occur in one third of the cases. Neurologic signs are variable and occur as diffuse or multifocal forebrain disease with brainstem and spinal cord involvement. The signs are peracute to acute in onset and progressive. Mortality rates are highest with EEE. Histopathology reveals gray matter predominance with multifocal to diffuse meningoencephalomyelitis. Diagnosis is made via serology (CF, HI, SN, and IgM capture ELISA). Results of CSF analysis are distinctive and reveal very high protein concentrations and severe neutrophilic pleocytosis. Treatment is mostly supportive care, which includes corticosteroids or nonsteroidal antiinflammatory agents and physical therapy. Long-term antiinflammatory therapy may be important for neurologic recovery. Efficacious vaccines are available but twice yearly vaccination is recommended. Mosquito control is important in reducing risk of infection.

Antiviral Therapy. Few reports address the use of antiviral agents in animals. Acyclovir is an antiherpes viral agent that inhibits the enzyme thymidine kinase and thus inhibits deoxyribonucleic acid (DNA) synthesis. This effect is 200 times greater for the viral enzyme than for the enzyme in mammalian cells.[180] Acyclovir can be given orally and intravenously. It penetrates into the CSF and aqueous humor at 30% to 50% of the plasma concentration. In human herpes encephalitis, the IV dose is 10 mg/kg every 8 hours. The dose should be reduced with renal failure because the drug is excreted in the urine. Encephalopathy is a rare side effect with high doses.

Foscarnet is effective against herpesvirus, cytomegalovirus, and the human immunodeficiency virus. It penetrates the CNS in good concentrations.[180]

The Transmissible Spongiform Encephalopathies (TSE)

The TSE are a group of slowly progressive, neurodegenerative diseases of the CNS. The group includes bovine spongiform encephalopathy (BSE, mad cow disease), scrapie in goats and sheep, chronic wasting disease in elk and deer, transmissible mink encephalopathy, and feline spongiform encephalopathy. The cause is a particle in which nucleic acids have not been demonstrated. These particles may represent infectious proteins derived from the normal host. Normal prion proteins (PrP) are located in nervous system membranes and are suspectable to proteases. Abnormal PrP are protease resistant (PrP-res). Protease resistant prions accumulate in the neurons and interfere with cell function and cause vacuole formation (Figure 15-17). There is a long latency period before clinical signs develop. The TSE are reportable diseases.

Bovine Spongiform Encephalopathy (BSE). BSE was first reported in dairy cattle in the United Kingdom. Infection was tied to the consumption of meat and bone meal contaminated with BSE-infected nervous tissue. BSE has been sporadically

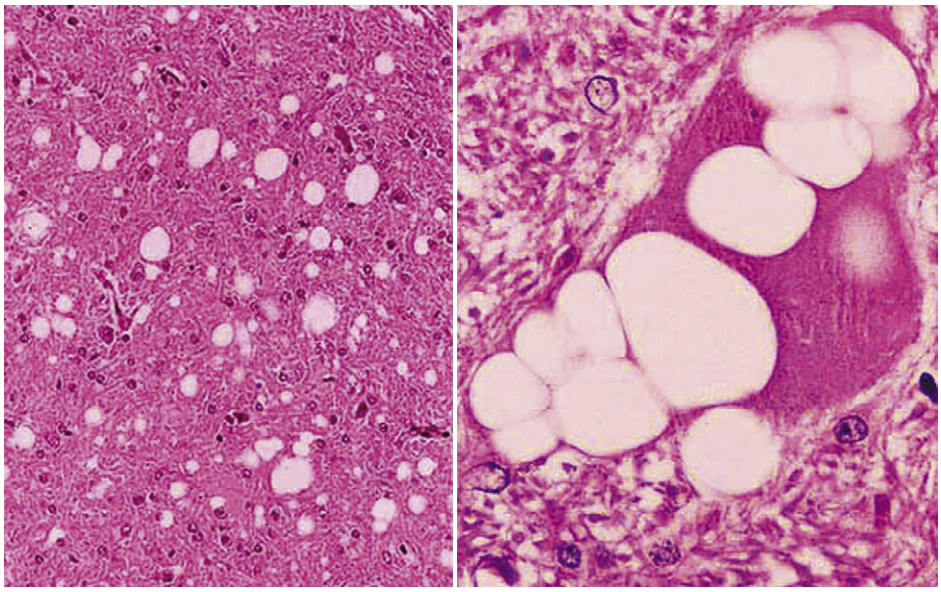


Figure 15-17 Spongiform change (vacuoles) in the caudal brainstem gray matter of a cow with bovine spongiform encephalopathy *(left image)* and large vacuoles in a large neuron (*right image*). (Courtesy Cornell University College of Veterinary Medicine.)

reported in Canada and a few cases have been reported in the United States. The incubation period can be long (2 to 8 years). The clinical signs include nervousness, aggression, frequent licking at the muzzle, muscle fasciculations, and bruxism. Cows are hypersensitive to external stimuli. Locomotor signs include ataxia, hypermetria, paresis, falling, and recumbency. There is no antemortem diagnostic test. Postmortem diagnosis includes histopathology, immunohistochemistry, and Western blot or ELISA on the brain. There is no treatment or vaccine. Human TSE, variant Creutzfeldt-Jakob disease, has been linked to consumption of brain and spinal cord tissue from BSE-infected cattle.

