REVIEW

Ischaemic stroke in dogs and humans: a comparative review

Cerebrovascular accidents, also known as strokes, are one of the major causes of disability and mortality among adult humans. The increased availability of magnetic resonance imaging in veterinary medicine means they are being increasingly recognised in dogs, too. Cerebrovascular accident is defined as the sudden onset of non-progressive, focal brain dysfunction as a result of ischaemic infarction or haemorrhage. Focal ischaemic stroke is caused by interruption of the arterial blood flow to a dependent area of brain parenchyma by a thrombus or an embolus. Once the diagnosis of ischaemic stroke is confirmed, potential sources of thrombosis or embolism should be investigated and treated accordingly. Dogs with ischaemic stroke tend to recover within several weeks with supportive care only.

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INTRODUCTION

The term 'cerebrovascular disease' is defined as any abnormality of the brain resulting from a pathological process compromising its blood supply (Kalimo and others 2002). Pathological processes that may result in cerebrovascular disease include occlusion of the lumen by a thrombus or embolus; rupture of the blood vessel wall; lesion or altered permeability of the vessel wall; and increased viscosity or other changes in the quality of the blood (Adams and Victor 1997).

Stroke or cerebrovascular accident (CVA) is the most common clinical presentation of cerebrovascular disease and is defined as the sudden onset of non-progressive, focal brain signs that occur secondarily to cerebrovascular disease (Sacco 1994a). By convention, these signs must continue for more than 24 hours to be diagnosed as stroke, which is usually associated with permanent damage to the brain. If the clinical signs resolve within 24 hours, the episode is called a transient ischaemic attack (Carolei and others 1998).

From a pathological point of view, the lesions affecting the cerebral blood vessels are divided into two broad categories: ischaemia with or without infarction as a result of obstructed blood vessels and haemorrhage caused by rupture of the blood vessel wall (Adams and Victor 1997). In humans, 77 per cent of strokes are ischaemic and 23 per cent are haemorrhagic (17 per cent intracerebral haemorrhage and 6 per cent subarachnoid haemorrhage) (Casso and others 1998).

PATHOPHYSIOLOGY OF ISCHAEMIC STROKE

As the brain has limited cellular storage capacity, it relies on a permanent supply of glucose and oxygen to maintain ionic pump function. The delivery of glucose and oxygen is compromised when cerebral blood flow (CBF) falls below a threshold level (ischaemic threshold). Ischaemia, defined as a reduction of CBF to a level incompatible with normal function, then develops. Since neurons have the highest demand for oxygen, neuronal function is first affected. This is followed, in declining order of vulnerability, by the function of oligodendrocytes, astrocytes, mesodermal microglia and fibrovascular elements (Collins and others 1989). If sufficient perfusion pressure is not re-established, severe ischaemia results in an area of dead tissue described as an infarct (Summers and others 1995).

Ischaemia is thus a continuum between normal cellular function and cell death. A focal ischaemic event results from a locally derived vascular obstruction (thrombus), or from a vascular obstruction transported to the brain from a distant site (thromboembolism) (Kalimo and others 2002). The development of an irreversible injury depends not only on the severity of the ischaemic insult, in other words the level of CBF, but also on its duration (Heiss and Rosner 1983).

Graded reductions in CBF are associated with specific molecular and biochemical events within brain cells. The primary effects of ischaemia are reduced

supply of substrate for energy metabolism (oxygen and glucose) and reduced removal of lactic acid. In severe ischaemia, these derangements directly cause neuronal and glial cell death (Sharp and others 1998). These primary abnormalities trigger secondary processes leading to cell death in regions of incomplete ischaemia and after reperfusion: calcium influx into cells, activation of proteases and lipases, production of free radicals and proinflammatory molecules, release of neurotransmitters, and induction of genes that promote cell death via apoptosis (Collins and others 1989, Dugan and others 1995, Mody and MacDonald 1995, Samdani and others 1997, Sharp and others 1998).

In contrast to the core, where ischaemia is severe and infarction develops rapidly, areas surrounding the core (called the penumbra) show a moderate decrease of CBF and thus tolerate longer durations of ischaemic stress. In the penumbra, neurons are still viable but are at risk of becoming irreversibly injured as the infarct evolves (Heiss and others 1994). Penumbra tissue has the potential for recovery and is therefore the target for intervention therapy in cases of acute ischaemic stroke (Kogure and Kogure 1997). The factors causing the evolution of the penumbra to irreversible injury are multiple and complex. The time window after which the penumbra is no longer viable depends on the degree of blood flow reduction, the region of the brain involved and the individual (Furlan and others 1996).

