Available online at www.sciencedirect.com
ScienceDirect
The Veterinary Journal 180 (2009) 290–303
The Veterinary Journal
www.elsevier.com/locate/tvjl

Review

Ischaemic and haemorrhagic stroke in the dog

Annette Wessmann [a,*], Kate Chandler [b], Laurent Garosi [c]

[a] Division of Companion Animal Science, Institute of Comparative Medicine, Faculty of Veterinary Medicine, University of Glasgow Veterinary School, 464 Bearsden Road, Bearsden, Glasgow G61 1QH, UK
[b] The Royal Veterinary College, Hawkshead Lane, North Mymms, Hertfordshire AL9 7TA, UK
[c] Davies Veterinary Specialists, Manor Farm Business Park, Higham Gobion, Hertfordshire SG5 3HR, UK

Accepted 20 December 2007

Abstract

Cerebrovascular disease results from any pathological process of the blood vessels supplying the brain. Stroke, characterised by its abrupt onset, is the third leading cause of death in humans. This rare condition in dogs is increasingly being recognised with the advent of advanced diagnostic imaging. Magnetic resonance imaging (MRI) is the first choice diagnostic tool for stroke, particularly using diffusion-weighted images and magnetic resonance angiography for ischaemic stroke and gradient echo sequences for haemorrhagic stroke. An underlying cause is not always identified in either humans or dogs. Underlying conditions that may be associated with canine stroke include hypothyroidism, neoplasia, sepsis, hypertension, parasites, vascular malformation and coagulopathy. Treatment is mainly supportive and recovery often occurs within a few weeks. The prognosis is usually good if no underlying disease is found.

Keywords: Cerebrovascular disease; Haemorrhage; Ischaemia; Canine; Magnetic resonance imaging

Introduction

Cerebrovascular disease refers to any abnormality of the brain resulting from a pathological process of the supplying blood vessels (Kalimo et al., 2002), such as thrombosis, embolism or haemorrhage (Victor and Ropper, 2001). Cerebrovascular accident (CVA), also termed stroke, is the most common clinical presentation of cerebrovascular disease and the third leading cause of death in humans (Kalimo et al., 2002). Prevalence data for stroke in dogs is lacking. However, the frequency of occurrence is suspected to be considerably lower in dogs than in humans, being observed in 1.5–2% of neurological case referrals in the authors' institutions.

Stroke is the sudden or abrupt onset of focal neurological deficits resulting from an intracranial vascular event and, by convention, with clinical signs lasting for at least 24 h (Victor and Ropper, 2001). Should the clinical signs last <24 h, the event is referred to as a transient ischaemic attack (TIA) (Victor and Ropper, 2001). Ischaemia is present if the blood flow to the tissue is insufficient to maintain normal cellular function (Summers et al., 1995). Severe ischaemia results in an area of necrosis, termed ischaemic necrosis or infarction. Secondary leakage of blood can lead to haemorrhagic infarction (Summers et al., 1995). Ischaemic stroke is caused by intracranial arterial or venous obstruction. Haemorrhagic stroke results from rupture of intracranial blood vessels. In human medicine, ischaemic events account for 77% of strokes, while haemorrhagic events account for 23% (Sacco et al., 1998). Although further studies are pending, the relative frequency appears to be similar in dogs (Joseph et al., 1988; McConnell et al., 2005).

Multiple classification schemes are available for strokes and an outline is given in Table 1, modified from the National Institute of Neurological Disorders and Stroke (1990). Ischaemic stroke can be classified by the territory that the affected blood vessel supplies, the size of the vessel (e.g., large arterial vessel disease: territorial infarct, Fig. 1; small perforating arterial vessel disease: lacunar infarct;

* Corresponding author. Tel.: +44 141 3305848; fax: +44 141 3303663.
E-mail address: a.wessmann@vet.gla.ac.uk (A. Wessmann).

1090-0233/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tvjl.2007.12.023

Table 1
Classification of stroke (modified from National Institute of Neurological Disorders and Stroke, 1990)

Ischaemic stroke	
Anatomical site (vascular territory)	Rostral cerebral artery
	Middle cerebral artery
	Caudal cerebral artery
	Rostral cerebellar artery
	Caudal cerebellar artery
	Perforating artery
	Basilar artery
	Vertebral artery
Size	Territorial infarct
	Lacunar infarct
Age	Recent
	Organising
Type (number of erythrocytes)	Non-haemorrhagic (pallid)
	Haemorrhagic (red)
Pathology	Arterial disease
	Venous disease
Mechanism	Thrombotic
	Embolic
	Haemodynamic
Aetiology (examples)	Embolus (fat, air, parasites, neoplasia, fibrocartilaginous)
	Hypercoagulable state
	Hypertension
	Atherosclerosis
	No underlying cause identified
Haemorrhagic stroke	
Anatomical site	Epidural
	Subdural
	Subarachnoid
	Intraparenchymal
	Intraventricular
Size	Small
	Large
Age	Hyperacute
	Acute
	Early subacute
	Late subacute
	Chronic
Aetiology (Examples)	Neoplasia
	Parasites
	Coagulopathy
	Vascular malformation
	No underlying cause identified

Fig. 2), the age of the infarct, the presence of secondary haemorrhage, the mechanism of the stroke and the suspected underlying cause. Haemorrhagic stroke can be classified according to the anatomical site of the haemorrhage (e.g. subdural, Fig. 3; intraparenchymal, Fig. 4), size of the lesion, age of the lesion or by the suspected underlying cause.

Anatomy of blood supply to the brain

The brain is supplied by five pairs of main arteries (Fig. 5). The rostral, middle and caudal cerebral arteries supply the cerebrum and the rostral and caudal cerebellar arteries supply the cerebellum. The cerebral arteries and the rostral cerebellar arteries arise from an elongated vascular ring at the base of the brain called the cerebral arterial circle (circulus arteriosus cerebri) or 'circle of Willis'. The caudal cerebellar arteries arise from the basilar artery. The cerebral arterial circle is formed by the internal carotid arteries and the basilar artery. The caudal communicating artery forms the lateral and caudal thirds of the cerebral arterial circle (Evans, 1993). The function of the arterial circle is to maintain a constant blood pressure in the end arteries. If occlusion of the artery occurs, these end arteries have insufficient anastomoses to maintain viability of the tissue supplied (Evans, 1993).

The main arteries are situated in the subarachnoid space and give rise to deep and superficial perforating arteries. The deep perforating arteries (proximal, distal and caudal) arise from the caudal communicating arteries and the basilar artery. They supply the deep parenchyma and grey matter of the thalamus, midbrain and part of the pons (Inoue et al., 1985; Kuwabara et al., 1988). The striate arteries arise from the cerebral arterial circle and supply the basal nuclei and thalamus (Evans, 1993). The superficial perforating arteries supply the deep white matter and the surface of the brain. Perforating arteries are end arteries and have limited collateral connections with neighbouring blood vessels until they divide into capillaries (Kuwabara et al., 1988). They meet without anastomoses in a junctional zone, where subcortical infarction can occur (Kuwabara et al., 1988; Kalimo et al., 2002). The cerebral arterial circle also receives a considerable input from anastomotic vessels derived from numerous branches of the external carotid artery (Jewell, 1952).

Pathophysiology of cerebrovascular disease

The brain depends more than any other organ on an adequate blood supply. Blood flow to the central nervous system (CNS) must efficiently deliver oxygen, glucose and other nutrients and remove carbon dioxide, lactic acid and other metabolic products. Several mechanisms exist to protect brain damage. Anastomoses ensure sufficient blood supply to the brain at all times. Pressure autoregulation helps to maintain a relatively constant cerebral blood pressure, despite variations in systemic blood pressure (Bouma et al., 1992). Chemical autoregulation results from the direct responsiveness of the vasculature of the brain to changes in partial pressure of carbon dioxide and, to a lesser degree, to changes in partial pressure of oxygen in arterial blood (Bouma et al., 1992). Increased regional brain metabolism, as seen in seizures, leads to increased cerebral blood flow (Ingvar, 1986). Any incident to the brain can alter these mechanisms of autoregulation.

Ischaemia

Insufficient blood supply leads to ischaemia or infarction, in which normal cellular function cannot be maintained (Summers et al., 1995; Adams et al., 2001; Victor and Ropper, 2001; Kalimo et al., 2002; Sacco et al., 2004;

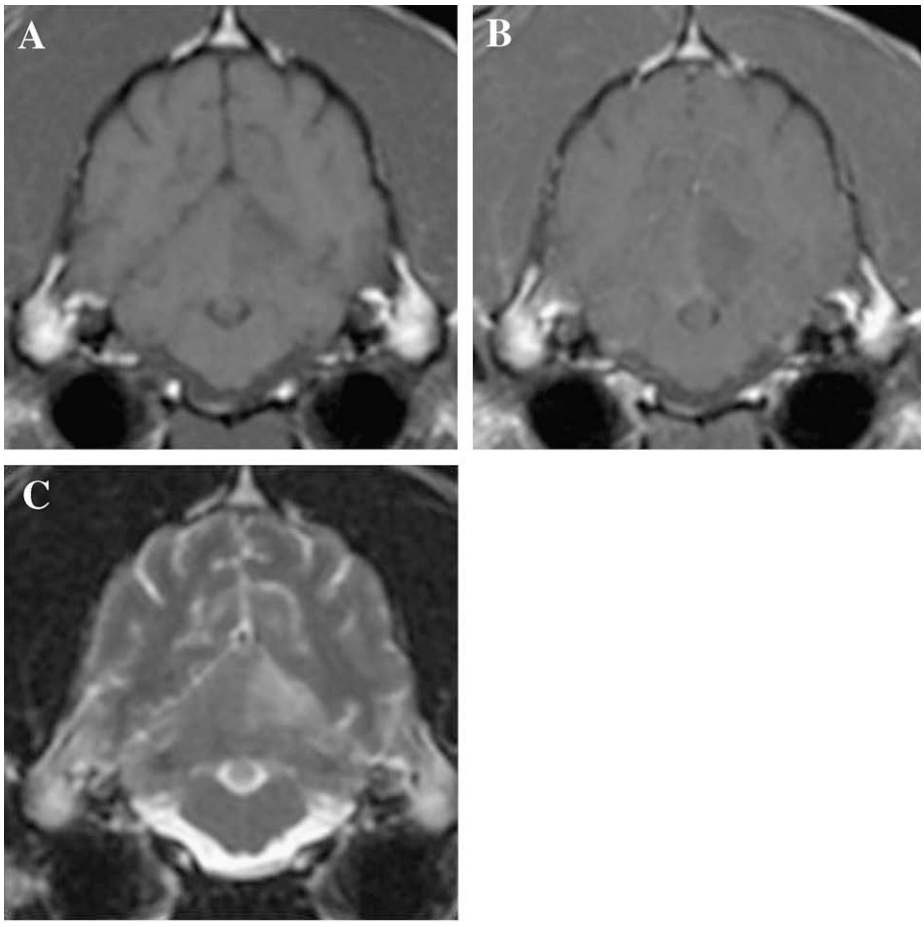

Fig. 1. Territorial infarct of unknown aetiology in the region of the left rostral cerebellar artery in a 10-year-old neutered male greyhound that presented with acute collapse followed by full recovery. The triangular wedge-shaped infarct is hypointense relative to the adjacent brain parenchyma on the T1-weighted image (A), with subtle gadolinium enhancement on the medial aspect of the lesion (B), and hyperintense on the T2-weighted image (C) (with thanks to V. Penning and R. Cappello).

