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CHAPTER 23

Disorders of the Brain

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CONGENITAL/DEVELOPMENTAL DISORDERS

Congenital Vestibular Disease

Definition and Causes

I. Dysfunction of the peripheral vestibular system is seen in young dogs and cats, possibly from a congenital defect.
II. The disorder is presumed to be inherited.
III. It has been reported in the following breeds:
  A. Dogs: Doberman pinscher, American cocker spaniel, German shepherd dog, Akita, beagle
  B. Cats: Siamese, Burmese
IV. Aggregates of lymphocytes occur within the inner ear of affected Doberman puppies, but the significance of these lesions is unclear.

Clinical Signs and Diagnosis

I. Onset of signs is usually 3 to 12 weeks of age.
II. Head tilt, vestibular ataxia, circling, and deafness may be seen.
III. Nystagmus is not a feature of this disorder.
IV. Diagnosis is one of exclusion: rule out other causes of vestibular signs.

Differential Diagnosis

I. Otitis media/interna
II. Ototoxicity: aminoglycoside antibiotics, topical antiseptics (iodophors, chlorhexidine)

Treatment and Monitoring

I. No treatment is available.
II. Compensation for the vestibular signs may occur over several weeks.
III. Deafness (if present) is typically permanent.

Hydrocephalus

Definition

I. It is an increase in the volume of cerebrospinal fluid (CSF) within the ventricular system or subarachnoid space of the brain (de Lahunta, 1983).
II. In compensatory hydrocephalus, CSF accumulates in spaces within the cranial cavity not occupied by brain parenchyma.
III. In obstructive hydrocephalus, obstruction to flow or absorption of CSF causes ventricular dilation (especially of the lateral ventricles) with subsequent loss of brain parenchyma.

Causes

I. Compensatory hydrocephalus may result from the following:
  A. Developmental malformations: cerebral hypoplasia or aplasia
  B. Destruction of brain parenchyma from in utero viral infections: feline panleukopenia
  C. Cerebral necrosis secondary to cerebrovascular accidents: acquired hydrocephalus
II. Obstructive hydrocephalus may result from the following:
  A. Fusion of rostral colliculi (midbrain) with CSF outflow obstruction at the mesencephalic aqueduct
  B. Dysfunction of the arachnoid villi with poor reabsorption of CSF through the dorsal sagittal venous sinus
III. Acquired hydrocephalus may result from the following:
  A. Mass lesions blocking CSF flow: neoplasia, abscess, granuloma
  B. Neoplasia preventing CSF absorption by the arachnoid villi
  C. Infections (viral, bacterial) or inflammation of the ependyma of the mesencephalic aqueduct or leptomeninges blocking flow of CSF
  D. Intraventricular hemorrhage blocking CSF outflow: leptomeningeal, intraventricular

Clinical Signs

I. No or variable signs may be seen, even in the presence of considerable ventricular dilatation.
II. Prosencephalic signs include disturbed consciousness (lethargy to severe depression), increased tendency to sleep, hypoactivity, propulsive circling, head pressing, seizures, behavioral changes, dementia, and visual deficits (with normal pupillary responses).
III. Motor deficits include spastic paresis, particularly if the brainstem is involved.
IV. Occasionally cerebellar ataxia may occur if there is involvement of the cerebellum.
V. Sensory deficits include proprioceptive ataxia.

Diagnosis

I. Presumptive diagnosis is based on physical examination findings.
   A. Animals with congenital hydrocephalus often have palpable open fontanelles and develop a dome-shaped calvaria.
   B. Ventral-lateral strabismus may be noted.
II. Imaging findings
   A. Skull radiographs may reveal a homogenous "ground glass" appearance within the calvaria and open cranial suture lines.
   B. Ventriculomegaly may be demonstrated by computed tomography (CT), magnetic resonance imaging (MRI), and occasionally ultrasonography.

Differential Diagnosis

I. Metabolic or toxic encephalopathies
II. Meningoencephalitis
III. Other congenital brain anomalies
IV. Degenerative encephalopathies

Treatment and Monitoring

I. Corticosteroids may decrease CSF production.
   A. Prednisone 0.25 to 0.5 mg/kg PO BID, then tapered to QOD
   B. Dexamethasone 0.05 mg/kg PO SID, then tapered to QOD
   C. May be discontinued in some dogs
II. Diuretics may decrease the volume of CSF.
   A. Furosemide 1 to 2 mg/kg PO BID
   B. Acetazolamide 0.1 mg/kg PO TID
III. Anticonvulsants may help control seizures.
   A. Phenobarbital 1 to 2 mg/kg PO BID
   B. Potassium bromide (KBr) 20 to 30 mg/kg PO SID
IV. Ventriculoperitoneal shunting of CSF to the abdominal cavity may be effective in some cases that are refractory to medical management, but complications include infections and shunt failure.
V. Prognosis is guarded to poor in severely affected animals.
VI. Animals with minimal clinical signs can often be managed long term.

Hydranencephaly and Porencephaly

Definition

I. Hydranencephaly is the congenital absence of a large portion of cerebrum in which cerebral cortex is absent and a fluid-filled, membranous sac takes its place (Summers et al., 1995).
II. Porencephaly is a disorder in which single or multiple cavities within the cerebrum usually communicate with the lateral ventricles or the subarachnoid space (Summers et al., 1995).

Causes

I. Hydranencephaly in cats is associated with in utero vaccine-induced feline panleukopenia infection.
II. Porencephaly may occur when in utero infection with feline panleukopenia virus occurs later in the period of fetal central nervous system (CNS) vulnerability, or from less virulent viruses.

Pathophysiology

I. The pathophysiology is not well understood.
II. Parvoviral destruction of cerebral tissues is one potential mechanism.
III. Hydranencephaly may arise from a fetal cerebrovascular accident that results in severe necrosis and resorption of cerebral tissue (Barone et al., 2000).

Clinical Signs

I. Signs typically occur within several weeks of birth and are proportional to the extent of cerebral loss.
II. Prosencephalic signs include blindness and behavioral abnormalities, such as compulsive behavior, indifference to surroundings, episodes of rage, and central blindness.

Diagnosis

I. Presumptive diagnosis is based on clinical signs.
II. Antemortem diagnosis can be made with MRI or CT.

Differential Diagnosis

I. Metabolic or toxic encephalopathies
II. Meningoencephalitis
III. Other congenital brain anomalies
IV. Degenerative encephalopathies

Treatment and Monitoring

I. Treatment is similar to that for hydrocephalus.
II. The prognosis is guarded to poor.

Lissencephaly and Pachygyria

Definition and Cause

I. Lissencephaly is a congenital abnormality in which the cerebral hemispheres have a smooth surface and absence of normal development of gyri and sulci (Summers et al., 1995).
II. Pachygyria is a condition in which the neocortex is much thicker than normal.
III. In most cases the cause is unknown, but lissencephaly may be genetic in the Lhasa apso.

Pathophysiology

I. The normal laminar pattern of the neuronal cell body organization is disrupted.
II. Bundles of white matter are randomly scattered throughout a thick cortex.
III. There is no development of corona radiata.

Clinical Signs

I. Lissencephaly is most commonly observed in the Lhasa apso.
II. Many dogs are difficult to house break but have relatively normal behavior.
III. Prosencephalic signs include seizures starting around 1 year of age, behavioral changes, and visual deficits.

Diagnosis

I. MRI reveals an absence of cerebral sulci and gyri, pachygyria, and decreased organization of white mater.
II. Definitive diagnosis is made by postmortem examination.

Differential Diagnosis

I. Metabolic or toxic encephalopathies
II. Meningoencephalitis
III. Other congenital brain anomalies, such as hydrocephalus
IV. Degenerative encephalopathies

Treatment and Monitoring

I. No definitive treatment exists.
II. Treat seizures symptomatically with anticonvulsants (see Chapter 22).
III. Prognosis is guarded.

CONGENITAL CEREBELLAR DISORDERS

Definition and Causes

I. These include developmental defects or malformations of the cerebellum.
II. The cause of most malformations is unknown; however, some may be genetic in origin.
III. Hypoplasia can result from in utero infections with feline and canine parvoviruses (Schatzberg et al., 2003).

Pathophysiology

I. Malformations
  A. Various forms of cerebellar agenesis and hypoplasia have been reported in dogs (Summers et al., 1995).
  B. A unique cerebellar malformation (Dandy-Walker syndrome) is characterized by a hypoplastic or aplastic cerebellum, cystic lesions of the caudal fossa or fourth ventricle, and hydrocephalus (Summers et al., 1995).
II. Hypoplasia
  A. The external germinal layer of the cerebellum is destroyed in utero by a parvovirus, with hypoplasia of the granule layer and disorganization of the Purkinje cells.
  B. Viruses or their resulting inflammation may destroy previously differentiated Purkinje neurons and cerebellar parenchyma, causing atrophy of the cerebellum (de Lahunta 1983).

Clinical Signs

I. Signs are present from the time the animal is able to walk and are usually nonprogressive.
II. Signs include a wide stance, spastic-hypermetric gait (cerebellar ataxia), loss of balance, and intention tremors.

Diagnosis

I. Presumptive diagnosis is based on clinical signs present at or soon after birth.
II. Multiple animals in the litter may be affected.
III. MRI may reveal a small cerebellum and increased amounts of CSF between the folia.
IV. Definitive diagnosis is made by postmortem examination.

Differential Diagnosis

I. Degenerative encephalopathies
II. Congenital cerebellar and abiotrophies
III. Meningoencephalitis

Treatment and Monitoring

I. No definitive treatment exists.
II. Clinical signs are typically nonprogressive.
III. Although signs persist, some animals make good pets.

Caudal Occipital Malformation and Syringohydromyelia

Definition

I. Occipital bone malformation and/or hypoplasia causes overcrowding of the caudal fossa and foramen magnum, obstruction of CSF, and syringohydromyelia.
II. Syringohydromyelia is a fluid-filled cavity within the spinal cord (syrinx) and central canal (hydromyelia).

Causes and Pathophysiology

I. Malformation of the occipital bone causes elongation and caudal displacement of the cerebellar vermis through the foramen magnum.
II. The spinal cord is pushed caudally by the medulla and may have a kinked appearance.
III. Occasionally, mild to moderate obstructive hydrocephalus is present.
IV. Syringohydromyelia may develop secondarily, but the pathogenesis is uncertain.

Clinical Signs

I. The Cavalier King Charles spaniel is overrepresented, but any breed may be affected.
II. Affected animals range in age from 6 months to 10 years.
III. Signs may manifest acutely or have an insidious course over months to years.
IV. An unusual manifestation is the observation of paroxysmal involuntary flank or neck scratching in Cavalier King Charles spaniels.
V. Spinal cord signs include cervical pain, cervical dystonia (torticollis), hyperesthesia, proprioceptive ataxia, abnormal postural reactions, varying degrees of paresis and hypermetria, and exercise intolerance.
VI. Intracranial signs include seizures and deficits of cranial nerves VII and VIII.
VII. Denervation of epaxial muscles and lesions in the dorsal tracks of the spinal cord can lead to muscle atrophy and scoliosis.