Scrapie. Scrapie is a TSE that affects sheep and goats. The prion is transmitted by ingestion or direct or indirect contact with infected placenta and birth fluids. The incubation is 1 to 7 years with clinical signs usually present at 2 to 5 years of age. Scrapie is most common in black-faced sheep (Suffolk, Cheviot, Hampshire). These breeds are genetically susceptible to the prion proteins. In addition to the signs described for cattle, sheep develop tremors, pruritus, wool break, and inducible nibbling reflex. When startled, sheep may tremble and fall down in a seizure. The signs progress slowly to recumbency and death (6 weeks to 1 year). The clinical signs in goats are similar. About 33% of infected goats regurgitate rumen contents.

The antemortem diagnosis of scrapie is based on clinical signs and third eyelid biopsy for immunohistochemistry of PrP-res. Postmortem diagnosis is made from histopathology of brain (vacuolation of gray matter) and immunohistochemistry of brain and/or lymphoid tissue. There is no treatment. The disease can be prevented by selecting ewes and rams that are genetically resistant to scrapie and by maintaining closed herds.

Feline Spongiform Encephalopathy. Spongiform encephalopathy has been reported to cause tremor in cats. A 7-year-old spayed female domestic shorthair cat presented for a 4-month history of progressive aggressive behavioral changes, tremor, and pelvic limb ataxia.[181] Histopathology revealed diffuse vacuolation of the neuropil and neuronal cell bodies most marked in the frontal lobe of the cerebral cortex. Due to the lack of plaques, which are associated with transmissibility, it is unclear if this is a true example of transmissible spongiform encephalopathy. Spongiform change was also reported in an 8-month-old female domestic shorthair cat that had a 2-week history of generalized ataxia and lethargy.[182] Neurologic examination also revealed head tilt, cervical spine ventroflexion, tetraparesis, tremor, and visual deficits. Histopathology revealed generalized vacuolation of the gray matter of the brain and spinal cord.

Rickettsial Infections (see Table 15-14)

The agents that cause Rocky Mountain spotted fever (RMSF) and canine ehrlichiosis may cause meningitis and encephalitis in addition to vasculitis and hematologic disorders.[183,184] Both diseases are transmitted by ticks and are limited to areas harboring the appropriate vector. Dogs with RMSF may have acute cervical pain and minimal signs related to brain or spinal cord disease. Dogs with neurologic ehrlichiosis usually have signs related to brainstem or spinal cord lesions. CSF may be normal or reveal increased protein and a mixed pleocytosis.[183] Confirmation of ehrlichiosis may be difficult in some dogs and is based on serologic tests and isolation of the organism.[185] Treatment is with tetracycline, minocycline, or doxycycline. Doxycycline is preferred because it penetrates the CSF in good concentrations. For doxycycline, a dose is 5 to 10 mg/kg every 12 hours IV or orally.

Parasitic Infections

Parasitic disease of the nervous system is uncommon. The most common parasitic diseases are summarized in Table 15-15.

Noninfectious Inflammatory Diseases

Immune Mediated Diseases

Polyradiculoneuritis (see Chapter 7) is probably an immune-mediated reaction to a transmissible agent in raccoon saliva. Postvaccinal rabies is rare (see Table 15-13). Both conditions are summarized in Table 15-16.

Meningoencephalomyelitis of Unknown Etiology (MUE) (see Table 15-17)

Several nonseptic inflammatory diseases may respond to medical therapy.[186,187,188] The causes of these diseases are

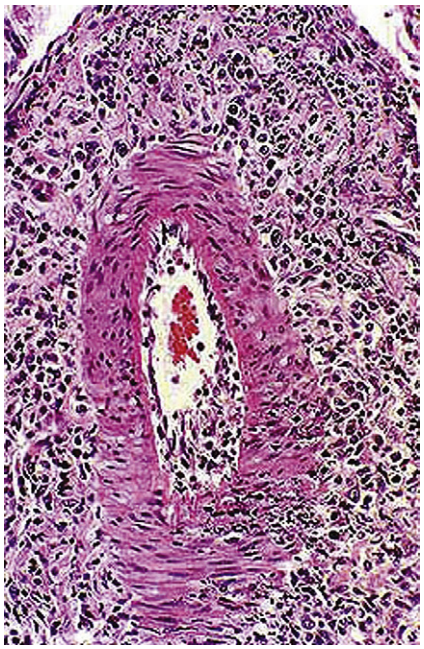


Figure 15-18 Canine juvenile polyarteritis (steroid responsive meningitis-arteritis). Note the prolific arterial inflammation with neutrophils. (Courtesy Cornell University College of Veterinary Medicine.)