Fox et al., 2005). Neuronal function appears to be unimpaired in humans with cerebral blood flow >40% of the normal value (Kalimo et al., 2002). A reduction of cerebral blood flow below this ischaemic threshold leads to hypoxia, hypoglycaemia and accumulation of potentially toxic metabolites, such as lactic acid, which contribute to cell damage (Kalimo et al., 2002). In animal experiments, complete obstruction of blood flow for >4–5 min produces irreversible cellular damage (Victor and Ropper, 2001).

Severe ischaemia causes direct cell death, whereas partial ischaemia can lead to secondary injury and reperfusion injury. Blood may accumulate if the ischaemic tissue is reperfused or if the venous drainage is occluded, resulting in haemorrhagic infarctions. Haemorrhagic infarctions carry a higher risk of clinical deterioration in humans (Adams et al., 2001; Kalimo et al., 2002). The damage depends on the severity and the duration of the ischaemia; repeated ischaemic episodes produce cumulative injury (Summers et al., 1995).

Cells with the highest demand for oxygen, the neurones, are affected first, followed by oligodendrocytes, astrocytes, mesodermal microglia and fibrovascular elements (Summers et al., 1995). Certain areas of the brain, such as the hippocampus, cerebral cortex, cerebellum, thalamus and basal nuclei, are more vulnerable to ischaemia than others (Panarello et al., 2004).

Necrosis or cell death occurs in the centre of an ischaemic lesion due to severe hypoperfusion (Kalimo et al., 2002). The necrotic area is surrounded by a zone of partially ischaemic tissue, with borderline levels of blood flow and metabolic function, called the penumbra (Adams et al., 2001). The penumbra has the capacity to recover normal cellular function if perfusion is restored and thus is the target for therapy in human medicine (Kalimo et al., 2002), but cell death may develop if the flow is not re-established or if the metabolic effects cannot be reversed (Adams et al., 2001; Garosi and McConnell, 2005).

At the molecular level, hypoperfusion leads to anaerobic glycolysis and a subsequent drop in adenosine triphosphate (ATP) production. Reduced intracellular ATP concentrations limit energy-dependent mechanisms within the cell that are required to protect cell homeostasis, for example maintenance of the resting membrane potential. A depolarised cell membrane permits the transmembrane flow of

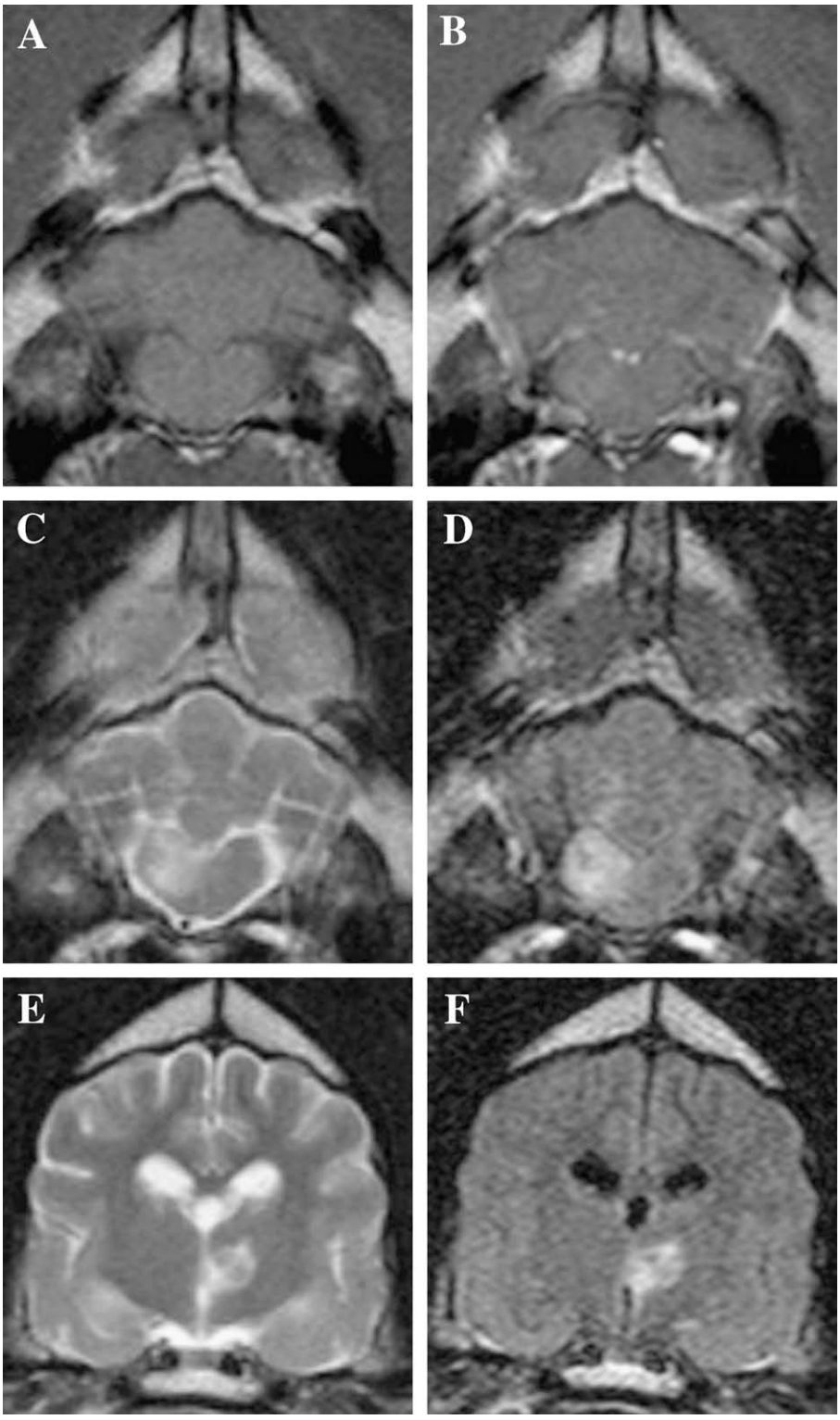

Fig. 2. Multiple lacunar infarcts in the territory of perforating arteries that supply the right brainstem (A–D) and the left thalamus (E, F). This 11-month-old male neutered cross-bred dog presented with an acute onset of non-ambulatory tetraparesis due to infarction secondary to a prostatic carcinoma. The dog improved during hospitalisation and then was lost to follow-up. The infarcts are isointense relative to brain parenchyma on the T1-weighted image (A), poorly enhancing with gadolinium (B) and hyperintense on T2-weighted images (C, E) and FLAIR (D, F).

multiple ions, such as sodium, potassium, chloride and calcium. Neuronal depolarisation leads to excitatory amino acid release and triggers a further increase in calcium influx due to voltage gated calcium channel activation. Rises in intracellular calcium concentrations result in synthesis of nitric oxide and the activation of enzymes, such as

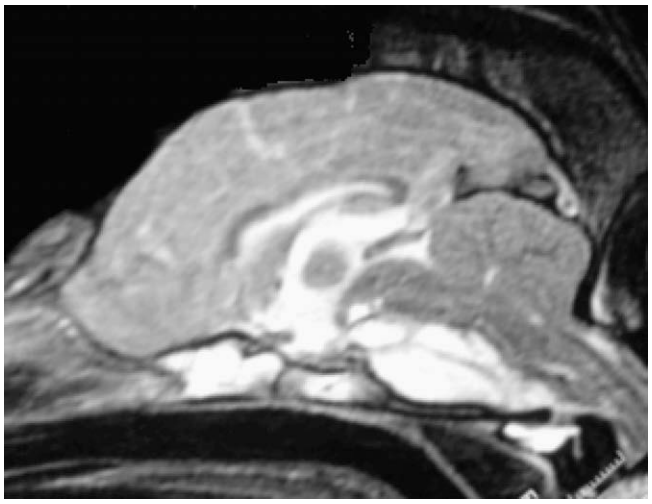

Fig. 3. Extra-axial haemorrhage ventral to the brainstem and likely to be sub-dural due to its mass effect in a 1-year-old male entire Cocker Spaniel that was presented with acute progressive brain stem signs with confirmed *Angiostrongylus vasorum* infestation. The dog was euthanased, but necropsy was not performed. The lesion is hyperintense relative to brain parenchyma on the T2-weighted image. The lesion was also isointense on the T1-weighted image, had no gadolinium uptake and was isointense on gradient echo sequences (not shown), suggestive of hyperacute haemorrhage or continuous haemorrhage.

phospholipidases, proteases and endonucleases, which destroy vital cell components. Elevated concentrations of calcium, in combination with metabolic acidosis, stimulate release of free radicals, contributing to irreversible neuronal injury. Genes are activated in ischaemia that enhance apoptosis, leading to cell death and release of inflammatory molecules (Adams et al., 2001; Panarello et al., 2004).

