SEIZURES AS A MANIFESTATION OF INTRACRANIAL DISEASE
with particular regard to brain tumours in dogs

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ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

Abstract

Seizures are one of the most common neurological disorders encountered in the canine patient. The susceptibility of the brain to a wide spectrum of structural and metabolic disorders means that the occurrence of seizures is indicative of an underlying condition of cerebrocortical dysfunction, not of a specific aetiology. However, all the pathological processes resulting in seizures may also occur without being accompanied by seizure activity. In addition, seizure activity in humans with brain tumours most commonly originates from cortical tissue that is distant from the tumour.

This dissertation focuses on seizures as a sign of intracranial dysfunction and through the presentation of selected canine clinical cases highlights the reasons and times at which seizures may be a clinical feature of intracranial neoplasia.

The majority of brain tumours associated with seizures affect the rostrotentorial structures, especially the frontal, olfactory, and parietal lobes. Of the sixteen cases presented here, ten had seizures as admitting complaint. Of these, two were diagnosed with idiopathic epilepsy, one with hydrocephalus and intracranial arachnoid cyst, and seven with brain tumours. All but one of these seven dogs had tumours located in the rostral fossa. Unexpectedly, one dog had a caudal fossa tumour. In this case, post mortem examination revealed the presence of metastasis within the forebrain.

At the time of presentation to a veterinarian, seizures may be the only clinical manifestation of an intracranial tumour. However, in most instances interictal neurological abnormalities are present. Conversely, animals affected with idiopathic epilepsy typically do not manifest interictal neurological deficits. In the case material here reported, two of the seven dogs presented for evaluation of seizure disorders and diagnosed with brain tumour did not exhibit interictal neurological abnormalities. These findings emphasise that a normal interictal neurological examination does not exclude the possibility that a structural brain abnormality is the cause of the observed seizure activity.

Overall, changes in mental status, behavioural derangement and ataxia are the neurological abnormalities most frequently observed in patients with intracranial neoplasia. Signs of vestibular dysfunction are a common manifestation of tumours affecting the caudal fossa

structures. In the series here reported, two of the three dogs diagnosed with hindbrain neoplasia exhibited signs of vestibular dysfunction at the time of presentation.

Combining the results of this study with a broad review of the literature pertaining to seizure disorders in dogs, this dissertation emphasises the non-specificity of seizures as a sign of intracranial disease / dysfunction and the need for a logical and systematic diagnostic evaluation.

This thesis is dedicated to:

My mother;
simply thanks for all her love

My father;
somebody said that I am a free spirit; you said that my heart is free
and encouraged me to follow it…
'I am missing you'

Christine Thomson;
for her patience and enthusiasm in guiding me through my approach
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well…I was forgetting Jimbo;
"I do like you. Sometimes I desire to kill you…"
but probably, "*at the end of the day*" you desire the
same with me.
However, that's just the way you are…
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Introduction

Definitions

Seizure

A seizure is the clinical manifestation of excessive and / or hypersynchronous discharge activity of populations of neurons in the cerebral cortex. This abnormal electrical activity produces characteristic paroxysmal discharges (epileptiform activity) on electroencephalographic (EEG) recordings. Each seizure is a discrete clinical event consisting in transient, self-limiting, stereotyped and involuntary changes in behaviour or neurological status. Seizures can manifest as anything from a subtle alteration in alertness to a generalised, tonic-clonic event (March 1998; Thomas 2000).

The definition of seizure given above implies a specific neuronal origin. In this dissertation the term "seizure" will be always used to refer to paroxysmal events of neuronal origin, whereas the term "seizure-like event/s" will be used to refer to paroxysmal events, which do not have a neuronal origin.

The clinical features of seizures can be separated into three components: the preictal stage or aura, the ictus and the postictal period. Preceding the seizure a prodromal period may occur.

Prodrome

The *prodrome* is a long-term indication of a forthcoming seizure manifested in man by disturbances of mood or behaviour, less frequently of subjective symptoms such as headache, nervousness, and anxiety. These manifestations occur hours to days before a seizure. Similarly, occasionally owners report that they know that their pet is going to seizure days in advance by changes in the animal's behaviour such as anxiety, restlessness, and uncontrolled barking. The pathophysiology of prodromes is not understood, but in contrast to auras, prodromes are long lasting (hours to days), not associated with electroencephalographic activity, and not part of the seizure. Prodrome is therefore a clinical definition. Prodromes are thought to reflect a preictal increase in excitability of an epileptogenic focus or of the entire brain (Podell 1996; Berendt & Gram 1999; Thomas 2000). However, this increased excitability does not result in EEG changes because the number of neurons firing in synchrony is probably not sufficient to generate electrical activity detectable at the scalp surface (Berendt & Gram 1999).

Aura

In human epileptology the aura is defined as the initial sensation / manifestation of a seizure before there are observable signs; it is caused by the initial abnormal electric activity of a single group of neurons, and therefore it represents the onset of a seizure. During this period, which can last seconds to minutes, human patients describe various sensations including dizziness, tingling, and anxiety. Because auras are usually subjective, they are difficult to characterise in animals. Nevertheless animals can exhibit stereotypic sensory or motor behaviour (pacing, licking), autonomic patterns (salivating, urinating, vomiting), or even unusual behaviour (hiding, excessive barking, increased or decreased attention seeking). During the aura, consciousness is unimpaired (Podell 1996; Berendt & Gram 1999; Thomas 2000). An aura is commonly seen prior to a generalised seizure, rarely prior to a partial one (Dodman et al 1992; Podell et al 1995).

Ictus

The ictus is the actual seizure event manifested by involuntary movements and / or abnormal sensations or behaviour, usually lasting from seconds to minutes (30 to 90 seconds in most cases). The ictus may be accompanied by disturbances of the autonomic nervous system, resulting in salivation, urination, defecation, pupillary dilation and piloerection.

Postictal period

After the ictal event comes the postictal period, which can last from minutes to days. Postictal signs are the clinical manifestation of transient abnormalities in brain function caused by the ictus. They may consist in unusual behaviour, disorientation, inappropriate bladder / bowel control activity, excessive or depressed thirst and appetite, fatigue, deep sleep, and actual neurologic deficits of weakness, blindness, or sensory and motor disturbances. The latter problems if asymmetric are known as Todd's paralysis and, are an indicator of a focal, contralateral cortical seizure focus. Often owners only observe the postictal period as evidence that their pet has had a seizure. Thus, careful questioning is needed by the clinician to decide if an animal did have a seizure. No correlation exists between the type, intensity, or duration of seizures and the duration of the postictal phase (Podell 1996; March 1998; Thomas 2000).

Interictal period

The interictal period is the time between resolution of any postictal signs and the beginning of the next ictus (Thomas 2000).

Status epilepticus

Status epilepticus has been defined as, a seizure lasting 20 to 30 minutes, which is an estimation of the duration necessary to cause brain damage (Shell 1999; Podell 2000). However, loss of brain homeostasis occurs within 1 to 2 minutes of seizure onset (Shell 1999). On the basis of this consideration, and the fact that isolated seizures rarely last more than a few minutes the following practical definition of status epilepticus has been proposed: "status epilepticus is a continuous seizure lasting at least 5 minutes, or two or more discrete seizures without full recovery of consciousness between seizures, even if the duration of each seizures is less than 5 minutes" (Shell 1999; Thomas 2000). The aim of this definition is to enhance the clinicians' ability to address the metabolic and physiologic changes, which follow status epilepticus more quickly (Shell 1999).

Cluster seizures

Cluster seizures (serial seizures, acute repetitive seizures) are two or more seizures occurring over a brief period (minutes to hours) but with the patient regaining consciousness between the seizures (Thomas 2000).

Epilepsy

The term "epilepsy" defines a *chronic* condition characterised by recurrent seizures.

Some authors refer to seizures, which are neuronal in origin, as to *epileptic seizure* cf. *nonepileptic seizures* (Podell 1996). The latter are paroxysmal events associated with transient alteration in neurologic function, but not accompanied by abnormal electrical discharges from the brain (Podell 1996; Knowles 1998). The term epileptic seizure is incorrect, because although seizures are always abnormal events, not all seizures are the result of a condition of chronic cerebrocortical dysfunction. A seizure can in fact be the natural reaction of a normal brain to a transient systemic insult or physiologic stress (extracranial metabolic or toxic insult, head injury). Seizures that occur at the time of a systemic disorder or brain insult are defined as *provoked seizures* or *reactive seizures* (RS). If the seizures stop when the underlying

condition resolves, the patient does not have epilepsy, as the seizures are not recurrent and an underlying chronic brain disorder is not present (Podell et al 1995; Podell 1996). In this dissertation paroxysmal events, which do not have a neuronal origin are referred to as "seizure-like event/s" because the term seizure always implies a neuronal origin.

Chronic recurrent seizures may be due to a wide spectrum of causes. Therefore, the term *epilepsies* is more appropriate than epilepsy. Epilepsies may be categorised as being symptomatic or idiopathic (Wolf 1997; Thomas 2000).

Symptomatic or *secondary epilepsies* (SE) are those in which seizures are the consequence of a structural brain lesion. Brain trauma, hydrocephalus, encephalitis, and neoplasia are examples of potential inducers of structural damage. Metabolic and toxic insults may also alter permanently the brain structure, hence causing SE (March 1998; Berendt & Gram 1999; Thomas 2000).

The designation of *idiopathic* or *primary epilepsies* (IE / PE) implies recurrent, unprovoked seizures in which no underlying brain abnormality exists or can be detected. Idiopathic epilepsy also implies that there are no interictal neurologic deficits (Knowles 1998). A functional defect probably underlies most forms of IE. A pre-existing (ion channel defects) or early development defect (persistent overabundance of excitatory circuits) affecting the cerebral cortex diffusely is considered the most likely causes of PE (Mischel & Vinters 1997; March 1998). This form of epilepsy is presumed to have a genetic component but definitive evidence for this in certain breeds is often difficult to find. The term *inherited* or *genetic epilepsy* should be used only when there is a known genetic cause for the epilepsy (Podell 1996; Thomas 2000).

The term *cryptogenic epilepsy* has been used, when recurrent seizures are presumed symptomatic, although diagnostic tests have failed to demonstrate an underlying cause (Berendt & Gram 1999; Thomas 2000). The definition of cryptogenic epilepsy is a clinical one and refers to patients with chronic recurrent seizure activity, which for history and physical/neurological examination findings would indicate symptomatic epilepsy, but the results of diagnostic tests are unremarkable. In these circumstances the term cryptogenic epilepsy is more appropriate than idiopathic epilepsy (Berendt & Gram 1999; Thomas 2000).

Types of seizures

Seizures may be classified by their clinical appearance as partial and generalised seizures (Wolf 1997; March 1998; Thomas 2000).

