An Update on Brain Disease

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An Update on Brain Disease: What Is It in the Brain?
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Introduction
The list of differential diagnoses encountered when dealing with a patient with brain disease is large. Huge. Enormous. However, the most common (and most important) that might be encountered in clinical practice are listed below. The non-infectious inflammatory diseases will be covered in a separate session, and we will cover the most important things here.

Differential Diagnoses

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Storage diseases
There are a large number of storage diseases which are the result of congenital deficiencies in (most commonly) a lysosomal acid hydrolase enzyme (for some storage diseases the underlying deficiency is unknown). The enzymatic pathway involved in degrading waste products contained within lysosomes is complex and multifactorial so that deficiency in any of these leads to a build up of undegraded products within lysosomes in cell cytoplasm which ultimately enlarge and cause the death of the cell. Although cells in all body organs are affected, neurons...
are especially vulnerable since they are post-mitotic, permanent cells (i.e., do not divide and replenish). Most of these conditions affect young animals at early ages, affect both males and females, and are autosomal recessively inherited. Most commonly the initial clinical signs suggest cerebellar dysfunction, but some (alpha-fucosidosis, ceroid lipofuscinosis in particular) may show up with prosencephalic signs first (seizures, odd behaviour, abnormal vision/blindness). Generally these diseases are progressive and non-treatable, although interestingly gene therapy has been shown to reverse clinical signs in a feline model of alpha-mannosidosis.

**Cerebellar abiotrophies**
Cerebellar abiotrophies differ from cerebellar hypoplasia (the main differential) in that they are conditions in which the cerebellum develops normally but then begins to degenerate. Classically these conditions are breed related, autosomal recessive in their mode of inheritance (where known), progressive in nature, and clinical signs occur within weeks to months of birth (some can be years later).

**L-2 Hydroxyglutaric Aciduria in Staffordshire Terriers**
This is a poorly characterized condition reported over the past few years in young-middle aged Staffordshire terriers. Initially reported in the UK, we have now seen 3 cases in Victoria (and several in New South Wales). Clinical signs include vague prosencephalic signs - abnormal behaviour, anxiety, plus difficulty/slowness in learning (owners may describe these dogs as dull) and abnormal, ataxic gait (difficult to localize). Signs may also include seizures. Onset is from 6 months onwards. The condition is caused by an inborn error of metabolism with excess secretion of L-2 hydroxyglutaric acid in the urine (organic acid). Diagnosis made on imaging (lack of distinction between grey and white matter on T2-weighted MRI scans with diffuse cerebral atrophy) and demonstration of excess organic acid in the urine (tests can be run at the Royal Children’s hospital). Prognosis is guarded but some dogs with mild signs may live a relatively normal life.
Hydrocephalus

Hydrocephalus is a pathological enlargement of the ventricles. Ventriculomegaly is enlargement of the ventricles – which may or may not be pathological. There is considerable breed related variation in ventricular size – brachycephalic dogs often having larger ventricles than other breeds (eg boxers, French bulldogs, Chihuahuas). Asymmetry may also be a normal finding. Enlargement also occurs with age – as cerebral cortex tissue volume decreases, so ventricles get larger to take up the extra space available (also known as hydrocephalus ex vacuo – this happens to us all at some point!). Hydrocephalus may occur due to obstruction in the ventricular system (obstructive or non-comunicating form; most commonly) or overproduction of CSF from the arachnoid granulations and choroid plexus (non-obstructive or communicating hydrocephalus; less commonly). Causes of obstruction may be either congenital (stenosis of the mesencephalic aqueduct, failure of opening of the lateral apertures of the fourth ventricle) or acquired (secondary to inflammatory disease or neoplasia or other cysts obstructing part of the system). Dilation of the system upstream of the obstruction results in clinical signs. In mature animals with acquired hydrocephalus the cause may not be determinable (probably minor inflammation or haemorrhage leading to blockage of the mesencephalic aqueduct). Clinical signs predominantly refer to the area affected – most commonly the prosencephalon but potentially also hindbrain if the fourth ventricle is affected. Seizures, behavioural changes, cortical blindness, dullness, head-pressing and circling are all reported. Occasionally vestibular signs may be present. Diagnosis requires imaging – either MRI or CT, or ultrasound in dogs where an open fontanelle is present for placement of the ultrasound probe. Treatment is either medical or surgical – reasonable long-term management is possible with corticosteroid therapy at anti-inflammatory doses. Carbonic anyhdrase inhibitors have also been used in acute stages of disease but cause significant electrolyte disturbances long term making them problematic. Surgical treatment involves placement of ventriculoperitoneal shunt which is placed via a small craniotomy and transfers fluid via a one-way, pressure-sensitive valve into the abdominal cavity for absorption by mesentery. Long term prognosis generally good, although shunt revision may be necessary to deal with blockage or infection which are common long term complications (at least in people). Interestingly a high
proportion of mathematicians (human ones) when given MRI are shown to have abnormally enlarged ventricles - make of that one what you will!!