Macroscopically, infarcts appear mostly as single, well circumscribed areas of cavitation or massive destruction, with loss of the original architecture of the tissue (malacia) (Fig. 6). Depending on the age of the lesion, microscopic examination reveals varying degrees of reactive changes. In acute lesions, the outlines of the original tissue (neurones and glial elements) may still be identifiable, although necrotic. Ischaemic change is characterised by marked eosinophilia when stained with haematoxylin and eosin, shrinkage of the cell and nuclear pycnosis (ischaemic change) (Fig. 7). As the lesion progresses, large numbers of macrophages replace the original tissue, before the defect undergoes scarring in the form of astrogliosis. Often, the defect is not filled and cystic lesions remain (Joseph et al., 1988; Summers et al., 1995; Rossmeisl et al., 2007).

Haemorrhage

Neuronal damage occurs in intracranial haemorrhage because extravasated blood leaks into the brain parenchyma or the subarachnoid space, causing distortion and compression of the adjacent tissue. Clot expansion occurs mostly within the first 6 h of haemorrhage and often is self-limiting, due to increased cerebral perfusion pressure and elastic resistance of the brain tissue (Auer and Sutherland, 2005). Oedema surrounding the clot may develop over several days. Ischaemia can occur as a consequence of compressed brain tissue or due to limited blood flow resulting from vascular damage (Auer and Sutherland, 2005). Depending on the severity of the haemorrhage, a mass effect may occur that causes a midline shift, alteration of the cerebral blood flow, increased intracranial pressure or obstructive hydrocephalus (Auer and Sutherland, 2005).

Initially, a haematoma is formed, visible as a mostly focal haemorrhagic lesion (Fig. 8) surrounded by petechial haemorrhages from torn vessels. The clot organises with time and the oedema and extravasated blood resolve over days to weeks. As a haematoma ages, it gradually becomes less oxygenated. Oxyhaemoglobin is converted to deoxyhaemoglobin and methaemoglobin in the first few days after haemorrhage, followed by erythrocyte lysis and breakdown of haemoglobin into ferritin and haemosiderin. Macrophages begin to phagocytose erythrocytes in the first 24 h and accumulate haemosiderin and lipid breakdown products over several days (Fig. 9). These haemosiderophages may persist throughout life within scar tissue formed by fibrillary astrocytes and around cysts (Stoffregen et al., 1985; Joseph et al., 1988; Summers et al., 1995; Thomas et al., 1997; Muhle et al., 2004). Persistent haemosiderin following head trauma is thought to be the cause of post-traumatic epilepsy, which may take years to develop in humans (Baumann et al., 2006).

Concurrent medical conditions

Cerebrovascular disease can be caused by primary intracranial CNS disease or occur secondarily to systemic (extracranial) disease (Joseph et al., 1988).

Ischaemia

Ischaemia results from arterial or venous obstruction caused by emboli or thrombi (Joseph et al., 1988). The obstructive material of an embolus originates from another vascular bed (artery-to-artery thromboembolism) or the heart (cardioembolism) and occludes a distant vessel. A thrombus is characterised by development of a blood clot within a vessel that causes vascular obstruction at the site of formation (Joseph et al., 1988).

Emboli causing cerebrovascular disease can arise from septic foci (endocarditis) (Cachin and Vandevelde, 1990; Cook et al., 2005), primary neoplasia (e.g. meningioma, intravascular lymphoma), metastatic neoplasia (e.g. neuroendocrine carcinoma, carcinoma of the prostate gland) (Joseph et al., 1988; Kent et al., 2001), migrating parasites or parasitic emboli (e.g. *Dirofilaria immitis*) (Patton and Garner, 1970; Kotani et al., 1975), fibrocartilaginous material (Axlund et al., 2004), fat (Muller et al., 1994), air or clot embolism secondary to surgery.

Cardioembolic stroke secondary to atrial fibrillation or septal abnormalities is a common cause of stroke in humans (Sila, 2006), but is rarely reported in dogs (Garosi

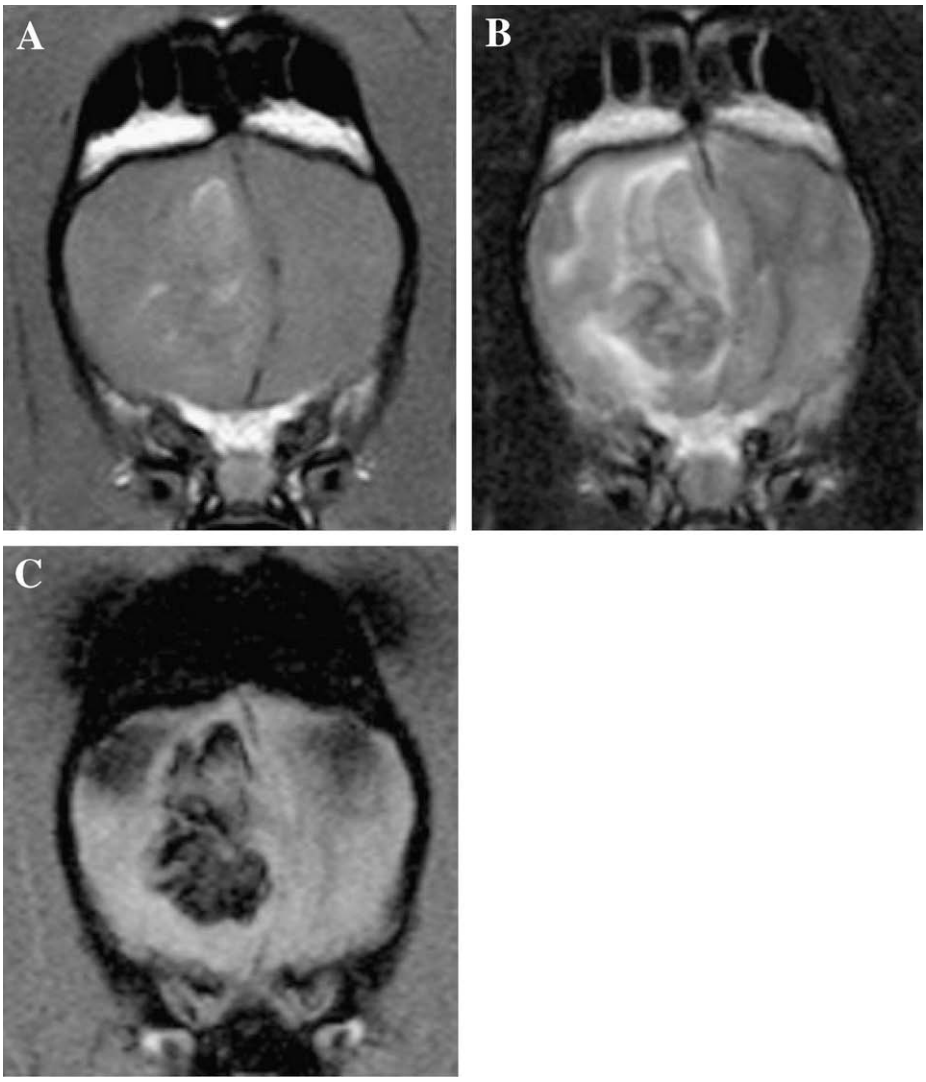

Fig. 4. Intraparenchymal haemorrhage in the right cerebral hemisphere causing a marked mass effect in a 9-month-old entire male German Shepherd dog with an acute presentation, followed by full recovery. The aetiology was unknown. The lesion is iso- and hyperintense relative to brain parenchyma on T1-weighted images (A), mainly hypo- and isointense in T2-weighted images, with hyperintense regions in the periphery of the lesion (B), consistent with oedema, and hypointense in gradient echo sequence (C).

et al., 2005a; Garosi and McConnell, 2005). However, clinical signs compatible with small cerebral emboli are more common in breeds predisposed to mitral valve disease (Pedersen, 2000).

Venous thrombosis is rare in dogs; the condition has been suspected in a dog with haemorrhagic cerebral infarction without an underlying cause being identified (Swayne et al., 1988). Atherosclerosis, an intimal disease characterised by deposition of fibrofatty plaques, is a common cause of thromboembolic stroke in humans and is also suspected to predispose dogs to cerebral thromboembolism (Patterson et al., 1985; Liu et al., 1986; Joseph et al., 1988; Hess et al., 2003). An underlying condition, especially hypothyroidism or diabetes mellitus, but also hyperadrenocorticism or hereditary hypercholesterolaemia, is almost always found in dogs with atherosclerosis (Patterson et al., 1985; Liu et al., 1986; Hess et al., 2003; Higgins et al., 2006).

Hypertension is the most common risk factor for stroke in humans in the western world and leads to cerebral ischaemia and haemorrhage. Chronic hypertension promotes the development of arterial atherosclerosis and lipohyalinosis of small penetrating arteries of the brain. Turbulence at the site of the atherosclerotic plaque can induce major arterial occlusion, with multilobar infarctions, or small artery occlusions that cause subcortical lacunar infarctions. Atherosclerosis also induces vascular remodelling in the form of ectasia and the vessel may rupture, resulting in direct intracranial haemorrhage, or increased deposition of collagen may lead to progressive stenosis, occlusion and infarction (Dukes, 1992; Auer and Sutherland, 2005). Hypertension is rarely primary in dogs, although the underlying cause is not always determined (Berg and Joseph, 2003). In a study of 33 dogs with brain infarctions, 30% had hypertension associated with concur-

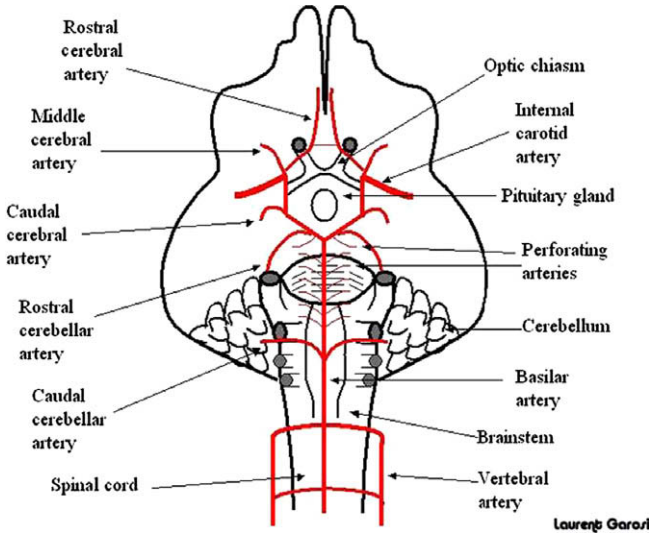

Fig. 5. Vascular supply of the brain and spinal cord, ventral view (simplified).