Diagnosis

I. MRI reveals varying degrees of ventriculomegaly, syringohydromyelia, compression of the cerebellum by the occipital bone, caudal displacement and herniation of the cerebellar vermis, and obstruction of the subarachnoid space at the foramen magnum.
II. CSF analysis occasionally reveals a mild elevation in nucleated cells and total protein.

Differential Diagnosis

I. Intervertebral disc disease
II. Meningoencephalitis
III. Neoplasia
IV. Atlantoaxial subluxation

Treatment and Monitoring

I. Prednisone 0.5 mg/kg PO QOD may control signs (Rusbridge et al., 2000).
II. Surgical management (subtotal occipital craniectomy, dorsal laminectomy of first cervical vertebra and durotomy to relieve obstruction) may be indicated for dogs with progressive signs (Dewey et al., 2005).
III. Prognosis is fair to good depending on the severity of clinical signs.

DEGENERATIVE DISORDERS

Neuronal Abiotrophies and Dystrophies

Definition and Causes

I. Many of these disorders (Table 23-1) are familial, hereditary, and cause degeneration of the CNS within the first few months of life (Summers et al., 1995).
II. Abiotrophies are characterized by early or premature neuronal degeneration and cell death.
  A. They are typically associated with an inherent lack of vital trophic or nutritive factors.
  B. They are categorized by the location of the affected neurons.
    1. Cerebellar abiotrophies are the most common and affect cerebellar Purkinje cells.
    2. Multisystem neuronal abiotrophies affect neurons throughout the CNS.
    3. Motor neuron abiotrophies affect motor neurons and cause lower motor neuron signs, with marked denervation atrophy and debilitating muscle contractures (arthrogryposis).
III. Neuraxonal dystrophies are a group of inherited (often autosomal recessive) disorders characterized by axonal swellings (spheroids) in preterminal portions of axons and synaptic terminals.
IV. Leukodystrophies (demyelinating disorders) are primary disorders of myelin synthesis.
  A. Leukodystrophies can involve CNS and peripheral nervous system (PNS) myelin.
  B. White matter involvement is usually regional, bilateral, and symmetrical.
V. Hypomyelinogenesis is absent, delayed, or abnormal production of myelin.
  A. Histologically, oligodendrocytes are diminished in number or may be dysfunctional.
  B. An X-linked inheritance pattern is known or suspected.
  C. Other possible causes include in utero infections or intoxications.
VI. Spongy degenerations are characterized by diffuse CNS vacuolation in the white and grey matter.
VII. Axonopathies are characterized by diffuse CNS degeneration that result predominantly in encephalomyelopathies and neuropathies.
  A. A subset of these disorders (spinocerebellar degenerations) induces bilaterally symmetrical degeneration of ascending and descending tracts of the spinal cord.
  B. Despite lesions predominantly affecting the spinal cord, progressive cerebellar signs are seen clinically.

Clinical Signs

I. With cerebellar abiotrophies, signs are noted in the first few weeks to months of life.
  A. Affected animals slowly develop progressive signs over months to years.
  B. Signs of cerebellar disease include a wide stance, spastic-hypermetric gait, loss of balance, intention tremors, and absent menace response.
II. With neuraxonal dystrophies signs of spinal cord and cerebellar dysfunction occur.
  A. Lesions occur diffusely throughout the CNS, but spinal cord lesions predominate.
  B. Affected breeds include the rottweiler, Chihuahua, German shepherd dog, and domestic short-haired cat.
III. Hypomyelinating disorders are characterized by generalized tremors, especially in the pelvic limbs.
  A. They often abate with rest.
  B. Signs may resolve spontaneously or persist indefinitely.

Diagnosis

I. Diagnosis is suspected based on the signalment and clinical signs (see Table 23-1).
II. MRI may be useful to demonstrate the distribution of lesions.
III. Definitive diagnosis often requires postmortem examination.

Differential Diagnosis

I. Disorders of intermediary metabolism
II. Metabolic disorders
III. Meningoencephalitis
IV. Neoplasia

Treatment and Monitoring

I. No definitive treatment exists for these degenerative disorders.
II. Prognosis is variable and often poor for long-term survival.

DISORDERS OF INTERMEDIARY METABOLISM

Definition and Causes

I. These disorders are caused by inherited errors in intermediary metabolism that arise from abnormal or deficient enzyme systems (Summers et al.,1995).
II. Some disorders are storage diseases.

TABLE 23-1

Breed-Associated Degenerative Disorders of the Brain

BREEDS	DISEASE	ONSET AND CLINICAL SIGNS	DIAGNOSIS
Cats			
Birman cat	Distal central-peripheral axonopathy	8-10 months; hypermetria, progressive paraparesis, plantigrade pelvic limb posture	Nerve biopsy
	Spongiform encephalopathy	7 weeks; hypermetria, paraparesis, depression	Histopathology
Domestic short-haired cat	Neuraxonal dystrophy	5-6 weeks; head tremors, ataxia, hypermetria	Histopathology
Egyptian mau	Spongiform encephalopathy	7 weeks; hypermetria, paraparesis, depression	Histopathology
Dogs			
Airedale terrier	Cerebellar degeneration	Cerebellar signs*	Histopathology
	Cerebellar hypoplasia	Cerebellar signs	Histopathology, MRI
Akita	Cerebellar abiotrophy	Cerebellar signs	Histopathology, MRI
American cocker spaniel	Neuronal degeneration	10-14 months; behavior and personality changes, absent menace response, variable hypermetria and falling	Histopathology
	Cerebellar signs	1-2 months; cerebellar signs that may stabilize by 12 months	Histopathology
	Neuraxonal dystrophy	2-4 months; hypermetria, ataxia, intention tremor	Histopathology
Australian kelpie	Cerebellar abiotrophy	6-12 weeks; cerebellar signs	Histopathology, MRI
Beagle	Cerebellar abiotrophy	3 weeks; cerebellar signs	Histopathology, MRI
Bernese mountain dog	Hypomyelination	2-8 weeks; fine tremor of the head and limbs, weakness, stiffness; may improve with age	Histopathology, MRI
Border collie	Cerebellar abiotrophy	6-8 weeks; cerebellar signs	Histopathology, MRI
Boxer	Progressive axonopathy	2 months; progressive ataxia and weakness; diminished proprioception, muscle tone, patellar reflexes; intact nociception	EMG and nerve conduction studies, nerve biopsy, histopathology
Brittany spaniel	Cerebellar abiotrophy	7-13 years; progressive cerebellar signs	Histopathology, MRI
Bullmastiff	Cerebellar abiotrophy	4-9 weeks; progressive cerebellar signs	Histopathology, MRI
	Spongiosis of gray matter	6-9 weeks; ataxia, hypermetria, intention tremor, decreased menace response, visual deficits, poor proprioception	Histopathology
Bull terrier	Cerebellar abiotrophy	Cerebellar signs	Histopathology, MRI
Cairn terrier	Cerebellar abiotrophy	Cerebellar signs	Histopathology, MRI
	Multifocal neuronal degeneration	4-7 months; progressive tetraparesis, cataplexy, cerebellar dysfunction	Histopathology
Chow chow	Hypomyelination	2-4 weeks; intention tremors, dysmetria, bunny hopping, improves after 1 year	Histopathology, MRI
Dalmatian	Leukodystrophy	3-6 months; visual deficits, progressive ataxia	Histopathology
English springer spaniel	Hypomyelination	1-2 weeks; severe tremors	Histopathology, MRI
Finnish harrier	Cerebellar abiotrophy	Cerebellar signs	Histopathology, MRI
Gordon setter	Cerebellar abiotrophy	6-30 months; slowly progressive cerebellar and vestibular signs	Histopathology, MRI
Jack Russell terrier	Spinocerebellar degeneration	2-4 months; cerebellar ataxia, progressive dysmetria and spasticity	Histopathology
Kerry blue terrier	Cerebellar abiotrophy	8-16 weeks; pelvic limb stiffness and head tremors, then dysmetria	Histopathology, MRI

Adapted with permission from Platt RS, Olby N: BSAVA Manual of Canine and Feline Neurology. 3rd Ed. British Small Animal Veterinary Association, Quedgeley, England 2004.

MRI, Magnetic resonance imaging; *EMG*, electromyography.

*Cerebellar ataxia (dysmetria, hypermetria), intention tremors of the head, wide based stance, and occasionally lack of menace with normal vision.

Continued

TABLE 23-1

Breed-Associated Degenerative Disorders of the Brain—*cont'd*

BREEDS	DISEASE	ONSET AND CLINICAL SIGNS	DIAGNOSIS
Labrador retriever	Cerebellar abiotrophy	12 weeks; cerebellar signs	Histopathology, MRI
	Axonopathy	Birth; crouched, short-strided gait in thoracic limbs, hypermetria, unable to stand by 5 months	Histopathology
Old English sheepdog	Cerebellar abiotrophy	Progressive cerebellar signs	Histopathology, MRI
Papillon	Neuroaxonal dystrophy	14 weeks; rapidly progressive ataxia and hypermetria, decreased postural reactions	Histopathology
Poodle	Cerebellar abiotrophy	Cerebellar signs	Histopathology, MRI
Rottweiler	Spongiform degeneration with encephalomyelopathy and polyneuropathy	6-16 weeks; progressive ataxia and dysmetria, laryngeal paralysis, congenital cataracts, microphthalmia	Histopathology
	Leukoencephalopathy	1-4 years; ataxia, tetraparesis, hypermetria, increased muscle tone/spinal reflexes, often more severe in thoracic limbs	Histopathology
	Neuraxonal dystrophy	Within 12 months; slowly progressive ataxia, hypermetria, wide-based stance, eventually intention tremors and nystagmus	Histopathology
Rough-coated collie	Cerebellar abiotrophy	4-8 weeks; progressive cerebellar signs	Histopathology, MRI
Saluki	Spongiosis of gray matter	Behavior changes, seizures, aimless wondering electroencephalography	Histopathology
Samoyed	Hypomyelination	3 weeks; generalized tremors, nystagmus, absent menace response	Histopathology, possibly MRI
	Cerebellar abiotrophy	Cerebellar signs	Histopathology, MRI
Shetland sheepdog	Hypomyelination	2-4 weeks; severe generalized tremors, difficulty standing, seizures, progressive debilitation	Histopathology, MRI
Weimaraner	Hypomyelination	3 weeks; generalized tremors, dysmetria; several dogs normal by 12 months	Histopathology, MRI

Pathophysiology

I. Storage disorders are characterized by defective lysosomal enzymes that are catabolic or obligatory to cellular processes (Skelly and Franklin, 2002).
   A. Loss or dysfunction of a degradative enzyme results in the accumulation of specific substrates in the lysosomes that distend cells with stored products.
   B. Lesions may be multisystemic or limited to the CNS and/or PNS.
   C. Most storage diseases are autosomal recessive traits (Table 23-2).

II. Disorders of intermediary metabolism affect enzyme systems that are not catabolic and do not result in stored substrate.
   A. They typically result in a unique, degenerative encephalopathy.
   B. Most are breed specific, with an autosomal recessive mode of inheritance (see Table 23-2).

Clinical Signs

I. Signs often reflect diffuse CNS involvement; however, cerebellar signs often predominate in storage diseases.
II. See Table 23-2 for specific signs.

Diagnosis

I. Diagnosis is often suspected based on signalment and clinical signs.
II. DNA testing is available for some disorders (see Table 23-2).
III. Diagnosis can be made through metabolite analysis of tissues or body fluids (urine or blood).