Partial seizures

Partial or focal seizures begin in a discrete cerebrocortical area and may or may not generalise. The appearance of the seizure reflects the location of the seizure focus. Partial seizures are defined as *simple partial* (SP) seizures when consciousness is not impaired and as *complex partial* (CP) seizures when consciousness is impaired (March 1998; Thomas 2000).

SP seizures are characterised by asymmetrical clinical manifestations, which reflect asymmetrical electrical activity in the brain (Selcer & Selcer 1990; Shell 1993a). There are many types of SP seizures depending on the cortical area affected. SP seizures are characterised by unilateral focal motor activity, involving isolated groups of muscles (for example, rhythmic contractions of facial or masticatory muscles). SP seizures are in fact also called "focal motor" seizures (March 1998). SP seizures may develop into CP seizures, and both types of partial seizures may secondarily generalise and develop into convulsions (secondary generalised seizures) (Podell 1996; Berendt & Gram 1999; Thomas 2000). The motor area of the cerebral cortex of domestic animals is small, allowing seizure activity to generalise rapidly (Oliver et al 1993b). The development of SP seizures into CP seizures is usually not identified because of obvious problems with the evaluation of subtle and/or rapid changes in consciousness (March 1998; Berendt & Gram 1999).

CP seizures, also called *psychomotor seizures*, are characterised by bizarre behavioural abnormalities accompanied by complex motor activity. Unprovoked aggression, extreme irrational fear (rage), jaw snapping, fly-biting, star-gazing, tail chasing, running, hiding, and senseless vocalisation have been described (Selcer & Selcer 1990; Dodman et al 1992; Sorjonen 1992; Shell 1993a; March 1998). Involuntary automatic motor behaviour such as swallowing movements, lip smacking or chewing, may occur at the time that consciousness is impaired. Episodic gastrointestinal disturbances, thought to be caused by abnormal limbic system function, have also been reported in dogs (Breitschwerdt et al 1979). CP seizures have a temporal or frontotemporal origin and epileptiform discharges are frequently bilateral (Dodman et al 1992; Sorjonen 1992; Dodman et al 1996; March 1998).

Partial seizures may also represent abortive forms of generalised, tonic-clonic seizures in animals receiving anticonvulsant medication (Knowles 1998).

Generalised seizures

Generalised seizures imply a diffuse disturbance of brain function from onset to termination (Podell 1996; Zifkin & Dravet 1997; March 1998). Clinical signs are symmetric in character and are usually associated with loss of consciousness (Shell 1993a; March 1998). With close observation, including videotaped review of seizures, it has become apparent that many patients suffer focal seizures with secondary generalisation (*secondary generalised seizures*) (Berendt & Gram 1999). Generalised seizures in which the first clinical signs indicate initial involvement of both cerebral hemispheres are referred to as *primary generalised seizures* (Shell 1993a; Berendt & Gram 1999).

Generalised seizures are subdivided into *convulsive* and *nonconvulsive*. The most common type of generalised convulsive seizure in dogs is a generalised, tonic-clonic seizure (Podell 1996; Thomas 2000). The first part of the seizure is the tonic phase, during which there is sustained contraction of all muscles. The animal loses consciousness and falls to its side in opisthotonus with the limbs extended. Respiration is often irregular or absent, and cyanosis is common. Autonomic release is also common. The tonic phase gives way to the clonic one, during which there is rhythmic contraction of muscles that manifests as paddling or jerking of the limbs and chewing movements. Occasionally tonic-clonic seizures occur in which consciousness is maintained (Chrisman 1991, Shell 1993a; Heynold et al 1997; Jaggy & Bernardini 1998; Thomas 2000). Very occasionally purely tonic or clonic seizures may be observed (Heynold et al 1997; Jaggy & Bernardini 1998). A*tonic seiz*ures and *myoclonic seizures* are also uncommon in domestic animals (Podell 1996). There are other causes of myoclonic jerks in animals, that is, not all myoclonic jerks are seizures (de Lahunta 2000b; Thomas 2000).

Generalised nonconvulsive seizures are also called absence seizures due to the transient loss of consciousness and lack of motor activity. True absence seizures have not been substantiated in either dogs or cats (Thomas 2000).

Epidemiological Issues

Seizures are one of the most common neurological disorders in the canine patient; for example 2 to 3% of one referral hospital's canine admissions were for evaluation and management of seizures (Podell et al 1995). Estimates of seizure incidence during an individual lifetime vary from 0.5% to 5.7% (LeCouteur 1995)

The relative frequency of structural symptomatic and idiopathic epilepsy varies between species. Idiopathic epilepsy is more common than structural symptomatic epilepsy in dogs, whereas the reverse is true in cats (Podell 1996; March 1998).

The true prevalence of idiopathic epilepsy is difficult to establish because of problems with the diagnosis and confident exclusion of other causes (Knowles 1998; Thomas 2000). Seizures in which an underlying cause is present but cannot be demonstrated by routine neurodiagnostic testing (so called cryptogenic epilepsy) are probably more common than is described in the veterinary literature (Thomas 2000). Refining neuroimaging and histological examination techniques in humans has resulted in an increase in epilepsies classified as symptomatic and a concomitant decrease in the proportion of cryptogenic and idiopathic epilepsies (Berendt & Gram 1999).

The textbook description of canine idiopathic epilepsy is that of bilaterally symmetrical generalised, tonic-clonic seizures, lasting approximately 1 to 3 minutes, initiating when the dog is 1 or 2 to 5 years old, common to certain breeds (de Lahunta 1983b; Oliver et al 1993b). More recent studies report that although most dogs with idiopathic epilepsy experience their first seizure between 6 months and 5 years of age, seizures occasionally start before 6 months or as late as 10 years of age (Heynold et al 1997; Jaggy & Bernardini 1998; Knowles 1998; Berendt & Gram 1999; Thomas 2000).

Breed-related inherited epilepsy in dogs has been documented in Beagles, Belgian Tervurens, Keeshounds, Dachshunds, and British Alsations German Shepherd dogs (Cunningham & Farnbach 1988; Shell 1993b; Hall & Wallace 1996; Famula et al 1997; Thomas 2000) and in a number of other breeds this is strongly suspected (Srenk & Jaggy 1996; Jaggy et al 1998; Knowles 1998). However, any breed may be affected. The mode of inheritance is still unknown (Schwardtz-Porsche 1994; Knowles 1998). As in most studies male dogs slightly

outnumber female dogs (Podell 1996; Thomas 2000) a sex linkage limitation, or modification cannot be excluded.

Causes of seizures

Causes of seizures are routinely ascribed as extra- or intracranial in origin.

Extracranial causes

Extracranial causes of seizures disrupt normal brain function; they are in turn divided into those that originate outside the body (e.g., toxins) and those that arise within the body but outside the nervous system (metabolic disorders) (LeCouteur 1995) (Table 1, page 11). Seizures in response to extracranial disease are called reactive seizures (Podell 1996).

There have been many articles published which review the extracranial causes of seizures with emphasis on the mechanism by which they generate seizures, and discussion of some general aspects of their diagnosis and therapeutic management. These aspects will not be addressed in this dissertation (Cuddon 1996; O'Brien 1998; Schwartz-Porsche 1999).

Intracranial causes of seizures

Intracranial causes of seizure disorders may be divided into functional and structural causes. Despite the absence of epidemiological studies aimed to establish the incidence of seizures specifically due to intracranial causes, the overall impression is that intracranial causes are by far the most common causes of seizures in dogs (LeCouteur 1995).

Functional and structural causes of seizures

Functional causes of seizures include primary epilepsy (LeCouteur 1995). Structural causes of seizures can represent any process that disrupts / changes the normal character of the brain tissue or vasculature, such as neoplasia, inflammation, vascular lesion and trauma (Table 3, page 13; Tab 4 page 14). Structural causes of seizures may also be described as progressive or non-progressive. Storage diseases and neoplasia are the most common types of progressive brain diseases (Shell 1993b; Jolly et al 1994; Podell et al 1995). Non-progressive brain diseases are those brain disorders that, although previously active, have become inactive but have left the brain in a "seizure-prone" state (hypoxic event, vascular accident, head trauma); morphological brain lesions may have occurred long before the first seizure occurs (LeCouteur 1995). Clinically it is important to distinguish between progressive and non-progressive brain

diseases because this influences both treatment options and prognosis (Schwartz-Porsche 1999).

In the canine species, symptomatic epilepsy is thought to be less common than idiopathic epilepsy. Intracranial causes of seizures have been widely reviewed elsewhere (Shell 1993b; LeCouteur 1995; Bagley 1997; Thomas 1998; Schwartz-Porsche 1999; Thomas 2000). A section of this dissertation is specifically designed to discuss brain tumours in dogs; conversely only brief notes of the other intracranial disorders, which may result in seizures, will be given in the context of the diagnostic approach to seizures.

Pathophysiology of seizure disorders

The specific pathophysiological mechanisms of seizures generation are complex and still not completely understood. In this dissertation only a brief description of the general mechanisms thought to underlay seizure activity will be given. Detailed considerations may be found in Engel & Pedley (1997), March (1998) and Westbrook (2000).

The potential for the generation and spread of paroxysmal neuronal discharges as found in seizure activity reflects features of the anatomical and functional organisation of the brain. Significant amongst these are: inherent neuronal properties such as burst firing (March 1998; Galarreta & Hestrin 1999); failure of local and regional inhibition of activity (March 1998; Westbrook 2000); features of inter-neuronal connectivity (Shell 1993a; Coulter 1997; Proctor & Gale 1997; March 1998).

After insult or as the consequence of disease, a spectrum of changes may occur that enhance the likelihood of a seizure developing. These include: changes in receptor density and / or sensitivity on neurons (McNamara & Wada 1997); changes in the performance of cellular ion pumps (Dichter & Wilcox 1997); loss of inhibitory circuits (March 1998); the development of kindling and mirror foci (Au Louis et al 1997; McNamara & Wada 1997); increased extra-cellular potassium levels (McNamara 1994; McNamara & Wada 1997).