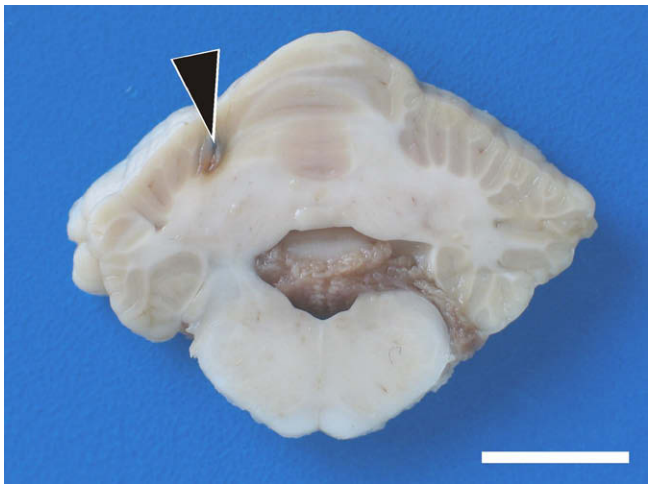

Fig. 6. Transverse section through the medulla oblongata and mid-cerebellum in a Bulldog with infarction of the rostral cerebellar artery. Note the discolouration due to thromboembolic occlusion (arrowhead) of a branch of the rostral cerebellar artery within the primary fissure. The grey-white transition in the adjacent ansiforme lobule is blurred when compared to the contralateral (unaffected) side (with thanks to Kaspar Matiasek). Bar = 1 cm.

rent medical conditions, such as chronic renal disease and hyperadrenocorticism (Garosi et al., 2005a).

Intracranial haemorrhage

Intracranial haemorrhage can originate from spontaneous rupture of small blood vessels, without an obvious underlying cause (Muhle et al., 2004; Subramaniam and Hill, 2005). Haemorrhage into primary and secondary brain tumours is common, for example in oligodendrogliomas, glioblastomas, ependymomas, haemangioendotheliomas (Fankhauser et al., 1965) or pituitary adenomas (Long et al., 2003). Haemangiosarcoma can also lead to haemorrhagic lesions, with secondary ischaemic necrosis (Waters et al., 1989).

Several extracranial diseases predisposing for disseminated intravascular coagulopathy, such as neoplasia (e.g. haemangiosarcoma, squamous cell carcinoma) (Joseph et al., 1988; Waters et al., 1989), von Willebrand's disease (Dunn et al., 1995) or *Angiostrongylus vasorum* infection (Garosi et al., 2005b; Wessmann et al., 2006) may also be associated with intracranial haemorrhage.

Congenital or acquired vascular malformations leading to intracranial haemorrhage are rarely recognised in veterinary medicine. Arteriovenous malformations (direct shunting between arteries and veins) or venous malformations (malformed veins separated by normal neural tissue) are considered to be congenital malformations. Clinical signs occur only if the vessel ruptures, resulting in intracranial haemorrhage (Hause et al., 1982; Joseph et al., 1988; Thomas et al., 1997). Aneurysms are acquired vascular dilatations caused by a weakened arterial or venous wall, with subsequent widening of the vascular lumen (Fox et al., 2005). Trauma-induced aneurysm of the cavernous sinus has been suspected in a dog with unilateral exophthalmos (Tidwell et al., 1997).

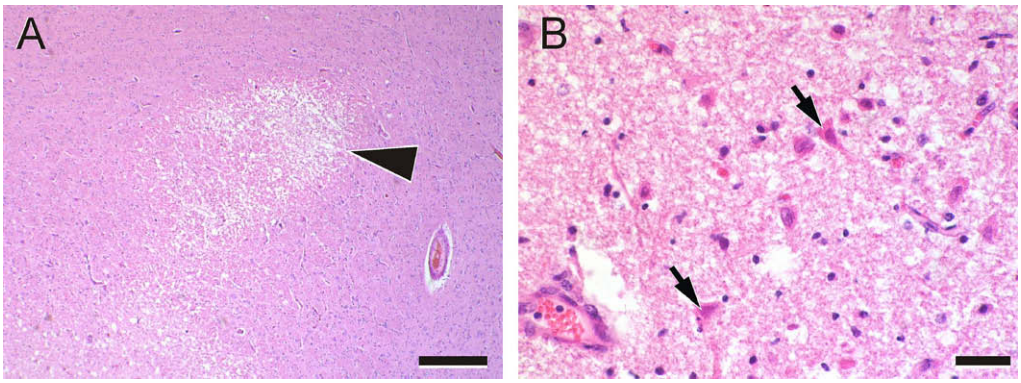

Fig. 7. Histological findings in brain infarction. Lacunar infarct of the thalamus in a dog. (A) Low power field showing spongiosis (arrowhead) of malperfused tissue. Original magnification 100x. Bar = 1 mm. (B) High power field with multiple neurones undergoing ischaemic nerve cell necrosis (arrows). Original magnification 200×. Bar = 50 μm. Haematoxylin and eosin (with thanks to Kaspar Matiasek).

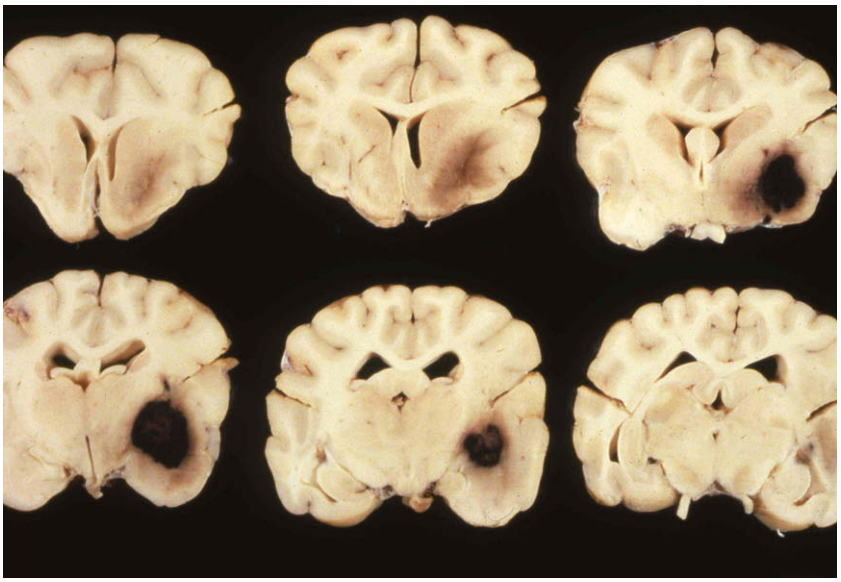

Fig. 8. Gross pathology of a 13-year-old male Welsh Corgi with forebrain signs showing a deep intracerebral haemorrhage with haematoma formation on the right side (maximally 1 cm × 1 cm) and involving the lentiform nucleus, amygdala and right optic tract. This space occupying lesion caused a mild midline shift to the opposite side. The adjacent rostral crus of the internal capsule displays malacic changes (with thanks to Brian Summers).

Other rare vascular diseases leading to intracranial haemorrhage in dogs are cerebral amyloid angiopathy (Uchida et al., 1990) and necrotising vasculitis (Sasaki et al., 2003). Cerebral amyloid angiopathy is caused by amyloid deposits in the arteries of the brain, which weakens the arterial walls; this is a common cause of intracranial haemorrhage in humans (Auer and Sutherland, 2005).

Clinical signs

A rapid onset of neurological deficits is the most characteristic sign of a stroke (Bogousslavsky et al., 1988; Victor and Ropper, 2001). The neurological deficits are often focal and are related to the localisation and extent of the lesion rather than being specific for cerebrovascular disease (Joseph et al., 1988; Victor and Ropper, 2001; Garosi et al., 2005a) or the type of stroke (Bogousslavsky et al., 1988; Joseph et al., 1988). Forebrain lesions may present with seizures, circling, contralateral hemiparesis and postural reaction deficits; cerebellar lesions may be associated with hypermetria, vestibular dysfunction or opisthotonus; and brainstem lesions may lead to ipsilateral cranial nerve deficits, hemi- or tetraparesis and head tilt or turning (Joseph et al., 1988).

Classically, the severity of the neurological deficits peak and then cease, except in fatal stroke. Embolic strokes often occur suddenly and the clinical signs peak immediately, whereas the clinical signs in thrombotic and haemorrhagic strokes can have a slightly delayed onset (Bogousslavsky et al., 1988; Victor and Ropper, 2001). Rarely, deterioration secondary to oedema formation continues for several days (Kitagawa et al., 2005). Significant deterioration is mostly a consequence of increased intracranial pressure or of a lesion incompatible with life (Kase et al., 2004). In humans, TIAs may precede a (usually thrombotic) stroke (Bogousslavsky et al., 1988; Victor and Ropper, 2001) and this is suspected to occur also in dogs (Joseph et al., 1988; McConnell et al., 2005). If systemic illness is present, the clinical signs precede the neurological deficits in the majority of cases (Joseph et al., 1988). Cerebrovascular disease can recur and relapses are most frequent in dogs where an underlying cause is identified (Garosi et al., 2005a).