Differential Diagnosis

I. Congenital cerebellar disorders or cerebellar abiotrophy (storage disorders)
II. Meningoencephalitis
III. Neoplasia
IV. Other degenerative encephalopathies

TABLE 23-2

Disorders of Intermediary Metabolism (Storage Diseases)

BREEDS	DISEASE	ONSET AND CLINICAL SIGNS	DIAGNOSIS
Cats			
Balinese cat	Niemann-Pick type A	Cerebellar/vestibular signs, depression, peripheral neuropathy	Enzyme assay in leukocytes, cultured fibroblasts
Domestic short-haired cat	Mannosidosis	Onset <6 months; connective tissue and skeletal malformation, possible peripheral neuropathy	DNA testing*
	GM_1 gangliosidosis	Cerebellar signs, dwarfism, facial dysmorphism	Oligosaccharide analysis in urine* Enzyme assay in skin fibroblasts, liver, leukocytes
	GM_2 gangliosidosis	Cerebellar/vestibular signs	Oligosaccharide analysis in urine* Enzyme assay in skin fibroblasts, liver, leukocytes
	Globoid cell leukodystrophy (Krabbe's disease)	Early cerebellar signs and ascending paralysis, cerebellar signs later or peripheral neuropathy	DNA testing† Peripheral nerve biopsy suggestive Enzyme assay in leukocytes, cultured fibroblasts
	Niemann-Pick type C	Ataxia, cerebellar/vestibular signs, peripheral neuropathy, possible hepatomegaly	Enzyme assay in leukocytes or cultured fibroblasts
	MPS VII	Progressive paraparesis	Urine metabolite screening*
	Mucolipidosis II (I-cell disease)	Dysmorphism, failure to thrive, delayed skeletal mineralization and abnormalities, retinal degeneration at 2.5 months of age	Inclusions in cultured fibroblasts, serum lysosomal enzyme assay
Korat cat	GM_2 gangliosidosis	Cerebellar/vestibular signs	Oligosaccharide analysis in urine* Enzyme assay in skin fibroblasts, liver, leukocytes
Norwegian forest cat	Glycogenosis	Incoordination, exercise intolerance	DNA testing*
Persian	Mannosidosis	Onset at 8 weeks; connective tissue and skeletal malformation, possible peripheral neuropathy	DNA testing* Oligosaccharide analysis in urine
Siamese	GM_1 gangliosidosis	Cerebellar signs, dwarfism, facial dysmorphism	Oligosaccharide analysis in urine* Enzyme assay in skin fibroblasts, liver, leukocytes
	Niemann-Pick type A	Cerebellar/vestibular signs, depression, peripheral neuropathy	Enzyme assay in leukocytes and cultured fibroblasts
	MPS VI	Dysmorphism, paraparesis from spinal abnormalities	DNA testing* Urine metabolite screening*
Dogs			
Akita	Glycogenosis (type III)	Muscular weakness, hepatomegaly	Liver, muscle, nervous system pathology
Bassett hound	Lafora's Disease	Myoclonic epilepsy	Intracytoplasmic PAS-positive inclusions in muscle biopsy
Beagle	GM_1 gangliosidosis	Cerebellar signs, dwarfism, facial dysmorphism	Oligosaccharide analysis in urine* Enzyme assay in skin biopsy fibroblasts, liver leukocytes
	Lafora's Disease	Myoclonic epilepsy	Intracytoplasmic PAS-positive inclusions in muscle biopsy

Adapted with permission from Platt RS, Olby N: BSAVA Manual of Canine and Feline Neurology. 3rd Ed. British Small Animal Veterinary Association, Quedgeley, England, 2004.

DNA, Deoxyribonucleic acid; *MPS,* mucopolysaccharidosis; *PAS*, periodic acid Schiff.

*DNA testing, oligosaccharide analysis, organic acid and metabolite screening in the urine, and serum lysosomal enzyme assays are performed by PennGenn/Section of Medical Genetics, Veterinary Hospital 4006, University of Pennsylvania, 3900 Delancey Street, Philadelphia, PA 19104.

†Lysosomal Diseases Testing Laboratory, Jefferson Medical College, Department of Neurology, 1020 Locust Street, Room 394, Philadelphia, PA 19107.

Continued

TABLE 23-2

Disorders of Intermediary Metabolism (Storage Diseases)—*cont'd*

BREEDS	DISEASE	ONSET AND CLINICAL SIGNS	DIAGNOSIS
Dogs—*cont'd*			
Beagle—*cont'd*	Globoid cell leukodystrophy (Krabbe's disease)	Early cerebellar signs and ascending paralysis, cerebellar signs later or periheral neuropathy	DNA testing† Peripheral nerve biopsy suggestive Enzyme assay in leukocytes, cultured fibroblasts
Border collie	Ceroid lipofuscinosis	Adult and juvenile forms Ataxia, seizures, progressive blindness (central ± retinal)	Lipopigment in skin biopsy
Boxer	Niemann-Pick type C	Ataxia, cerebellar/vestibular signs, peripheral neuropathy, possible hepatomegaly	Enzyme assay in leukocytes, cultured fibroblasts
Cairn terrier	Globoid cell leukodystrophy (Krabbe's disease)	Early cerebellar signs and ascending paralysis, cerebellar signs later or peripheral neuropathy	DNA testing† Peripheral nerve biopsy suggestive Enzyme assay in leukocytes, cultured fibroblasts
Dachshund	Lafora's Disease	Myoclonic epilepsy	Intracytoplasmic PAS-positive inclusions in muscle biopsy
	Ceroid lipofuscinosis	Ataxia, seizures, progressive blindness (central ± retinal) Adult and juvenile forms	Lipopigment in skin biopsy
Dashshund, wire-hired	MPS III-A	Ataxia, intention tremor, dysuria	Urine metabolite screening*
English setter	Ceroid lipofuscinosis	Ataxia, seizures, progressive blindness (cental ± retinal) Adult and juvenile forms	Lipopigment in skin biopsy
English springer spaniel	Fucosidosis	Onset at 1-4 years; cerebral signs	DNA testing to detect carrier or affected dogs*
	GM_1 gangliosidosis	Cerebellar signs, dwarfism, facial dysmorphism	Oligosaccharide analysis in urine* Enzyme assay in skin fibroblasts, liver, leukocytes
	Glycogenosis	Incoordination, exercise intolerance	Liver, muscle, nervous system pathology
German shepherd dog	Glycogenosis (type III)	Muscular weakness, hepatomegaly	Liver, muscle, nervous system pathology
German short-haired pointer	GM_2 gangliosidosis	Cerebellar/vestibular signs	Oligosaccharide analysis in urine* Enzyme assay in skin fibroblasts, leukocytes
Irish setter	Globoid cell leukodystrophy (Krabbe's disease)	Early cerebellar signs and ascending paralysis, cerebellar signs later or peripheral neuropathy	DNA testing† Peripheral nerve biopsy suggestive Enzyme assay in leukocytes, cultured, fibroblasts
Japanese spaniel	GM_2 gangliosidosis	Cerebellar/vestibular signs	Oligosaccharide analysis in urine* Enzyme assay in skin fibroblasts, liver, leukocytes
Labrador retriever	MPS II	Incoordination, exercise intolerance, visual deficits	Urine metabolite screening*
Lapland dog	Glycogenosis (type II)	Muscle weakness, vomiting, megaesophagus, cardiac and respiratory abnormalities	Liver, muscle, nervous system pathology, EMG abnormalities
Maltese	Malonic aciduria	Seizures, stupor	Organic acid screening*
Miniature pinscher	MPS VI	Dysmorphism, paraparesis from spinal abnormalities	DNA testing* Urine metabolite screening*
Mix-breed dogs	MPS VII	Pelvic limb weakness, joint laxity, atrioventricular valve incompetence	DNA testing* Urine metabolite screening*

EMG, Electromyography.

TABLE 23-2

Disorders of Intermediary Metabolism (Storage Diseases)—*cont'd*

BREEDS	DISEASE	ONSET AND CLINICAL SIGNS	DIAGNOSIS
Dogs—*cont'd*			
Plott hound	MPS I	Dysmorphism, paraparesis from spinal abnomalities	Urine metabolite screening*
Poodle	Globoid cell leukodystrophy (Krabbe's disease)	Early cerebellar signs and ascending paralysis, cerebellar signs later or peripheral neuropathy	DNA testing† Peripheral nerve biopsy suggestive Enzyme assay in leukocytes, cultured fibroblasts
Portuguese water dog	GM_1 gangliosidosis	Cerebellar signs, dwarfism, facial dysmorphism	Oligosaccharide analysis in urine* Enzyme assay in skin fibroblasts, liver, leukocytes
Siberian husky	GM_1 gangliosidosis	Cerebellar signs, dwarfism, facial dysmorphism	Oligosaccharide analysis in urine* Enzyme assay in skin fibroblasts, liver, leukocytes
Silky terrier	Glucocerebrosidosis (Gaucher disease)	Onset at 4-10 months; cerebellar signs, ataxia, seizures, dementia	Enzyme assay (β-glucosidase) in leukocytes
Staffordshire bull terrier	L-2-hydroxyglutaric aciduria	Onset at 6-8 months; ataxia, hypermetria	Urine organic acid screening*
Sydney silky dog	Glucocerebrosidosis (Gaucher disease)	Ataxia, seizures, progressive blindness (central ± retinal) Adult and juvenile forms	Enzyme assay in leukocytes, cultured fibroblasts
Tibetan terrier	Ceroid lipofuscinosis	Early cerebellar signs and ascending paralysis; late cerebellar signs or peripheral neuropathy	Lipopigment in skin biopsy
West highland white terrier	Globoid cell leukodystrophy (Krabbe's disease)	Ataxia, intention tremor	DNA testing† Peripheral nerve biopsy suggestive Enzyme assay in leukocytes, cultured fibroblasts

Treatment and Monitoring

I. Definitive treatment does not exist.
II. Prognosis is variable and often poor for long-term survival.

INFECTIOUS DISORDERS

Rickettsial Meningoencephalitis

Definition and Causes

I. Rickettsial disorders that can infect the brain include Rocky Mountain spotted fever *(Rickettsia rickettsii),* ehrlichiosis, and salmon poisoning (Greene, 2006).
II. Rocky Mountain spotted fever is transmitted by *Dermacentor andersoni*, *Dermacentor variabilis,* and *Amblyomma americanum* ticks.
III. Canine ehrlichiosis *(Ehrlichia canis)* is transmitted by the brown dog tick, *Rhipicephalus sanguineus*.
IV. Salmon poisoning *(Neorickettsia helminthoeca)* is acquired by consumption of salmonid and other fish that carry the metacercaria of the fluke, *Nanophyetus salmincola,* which is the intermediate host.

Clinical Signs

I. Signs arise from a nonsuppurative meningoencephalitis composed mostly of plasma cells.
II. See Chapter 115 for systemic signs.
III. Neurological signs reflect diffuse brain involvement.