Table 1. Extracranial causes of seizures

Metabolic disorders

Hypoxia

- Congenital and acquired cardiac disease
- Respiratory disturbances
- Polycythemia

Hypoglycaemia

- Table 2, page 12

Hepatoencephalopathy

- Portosystemic shunt
- Severe liver diseases

Hypocalcaemia

- Periparturition
- Hypoparathyroidism
  - Immune-mediated lymphocytic parathyroiditis

Hypercalcaemia

- Primary hyperparathyroidism
  - Functional adenoma
- Pseudohyperparathyroidism
  - Lymphosarcoma, anal sac adenocarcinoma
- Osteolysis secondary to neoplasia
- Acute and chronic renal failure
- Hypoadrenocorticism

Electrolyte and acid-base status imbalances

- Hyper- and hyponatremia
- Nonketotic hyperosmolar diabetes

Hyperlipidemia

- Fat emboli in Miniature Schauzers
- Hypothyroidism

Renal encephalopathy

- Uremia
- acid-base, fluid and electrolytes abnormalities
- hypertension

Pancreatic encephalopathy

Thiamin deficiency

- (terminal stages)

Intoxication

- Organophosphates, carbamates
- Chlorinated hydrocarbons
- Rodenticides, herbicides
- Heavy metals (especially lead)
- Drug related (e.g. ivermectin)
- Plant toxins and mycotoxins
- Animal toxins (e.g. bee and wasp venom)

(Cuddon 1996; Podell 1996; O'Brien 1998; Schwartz-Porsche 1999; Thomas 2000)

Table 2. Causes of hypoglycaemia in dogs

Increased glucose consumption
- Excess of insulin
  - Insulin-secreting tumours (insulinoma)
  - Therapeutic overdose
  - Extrapancreatic neoplasia (insulinlike substances)
- Hunting dog hypoglycaemia

Insufficient glucose supply
- Inadequate blood supply
- Inadequate glucose production
  - Hepatic diseases
  - Neonatal and transient juvenile hypoglycaemia
  - Substrate deficiencies (starvation, malabsorption)
  - Enzyme deficiencies
    - Glycogen storage disease
    - Glucose-6-phospatase deficiency (Von Gierke's disease)
    - Acid α-glucosidase deficiency (Pompe's disease)
    - Amylo-1-6 glucosidase deficiency (Cori's disease)

Sepsis

(Cuddon 1996)

Table 3. Intracranial structural causes of seizures

Degenerative

Storage diseases
GM2 gangliosidosis, metachromatic leukodystrophy,
Glycoproteinosis, glycogenosis, ceroid lipofuscinosis

Anomalous

Hydrocephalus
Acquired, congenital
Malformations
Lissencephaly

Neoplastic

Primary brain tumour
Metastatic brain tumour

Infectious-Inflammatory

(meningitis and/or encephalitis)
Viral
Canine distemper, rabies
Bacterial
Various types (e.g., Spirochaetes)
Fungal
Cryptococcosis
Protozoal
Toxoplasmosis
Neosporosis
Rickettsia rickettsii and Ehrlichia canis
Parasitic
Aberrant migration (e.g., *Cuterebra* species larvae)
Granulomatous meningoencephalitis /-encephalomyelitis (Table 4, page 14)
Necrotizing encephalitis
Unknown causes

Traumatic (head trauma)
acute → haemorrhages / hypoxia
delayed → scars

Vascular

Intracranial haemorrhage
Brain infarction
embolism from underlying cardiac disease (e.g., bacterial endocarditis)
hypertension
cerebral artery atherosclerosis secondary to hypothyroidism
Hypertensive encephalopathy
Essential hypertension
Secondary hypertension
acute and chronic renal failure
glomerulonephritis
hyperadrenocorticism

(Shell 1993a; Jolly et al 1994; Podell 1996; Bagley & Gavin 1998;Thomas 1998; Schwartz-Porsche 1999; Thomas 2000)

Table 4. Granulomatous meningoencephalomyelitis

Signalment

Dogs of all breeds, both sexes and all ages. However most commonly diagnosed in young to middle-aged dogs (3-6 years), especially toy and small breeds of dogs, and terriers and poodles (Muñana & Luttgen 1998; Thomas 1998)

Histopathology

The hallmark of GME is the presence of large inflammatory perivascular cuffs consisting primarily of lymphocytes and macrophages; few plasma cells and, infrequently, neutrophils are also seen. Leptomeningeal infiltrates and granulomatous lesions in the neuropil are also common findings in dogs with GME (Summers et al 1995; Kipar et al 1998; Muñana & Luttgen 1998)

Histopathologic classification and related clinical presentation

Disseminated GME		
Lesions distributed widely throughout the CNS, but are primarily in the white matter of the cerebrum, cerebellum, caudal aspect of the brainstem and cervical spinal segments	→	acute onset and rapid progression of multifocal CNS signs; death generally occurs within 1 to 3 weeks
Focal GME		
Single granulomatous mass, most commonly located in the cerebral white matter or brainstem. Smaller, disseminated lesions are usually present as well	→	more gradual / often insidious onset and slow progression (over 3 to 6 months) of clinical signs suggesting a single space-occupying lesion within the brain or spinal cord
Ocular form		
Rare; optic nerves and optic chiasm involvement	→	acute onset of visual impairment, midriatic unresponsive pupils and retinal haemorrhages

(Braund 1985; Muñana & Luttgen 1998; Thomas 1998)

Common clinical signs

Signs of neurological dysfunction vary with the location of the lesion

Neck pain
Ataxia
Paresis
Abnormal behaviour
Blindness
Vestibular dysfunction
Seizures (20%)

Differential diagnosis

Canine distemper virus encephalitis; Fungal and Protozoal granulomatous encephalomyelitis (Muñana & Luttgen 1998; Thomas 1998), sporadic necrotizing meningoencephalitis (small breeds: pug, maltese, Yorkshire Terriers), granulomatous leptomeningitis in beagles (associated with *E.coli* infection) (Kipar et al 1998)

Intracranial neoplasia in dogs

Epidemiology and classification

Epidemiology

Intracranial tumours occur relatively frequently in dogs. The incidence of intracranial neoplasia occurring in veterinary patients has not recently been evaluated; previously reported incidence of primary brain tumours in the canine species is 14.5 a year per 100,000 dogs at risk (Vandevelde 1984). Metastatic disease appears to be less common (Moore et al 1996). However, the actual incidence of intracranial neoplasia is probably unknown because: a) the access to advanced imaging modalities, which allow ante-mortem diagnosis of intracranial space-occupying lesions (computed tomography and magnetic resonance imaging), has limited availability and represents a significant cost to the owner; b) the cranial vault is uncommonly evaluated as a site of metastatic disease at routine post-mortem examination (Bagley & Gavin 1998). In addition, improved therapy for neoplasia has resulted in longer survival and change in metastatic behaviour for some cancers, leading to increased incidence of intracranial metastasis. This has been shown to be particularly true for lymphoreticular neoplasia because lymphocytes can cross the blood-brain barrier (BBB) (Couto et al 1984; Moore et al 1996).

Although, brain tumours occur in dogs of all breeds, both genders and any age, the incidence increases over five years of age, and the relative risk increases in certain breeds. The median age for dogs for being diagnosed with a brain tumour is 9 years (Kraus & McDonnell 1996; Moore et al 1996; Bagley 1999; LeCouteur 1999). Interestingly, brain tumours are over-represented in immature dogs (<6 months): intracranial tumours are second only to tumours of the haematopoietic system in dogs of this age group (Keller & Madewell 1992; Spugnini et al 1995). Brain tumours that can occur in dogs younger than 5 years of age include medulloblastoma, ventricular tumours (e.g., ependymoma, choroid plexus papilloma), and tumours of congenital maldevelopment such as epidermoid / dermoid cysts, craniopharyngiomas and teratomas (LeCouteur 1990; Moore et al 1996). Teratomas may be associated with the onset of clinical signs late in life (Targett et al 1998). Gliomas and meningiomas have also been reported (Cox et al 1990; Keller & Madewell 1992; Triolo et al 1994).

Breeds such as Golden Retriever, mixed breed, Labrador Retriever, Boxer, Collie, Doberman Pinscher, Schnauzer, Scottish Terrier, and Old English Sheepdog have been reported to develop intracranial tumours more commonly than other breeds (Heidner et al 1991; Kraus & McDonnell 1996; Moore et al 1996; Bagley 1999; LeCouteur 1999).

Breed predisposition for certain tumours types has been reported: glial cell tumours (astrocytomas, oligodendrogliomas) and pituitary tumours have a predilection for brachycephalic breeds. Conversely, meningiomas have a similar incidence in all breeds of dogs, although marginally higher in the dolicocephalic ones (Moore et al 1996; Dewey et al 2000).

Overall, meningiomas and astrocytomas are the most common types of intracranial neoplasia in dogs (Moore et al 1996; LeCouteur 1999; Dewey et al 2000). Some reports indicate meningioma (Heidner et al 1991) as the most common tumour type, whereas in others astrocytoma is (Zaki 1977). These differences may reflect a change in the incidence of tumours, changing in breed popularity, geographic differences or other unknown reasons. Similar consideration has to be made regarding the incidence of astrocytoma and oligodendroglioma. Astrocytoma is reported to be the most common glial cell tumour of dogs in the United States of America, whereas in some European countries oligodendroglioma appears to be the most common (Moore et al 1996).

Gender predisposition is not well established. Some studies report a higher incidence of brain tumours in males (Zaki & Nafe 1980; Moore et al 1996) although a higher proportion of females appear to develop meningiomas, perhaps as a consequence of oestrogen receptors identified in this tumour type in both dogs and humans (Speciale et al 1990; Spugnini et al 1995; Moore et al 1996).

Classification

Classification of brain tumours is generally based on histological and cytological criteria capable of determining the cell type of tumour origin, the growth characteristic of the tumour and the degree of differentiation within the tumour. Such determinations provide the clinicians with a basis for making a prognosis and determining therapeutic options (LeCouteur 1999).

Primary and secondary brain tumours

Intracranial neoplasms may be classified as either primary or secondary, depending on their cell of origin. Primary brain tumours arise from the brain parenchymal tissue (glial cells, neurons), cells comprising the outer and inner lining of the brain (meninges and ependyma, respectively), vascular elements (choroid plexus) and lymphoid tissues (LeCouteur 1990; Dewey et al 2000). Secondary tumours include all metastatic tumours. These may reach the brain by haematogenous metastasis from a primary tumour located outside the nervous system or by local invasion (or extension) from adjacent non-neuronal tissue (e.g., nasal and frontal sinuses tumours, middle ear and calvarial tumours) (LeCouteur 1999). As the central nervous system (CNS) lacks a lymphatic system, CNS metastases most likely occur by haematogenous routes; this partially explains the high incidence of infarction and / or haemorrhage observed with CNS metastases (Fenner 1990). The cortical grey / white matter junction is a common area of metastases due to increased vascularity; brain stem and cerebellar metastases are less frequently seen (Bagley & Gavin 1998; Moore & Taylor 1988).

Local extension from nasal adenocarcinoma or metastases from mammary, prostatic or pulmonary adenocarcinoma, lymphosarcoma and haemangiosarcoma are the most frequently encountered secondary tumours in dogs (Moore & Taylor 1988; Sackman et al 1989; Nafe 1990; Mori et al 1991; Bagley & Gavin 1998). Tumours that readily metastasise to the lungs are more likely to metastasise to the brain (Bagley & Gavin 1998), because 15% of cardiac blood flow returning from the lungs goes to the brain (Johnson 1990). Calvarial tumours that may affect the brain by means of local extension include osteosarcoma and multilobular osteochondrosarcoma (Straw et al 1989).

