Neurovascular Disorders

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Neurovascular disorders encompass those conditions that result in cerebrospinal ischemia, infarction, and hemorrhage. Various vascular and parenchymatous changes have been reported in dogs and cats in association with vascular anomalies (e.g., aneurysms, telangiectatic hamartomas), cerebral arteriosclerosis, mineral and pigment deposition, malacias and necrosis, cerebral infarction-thrombosis-embolism, inflammatory processes, cerebral hemorrhage, and vascular neoplasms, including intravascular lymphoma (malignant angioendotheliomatosis) [1,110]. Cerebral ischemia connotes insufficient blood supply to the brain to maintain normal cellular functions. It has been stated that ischemia can be viewed as hypoxia plus hypoglycemia [2].

Brain ischemia may be:

a. focal resulting from narrowing/occlusion of cervicocranial vessels or from hypoperfusion of the brain associated with atherothrombosis or embolism, or
b. global resulting from systemic hypoperfusion [3].

In atherothrombosis, a localized thrombus forms on an atherosclerotic plaque resulting in disruption of blood flow and subsequent ischemia and/or infarction. In embolism, a brain or spinal cord artery is suddenly occluded by embolic material, usually a thrombus that arises from a distant site such as the heart. Hypovolemia or cardiac pump failure causes a global decrease in cerebral blood flow and can lead to infarction in the border zones between major cerebral arteries (called watershed infarction). Impaired blood supply to the brain results in a decline in tissue PO2 levels, called stagnant hypoxia, which is tantamount to ischemia [4]. Cells in the central nervous system (CNS) show selective vulnerability to the effects of ischemia and hypoxia (often considered together as hypoxia-ischemia [2]). Due to the high demand of neurons for oxygen, neurons are first affected by hypoxia-ischemia followed by oligodendrocytes, then astrocytes, and finally vascular cells [4]. If neurons are the only cells affected, the tissue damage is termed "selective neuronal necrosis". If all cellular elements are affected, the lesion is called "pan-necrosis" or "infarction". The spinal cord is less sensitive to hypoxia-ischemia than is the brain [5], while neonatal animals are more resistant to hypoxia-ischemia than are adults [2]. Axons are more sensitive to hypoxia-ischemia than their myelin sheaths [2]. In general, the incidence of neurovascular disorders based on pathological studies is low in dogs and cats [1,6]. Yet several reports argue that neurovascular disorders may be more common than the literature suggests and that the increased availability of advanced imaging techniques has heightened the awareness of these often devastating conditions [7-9].

The following neurovascular disorders of the CNS will be discussed:

Cardiac Arrest
Feline Ischemic Encephalopathy
Fibrocartilaginous Embolization
Hemorrhage
Hemorrhagic Myelomalacia
Infarction
Seizures and Cerebral Necrosis
Traumatic Feline Ischemic Myelopathy
Cardiac Arrest
Cardiac arrest during anesthesia may have devastating effects on the brain. In one report involving 2 cats and 2 dogs, cardiac arrest of variable duration (for at least 7 to 8 minutes in one cat) occurred during anesthesia [10]. Post-operatively, animals showed blindness, sometimes accompanied by dilated pupils that later became miotic or anisocoric, and were variably unresponsive to light. Initially some animals were recumbent and opisthotonic with rigid limb extension. The hind limbs tended to relax within several days. Transient positional nystagmus was observed in one dog. Several animals were hyperexcitable and some had seizures. One 6 year old Domestic shorthair cat presented with a 2-week history of blindness following general anesthesia had normal pupillary light response and dazzle response [102]. Microscopically, extensive lesions of ischemic necrosis (characterized by neuronal cytoplasmic eosinophilia, shrinkage, nuclear pyknosis, and neuronal dissolution) were observed in the cerebral cortex, cerebellar vermis (involving Purkinje cells with astrocytic proliferation in the molecular layer), basal ganglia, thalamus, and caudal colliculi [10]. Hemorrhage into the cerebral cortex was observed, and ischemic necrosis was present in several cranial nerve nuclei (usually bilaterally symmetrical), the mammillary body, the interpeduncular ganglion, and the acoustic tubercle. Secondary Wallerian degeneration and/or edema of white matter were seen. Microcavitation of affected cerebral cortex occurred soon after the cardiac arrest. The distribution of lesions suggested a particular susceptibility of affected areas to hypoxia/anoxia. The most severe lesions occurred in the more dorsal convolutions of the cerebral cortex, especially those bordering the longitudinal fissure. The involvement of the basal ganglia and hippocampus also suggested specific tissue vulnerability. Cerebral malacia, also located in the cerebral cortex and in the region of the basal ganglia (caudate nucleus, internal capsule, and putamen), has been found in dogs and cats with chronic congestive heart failure associated with atrioventricular valvular insufficiency and intramural coronary arteriosclerosis [1,6].

Feline Ischemic Encephalopathy
Feline ischemic encephalopathy (FIE) is an ischemic necrosis of cerebral tissue that occurs sporadically in male and female cats of all ages (e.g., from 7 months to 11 years), especially in summer months [17-21]. Clinical signs are usually acute in onset, non-progressive, and variable (probably reflecting location of lesions and associated brain edema), and typically suggest unilateral cerebral or brainstem involvement. Signs may include depression, head tilt, anisocoria, circling, seizures, and change in attitude/behavior, often to the point of aggression. Seizures are often the initial presenting or historical clinical sign [19,21], and they may be mild and/or of the partial category, and of low frequency [22]. Mydriasis and visual impairment may be present. Clinical signs may be modified or disappear with time (several days to weeks). Multiple episodes may occur.
Hematology, blood chemistries, and skull radiographs are usually normal. Cerebrospinal fluid (CSF) analysis may be normal or reveal a mild to moderate pleocytosis (usually monocytic) and mild protein increase. An increased proportion of large foamy macrophages has been observed in CSF from 2 to 7 months after onset of seizures [22]. A presumptive diagnosis may be made using MRI. In one study of 6 affected cats, T2 weighted MRI revealed mild-to-marked asymmetry of the cerebral hemispheres and bilateral, but asymmetric enlargement of the subarachnoid space, suggesting compensatory pooling of CSF over atrophied gyri and widened sulci, especially involving the temporal lobes [22].