Diagnosis

I. CSF analysis reveals a mononuclear pleocytosis, with mild to moderate elevations in protein content.
II. A complete blood count (CBC) may reveal thrombocytopenia, anemia, and leukopenia early in the course, followed by leukocytosis.
III. Intracytoplasmic ehrlichia morulae are occasionally identified in blood and CSF mononuclear cells.
IV. Definitive diagnosis is based on elevated serum titers, a four-fold rise in antibody titer, or positive polymerase chain reaction (PCR) assays (see Chapters 2 and 115).

Differential Diagnosis

I. Immune-mediated, noninfectious meningoencephalitis
II. Other CNS infections
III. CNS neoplasia: lymphoma, metastatic neoplasia

Treatment and Monitoring

I. Doxycycline is given 5 to 10 mg/kg PO BID for 2 to 3 weeks.
   A. Antibiotics may be effective if initiated early in disease course.
   B. Dogs may respond dramatically within 1 to 2 days, but prognosis is guarded to poor when severe neurological deficits are present.
II. Recovery may be prolonged, and residual neurological deficits are possible.

Mycotic and Algal Infections

Definition and Causes

I. Most mycotic infections are regional diseases that produce pyogranulomatous inflammation of the CNS and are treated similarly (Lavely and Lipsitz, 2005).
   A. Mycoses that may affect the CNS include *Cryptococcus ghatti*, *Blastomyces dermatitidis*, *Histoplasma capsulatum, Coccidioides immitis, Aspergillus* spp., phaeohyphomycosis, and hyalohyphomycosis.
   B. *Cryptococcus neoformans* may be the most common CNS mycotic infection.
II. Protothecosis is a rare CNS infection of dogs caused by the achlorophyllous algae, *Prototheca wickerhamii* and *Prototheca zopfii*.

Pathophysiology

I. Cryptococcosis is typically acquired from the environment (e.g., pigeon droppings, dead trees) rather than directly from infected animals.
II. The natural route of these infections is thought to be via the respiratory tract, with subsequent hematogenous and lymphogenous dissemination.

Clinical Signs

I. Clinical signs may reflect a focal mass lesion or a diffuse, multifocal process.
II. Signs also reflect the location of the lesions within the CNS and are variable.
III. A profound elevation in intracranial pressure may cause severe changes in mentation (depression, stupor, coma).
IV. Ocular and nasal discharge may be noted.
V. See Chapter 111 for systemic signs.

Diagnosis

I. Diagnosis of cryptococcosis utilizes the latex agglutination test (LAT), which detects capsular antigen in serum, urine, or CSF.
II. Serological testing for other agents is described in Chapters 2 and 111.
III. CSF analysis sometimes reveals cryptococcal organisms by staining with India ink.
   A. Mononuclear, neutrophilic, or eosinophilic pleocytosis, and elevated protein levels are often present.
   B. Fungal culture of CSF is usually unrewarding.
IV. MRI may show multiple inflammatory lesions that are hypointense on T1-weighted images and hyperintense on T2-weighted images, with multifocal parenchymal and leptomeningeal enhancement.

Differential Diagnosis

I. Immune-mediated, noninfectious meningoencephalitis
II. Other CNS infections
III. CNS neoplasia: lymphoma, metastatic neoplasia

Treatment and Monitoring

I. Amphotericin B may be given at 0.1 to 0.5 mg/kg IV, SC three times weekly.
   A. Animals treated with amphotericin B require weekly assessment of renal function, and it is contraindicated in animals with renal dysfunction.
   B. Liposome encapsulated preparations may be safer.
II. Imidazole drugs may be tried alone or in conjunction with amphotericin.
   A. Fluconazole 5 to 15 mg/kg PO BID (preferred)
   B. Itraconazole 5 to 10 mg/kg PO BID
III. For cryptococcosis, the LAT is monitored monthly during treatment.
   A. Treatment is discontinued after two negative LAT tests are documented 1 month apart or 1 month after resolution of clinical signs.
   B. Treatment is often prolonged (3 to 12 months).
   C. Prognosis is guarded, especially for disseminated disease.

Canine Distemper Encephalomyelitis

Definition and Cause

I. Canine distemper virus is a multisystemic disease affecting the respiratory, alimentary, urogenital, ocular, and nervous systems in dogs.
II. It is an RNA Morbillivirus of the family Paramyxoviridae.

Pathophysiology

I. Several forms and stages of CNS disease exist (Summers et al., 1995).
II. Lymphocytic meningoencephalomyelitis occurs during the first week of exposure.
   A. No neurological signs are seen during this phase.
   B. Infection may be self-limiting or may progress to affect either grey or white matter (more commonly).
III. Grey matter disease occurs approximately 1 week after initial infection.
   A. Typical sites of infection include the cerebral cortex, brainstem, and spinal cord.
   B. Grey matter disease typically occurs in puppies at 6 to 12 weeks of age; certain viral strains may cause disease in adult dogs.
   C. Postvaccinal disease (inadequately attenuated virus) can occur 7 to 10 days after vaccination and may result in severe brainstem lesions and death.
   D. Old-dog encephalitis is a rare, chronic form of the disease.
   E. Pathologic lesions include neuronal degeneration, gliosis, and eosinophilic inclusions in neurons and glial cells.

IV. White matter disease is the most common form of infection and occurs approximately 1 month after initial infection.
   A. Demyelination is the hallmark finding.
   B. Lesions occur in sites that are adjacent to CSF pathways (optic tracts, hippocampus, cerebellar peduncles, spinal cord).
   C. White matter lesions may be noninflammatory for 1 month, then progress to nonsuppurative meningitis and perivascular encephalitis.
   D. Inflammatory lesions ultimately become necrotizing.
   E. Eosinophilic inclusions can be observed in glial cells.

Clinical Signs

I. With grey matter disease, signs reflect nonsuppurative meningitis.
   A. Seizures, stupor, hysteria, and ataxia can be observed.
   B. Dogs may die within 2 to 3 weeks, recover, or develop white matter disease.
II. With white matter disease, signs are multifocal and variable.
   A. Commonly observed signs include cerebellovestibular ataxia and spinal cord paresis.
   B. Occasionally myoclonus develops of a single limb or the temporalis and/or masseter muscles.
   C. Some dogs die 4 to 5 weeks after initial infection, and some may recover with minimal CNS injury.
   D. Other dogs may have persistent CNS demyelination and nonsuppurative inflammation, with or without clinical signs.

Diagnosis

I. Presumptive diagnosis is based on history, signalment, vaccination status, and clinical signs, especially in nonvaccinated dogs.
II. Immunofluorescent or immunocytochemical techniques can detect canine distemper viral antigen in brain sections and other tissues (mononuclear cells in blood, conjunctival or tracheal washes, foot pad biopsies).
III. CSF analysis reveals moderate pleocytosis of mononuclear cells (lymphocytes, macrophages).
   A. Neutralizing antibody in CSF develops 2 to 3 weeks after onset of disease.
   B. The immunoglobulin G (IgG) index (calculated quotient of IgG and albumin levels in CSF compared to serum that detects intrathecal IgG synthesis) is elevated in most dogs except those with acute, noninflammatory distemper.
IV. Reverse transcriptase PCR of urine, CSF, and conjunctival swabs may identify the virus.

Differential Diagnosis

I. Affected puppies: congenital and developmental diseases
II. Immune-mediated or noninfectious meningoencephalitis
III. Other causes of infectious meningoencephalitis: bacteria, parasites, protozoa, rickettsia
IV. Other viral CNS infections
   A. Borna disease (staggering disease), LaCrosse virus
   B. Canine herpesvirus
   C. Rabies
   D. Tickborne encephalitis virus
   E. Eastern equine encephalitis virus
   F. West Nile virus
V. CNS neoplasia: lymphoma, metastatic disease

Treatment and Monitoring

I. No definitive treatment exists for the virus.
II. Treatment is largely supportive (fluid therapy, nutritional support).
III. Euthanasia is considered for dogs with progressive neurological signs that lead to incapacitation.

Feline Infectious Peritonitis Meningoencephalitis

Definition and Cause

I. Feline infectious peritonitis (FIP) is a fatal, systemic immunopathologic disease caused by a feline coronavirus.
II. Although meningitis may accompany the more acute form of peritoneal exudation, a second form affects the CNS and eye with little or no peritoneal involvement (Foley et al., 1998).

Pathophysiology

I. The underlying pathogenesis involves a type III immune reaction and immune complex-induced vasculitis.
II. This CNS infection is characterized by meningitis, ependymitis, and encephalomyelitis (Summers et al., 1995).
III. The mesencephalic aqueduct may be obstructed, causing hydrocephalus and hydromyelia.
IV. Focal brain or spinal cord lesions may also occur.

Clinical Signs

I. Signs are usually nonspecific, but often include profound cerebellovestibular involvement.
II. Signs from focal lesions reflect the site of the lesion.
III. See Chapter 112 for systemic signs.

Diagnosis

I. Antemortem diagnosis is very challenging.
II. CSF analysis reveals profound neutrophilic or mononuclear pleocytosis, with high elevations of protein.
III. Identification of antibody titers in CSF is supportive.
IV. Serum titers are difficult to interpret (see Chapter 112).
V. Serum hypergammaglobulinemia and increased fibrinogen levels may occur.
VI. MRI may show marked dilation of the ventricular system and enhancement of ependymal (periventricular) surfaces and the choroid plexus.
VII. Definitive diagnosis requires histopathology.

Differential Diagnosis

I. Congenital or developmental diseases
II. CNS neoplasia: lymphosarcoma
III. Other viral diseases: feline immunodeficiency virus, Borna disease

IV. Bacterial meningoencephalitis
V. Toxoplasmosis

Treatment and Monitoring

I. Because no definitive treatment exists, supportive care (fluid therapy, nutritional support) may be tried.
II. Prednisone 2 to 4 mg/kg PO SID to BID may provide palliative relief.
III. The prognosis is grave for long-term survival.

Bacterial Meningoencephalitis

Definition and Causes

I. It is inflammation of the brain and/or meninges from aerobic or anaerobic bacterial infections.
II. Organisms that can infect the CNS include *Pasteurella, Staphylococcus, Actinomyces, Nocardia, Streptococcus,* and *Klebsiella* spp., and *Eschericia coli*.

Pathophysiology

I. A variety of mechanisms allow bacterial entry into the CNS.
   A. Hematogenous spread from distant foci: lung abscess, vegetative endocarditis, urinary tract infection
   B. Direct extension from nasal and paranasal sinuses, ears, and eyes
   C. Secondary to trauma and wound contamination (bite wound)
   D. Meningeal spread along nerve roots
   E. Contaminated surgical instruments: spinal needles
II. Organisms usually disseminate through CSF pathways and produce meningitis and microabscesses of the brain and spinal cord.
III. Formation of inflammatory cytokines and tumor necrosis factor by monocytes and neural cells leads to altered blood-brain barrier permeability, recruitment of neutrophils, and purulent exudates in the subarachnoid space.
IV. Vasculitis leads to vasogenic brain edema.
V. Toxic oxygen metabolites released from degranulating leukocytes also cause cytotoxic brain edema.

Clinical Signs

I. Clinical signs begin acutely.
II. Systemic signs include fever, vomiting, bradycardia, anorexia, shock, and hypotension.
III. Neurological signs consist of hyperesthesia, cervical pain and rigidity (common), seizures (occasionally), and cranial nerve deficits (Radaelli and Platt, 2002).