**Cerebellar hypoplasia**
As distinct from cerebellar abiotrophies (where the cerebellum is normal at birth and then undergoes degeneration), cerebellar hypoplasia implies an underdeveloped cerebellum which is present at birth. The most common cause in domestic animals is in utero infection with feline panleukopaenia virus (feline parvovirus) during the third trimester of pregnancy. The Purkinje neurons of the cerebellum are particularly vulnerable to infection and in their absence normal formation of the cerebellar layers (granule cell layer, purkinje cell layer, molecular layer) fails to occur. To be covered in more detail in the ‘tilters and rollers’ session.

**Hepatic encephalopathy**
The pathogenesis of hepatic encephalopathy is poorly understood. Hepatic insufficiency from a number of causes, including acute liver failure, chronic liver failure (including cirrhosis), congenital portosystemic shunts and congenital urea cycle enzyme abnormalities can all result in secondary prosencephalic disease. As a consequence, various substances pass from the portal circulation directly into the systemic circulation without undergoing detoxification. These include ammonia (probably integral to the pathogenesis of dysfunction), various amino acids (especially the aromatic amino acids phenylalanine, tyrosine, and tryptophan), short-chain fatty acids, mercaptan and various biogenic amines, indoles and skatoles, incriminated in causing HE. Increased intracellular osmolality from too-rapid glutamine accumulation (ammonia metabolized by astrocytes to glutamine) may result in cerebral oedema, which also may play a role in development of cerebral hyperaemia and increased intracranial pressure. Glutamine, short-chain fatty acids, aromatic amino acids, and mercaptans are sodium/potassium ATPase inhibitors. Other theories pertaining to the pathogenesis of HE include perturbed monoamine neurotransmission as a result of altered plasma amino acid metabolism; imbalance between excitatory amino acid neurotransmission (glutamate), and inhibitory amino acid neurotransmission (gamma -aminobutyric acid); and increased cerebral concentration of an endogenous benzodiazepine-like substance.
Clinical signs relate to prosencephalic disease: behavioural changes (vocalizing, aggression), dullness, ataxia, circling, aimless wandering, blindness, seizures, head-pressing. In severe cases this can progress to stupour or coma. Diagnosis is made on biochemistry panels plus pre- and post-prandial bile acid tolerance tests. Ammonia levels can also be measured but are very labile – if you cannot run the test quickly or don’t trust your lab, do not use this as your main test. Treatment is directed at underlying hepatic disease (lactulose, lactulose enemas, intestinal antibiotics to reduce bacterial flora such as metronidazole, dietary management with low protein/high biological value protein diets). Ligation of portosystemic shunts (or coil embolism) is the treatment of choice for animals with congenital shunts.

**Note:**

1. When treating animals with seizures secondary to hepatic insufficiency avoid anticonvulsants that are metabolized by the liver – e.g. phenobarbitone, diazepam etc. Use potassium bromide or keppra as first-line therapy.

2. Animals that have portosystemic shunts ligated may develop seizures shortly post-operatively, for reasons that are poorly understood (and not related to HE pre-shunt ligation; various causes have been postulated including the existence of endogenous benzodiazepine-like ligands). These seizures are frequently very difficult to control if they occur – potassium bromide at 100mg/kg PO QID for 24 hrs followed by 30 mg/kg PO SID dosing is recommended but not always effective. Propofol CRIs have also been reported to be effective.

