CANINE STROKE

Simon Platt BVMS, Dipl.ACVIM (Neurology), Dipl.ECVN, MRCVS
Department of Small Animal Medicine & Surgery, College of Veterinary Medicine, University of Georgia, 501 DW Brooks Drive, Athens GA, USA 30602

Introduction
Previously considered uncommon, cerebrovascular accidents (CVA) are increasingly recognized in dogs and cats with the advances of neuro-imaging. Most types of CVA that are seen in humans have been documented in dogs. Recovery from cerebrovascular disorders in animals is probably more spectacular than in humans because animals have a less prominent pyramidal system. A ‘stroke’ is a suddenly developing focal neurological deficit resulting from a cerebrovascular accident. The causes of strokes can be divided into two basic groups:
1. obstruction of the blood vessels leading to ischemia, and
2. rupture of blood vessel walls leading to hemorrhage.
Cerebral ischemia is the reduction, although not necessarily the cessation, of blood flow to a level incompatible with normal function; the impairment may be global or regional. Ischemia, viewed simplistically as hypoxia plus hypoglycemia, will affect the most sensitive elements in the tissue, and if severe, persistent, or both, perturb all components. In its mildest form, impaired regional cerebral blood flow causes a transient ischemic attack (TIA). TIA has an abrupt onset but is a rapidly diminishing neurological deficit of vascular origin, which lasts for less than 24 hours. This is well documented in humans but has not been studied in dogs, although the author does believe that this occurs in dogs, occasionally as a historical precursor to an infarction.
Severe ischemia, which in the CNS would produce necrosis of the neurons and glial elements, results in an area of dead tissue termed an infarct. Infarction can result from arterial obstruction or venous thrombosis; arterial infarction can be due to either obstruction from thrombosis or embolism or to occlusion from blood vessel abnormalities such as vasculitis. A number of classification systems for ischemic stroke have been proposed in humans. The most commonly used clinical systems divide ischemic stroke into three major stroke subtypes: large artery or atherosclerotic infarctions, cardioembolic infarctions and small vessel or lacunar infarctions. Atherosclerotic infarctions are the most common subtype documented in people. Although the frequency of the three different subtypes is, as yet, unknown in dogs, atherosclerosis has been reported in dogs; it is especially seen in older dogs, dogs with hypothyroidism and miniature schnauzers with idiopathic hyperlipoproteinemia. Other diseases associated with infarction in dogs include sepsis, coagulopathy, neoplasia and heartworm infections.
Cerebrovascular accidents can, on occasion, result from hemorrhage. This can occur within or around the brain and may result in rapid cerebral dysfunction often by alteration in cerebral volume (mass effect). It is classified as epidural, subdural, subarachnoid, intraparenchymal (primary or secondary), or intraventricular. When the bleeding is substantial enough to form an excessive additional volume within the CNS, the results can be fatal. The presence of a hematoma initiates edema and neuronal damage in surrounding parenchyma. Fluid begins to collect immediately in the region around the hematoma, and edema usually persists for up to 5 days, and in some cases as much as 2 weeks. Early edema around the hematoma results from the release and accumulation of osmotically active serum proteins from the clot.
The source of primary intraparenchymal hemorrhage is incompletely understood but human patients often have systemic hypertension with concurrent fibrinoid degeneration of arteries in the brain. Hypertension in dogs may be primary or secondary to disorders such as renal disease and hyperadrenocorticism; these animals may be predisposed to intracranial hemorrhage. A variety of secondary causes of hemorrhage exist in dogs. Dogs with brain infarction can have associated hemorrhage, as can dogs with intracranial tumors, vasculitis or coagulopathies.