Diagnosis

I. CSF analysis typically shows a profound neutrophilic pleocytosis and protein elevation.
   A. Organisms sometimes may be seen on CSF cytology.
   B. Bacterial culture of CSF (aerobic and anaerobic) provides a definitive diagnosis, but negative cultures do not rule out the disease.
II. Blood and urine cultures may yield a pathogenic organism.
III. A CBC may reveal a neutrophilic leukocytosis and left shift.
IV. MRI and CT can show meningeal, brain and/or ventricular enhancement, as well as abscessation.

Differential Diagnosis

I. Immune-mediated meningoencephalitis, especially steroid-responsive meningitis/arteritis
II. Intervertebral disc disease
III. Other CNS infections
IV. CNS neoplasia: lymphoma, metastatic neoplasia
V. Systemic bacterial infections

Treatment and Monitoring

I. Preferred antibiotic therapy is based on culture results and is continued for several weeks after clinical signs have resolved.
II. Empirical treatment choices in dogs are as follows:
   A. Chloramphenicol 50 mg/kg IV, IM, SC, PO BID
   B. Metronidazole 10 to 15 mg/kg PO TID
   C. Enrofloxacin 10 mg/kg IV, PO SID
   D. Azithromycin 5 to 10 mg/kg PO SID
   E. Trimethoprim-sulfonamide 15 to 30 mg/kg PO BID
III. Corticosteroids are generally contraindicated, but anti-inflammatory doses may be beneficial upon initiation of treatment.
IV. Prognosis is guarded.
   A. Death is common even if appropriate therapy is administered.
   B. Relapses are frequently encountered.

Toxoplasmosis

Definition and Cause

I. Toxoplasmosis may be the most common protozoa to affect the CNS in dogs and cats.
II. The causative agent is *Toxoplasma gondii.*

Pathophysiology

I. Organisms may form cysts in the CNS and in the skeletal and heart muscles.
II. Parasites are mainly intracellular, and subclinical infection may persist for life.
III. Activation may occur with severe immunosuppression, especially from viral infections.
IV. Nonsuppurative (focal or multifocal) necrotizing meningoencephalomyelitis occurs in the CNS, whereas radiculitis and myositis develop in the PNS.
V. Chorioretinitis commonly accompanies CNS lesions.
VI. Lesions may also occur in lungs, liver, spleen, and lymph nodes.

Clinical Signs

I. The disease most commonly affects animals <1 year of age or animals that are immunocompromised.
II. Clinical signs relate to either focal (granulomas) or multifocal CNS disease.

III. Possible signs include hyperexcitability, depression, intention tremors, paresis, paralysis, head tilt, and seizures.
IV. Spinal cord signs are more common in cats.
V. See Chapter 116 for systemic signs.

Diagnosis

I. Definitive diagnosis is often difficult to establish (see Chapter 116).
II. CSF analysis may demonstrate a mononuclear, neutrophilic, or eosinophilic pleocytosis, with elevated protein levels.
III. PCR may reveal the presence of the organism in CSF, muscle, or liver biopsies.
IV. Electromyography (EMG) may show abnormal spontaneous activity in animals with muscle and nerve involvement, and nerve conduction velocities may be decreased in animals with nerve involvement.
V. MRI or CT may reveal focal or multifocal CNS lesions.

Differential Diagnosis

I. Dogs
  A. *Neospora caninum*
    1. Most often affects dogs <2 years of age
    2. Predilection for lumbosacral nerve roots (radiculitis, neuritis, see Chapter 24)
    3. May cause encephalitis (especially cerebellitis) in adult dogs
  B. Sarcocystosis, encephalitozoonosis, trypanosomiasis
  C. Acanthamebiasis, babesiosis
  D. Leishmaniasis
  E. Autoimmune, bacterial, viral meningoencephalitis
  F. Neoplasia: lymphosarcoma, histiocytic tumors
II. Cats
  A. FIP
  B. Neoplasia: lymphosarcoma
  C. Borna disease
  D. Bacterial meningoencephalitis

Treatment and Monitoring

I. Clindamycin is the drug of choice and is given at 10 to 20 mg/kg PO, IM BID for 3 to 6 weeks.
II. Alternatively, trimethoprim-sulfonamide (15 to 20 mg/kg PO BID) is combined with pyrimethamine at 1 mg/kg PO SID for 4 to 8 weeks.
III. Prognosis is guarded with CNS involvement, but some animals survive with minimal residual neurological deficits.

NONINFECTIOUS INFLAMMATORY DISORDERS

Granulomatous Meningoencephalomyelitis

Definition and Cause

I. Granulomatous meningoencephalomyelitis (GME) is an idiopathic (mononuclear) meningoencephalomyelitis that most commonly occurs in young to middle-age dogs.
II. GME is thought to be an immune-mediated (delayed-type hypersensitivity) disease based on the presence of major histocompatibility complex class II and cluster differentiation (CD3) antigen-positive lymphocytes (Kipar et al., 1998).

Pathophysiology

I. Three morphological forms exist, namely disseminated, focal, and ocular disease (Summers et al., 1995).
II. Lesions consist of perivascular, concentric proliferations of inflammatory cells predominantly in the white matter.
III. Perivascular cellular accumulations consist of lymphocytes, plasma cells, and mononuclear cells.

Clinical Signs

I. Onset ranges from 9 months to 10 years of age.
II. Signs may be acute, rapidly progressive and fatal, or chronic and insidious.
III. The focal form of GME results in focal deficits, whereas the disseminated form causes multifocal signs.
IV. Neurological signs reflect lesion location and distribution.
  A. Brainstem (varying degrees of depression and spastic tetraparesis, vestibular ataxia, head tilt, abnormal nystagmus) and cerebellar signs are most common.
  B. Prosencephalic signs include seizures, depression, circling, and visual deficits.
  C. The ocular form causes visual deficits, anisocoria, and abnormalities in pupillary light reflexes.
V. A fever is often present.

Diagnosis

I. The CSF usually reveals a mild to severe pleocytosis of monocytes and lymphocytes, with mild protein elevation.
II. MRI and CT may reveal multifocal lesions, predominantly in the white matter of the CNS.
III. Definitive diagnosis requires histopathology.

Differential Diagnosis

I. Necrotizing meningoencephalitis
II. Necrotizing leukoencephalitis
III. Infectious meningoencephalitis
IV. CNS neoplasia: lymphoma, metastatic neoplasia

Treatment and Monitoring

I. Immunosuppression is the primary therapy.
II. Prednisone is given at 1.0 to 3.0 mg/kg PO BID for 1 month, then gradually tapered over several months to 0.5 mg/kg PO SID to QOD.
III. Additional drugs may allow a reduction in prednisone and ameliorate its side effects.
  A. Cytosine arabinoside 50 mg/m^2 SC BID for 2 days, repeated every 3 weeks (Zarfoss et al., 2006)
  B. Cyclosporine 5 to 10 mg/kg PO BID (Adamo and O'Brien, 2004)
  C. Others: leflunomide, procarbazine, CCNU (lomustine)
IV. Radiation therapy may be beneficial for the focal form.
V. GME is rarely cured and often requires lifelong therapy to control the inflammation.

Necrotizing Meningoencephalitis

Definition and Cause

I. It is an idiopathic meningoencephalitis of young pugs, Maltese, Shih tzus, and occasionally other small-breed dogs (Cordy and Holliday, 1989; Stalis et al., 1995).
II. It is presumed to be an immune-mediated disease.

Pathophysiology

I. Lesions consist of nonsuppurative meningoencephalitis and mild cerebral necrosis.
II. It typically affects the cerebral hemispheres, with inflammation extending from the leptomeninges through the cortex and into the corona radiata.
III. This pattern leads to a loss of demarcation between cortical grey and white matter in the brain.

Clinical Signs

I. Onset ranges from 9 months to 4 years of age.
II. Signs may be rapidly progressive and fatal.
III. Signs consist of prosencephalic signs, such as seizures, depression, circling, and visual deficits.
IV. Motor and sensory problems (ataxia, paresis), brainstem and cerebellar signs are also possible.

Diagnosis

I. CSF analysis shows a moderate to severe pleocytosis composed of monocytes and lymphocytes, with mild protein elevation.
II. MRI findings mirror the topography of the histopathologic lesions.
III. MRI typically demonstrates multifocal lesions in the superficial cortical grey matter at the junction of the cerebrum and leptomeninges.

Differential Diagnosis

I. Granulomatous meningoencephalomyelitis
II. Necrotizing leukoencephalitis
III. Infectious meningoencephalitis
IV. CNS neoplasia: lymphoma, metastatic neoplasia
V. Metabolic, toxic encephalopathies
VI. Other causes of seizures: see Chapter 22

Treatment and Monitoring

I. Immunosuppression is the primary therapy and is similar to that for GME.
II. The prognosis is grave.
III. If a response is seen to immunosuppression, lifelong therapy is necessary to control the inflammation.

Necrotizing Leukoencephalitis

Definition and Cause

I. It is an idiopathic (mononuclear) meningoencephalitis of young Yorkshire terriers, Chihuahuas, and occasionally other small-breed dogs (Tipold et al., 1993).
II. It is presumed to be an immune-mediated disease.

Pathophysiology

I. Lesions consist of nonsuppurative meningoencephalitis and moderate to severe cerebral necrosis.
II. Gross cavitations occur in periventricular cerebral and diencephalic (thalamocortical) white matter.

Clinical Signs

I. Onset is from 1 to 5 years of age.
II. The clinical course is slowly progressive, usually over many weeks to months.
III. Clinical signs reflect caudal brainstem or prosencephalic lesions.
IV. Brainstem signs often predominate and include varying degrees of depression, spastic tetraparesis, vestibular ataxia, head tilt, and abnormal nystagmus.
V. Prosencephalic signs consist of seizures, propulsive activity, and visual deficits.

Diagnosis

I. The CSF analysis usually reveals a moderate to severe pleocytosis of monocytes and lymphocytes and a mild protein elevation.
II. MRI and CT may show multifocal cavitating lesions predominantly in deep white matter.

Differential Diagnosis

I. Granulomatous meningoencephalomyelitis
II. Necrotizing meningoencephalitis
III. Infectious meningoencephalitis
IV. CNS neoplasia: lymphoma, metastatic neoplasia
V. Metabolic or toxic encephalopathies
VI. Other causes of seizures: see Chapter 22

Treatment and Monitoring

I. Immunosuppression is the mainstay of therapy (see under GME).
II. The prognosis is grave and therapy may be life-long.

Canine Meningeal Polyarteritis

Definition and Cause

I. The disease is a neutrophilic meningitis of young dogs that is characterized by episodes of severe pain, depression, and fever (Cizinauskas et al., 2000).
II. It is presumed to be immune-mediated.
III. It is also known as *steroid-responsive* (or *sterile*) *meningitis-arteritis, immune-mediated meningitis, Beagle pain syndrome, systemic necrotizing vasculitis,* and *juvenile polyarteritis syndrome.*

Pathophysiology

I. Inflammation occurs in the leptomeningeal arteries.
II. Leptomeningeal vascular lesions may be accompanied by lymphocytic thyroiditis, amyloidosis (splenic, hepatic, renal), or polyarthritis (Webb et al., 2002).