**Hypoglycaemia**

There are 2 main causes for hypoglycaemia: insulin-secreting tumours (insulinomas) of the pancreas, and overdosage of diabetic patients with insulin (especially when not eating). Young puppies (less than 3 months of age) are also prone to hypoglycaemia in association with cold, starvation or GI disease. Hypoglycaemia may also be seen in animals with portosystemic signs. Clinical signs associated with hypoglycaemia include behavioural changes, weakness, ataxia, collapse, transient blindness and seizures. In addition sympathoadrenal signs (nervousness,
muscle tremors, restlessness, hunger) may occur preceding CNS signs. Signs are often intermittent, becoming become more frequent as the disease progresses, and may be associated with periods of fasting, exercise or excitement. Rarely, polyneuropathies may also occur with hypoglycaemia - tetraparesis/plegia, facial nerve signs, hyporeflexia and hypotonia most commonly seen. CNS signs occur because neurons are unable to synthesise or store glucose and rely almost entirely on glucose derived from the blood. Diagnosis requires demonstration of hypoglycaemia in a fasting blood sample, together with elevated insulin levels (in animals with insulinoma - paired samples required; some tumours secrete insulin-like growth factor which does not register as insulin, making diagnosis trickier). Treatment is directed at removing underlying cause of hypoglycaemia plus administration of dextrose solutions (5%). In animals with inoperable insulinomas, prednisolone and diazoxide can be used but prognosis is guarded-poor with survival of 90 days only (vs 12-14 months for resectable tumours).

**Hypothyroidism**

Signs of neurological dysfunction are relatively common in animals with hypothyroidism, but these are usually associated with the peripheral nervous system (vestibular signs, generalized polyneuropathy with flaccid paralysis). Extremely rarely, hypothyroidism can cause a severe form of CNS disease known as myxoedema coma. Dogs present with bradycardia, hypothermia and stupour/coma together with hypoventilation, hypoxia and hypotension. Usually there is no shivering despite hypothermia. Pathogenesis is unknown, although often the degree of hypothyroidism is severe and an inciting cause may be noted (eg respiratory depressant drugs, concomitant disease, surgery etc). Other signs of hypothyroidism are present. Prognosis is guarded - aggressive warming (including flushing bladder with warm water as well as external heat sources), fluid therapy and administration of thyroxine recommended.
Neoplasia Affecting the Brain
Tumours affecting the brain can arise as one of several forms:

- **Primary tumours** arise from cells and structures of the brain itself
- **Secondary tumours** arise from cells and structures adjacent to the brain
- **Metastatic tumours** arise as a spread of a tumour at a distant site

Of these, the most common tumours that affect dogs (and humans) are primary tumours. They occur with a slightly greater incidence than in people (14-15 per 100,000 dogs vs 8-9 per 100,000 people at risk). The most common types of primary brain tumours include:

- Meningiomas
- Astrocytomas
- Oligodendrogliomas
- Choroid plexus papillomas
- Pituitary macroadenomas
- Ependymomas
- Primitive neuroectodermal tumours (PNETs)

Meningiomas are the most common brain tumours seen in both dogs and cats (approximately 45% of all primary brain tumours in dogs). They are thought to arise from arachnoid cap cells of the meninges and occur anywhere along a meningeal surface (eg cerebral convexity, falx cerebri, at the cerebellopontine angle, in the olfactory lobe), or within a ventricle. They can occur as a discrete focal mass, as an en-plaque form or with large cystic components within them. On imaging they have a broad-based dural attachment and are often associated with hyperostosis of the overlying bone (approximately 50% of the time in cats). Contrast enhancement is typically homogenous. Non contrast-enhancing areas associated with necrosis are not uncommon in dogs. Histopathologically they appear benign - in cats they are often well-encapsulated and removable surgically but in dogs tend to creep into the Virchow-robin spaces surrounding meningeal vessels so microscopic disease usually remains after debulking.
Astrocytomas and oligodendrogliomas together are often referred to as gliomas. Astrocytomas are thought to arise from an astrocyte precursor cell while oligodendrogliomas are thought to arise from an oligodendrocyte precursor, although this is by no means certain. They occur with approximately equal frequency - approximately 17% and 14% of all primary brain tumours in dogs, respectively. Astrocytomas in humans are graded using a 4-grade classification scheme by the world health organization - WHO Grade I being a very small subset (pilocytic astrocytomas), grade II encompassing most astrocytomas, Grade III Anaplastic astrocytoma and Grade IV Glioblastoma multiformae. Oligodendrogliomas may occur more frequently in boxers and more commonly in periventricular white matter. They can also spread along CSF pathways. Imaging features of both types suggest an intraaxial tumour (arising from within the brain tissue). On MRI oligodendrogliomas are frequently hypointense on T1-weighted scans and hyperintense on T2-weighted scans, as befitting their mucinous appearance grossly. Astrocytomas tend to be more solid in appearance on imaging with greater and more heterogenous contrast uptake.