In some studies, no age, sex, or breed predisposition in the occurrence of canine stroke has been demonstrated (Joseph et al., 1988; Garosi et al., 2005a; McConnell et al., 2005). In contrast, McConnell et al. (2005) observed a higher frequency of male dogs with cerebrovascular disease (58%); similarly, a higher frequency in males has been found in humans. Cavalier King Charles Spaniels and greyhounds were overrepresented in one study of brain infarcts (Garosi et al., 2005a). Small breed dogs were more likely to have cerebellar territorial infarcts and large breed dogs were more likely to have lacunar thalamic-midbrain infarcts (Garosi et al., 2005a).

Diagnostic imaging

Imaging of the brain is the core diagnostic tool in the clinical investigation of cerebrovascular disease. Computed tomography (CT) or magnetic resonance imaging (MRI) help (1) to diagnose cerebrovascular disease and rule out other intracranial diseases, (2) to differentiate between ischaemic and haemorrhagic lesions, (3) to identify the location of the lesion, (4) to identify the size of the lesion and (5) to identify the age of the lesion. Examples of diagnostic image modalities for ischaemia and haemorrhage in the brain are given in Tables 2 and 3, respectively.

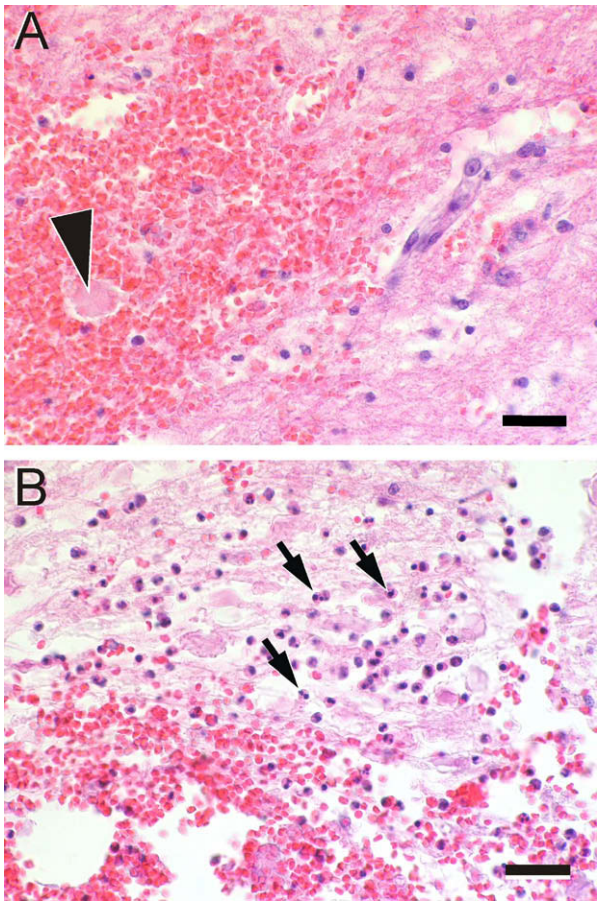

Fig. 9. Acute parenchymal haemorrhage in a dog characterised by extravasation of erythrocytes and absence of haemosiderophages. (A) Vascular compromise is accompanied by axonal spheroids (arrowhead). Original magnification 200×. Bar = 100 μm. (B) About 4 h later, polymorphonuclear leucocytes (arrows) enter the site of lesion. Original magnification 100×. Bar = 50 μm. Haematoxylin and eosin (with thanks to Kaspar Matiasek).

Ischaemia (Table 2)

CT is often the initial screening tool to exclude haemorrhage in humans with suspected stroke. Established areas of infarction present as subtle hypodense lesions on CT due to the influx of water associated with cerebral oedema (Kalafut et al., 2000). Subtle findings of infarction in the hyperacute stage (<24 h) are often difficult to interpret and may include loss of delineation between grey and white matter, loss of parenchymal hypodensity, obliteration of sulci secondary to oedema formation and subtle mass effect (Tidwell et al., 1994; Culebras et al., 1997; Kalafut et al., 2000).

Table 2
Examples of diagnostic image modalities for ischaemia

Modality		Image characteristic/function
CT		Hypodense
MRI	T1-WI	Hypointense
	T2-WI	Hyperintense
	FLAIR	Hyperintense
	DWI	Hyperintense (detects cytotoxic oedema in hyperacute stroke)[a]
	ADC	Cytotoxic oedema: Hypointense[a] Vasogenic oedema: Hyperintense
	PWI	Detects penumbra (DWI/PWI mismatch)
	MRA	Detects vaso-occlusive disease and vascular malformation

CT: Computed tomography; MRI: Magnetic resonance imaging; WI: Weighted image; FLAIR: Fluid attenuated inversion recovery; DWI: Diffusion weighted image; ADC: Apparent diffusion coefficient; PWI: Perfusion weighted image; MRA: Magnetic resonance angiography.
[a] Only during first 10 h to 4 days; after that intracellular water is released and the water proton mobility is increased.

With the advent of functional MRI, CT offers no advantage in the diagnosis of ischaemic stroke, aside from helping to rule out diseases that mimic stroke (Heiland, 2003). MRI is superior to CT for detection of ischaemia, due to its excellent soft tissue contrast and its ability to detect subtle lesions (Heiland, 2003). Non-haemorrhagic infarcts are classically well demarcated, wedge-shaped, with minimal mass effect and often affecting the grey matter (Berg and Joseph, 2003; McConnell et al., 2005; Garosi et al., 2006) (Figs. 1 and 2).

Conventional MRI sequences classically reveal hypointensity on T1-weighted images (WI), hyperintensity on T2-WI and fluid attenuated inversion recovery (FLAIR) images (McConnell et al., 2005). Weak contrast enhancement may occur in the periphery and may be observed 7–10 days after the onset of the stroke (Berg and Joseph, 2003; McConnell et al., 2005; Garosi et al., 2006). Difficulties in differentiating acute from old ischaemic lesions by conventional MRI (Lindgren et al., 2000) can be overcome with functional MRI techniques.

Diffusion-weighted imaging (DWI) displays the ischaemic core of a stroke as hyperintense within minutes of onset and is highly sensitive for the diagnosis of ischaemic stroke (Mullins et al., 2002; Heiland, 2003). DWI relies on cytotoxic oedema within ischaemic cells causing reduced diffusion due to limited Brownian motion of water molecules (Neumann-Haefelin et al., 1999; Schaefer et al., 2000; Heiland, 2003). The contrast between grey and white matter in DWI is due to T2-weighted contrast. Thus,

Table 3
Examples of diagnostic image modalities for haemorrhage

Modality	Image characteristic				
CT	Acute: Hyperdense		With time: Isodense		
MRI	Hyperacute (<24 h)	Acute (1–3 days)	Early subacute (3–7 days)	Late subacute (7–14 days)	Chronic (>14 days)
T1-WI	Isointense	Iso- to hypointense	Hyperintense	Hyperintense	Iso- to hypointense
T2-WI	Hyperintense	Hypointense	Hypointense	Hyperintense	Hyperintense
GRE	Hypointense in all stages				

CT: Computed tomography; MRI: Magnetic resonance imaging; GRE: Gradient echo image; WI: Weighted image.

hyperintense lesions on conventional T2-weighted images may also appear hyperintense on DWI due to the residual T2 component; this is known as 'T2 shine through' (Schaefer et al., 2000; McConnell et al., 2005).

Apparent diffusion coefficient (ADC) maps quantify the degree of water proton mobility from one magnetic field to another (Fisher and Albers, 1999). True reduced diffusion (cytotoxic oedema) appears hypointense on the ADC map and thus confirms acute ischaemia. In contrast, vasogenic oedema, as seen in neoplasia or chronic stroke, is hyperintense on ADC maps and DWI, where the diffusion is higher due to a relative increase in water in the extracellular compartment (Schaefer et al., 2000; Garosi and McConnell, 2005; McConnell et al., 2005) (Table 2).

Perfusion-weighted imaging (PWI) contributes to DWI and reveals the volume of hypoperfused tissue in the ischaemic core and the surrounding penumbra. It relies on the dynamic magnetic susceptibility effects (T2 images) within the brain during the first pass of an intravenously injected gadolinium-based contrast agent. Hyperacute strokes (<24 h) often have larger lesions on PWI compared to DWI and this volume mismatch has some correlation with the ischaemic penumbra (Neumann-Haefelin et al., 1999; Schaefer et al., 2000; Heiland, 2003; Garosi and McConnell, 2005).

Three dimensional time-of-flight magnetic resonance angiography (3D TOF MRA) is a non-invasive method to visualise the intracranial vasculature (Fig. 10). As blood flows within the vessel, it appears bright on 3D TOF MRA relative to the surrounding tissue. The hyperintensity depends on the blood flow and the path of the vessel through the acquired image volume. This imaging technique is used for identifying vaso-occlusive disease, aneurysms and arteriovenous malformations (Tidwell et al., 1997; Kent et al., 2001; Garosi and McConnell, 2005).

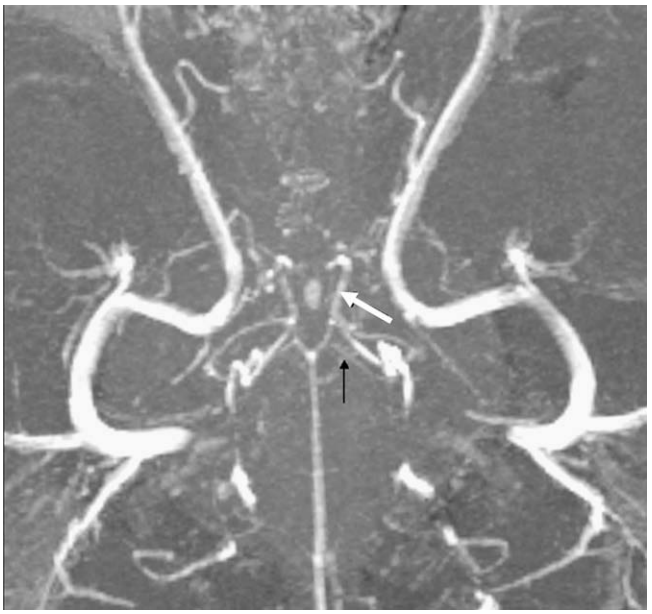

Fig. 10. Time-of-flight magnetic resonance angiogram in a dog with acute right-sided peripheral vestibular syndrome. No abnormalities were detected in this imaging study or a full MRI study. The cerebral arterial circle (white arrow) and rostral cerebellar artery (black arrow) can be clearly seen. (With thanks to Holger Volk and Giunio Cherubini).