Clinical Signs

I. Affected dogs range in age from 6 months to a few years.
II. It affects the beagle, Bernese mountain dog, boxer, German short-haired pointer, and is sporadically reported in other breeds.
III. The predominant clinical signs are profound neck pain, depression, anorexia, and fever.
IV. Occasionally, ataxia and varying degrees of paresis are also present (see Chapter 24).
V. The clinical course is typically acute in onset.

Diagnosis

I. Signalment and clinical signs are suggestive.
II. CSF analysis reveals the following:
   A. CSF has a severe neutrophilic pleocytosis, with excessive protein and phagocytosed red blood cells (RBCs).
   B. Neutrophils in CSF do *not* show toxic changes, and intracellular bacteria are not observed.
   C. CSF aerobic and anaerobic bacterial cultures are negative.
   D. Consistent elevation of CSF and serum immunoglobulin (Ig) A concentrations occur.
III. Occasionally peripheral neutrophilia with a left shift and an elevated serum α2-globulin fraction are found.
IV. CT or MRI may demonstrate contrast enhancement of the meninges, spinal cord, or brain.

Differential Diagnosis

I. Intervertebral disc disease
II. Bacterial meningoencephalitis
III. Other immune-mediated meningoencephalitides
IV. CNS neoplasia

Treatment and Monitoring

I. Long-term immunosuppression is achieved with prednisone at 1 to 2 mg/kg PO BID, then tapered monthly over 6 months.
II. In refractory cases, azathioprine (1.5 mg/kg PO SID to QOD) may be added and eventually alternated with prednisone QOD.
III. Prognosis is guarded to favorable; recurrences are common.
IV. Monitor for recurrences, and consider repeating the CSF analysis if clinical signs persist.

Eosinophilic Meningoencephalitis

Definition and Cause

I. Eosinophilic meningoencephalitis is an uncommon disease, primarily of rottweilers and golden retrievers, that is characterized by severe, multifocal neurological signs (Smith-Maxie et al., 1989; Schultze et al., 1986).
II. It is presumed to be an immune-mediated disease.

Clinical Signs

I. Prosencephalic signs consist of behavioral and mentation changes, circling, pacing, head pressing, blindness, and generalized or partial seizures.
II. Brainstem signs include episodic collapse, facial paralysis, absent gag reflex, reduced pupillary light reflexes, torticollis, and varying degrees of ataxia and incoordination.

Diagnosis

I. CSF analysis shows variable pleocytosis, with 21% to 98% eosinophils, and elevated protein content.
II. Mild to moderate systemic eosinophilia may be observed.
III. Serology for infectious diseases is negative.

Differential Diagnosis

I. Other CNS infections: primary protozoal, fungal, parasitic
II. Other noninfectious meningoencephalitides
III. CNS neoplasia

Treatment and Monitoring

I. Prednisone therapy (and possibly additional immunosuppressive agents) is instituted similar to that for GME.
II. Prognosis is favorable to guarded.

IDIOPATHIC DISORDERS

Idiopathic Tremor Syndrome

Definition and Cause

I. Idiopathic tremor syndrome (shaker dog disease) is a meningoencephalitis of young, small, white dogs (de Lahunta, 1983).
II. Occasionally, dogs with pigmented coats are affected.
III. The exact pathogenesis remains uncertain, although it may be immune-mediated.
IV. Mild lymphoplasmacytic meningoencephalitis is the predominant lesion.

Clinical Signs

I. It most commonly affects Maltese and West Highland white terriers.
II. Other affected breeds include the bichon frisé, Spitz, samoyed, beagle, dachshund, and Yorkshire terrier.
III. The predominant clinical sign is continuous, whole-body tremors that worsen with exercise, stress, and excitement, but disappear with sleep.
IV. Neurological examination often is normal, with the exception of generalized tremors.
V. When present, neurological signs may include absent menace response, spontaneous nystagmus, poor to absent oculocephalic reflexes (physiological nystagmus), vestibular or cerebellar ataxia, head tilt, varying degrees of paresis, and seizures.

Diagnosis

I. CSF analysis reveals mild lymphocytic pleocytosis, with normal or mildly elevated protein levels.
II. MRI typically is normal, but may disclose symmetrical ventricular enlargement in some dogs.

Differential Diagnosis

I. Metabolic or toxic encephalopathies
II. Meningoencephalitis
III. Dysmyelinogenic disorders

Treatment and Monitoring

I. Prednisone is administered at 1 to 2 mg/kg PO SID for 4 weeks, then tapered to 0.5 to 1 mg/kg PO SID for 2 weeks, then to QOD for 2 weeks, then to every 72 hours for 4 weeks.
II. Diazepam 0.25 mg/kg PO BID to TID or propanolol 1 mg/kg PO TID may be beneficial in refractory cases.
III. Prognosis is favorable, with tremors usually decreasing by the end of the first week of therapy.
IV. Relapses can occur and may require additional immunosuppressive therapy (e.g., azathioprine).

Trigeminal Neuropathy

Definition and Cause

I. It is an idiopathic disorder characterized by acute onset of trigeminal nerve paresis or paralysis (de Lahunta, 1983).
II. It may be an immune-mediated condition.

Clinical Signs

I. Clinical signs include an acute onset of jaw paresis or paralysis with an inability to close the mouth, drooling, and difficult prehension of food and water.
II. Trigeminal sensory deficits are common.
III. Horner's syndrome (from effects on postganglionic sympathetic fibers incorporated in segments of the ophthalmic branch of the trigeminal nerve) is occasionally seen.
IV. Occasionally, the facial nerve is also involved.

Diagnosis

I. EMG of the muscles of mastication is abnormal.
II. CSF analysis may reveal a mild mononuclear pleocytosis, often with normal or mildly elevated protein content.
III. Definitive diagnosis of trigeminal neuropathy requires biopsy of the trigeminal nerve, but it is rarely done.

Differential Diagnosis

I. Lymphoma infiltrating the trigeminal nerves
II. Polyradiculoneuritis
III. Rabies
IV. Masticatory muscle myositis

Treatment and Monitoring

I. The condition is often self-limiting, with recovery occurring over 3 to 4 weeks to several months.
II. Corticosteroids do not seem to affect the clinical course.
III. Fluid and nutritional support may be necessary for animals unable to eat and drink on their own.
IV. The severity of muscle atrophy, clinical course, and recovery depends upon the extent of axonal degeneration.
V. Prognosis is favorable in most cases, but can be guarded in severely affected animals.

Idiopathic Facial Nerve Paralysis

Definition and Cause

I. It is a disorder of mature dogs and cats that is characterized by facial palsy or paralysis (Kern and Erb, 1987).
II. The cause is unknown.

Clinical Signs

I. Predisposition exists in the American cocker spaniel, Pembroke Welsh corgi, boxer, English setter, and domestic long-haired cat.
II. Clinical signs include ear drooping, commissural paralysis of the lip, sialosis, deviation of the nose away from the affected side, and collection of food on the paralyzed side of the mouth.
III. Menace response and palpebral reflexes are absent ipsilaterally.
IV. Facial paralysis is usually unilateral, but may be bilateral in some animals.
V. Horner's syndrome is not seen.

Diagnosis

I. Diagnosis is often presumptive, based on clinical signs and exclusion of other disorders.
II. EMG may reveal spontaneous denervation potentials in superficial facial muscles.

Differential Diagnosis

I. Polyradiculoneuritis (coonhound paralysis)
II. Endocrine disorders: hypothyroidism, insulinoma
III. Laryngeal paralysis syndrome
IV. Myasthenia gravis, botulism
V. Trauma near the stylomastoid foramen or in conjunction with petrosal bone fracture
VI. Middle ear infection, neoplasia
VII. Surgery of the external or middle ear, or side of the face
VIII. Extracranial tumors

Treatment and Monitoring

I. Application of ophthalmic lubricants helps prevent corneal drying.
II. Prognosis for a complete return to function is guarded.
III. Chronic lip paralysis may result in permanent contracture, and the inability to close the eyelids often leads to keratitis.

Peripheral Vestibular Syndrome

Definition and Cause

I. It is an acute disorder that occurs in cats of all ages and in older dogs (de Lahunta, 1983).
II. Mechanism and cause are unknown.
III. Most feline cases (80%) occur in the summer (Burke et al., 1985).

Clinical Signs

I. Clinical signs occur acutely.
II. Only signs of peripheral vestibular dysfunction (no evidence of facial nerve paralysis or Horner's syndrome) are present.

III. Signs include head tilt, asymmetrical ataxia, and horizontal or rotatory nystagmus with the fast phase directed away from the head tilt.
IV. More severe signs of falling, rolling, and vomiting (especially in dogs) are seen occasionally.

Diagnosis

I. Presumptive diagnosis is based on signalment, history, clinical signs, and exclusion of other etiologies.
II. Absence of otoscopic and radiographic abnormalities of the middle ear is supportive.
III. MRI or CT scan is normal.
IV. CSF analysis is normal.

Differential Diagnosis

I. Otitis media/interna
II. Neoplasia
III. Cerebrovascular accident of brainstem

Treatment and Monitoring

I. Supportive care is administered, as needed.
II. Affected animal tends to stabilize in a few days and improve gradually over several weeks.
III. Prognosis for spontaneous remission is good; however, residual deficits (e.g., mild head tilt) may occur.

PARASITIC DISORDERS

Parasitic Encephalomyelitis

Definition

I. Aberrant migration of parasite larvae through the CNS results in parenchymal damage and neurological signs (Braund, 2005).
II. It is also known as *cerebral larval migrans.*

Causes

I. *Toxocara canis*
II. *Ancylostoma caninum*
III. *Angiostrongylus cantonensis*
IV. *Dirofilaria immitis*
V. *Angiostrongylus vasorum*
VI. *Cysticercus cellulosae*
VII. *Baylisascaris procyonis*
VIII. *Coenurus serialis*

Pathophysiology

I. Migrating larvae damage neural tissue by two mechanisms.
II. Necrosis can occur in tissue along the migratory pathway.
III. Migrating larvae evoke an inflammatory response, which causes ischemia, edema, and toxic injury to myelin, axons, and neurons.

Clinical Signs

I. Clinical signs are acute in onset and rapidly progressive.
II. Signs reflect the location of the migratory pathway.
   A. Prosencephalon signs include blindness, circling, behavioral changes, seizures, and postural reaction deficits.
   B. Brainstem signs include varying degrees of ataxia and paresis, changes in mentation, cranial nerve deficits, head tilt, and spontaneous nystagmus.
   C. Cerebellar signs include a wide stance; a spastic, hypermetric gait; loss of balance; intention tremors; and absent menace response.
III. Neurological signs may reflect focal or multifocal disease.

Diagnosis

I. CSF is characterized by an eosinophilic or neutrophilic pleocytosis, and protein elevation.
II. A positive test for *D. immitis* is suggestive.
III. Definitive diagnosis requires histological demonstration of the parasite within the CNS.

Differential Diagnosis

I. Infectious meningoencephalitis
II. Eosinophilic meningoencephalomyelitis
III. GME
IV. Neoplasia

Treatment and Monitoring

I. No successful therapy to date
II. Guarded prognosis

Intracranial Myiasis

Definition and Cause

Aberrant migration of *Cuterebra* spp. larvae can occur within the CNS of cats and dogs (rarely) (Glass et al., 1998).