Clinical signs
CVA are characterized clinically by a peracute or acute onset of focal, asymmetrical and non-progressive brain dysfunction. Worsening of edema (associated with secondary injury phenomenon) can result in progression of neurological signs for a short period of 24-72 hours. Hemorrhage may be an exception to this description and be presented with a more progressive onset. Clinical signs usually regress after 24-72 hours; this is attributable to diminution of the mass effect secondary to hemorrhage and reorganization or edema resorption. With brainstem involvement, neurological examination of the cranial nerves will define the exact location and extension of the lesion. With forebrain lesions, the clinical sign may vary from simple disorientation to death. A unilateral lesion will induce ipsilateral circling, hemi-inattention syndrome, contralateral central blindness, as well as...
contralateral ataxia and proprioception deficits. Seizures are reported to be very common in association with CVA in dogs.

Diagnosis
Blood and urine analysis is indicated to identify the possible underlying causes described above. Thyroid function (FT4, TT4, and endogenous cTSH levels), a coagulation profile (including a buccal mucosal bleeding time, a prothrombin time, a partial thromboplastin time and fibrinogen degradation products) and, if possible, multiple systolic blood pressures and an ECG, should be evaluated in any animal suspected of CVA. A fecal analysis should be performed to rule out parasitic infestation. Blood and urine cultures are indicated in case of sepsis. Cerebrospinal fluid analysis is unlikely to confirm a diagnosis of CVA but may help to rule out inflammatory CNS disease or may, on occasion, reveal recent haemorrhage (xanthochromia), normal to increased protein and a mild neutrophilic or mononuclear pleocytosis. Imaging studies of the brain (computed tomography, CT, or magnetic resonance imaging, MRI) are necessary to confirm the clinical neurolocalisation, re-enforce the suspicion of CVA, identify associated mass effect and rule-out other causes of focal brain disorders (trauma, tumor, inflammation). CT also allows rapid image acquisition, in addition to the fact that changes associated with ischemia/infarction can be detected as early as 3 to 6 hours after the onset. Enhancement usually appears after 24-48 hours and is most evident after 1 or 2 weeks especially in the periphery where neovascularisation exists.

MR imaging is more sensitive than is CT in early infarction, with changes seen within an hour of onset. Magnetic resonance imaging is more sensitive in the detection of edema, provides multiplanar views, and lacks beam-hardening artifact when compared with CT. The conventional imaging findings in evolving cerebral infarction are well characterized and follow a temporal evolution similar in many ways to that seen on CT. These changes seen in ischemic parenchyma rely on an increase in tissue water content. Gradually, during the acute stage, the T2-weighted image becomes more hyperintense in the ischemic region, particularly over the first 24 hours. These signal changes seen in the first 24-hours are best appreciated in grey matter and are well visualized in deep grey matter structures such as the thalamus or basal ganglia, in addition to cortical grey matter. Gadolinium enhances infarcts because of vascular rupture but does not enhance ischemia or edema. Computed tomography is very sensitive for acute hemorrhage, with a linear relationship demonstrated between CT attenuation and hematocrit. In a patient with a normal hematocrit, acute hemorrhage is seen as an area of increased attenuation, which tends to increase for the first 72 hours and then slowly decreases to isodensity at about 1 month post-hemorrhage. The periphery of the lesion may enhance from approximately 6 days to 6 weeks after onset, on a CT scan.

Treatment
Ischemic stroke
Treatment of an ischemic stroke revolves around three principles:
1. monitoring and correction of basic physiologic variables (e.g. oxygen level, fluid balance, blood pressure, body temperature);
2. inhibition of the biochemical and metabolic cascades subsequent to ischemia to prevent neuronal death (concept of neuroprotection); and
3. restoration or improvement of cerebral blood flow by thrombolysis in the presence of a thrombus.

The potentially salvageable portion of the ischemic zone (ischemic penumbra) is the presumed therapeutic target for both thrombolytic and neuroprotective stroke therapy. The time period during which injury may be reversible is called the therapeutic window. It is estimated that this ‘window of opportunity’ is approximately 3-4 hours before the irreversible neurological damage occurs. Fortunately, the vast majority of ischemic stroke patients have no major difficulty maintaining their airways, breathing efforts or circulatory competence early in their clinical course.