Pituitary gland neoplasms (adenomas and carcinomas) and tumours arising from cranial nerves (e.g., nerve sheath tumour of the IIIrd or VIIth cranial nerves) are considered secondary brain tumours, as they affect the brain by means of local extension (LeCouteur 1999). Some authors refer to tumours that affect the brain but which are not strictly derived from the nervous system to as CNS-associated tumours, and include in this category: pituitary tumours, germ cells tumours[1], craniopharyngiomas, chordomas and osteochondrosarcomas. Of these,

[1] These are also referred to as suprasellar germ cells tumours because most commonly located in the pineal and suprasellar region.

pituitary tumours and osteochondrosarcomas occur relatively frequently in dogs (Moore et al 1996).

In general, lymphoma is classified as a secondary brain tumour, because it almost always occurs simultaneously with the development of, or late in the course of therapy for, multicentric lymphoid neoplasia originating from a primary focus outside the CNS (Britt et al 1984; Couto et al 1984; Johnson 1990; LeCouteur 1990). Occasionally, however, lymphoma involves the CNS in absence of systemic disease, in which case it is classified as primary CNS lymphoma (Johnson 1990).

Cytological and biological malignancy

In assessing the malignant potential of a brain tumour, the difference between cytological and biological malignancy has to be emphasised. Cytological malignancy is a morphological assessment of anaplasia, whereas biological malignancy is related to the life-threatening potential of the mass in itself (LeCouteur 1999). Most cytologically malignant brain tumours are also biologically malignant, despite the treatments presently available. Cytologically benign brain tumours may be biologically malignant because of various secondary effects e.g. increased intracranial pressure (ICP).

The capability of a brain tumour to: locally infiltrating normal brain parenchyma, spreading along the surface of the brain to local sites, or spreading by cerebrospinal fluid (CSF) to other sites within the cranial vault and / or the spinal cord, influences its biological malignancy. Multiple space-occupying lesions usually carry a worse prognosis than single masses (Le Couteur 1999). Most primary brain tumours of dogs are solitary. However, multiple CSF metastases of medulloblastoma (LeCouteur 1990) and choroid plexus papilloma (LeCouteur et al 1981) have been reported. Multiple tumours of different histologic type are rare (e.g., pituitary carcinoma, meningioma) (Patnaik et al 1986; Johnson 1990; Schulman et al 1992). Primary brain metastases to non-CNS sites can occur but are uncommon (Schulman et al 1992; Moore et al 1996; Furushima et al 1989).

Tumour types

This dissertation concentrates on meningiomas and glial cell tumours these being the tumour types more frequently encountered in dogs. Table 11 (page 28-30) summarises the

classification of primary brain tumours in human patients according to the World Health Organisation (WHO, 1993); not all these tumour types have been described in dogs.

Meningiomas

HISTIOGENESIS

Meningiomas arise from the mesenchymal arachnoid layer of the meninges; they develop from the periphery of the brain parenchyma and expand inward. However, despite the striking ultrastructural similarities between arachnoid cells and meningiomas cells, the ultimate histogenesis of meningiomas remains to be established (Lantos et al 1997).

BEHAVIOUR

Canine intracranial meningiomas are most often at the convexities of the cerebral hemispheres, in the midline attached to the falx cerebri or to the tentorium cerebelli, or at the lateral / ventral surface of the brain at the rostral and middle fossa (Braund 1984; Braund & Ribas 1986). Meningioma may also arise intraventricularly from the tela choroidea, mimicking a choroid plexus tumour (Bagley & Gavin 1998). Retrobulbar, paranasal and frontal sinus localisation are uncommon, but have been described (Patnaik et al 1986, Patnaik 1989; Moore et al 1996).

Growth is usually slow and within meningeal layers; lesions are usually discrete and may be delineated by a thin investing capsule (Kraft 1990). Meningiomas may compress or extend into adjacent brain tissue causing pressure atrophy and a mass effect. Meningiomas are often adherent to the dura mater. Attachment to the dura can be broad-based (narrow), sessile (pedunculated) or complete (meningioma *en plaque*). Meningiomas may be spheroidal, or lobate, with a regular or a nodular surface (Kraft 1990).

Hyperostosis, a proliferative bony response that is a hallmark of human meningiomas, is a common finding in dogs (Braund & Ribas 1986; Kraft 1990). Currently hyperostosis is believed to result from high activity of the enzyme alkaline phosphatase (AP) in the neoplastic cells and/or a change in local blood supply (Lantos et al 1997). Alternatively, meningiomas may produce bone erosion as a result of pressure atrophy of the calvarium (Bagley 1996b).

In dogs, meningiomas tend to be more infiltrative into surrounding cortical parenchyma than in cats where meningiomas are often multiple and always well encapsulated (LeCouteur

1999). Predominantly cystic meningiomas, most commonly involving the olfactory area, have been described (Bagley et al 1996; Bagley 1999).

HISTOLOGICAL FEATURES

The major histological features of the three subtypes most commonly encountered are summarised in Table 5, page 20. Two or more subtypes are often present within the same tumour mass (Kraft 1990). Meningothelial and transitional subtypes are most common in dogs (Johnson 1990). In most cases a single H&E-stained section secures the diagnosis, and immunostaining is performed only to further confirm it (Johnson 1990). Sarcomas of the meninges have been described in dogs. They may occur as discrete masses or as a diffuse sarcomatosis of the meninges (Moore et al 1996).

Table 5. Histology and Immunocytochemistry of meningiomas

	Histology	Immunohistochemistry
Meningothelial	Nests, lobules of meningothelial cells with round to oval nuclei and abundant cytoplasm. Cell membrane is not well defined and the overall impression is that of a syncytium (also called *syncytial meningiomas*)	positive vimentin and EMA* reactivity
Fibroblastic	Bundles of elongated fibroblastic-like cells	
Transitional	Islands of meningothelial cells alternate with interlacing bundle of spindle-shaped cells. They have a striking tendency for whorl formation. They may contain *psammoma bodies*	

*Epithelial Membrane Antigen proved for humans, not for canine meningiomas

(Johnson 1990; Kraft 1990; Summers et al 1995; Moore et al 1996)

GRADING AND PROGNOSIS

Although, typically solitary and benign (WHO Grade I), histologically malignant meningiomas are described (Moore et al 1996). In human meningiomas, the histological pattern in itself appears to be of little prognostic importance, with the exception of the aggressive papillary variant (WHO Grade II or III). This variant has also been reported in dogs (Schulman et al 1992). In contrast, the presence of necrosis, mitotic figures and infiltration of brain parenchyma, are considered indicators of poor prognosis. These features

cannot be taken as prognostic indicators in dogs: areas of focal necrosis with pools of neutrophils, and invasion along the Virchow-Robin spaces, are all common findings in canine meningiomas (Johnson 1990; Summers et al 1995; Moore et al 1996).

Gliomas

Gliomas arise from neuroglial cells of the parenchyma, which include astrocytes, oligodendrocytes, ependymal cells, and choroid plexus cells (McLendon et al 1998).

ASTROCYTOMAS

Histogenesis

Astrocytomas are tumours of neuroepithelial origin, which arise from neoplastic transformation of astrocytes in different stages of maturity (Frenier et al 1990).

Behaviour

Astrocytomas are diffusely infiltrating neoplasms, preferentially located in the cerebral hemispheres (especially the fronto-temporal region and the piriform lobe) and diencephalon (Johnson 1990; Moore et al 1996). However, brainstem localisation has also been reported (Johnson 1990; Kraft & Gavin 1999).

Histological features

Astrocytomas are characterised by a wide range of histopathological features and biological behaviour (Moore et al 1996). These are summarised in Table 6, page 22.

Grading and prognosis

The two grading systems, both of which have prognostic significance (Lantos et al 1997), used in man are summarised in Table 7, page 22. Increasing grade is consistent with the degree of aggression of the tumour. However, astrocytomas show a consistent tendency to diffuse infiltration of adjacent and distant brain structures largely irrespective of histological grade, in addition to an inherent tendency for progression to a more malignant phenotype (Lantos et al 1997). Whether this anaplastic progression also occurs in dogs is not known (Moore et al 1996). In addition, other glial neoplasms, mainly oligodendrogliomas, may also become highly anaplastic and morphologically indistinguishable from glioblastomas (Moore et al 1996).

Glioblastoma multiforme appears to be less common in dogs than in humans and it has been reported in brachycephalic breeds (Moore et al 1996). In addition, the extremes of nuclear pleomorphism with exuberant multinucleated giant cells seen in human glioblastomas are

much less common; the canine variant often qualifies as a small cell glioblastoma (Summers et al 1995).

Table 6. Classification, histology and immunohistochemistry of astrocytic tumours

	Histology	Immunohistochemistry
Low grade Astrocytomas	Slight hypercellularity and pleomorphism with no mitosis though atypical nuclei may be observed[2,5]. Fibrillary, protoplasmic and gemistocytic tumours are found in man and the dog[4,5,6]. Fibrillary tumours are the commonest in the dog[2,5].	*GFAP* *(Glial fibrillary acidic protein)* In man expression directly correlates with the degree of differentiation and this may be true of canine tumours[1,3,4,5,6] (Table 10, page 26) *S-100* Expressed in human tumours but not of diagnostic relevance[6]
Anaplastic astrocytomas	Focal moderate hypercellularity with pleomorphism and mitotic figures[4,5,6].	
Glioblastoma	Hypercellular, pleomorphic with obvious mitosis. A hallmark finding is vascular proliferation and necrosis; the latter may account up to 80% of the tumour mass[5,6].	

[1]Vandevelde et al 1985; [2]Frenier et al 1990; [3]Johnson 1990; [4]Summers et al 1995; [5]Moore et al 1996; [6]Lantos et al 1997

Table 7. Grading of astrocytic tumours

Low-grade astrocytomas	Grade II*	WHO Grade I and II
Anaplastic astrocytomas	Grade III	WHO Grade II and III
Glioblastoma	Grade IV	WHO Grade III and IV

(Frenier et al 1990; Summers et al 1995; Moore et al 1996; Lantos et al 1997)

*Grade I astrocytomas is used to designate human juvenile pilocytic astrocytomas and subependymal giant cells astrocytoma. The pilocytic variant has also been reported in the dog (Moore et al 1996) (Table 11, page 28)

OLIGODENDROGLIOMAS

Histogenesis

Oligodendrogliomas are tumours of neuroepithelial origin arising from oligodendrocytes (Moore et al 1996).

Behaviour

These tumours can occur anywhere in the white matter but are more commonly found in the diencephalon and cerebral hemispheres, with the frontal and pyriform lobes (especially the frontal lobe) being more frequently affected (Moore et al 1996).

Growth occurs by infiltration and encroachment of surrounding tissues (Moore et al 1996). Despite a capacity for infiltrative spread that is shared with astrocytoma, oligodendrogliomas tend to have relatively well delineated macroscopic borders, especially in the deep white matter (Johnson 1990; Summers et al 1995).