A number of classifications for ischaemic stroke have been proposed in humans (Sacco 1994a). Ischaemic stroke can be classified depending on the vascular territory involved (Kalimo and others 2002); the number of red blood cells found in the necrotic tissue, dividing infarcts into pallid (pale) or haemorrhagic (red) infarcts (Kalimo and others 2002); the size of vessels involved, dividing infarcts into territorial (large vessel disease) or lacunar (small vessel disease) infarcts (Adams and Victor 1997, Gan and others 1997, Kalimo and others 2002); and the suspected underlying cause (Bougousslavsky and others 1988, Sacco 1994a,b, Marks 2002).

THE STROKE SYNDROME

In all forms of stroke, it is the abruptness with which the neurological deficits develop that defines the disorder as being vascular (Adams and Victor 1997). This is in comparison with other diseases affecting the brain such as metabolic disorders, which tend to wax and wane in severity with time, and the inflammatory or neoplastic diseases, in which the onset is more insidious and the course progressive. The other important clinical feature that defines a stroke is the fact that, after a short time, the neurological deficits stop progressing and then regress in all except fatal strokes. Worsening of the oedema can result in slight progression of neurological signs for 24 to 72 hours.

A stroke should be considered in any dog presented with peracute onset of focal and non-progressive brain dysfunction (Platt and Garosi 2003). In ischaemic stroke, the specific neurological deficit relates to the location and size of the infarct. The territory of any artery (large or small, deep or superficial) may be involved. In humans, the clinical picture that results from an occlusion of any one artery differs in minor ways from one patient to another. However, there is sufficient uniformity to justify the assignment of a typical syndrome to each of the major arteries (Adams and Victor 1997).

In focal cerebral ischaemia, the blood flow through an artery is compromised to such an extent that the tissue in its supply territory becomes ischaemic. In its mildest form, the impaired regional CBF causes a transient ischaemic attack (TIA). These are brief episodes of focal loss of brain function attributable to ischaemia, involving one of the vascular systems and lasting less than 24 hours (Carolei and others 1998). The cause of TIA in humans is most often small emboli from extracranial sources, either cardiac or from atherosclerotic plaques in the carotid or vertebrobasilar arteries. Similar paroxysmal events have been reported in dogs with suspected or histologically proven infarction (Thomas and others 1996, Garosi and others 2005a, McConnell and others 2005), but the underlying cause remains undetermined.

CEREBRAL ARTERIAL BLOOD SUPPLY AND DISTRIBUTION

The brain is a complex and heterogeneous organ dependent on its blood supply. The major afferent blood supply to the brain arises from the paired internal carotid arteries and paired vertebral arteries. The internal carotid arteries and the single basilar artery, a continuation of the spinal artery and fused vertebral arteries, are joined on the ventral surface of the brain into an elongated vascular ring called the cerebral arterial circle (circulus arteriosus cerebri), or the circle of Willis in humans.

The arterial supply in dogs is radically different from that in humans and other primates. In humans, the internal carotid artery is the most important source of blood to the brain, whereas in dogs the cerebral arterial circle receives a substantial contribution from anastomotic vessels derived from numerous extensive branches of the external carotid artery (Jewell 1952). Compared with humans, the vertebral arteries in dogs assume a greater importance in terms of the total blood supply to the brain, irrigating the rostral thalamus, hypothalamus and caudal cerebral cortex (Jewell 1952, Wellens and others 1975) (Fig 1). Because of the numerous intraextracranial anastomoses, many alternative routes ensure an adequate blood supply to the dog's brain, thus protecting the brain against the effects of cerebral arterial occlusion (Jewell 1952). These differences make the dog unsuitable for many experimental models of cerebral ischaemia and may explain why cerebrovascular disease is less common in dogs than in humans.