Haemorrhage (Table 3)

CT was previously the primary diagnostic tool for detection of haemorrhage in stroke patients. A haematoma appears as a firm, homogeneously hyperdense image, whereas petechial haemorrhages are seen as hyperdense points, which may coalesce to an irregular hyperdense area (Hoggard et al., 2002). With time, the lesion appears isodense and with variable contrast enhancement (Hoggard et al., 2002).

Multimodal MRI is as reliable as CT in diagnosing hyperacute intracranial haemorrhage and superior in detecting subtle microhaemorrhages or underlying parenchymal disease (e.g. vascular lesions, tumours) (Schellinger et al., 1999; Hoggard et al., 2002) (Figs. 3 and 4). The various forms of haemoglobin seen at different time points of the haemorrhage have different magnetic properties, depending on whether they contain unpaired electrons. This is useful to determine the age of the haematoma.

Five distinct stages of MRI appearance of intracranial haemorrhage have been defined: hyperacute (<24 h; intracellular oxyhaemoglobin; long T1 and T2; isointense on T1-WI, hyperintense on T2-WI), acute (1–3 days; intracellular deoxyhaemoglobin; long T1, short T2; iso- to hypointense on T1-WI, hypointense on T2-WI), early subacute (4–7 days; intracellular methaemoglobin with intact erythrocytes; short T1, short T2; hyperintense on T1-WI, hypointense on T2-WI), late subacute (7–14 days; extracellular methaemoglobin with erythrocyte lysis; short T1, long T2; hyperintense on T1-WI and T2-WI) and chronic (>2 weeks; ferritin and haemosiderin; long T1, short T2; iso- to hypointense on T1-WI, hyperintense on T2-WI) (Bradley, 1993; Thomas et al., 1997; Wasenko et al., 2002).

The transition from hyperacute to acute haemorrhage is characterised by a change from oxygenated to deoxygenated blood, starting in the periphery of the haemorrhage, causing a hypointense rim surrounding a hyperacute haemorrhage in a T2-WI. It is postulated that small amounts of deoxyhaemoglobin are already present within the first few hours of intracranial haemorrhage, thus aiding early stroke diagnosis (Atlas and Thulborn, 1998; Wasenko et al., 2002). Acute and subacute haemorrhages are usually associated with vasogenic oedema of the surrounding neuropile, which appears as a hyperintense zone in T2-weighted images (Hayman et al., 1991; Bradley, 1993; Kang et al., 2001; Wasenko et al., 2002).

Gradient echo (GRE) MRI is highly sensitive for detection of blood products and also detects chronic haemorrhage, which may be invisible on CT (Hoggard et al., 2002) (Fig. 4C). GRE images use a gradient to rephase protons and thus susceptibility effects become more prominent. Haemosiderin is strongly paramagnetic, leading to a low signal in GRE images (Hayman et al., 1991). These susceptibil-

ity effects are also seen with gas, mineralisation, fibrous tissue or iron deposits, which appear hypointense in T2-weighted images and in GRE images (McConnell et al., 2005).

Ancillary diagnostic investigation

Baseline diagnostic tests for dogs with suspected cerebrovascular disease should include complete blood cell counts, full serum biochemistry and urinalysis (Garosi et al., 2005a). Assessment of thyroid and adrenal function, coagulation profile, multiple systolic blood pressure measurements and electrocardiogram are also warranted in dogs presenting with stroke. D-dimer determination and antithrombin III level are useful as screening tests to include in the routine coagulation profile, along with prothrombin time, activated partial thromboplastin time and fibrinogen degradation products.

Echocardiography is warranted in the evaluation of heart disease, such as endocarditis or valvular disease (Cook et al., 2005; Garosi et al., 2005a). Blood cultures are warranted if a septic embolus is suspected (Cook et al., 2005). Thoracic radiography and abdominal ultrasound can be used to screen patients for primary or metastatic neoplasia or pneumonia. Faecal analysis may be performed to rule out parasitic infestation, such as *A. vasorum* (Garosi et al., 2005b; Wessmann et al., 2006).

Cerebrospinal fluid (CSF) analysis aids in ruling out other differential diagnoses, such as inflammatory CNS disease, but cannot be used for diagnosis of cerebrovascular accidents, in which findings typically are non-specific: increased protein concentration, mild neutrophilic or mononuclear pleocytosis (<30 cell/μL), xanthochromia or haemosiderosis; CSF may also be normal (Vandevelde and Spano, 1977; Joseph et al., 1988; Berg and Joseph, 2003; Kitagawa et al., 2005; Garosi et al., 2006).

Electrophysiological investigations, such as electroencephalography (EEG) and evoked potentials, are often non-specific for a certain disease process and thus of limited diagnostic value in the diagnosis of stroke (Klemm, 1989; Adams et al., 2001). Experimentally, EEG has been used to predict ischaemic or infarcted regions of the brain (Sakamoto et al., 1978). Somatosensory evoked potentials and brainstem auditory evoked potentials showing diminished potentials were suggestive of large neurological dysfunction and thus a worse outcome (Mullan et al., 1993; Steiner et al., 1998).

Treatment

Most dogs with strokes recover with time on supportive care only (Garosi et al., 2005a). No specific treatment is available that affects the outcome of either ischaemic or haemorrhagic strokes. Treatment focuses on prevention of secondary brain damage or complications, such as increased intracranial pressure or seizures, and identifying and treating the underlying causes (Garosi et al., 2005a). Close monitoring is important, especially within the first few hours after stroke onset, where a significant deterioration may occur.

Oxygen supplementation is necessary only if hypoxia is present. Maintaining blood pressure ensures cerebral perfusion and may improve collateral blood supply (Garosi and McConnell, 2005). Aggressive treatment of hypertension, resulting in low blood pressure and consequently reduced cerebral perfusion, can be detrimental, especially if increased intracranial pressure is present (Thurman and Jauch, 2002). Increased intracranial pressure should be treated aggressively and may involve administration of mannitol, oxygen supplementation and head elevation by 20–30° (Bagley et al., 1996). Mild hypothermia may reduce ischaemic neuronal injury, as in humans (Schwab, 2005).

Hyperglycaemia is negatively associated with outcome in dogs with head injuries and should be avoided (Syring et al., 2001). Hyperglycaemia produces profound brain oedema and perihaematomal cell death in experimental intracranial haemorrhage (Subramaniam and Hill, 2005). Glucocorticoid treatment has no proven beneficial effect for ischaemic or haemorrhagic stroke in the clinical setting, whereas it may predispose the patient to complications, such as infection and hyperglycaemia (De Reuck et al., 1988, 1989; Garosi and McConnell, 2005).

The application and efficacy of specific treatments for ischaemic stroke in humans remains controversial. Neuroprotective therapy is designed to inhibit the acute cellular and metabolic consequences of the stroke and relies on the principle that delayed neuronal injury occurs after ischaemia (Hickenbottom and Grotta, 1998; Ovbiagele et al., 2003). Neuroprotective drugs, including calcium channel antagonists, glutamate receptor antagonists such as *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonists and other neurotransmitter modulators, produce a dramatic decrease in stroke volume in experimental studies, but clinical efficacy has not been demonstrated or remains to be evaluated (Hickenbottom and Grotta, 1998; Labiche and Grotta, 2004).

Thrombolytic treatment is controversial due to the risk of haemorrhage. Tissue plasminogen activator or streptokinase converts plasminogen to plasmin, which is a proteolytic enzyme capable of hydrolysing fibrin, fibrinogen and other clotting proteins (Victor and Ropper, 2001). Tissue plasminogen activator given intravenously within 3 h of stroke onset appears to be most effective in humans with ischaemic stroke and should only be applied after intracranial haemorrhage or haemorrhagic transformation of infarcts are excluded (Victor and Ropper, 2001; National Institute of Neurological Disorders Stroke rt-PA Stroke Study Group, 2005). Fibrinolytic therapy has been used for aortic thromboembolism, but has not been used for treating ischaemic stroke in veterinary patients (Pion, 1988).

Severe intracranial haemorrhage may benefit from surgical evacuation (Adamo et al., 2005). However, early surgical evacuation of intraparenchymal haematomas did not

significantly affect long-term outcome compared with standard medical care in humans (Subramaniam and Hill, 2005). Haemostatic therapy with procoagulant drugs is currently being evaluated in human medicine and may reduce the rate of repeat haemorrhage if administered early. Activated recombinant factor VIIa shows promise in the prevention of intraparenchymal haematoma expansion (Subramaniam and Hill, 2005).

Prognosis

The prognosis depends on the type and localisation of the stroke, the severity of the neurological dysfunction, occurrence of deterioration or complications and finally the underlying cause, if identified (Garosi and McConnell, 2005). Most dogs recover within weeks after the onset of stroke (Garosi et al., 2005a; McConnell et al., 2005; Garosi et al., 2006). Cases with progressive perilesional oedema, ongoing vascular lesions or continuous haemorrhage often have a delayed recovery, if at all (Joseph et al., 1988; Victor and Ropper, 2001). Dogs with concurrent medical conditions causing ischaemic stroke have a shorter survival than dogs in which no concurrent medical condition can be identified (Garosi et al., 2005a). Haemorrhagic stroke is far less common than ischaemic stroke, but is associated with higher mortality (Bogousslavsky et al., 1988; Sacco et al., 1998; McConnell et al., 2005; Subramaniam and Hill, 2005). Intraventricular haemorrhage is associated with a worse outcome and a higher mortality in humans (Subramaniam and Hill, 2005).