Choroid plexus papillomas arise from the choroid plexus of either the lateral, third or fourth ventricles. Since they arise from essentially a collection of blood vessels they tend to enhance very strongly and uniformly following contrast administration on imaging studies. Most are histologically benign but a few can be anaplastic (chorid plexus carcinoma). They can also seed along CSF pathways and implant in other parts of the neuraxis. Pituitary macroadenomas arise from the hypophyseal stalk and expand dorsally into the thalamus/hypothalamus, and on imaging appearance commonly look like ‘mushroom clouds’. Ependymomas and PNETs occur relatively uncommonly - ependymomas arise from ependymal cells lining the ventricular system, whilst the PNET’s origin is currently unknown. Secondary tumours most commonly include adenocarcinomas arising from the nasal epithelium and invading the brain, and either osteosarcomas, fibrosarcomas or multilobulated tumours of bone arising from the skull that compress the brain. Metastatic tumours all arise from tumours that spread haematogenously (since there is no lymphatic drainage within the brain). Common candidates include lymphoma, metastatic carcinoma (from mammary gland, lung and GIT most commonly) and
haemangiosarcoma. Histiocytic sarcoma can also occur in the brain (both as a metastatic tumour and as a primary brain tumour).

Clinical signs associated with tumours reflect their site of origin. In the case of meningiomas it is common for tumours to have been present for several months before the onset of clinical signs as these tumours grow slowly, allowing the brain to accommodate. Tumours arising in the prosencephalon often cause seizures and cortical blindness. Seizures without interictal abnormalities may be seen with tumours arising on ventral midline or in the rostral parts of the prosencephalon. Diagnosis requires either MRI or CT scanning. CSF taps may show albuminocytologic dissociation (increased protein with normal cell counts) in tumours with significant necrosis, and very occasionally may reveal neoplastic cells (with lymphoma most commonly, but also metastatic carcinomas and very occasionally with oligodendrogliomas or choroid plexus papillomas). It is usually worth performing a metastis check - thoracic radiographs and abdominal radiographs/ultrasound - prior to MRI/CT if you have a patient with tumour high on your differential list.

Treatment requires surgical debulking (where location allows) followed by irradiation with megavoltage sources. Typical hyperfractionated dose schedules include 2-3 Gy daily doses up to a maximum of approximately 50 Gy. Survival times in dogs are now being reported to approach a median of 2 years, with some patients living 3 or 4 years following diagnosis. At present there is little evidence to support different treatment modalities for different tumour types, with the exception of meningiomas in cats, for whom surgical debulking alone often results in survival times of up to 4-5 years. However, in people some tumour types (particularly oligodendrogliomas) are chemosensitive, associated with particular patterns of genetic material rearrangements in these tumours (loss of heterozygosity of the short arm of chromosome 1 and the long arm of chromosome 19) and it may be that in the future the same features may be identified in canine oligodendrogliomas.
Thiamine deficiency

Thiamine (vitamin B1) deficiency occurs sporadically in dogs and cats either if commercial rations are naturally low in thiamine or if food is treated with excessive heat or sulfites/sulfur dioxide preservatives. All-fish diets also at risk since many species of fish contain thiaminases. Thiamine is essential for carbohydrate metabolism (especially glucose) via the Krebs cycle. Deficiency leads to increased levels of pyruvate and lactate, together with reduced red blood cell transketolase activity. Brain and heart are the most susceptible tissues since they are dependent on glucose or lactate-pyruvate for energy. Clinical signs include anorexia, vomiting, depression, wide-based hindlimb stance, kyphosis, ataxia, progressive spastic paraparesis, crouching hindlimb gait, torticollis, head ventroflexion, circling, exopthalmos, generalized tonic-clonic seizures, weakness, opisthotonus, menace deficits, tremors and occasionally nystagmus. Some dogs show signs of hysteria. With severe lesions semicoma, persistent crying, opisthotonus, limb spasticity and death may occur. ECG abnormalities in dogs and cats are also reported including bradycardia, tachycardia, sinus arrhythmias, QRS prolongation, P waves with notched peaks, elevation of ST segment and T wave flattening or inversion may occur. Lesions consist of polioencephalomalacia, bilaterally symmetrical in periventricular grey matter, brainstem nuclei (basal nuclei, red nucleus, caudal colliculi, oculomotor nuclei, vestibular nuclei, rostral olives), cerebellar peduncles, cerebellar nodulus and in ventromedial and dorsomedial occipital cortex and dorsomedial parietal cortex. Treatment requires prompt administration of thiamine hydrochloride 25-50 mg/day IM in dogs (10-20 mg IM cats) over several days. Complete remission of clinical signs usually occurs, although some cats have been reported to have residual learning deficits experimentally.