There is no evidence that glucocorticoid treatment provides any beneficial neuroprotection in stroke. Aside from the lack of proven benefit in veterinary stroke patients, the use of glucocorticoids may increase the risk of gastrointestinal complications and infection. Treatment strategies for ischemic stroke considered in man utilizing other neuroprotective agents (N-methyl-D-aspartate [NMDA] antagonists, Ca2+ channel blockers, sodium channel modulators) or anti-platelets and thrombolytic therapy remain to be evaluated clinically in dogs. Although the above neuroprotective agents have resulted in a dramatic decrease in the size of stroke lesion in experimental animal models, these agents have either failed to prove their efficacy in clinical trials or are awaiting further investigation. At the time of writing, there is no definitive data in humans or animals to confirm a significant improvement in clinical outcome in patients with acute ischemic stroke treated with unfractionated heparin as thrombolytic therapy. Despite conflicting results regarding its efficacy, intravenous recombinant tissue plasminogen activator (TPA) is sometimes used in human stroke patients if it can be given within the first 3 hours. This critical time window makes the use of thrombolytic treatment
unrealistic in veterinary neurology. Furthermore, this type of treatment carries a significant risk of intracranial hemorrhage following treatment. Antiplatelet therapy with low-dose aspirin (0.5 mg/kg PO SID) can be used prophylactically to prevent clot formation in proven cardiac sources of an embolus.

**Hemorrhagic stroke**
The medical management of dogs with intracranial hemorrhage commonly includes: stabilization of the patient (airway protection, monitoring and correction of vital signs); assessment and monitoring of the neurological status; determination and treatment of potential underlying causes of the hemorrhage; assessment for the need for specific treatment measures including management of raised intracranial pressure (ICP).

The risk of neurological deterioration and cardiovascular instability is highest during the first 24 hours after the onset of an intracranial hemorrhage, as the space-occupying lesion slowly expands and cerebral vasogenic edema develops. Careful monitoring including assessment of vital parameters (e.g., oxygen levels, fluid balance, blood pressure, body temperature) as well as neurological status, is therefore essential during this initial period.

There is no evidence in humans to support the routine use of oxygen for the treatment of hemorrhagic stroke, in the absence of hypoxia. In a rapidly deteriorating animal, hyperventilation can temporarily be used to reduce ICP. The aim of hyperventilation is to reduce cerebral blood volume and hence ICP, by causing a hypocapnic vasoconstriction. However, excessive hyperventilation can be accompanied by a reduction in global cerebral blood flow, which may drop below ischemic thresholds, therefore it is not a recommended therapy unless the PaCO₂ can be closely monitored with capnography or arterial blood gas analysis.

Mannitol has traditionally been used to treat intracranial hypertension associated with pathologies such as head trauma, brain tumors or encephalitis. There is insubstantial evidence to suggest that mannitol exacerbates intracranial haemorrhage; therefore osmotic diuretics are routinely used in the control of ICP in human patients with known intracranial hemorrhage. Mannitol therapy (0.25 - 1.0 g/kg IV over 10 to 20 minutes up to q 8h) may be initiated to treat suspected elevated ICP secondary to hemorrhagic stroke. Mannitol’s main effect is to enhance cerebral blood flow by reducing blood viscosity. Surgical evacuation of the hematoma can be employed in dogs with large hematomas (mostly subarachnoid) and a deteriorating neurological status.

**Prognosis**
The prognosis for ischemic or hemorrhagic stroke depends overall on the initial severity of the neurological deficit, the initial response to supportive care and the severity of the underlying cause if one has been identified. Fortunately, most cases of ischemic stroke recover within several weeks with only supportive care. In a recent retrospective study of 33 dogs with MRI or necropsy evidence of brain infarction, there was no association between the region of the brain involved (telencephalic, thalamic/midbrain, cerebellum), the type of infarction (territorial or lacunar) and the outcome. However, dogs with a concurrent medical condition had a significantly shorter survival time than those dogs with no identifiable medical condition. Dogs with a concurrent medical condition also were significantly more likely to suffer from recurrent neurological signs due to subsequent infarcts.