Conclusion

Cerebrovascular diseases are increasingly being recognised in veterinary medicine. Advanced diagnostic imaging can be used to recognise the presence and type of stroke in dogs, which helps in formulation of a treatment plan and determining prognosis. Further studies are required to improve our understanding of cerebrovascular diseases in dogs and to develop treatment options for stroke in this species.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

References

Adamo, P.F., Crawford, J.T., Stepien, R.L., 2005. Subdural hematoma of the brainstem in a dog: magnetic resonance findings and treatment. Journal of the American Animal Hospital Association 41, 400–405.

Adams, H.P., Hachinski, V., Norris, J.W., 2001. Ischemic Cerebrovascular Disease. Oxford University Press, New York.

Atlas, S.W., Thulborn, K.R., 1998. MR detection of hyperacute parenchymal hemorrhage of the brain. American Journal of Neuroradiology 19, 1471–1477.

Auer, R.N., Sutherland, G.R., 2005. Primary intracerebral hemorrhage: pathophysiology. Canadian Journal of Neurological Sciences 32 (Suppl. 2), S3–S12.

Axlund, T.W., Isaacs, A.M., Holland, M., O'Brien, D.P., 2004. Fibrocartilaginous embolic encephalomyelopathy of the brainstem and midcervical spinal cord in a dog. Journal of Veterinary Internal Medicine 18, 765–767.

Bagley, R.S., Harrington, M.L., Pluhar, G.E., Keegan, R.D., Greene, S.A., Moore, M.P., Gavin, P.R., 1996. Effect of craniectomy/durotomy alone and in combination with hyperventilation, diuretics, and corticosteroids on intracranial pressure in clinically normal dogs. American Journal of Veterinary Research 57, 116–119.

Baumann, C.R., Schuknecht, B., Lo Russo, G., Cossu, M., Citterio, A., Andermann, F., Siegel, A.M., 2006. Seizure outcome after resection of cavernous malformations is better when surrounding hemosiderin-stained brain also is removed. Epilepsia 47, 563–566.

Berg, J.M., Joseph, R.J., 2003. Cerebellar infarcts in two dogs diagnosed with magnetic resonance imaging. Journal of the American Animal Hospital Association 39, 203–207.

Bogousslavsky, J., Van Melle, G., Regli, F., 1988. The Lausanne stroke registry: analysis of 1000 consecutive patients with first stroke. Stroke 19, 1083–1092.

Bouma, G.J., Muizelaar, J.P., Bandoh, K., Marmarou, A., 1992. Blood pressure and intracranial pressure-volume dynamics in severe head injury: relationship with cerebral blood flow. Journal of Neurosurgery 77, 15–19.

Bradley Jr., W.G., 1993. MR appearance of hemorrhage in the brain. Radiology 189, 15–26.

Cachin, M., Vandevelde, M., 1990. Cerebral infarction associated with septic thromboemboli in the dog. In: Proceedings of the 8th Annual Meeting of the Veterinary Internal Medicine Forum, ACVIM. p. 1136.

Cook, L.B., Coates, J.R., Dewey, C.W., Gordon, S., Miller, M.W., Bahr, A., 2005. Vascular encephalopathy associated with bacterial endocarditis in four dogs. Journal of the American Animal Hospital Association 41, 252–258.

Culebras, A., Kase, C.S., Masdeu, J.C., Fox, A.J., Bryan, R.N., Grossman, C.B., Lee, D.H., Adams, H.P., Thies, W., 1997. Practice guidelines for the use of imaging in transient ischemic attacks and acute stroke. A report of the Stroke Council, American Heart Association. Stroke 28, 1480–1497.

De Reuck, J., De Bleecker, J., Reyntjens, K., 1989. Steroid treatment in primary intracerebral haemorrhage. Acta Neurologica Belgica 89, 7–11.

De Reuck, J., Vandekerckhove, T., Bosma, G., De Meulemeester, K., Van Landegem, W., De Waele, J., Tack, E., De Koninck, J., 1988. Steroid treatment in acute ischaemic stroke. A comparative retrospective study of 556 cases. European Neurology 28, 70–72.

Dukes, J., 1992. Hypertension: a review of the mechanisms, manifestations, and management. Journal of Small Animal Practice 33, 119–129.

Dunn, K.J., Nicholls, P.K., Dunn, J.K., Herrtage, M.E., 1995. Intracranial haemorrhage in a Dobermann puppy with von Willebrand's disease. Veterinary Record 136, 635–636.

Evans, H.E., 1993. The Heart and Arteries. In: Evans, H.E. (Ed.), Miller's Anatomy of the Dog. W.B. Saunders Company, Philadelphia, pp. 586–681.

Fankhauser, R., Luginbuhl, H., McGrath, J.T., 1965. Cerebrovascular disease in various animal species. Annals of the New York Academy of Sciences 127, 817–860.

Fisher, M., Albers, G.W., 1999. Applications of diffusion-perfusion magnetic resonance imaging in acute ischemic stroke. Neurology 52, 1750–1756.

Fox, P.R., Petrie, J.-P., Hohenhaus, A.E., 2005. Peripheral vascular disease. In: Ettinger, S.J., Feldman, E.C. (Eds.), Textbook of Veterinary Internal Medicine, vol. 2. Elsevier Saunders, St. Louis, pp. 1145–1165.

Garosi, L.S., McConnell, J.F., 2005. Ischaemic stroke in dogs and humans: a comparative review. Journal of Small Animal Practice 46, 521–529.

Garosi, L., McConnell, J.E., Platt, S.R., Barone, G., Baron, J.C., DeLahunta, A., Schatzberg, S.J., 2005a. Results of diagnostic investigations and long-term outcome of 33 dogs with brain infarction (2000–2004). Journal of Veterinary Internal Medicine 19, 725–731.

Garosi, L.S., Platt, S.R., McConnell, J.F., Wrayt, J.D., Smith, K.C., 2005b. Intracranial haemorrhage associated with *Angiostrongylus vasorum* infection in three dogs. Journal of Small Animal Practice 46, 93–99.

Garosi, L., McConnell, J.F., Platt, S.R., Barone, G., Baron, J.C., DeLahunta, A., Schatzberg, S.J., 2006. Clinical and topographic magnetic resonance characteristics of suspected brain infarction in 40 dogs. Journal of Veterinary Internal Medicine 20, 311–321.

Hause, W.R., Helphrey, M.L., Green, R.W., Stromberg, P.C., 1982. Cerebral arteriovenous malformation in a dog. Journal of the American Animal Hospital Association 18, 601–607.

Hayman, L.A., Taber, K.H., Ford, J.J., Bryan, R.N., 1991. Mechanisms of MR signal alteration by acute intracerebral blood: old concepts and new theories. American Journal of Neuroradiology 12, 899–907.

Heiland, S., 2003. Diffusion- and perfusion-weighted MR imaging in acute stroke: principles, methods, and applications. Imaging Decisions MRI 7, 4–12.

Hess, R.S., Kass, P.H., Van Winkle, T.J., 2003. Association between diabetes mellitus, hypothyroidism or hyperadrenocorticism, and atherosclerosis in dogs. Journal of Veterinary Internal Medicine 17, 489–494.

Hickenbottom, S.L., Grotta, J., 1998. Neuroprotective therapy. Seminars in Neurology 18, 485–492.

Higgins, M.A., Rossmeisl, J.H., Panciera, D.L., 2006. Hypothyroid-associated central vestibular disease in 10 dogs: 1999–2005. Journal of Veterinary Internal Medicine 20, 1363–1369.

Hoggard, N., Wilkinson, I.D., Paley, M.N., Griffiths, P.D., 2002. Imaging of haemorrhagic stroke. Clinical Radiology 57, 957–968.

Ingvar, M., 1986. Cerebral blood flow and metabolic rate during seizures. Relationship to epileptic brain damage. Annals of the New York Academy of Sciences 462, 194–206.

Inoue, T., Kobayashi, S., Sugita, K., 1985. Dye injection method for the demonstration of territories supplied by individual perforating arteries of the posterior communicating artery in the dog. Stroke 16, 684–686.

Jewell, P.A., 1952. The anastomoses between internal and external carotid circulations in the dog. Journal of Anatomy 86, 83–94.

Joseph, R.J., Greenlee, M.S., Carrillo, J.M., Kay, W.J., 1988. Canine cerebrovascular disease: clinical and pathological findings in 17 cases. Journal of the American Animal Hospitalisation Association 24, 569–576.

Kalafut, M.A., Schriger, D.L., Saver, J.L., Starkman, S., 2000. Detection of early CT signs of >1/3 middle cerebral artery infarctions: interrater reliability and sensitivity of CT interpretation by physicians involved in acute stroke care. Stroke 31, 1667–1671.

Kalimo, H., Kaste, M., Haltia, M., 2002. Vascular diseases. In: Graham, D.I., Lantos, P.L. (Eds.), Greenfield's Neuropathology, vol. 1. Arnold, London, pp. 281–355.

Kang, B.K., Na, D.G., Ryoo, J.W., Byun, H.S., Roh, H.G., Pyeun, Y.S., 2001. Diffusion-weighted MR imaging of intracerebral hemorrhage. Korean Journal of Radiology 2, 183–191.

Kase, C.S., Mohr, J.P., Caplan, L.R., 2004. Intracerebral hemorrhage. In: Mohr, J.P., Choi, D.W., Grotta, J.C., Weir, B., Wolf, P.A. (Eds.), Stroke: Pathophysiology, Diagnosis, and Management. Churchill Livingstone, Philadelphia, pp. 327–376.

Kent, M., DeLahunta, A., Tidwell, A.S., 2001. MR imaging findings in a dog with intravascular lymphoma in the brain. Veterinary Radiology and Ultrasound 42, 504–510.

Kitagawa, M., Okada, M., Kanayama, K., Sakai, T., 2005. Traumatic intracerebral hematoma in a dog: MR images and clinical findings. Journal of Veterinary Medical Science 67, 843–846.

Klemm, W.R., 1989. Electroencephalography in the diagnosis of epilepsy. Problems in Veterinary Medicine 1, 535–557.

Kotani, T., Tomimura, T., Ogura, M., Yoshida, H., Mochizuki, H., 1975. Cerebral infarction caused by *Dirofilaria immitis* in three dogs. Japanese Journal of Veterinary Science 37, 379–390.