Idiopathic Cerebellitis/Shaker dog disease/White hairy shaker syndrome

Another one for the ‘tilters and rollers’ session. Condition affecting mature dogs, often Maltese and West Highland White Terriers, but also Bichon Frisé, Spitz, Samoyed, Beagle, Dachshund, Yorkshire Terrier dogs and Springer spaniels. Synonyms include idiopathic tremors of adult dogs, sporadic acquired tremors of adult dogs, and "little white shakers" since many dogs are white.
Cryptococcosis
The incriminating organism is Cryptococcus neoformans (var neoformans or var gatii most commonly). Ubiquitous in the environment. Infection causes either focal or multifocal signs in dogs and cats – seizures, depression, circling, ataxia, and cranial nerve deficits. Signs may be frustratingly vague – the ‘not quite right’ patient with possible neck pain and not much else.. Entry via cribiform plate has been incriminated in at least one case. Histopathology shows impressive meningitis with strong inflammatory response in dogs and mild inflammation in cats. Organisms may be seen in perivascular spaces, parenchyma or meninges – small round to oval nuclei (yeast form of the organism, occasionally budding forms noted – peanut shaped) with clear ‘halo’ of cytoplasm (the capsule) which stains strongly for PAS. Diagnosis possible with Cryptococcus latex agglutination test which detects antigen and can be performed on CSF, urine or serum. CSF shows mononuclear pleocytosis and occasional organisms (clear halo can be visualized following India ink preparations). Treatment with combination of amphotericin B (0.1-0.5 mg/kg IV three times weekly) and flucytosine (120 mg/kg daily, divided into 4 equal doses). Toxic epidermal necrolysis is sometimes seen as a side effect. Chronic therapy required (probably lifelong) and recurrence is not uncommon, sometimes after therapy for a year or more. Prognosis is guarded, although some animals have been successfully treated.

Fungal encephalitis
Sporadic cases of this disease are seen, more common in German shepherds. Multiple organisms have been incriminated, including Blastomyces dermatitidis, Histoplasma capsulatum and Coccidioides immitis along with Aspergillus spp and others. This results in phaeomycosis or mycotic encephalitis (when it reaches the brain). Diagnosis and treatment both challenging – imaging suggests widespread oedema and inflammation (often patchy, multifocal contrast enhancement), CSF shows a mixed cell pleocytosis (may be very high cell counts with relatively large numbers of neutrophils) reflecting the granulomatous inflammation associated with infection. Treatment with amphotericin B and fluconazole has been recommended, with surgical resection of lesions if possible. Prognosis is grave and most cases are fatal.
Bacterial meningoencephalitis and abscessation
Bacterial infection of the CNS is incredibly rare in dogs and cats. It is usually secondary to penetrating injury, migrating foreign body, or severe otitis media/interna with erosion through into the calvarium, although haematogenous spread can occur. Either abscess formation or empyema (collection of pus outside the arachnoid or dura mater) can occur. Diagnosis is based on imaging findings (particularly irregular, patchy contrast uptake; ring enhancement may occur if abscess formation occurs) and CSF (neutrophilic pleocytosis, often with a very high WCC). Systemic signs of disease (including pyrexia) usually are not present. Culture and sensitivity can be attempted from CSF but usually are negative (try inoculating a blood culture bottle with a CSF sample). If treatment cannot be based on culture results pick a mixture of broad-spectrum antibiotics with CSF-penetrating abilities: ampicillin + chloramphenicol. Enrofloxacin, metronidazole, trimethoprim-sulphur. Prognosis is guarded in most cases – if an abscess is detected, surgical removal indicated. Successful management of cases with intracranial spread from otitis media/interna reported following ventral bulla osteotomy and 1-3 months of antibiotic therapy.