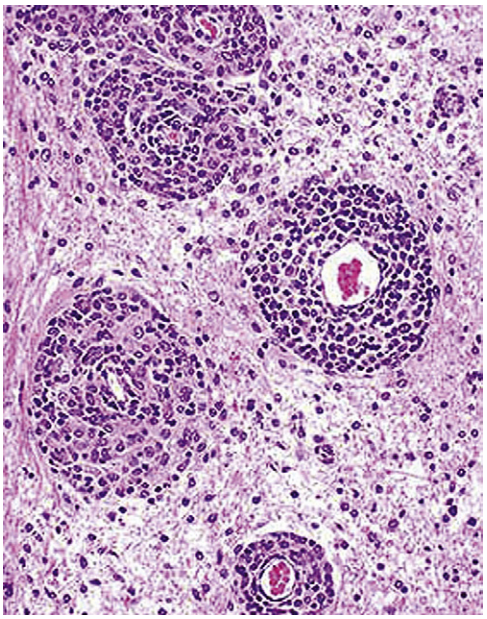


Figure 15-19 Perivascular cuffs of lymphocytes, plasma cells, and histiocytes in the cerebral white matter of a dog. These lesions are typical of granulomatous meningoencephalomyelitis. (Courtesy Cornell University College of Veterinary Medicine.)

not currently known, but immune-mediated mechanisms are suspected. Accordingly, corticosteroids and other immunosuppressive drugs may be beneficial with certain diseases. Differentiating these diseases from bacterial or viral infections is difficult because the clinical signs and CSF findings may be similar with both types of inflammation (see Chapter 4).

Steroid-Responsive Meningitis-Arteritis (SRMA)

Steroid-responsive meningitis-arteritis occurs in large-breed dogs, usually less than 2 years of age (Figure 15-18).

Cervical spinal hyperesthesia occurs in more than 90% of affected dogs. Neutrophilic leukocytosis with left shift and fever occurs in two thirds of affected dogs. Boxers, Bernese mountain dogs, beagles, weimaraners, and Nova Scotia duck tolling retriever dogs may be predisposed to this disease.[187-193] Dogs with noninfectious, nonerosive, idiopathic immune-mediated polyarthritis (IMPA) commonly have spinal pain, and about 50% of these dogs have concurrent SRMA.[188] Analysis of CSF usually reveals marked increases in protein and neutrophils. Bacterial cultures from the CSF are negative. IgA concentrations are increased in both the plasma and the CSF. Measurement of acute phase proteins in CSF may also aid in the diagnosis and management of affected dogs.[194,195] Most dogs respond dramatically to prednisone, 2 to 4 mg/kg every 24 hours.[194] In dogs not responding to prednisone alone, additional immunosuppressive therapy may be needed. Once the signs are controlled, the dose of prednisone is decreased to alternate-day therapy, and then the total dose is gradually reduced over months. Relapses are common when the corticosteroid dose is too low or is discontinued.

Necrotizing Meningeal Vasculitis

Necrotizing meningeal vasculitis is a severe form of SRMA.[186,187,194] Necrotizing vasculitis also occurs in young dogs, especially beagles, Bernese mountain dogs, and German shorthaired pointers. Although the prognosis in affected beagles is guarded, other breeds may respond well to prednisone at 2 to 4 mg/kg every 24 hours using the aforementioned reducing-dosage regimen.

Granulomatous Meningoencephalomyelitis (GME)

GME is a common nonseptic inflammatory disease that affects young to middle-aged small-breed dogs.[186,187,188,196,197] Females are more often affected.[188] The exact cause is unknown, but studies of inflammatory cells in dogs with GME suggest a T cell–mediated delayed type of hypersensitivity.[198] Neurologic signs may be acute or chronic. Clinically, GME has been characterized into three clinical presentations: focal, disseminated, or ocular.[199,200] Cervical pain is a common finding. About 50% of affected dogs have focal signs referable to the forebrain, and about 50% have forebrain and brainstem disease.[196] Central vestibular signs are common manifestations of acute disease.[197] Rarely, involvement of the peripheral nervous system may be observed.[201]

A definitive diagnosis is based on histopathologic examination of the CNS. Microscopically, the hallmark of GME is perivascular cuffs of granulomatous inflammation (Figure 15-19).[202]

Presumptive antemortem diagnosis is based on a combination of signalment, anamnesis, clinicopathologic data, and exclusion of other disease capable of producing similar clinical signs. Since the definitive diagnosis of GME necessitates histologic evaluation of CNS tissue, the term meningoencephalomyelitis of unknown etiology (MUE) has been used to describe dogs without a definitive diagnosis.