Lesions are usually unilateral and may involve up to 75% of one cerebral and/or cerebellar hemisphere. Grossly, the involved hemisphere may appear atrophic and ridged with wide sulci [19,21]. The sunken, depressed area is often found in the parietal-temporal field of the cerebrum [2]. In some instances, there is loss of the pyriform lobe, amygdala, parahippocampal gyrus, caudatum, globus pallidus, putamen, internal and external capsules, and subcortical white matter, with associated moderate dilatation of lateral and third ventricles [21]. These gross changes are frequently found in cats with an extended clinical course. Histopathological findings are characterized by severe parenchymal atrophy and cystic degeneration, gliosis, and phagocytic macrophage infiltration. Perivascular, lymphocytic cuffing around small capillaries has been seen [21]. The major area of infarction is frequently in the distribution of the middle cerebral artery. Vascular occlusive lesions, including thrombosis and vasculitis, have been found only occasionally [2]. Affected animals do not have cardiomyopathy.

The cause of this enigmatic ischemic condition has been uncertain. Clinical similarities between FIE and Cuterebra infection of the brain were noted some time ago [17], and preliminary evidence for this pathogenesis has now been reported [2]. More recently, 10 cats with primary CNS infection by larvae of Cuterebra flies were documented at Cornell University [112]. Clinical abnormalities noted in all cats were progressive and most commonly consisted of depression, blindness, and behavior changes. Affected cats presented in July through September. The diverse histopathological changes were unique to this aberrant migration and consisted of a combination of five characteristic features: parasitic track lesion in 7 cats, superficial laminar cerebrocortical necrosis (associated with dark and shrunken neurons) in all cats, cerebral infarction in 8 cats, subependymal rarefaction and astrogliosis with or without ependymal cell loss in 7 cats (especially involving the lateral ventricles), and patchy subpial astrogliosis restricted to the brain stem and spinal cord in 7 cats. The last four-mentioned changes occurred throughout the parenchyma unassociated with the track lesion or the parasite in the affected tissue. The larvae were recovered most commonly in the region of the olfactory bulbs and peduncles, optic nerves, and cribriform plate, suggesting entry from the nasal cavity. Many of the changes noted were suggestive of a toxic factor elaborated by the parasite and/or the host tissues and circulated within the CSF, as well as vascular compromise as a component in those cats with brain infarction. Based on the prevalence of infarction associated with this syndrome, the lack of reported cases of such lesions in regions of the world devoid of the fly (e.g., Australia and New Zealand), and the clinical and pathological similarities to FIE, it seems likely that aberrant Cuterebral larval migration in the brain is the putative cause of feline ischemic encephalopathy.

Treatment is largely supportive. Prognosis is often favorable since many of the signs seen initially will ameliorate; however, behavioral changes and uncontrollable seizures may persist.

Fibrocartilaginous Embolization

Fibrocartilaginous embolization (FCE) is an ischemic necrosis of spinal cord parenchyma that has been associated with fibrocartilaginous emboli in spinal cord vasculature of dogs [23-29]. The disorder has been reported mainly in dogs of either sex, immature as early as 4 months of age [30] and adult, of small and large non-chondrodystrophoid breeds. Almost 50% of confirmed cases have been giant-breed dogs [31]. Young Irish Wolfhounds (between 8 and 13 weeks of age), of either gender (but especially males) appear to be predisposed to this condition [32]. In small breeds, the Miniature Schnauzer is often affected [33]. FCE has been reported less commonly in cats [34-37,107].

The pathogenesis is not well understood. Intervertebral disk material is considered to be the source of the fibrocartilage and it has been hypothesized that disk material may somehow be "injected" into spinal cord vessels. For a review of several hypotheses, see Cauzinille [31]. The fact that this disorder occurs in young adult non-chondrodystrophoid breeds of dogs that are not prone to disk disease at this age is enigmatic (approximately 80% of affected dogs are between 3 and 6 years of age) [31], especially since the condition has not been reported in chondrodystrophoid breeds of dogs, which are at high risk of disk disease. Fibrocartilaginous emboli have been demonstrated, however, in pulmonary vessels of chondrodystrophoid breeds of dogs with signs of clinical disk disease. The role of trauma remains unclear. According to one review, approximately 60% of confirmed canine cases had an antecedent history of trauma or exercise [38].
Onset of signs is typically hyperacute, usually within minutes to several hours. Signs usually do not progress beyond the first 24 hours [33], except for those rare cases in which hemorrhagic myelomalacia develops. Clinical signs of FCE will reflect location of the lesion within the spinal cord. Signs may be unilateral or bilateral, depending on the site of infarction and the degree of damage [29]. While any level of the spinal cord may be affected, cervical or lumbar cord segments are commonly involved, especially at the level of the cervicothoracic (see cervicothoracic syndrome) and lumbosacral (see lumbosacral syndrome) intumescences [31]. Infarction at the level of the cervicothoracic or lumbosacral spinal cord may result in a neuropahtic syndrome as a result of necrosis of ventral horn cells within the spinal cord gray matter. Clinical signs will be characterized by depressed reflexes, reduced muscle tone, and muscle atrophy after 5 to 7 days. According to the level of the spinal cord injury and its extent, Horner’s syndrome and or loss of the cutaneous trunci reflex may be noted. If the lumbosacral cord is involved, there may be paralysis and analgesia of the tail, anal sphincter, bladder and rectum. Affected animals do not typically show evidence of pain, although there may be historical reports of pain or discomfort prior to neurological deficits [9]. Signs of a thoracolumbar syndrome will be seen with spinal cord lesions between T3 and L3 cord segments. In cats, emboli have been reported in cervical and lumbosacral cord regions.