Histological features

The most striking feature of smear preparations of oligodendrogliomas is the cytological uniformity (Lantos et al 1997). The histological features are summarised in Table 8, page 23. The histopathological diagnosis of oligodendroglioma relies primarily on the recognition of the few typical morphological features described (Table 8). These are complemented by immunohistochemical features, which alone, however, are not specific for this group of tumours.

Table 8. Histological and Immunohistochemical characteristics of Oligodendrogliomas

	Histology	Immunohistochemistry
Well-differentiated oligodendrogliomas	Typical honeycomb or fried eggs appearance; dense packing of isomorphic cells demarcated by a delicate fibrovascular strroma. Cells have small, round chromatin-rich nuclei, empty-looking cytoplasm and sharp cellular boundaries. Microcysts of mucinous matrix are frequent within the mass[1,2].	*MBP* (*myelin basic protein*) and *GFAP* negative[1,2,3,4] variable MAG* and Leu-7[5] antigen immunoreactivity in dogs and humans but not of diagnostic relevance[1,4] Reticulin staining used to emphases the typical "chicken wire" pattern of blood vessels[2]
Anaplastic oligodendrogliomas	Frequent mitosis and moderate nuclear pleomorphism, with ovoid to fusiform vesicular nuclei[2,3]. Sometimes features similar to glioblastoma multiforme[2,3].	MBP negative[2,4]; variable GFAP** immunoreactivity[4] *myelin-associated glycoprotein **proved in humans

[1]Johnson 1990; [2]Summers et al 1995; [3]Moore et al 1996; [4]Lantos et al 1997

CHOROID PLEXUS TUMOURS

Histogenesis

They are neuroepithelial in origin, and arise from the cells of the choroid plexus (Summers et al 1995; Moore et al 1996).

Behaviour

Choroid plexus tumours are relatively common in dogs (Moore et al 1996). They arise most commonly in the fourth ventricle but can occur in the lateral and third ventricles (Zaki & Nafe 1980; Johnson 1990; Moore et al 1996). They are usually well-defined, expansive masses that grow slowly into the ventricular system and cause compression of adjacent brain tissue. They may cause hydrocephalus both due to obstruction (Moore et al 1996) and increased CSF production (Johnson 1990). Haemorrhages are frequent (Moore et al 1996).

Histological features

Histological features are summarised in Table 9, page 25. In most instances recognition of the features described allows a confident diagnosis of choroid plexus tumour. However, choroid plexus carcinomas may be particularly difficult to distinguish from secondary carcinomas (Johnson 1990); many immunohistochemical markers may be necessary to secure the diagnosis (Lantos et al 1997).

EPENDYMAL TUMOURS

Histogenesis

They are neuroepithelial in origin, and arise from the ependymal cells lining the ventricular system (Dewey et al 2000).

Behaviour

Ependymal tumours are uncommon in dogs (Moore et al 1996). They can occur anywhere along the ventricular system (Moore et al 1996), but most often they develop in the lateral ventricles (Johnson 1990; Nafe 1990). Conversely, in human beings, they most often develop in the caudal fossa in the fourth ventricle. The ratio between infratentorial and supratentorial (lateral ventricles) ependymomas in people is about 60:40 (Lantos et al 1997).

They are usually poorly defined, highly infiltrative and destroy surrounding neuronal tissue. They are capable of intracranial metastases via CSF pathways: portions readily break off the primary mass because of the absence of extensive supporting stroma (Moore et al 1996). They frequently cause internal obstructive hydrocephalus (Johnson 1990; Moore et al 1996).

Histological features

The histological features of ependymal tumours are summarised in Table 9, page 25. In most cases a single H&E-stained section secures the diagnosis. Immunocytochemically, human ependymomas express vimentin and GFAP, but infrequently cytokeratin (Johnson 1990; Moore et al 1996; Lantos et al 1997). In this respect they show transition toward glial cells in contrast to the epithelial nature of the plexus papilloma, which is keratin-positive and less frequently GFAP-positive (Summers et al 1995; Lantos et al 1997) (Table 9).

Table 9. Histological and Immunohistochemical characteristics of ependymomas and choroid plexus tumours

	Histology	Immunohistochemistry
Ependymomas	Highly cellular, well-vascularised tumours. Cells with ovoid, deeply chromatic, fairly uniform, polar nuclei and indistinct eosinophilic cytoplasm. Growth occurs as solid sheets. Characteristic is the presence of perivascular pseudo-rosettes and true rosettes. The cells that compose the rosettes may have surface cilia and / or basal bodies[3,4]. Mucinous change and cyst formation may be seen[4].	immunohistochemical properties proved in humans but not well established in dogs[1,3,5]: Vimentin and GFAP positive[3,4,5] Cytokeratin negative[3,4]
Anaplastic ependymomas	Moderate nuclear pleomorphism and necrosis[4,6]. They may merge into glioblastoma multiforme[4].	
Choroid plexus papilloma	Typical stereotyped branching papillary structures formed by cuboidal to columnar epithelium with regular, ovoid nuclei supported by a richly vascular stroma. Mitoses are absent[3,4]. Focal keratinisation of cells may occur[2]. Haemorrhages, calcification and cysts are frequent[3,4,5].	GFAP* and S-100 negative[1,2,3] Cytokeratin and carcinoembryonic antigen positive[2,3]
Choroid plexus carcinoma	Loss of papillary architecture with features of anaplasia, necrosis and frank local invasiveness[3,6].	*occasionally positive in humans[5,6]

[1]Vandevelde et al 1985; [2]Ribas et al 1989; [3]Johnson 1990; [4]Summers et al 1995; [5]Moore et al 1996; [6]Lantos et al 1997

MIXED GLIOMAS

Many canine glial cells tumours are composed of mixed cell types including astrocytic, oligodendroglial and / or ependymal cells, thus justifying similarly to the human counterpart a diagnosis of mixed glioma (Johnson 1990; Summers et al 1995; Moore et al 1996).

Other primary brain tumours

Primary brain tumours derived from other cell types are rarely described in the dog. They include neuronal cell tumours (e.g., gangliocytomas); (Moore et al 1996); haemangioblastoma (LeCouteur 1999); primary lymphoma (Dewey et al 2000, Long et al 2000) and embryonal tumours (LeCouteur 1990; Moore et al 1996), as well as pathologic entities of still controversial classification such as microgliomatosis and gliomatosis cerebri (Vandevelde et al 1981; Cuddon & Smith-Maxie 1984; Summers et al 1995; Moore et al 1996; Lantos et al 1997).

One case of primary intracranial malignant plasma cell tumour (Sheppard et al 1997) and one case of primary malignant hystiocytosis (Chandra & Ginn 1999) has also been reported.

Pituitary tumours

Most pituitary tumours arise from the pars distalis and less frequently from the pars intermedia. They can be classified as adenomas or adenocarcinomas, with most being adenomas. Many are functional tumours derived from chromophobe cells that produce adrenocorticotropic hormone resulting in hyperadrenocorticism (Moore et al 1996). Pituitary macroadenomas / carcinomas may also result in signs primarily related to CNS dysfunction because of dorsal enlargement with encroachment on diencephalic structures and hypothalamic dysfunction (Sarfaty et al 1988).

Immunocytochemical studies reveal staining for ACTH, β-lipoprotein and β-endorphin in both pars distalis and intermedia adenomas of the dog. Strong α-melanin stimulating hormone immunoreactivity occurs in pars intermedia tumours (Summers et al 1995).

Table 10. Immunohistochemistry characteristic of primary brain tumours in dogs and human beings

	vimentin	GFAP	S-100	MBP	cytokeratin
Meningiomas	◇ (D) / ○ (H)	◆(D) / ● (H)			◆ (D) / ● (H)
Low grade astrocytomas	◆(D) / ○ (H)	◇ (D) / ○ (H) Strong and uniform	○ (H)		
Anaplastic astrocytomas	○ (H) variable	? (D) / ○ (H) but less consistent than low grade astrocytomas			
Glioblastoma multiforme	○ (H) variable	○ (H) Highly variable degree and extent of positivity			
Well-differentiated oligodendrogliomas	◆ (D) / ● (H)	◆ (D) / ● (H)		◆ (D) / ● (H)	
Anaplastic oligodendrogliomas	○ (H) variable	○ (H) variable		◆ (D) / ● (H)	
Ependymomas	? (D) / ○ (H)	○ (H) (◆ in dogs?)			● (H) occasional ○ (H)
Choroid plexus tumours		◆ (D) / ● (H) occasional ○ (H)	◆ (D) / ● (H)		◇ (D) / ○ (H)

Immunoreactivity: (◇) positive in the dog; (○) positive in humans; (◆) negative in the dog; (●) negative in humans; (?) unknown or uncertain

(Vandevelde et al 1985; Johnson 1990; Summers et al 1995; Lantos et al 1997)

Table 11. WHO (1993) Classification of the CNS tumours (Lantos et al 1997)

Tumours of neuroepithelial origin

Astrocytic tumours

Diffuse astrocytoma

Low grade astrocytoma (Grade II)

3 subtypes: fibrillary, gemistocytic, protoplasmic

Anaplastic astrocytoma (Grade III)

Glioblastoma (Grade IV)

Variants: giant cell glioblastoma, gliosarcoma

pylocitic astrocytoma (Grade I)

subependymal giantcell astrocytoma (Grade I)

pleomorphic xanthoastrocytoma (Grade II)

Oligodendroglial tumours

Oligodendroglioma (Grade II)

Anaplastic (malignant) oligodendroglioma (Grade IV)

Mixed gliomas

Oligoastrocytoma (Grade II)

Anaplastic oligoastrocytoma (Grade III)

Ependymoastrocytoma (Grade II)

Oligoependymomas (Grade II)

Ependymal tumours

Ependymoma (Grade II)

3 subtypes: cellular, papillary and clear cell

Anaplastic (malignant) ependymoma (Grade III)

Myxopapillary ependymoma (Grade I)

Subependymoma (Grade I)

Choroid plexus tumours

Choroid plexus papillomas (Grade I)

Choroid plexus carcinoma

Neuroepithelial tumours of uncertain origin

Astroblastoma

Polar spongioblastoma

Gliomatosi cerebri (Grade III or IV)

Neuronal cell tumours

Gangliocytoma

Dysplastic gangliocytomas of the cerebellum

Central neurocytoma

Variant: atypical central neurocytoma

Table 11 (cont). WHO (1993) Classification of the CNS tumours (Lantos et al 1997)

Mixed neuronal-glial tumours

Gangliogliomas

Variant: anaplastic (malignant) gangliogliomas

Ganglioneuromas

Desmoplastic infantile gangliogliomas

Dysembryoplastic neuroepithelial tumours

Tumours of the pineal region

Pineal parenchyma tumours

Pineocytomas (Grade II)

Pineoblastoma (Grade IV)