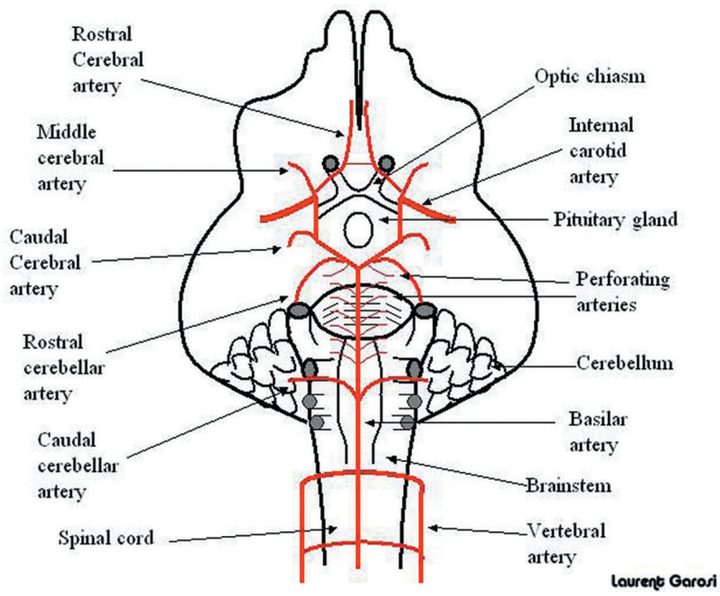

FIG 1. Ventral view of the brain and spinal cord of a dog, showing the vascular supply (simplified)

The major arteries supplying the cerebrum and cerebellum are the same in both humans and dogs, and magnetic resonance imaging (MRI) reveals a similar appearance of infarcts. Occlusion of one of these main arteries results in a large infarct, also called a territorial infarct (Kalimo and others 2002).

Table 1. Cerebral arterial blood supply and distribution*

Arterial supply	Distribution
Rostral cerebral artery	Rostromedial and dorsal surfaces of the cerebral cortex along each side of the medial longitudinal fissure
Middle cerebral artery	Lateral surface of the cerebral cortex
Caudal cerebral artery	Caudomedial and dorsal surfaces of the cerebral cortex along each side of the medial longitudinal fissure
Rostral cerebellar artery	Rostral part of the cerebellar hemisphere, vermis and dorsolateral brainstem
Caudal cerebellar artery	Caudal and ventral cerebellum Lateral medulla
Striate arteries	Globus pallidus, putamen, internal capsule, claustrum and part of the caudate nucleus
Proximal perforating arteries arising from the caudal communicating artery	Rostromedial thalamus
Distal perforating arteries arising from the caudal communicating artery	Caudolateral thalamus and subthalamus
Caudal perforating arteries arising from the basilar bifurcation and paramedian branches arising from the proximal portion of the caudal cerebral artery	Median and paramedian region of the caudal thalamus, midbrain and upper pons

*From Gillilan (1964, 1976), Anderson and Kubicek (1971), Nanda (1975), Inoue and others (1985), Kuwabara and others (1989), Brenowitz and Yonas (1990), Evans (1996), St-Jacques and others (1996)

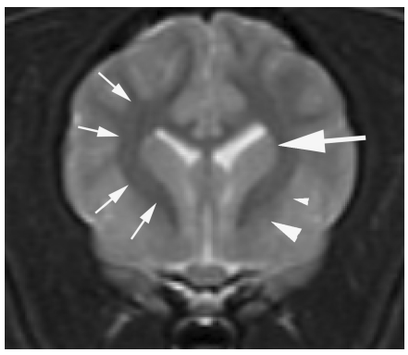

FIG 2. Transverse T2-weighted magnetic resonance (MR) image of the brain of a normal Cavalier King Charles spaniel at the level of the optic chiasm, showing the main regions of the brain supplied by the striate artery in dogs. The left caudate nucleus (large arrow), putamen (small arrowhead), globus pallidus (large arrowhead) and right internal capsule (small arrows) are identified

The branches of the main arteries running in the subarachnoid space penetrate the brain parenchyma. These intraparenchymal branches include both deep and superficial perforating arteries (Kalimo and others 2002). These penetrating branches are end arteries that have limited collateral connections with neighbouring blood vessels until they divide into capillaries (Nishimaru 1963). The capillaries do interconnect, but their collateral flow is relatively local and limited, such that the occlusion of a perforator artery usually results in a small area of ischaemic damage, commonly described as a lacunar infarct (Kalimo and others 2002). Specific vascular territories of the canine brain are summarised in Table 1 and Fig 2.