Pathologically, malacia and necrosis of spinal cord gray and white matter are present, often extending over several spinal cord segments. The margins of the lesions tend to be well delineated from normal tissue, with new vascular proliferation and macrophage infiltration evident within a few days [39]. Gitter cells are prominent in the infarcted areas and cavities may form [37]. There may be evidence of emboli in one or more spinal cord vessels (arteries, arterioles and/or veins) or occasionally, in nerve root vasculature, having histological and histochemical staining characteristics of fibrocartilage seen in intervertebral disks [39]. Infarcted areas are usually ischemic but may be hemorrhagic. In addition to the phagocytic mononuclear cells, neutrophils are often abundant within the lesions. Lesions are frequently asymmetric [29]. Gritty cholesterol masses, presumably secondary to myelin breakdown products within infarcted areas, were found in spinal cord white matter in 3 dogs with fibrocartilaginous emboli [23].

Prognosis is guarded and depends on the location and extent of infarction, as well as prompt initiation of medical therapy [40,41]. Animals with extensive gray matter involvement of the cervicothoracic and/or lumbosacral spinal cord segments and those that subsequently develop hemorrhagic myelomalacia have a poor prognosis. Conversely, animals with upper motor neuron signs (associated with a lesion between T3 and L3) have a better prognosis [40,42]. Prognosis may also be related to dog size. In one study, mortality in Miniature Schnauzers associated with fibrocartilaginous embolic myelopathy was significantly lower than mortality rates reported for affected large and giant breeds [33]. Treatment using a high-dose of methylprednisolone succinate (MPS) has been recommended - slow intravenous bolus of MPS, 30 mg/kg, followed by 5.4 mg/kg/hour for 24 to 48 hours [31]. Patients should receive the MPS as soon as possible after onset of neurological signs (e.g., within 6 hours) to maximize chances of recovery. Any improvement should be apparent in 10 to 14 days [43]. Residual effects are common [33,40,41]. Excellent nursing care is essential for non-ambulatory patients (see Spinal Trauma for more information).

Hemorrhage
In cerebral hemorrhage, blood leaks from the vessel (usually a small artery) directly into the brain, one of the ventricles, or the subarachnoid space. Epidural, subdural, subarachnoid and intraparenchymal hemorrhages may be observed in dogs and cats following head injury [44,45] and bleeding into the inner ear is not infrequent [46]. Note that the term "extradural" is more anatomically correct than "epidural" because of absence of any epidural space within the cranium [108]. Variably sized perivascular hemorrhages will also be seen in an area of contusion. Contrecoup hemorrhages result from tearing of leptomeningeal and parenchymal blood vessels [44]. Subdural hematomas may occur as focal intradural mass lesions or as diffuse lesions over the cerebral cortex, sometimes associated with massive accumulations of blood [45,47]. Subdural hematomas may be a complication of hydrocephalus. It has been suggested that hydrocephalus resulting in a widened subarachnoid space may predispose to tearing of cerebral vessels where they cross the subdural space [108]. In some centers, hemorrhage associated with hydrocephalus is observed as a necropsy finding more frequently in the ventricles due to tearing of the internal capsule [108]. Subarachnoid hemorrhage is a common consequence of cranial trauma in animals and is usually associated with extensive parenchymal damage [44]. Hemorrhage into the brain substance (intraparenchymal) from damaged vessels is commonly observed. This form of bleeding may be short-lived due to vessel spasm and
microthrombi formation [48]. Brain hemorrhages may quickly become space-occupying masses (hematomas) that, like brain tumors, compress brain parenchyma, and if unchecked, may lead to widespread brain edema, brain herniation, mid-line shifts, ischemia, brainstem compression and development of deep pontine hemorrhages (Duret hemorrhages) [44]. As herniation progresses, petechial or small ecchymotic hemorrhages may be found in the medulla oblongata and in the herniated cerebellar vermician lobe.

In spinal trauma, subdural hemorrhage is commonly found. Epidural hemorrhage is a frequent finding in severe disk disease. Petechial hemorrhages are commonly observed in injured spinal cord segments (see Disk Disease and Spinal Trauma). Dural laceration, epidural, subdural, and intramedullary hemorrhage, along with malacia and swelling of the spinal cord at the T12 - 13 interspace, were reported in a racing Greyhound that fell in a race and developed acute hind limb paralysis [49]. Subperiosteal vertebral hematoma in the dog, unassociated with spinal trauma, appears to be a rare vascular accident of an epidural nature [50]. In this report, a 13 month old dog had non-weight bearing paraparesis and total anesthesia to the hind limbs, anus and tail. Myelography revealed an extradural compressive lesion in the body of L3. At necropsy, a subperiosteal hematoma encircled the cord on all but the ventral aspects. There was no evidence of free blood in the spinal canal. At the level of L3, the spinal cord appeared swollen, with axonal degeneration, hematomyelia, and gliosis. The cause of the hematoma was not determined. Interestingly, the authors reported a second case in a 7 year old Labrador Retriever with identical signs and necropsy findings [50].