Mixed pineocytoma and pineoblastoma

Craniopharyngioma

Germ cell tumours

Glial tumours

Primary and secondary astrocytomas

Mesenchymal tumours

Primary and secondary meningiomas, angiomas

Ependymomas and Choroid plexus tumours

Primary (rare) and secondary

Ganglionic tumours

Gangliocytoma, gangliogliomas

Non-neoplastic masses

Pineal cysts

Embryonal tumours (Grade IV)

Medulloepitheliomas

Ependymoblastoma

Central neuroblastic tumours

central neuroblastoma

olfactory neuroblastomas

Primitive neuroectodermal tumours (PNET)

Medulloblastomas

Variants: desmoplastic m., melanotic m., lipomatous m., medullomyoblastomas

Extracerebellar primitive neuroectodermal tumours

Tumours of the meninges

Tumours of meningothelial cells

Meningiomas (benign meningiomas) (Grade I)

11 subtypes: meningothelial, fibrous (fibroblastic), transitional, psammomatous, angiomatous, microcystic, secretory, clear cell, chordoid, lymphoplasmacyte-rich, metaplastic

atypical meningiomas (Grade II)

papillary meningiomas (Grade II)

anaplastic (malignant) meningiomas (Grade III)

Table 11 (cont). WHO (1993) Classification of the CNS tumours (Lantos et al 1997)

Mesenchymal, non- meningothelial tumours (MN-M)

benign MN-M tumours

chondromas, osteochondromas, osteomas, lipomas, fibrous histiocytomas

malignant MN-M tumours

haemangiopericytomas, fibrosarcomas, chondrosarcomas, rhabdomysarcomas, meningeal sarcomatosis, malignant fibrous histiocytomas

Tumours of uncertain histogenesis

Haemangioblastomas

Germ cell tumours

Germinoma
Embryonal carcinoma
Endodermal sinus tumour
Choriocarcinoma
Teratoma

Lymphomas

Primary malignant lymphomas

Primary B cell lymphomas
Primary T cell lymphomas

Secondary lymphomas

Lymphomatous leptomeningitis
Dural involvement
Intravascular malignant lymphomatosis
Lymphomatoid granulomatosis

Plasma cell tumours

Solitary plasmacytomas
Multiple myelomatosis

Chordomas

Variant: chondroid chordomas

Cysts and tumour-like conditions

Epidermoid cysts
Dermoid cysts
Colloid cysts
Enterogeneous cyst
Neuroglial cysts
Glial cysts of the pineal gland
Cysts of the choroid plexus
Arachnoidal cysts
Plasma cell granuloma

Pathologic effects, historical and clinical features of brain tumours

Brain tumour-induced pathology

Brain tumours cause cerebral dysfunction through primary and secondary pathologic effects; these are summarised in Table 12 (page 31).

Primary brain tumours are often slow growing, allowing intracranial structures to initially adapt successfully to the increasing pressure (North & Reilly 1990; Bagley 1996b; LeCouteur 1999). Exhaustion of the compensatory mechanisms may result in sudden onset of severe neurological dysfunction in absence of premonitory signs, or in rapid deterioration of previously vague clinical signs (e.g., subtle behavioural changes). Acute onset of neurologic deficits may also occur following tumour-associated acute haemorrhage, infarction, or obstructive hydrocephalus. Rapidly growing tumours do not permit the same degree of compensation and in such cases a sudden onset of severe neurological dysfunction is frequently observed (LeCouteur 1999, Dewey et al 2000).

Table 12. Pathologic effects of intracranial neoplasia

Primary effects	*Secondary effects*
• Infiltration of normal nervous tissue • Compression/encroachment of adjacent anatomic structures • Disruption of cerebral blood circulation Local ischemic necrosis	• Vasogenic cerebral oedema • Inflammation • Haemorrhages • Disturbance of CSF flow dynamics obstructive Hydrocephalus • Elevated ICP • Brain herniation caudal transtentorial herniation foramen magnum herniation

Carrillo et al 1986; Johnson 1990; North & Reilly 1990; Bagley 1996b; Kraus & McDonnell 1996; LeCouteur 1999; Dewey et al 2000; Webb & Muir 2000

Historical features of brain tumours

Historical and presenting clinical signs of patients with intracranial neoplasia are variable and reflect the location, size and associated pathologic effects of the tumour (LeCouteur 1999; Nafe 1990). In dogs with brain tumours, the most common presenting clinical sign of dysfunction is seizure activity (LeCouteur 1999; Dewey et al 2000).

With the exception of seizure activity, the onset of neurological dysfunction is often insidious over weeks to months, especially with meningiomas (Nafe 1990). Many dogs have a long history of 'vague', intermittent signs, such as: disorientation, hiding during the day, lethargy, change in appetite and water consumption, unsteadiness, stumbling, getting stuck in corners, bumping into objects (Kraus & McDonnell 1996). It is very likely that both owner and veterinarian do not recognise these non-specific early signs, which are often initially attributed to "old age" (Mandigers et al 1994; LeCouteur 1999). However, even with a slowly growing tumour subacute or acute development of neurologic dysfunction may occur, following exhaustion of brain compensatory mechanism. Other potential explanations include tumour-associated acute haemorrhage, infarction or obstructive hydrocephalus (LeCouteur 1999).

Location and effective size influence the clinical presentation of a brain tumour independently from the inherent growth characteristics of the tumour itself (Foster et al 1988; Nafe 1990; LeCouteur 1999).

Localising the lesion

Although definitive localisation of the tumour is achieved by imaging, a clinically developed localisation of the lesion is helpful in early prognostication and counselling of the client and in planning further investigation. A clinical appreciation is developed from a consideration of the history and clinical findings (see Lesion localisation, page 132). However, dogs with symptoms of intracranial neoplasia are often presented at later stage of illness when the secondary effects make exact anatomical localisation of the lesion difficult (Mandigers et al 1994).

Brain tumours cause clinical signs that localise to forebrain, brainstem and cerebellum; clinical signs are referred to as multifocal when indicative of the involvement of several areas of the CNS (Moore et al 1996). Intracranial CNS structures, as well as clinical signs arising from their dysfunction, are also often referred to as rostrotentorial or rostral fossa and caudotentorial or caudal fossa structures. Although the classification of these portions may be arbitrary and overlapping, it is often useful.

The strict location of the diencephalon (forebrain Vs brainstem) remains controversial in veterinary anatomy (Jenkins 1978). For the purpose of this dissertation, I consider the forebrain to comprise of the telencephalon (cerebral hemispheres) and the diencephalon

(thalamus, epithalamus, metathalamus, subthalamus, and hypothalamus) because of the strict functional and anatomical correlation existing between these two portions in the adult brain. The forebrain structures are also referred to as rostral fossa or rostrotentorial structures. Located caudally to the diencephalon are the mesencephalon (or midbrain; middle fossa) and the caudal fossa structures, the latter including the metencephalon (ventral pons and dorsal cerebellum) and the myelencephalon (medulla oblongata). The brainstem encompasses the myelencephalon, the ventral portion of the metencephalon (pons) and the mesencephalon, thus including both caudal fossa (except for the cerebellum) and middle fossa structures. Some authors locate the diencephalon in the brainstem (Jenkins 1978; de Lahunta 1983a; Hogg 1987).

Overview of the management of primary brain tumours

Treatment for brain tumours in dogs depend upon tumour type, tumour location, natural history of the tumour, associated morbidity / mortality of the treatment modality, and cost (Bagley 1999). Treatment modalities can be divided into supportive and definitive therapy. For the purposes of this dissertation, supportive therapy refers to treatments aimed at the alleviation of secondary effects of the tumour, whereas definitive therapy is directed toward diminishing tumour volume or eliminating the tumour (Dewey et al 2000). The ultimate goal of both strategies is to provide the patient with a good quality of life for as long as possible.

Supportive therapy

Supportive therapy is usually recommended regardless of whether the client elects to pursue definitive therapy. Clinicians must emphasise the limitations of supportive therapy (Dewey et al 2000). Waning of the palliative effects of supportive therapy and exhaustion of compensatory brain mechanisms results in recurrence of clinical signs, usually within several weeks to several months. Recurrence of clinical signs is often sudden and dramatic (Moore et al 1996; LeCouteur 1999; Dewey et al 2000).

Corticosteroid medication

Supportive therapy consists initially of an anti-inflammatory regimen of oral corticosteroids, more commonly prednisolone (0.5 mg/kg every 12 hours), which can be increased or decreased depending on patient response (Dewey et al 2000). Other authors advise an initial dose of prednisolone varying between 2 to 4 mg/kg/day, which is then tapered during 1 to 2

weeks to the lowest effective dose to alleviate clinical signs (Kraus & McDonnell 1996). However, at this dose side effects of corticosteroids medication such as polyuria, polydipsia, polyphagia and panting are more severe than at anti-inflammatory doses and serious side effects such as haemorrhagic gastroenteritis are more likely to occur. Corticosteroids medication should be discontinued if haemorrhagic gastroenteritis ensues (Kraus & McDonnell 1996). Prednisolone therapy is believed to exert its beneficial therapeutic effects by decreasing ICP through reducing tumour-associated vasogenic oedema and decreasing CSF production. Via reducing vasogenic oedema prednisolone therapy also reduces the effective mass of the tumour (Bagley 1996b; Dewey et al 2000).

Anticonvulsant therapy

If seizure activity is part of the patient's clinical signs, anticonvulsant medication should be prescribed (Dewey et al 2000). For the control of seizure activity in patients with brain tumours, established treatment protocols for idiopathic epilepsy are commonly used (Lane & Bunch 1990, Podell 1996). The anticonvulsant drug most commonly used as adjunctive therapy for brain tumour is phenobarbitone; the recommended dose varies between 2 to 5 mg/kg every 12 hours orally. Phenobarbitone has shown to be effective in lessening seizure frequency and duration in patients with brain tumours, however some animals may require combination of phenobarbitone and potassium bromide (KBr) (Boothe 1998). Some authors report to have been successful in controlling seizure activity in dogs with brain tumours using KBr as a sole anticonvulsant agent, but no indication is given regarding tumour's characteristics and type, duration and frequency of seizures (Dewey et al 2000). However, seizures in dogs with brain tumours are more likely to be difficult to control or refractory to standard antiepileptic drugs (Bagley & Gavin 1998).

Other factors that need to be considered in dogs with brain tumours on antiepileptic medication include the effects of concurrently administered drugs on the antiepileptic drug metabolism and elimination. It is not uncommon for dogs with brain tumours to receive combination of antiepileptic drugs, corticosteroids, antinuclear medications, diuretics, and antibiotics. Increasing the number of drug therapies, increases the potential for drug interactions, and may significantly alter antiepileptic concentration (Bagley & Gavin 1998).

Most animals, prior to specific diagnosis of a brain tumour are placed on anticonvulsant medication for treatment of seizure activity. If definitive therapy is undertaken, these anticonvulsants are continued throughout the therapy. If an animal is not receiving anticonvulsants at the time of surgical therapy, anticonvulsant therapy is initiated prior to surgery, with the aim to decrease postsurgical seizure activity. Ideally, steady state serum levels of anticonvulsant should be achieved prior to surgery (Bagley & Gavin 1998). Guidelines for the management of seizures in the postoperative period have been reported elsewhere (Spugnini et al 1995; Bagley & Gavin 1998).