NEUROIMAGING OF ISCHAEMIC STROKE

Imaging studies of the brain are necessary to rule out other causes of acute-onset neurological signs and to confirm a suspicion of stroke. They are also necessary to define the vascular territory involved, the extent of the lesion, and to distinguish between ischaemic and haemorrhagic stroke. MRI is the most sensitive imaging modality for diagnosing ischaemic stroke.

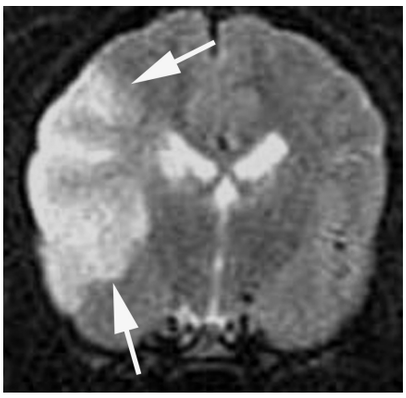

FIG 3. Transverse T2-weighted MR image of the brain of a dog with a territorial infarct in the region supplied by the right middle cerebral artery. Observe the sharp demarcation between affected and non-affected tissue discriminating territorial infarcts from other lesions. The increase in signal is predominantly within the grey matter and usually homogeneous in appearance. A mild mass effect is present. This finding, when present, occurs within the first week postinfarction

Changes are evident within hours of onset.

Computed tomography

Computed tomography (CT) images are frequently normal during the acute phase of ischaemia. Therefore, the diagnosis of ischaemic stroke using CT relies upon the exclusion of mimics of stroke. Early signs of ischaemia seen on CT images can be subtle and difficult to detect even by experienced readers. Signs include parenchymal hypodensity, loss of grey-white matter differentiation, subtle effacement of the cortical sulci, and local mass effect (Schriger and others 1998, Grotta and others 1999). Until recently, CT was the preferred imaging modality in humans to determine the presence of haemorrhage in early stroke. Haemorrhage appears hyperdense in the early stages. Recent developments in MRI mean that CT now offers no advantage over it in the diagnosis of ischaemic stroke.

Conventional MRI

With conventional MRI, ischaemic stroke can be seen within 12 to 24 hours of onset and can be distinguished from haemorrhagic lesions. Although infarcts can sometimes be difficult to differentiate from other pathological processes, such as inflammatory diseases, they tend to have certain distinguishing characteristics on conventional magnetic resonance images (Thomas 1996, Thomas and others 1996, De La Paz and Mohr 1998, McConnell and others 2005) (Figs 3 and 4).

Functional MRI

Several functional MRI techniques have been developed for early diagnosis and follow-up treatment of strokes in humans. They include diffusion and perfusion imaging and magnetic resonance angiography (Figs 5, 6 and 7). Diffusion and perfusion MRI techniques have made it possible to distinguish between the two compartments (central core and peripheral penumbra) of ischaemic tissue (Sartor and Fiebach 2003). With perfusion-weighted images (PWI), the blood supply of the tissue and area of hypoperfusion can be monitored, whereas diffusion-weighted images (DWIs) approximately reflect the irreversibly damaged infarcted core (Heiland 2003). The volume difference between the two, also termed PWI/DWI mismatch, has some correlation with the ischaemic penumbra (Sartor and Fiebach 2003). DWIs are used commonly in humans to improve the sensitivity and specificity of diagnosing acute stroke, making it an ideal sequence for positive identification of hyperacute stroke, ruling out stroke mimics (Geijer and others 1999).

In addition to its use for tissue evaluation, MRA can non-invasively assess the intracranial vascular status of stroke patients.

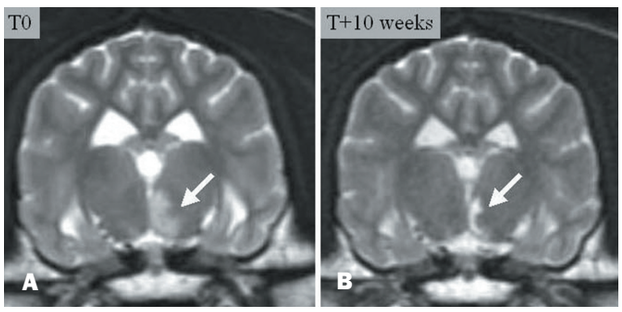

FIG 4. Transverse T2-weighted MR images of the brain of a greyhound with a lacunar infarct in the paramedian region of the caudal thalamus. (A) At onset. Typical small, comma-shaped lacunar infarct (arrow), observed within the grey matter. The lesion is more sharply defined, homogeneous and hyperintense than is typically seen with inflammatory disease. (B) At 10 weeks. The lesion is smaller and more sharply marginated (arrow) due to necrosis and atrophy of the affected parenchyma