The diagnosis of MUE should be pursued in a logical manner (see Chapter 4). Briefly, minimum database (complete blood count, chemistry profile, and urinalysis) often discloses nonspecific abnormalities. Analysis of CSF is critical to establishing a presumptive antemortem diagnosis. Mononuclear pleocytosis, activated macrophages, occasionally neutrophils, and rarely mast cells with increases in protein content are common CSF abnormalities. Cross-sectional imaging also is important in the diagnostic workup. MRI of the brain is the imaging modality of choice. With MRI, multifocal hyperintensities on T2-weighted and fluid attenuated inversion recovery sequences predominantly affecting the white matter are observed. Enhancement patterns vary on T1-weighted sequences after administration of contrast

media. A focal space occupying mass or abnormalities involving the optic nerves may be observed in animals with the focal or ocular forms, respectively.[203] Abnormal findings from CSF analysis and MRI of the brain can be found in other forms of MUE. Therefore, the value in pursuing these diagnostics tests is not only in documenting abnormalities but in excluding other disease processes; the greatest importance of which is eliminating infectious disease from consideration. Given the treatment of GME is centered on immunosuppression, misdiagnosis may be devastating in animals with infectious disease. Therefore, depending on the clinician's index of suspicion, further diagnostic testing aimed at the identification of an infectious etiology may be warranted. Likewise, CNS lymphoma may occur with clinical signs of multifocal signs and have MRI findings and lymphocytic pleocytosis that are difficult to differentiate from GME. PCR for the antigen receptor rearrangements may be useful in the diagnosis of CNS lymphoma.

Response to prednisone therapy is highly variable. Some dogs respond to prednisone (2 to 4 mg/kg every 24 hours, using the aforementioned reducing-dosage regimen), but relapses and progression of neurologic signs are common in many dogs. Cytosine arabinoside, given as a single agent or in combination with prednisone, is a more effective treatment.[204,205] In one study of 10 dogs treated with cytosine arabinoside and prednisone, all dogs achieved partial or complete remission and the median survival time was 531 days; five dogs were still alive at the end of the study.[206] Cytosine arabinoside is administered in cycles. Each cycle consists of administering the drug at a dose of 50 mg/m^2 given subcutaneously twice a day for 2 consecutive days. Cycles are initially repeated every 3 weeks. With time, gradual lengthening of the interval between cycles can be done. In severely affected animals, initial administration of 600 mg/m^2 given as a constant rate infusion over 2 days may be beneficial.[207] To monitor for myelosuppression, a CBC should be performed 10 to 14 days following the first course of treatment and every 2 to 3 months throughout the course of therapy. Cyclosporine may also be effective in treating GME. Two protocols have been reported.[205,208] In one, cyclosporine was administered at 10 mg/kg every 24 hours for 6 weeks. The dose was then reduced to 5 mg/kg per day. Prednisone was also administered at 2 to 4 mg/kg daily for 3 to 4 weeks. In another protocol, cyclosporine was administered at 3 to 10 mg/kg every 12 hours. Serum cyclosporine levels were followed but the drug was not detected in the CSF, even in dogs with good clinical response. In one study of 10 dogs treated with cyclosporine and prednisone, all dogs responded and the median survival time was 930 days.[208] Procarbazine has also been used as an adjunctive therapy combined with prednisone.[209] The dosage administered was 25 to 50 mg/m^2 orally once daily. The combination of procarbazine and prednisone in 21 dogs provided a median survival time of 14 months. Seven dogs experienced myelosuppression and three dogs had hemorrhagic gastroenteritis. Other immunosuppressive drugs used in the treatment of GME include mycophenolate mofetil (20 mg/kg orally twice daily) and leflunomide (1.5 to 4.0 mg/kg orally once daily).[210]

Radiation treatment is effective for dogs with focal GME.[173] The prognosis for survival is better for dogs with focal disease.[196]

Necrotizing Meningoencephalitis (NME) and Necrotizing Leukoencephalitis (NLE)

These breed-specific diseases are seen most commonly in young adult dogs. They are fatal disorders that cause a nonsuppurative inflammation and necrosis of the brain. Variants have been reported in the pug, Yorkshire terrier, Maltese, Pekingese, French bulldog, Chihuahua, and shih-tzu.[211] NME is most common in the pug and Maltese and NLE is most common in Yorkshire terriers and French bulldogs. In pugs, the mean age of onset of clinical signs is 18 months (range 4 to 113 months). Females are more commonly affected than males. Most pugs with NME have a mononuclear pleocytosis.