In contrast to the high incidence in man, massive intracerebral hemorrhage resulting from spontaneous rupture of vessels and/or saccular aneurysms is rarely reported in animals [1,51,52]. In humans, this type of hemorrhage is usually associated with hypertension and degenerative and fibrotic changes in the intracerebral arteries. Neurological signs attributable to strokes (presumably hemorrhagic) have been seen in cats with severe systemic hypertension (signs included acute blindness and retinal hemorrhage/detachment) [53]. In dogs, spontaneous intracranial hemorrhages tend to be single, located in the cerebrum, and often in the area of the hippocampus-amygdala [44,51]. Cerebrovascular microaneurysms and variably sized ring-like hemorrhages are sometimes seen in older dogs, usually from 9 to 11 years of age, or older, in association with an amyloid (congophilic) angiopathy [52,54,55]. In these dogs, amyloid deposits were observed mostly in the wall of cerebral arterioles and capillaries showed hyaline degeneration. The accumulation of amyloid fibrils measuring about 10 nm in diameter was seen in the cerebral vessel wall by electron microscopy. The hemorrhages, which were quite large in some dogs, were associated with the vessels involved in the amyloid angiopathy [54]. The hemorrhages occurred mainly in the upper layers of the cerebral cortex. Cerebellar cortex, white matter, subcortical and brainstem gray matter were rarely involved. Clinical signs included seizures, behavioral changes, and motor disturbances. In a dog with a 2 year history of exophthalmos occurring 2 years after head trauma, an enlarged cavernous sinus and associated ophthalmic Plexus were believed to represent an arterialized aneurysm, most likely the result of traumatic arteriovenous fistulation [56]. Intracranial and intraspinal hemorrhage has been occasionally reported in dogs in association with arteriovenous vascular malformations e.g., telangiectatic hamartomas and angiomas [1,57,58]. Hemorrhage into primary and secondary brain tumors is frequently observed in dogs, especially oligodendrogliomas, glioblastomas, ependymomas, and hemangioendotheliomas [1]. Hemorrhage within a pituitary adenoma leading to secondary compression of the hypothalamus resulted in signs of hyperthermia, hypernatremia and collapse (“pituitary apoplexy”) in a 7 year old female German Shorthaired Pointer [103]. Hemorrhage has been observed in the CNS of dogs with intravascular lymphoma (malignant angioendotheliomatosis) [110,116]. Intracystic hematomas have been found in dogs with intracranial intra-arachnoid cysts [111].

Miscellaneous hemorrhages of diverse etiologies have been reported in the CNS of dogs and cats, including migrating parasitic disorders, e.g., cuterebrasis in dogs and cats [1,59]; protozoan infections, e.g., toxoplasmosis in dogs [1], bacterial meningitis [1]; viral diseases, often associated with attendant vasculitis, e.g., canine hepatitis [1], parvovirus [60], and canine herpes virus [61]; nutritional disorders, e.g., thiamine deficiency in cats leading to necrosis and hemorrhage of the hippocampus, midbrain, and medulla oblongata [1]; toxins, e.g., warfarin poisoning [62]; systemic metabolic disorders, e.g., disseminated intravascular coagulopathies, platelet dysfunction, and coagulation factor deficiencies [7,63]; infarction with diapedetic hemorrhages associated with thromboemboli, septic thrombi or neoplastic emboli [1,64]; and chronic serum hyperosmolality, e.g., diabetes mellitus or hypernatremia, in which shrinkage of brain tissue may cause tearing of vessels, leading to subarachnoid or subdural hemorrhage [65]. Cerebral hemorrhage has also been found in dogs with salt poisoning [66].

CNS hemorrhage may occur after therapeutic or diagnostic procedures. Mild, moderate or severe patchy hemorrhagic leptomenigitis was seen at 24 hours after subarachnoid injections of non-ionic contrast agents iopamido1 or metrizamide [67]. Variable degrees of hemorrhage have been reported in intracranial pressure monitoring [63]. Hemorrhagic complications resulting in progressive seizure activity and respiratory arrest were reported with L-asparaginase
administration for the treatment of tumors [68]. In this instance, a triangular wedge of hemorrhagic infarction was found in the cerebrum of a 9 year old Labrador Retriever - the base of the triangle was oriented along the surface of the cortex while the apex extended into the white matter. Additional findings in this dog included multifocal hemorrhagic foci, fibrinoid degeneration of vessels, and thrombosis. A drug-related deficiency in serum antithrombin III may have predisposed this dog to hemorrhagic thrombomobolism.

Onset of signs in animals with sudden hemorrhage is usually acute [7,69]. Clinical signs seen will reflect the location of the hemorrhage and development of any secondary effects, e.g., brain swelling and herniation. Involvement of the pyriform lobe or ventral region of the temporal lobe may cause brainstem compression leading to ipsilateral vestibular signs [69]. However, in one review of 17 dogs with cerebrovascular disease, all dogs in which hemorrhage was a dominant pathologic finding had evidence of a focal neurological deficit [7]. Presence of macrophages containing red blood cells or hemosiderin ("siderophages") in CSF may suggest a recent hemorrhagic episode, although these cells may persist for weeks or months [44]. Coagulation profiles, including platelet count, prothrombin time, activated partial thromboplastin time, thrombin time, and fibrin split products, and specific coagulation factors (e.g., plasma von Willebrand factor antigen) should be performed in animals with suspected coagulation disorders [7,63]. Prognosis of animals with hemorrhage is guarded. The advent of advanced imaging techniques, such as magnetic resonance imaging and computerized tomography, should facilitate the diagnosis of cerebral hemorrhage, cerebral ischemic infarction, and aneurysms in animals [8,56,70,71]. Reports on treating hemorrhage in animals are limited, although successful surgical removal (craniectomy and surgical drainage) of a subacute subdural hematoma has been reported [71].