Kuwabara, S., Uno, J., Ishikawa, S., 1988. A new model of brainstem ischemia in dogs. Stroke 19, 365–371.

Labiche, L.A., Grotta, J.C., 2004. Clinical trials for cytoprotection in stroke. NeuroRx 1, 46–70.

Lindgren, A., Staaf, G., Geijer, B., Brockstedt, S., Stahlberg, F., Holtas, S., Norrving, B., 2000. Clinical lacunar syndromes as predictors of lacunar infarcts. A comparison of acute clinical lacunar syndromes and findings on diffusion-weighted MRI. Acta Neurologica Scandinavica 101, 128–134.

Liu, S.K., Tilley, L.P., Tappe, J.P., Fox, P.R., 1986. Clinical and pathologic findings in dogs with atherosclerosis: 21 cases (1970–1983). Journal of the American Veterinary Medical Association 189, 227–232.

Long, S.N., Michieletto, A., Anderson, T.J., Williams, A., Knottenbelt, C.M., 2003. Suspected pituitary apoplexy in a German shorthaired pointer. Journal of Small Animal Practice 44, 497–502.

McConnell, J.F., Garosi, L., Platt, S.R., 2005. Magnetic resonance imaging findings of presumed cerebellar cerebrovascular accident in twelve dogs. Veterinary Radiology and Ultrasound 46, 1–10.

Muhle, A.C., Kircher, P., Fazer, R., Scheidegger, J., Lang, J., Jaggy, A., 2004. Intracranial haemorrhage in an eight-week-old puppy. Veterinary Record 154, 338–339.

Mullan, J.C., Korosue, K., Heros, R.C., 1993. The use of somatosensory evoked potential monitoring to produce a canine model of uniform, moderately severe stroke with permanent arterial occlusion. Neurosurgery 32, 967–973.

Muller, C., Rahn, B.A., Pfister, U., Meinig, R.P., 1994. The incidence, pathogenesis, diagnosis, and treatment of fat embolism. Orthopaedic Review 23, 107–117.

Mullins, M.E., Schaefer, P.W., Sorensen, A.G., Halpern, E.F., Ay, H., He, J., Koroshetz, W.J., Gonzalez, R.G., 2002. CT and conventional and diffusion-weighted MR imaging in acute stroke: study in 691 patients at presentation to the emergency department. Radiology 224, 353–360.

National Institute of Neurological Disorders and Stroke, 1990. Special report from the National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases III. Stroke 21, 637–676.

National Institute of Neurological Disorders Stroke rt-PA Stroke Study Group, 2005. Recombinant tissue plasminogen activator for minor strokes: the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study experience. Annals of Emergency Medicine 46, 243–252.

Neumann-Haefelin, T., Wittsack, H.J., Wenserski, F., Siebler, M., Seitz, R.J., Modder, U., Freund, H.J., 1999. Diffusion- and perfusion-weighted MRI. The DWI/PWI mismatch region in acute stroke. Stroke 30, 1591–1597.

Ovbiagele, B., Kidwell, C.S., Starkman, S., Saver, J.L., 2003. Neuroprotective agents for the treatment of acute ischemic stroke. Current Neurology and Neuroscience Report 3, 9–20.

Panarello, G.L., Dewey, C.W., Barone, G., Stefanacci, J.D., 2004. Magnetic resonance imaging of two suspected cases of global brain ischemia. Journal of Veterinary Emergency and Critical Care 14, 269–277.

Patterson, J.S., Rusley, M.S., Zachary, J.F., 1985. Neurologic manifestations of cerebrovascular atherosclerosis associated with primary hypothyroidism in a dog. Journal of the American Animal Hospital Association 186, 499–503.

Patton, C.S., Garner, F.M., 1970. Cerebral infarction caused by heartworms (*Dirofilaria immitis*) in a dog. Journal of the American Veterinary Medical Association 156, 600–605.

Pedersen, H.D., 2000. Mitral Valve Prolapse in the Dog. Pathogenesis, pathophysiology, diagnosis and comparative aspects of early myxo-

matous mitral valve disease. Thesis. The Royal Veterinary and Agricultural University, Copenhagen, Denmark.

Pion, P.D., 1988. Feline aortic thromboemboli and the potential utility of thrombolytic therapy with tissue plasminogen activator. Veterinary Clinics of North America Small Animal Practice 18, 79–86.

Rossmeisl, J.H., Rohleder, J.J., Pickett, J.P., Duncan, R., Herring, I.P., 2007. Presumed and confirmed striatocapsular brain infarctions in six dogs. Veterinary Ophthalmology 10, 23–36.

Sacco, R.L., Boden-Albala, B., Gan, R., Chen, X., Kargman, D.E., Shea, S., Paik, M.C., Hauser, W.A., 1998. Stroke incidence among white, black, and Hispanic residents of an urban community: the Northern Manhattan Stroke Study. American Journal of Epidemiology 147, 259–268.

Sacco, R.L., Toni, D., Brainin, M., Mohr, J.P., 2004. Classification of ischaemic stroke. In: Mohr, J.P., Choi, D.W., Grotta, J.C., Weir, B., Wolf, P.A. (Eds.), Stroke: Pathophysiology, Diagnosis, and Management. Churchill Livingstone, Philadelphia, pp. 61–74.

Sakamoto, T., Tanaka, S., Yoshimoto, T., Watanabe, T., Suzuki, J., 1978. Experimental cerebral infarction. Part 2: Electroencephalographic changes produced by experimental thalamic infarction in dogs. Stroke 9, 214–216.

Sasaki, M., Pool, R., Summers, B.A., 2003. Vasculitis in a dog resembling isolated angiitis of the central nervous system in humans. Veterinary Pathology 40, 95–97.

Schaefer, P.W., Grant, P.E., Gonzalez, R.G., 2000. Diffusion-weighted MR imaging of the brain. Radiology 217, 331–345.

Schellinger, P.D., Jansen, O., Fiebach, J.B., Hacke, W., Sartor, K., 1999. A standardized MRI stroke protocol: comparison with CT in hyperacute intracerebral hemorrhage. Stroke 30, 765–768.

Schwab, S., 2005. Therapy of severe ischemic stroke: breaking the conventional thinking. Cerebrovascular Diseases 20 (Suppl. 2), 169–178.

Sila, C.A., 2006. Heart diseases and stroke. Current Neurology and Neuroscience Reports 6, 23–27.

Steiner, T., Jauss, M., Krieger, D.W., 1998. Hemicraniectomy for massive cerebral infarction: Evoked potentials as presurgical prognostic factors. Journal of Stroke and Cerebrovascular Diseases 7, 132–138.

Stoffregen, D.A., Kallfelz, F.A., DeLahunta, A., 1985. Cerebral hemorrhage in an old dog. Journal of the American Animal Hospital Association 21, 495–498.

Subramaniam, S., Hill, M.D., 2005. Controversies in medical management of intracerebral hemorrhage. Canadian Journal of Neurological Sciences 32 (Suppl. 2), S13–S21.

Summers, B.A., Cummings, J.F., DeLahunta, A., 1995. Central nervous system hypoxia, ischemia, and related disorders. In: Summers, B.A., Cummings, J.F., DeLahunta, A. (Eds.), Veterinary Neuropathology. Mosby-Year Book, St. Louis, pp. 237–249.

Swayne, D.E., Tyler, D.E., Batker, J., 1988. Cerebral infarction with associated venous thrombosis in a dog. Veterinary Pathology 25, 317–320.

Syring, R.S., Otto, C.M., Drobatz, K.J., 2001. Hyperglycemia in dogs and cats with head trauma: 122 cases (1997–1999). Journal of the American Veterinary Medical Association 218, 1124–1129.

Thomas, W.B., Adams, W.H., McGavin, M.D., Gompf, R.E., 1997. Magnetic resonance imaging appearance of intracranial hemorrhage secondary to cerebral vascular malformation in a dog. Veterinary Radiology and Ultrasound 38, 371–375.

Thurman, R.J., Jauch, E.C., 2002. Acute ischemic stroke: emergent evaluation and management. Emergency Medicine Clinics of North America 20, 609–630.

Tidwell, A.S., Mahony, O.M., Moore, R.P., Fitzmaurice, S.N., 1994. Computed tomography of an acute hemorrhagic cerebral infarct in a dog. Veterinary Radiology and Ultrasound 35, 290–296.

Tidwell, A.S., Ross, L.A., Kleine, L.J., 1997. Computed tomography and magnetic resonance imaging of cavernous sinus enlargement in a dog with unilateral exophthalmos. Veterinary Radiology and Ultrasound 38, 363–370.

Uchida, K., Miyauchi, Y., Nakayama, H., Goto, N., 1990. Amyloid angiopathy with cerebral hemorrhage and senile plaque in aged dogs. Japanese Journal of Veterinary Science 52, 605–611.

Vandevelde, M., Spano, J.S., 1977. Cerebrospinal fluid cytology in canine neurologic disease. American Journal of Veterinary Research 38, 1827–1832.

Victor, M., Ropper, A.H., 2001. Cerebrovascular diseases. In: Wonsiewicz, M.J., Medina, M.P., Navrozov, M. (Eds.), Adams and Victor's Principles of Neurology. McGraw-Hill, New York, pp. 821–924.

Wasenko, J.J., Lieberman, K.A., Rodziewicz, G.S., Holsapple, J.W., 2002. Magnetic resonance imaging characteristics of hyperacute hemorrhage in the brain and spine. Clinical Imaging 26, 330–337.

Waters, D.J., Hayden, D.W., Walter, P.A., 1989. Intracranial lesions in dogs with hemangiosarcoma. Journal of Veterinary Internal Medicine 3, 222–230.

Wessmann, A., Lu, D., Lamb, C.R., Smyth, J.B.A., Mantis, P., Chandler, K., Boag, A., Cherubini, G.B., Cappello, R., 2006. Brain and spinal cord haemorrhages associated with *Angiostrongylus vasorum* infection in four dogs. Veterinary Record 158, 858–863.