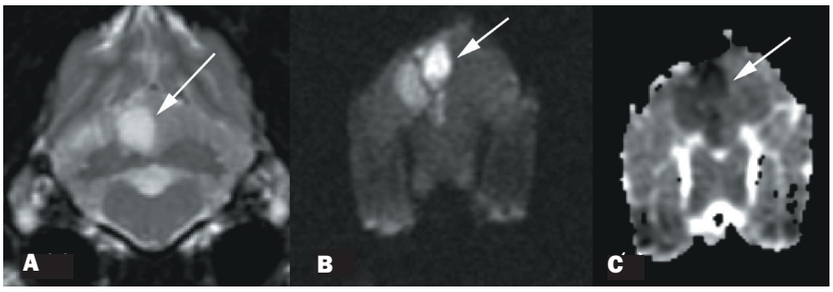

FIG 5. (A) Transverse T2-weighted magnetic resonance angiography (MRA) image of the brain of a whippet with an acute cerebellar infarct (arrows), (B) oblique diffusion-weighted image (DWI), and (C) apparent diffusion coefficient. Trapping of water within cells due to lack of energy results in a restricted diffusion of water within the brain, which appears as increased signal in (B) and reduced signal in (C). The use of DWI allows ageing of infarcts and helps exclude other lesions resembling infarcts

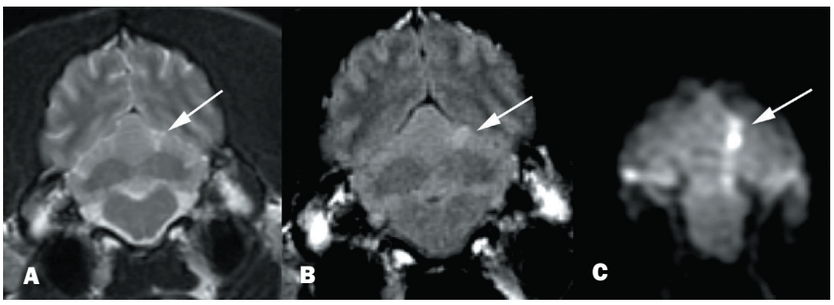

FIG 6. (A) Transverse T2-weighted MRA image of the brain of a dog with small cortical cerebellar infarct (arrows), (B) fluid attenuated inversion recovery (FLAIR) and (C) DWI images. Small infarcts may be overlooked on standard MR images especially if adjacent to the ventricles. In this case, the lesion is significantly more apparent on the FLAIR and DWI images than on the T2-weighted image

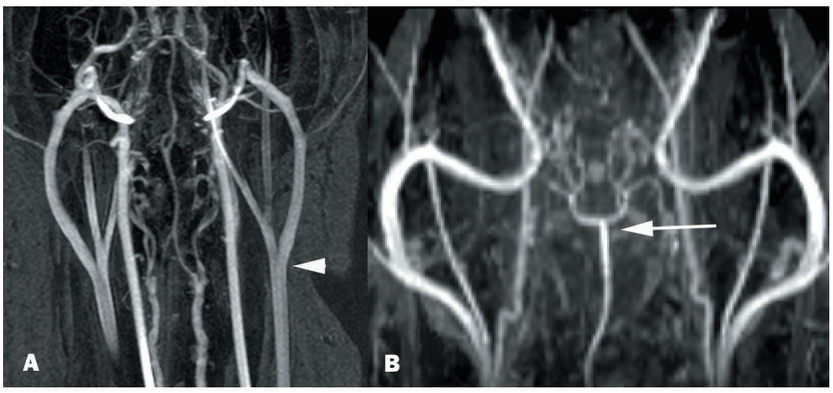

FIG 7. (A) Contrast-enhanced MRA of the carotid arteries (arrowhead) and (B) time-of-flight (TOF) MRA of the intracranial and extracranial arterial supply in a dog. Contrast-based techniques result in better quality images than non-contrast TOF techniques. The basilar artery and cerebral arterial circle can be seen on the TOF image (arrow) but are difficult to interpret due to superimposition of other vessels and fat in the skull

The use of MRA in dogs has been described and may allow identification of underlying vascular lesions in cases of canine stroke (Kent and others 2001) (Fig 7).