**Hemorrhagic Myelomalacia**

This destructive spinal cord lesion is probably the most undesirable complication of spinal trauma. Synonyms include progressive diffuse myelomalacia, progressive hemorrhagic myelomalacia, hematomyelia, ascending syndrome, and ascending cord necrosis. This condition may occur within a few hours to one day after the initiating injury, such as external spinal trauma, or more commonly, acute, massive intervertebral disk extrusion. In one study, type III disk protrusion, in which disk material spreads along the epidural space for a distance of one or more vertebrae and may completely encircle the dura, was found in 7 of 8 affected dogs [72]. Hemorrhagic myelomalacia may also occur after fibrocartilaginous embolization [109]. The thoracolumbar spinal cord is usually involved. Clinical signs reflect the nature and level of the lesion. Initially, with a thoracolumbar cord lesion, an animal will show signs of acute onset, total paraplegia with exaggerated pelvic limb reflexes [73]. As a result of edema and hemorrhage, the cord malacia can descend to involve the lumbosacral segments, and clinical signs of flaccid paraplegia with pelvic limb atonia and areflexia will develop within 2 to 3 days. The tail will be flaccid and the anus dilated and unresponsive to stimuli. Pain perception is absent in all these areas. As the disorder progresses rostrally, the thoracic limbs may become flaccid and analgesic, bilateral Horner’s syndrome may occur, and a line of analgesia may be detected at the cranial thoracic region [74]. Breathing may become diaphragmatic. If the spinal cord malacia ascends to lower- or mid-cervical levels, respiratory paralysis will occur, followed by death. The myelographic signs include a variable degree of contrast medium infiltration into the spinal cord and/or spinal cord swelling [109].

The pathological lesion is a combination of ischemic and hemorrhagic infarction of spinal cord parenchyma. In areas of total transverse necrosis (involving both neural and mesenchymal elements), the disruption of normal architecture may be so marked that anatomical divisions of gray and white matter are lost. There is diffuse softening, hemorrhagic infiltration, extreme demyelination, and marked polymorphonuclear infiltration in the cord substance. Neurons show ischemic cell changes ranging from loss of Nissl substance and a prominent nucleolus to shrunken cells with homogeneous pink neuronal cytoplasm and pyknotic nuclei, often with small basophilic dots representing degenerating axonal terminal boutons. Some degenerating neurons are vacuolated. Eventually, only a faint cell outline (ghost cell) is seen. The majority of intramedullary blood vessels may be necrotic. Large accumulations of lipid phagocytes may be seen in some segments. In less severe lesions, localized infarcts of the white matter that are triangular in shape with the apex to the periphery may be present [72]. Hemorrhagic myelomalacia is characterized by rostral or caudal extension of hemorrhage and necrotic tissue in the central canal area or at the base of the dorsal funiculus. Extramedullary vessels (arteries and veins) may be thrombosed or ruptured, resulting in severe subdural and subarachnoid hemorrhage. Intraradicular hemorrhage is often seen and nerve roots may show evidence of Wallerian degeneration. The underlying mechanism for the proposed occlusive vascular damage is uncertain, although vasospasms and reduced collateral circulation have been implicated [72], perhaps secondary to release of catecholamines [74].

Spinal cord damage is permanent. There is no treatment. It should be noted that this condition could develop even after immediate surgical decompression of acute disk extrusion.
Infarction

Infarction or necrosis (malacia) of the CNS parenchyma may result from cerebrospinal vascular occlusion associated with an embolus. The embolic material may represent white platelet-fibrin and red erythrocyte-fibrin thrombi, cholesterol crystals, fragments of atherosclerotic plaques, calcified fragments of valves and plaques, air, fat, myxomatous tumor fragments, or bacterial vegetations or other foreign bodies including parasites [3]. Miscellaneous occlusive conditions that can cause brain ischemia in humans include coagulation disorders, immunological abnormalities and vasculitides [3]. Similar conditions are rarely seen clinically in dogs and cats [53]. Some infarcts are devoid of blood and therefore pallid (pale infarction). Others show extravasation of blood from many small vessels within the infarcted tissue (red or hemorrhagic infarction) [75]. In one report of canine cerebrovascular disease, most infarcts were hemorrhagic [7]. Based on published reports and necropsy studies, the incidence of CNS infarction is relatively low in dogs and cats [1,6]. Infarction most commonly occurs in association with fibrocartilaginous emboli in dogs and with ischemic encephalopathy in cats. Hemorrhagic myelomalacia is sometimes associated with acute, severe spinal cord trauma, such as intervertebral disk extrusion. Aortic thromboemboli in cats typically results in neuromuscular pelvic limb ischemia, rather than spinal cord infarction (see ischemic neuromyopathy). Note that one potential complication of hyperadrenocorticism in dogs is thromboembolism, possibly related to coagulation protein loss in urine, and signs of pelvic limb weakness, pain and collapse as a result of occlusion of the distal aorta and/or the iliac arteries [104].