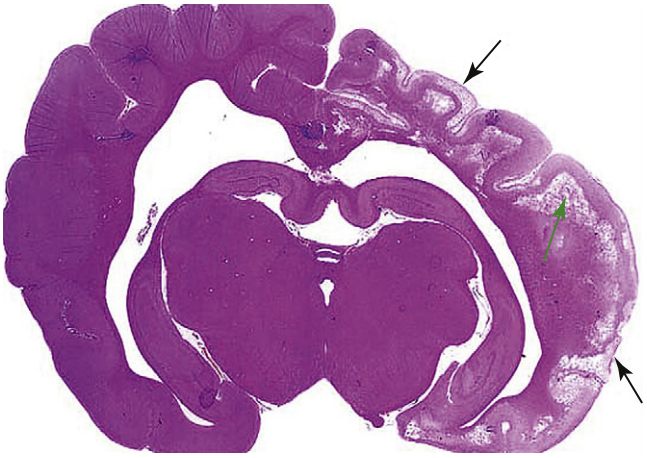


Figure 15-20 Brain from Maltese dog treated for intractable seizures. Note the laminar loss of cortical tissue *(black arrows)* and cribriform changes in the white matter *(green arrows)*. These are the lesions of necrotizing meningoencephalitis. (Courtesy Cornell University College of Veterinary Medicine via Dr. R. Higgins, University of California, Davis.)

As with GME, definitive diagnosis requires histopathologic evaluation of the brain. Gross evaluation of the brain in dogs with NME discloses abnormalities limited to the gray/white matter junction of the cerebrum (Figure 15-20).

Microscopically, the lesion affects gray and white matter, meninges, and choroid and consists of inflammatory infiltrate composed of lymphocytes, plasma cells, and macrophages. In addition, areas of liquefactive necrosis and cavitation occur. In dogs with NLE, gross lesions predominate in the deep white matter of the cerebrum and thalamus. Similar to NME, inflammation composed of lymphocytes, plasma cells, and macrophages exist along with necrosis and cavitation of the white matter. Typical white matter lesions involve the thalamus, internal capsule, centrum semiovale, and corona radiata.

Although there are gross anatomic differences in the distribution of the lesions in NME and NLE, these diseases may represent a spectrum of a single disease process rather than separate entities. In fact, although NME or NLE has been reported to affect specific breeds, occasionally NLE has been observed in a breed normally thought to be affected with NME and vice versa.[212,213]

Presumptive diagnosis can be relatively accurately established based on signalment (specifically breed), clinicopathologic data, and exclusion of other disease processes that may result in similar clinical signs. Importantly, a relatively accurate presumptive diagnosis can be made based on MRI findings. Magnetic resonance imaging characteristics and topography of the lesion mirrors the gross and histologic findings (Figure 15-21).[212,213]

Treatment is pursued using the same drug combinations as with GME. Overall, the prognosis is guarded depending on the severity of clinical signs and extent of necrosis of the brain. The mean survival time in one study was 93 days.[211]

Eosinophilic Meningoencephalomyelitis (EME)

Eosinophils are rarely found in CSF. When the percentage is less than 5%, it is a nonspecific finding and can be found in several CNS disorders. When eosinophil counts exceed 20%,

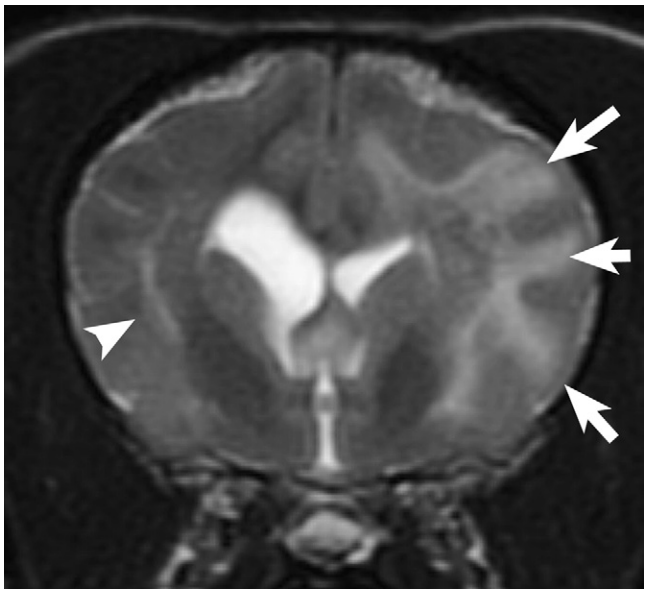


Figure 15-21 Axial T2W image of the brain of an adult Dachshund dog with meningoencephalitis of unknown origin. There is excessive hyperintensity of the white matter (internal capsule, centrum semiovale, and corona radiate) of the left cerebrum *(arrows)*. There is also edema in internal capsule of the right cerebrum *(arrowhead)*.