UNDERLYING CAUSES OF ISCHAEMIC STROKE

Ischaemic strokes have been reported infrequently in the veterinary medical literature when compared with the medical literature (Fankhauser and others 1965, Patton and Garner 1970, Kotani and others 1975, Patterson and others 1985, Liu and others 1986, Bagley and others 1988, Joseph and others 1988, Swayne and others 1988, Cachin and Vandevelde 1990, Norton 1992, Tidwell and others 1994, Thomas 1996, Kent and others 2001, Berg and Joseph 2003, Platt and Garosi 2003, Axlund and others 2004, Garosi and others 2005a,b, McConnell and others 2005). Apart from recent reports by Garosi and others (2005a,b), most have been based on postmortem results in dogs that died or were euthanased as a result of the severity of the ischaemic stroke and/or the suspected underlying cause of the stroke. This may affect the prevalence and type of underlying causes, as it is likely that only the most severely affected dogs, or dogs in which infarction occurred secondarily to a disease with a poor prognosis (neoplasia), would die or be euthanased.

In embolic strokes, the occlusion is due to an embolic fragment that has broken away from a thrombus that has formed either in another vascular bed (artery-to-artery thromboembolism) or in the heart (cardioembolism). Thromboembolic diseases that have been histopathologically confirmed to underlie brain infarct in dogs include septic (Cachin and Vandevelde 1990, Cook and others 2005), parasitic (*Dirofilaria immitis*) (Kotani and others 1975), metastatic tumour cell (Joseph and others 1988) and fibrocartilaginous embolisms (Axlund and others 2004). The biggest clinical problem with embolisms is identifying the source, especially antemortem. Emboli breaking loose from thrombi formed on atherosclerotic, often ulcerated, lesions in the extracranial arteries are the most common source of artery-to-artery embolism in man (Kalimo and others 2002). Other uncommon sources include emboli composed of tumour cells, which either detach from a neoplasm located within the cardiovascular system or proliferate freely in the circulating blood (cardiac myxoma, intravascular malignant lymphoma, and so on) (Haught and others 1991, Kalimo and others 2002), as well as fat (Muller and others 1994) or air embolisms. There are many causes of emboli arising from the heart in humans. The prevalence of cardioembolic stroke in dogs is as yet unknown.

Aside from embolic disease, most ischaemic strokes in humans can be attributed to atherosclerosis and chronic hypertension, with both conditions interacting in a variety of ways (Adams and Victor 1997). The atheromatous plaques serve as sites of thrombosis by progressively narrowing the lumen of an artery, causing stenosis, reduction of blood flow and damage to the endothelium. The atherosclerotic thrombosis involves the deposition of fibrin and platelets (Kalimo and others 2002). In addition to vascular occlusion at the site of atherosclerosis, infarcts are also produced by emboli arising from atheromatous lesions situated proximally to otherwise healthy branches

located more distally in the arterial tree (Fisher and Karnes 1965). Chronic hypertension, hyperlipidaemia and diabetes mellitus are the main risk factors for atherosclerosis in humans (Valtonen and Oksanen 1972, Adams and Victor 1997).

Atherosclerosis is generally considered a rare phenomenon in dogs (Fox and others 2000) but has been reported, particularly in dogs with hypothyroidism (Hess and others 2003) and miniature schnauzers with idiopathic hyperlipoproteinaemia (Rogers and others 1975, Patterson and others 1985, Liu and others 1986, Joseph and others 1988). Recently, diabetes mellitus has also been identified as being more prevalent in dogs with atherosclerosis compared with dogs without atherosclerosis on postmortem examination (Hess and others 2003). However, in contrast to humans, infarction in dogs has rarely been associated with atherosclerosis, but when it does occur, has been considered a complication of hypothyroidism (Fankhauser and others 1965, Suzuki 1972, Patterson and others 1985, Liu and others 1986).

In a study by Garosi and others (2005b), thyroid function was tested in 33 dogs with ischaemic stroke. None of these dogs was diagnosed with primary hypothyroidism, an endocrine disease frequently incriminated in the veterinary literature as an underlying cause of cerebrovascular disease (Patterson and others 1985, Liu and others 1986, Thomas 1996). Other uncommonly reported causes of thrombosis in dogs include occlusion of blood vessels with neoplastic cells in cases of intravascular lymphoma (Kent and others 2001).