Cerebellar infarction caused by primary arterial thrombosis has been reported in a 12 year old German Shepherd dog with acute onset of seizures, moderate opisthotonus, and menace deficit in the left eye [76]. The dog remained recumbent for several days before slowly improving to the point it could stand unassisted. At this time, the dog showed predominantly cerebellar signs, including swaying backward and forward, lurching to either side, ataxia-dysmetria, and falling. Grossly, a soft, hemorrhagic area was found in the rostral and middle parts of the left cerebellar hemisphere. Microscopically, a well-demarcated area of hemorrhagic necrosis was present with marked disruption of the granular layer and accompanying neuronal and Purkinje cell degeneration. Moderate diffuse reactive astrocytosis was admixed with a primarily mononuclear cell infiltrate. In less severely affected areas, a moderate multifocal to coalescing spongiosis was seen primarily within gray matter. A mural thrombus was found in the rostral cerebellar artery. Interestingly, mild to moderate myocardial degeneration was also noted. A similar case was reported in an 11 year old, female Shetland Sheepdog, 4 days after an acute onset of seizures, mental depression, circling to the left, postural deficits of the right limbs, and a right menace deficit [77]. CSF was clear and colorless and protein content was 35 mg/dl with normal cell count. Using CT scans, a ring-enhancing, intra-axial lesion associated with edema and non-uniform ventricular compression was identified in the left frontal lobe. An area of ill-defined hyperdensity, compatible with hemorrhage, was seen on corresponding CT images before contrast enhancement. At necropsy, a focal, hemorrhagic infarct, characterized by liquefactive necrosis, marked gliosis and neovascularization, was found. The etiology of the infarction could not be identified. The CT findings were similar to those seen in man with cerebral infarction due to embolic occlusion and subsequent hemorrhage. MRI scans may be better than CT in the diagnosis of cerebral infarction in the acute phase (lesions <1 week duration) [77].

Venous thrombosis is rarely reported in the veterinary literature. As a result of the extensive cerebral venous network and presence of collateral vessels in animals and humans, thrombosis must be extensive before blood flow becomes greatly reduced and hypoxia-ischemia ensues [78]. A multitude of different conditions can cause venous thromboses in humans, including infections, altered hormonal status in young women during pregnancy, the puerperium, or associated with the intake of oral contraceptives, altered state of coagulability, congenital or congestive heart disease, and certain hematological disorders such as thrombocytopenia [78]. Cerebral hemorrhagic infarction associated with venous thrombosis was found in a 10 year old crossbred bitch with a history of peracute onset of seizures, left-sided hemiparesis and compulsive circling to the right [79]. The direct and consensual pupillary light reflex was absent in the left eye. Grossly, the right head of the caudate nucleus and rostral diencephalons were hemorrhagic and edematous. The right caudate nucleus was the most severely affected area and was characterized by hemorrhage, edema, and ischemic neurons. The right optic tract was severely edematous and associated oligodendrogial nuclei were pyknotic. Astrocytes were swollen and surrounded by vacuoles. Medium to small diameter blood vessels within the affected regions showed fibrinoid necrosis, erythrocytic dialedesis, and fresh fibrin thrombi. Perivascular accumulations of a few neutrophils and macrophages were seen at the margins of the hemorrhagic lesion as well as in the neuropil of the right caudate nucleus. There was an occluding thrombus in the right basal vein extending from the rostral perforating substance to the dorsolateral branch of the basal vein. At the rostral limits, the thrombus had undergone organization and endothelial-associated recanalization. The left basal vein contained a fresh multilaminated occluding thrombus at the level of the hypothalamus. The etiology of the thrombi was not determined, although special stains failed to reveal bacteria or fungi in any thrombi. In humans, occlusion of a cerebral vein may lead to an infarctive stroke. The slower evolution of signs and its greater epileptogenic and hemorrhagic tendency favors venous over arterial thrombosis [75].
In contrast with humans, infarction in dogs and cats is rarely seen associated with atherosclerosis (arterial xanthomatosis) but when it does occur, it may be as a complication of hypothyroidism (in dogs) [1]. Atherosclerosis usually involves the intima of muscular and musculoelastic arteries and microscopically, the lesions include smooth muscle cells, collagenous and elastic fibers, fat-storing foam cells, extracellular lipids, cholesterol, calcium and amorphous debris [1]. One report on primary hypothyroidism involved a 6-year-old Doberman Pinscher presented with sudden onset of seizures, disorientation and circling [80]. The dog had an 18-month history of episodic head tilt and ataxia. The condition deteriorated so that the dog was recumbent and comatose with marked extensor rigidity. Serum T3 and T4 values were low and cholesterol values were very high (2,130 mg/dl). CSF analysis was normal. An EEG trace revealed diffuse flattening in all leads, except for periodic spike- and slow-wave discharge associated with the right frontal lobe of the cerebral cortex. Grossly, both lobes of the thyroid gland were pale, small and thin. All visible arteries on the ventral and lateral surfaces of the brain were opaque yellow, firm, and tortuous. A shallow depression was noted over the dorsolateral aspect of the left parietal lobe of the cerebrum and the lumen of the branch of the middle cerebral artery supplying this region appeared obliterated.

Microscopically, arteries throughout the body, especially in branches of the cerebral and coronary arteries had severe atherosclerosis characterized by intimal and medial fibromuscular thickening, cholesterol deposition, and accumulation of foamy macrophages and lipid vacuoles. In the brain, wide bands of pseudolaminar necrosis were seen in the peripheral gray matter of the left parietal lobe. The necrotic areas were composed of shrunken, degenerating neurons, small vacuoles suggestive of myelin degeneration, and numerous gitter cells. Similar focal areas were found in left and right cerebral cortices, along with multifocal, acute necrotizing vasculitis. A cholesterol granuloma was found in the white matter of the right parietal lobe. A few neurons in the caudal and medial vestibular nuclei were shrunken and degenerating. A lymphocytic thyroiditis was also present. In another study involving 21 dogs with atherosclerosis, common findings in dogs tested were hypercholesterolemia, lipidemia, and hypothyroidism [81]. Three dogs showed neurological signs, including disorientation, coma, circling to one side and loss of vision. Severe atherosclerotic changes and obstruction were present in the bifurcations of the arterial circle of Willis and rostral cerebral arteries and there was focal infarction in the cerebral hemispheres.