an eosinophilic pleocytosis exists and the most common causes are parasitic migration, cryptococcosis, neosporosis, and idiopathic EME. Idiopathic EME occurs in both large- and small-breed dogs with a median age of 3.5 years.[214] There is no gender bias and about 75% of dogs respond to prednisone therapy (0.33 to 1 1 mg/kg q12h).

CASE STUDIES

Key: *0*, Absent; *+1*, decreased; *+2*, normal; *+3*, exaggerated; *+4*, very exaggerated or clonus: *PL*, pelvic limb; *TL*, thoracic limb; *NE*, not evaluated.

CASE STUDY 15-1 *CASEY*

veterinaryneurologycases.com

▪ Signalment
Mastiff, female spayed, 1.5 years old

▪ History
Clinical signs began several days ago. Dog has experienced vomiting, diarrhea, dry eyes and nose, urinary incontinence, and weight loss. All vaccinations are current.

▪ Physical Examination Findings
Dog is dull and dehydrated. The bladder is distended and easily expressed. Gas-filled intestinal loops can be palpated. Both eyes are very dry and the planum nasale is dry and crusted. Both pupils are widely dilated and do not respond to a strong light source. Third eyelids are prolapsed.

▪ Neurologic Examination
Mental status
Dull

Gait and posture
Normal

Postural reactions
Normal

Spinal reflexes
Normal except the perineal reflex is weak and anal tone is reduced.

Cranial nerves
Pupils are dilated and do not respond to strong light source.

Sensory evaluation
Normal

▪ Lesion Localization
Generalized disease of autonomic nervous system

▪ Differential Diagnosis
1. Dysautonomia
2. Botulism

▪ Diagnostic Plan
Dilute pilocarpine in left eye (immediate constriction); poor wheal and flare to intradermal histamine phosphate injection.

▪ Diagnosis
Dysautonomia

▪ Treatment
Dilute pilocarpine in each eye daily. Cisapride was administered twice a day to promote esophageal motility.

▪ Outcome
This case responded poorly to treatment,

CASE STUDY 15-2 *MCCOY* veterinaryneurologycases.com

■ Signalment
Pus, female spayed, 3 years old

■ History
Two months prior to presentation, the dog was brought in because of a paralyzed tail. A cauda equina syndrome was presumptively diagnosed and the dog seemed to respond to nonsteroidal antiinflammatory drugs. On this visit, the dog was seen for severe ataxia. Owner declined diagnostic testing and the dog was placed on prednisone and doxycycline. Three days later, the dog's condition had worsened and seizures developed. The dog was treated with phenobarbital and referred. All vaccinations are current.

■ Physical Examination Findings
See neurologic examination.

■ Neurologic Examination
Mental status
Dull and poorly responsive to auditory stimuli

Gait and posture
Unable to stand without assistance. She is very ataxic and falls both left and right. Left head tilt is present.

Postural reactions
1. Proprioceptive placing: normal in left front leg and very depressed in all other limbs
2. Hopping: +1 in thoracic limbs and 0 in pelvic limbs

Spinal reflexes
1. Patellar: +3 in both limbs
2. Withdrawal: normal

Cranial nerves
Menace response: reduced
Palpebral reflex: normal
Pupils: very dilated and no PLRs absent
Vertical nystagmus

Sensory evaluation
Normal

■ Lesion Localization
Forebrain based on seizures
Left cranial medulla based on vestibular signs and postural deficits
Retina/optic nerves bilateral based on reduced menace responce and absent PLRO

■ Differential Diagnosis
1. Viral encephalitis
2. Pug dog encephalitis
3. Protozoal encephalitis
4. Rickettsial encephalitis

■ Diagnostic Plan
CSF and immunocytochemistry analysis; cross-sectional imaging and serology

■ Results
CSF: mild increase in protein; normal cell count; CSF cells positive on immunofluorescent antibody for canine distemper; MRI and serology not performed

■ Diagnosis
Canine distemper encephalomyelitis

■ Treatment
Euthanasia

CASE STUDY 15-3 *RASCAL* veterinaryneurologycases.com

■ Signalment
Abyssinian cat, male castrated, 1 year old

■ History
The cat had severe paraparesis. Clinical signs began 3 weeks ago with lameness of the right thoracic limb that was managed with NSAIDs. Weakness and ataxia also became evident in the pelvic limbs. Muscular atrophy developed rapidly in the pelvic limbs. The cat has had two episodes of pyrexia and anorexia. Vaccinations are current.