Pathophysiology

I. Larvae may migrate through the nose, ethmoids, and cribriform plate and enter the brain through the olfactory lobe.
II. Alternatively, larvae can migrate through foramina of the skull, travel through the external and middle ear, penetrate the mastoid region, invade venous sinuses and meninges, or enter hematogenously after penetrating a large vessel.
III. Microscopic necrosis of the brain occurs secondary to ischemia.
IV. Lesions are usually unilateral in regions supplied by the middle cerebral artery (see Cerebral Vascular Disease).
V. It is hypothesized that the larvae produce a toxin that causes vasospasm and cerebral infarction and may cause superficial laminar cerebrocortical necrosis (Williams et al., 1998).

Clinical Signs

I. Animals are often affected in summer months, when adult flies deposit their ova.
II. Typically outdoor cats (rarely dogs) are affected.
III. Many cats have signs consistent with upper respiratory disease (especially sneezing) before the appearance of neurological signs.
IV. Neurological signs are peracute in onset.
V. Prosencephalic signs, including unilateral postural reaction deficits, unilateral facial (and occasionally whole-body)

hypalgesia, and a menace deficit with a dilated, nonresponsive pupil from involvement of the optic tracts are noted.
VI. Seizures and profound behavioral and mentation changes are often present.

Diagnosis

I. CSF analysis may be normal or show a mild to moderate pleocytosis (neutrophilic, mononuclear, or occasionally eosinophilic), with mild protein elevation.
II. MRI may reveal the migratory path of the larvae, cerebrocortical lesions, and evidence of a focal or regional infarction.
III. Definitive diagnosis requires histopathology.

Differential Diagnosis

I. Other infectious or parasitic meningoencephalitis
II. Eosinophilic meningoencephalitis
III. Neoplasia

Treatment and Monitoring

I. The following may be beneficial, but controlled studies have not been done.
   A. Pretreat with diphenhydramine 4 mg/kg IM.
   B. Give ivermectin 400 µg/kg SC and dexamethasone 0.1 mg/kg IV.
   C. Repeat the treatment 24 to 48 hours later.
II. A third-generation cephalosporin, trimethoprim-sulfa drug, or metronidazole may be given to prevent bacterial infection associated with larval migration.
III. Although prognosis is guarded; some cats may recover over weeks to months with residual neurological deficits.

METABOLIC/TOXIC DISORDERS

General Information

Definition and Causes

I. These include disturbances in cerebral function from metabolic derangements or toxicoses that usually manifest as diffuse prosencephalic signs.
II. See Table 23-3 for a list of causes.

Pathophysiology

I. Energy deprivation leads to alterations in neuronal resting membrane potentials, and may disrupt neurotransmitter function and metabolism.
II. Certain toxins and metabolic abnormalities may interfere with energy metabolism in the brain, potentially causing neuronal death.
III. Electrolyte imbalances may alter neuronal excitability and neurotransmission.
IV. Changes in serum osmolality and water content lead to altered osmotic balance in neural cells, which may cause either brain cell swelling (edema) or dehydration.

Clinical Signs

I. Metabolic encephalopathies typically cause diffuse, symmetrical prosencephalic signs, such as seizures, altered mentation (confusion, disorientation, dementia, pacing, head pressing), circling, and altered consciousness (obtundation, stupor, coma).
II. Onset may be acute or chronic, and signs may wax and wane.
III. Motor signs include tremors, myoclonus, and varying degrees of paresis/paralysis.

TABLE 23-3

Causes of Metabolic or Toxic Encephalopathies

DISORDER	CAUSES
Hypoxia	Cardiopulmonary failure, disturbances in hemoglobin function, carbon monoxide poisoning, methemoglobinemia, cellular hypoxia (cyanide poisoning)
Hypoglycemia	Pancreatic beta-cell tumor (insulinoma), iatrogenic insulin overdose, hepatic dysfunction, septicemia, hypoadrenocorticism, paraneoplastic syndromes (e.g., leiomyosarcoma, hepatoma, lymphoma), neonatal animals, hunting dogs, storage diseases
Acidosis, alkalosis, hyperosmotic states	Hyperglycemia (diabetes mellitus), hypernatremia, dehydration, diabetes insipidus, nonketotic, hyperosmolar diabetes mellitus, hyperaldosteronism
Hypoosmotic states, hyponatremia	Hypoadrenocorticism, water intoxication, inappropriate secretion of antidiuretic hormone
Alterations in calcium homeostasis	
Hypercalcemia	Paraneoplastic syndromes, rodenticide toxicity (cholecalciferol-containing products), hyperparathyroidism, Vitamin D toxicity, renal disease, hypoadrenocorticism, certain granulomatous diseases
Hypocalcemia	Eclampsia, hypoparathyroidism
Endogenous neurotoxins	Hepatic insufficiency/failure, renal failure, pancreatitis
Endocrine disorders	Hyperthyroidism, hypothyroidism

Diagnosis

I. Other evidence of metabolic disturbances may be identified from the history or the physical examination.
II. A minimum laboratory database includes a complete blood count, biochemistry profile, and urinalysis.
III. Other diagnostic tests are considered based on initial findings.
  A. Serum bile acids
  B. Blood gas analysis
  C. Measurement of serum osmolality
  D. Endocrine function tests
  E. Cardiopulmonary function tests: electrocardiography, blood pressure measurement, radiography, echocardiography
  F. Abdominal radiography and ultrasonography

Differential Diagnosis

I. Degenerative encephalopathies
II. Meningoencephalitis
III. Neoplasia
IV. Brain malformations

Treatment and Monitoring

I. Ensure an adequate airway; support breathing and circulation if the animal is comatose.
II. Correct the underlying metabolic disturbance.
III. Consider anticonvulsants for seizures.
IV. Take care when treating seizures in animals with hepatic insufficiency, because they are unable to metabolize many anticonvulsants.
  A. Give diazepam (0.5 mg/kg IV), but reduce the dosage if hepatic encephalopathy is a primary concern.
  B. Give phenobarbital initially at 2.0 mg/kg PO, IV, IM BID, with caution.
    1. Metabolism may be compromised with hepatic dysfunction.
    2. Acidosis causes increased penetration of barbiturates into the brain.
  C. Seizures may be difficult to control until the underlying metabolic imbalance is corrected.
V. Administer dextrose if hypoglycemia is identified (see Chapter 46).
VI. In most cases, neurological signs resolve once the metabolic disturbance is corrected.

Hepatic Encephalopathy

See Chapter 37.

Cerebrovascular Disease

Definition

I. Cerebrovascular disease refers to conditions that result in brain ischemia, infarction, or hemorrhage.
II. These conditions include the following:
  A. Cerebrovascular accidents: thromboembolism and infarction, hemorrhage (Garosi et al., 2005)
  B. Vascular anomalies: aneurysm, hamartoma
  C. Cerebral arteriosclerosis secondary to severe hypothyroidism
  D. Meningoencephalitis
  E. Intravascular neoplasms: lymphoma

Causes and Pathophysiology

I. Cerebral ischemia occurs as a result of insufficient blood supply to the brain.
  A. Dogs may have transient ischemic attacks, possibly from vasospasm.
    1. Attacks are often of unknown etiology.
    2. Occasionally they are associated with hypertension.
  B. Feline ischemic encephalopathy (FIE) occurs in the late summer, most commonly in eastern North America.
    1. Aberrant migration of *Cuterebra* spp. larva is thought to be the primary cause (Glass et al., 1998).
    2. It is hypothesized that a toxin from the larva causes vasospasm (of the middle cerebral artery), resulting in a unilateral ischemic brain lesion (Williams et al., 1998).
II. Hypoperfusion of the brain is associated with atherothrombosis or embolism.
  A. With atherothrombosis, a localized thrombus forms and disrupts blood flow, with subsequent ischemia and/or infarction.
  B. With embolization, an artery is suddenly occluded, usually by a thrombus that arises from a distant site, such as in the heart (blood clot) or a neoplasm (e.g., neoplastic cells from hemangiosarcoma).
III. Systemic hypoperfusion causes a decrease in cerebral blood flow and can lead to infarction in the border zones between major cerebral arteries (watershed infarction).
IV. Impaired blood supply to the brain results in a decline in tissue oxygen levels (stagnant hypoxia), which cause brain ischemia.

Clinical Signs

I. Clinical signs are peracute and may be followed by progressive recovery over days to weeks.
II. Clinical signs reflect the location of brain infarction.
III. Although gait deficits are not typically seen with prosencephalic lesions, a transient gait deficit (hemiparesis) may be seen with prosencephalic infarcts.
IV. Vestibular signs may be seen with thalamic infarcts.

Diagnosis

I. Serial blood pressure measurements may indicate hypertension.
II. Results of a CBC, biochemistry profile, and urinalysis vary, depending on the presence of an underlying systemic disease.
III. Additional tests may include urine protein: creatinine ratio, serum antithrombin III activity, coagulation profile, and endocrine testing for hyperadrenocorticism, thyroid diseases, and pheochromocytoma.
IV. Thoracic radiography and abdominal ultrasonography may reveal evidence of an underlying disease.

V. MRI (and occasionally CT) may reveal ischemic brain lesions.
VI. CSF analysis usually shows normal to mild increases in nucleated cells, with elevated protein content.

Differential Diagnosis

I. Meningoencephalitis
II. Metabolic encephalopathy
III. Neoplasia

Treatment and Monitoring

I. No definitive treatment for the neurologic signs has been defined in animals.
II. Osmotic therapy (as described for cranial trauma) may be beneficial in severely affected animals.
III. Treatment is usually directed at the underlying disease.
IV. Prognosis and recovery are highly variable.

NUTRITIONAL DISORDERS

Thiamine Deficiency

Definition and Causes

I. Metabolic encephalopathy can arise from thiamine deficiency (de Lahunta, 1983).
II. Commercial rations or homemade diets may be low in thiamine.
III. Overcooking food before feeding or during food processing can affect thiamine levels.
IV. Thiamine can be destroyed by sulfites or sulfur dioxide used as a preservative in canned food.
V. All-fish diets may result in thiamine deficiency, as many fish contain thiaminase.
VI. Severe hepatic or renal disease can be associated with thiamine deficiency.

Pathophysiology

I. Thiamine is essential for complete oxidation of glucose through the Krebs cycle.
II. Tissues that derive energy from glucose or lactate-pyruvate are compromised.
III. Several proposed mechanisms for neuronal cell death include impaired vascular function, increased blood-brain barrier permeability, N-methyl-D-aspartic acid receptor-mediated excitotoxicity, and increased free radical formation (Leong and Butterworth, 1996).
IV. CNS lesions include bilateral, symmetrical degeneration of brainstem nuclei (caudal colliculi, vestibular, lateral geniculate, oculomotor and red nuclei), and cortical lesions (less common).

Clinical Signs

I. Signs are related to dysfunction of brainstem nuclei and include vestibular ataxia, seizures, dilated pupils, opisthotonus, coma, and death.
II. Severe head and neck ventriflexion is often present from neuromuscular weakness.
III. Dogs may have signs of central (bilateral) vestibular disease or cervical myelopathy (Garosi et al., 2003).