Definitive therapy

Definitive therapy is directed at long-term control or cure by eliminating neoplastic tissue and inhibiting further tumour growth. Modes of definitive therapy include surgery, radiation therapy, and chemotherapy. Surgical removal / debulking and / or megavoltage radiation therapy are the most common definitive therapies for canine brain tumours. Modalities described are summarised in Tab 13, page 37.

Surgery

Dogs with superficially located tumours of the cerebral hemispheres and cerebellum are the best candidates for surgical intervention (Dewey et al 2000). If the tumour is located in areas of the brain where access and exposure is limited, the risk of surgical morbidity increases remarkably (caudal fossa, brain stem) (LeCouteur 1999). Poor surgical access often leads to increased surgical mortality. If the tumour is within the parenchyma or within a ventricle, it is impossible to access these lesions without damage to the surrounding and / or overlying brain tissue (LeCouteur 1999; Dewey et al 2000). Many intracranial tumours have multiple vessels supplying blood flow lending to the risk of haemorrhages during resection. Possibly from these factors and others, dogs have historically had less than encouraging results with surgical treatment of brain tumours (Bagley & Gavin 1998, Heidner et al 1991, Niebauer et al 1991). However, with advances in surgical techniques and equipment, as well as improved monitoring, surgical removal of brain tumours in dogs is an increasingly viable treatment option (Bagley & Gavin 1998).

When location of the mass makes surgical intervention possible, this should always be performed regardless of tumour type and degree of aggression. Removal of all grossly visible

neoplasia provides some therapeutic benefit to the patients by decreasing ICP (decompression effect of craniectomy / durotomy). In addition it may render the patient a better candidate for other therapy (e.g. radiation therapy) (LeCouteur 1999; Dewey et al 2000).

Radiation therapy

Experience in veterinary radiation oncology indicates that many patients with brain tumours benefit from radiation treatment, both when it is used as an adjunctive therapy to surgery, or as the sole definitive therapy for mass lesions that are difficult to access surgically, such as brainstem, pituitary tumours and both rostral and caudal fossa tumours located on the floor of the calvarium (Gavin et al 1995, Kraus & McDonnell 1996; Burk & Giel 1997; LeCouteur 1999; Dewey et al 2000).

Radiation therapy is most effective at controlling tumour growth and only rarely will eradicate the tumour completely (Bagley & Gavin 1998); brain tumours are defined as "moderately radiosensitive" meaning that treatment by radiation therapy alone is most often palliative (Thrall 1997; Blackwood & Dobson 1998; Smith et al 2000). However, as CNS tumours generally have a low metastatic potential, local control offers potential benefits (Gavin et al 1995).

External beam, megavoltage irradiation is currently recommended for the therapy of brain tumours in dogs (LeCouteur 1999; Dewey et al 2000). Other modalities of delivering radiation therapies have been described including brachytherapy (Heidener et al 1991; Evans et al 1993; Gavin et al 1995); Boron Neutron Capture Therapy (BNCT) (Gavin et al 1994; Bagley et al 1999b; Coderre & Morris1999); X-ray phototherapy (XPT) (Iwamoto et al 1990; Norman et al 1991; Iwamoto et al 1992; Norman et al 1997).

Chemotherapy

Cytotoxic drugs have had a limited role in the treatment of intracranial neoplasia in dogs mainly because of their poor ability to cross the blood-brain barrier, even when its permeability is increased by the presence of a tumour.

In some tumours, primarily those of glial origin, some control has been achieved with the use of nitrosourea compounds (lomustine and carmustine), but the survival time was not significantly increased in comparison to animals receiving only supportive therapy. However

the data reported is incomplete and does not allow objective evaluation of efficacy of these drugs (Cook 1990, Dimski & Cook 1990; Fulton & Steinberg 1990).

Table 13. Treatment modalities for brain tumour in dogs

Supportive therapy

Corticosteroids[14]

Anticonvulsants

Phenobarbitone and Potassium Bromide[8]

Definitive therapy

Surgery

a) Meningiomas
   Usually benign and poorly invasive[13, 14]
b) Gliomas
   Usually malignant and invasive[13,14]
c) Pituitary tumours
   potentially accessible to a skilled surgeon[9, 15, 16]
d) Osseous tumours of the skull
   potentially excisable even if malignant provided localized[13]
e) Metastatic and multicentric tumours in the brain
   Usually not surgical but removal of a solitary metastatic lesion might be considered[13]
f) Nasal and orbital tumours
   once in the brain usually hopeless[13]
g) Dermoid/epidermoid cysts
   Slow growing and excisable if accessible[13]
h) Intracranial granulomas
   Slow growing and excisable if accessible[13, 10]

Radiation therapy

a) Focused radiation
   Orthovoltage (X-rays)[1,3,4] and Megavoltage (X-rays or γ-rays)[12,13,14] linear accelerator
   Cobalt 60 teletherapy units[3,6]
   Boron neutron capture[11]
b) Whole brain radiation
   (only for GME[10])
c) Hypoxic cell sensitizers (with radiation therapy)[5]

Chemotherapy

a) carmustine (BCNU)[2]

[1]Turrel et al 1984; [2]Fulton & Steinberg 1990; [3]Heidner et al 1991; [4]Evans et al 1993; [5]Moore et al 1996; [6]Burk & Giel 1997; [7]Bagley & Gavin 1998; [8]Boothe 1998; [9]Lantz et al 1988; [10]Muñana & Luttgen 1998; [11]Bagley 1999; [12]Brearley et al 1999; [13]LeCouteur 1999; [14]Dewey et al 2000; [15]Meij 2000b; [16]Meij 2000a

Aims of dissertation

The goal of this dissertation is to examine seizures as a manifestation of intracranial disease in the dog and in particular to consider how the presenting features of a patient reported to have seizures may alert a clinician to the possibility of intracranial neoplasia. Such patients benefit from intracranial imaging in their assessment but because of the relatively limited availability of the relevant technologies and their associated costs the decision to seek such investigation may require some justification for an owner.

Case Assessment Protocols

Case selection

The sixteen canine clinical cases presented in this dissertation were selected from those referred to the Neurology Service of the Small Animal Hospital at the University of Glasgow Veterinary School (UGVS). Accessions included were seen during the period October 1999 to September 2000 and are patients referred for investigation of seizure disorders and / or neurological abnormalities other than seizure activity suggestive of intracranial disease.

Investigation of cases

Clinical assessment

The signalment was obtained in all cases. The historical details described include information from the referring veterinary surgeon and the owner. All cases underwent a full physical examination. A neurological examination was performed, as detailed by Oliver *et al* (1993a), including a fundic examination. For both physical and neurological examination only significant abnormal findings are described, though unremarkable findings were recorded.

History and physical examination

History taking and physical examination followed the standardised form in use in the Small Animal Hospital at UGVS (see Figure 1 (history), page 41; Figure 2, page 42).

Further questions were asked of the owner(s) as appropriate. Specifically, owners of dogs presented for evaluation of seizures were questioned about: any similar episodes; any traumatic incidents; exposure to toxins; behavioural changes; the nature of the seizures, including events that might have occurred before or after the seizure(s), changes in consciousness, pattern of muscle activity, urination / defecation, and duration. Seizure pattern was defined by questioning the owner about seizure frequency; particular note was made of any perceived change in the pattern of seizures. The owners where also asked if they had noticed any correlation between seizures and time of the day and/or activity (feeding, sleeping, exercise, etc).

MEDICAL HISTORY

LENGTH OF TIME IN OWNERS' POSSESSION	
WHERE OBTAINED	

1. CHIEF COMPLAINT	
2. PRESENT ILLNESS Onset/duration First signs/progression Treatment	
3. PAST HISTORY Ownership Past illnesses Surgery/trauma Vaccinations/dates	
4. DIET & ENVIRONMENT Food/type amount Housing/exercise General environment Other animals	
5. SYSTEM REVIEW A General B Integument C Eyes, ears, nose, throat D Musculoskeletal E Cardiovascular F Respiratory G Gastrointestinal H Genito-urinary	

Figure 1. UGVS Small Animal Hospital standardised history form

PHYSICAL EXAMINATION

General Appearance			
Weight	Temp	Pulse	Resp
Hydration			

SYSTEM	PHYSICAL FINDINGS	SYSTEM	PHYSICAL FINDINGS
1. Mucous Membranes ❑ Normal ❑ Abnormal		8. Circulatory ❑ Normal ❑ Abnormal	
2. Ears ❑ Normal ❑ Abnormal		9. Respiratory ❑ Normal ❑ Abnormal	
3. Skin Mamm Glands ❑ Normal ❑ Abnormal		10. Digestive ❑ Normal ❑ Abnormal	
4. Lymph Nodes ❑ Normal ❑ Abnormal		11. Abdominal Palpation ❑ Normal ❑ Abnormal	
5. Musculoskeletal ❑ Normal ❑ Abnormal		12. Genital ❑ Normal ❑ Abnormal	
6. Neural ❑ Normal ❑ Abnormal		13. Urinary ❑ Normal ❑ Abnormal	
7. Eyes ❑ Normal ❑ Abnormal		14. Rectal ❑ Normal ❑ Abnormal	

COMMENTS

Figure 2. UGVS Small Animal Hospital physical examination form

If, at the time of presentation, the animal was on anti-epileptic medication dose regimen and time of administration were recorded; this information providing an early indication regarding adequacy of dose and management from both the point of design and implementation.

All clients with a dog presented for evaluation of neurological abnormalities other than seizures, or whose animal manifested other neurological signs in addition to seizures, were questioned about period of time for which such signs had been present and the progression of signs during this time. In addition, response to any medication started at the referring veterinary practice was noted, with particular regard to systemic steroid medication.

Neurological examination

A full neurological examination was performed and results recorded in a standardised form in use at UGVS (see pages 44-45).

In the consulting room while the history was taken, the animals were allowed to interact unimpeded with the environment to evaluate mentation, posture, gait, response to visual, auditory and tactile stimuli, and the presence of behavioural abnormalities such as circling, pacing, and head pressing. The gait was evaluated for lameness, co-ordination and weakness.

The proprioceptive, strength and reflex tests outlined on the neurological examination form (page 44) were undertaken to further characterise any deficits or abnormalities in gait and posture. The specific goal was to characterise any abnormalities as to whether they involved spinal cord / neuromuscular disease or were of likely intracranial origin. Strong indicators of intracranial disease were thought to be conscious proprioceptive abnormalities with otherwise normal gait and proprioceptive deficits in association with specific cranial nerve abnormalities.

University of Glasgow Veterinary Hospital
Neurological Examination

Date _____
Student _____

Attach Label Here

1) *SUBJECTIVE* .....
.....
.....