■ Physical Examination
The rectal temperature is normal. Cat is thin with generalized muscle atrophy. Enlarged popliteal lymph nodes are present.

■ Neurologic Examination
Mental status
Alert and responsive

Posture
Normal

Gait
Severe paraparesis. The tail is paralyzed.

Postural reactions
Hopping and proprioceptive deficits are noted in both pelvic limbs. Hopping is decreased in the right thoracic limb.

Spinal reflexes
Spinal reflexes are increased in all limbs except the left pelvic limb where the patellar reflex is absent and hock flexion is decreased during flexion. Perineal reflex is absent.

Cranial nerves
The menace response is reduced and the pupils are widely dilated (medication to examine retinas). Pupillary light reflexes cannot be evaluated due to administration of cycloplegic drugs.

CASE STUDY 15-3 *RASCAL*—cont'd

Palpation
The urinary bladder is distended.

Sensory evaluation
Hyperesthesia is noted in the LS region. Noxious stimuli are poorly perceived from the tail.

▪ Lesion Localization
At least two and maybe three spinal cord lesions are present. In addition, disease of multiple spinal nerves (neuritis) or muscle may also be present to explain the generalized muscle atrophy.
1. T3-L3 based on paraparesis and increased spinal reflexes
2. Left L4-S2 based on absent patellar and flexor reflexes
3. Cauda equina based on sensory examination of tail and decreased perineal reflex

▪ Differential Diagnosis
There are multifocal lesions making inflammatory disease much more likely than degenerative or neoplastic processes.
1. Protozoal myelitis-neuritis (toxoplasmosis and neosporosis)
2. Mycotic myelitis-neuritis (cryptococcosis, histoplasmosis, blastomycosis, aspergillosis)
3. FIP
4. Lymphoma

▪ Diagnostic Plan
1. CBC
2. Fine-needle lymph node biopsy
3. Thoracic and LS radiographs
4. MRI
5. CSF analysis

▪ Results
Fundic examination revealed severe bilateral chorioretinitis. Lymph node aspirate isolated histoplasma organisms. Radiographs of the lumbosacral spine did not reveal any skeletal lesions. Cross-sectional imaging and CSF analysis not performed.

▪ Diagnosis
Histoplasmosis with myelitis and neuritis (likely fungal granulomas)

▪ Treatment
Itraconazole (cat greatly improved and regained ability to urinate)

CASE STUDY 15-4 *SADIE*

 veterinaryneurologycases.com

▪ Signalment
Boxer, 9-month-old female intact

▪ History
The dog has a 2-day history of anorexia, decreased activity, and stiff gait. There is no history of trauma. She lives in northeastern Kansas, is well vaccinated, and eats a premium dog food. The dog was examined in early September.

▪ Physical Examination Findings
The abnormalities include a stiff gait and rectal temperature of 104.5° F. Ticks are present on the dog.

▪ Neurologic Examination
Mental status
Responsive to her environment

Gait and posture
Discomfort evident when handled or picked up. A stiff gait and reluctance to walk are noted. There is no head tilt circling, or ataxia.

Postural reactions
Normal

Spinal reflexes
Normal

Cranial nerves
Normal

Sensory evaluation
Marked hyperesthesia is elicited upon palpation over the thoracolumbar and cervical vertebral column.

▪ Lesion Localization
There are no findings suggestive of intramedullary spinal cord disease, especially with the presence of paraspinal pain. The hyperesthesia suggests disease involving the TL and cervical vertebra or meningeal disease. Muscles and joints also have pain sensitive fibers.

▪ Differential Diagnosis
1. Steroid responsive meningitis-arteritis
2. Rickettsial (RMSF) meningitis
3. GME
4. Discospondylitis
5. Metastatic neoplasia
6. Intervertebral disk disease
7. Polymyositis
8. Polyarthritis

▪ Diagnostic Plan
1. CBC, biochemical profile, UA
2. Thoracic radiographs and abdominal ultrasound to rule-out metastatic disease; spinal radiography
3. Serology: RMSF and *Ehrlichia canis*
4. CSF analysis

CASE STUDY 15-4 *SADIE*—cont'd

Results
1. The primary abnormality on the CBC was a platelet count of 90,000. The biochemical profile and UA were normal.
2. Thoracic radiographs and abdominal ultrasound within normal limits;
3. Negative serology for RMSF and *Ehrlichia canis*
4. No CSF analysis was performed

Diagnosis
Given the clinical signs and the presence of ticks, RMSF meningitis was suspected.