Cerebral infarction associated with septic thromboemboli has been reported in dogs [1,9]. In one report on 10 dogs, most were older than 5 years of age and there was an acute onset of severe neurological signs (cerebral syndrome with lateralizing signs) in 8 of the dogs [9]. CSF analysis revealed marked pleocytosis (including neutrophils) and elevated protein levels in 8 of 9 dogs tested. Seven dogs died or were euthanized, while 3 were treated successfully with antibiotics. Pathological changes included focal infarction, sometimes with abscess formation, vascular changes, thrombosis, and hemorrhage. In four dogs, a primary infection focus was found outside of the CNS. *Staphylococcus aureus* and β*-Streptococcus* were isolated in two cases.

Infarction has occasionally been observed secondary to embolic metastatic tumors cells in dogs [7], including mammary adenocarcinoma and other malignant neoplasms [1]. Multiple CNS ischemic infarction may occur in animals with intravascular lymphoma (malignant angioendotheliomatosis) associated with vessel thrombosis [110,113].

Infarction secondary to migrating parasites and/or parasitic emboli (see Parasitic Encephalomyelitis) is also occasionally reported in dogs, most frequently associated with heartworms (*Dirofilaria immitis*) [82,83]. In these reports, clinical signs were usually sudden in onset and included generalized seizures, blindness, ataxia, dysphagia, circling, and coma. Worms were found obstructing several vessels, including the anterior and posterior communicating arteries and the middle cerebral artery. Thrombosis of the anterior cerebral artery and meningeal arteries was also seen in one dog [82]. Variably sized areas of infarction were found in frontal, temporal, parietal, or occipital lobes of the cerebrum, depending on location of the arterial occlusion. In some dogs, the infarction was massive and involved virtually one complete cerebral hemisphere. Focal malacic lesions were occasionally present in the thalamus and lateral geniculate body. The malacic areas mainly comprised extensive ischemic changes in neurons, numerous foamy macrophages (gitter cells), and variable numbers of neutrophils. An intense granulomatous inflammation was sometimes found involving the arteries. Note that spinal cord infarction may also occur as a result of parasites and/or parasitic emboli.

Spinal cord infarction in cats has been induced by experimental X-irradiation [84]. In this study, the thoracolumbar spinal cord of 4 cats was subjected to 4000 RADS of X-irradiation. Between 3 and 5 months later, the cats developed hind limb weakness, showed proprioceptive deficits, and became uncoordinated. Microscopically, small infarcts were found in the white matter of the irradiated area of spinal cord, accompanied by neuronal death and edema of the gray matter close to the central canal. Ultrastructurally the infarcts were shown to stem from necrosis and thrombosis of small blood vessels. While CSF studies may suggest septic, neoplastic or parasitic etiologies, antemortem diagnosis of ischemic or hemorrhagic infarcts are more likely to center on the use of specialized imaging techniques, such as MRI [77,85,113]. Prognosis appears to be very guarded.
To date, detailed treatment strategies are lacking in animals. In humans, ischemic stroke management may include [3]:

a. recanalization (thrombolytic therapy) of occluded vessels,
b. maximizing blood volume and cerebral blood flow and reducing blood viscosity,
c. maintaining sufficient perfusion pressure (through careful control of blood pressure, reduction of cerebral edema, and lowering of intracranial pressure) and
d. blocking the progression of occlusive processes using anticoagulants and agents that alter platelet function.

**Seizures and Cerebral Necrosis**

In humans, severe seizural activity is frequently associated with cognitive problems and with widespread neuronal ischemic necrosis in the neocortex, hippocampus and other selective neuronal populations [11,86-88]. This selective distribution may reflect a disruption of neuronal energy metabolism. A similar neuronal vulnerability is seen in patients with hypoglycemia and cerebral ischemia [5,89], suggesting a similar pathogenesis for hypoxic-ischemic conditions. In humans, lesions induced by status epilepticus (SE) may be epileptogenic by leading to misdirected regeneration. Major increases in cerebral blood flow (CBF) protect the brain in early SE, but CBF falls in late SE as blood pressure falters [87]. At the same time, large increases in cerebral metabolic rate for glucose and oxygen continue throughout SE. Adenosine triphosphate (ATP) depletion and lactate accumulation are associated with hypermetabolic neuronal necrosis. Excitotoxic mechanisms mediated by both N-methyl-D-aspartate (NMDA) and non-NMDA glutamate receptors open ionic channels permeable to calcium and play a major role in neuronal injury from SE. Hypoxia, systemic lactic acidosis, CO, narcosis, hyperkalemia, hypoglycemia, shock, cardiac arrhythmias, pulmonary edema, acute renal tubular necrosis, high output failure, aspiration pneumonia, hyperpyrexia, blood leukocytosis and CSF pleocytosis are common and potentially serious complications of SE [87].