Protozoal diseases (toxoplasmosis, neosporosis)
Toxoplasma gondii and Neospora caninum are 2 apicomplexan protozoal parasites for which cats and dogs are the definitive host, respectively. Rarely multifocal disease can be caused by infection anywhere within the neuraxis (brain or spinal cord). Most commonly the initial infection is subclinical, but immune system compromise leads to reactivation of this subclinical infection and release of the encysted tachyzoites from cell mediated/humoural immunity. Signs relate to the site of infection but typically multifocal signs including prosencephalic, hindbrain and vestibular signs may be seen. Concurrent chorioretinitis may occur – fundic examination is important. Diagnosis includes haematological and biochemistry testing along with serological testing. Results of CSF testing may be abnormal, with elevated protein content and a mixed monocytic-polymorphonuclear pleocytosis and sometimes eosinophils. Serum creatine kinase levels are often increased. Protozoan meningoencephalitis may also be detected using MRI scans. Prognosis is guarded in any animal with signs of CNS disease. A 4 to 8 week regimen of
trimethoprim-sulfonamide (at 15 - 20 mg/kg combined dose, PO, bid) and pyrimethamine (at 1 mg/kg, PO, daily) has successfully treated animals with TX-NS-induced encephalomyelitis. Clindamycin is considered to be the drug of choice for treating toxoplasmosis, at a dose of 10 to 40 mg/kg/day, PO or IM, divided bid to tid. This dose can also be used for treating dogs with neosporosis. Clindamycin crosses the blood-brain barrier. Oral and parenteral dosages are similar because of the good intestinal absorption of clindamycin. Oral clindamycin can cause anorexia, vomiting, or diarrhea in dogs and cats. Pyrimethamine may also be used in conjunction but beware of aplastic anaemia - supplement with folate (brewer’s yeast is the easiest source – try health food stores).

**Granulomatous meningoencephalitis (GME)**

Sporadic inflammatory, non-infectious condition affecting anywhere along the neuraxis of (more commonly) small, young to middle-aged dogs. Large breed dogs also sporadically affected. GME occurs in one of 3 forms: focal form, where a single lesion (granuloma) is present, diffuse (or disseminated) form in which multiple lesions are present, and an ocular form, characterized by inflammation within the eye alone. Lesions consist of large accumulations of mononuclear cells (lymphocytes, plasma cells and bizarre histiocytic macrophages) perivascularly, although they may spill out into the surrounding tissue between vessels. Secondary oedema, reactive gliosis and neuronal death occurs. Mitotic figures often very common. There is some debate as to whether these lesions may represent a form of neoplasm (probably lymphoid or histiocytic) or are immune-mediated in nature (most evidence currently supports the latter theory). Diagnosis based on history and signalment (particularly multifocal disease in a small breed, young to middle aged dog), imaging (MRI more likely to show up the multifocal inflammatory encephalitis and meningitis but CT may help) and CSF (showing moderate mononuclear pleocytosis, with a predominant lymphocytic/monocytoid population). Treatment consists of aggressive immunosuppression – initially with corticosteroids at immunosuppressive doses, then with one of a number of other agents: cytosine arabinoside (different protocols exist; some suggest an initial dose of 600 mg/m2 followed 4 wks later by 400 mg/m2 doses every 4 wks; take haemograms to monitor for bone marrow suppression before each dose and a week subsequent), cyclosporine being most successful, with others used including mycophenylate,
azathioprine. Prognosis is poor for cure, but long term ‘remission’ for 2-3 years can sometimes be achieved. Prognosis generally thought to be poorer or the disseminated form of the disease.

**Cerebrovascular Accidents**
These are being recognized increasingly commonly in dogs thanks to the advent of MRI. Two major forms of infarction occur – haemorrhagic (associated with bleeding into the brain) and ischaemic (associated with embolic disease). Clinical signs associated with the area of the brain affected – commonly these are the cerebral cortex, thalamus and cerebellum. Large ischaemic infarcts tend to affect vascular territories but small haemorrhagic infarcts can occur in smaller vascular territories (eg lacunar infarct of the striate vessels in the thalamus). Diagnosis requires imaging – CT may show up large areas of haemorrhage, but ischaemic events may not show up unless MRI is performed. Causes of the vascular event should be searched for – commonly including coagulopathies (check coagulation profiles, urinalysis for protein-losing nephropathies), hypertension (secondary to renal disease, hyperadrenocorticism), and hypothyroidism. Frequently no identifiable cause is found. If signs are not too severe many animals respond to supportive care and recover fully.