Treatment
Dog was placed on oral doxycycline. The dog dramatically responded to treatment. Convalescence RMSF titers were 1:256.

CASE STUDY 15-5 *VICTOR*

Signalment
Miniature schnauzer, intact male, 14 months old

History
The dog has been anorexic and lethargic for the past 2 days. He vomited one to two times in last 48 hours. Dog has right head tilt, circles and falls to the right, and bumps into objects on the right side. Owners report that the dog is reluctant to open his mouth and whines when his mouth is opened. Another veterinarian also found a mild fever and modest thrombocytopenia (165,000 platelets/μL).

Physical Examination Findings
The liver was not palpable on abdominal palpation. Rectal temperature at admission was 103.2° F.

Neurologic Examination
Mental status
Dull, confused, and disoriented

Gait and posture
Right head tilt; drifts and falls to the right, right hemiparesis, circles both directions but mostly to the right side. Visual deficits are suspected on right side.

Postural reactions
Very decreased on the right side

Spinal reflexes
All spinal reflexes are intact

Cranial nerves
Menace response: OD—absent; OS—normal
Palpebral reflex: normal
PLR: intact
Physiologic nystagmus is intact. There is no pathologic nystagmus but a ventrolateral strabismus is observed in the right eye
Facial sensation: normal
Swallowing/gag: normal
Tongue movement: normal

Sensory perception
Normal

Lesion Localization
Left cerebral cortex; right brainstem (rostral medulla—central vestibular disease)

Differential Diagnosis
1. Rickettsial encephalitis
2. Viral encephalitis
3. Meningoencephalomyelitis of unknown origin
4. Fungal encephalitis
5. Toxoplasmosis/neosporosis
6. Hepatoencephalopathy

Diagnostic Plan
1. Fundic examination
2. CBC, biochemical profile, UA
3. Bile acids
4. Abdominal radiographs/ultrasonography
5. MRI
6. CSF analysis

Results
1. CBC: platelets 162,000 (200,00 to 500,000 cells/μL); CK 501 (22 to 491); ALT 76 (3 to 69)
2. UA: normal
3. Abdominal radiographs: small liver
4. Bile acids: pre-5.3; postprandial 23.8 (5 to 23)
5. CSF: WBC—488; RBC—173; Total protein—94.39; cytology—100% lymphocytes
6. PCR and serology for *Ehrlichia*: negative
7. *Toxoplasma gondii* and *Neospora caninum*: negative titers (IFA) at 1:50
8. MRI not performed

Diagnosis
Meningoencephalitis of unknown etiology; possibly GME

Treatment
Initially chloramphenicol and prednisone was administered. The dog was maintained on an immunosuppressive dose of prednisone.

Outcome
1. Recheck 1 month: Improved
2. Recheck 2 months: Much improved
3. Recheck 3 months: Signs in remission. The dog developed severe iatrogenic Cushing. The dose of prednisone was reduced to every other day. Other immunosuppressive agents (e.g., cytosine arabinoside) were considered.

CASE STUDY 15-6 *OTTO* veterinaryneurologycases.com

▪ Signalment
Miniature schnauzer, male, 16 weeks old

▪ History
Otto developed clinical signs at 8 weeks of age and signs have progressively worsened. There are no other clinical signs. He eats, drinks, and is growing normally. Owner describes clumsy gait and falling right and left.

▪ Physical Examination Findings
No abnormalities found except for neurologic examination findings.

▪ Neurologic Examination
Mental status
Alert and responsive

Gait and posture
There was a base wide stance. Gait showed severe cerebellal ataxia, hypermetria, and falling to right. Intention tremors were evident upon eating.

Postural reactions
+1 hopping in left thoracic and pelvic limbs.

Cranial nerves
Normal

Spinal reflexes
Patellar reflex on left side is +3. All other reflexes are normal.

Sensory evaluation
Normal

▪ Lesion Localization
The prominent clinical signs localized to the cerebellum. Dog probably has either brainstem and/or cervical spinal cord lesion to explain the postural reaction deficits.

▪ Differential Diagnosis
1. Cerebellar abiotrophy
2. Lysosomal storage disease
3. Canine distemper virus
4. Other infectious inflammatory disease

▪ Diagnostic Plan
1. CSF analysis
2. Serology for distemper, toxoplasmosis, neosporosis, and rickettsial agents.
3. MRI
4. Urine organic acid screening

▪ Results
1. CSF: Normal
2. Serology results were for negative infectious agents
3. MRI and urine screening not performed

▪ Treatment
No treatment was administered because dog most likely has a neurodegenerative disease

▪ Outcome
Dog developed rapid progression of neurologic signs and was euthanized at 6 months of age. Necropsy and histopathology confirmed cerebellar abiotrophy with degenerative lesions also in the brainstem.

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