In the Western world, arterial hypertension is the main risk factor for stroke in humans. Hypertension promotes intracerebral haemorrhage, as well as atherosclerotic macro- and microangiopathy, resulting in ischaemic stroke (Dufouil and others 2001). Garosi and others (2005b) found a prevalence of hypertension of less than 30 per cent in 33 dogs with ischaemic stroke. When hypertension was documented in these dogs, an underlying cause, in particular chronic kidney disease or hyperadrenocorticism, was found. Other causes of hypertension included phaeochromocytoma.

It is common to find hypertension associated with acute strokes in humans since the secretion of catecholamines will provoke hypertension. This response may be a temporary response to stress, and some authors have argued that the elevated blood pressure is to ensure adequate cerebral perfusion pressure in the infarct's penumbra zone (Yatsu and Zivin 1985, Droste and others 2003). After ischaemic stroke has been diagnosed, it is necessary to continuously monitor blood pressure to differentiate stroke-induced hypertension from hypertension-related stroke. Monitoring is also important in humans, and in dogs presented with medical conditions associated with a high prevalence of hypertension that are normotensive on initial measurement of blood pressure.

Despite efforts to arrive at a diagnosis, the cause of the infarction remains undetermined in up to 40 per cent of human cases (Sacco 1994b). This subtype of infarct of undetermined cause has been termed cryptogenic. Emerging technologies have led to the suggestion that some cases of cryptogenic infarct may be explained by haematological disorders causing hypercoagulable states (Kalimo and others 2002).

In the study by Garosi and others (2005b), arterial thrombosis and a hypercoagulable state was documented in four dogs (one dog with protein-losing nephropathy, two dogs with untreated hyperadrenocorticism and one dog with haemangiosarcoma). Other reports of histopathologically confirmed brain infarct in dogs mention the presence of mural thrombi in the cerebral arteries, but the cause of the formation of the thrombus was not determined (Bagley and others 1988, Joseph and others 1988).

Hypercoagulable states have become increasingly recognised for their role in thrombogenesis (Bick and Kaplan 1998). While primary hypercoagulable states remain poorly characterised in animals, secondary hypercoagulable states are well recognised as predisposing factors for thrombosis. Conditions such as hyperadrenocorticism, protein-losing nephropathy, protein-losing enteropathy and neoplasia have all been associated with thromboembolism (Fox and others 2000). Spaniels and particularly Cavalier King Charles spaniels seem to be predisposed to cerebrovascular accidents, since an increased incidence of cerebellar infarction has been documented in this breed (McConnell and others 2005). The reasons are unclear but may be due to the prevalence of heart disease, alterations in coagulation and platelet morphology, or possible connective tissue pathology and anatomical variation (Chiari malformation).

Haemostatic abnormalities associated with stroke in humans may be broadly classified as familial or acquired (Coull and Clark 1993). Principal among the familial thrombotic coagulopathies are deficiencies in the concentration or function of protein-C, protein-S and antithrombin III. The acquired disorders of haemostasis associated with stroke probably constitute a larger proportion of the important stroke-related coagulopathies. Many of the acquired haemostatic abnormalities exist within a special clinical setting, such as with malignancy or with myeloproliferative diseases, nephrotic syndrome or liver disease. Most of the haemostatic disorders in stroke are associated with dysfunction of vascular endothelium and abnormalities of, or interference with, the natural anticoagulant proteins (Coull and Clark 1993). Further studies are required to investigate the possible relationship between haemostatic disorders and ischaemic stroke in humans as well as in dogs.

TREATMENT OF ISCHAEMIC STROKE

Once the diagnosis of stroke has been made, potential underlying causes should be investigated and treated accordingly.

Theoretically, there are three approaches to the treatment of ischaemic stroke: monitoring and correction, if there is deviation from the normal range, of basic physiological variables (oxygen level, fluid balance, blood pressure, body temperature); inhibition of the biochemical and metabolic cascades after ischaemia to prevent neuronal death (the concept of neuroprotection); and restoration or improvement of cerebral blood flow by thrombolysis in cases of a thrombus.