Diagnosis

I. History, signalment, clinical signs, and response to treatment allow a presumptive diagnosis.
II. MRI may disclose symmetrical lesions in affected brainstem nuclei (Garosi et al., 2003).
III. Serum levels of pyruvate and lactate may be increased.
IV. Red blood cell transketolase activity is usually decreased.

Differential Diagnosis

I. Meningoencephalitis
II. Metabolic or toxic encephalopathies
III. Neoplasia
IV. Other causes of central vestibular disease

Treatment and Monitoring

I. Even in severely affected animals, prognosis is fair to good if signs are recognized early.
II. Thiamine HCl (vitamin B_1) is administered at 25 to 50 mg/day IM to dogs for 3 to 7 days, and at 10 to 20 mg/day IM to cats until signs abate, or for 21 days.
III. Higher doses may be required in some animals.
IV. Dietary abnormalities should also be corrected.

NEOPLASIA

Definition

I. Primary brain tumors arise from neuroectodermal or mesodermal cells that are normally present within or associated with the brain (Summers et al., 1995).
II. Secondary tumors originate from surrounding tissues and extend into the brain or arise from hematogenous metastasis.
III. Classification of brain tumors (primary or secondary) is based on characteristics of the constituent cell types (Bagley et al., 1993).

Causes and Classification

I. Primary tumors
  A. Tumors of neuroepithelium
    1. Astrocytic tumors: astrocytoma, glioblastoma multiforme
    2. Oligodendroglial tumors: oligodendroglioma
    3. Mixed glial tumors: oligoastrocytoma, gliomatosis cerebri
    4. Embryonal tumors: primitive neuroectodermal tumors (PNETs), medulloblastoma
    5. Ependymoma
    6. Choroid plexus tumors
  B. Tumors of meninges: meningioma, meningeal sarcoma
  C. Tumors of hematopoietic tissue: lymphoma, histiocytic tumors
  D. Nerve sheath tumors
  E. Tumors of the sellar region
    1. Pituitary tumors: adenoma, adenocarcinoma
    2. Suprasellar germ cell tumors

II. Metastatic tumors
  A. Hemangiosarcoma
  B. Urogenital tumors: prostatic carcinoma, mammary gland adenocarcinoma
  C. Malignant melanoma
III. Secondary tumors of adjacent tissues
  A. Tumors arising from the calvaria: osteosarcoma, multilobulated tumor of bone
  B. Local extension of regional tumors
    1. Nasal tumor: adenocarcinoma, fibrosarcoma
    2. Tumors arising from the ear or osseous bullae: adenocarcinoma, squamous cell carcinoma

Pathophysiology

I. Direct effects of tumor growth include compression and invasion of normal brain parenchyma.
II. Indirect effects are often more significant than direct effects.
  A. Damage to the blood-brain barrier can result in cerebral edema.
  B. Obstruction to CSF flow causes secondary hydrocephalus.
  C. Brain herniation can occur as a result of increased intracranial pressure from an enlarging space-occupying mass within the rigid calvaria.
  D. Hemorrhage is also a possibility.

Clinical Signs

I. Breed predisposition has been reported for several tumors.
  A. Brachycephalic breeds (especially the boxer, English bulldog, and Boston terrier) are predisposed to gliomas (astrocytomas, oligodendrogliomas, mixed tumors) and pituitary tumors.
  B. Dolichocephalic dogs and Siamese cats may be predisposed to meningiomas.
II. Onset of disease may be acute or insidious, depending on the location, rate of growth, and indirect effects of the tumor.
III. Neurological signs reflect the location of the tumor.
  A. Cerebral or thalamic tumors (prosencephalic tumors) may cause seizures, circling, behavioral changes, contralateral postural reaction deficits, contralateral visual deficits, and contralateral nasal hypalgesia.
  B. Brainstem tumors can induce vestibular signs, ipsilateral postural reaction deficits, cranial nerve deficits, ataxia (both proprioceptive and vestibular), and changes in mentation.
  C. Cerebellar tumors can result in a wide stance; spastic, hypermetric gait (cerebellar ataxia); loss of balance; intention tremors; ipsilateral postural reaction deficits; and ipsilateral, absent menace response without visual deficits.
  D. Tumors of the floor of the calvaria may cause deficits of the oculomotor, trochlear, abducens nerves, and the ophthalmic branch of the trigeminal nerve.
    1. Disruption of the sympathetic innervation to the head may also occur.
    2. Clinical signs may include ophthalmoplegia, Horner's syndrome, mydriasis, and trigeminal sensory deficits involving the eye and the medial canthus.
IV. Metastatic tumors may involve single or multiple areas within the CNS and be associated with focal or multifocal signs.
V. Tumors involving the frontal and olfactory lobes of the cerebrum may cause seizures or changes in mentation without other deficits.

Diagnosis

I. A minimum database includes a CBC, biochemistry profile, urinalysis, and three radiographic views of the thorax.
II. MRI and CT may allow a presumptive diagnosis.
  A. Meningiomas often are extraaxial (on the periphery of the brain), have a broad-based attachment, and exhibit strong, homogeneous contrast enhancement.
  B. Glial tumors often are intraaxial (within brain parenchyma), display variable contrast enhancement, and occasionally have a ring-enhancement pattern.
  C. Choroid plexus tumors are located intraventricularly or at the cerebellomedullary angle and typically exhibit strong, uniform contrast enhancement.
  D. Tumors can occur in the ventricles, such as choroid plexus and ependymal tumors.
  E. Secondary consequences include compression of normal brain structures with shifting of midline structures, obstructive hydrocephalus, and cerebral (vasogenic) edema.
III. CSF analysis often reveals nonspecific abnormalities.
  A. An increased protein concentration and a normal cell count are typical.
  B. Neoplastic lymphocytes may be seen with lymphoma.
  C. Meningiomas may result in a neutrophilic pleocytosis from tumor necrosis.
  D. An increased risk of brain herniation is associated with elevated intracranial pressure and is a contraindication to CSF tap.
IV. Definitive diagnosis requires histopathologic evaluation.

Differential Diagnosis

I. Metabolic or toxic encephalopathies
II. Meningoencephalitis: infectious, noninfectious
III. Vascular disorders
IV. Other causes of seizures, altered mentation

Treatment and Monitoring

I. Certain treatments are directed at the secondary consequences.
  A. Osmotic diuretics are used to draw edema out of the brain.
    1. Give mannitol at 0.25 to 1.0 g/kg IV over 10 to 15 minutes.
    2. Administer furosemide (0.7 mg/kg IV) 15 minutes after mannitol to prolong the effects of mannitol.
    3. Administer hypertonic saline at 1.0 to 2.0 mL/kg IV over 10 to 15 minutes.

4. Repeat osmotic therapy up to every 6 hours unless the animal becomes dehydrated or hypovolemic.
5. Evaluate packed cell volume (PCV) and total solids (TS) before administration of osmotic therapy to evaluate hydration status.
6. Do not use osmotic therapy in dehydrated, hypovolemic animals, or in animals with decreased cardiac function.

B. Prednisone (0.5 to 1.0 mg/kg PO, IV) can be administered to reduce peritumoral (vasogenic) edema and inflammation.
C. Anticonvulsants are administered for seizures.
1. Phenobarbital (2.0 to 4.0 mg/kg PO, IM, IV BID) is usually the first option.
2. KBr (30 mg/kg PO SID) may also be added.
3. Animals with intracranial neoplasia may become extremely sedate with anticonvulsants.
4. Dosages less than the recommended amount may be used initially to avoid extreme sedation.

II. Definitive treatment includes surgery and/or radiation therapy.
A. Surgery allows for tumor resection or cytoreduction and provides a histological diagnosis.
B. Surgery often is reserved for tumors that are extraaxial (superficial), and more easily approached and removable.
C. Radiation therapy (alone or in combination with surgery) has been shown to increase survival time (Axlund et al., 2002; Bley et al., 2005).
D. Overall prognosis is fair to guarded and depends on the location and type of tumor.

CRANIAL TRAUMA

Definition and Causes

I. Neurological dysfunction secondary to head trauma is caused by brain contusion, laceration, edema, or hemorrhage.
II. Trauma may occur from a fall, automobile accident, or blunt or penetrating injuries.

Pathophysiology

I. Depressed skull fractures may cause compression and injury to underlying brain parenchyma.
II. Angular acceleration of the brain can cause diffuse, axonal injury.
III. The impact of the brain against the skull results in coup (occurring in tissue under the area of impact) and contrecoup injuries (occurring in tissue on the side opposite the impact).
IV. Hemorrhage and hematoma formation can compress brain parenchyma.
V. The end result is vasogenic edema of the brain.

Clinical Signs

I. Signs may be indicative of focal or diffuse brain disease.
II. Prosencephalic injury may result in loss of consciousness in severe cases, but more frequently leads to circling, altered mentation, and contralateral postural reaction deficits, blindness, and facial hypalgesia.
III. Brainstem injury typically causes altered mentation (depression, obtundation, or sometimes a comatose state), pupillary changes, and loss of conjugate eye movements
IV. Cerebellovestibular injury can result in dysmetria, cerebellar or vestibular ataxia, dysequilibrium, head tilt, and spontaneous or positional nystagmus.
V. Evidence of progressive clinical signs suggests cerebral edema, herniation, or hematoma formation.

Diagnosis

I. Signs of brain dysfunction in an animal known to have suffered an injury are suggestive.
II. Abrasions, penetrating wounds, or other evidence of head trauma are supportive.
III. Although difficult to interpret, radiographs may reveal skull fractures.
IV. MRI or CT can identify skull fractures, areas of hemorrhage, hematoma formation, and edema within the brain.

Differential Diagnosis

I. Other disorders are considered if trauma was not witnessed or if external evidence of trauma is absent.
II. Consider metabolic and toxic encephalopathies, as well as inflammatory, vascular, and neoplastic disorders.

Treatment and Monitoring

I. Nonspecific therapy is often initiated before or in conjunction with specific therapies.
A. Ensure airway patency, adequate ventilation, and stabilize cardiovascular function.
B. Institute fluid therapy to correct any hypovolemia and associated hypotension.
C. Provide oxygen to prevent further tissue hypoxia.
D. Turn recumbent animals every 6 hours, and keep them clean and well padded.
E. Provide nutritional support after they are stabilized.

II. Specific therapy is directed at reducing cerebral edema and intracranial pressure.
A. Recumbent animals are positioned with their heads slightly elevated (15 to 30 degrees).
B. Osmotic therapy is started for cerebral edema.
1. Mannitol 0.25 to 1.0 g/kg IV over 10 to 15 minutes
2. Hypertonic saline 7% 1 to 5 mL/kg IV over 3 to 5 minutes
3. Furosemide (0.7 mg/kg IV) can be given 15 minutes after mannitol to prolong its effect.
4. Osmotic therapy can be repeated every 6 to 8 hours unless dehydration or hypernatremia develops.
5. Electrolytes, PCV, and TS are monitored closely with osmotic therapy.

C. Osmotic therapy is contraindicated in hypovolemic animals and those with clinical signs suggestive of active intracranial hemorrhage.
D. Surgery is indicated for depressed skull fractures or if the animal's condition deteriorates despite medical management.

III. Prognosis depends on the severity and location of the injury.
IV. Although most improvements are seen within the first month of the injury, recovery may take weeks to months.
V. Long-term sequelae may include seizures and persistent neurological deficits.

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