The association between seizures and brain pathology remains enigmatic in dogs and cats. In one report of neuropathological changes in the brains of 40 dogs with seizures, 12 cases of which were considered to be idiopathic epilepsy including several dogs with status epileptics, Palmer [90] found no evidence of neuronal ischemic changes, and concluded that seizures, per se, did not appear to result in brain pathology. Summers and colleagues reported a similar experience [2]. More recently, a morphologic and morphometric study of dogs with medically intractable epilepsy failed to find evidence of temporal lobe pathology [105], although heterotopic neuron clusters were found in one affected dog, suggesting that neuronal migration disorders might be a contributing factor to the epilepsy. There are several reports of seizures and cerebral necrosis or polioencephalomalacia in dogs, with selective involvement of areas in the brain suggestive of hypoxia-ischemia, including neocortex, hippocampus, pyriform cortex, basal nuclei and thalamic nuclei [91-96,115]. Microscopic changes include neuronal degeneration characterized by numerous eosinophilic shrunken nerve cells with pyknotic or lytic nuclei. Central chromatolysis with eccentric, pyknotic nuclei was sometimes seen. Occasionally, there was marked infiltration of vessels with lymphocytes and histiocytes. Microgliosis and astrogliosis were prominent. The clinical, neuropathological, and epidemiological findings suggested that the seizures in these cats were triggered by primary structural brain damage, perhaps resulting from excitotoxicity, and were not the result of idiopathic seizures. The cause remained unknown, but epidemiological analysis suggested an environmental factor, probably a toxin.
Unequivocal brain lesions associated with seizures have been reported, however, in an epilepsy-prone colony of beagle dogs that died as a result of the disorder [98]. Grossly, various degrees of brain swelling with flattening of the cerebrocortical sulci, and sometimes coning of the cerebellum with compression of the caudal cerebellar folia, were seen in a few dogs. Approximately 50% of the 68 dogs had a relatively specific pattern of acute brain damage on microscopic examination. In all affected areas, there was a triad of lesions consisting of perineuronal and perivascular astrocytic swelling, perineuronal basophilic incrustations, and ischemic cell change in neurons, especially the small cells. The lesions were often bilateral but asymmetrical. In the cerebral cortex, the rostral cerebrum was usually more severely involved than other areas, particularly the medial aspect of the frontal lobes and the cingulate gyrus. With increasing severity the lesions extended to the depths of the sulci and to the tips of the gyri of the lateral and dorsolateral convexities of the cerebrum. The most common areas of involvement were the cerebral cortex (especially neurons in layers II and III), basal nuclei (especially the globus pallidus, bilaterally), claustrum, amygdala, septal nuclei, dorsal thalamic nuclei, isthmus of the pyriform lobe, and hippocampus (particularly the dorsal horn, and especially involving the H1 field and endofolium). The cerebellum was affected only rarely. In addition, intraneuronal inclusions identical to Lafora’s bodies found in myoclonus epilepsy of man were detected in thalamic nuclei of 6 dogs, but were considered to be incidental findings and unrelated to the seizures. Similar cortical findings have been reported in a 5 year old Shetland Sheepdog with a 3 year history of seizural episodes that ended in status epilepticus [99]. Grossly, both cerebral hemispheres, the hippocampal ventral horn and the posterior portions of the cingulate gyrus were reduced in size, and the lateral ventricles were mildly dilated. Microscopically, lesions were characterized by neuronal loss, gemistocytic to fibrillary astrocytosis, and vascular proliferation. The distribution was bilateral and symmetrical and involved the limbic parts of the cingulate gyrus, amygdala, dorsal and ventral hippocampus and dorumedial nucleus of the thalamus. The most severe lesions were in the cingulate gyri and medial aspects of the frontal lobes, and the cortex in these areas was significantly reduced in size. The H1 field and endofolium of the hippocampus showed moderate neuronal loss and gliosis, while the dentate gyrus and H2 field were minimally affected. The extensive and chronic lesions were considered to be the result of recurring seizures during the course of the disease. Acute lesions such as edematous neuropil found in the thalamus may have resulted from the violent seizures prior to euthanasia. The type and distribution of lesions seen in these dogs were reportedly similar to those seen in dogs with experimentally-induced hypoxia [15,16]. Bilateral neuronal atrophy of the hippocampus with extensive gliosis and ventricular enlargement has also been reported in a 3.5 year old Poodle with epilepsy, although the author speculated that the lesions were the cause rather than the result of the seizures [100]. The infrequent reports of morphologic changes in dogs with seizures may suggest a degree of species insusceptibility and may also reflect such vagaries as intensity and frequency of seizures, duration, and degree of therapeutic control prior to death [2]. Reversibility of lesions may be another explanation. Reversible post-ictal imaging abnormalities (resolution of lesions was noted from 10 to 16 weeks) in the piriform/temporal lobes, characterized by varying degrees of hyperintensity on T2-weighted images and hypointensity on T1-weighted images, have been described in 4 dogs [114]. A surgical biopsy of the temporal cortex and hippocampus from an animal with an olfactory meningioma revealed edema, neovascularization, reactive astrocytosis, and acute neuronal necrosis. These histological findings are similar to the above-mentioned lesions seen in dogs with seizures. The authors emphasize that repeat imaging after seizure control may help differentiate between seizure-induced changes and primary multifocal parenchymal abnormalities. Similar reversible lesions have been documented in human patients following seizures [117]. The advent of high-resolution MRI may facilitate demonstration of changes such as hippocampal atrophy and abnormal signal intensities that are correlated with mesial temporal sclerosis in many human patients (in which seizures arise from the hippocampus or amygdala) [101].

**Traumatic Feline Ischemic Myelopathy**

Summers and colleagues have described a unique ischemic myelopathy in cats in which affected animals were found with paralysis of the hind limbs and analgesia of the tail, anus, perineum, pelvic limbs, and caudal abdominal wall [39]. Necropsy studies revealed presence of abdominal trauma including sublumbar retroperitoneal hemorrhage, kidney avulsion or peritoneal hemorrhage. The vertebral column, vertebral canal, and spinal cord were grossly normal. Transverse sections of the spinal cord indicated discolored gray and soft areas of the central spinal cord extending from L2 through the caudal segments. Microscopically, there was severe, bilateral ischemic degeneration of the ventral gray columns including the central canal and associated gray and white matter and basal areas of the dorsal gray columns. The cranial extent of the lesion was from L1 to L3. Lesions varied from acute ischemic necrosis and macrophage infiltration to more chronic astrogliosis. The lesions were in the distribution of the branches of the ventral spinal artery. It was hypothesized that the cats were run over by vehicle tires causing contusion of the abdominal soft tissues and vasoospasm/thrombosis of the lumbar arteries for a sufficient period to induce spinal cord ischemia. It was noted that ischemic infarction occurred in the lumbar epaxial muscles, which are also supplied by the branches of the same lumbar arteries.
References

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