In ischaemic stroke, irreversible neuronal injury begins within minutes. The area of markedly decreased perfusion surrounding the ischaemic penumbra is potentially salvageable if significant arterial flow can be quickly restored. Thus, the penumbra is the therapeutic target of most emergent stroke treatments (Hakim 1998). It is estimated that the penumbra is lost and irreversible lesions occur within six hours (Hakim 1998, Zivin 1998). Survival of neurons and other cells in the occluded territory depends on collateral arterial blood supply. The degree of compensatory blood flow determines whether cells die rapidly and form an infarct or survive by simply increasing the oxygen extraction from the blood. The perfusion pressure through the collateral arteries (and, in practice, the systemic arterial blood pressure) and the time between onset of ischaemia and reperfusion are the two most important factors influencing outcome (Hossmann 1988).

Monitoring of vital parameters

Fortunately, the vast majority of acute ischaemic stroke patients have no major difficulty maintaining their airway, breathing efforts or circulatory competence early in the clinical course (Thurman and Jauch 2002). Complications are usually associated with secondary occurrence of vasogenic oedema. Although patients are frequently placed on supplemental oxygen, there is no evidence in humans to support the routine use of oxygen in the absence of hypoxia (Adams and others 2004). Maintenance of systemic arterial blood pressure within the physiological range is essential because perfusion pressure is the primary force for improving the collateral blood supply.

Hypertension in cases of acute stroke presents several clinical dilemmas in humans. Many stroke victims share hypertension as an underlying risk factor, but the elevated blood pressure may be induced to ensure an adequate cerebral perfusion pressure in the infarct's penumbra zone (Yatsu and Zivin 1985, Droste and others 2003). Aggressive lowering of blood pressure should therefore be avoided during acute ischaemic stroke unless the patient is at a high risk of end-stage organ damage (Thurman and Jauch 2002).

Neuroprotection

There is no evidence that glucocorticoid therapy provides any beneficial effect (De Reuck and others 1988). The use of other agents in animals (N-methyl D-aspartate or alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid antagonists, calcium channel antagonists, sodium channel modulators, glycine antagonists, inhibitors of nitric oxide synthase) has resulted in a dramatic decrease in stroke volume in experiments, but these agents have either failed to prove their efficacy in clinical trials or are awaiting further investigation (Hickenbottom and Grotta 1998, Ovbiagele and others 2003).

Thrombolytic therapy

The potential benefits of thrombolytic therapy in humans depend on the effectiveness of the route of administration, and the time window during which it is given. Intravenous tissue plasminogen activator (tPA) is the first and currently only drug for the treatment of acute ischaemic stroke approved by the US Food and Drug Administration (National Institute of Neurological Disorders and Stroke rtPA Stroke Study Group 1995). Recent trials of thrombolytic therapy in acute ischaemic stroke have provided conflicting results. Only one trial of tPA suggested that thrombolytic therapy was definitely beneficial if given intravenously within the first three hours (National Institute of Neurological Disorders and Stroke rtPA Stroke Study Group 1995). If true, this critical time window makes the use of thrombolytic treatment unrealistic in veterinary neurology. Furthermore, administration of thrombolytic therapy carries a significant risk of brain haemorrhage (National Institute of Neurological Disorders and Stroke rtPA Stroke Study Group 1997).

Thrombolysis requires further testing in large randomised trials because the risks seem substantial, and the overall benefit is still uncertain: the time window for effective treatment remains unclear, there is no objective evidence to suggest that tPA is safer than streptokinase, and the apparent hazards and benefits may be similar when differences in trial design and baseline variables are adjusted for (Wardlaw and others 1997).

Table 2. Medical conditions commonly associated with ischaemic stroke in dogs

Hypertension (and potential underlying causes)
Endocrine disease (hyperadrenocorticism, hypothyroidism, diabetes mellitus)
Kidney disease
Heart disease
Metastatic disease

PROGNOSIS OF ISCHAEMIC STROKE

The prognosis of ischaemic stroke depends mainly on the neuroanatomical location of the stroke, the initial severity of the neurological deficit, the presence of secondary pathological effects (extracellular oedema, haemorrhagic transformation, increased intracranial pressure) and, especially, the underlying cause if one is identified. Most dogs with ischaemic stroke tend to recover within several weeks with only supportive care. The presence of a concurrent medical condition was a significant factor in the occurrence of subsequent infarct in the case series reported by Garosi and others (2005b). Once a diagnosis of brain infarct has been made, potential underlying causes should be investigated and treated accordingly (Table 2).

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