2) *OBJECTIVE*

Observation

Mental	Alert		Depressed		Disorientated		Stupor		Coma
Posture	Normal		Head Tilt		Tremor		Falling		
Gait	Normal		Ataxia		Stiffness		Dysmetria		Circling
Limbs affected	Pelvic Limbs		Tetra		Hemi		Mono		
Other (e.g. fits)									

Key: 4=exaggerated, clonus; 3=increased; 2=normal; 1=decreased; 0=none; NE=not evaluated

Weakness	Left Fore	Right Fore	Left Rear	Right Rear
Hopping				
Wheelbarrow				
Ext. postural thrust				
Hemistand/walk				

Proprioception	Left Fore	Right Fore	Left Rear	Right Rear
Paw Position				
Reflex Step				
Hip Sway				
Placing-tactile				
Placing-visual				

UMN or LMN	Left Fore	Right Fore	Left Rear	Right Rear
Muscle Bulk				
Muscle Tone				
Ext. Carpi Rad.				
Patellar				
Pedal				

Panniculus and Sacral Segments

Panniculus	Cut-off		If Yes: Level on L		Level on R	
Anal reflex	Left		Right			
Tail	Voluntary movement					
Bladder	Control		Bladder size		Ease of expression	

Pain

Hyperaesthesia	Cervical		Thoracic		Lumbar		L-Sacral	
Superficial Pain	L-Fore		R-Fore		L-Hind		R-Hind	
Deep Pain	L-Fore		R-Fore		L-Hind		R-Hind	

Figure 3. Neurological examination form from UGVS – general observation and cord tests.

Cranial Nerves

	L	R
Vision 2		
Menace 2,7		
PMR - stim L 2,3		
PMR - stim R 2,3		
Pupil size 2,3,Symp.		
Fundic Exam		
Vest. eye move.		
Strabismus 8,3,4,6		
Nystagmus 8,3,4,6		

	L	R
Facial Sens. *max*		
mandibular		
ophthalmic 5		
Mast. muscle 5		
Facial muscle 7		
Palpebral 5,7		
Gag 9,10		
Tongue 12		
Sympathetic		

Comments CN

Summary of Neurological Exam: .....

.....

.....

) ASSESSMENT

.ocation:

		location:
Peripheral NS		
Neuromuscular		
Spinal Cord	C1 to C5	
	C6 to T2	
	T3 to L3	
	L4 to S1	
	S1 to S3	
Brain	Forebrain	
	Brain Stem	
	Vestibular	central? peripheral?
	Cerebellar	
Normal		

ustification for localisation: .....

.....

.....

) PLAN

ifferential Diagnoses:

. .....
. .....
. .....
. .....
. .....

Tests:

1. .....
2. .....
3. .....
4. .....
5. .....

Figure 4. Neurological examination form from UGVS – cranial nerves and localisation.

The cranial nerve examination outlined on the neurological examination form (page 45) was undertaken to further characterise any deficits or abnormalities in the function of structures of the head, head position and posture. The pattern of abnormalities was further used as evidence for intracranial localisation to the two major anatomical divisions of the brain (rostral and caudal fossa). Strong indicators of forebrain disease were abnormalities of visual pathways thought not to be of retinal origin. Strong indicators of brainstem dysfunction were specific deficits of cranial nerves III-XII, thought not to be peripheral in nature. A full fundic examination was provided by the Ophthalmology Service if required.

Based on these findings the pathologic process was ascribed as affecting the forebrain, the brainstem or the cerebellum; alternatively, the author referred the neuroanatomical localisation as to the forebrain, midbrain or hindbrain. In some cases the lesion was characterised as multifocal or diffuse.

Lesion localisation, history and signalment were used to logically establish a list of differential diagnoses and plan further diagnostic work-up accordingly.

Ancillary investigations

Further diagnostic procedures were performed in all cases in order to rule out other potential causes of the clinical signs (with particular regard to extracranial causes of seizures and/or primary extracranial neoplasia) and to evaluate general health prior to anaesthesia. The full details of the diagnostic evaluation of each case is summarised in Table 18 (page 122).

Clinical pathology

Haematology, biochemistry, and urinalysis panels

Routine haematological and biochemical evaluation was performed in all cases. Results of pre-referral investigations were used if this was recent and appropriate. Urinalysis was performed as indicated. Parameters analysed, results of all tests and reference ranges quoted by the UGVS laboratories and specialist laboratories used by them are reported in Table 20 (page 126).

Serology

Serology was undertaken on serum and CSF samples.

Distemper antibodies were measured by a standardised neutralisation technique[2]. Toxoplasma antibodies titres were determined using a dye test[3]. *Neospora caninum* antibodies were detected using an indirect fluorescent antibody test (IFAT) and the titres determined using a standardised neutralisation technique[4].

Evaluation of pituitary and thyroid function

Investigations varied with individual cases.

An ACTH[5] stimulation test was used in the assessment of rostral lobe pituitary function. Serum cortisol concentration was determined before, and at 30 minutes after intravenous administration of 0.25 mg of tetracosactrin (Synacthen, Alliance Pharmaceuticals Ltd) (Herrtage 1998a)

Basal serum insulin-like growth factor (IGF-I) concentration[6] was measured as an indirect measure of growth hormone (GH) and as an indicator of increased rostral pituitary lobe function (Feldman & Nelson 1996, Herrtage 1998a).

Plasma thyroxine (T4) and thyroid stimulating hormone (TSH) were measured in conjunction as a technique for assessing for hypothyrodism (Herrtage 1998a).

Anticonvulsants

Serum phenobarbitone level was determined where indicated. In some cases, monitoring of the serum phenobarbitone level was also performed at the referring veterinary practice.

CSF analysis

See CSF analysis, page 49.

Diagnostic imaging

Conventional radiographic investigation

These were undertaken using an SMR Galaxy 15HF unit (SMR Medical Imaging, Blackpool, UK). The cassette systems were all rare earth (Quanata Fast Detail and Sterling Ultra Vision

[2] Canine Infectious Disease Research Unit, UGVS
[3] Scottish Toxoplasma Reference Laboratory, Raigmore Hospital NHS Trust, Inverness
[4] Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA
[5] Cambridge Specialist Laboratory Services, Stapleford, Cambridge CB2 5XY
[6] Cambridge Specialist Laboratory Services, Stapleford, Cambridge CB2 5XY

Rapid, Cronex) and an optimised radiographic film (Cronex Medical Xray film) was used. Films were developed using an automatic processor (Cronex CX-130).

In cases with suspected extracranial neoplasia and / or when considered indicated on the basis of the physical examination findings, conventional radiographic studies were undertaken. These included survey radiographs of chest, abdomen, vertebral column, nasal cavity, skull and distal limbs. Specifically, in cases with suspected extracranial neoplasia, left and right inflated views of the thorax were obtained to evaluate the lung field for metastatic disease.

Computed Tomography

All cases underwent computed tomographic (CT) studies of the brain and skull, using a third generation transverse slice CT unit (Excel 2400 Elite®, Elscint Ltd, Haifa, Israel). Dogs were positioned in sternal recumbency with the forelimbs pulled alongside the chest (so that the paws were outside of the imaging field of view) and the head extended and supported on a radiolucent headrest.

Scanning was undertaken at 120 KV, 300 mAs, with a 240 mm diameter scan field size, 256x256 image matrix, standard resolution and soft tissue reconstruction filter. A bed increment of 5mm and a 5mm slice width were selected to maximise the imaging of the brain parenchyma. If considered necessary areas of interest were rescanned using a bed increment and a slice width less then 5mm. The scanning area extended from the occipital protuberance to the cribriform plate, but in some dogs it was extended rostrally and / or caudally. Images were acquired using a scan angle of 360° and a scan time of 2 seconds.

Post-contrast scans were taken following intravenous administration of 2ml/kg of the non-diffusible iodinated compound sodium iothalamate- (70% weight/volume, 420 mg iodine/ml, Conray 420, Mallinckrodt Medical Ltd, Northampton, England, UK). Post-contrast slices were taken at the same levels as the initial study starting ~20 seconds after finishing delivering the contrast agent.

Images were reviewed using different windows (bone window) to highlight particular structures and contrast uptake. Sagittal and dorsal views were also examined to assess location of a lesion and its extent.

CT images were evaluated qualitatively for the presence of: a) areas of abnormal attenuation of soft tissue and bone, b) mass effect (e.g. displaced falx cerebri and / or distorted ventricular system) and c) abnormal contrast enhancement (Table 14, page 49). Changes in density were also assessed quantitatively (Tidwell 1999). The current literature describes general criteria that aid in identifying the nature of a space-occupying lesion and specifically describes the attributes of some common tumours (Kraft & Gavin 1999). The CT appearance of the most common intracranial tumour types are summarised in Table 15 (page 51). The CT findings for the cases presented in this dissertation are summarised in Table 19 (page 123).

Table 14. Imaging features used to characterise intracranial space-occupying lesions

Number	Singular or multiple
Axial origin	Extra-axial or Intra-axial
Anatomic site	Specific anatomic location (sella, nasal passages, dura, ventricular system, cerebrum)
Shape	Ovoid to spherical, lenticular, broad-based, lobular, plaque-like, amorphous or infiltrative
Margins	Smooth or irregular; well-defined or poorly defined
Pattern of growth	Growth displacing, or replacing adjacent structures, and growth extension (mass effect)
Density	Hypodense, isodense, hyperintense
Contrast enhancement	Intensity (none, mild, moderate, strong) and pattern (uniform, non-uniform, or ring)
Other pathological features	Evidence for hydrocephalus, oedema, haemorrhage, necrosis, mineralisation, hyperostosis, osteolysis, cysts

CSF analysis

CSF samples were collected, if thought to be of potential diagnostic value, from patients where any perceived risk was felt justified. Although, CSF parameters are often altered by the presence of brain tumours, in most instances the abnormalities are non-specific and often only of value in supporting other findings (Bailey & Higgins 1986; Dewey et al 2000; Webb & Muir 2000). CSF analysis is of particular value in identifying evidence of inflammation and possible tumour identification, following cytology (Christopher et al 1988; Grevel & Machus

1990; Kraus & McDonnell 1996). The potentially low diagnostic yield and the risk of herniation associated with taps in patients with raised ICP means that at UGVS CSF analysis follows intracranial imaging. The presence of an intracranial mass and /or clinical evidence of increased ICP usually precluded a tap. The anaesthetic protocol followed was designed to minimise risks associated with raised ICP (see Anaesthetic protocols page 50). If a tap was undertaken in a case with suspected raised ICP the patient was hyperventilated prior to sampling and mannitol (Mannitol intravenous infusion BP 20% w/v, Galen Research Laboratories Ltd) administered.

CSF was collected from the cerebellomedullary cistern (Rusbridge 1997) using a 3 inch 20 or 22 gauge spinal needle selected according to patient size (Yale® Spinal, BD, Spain). The collection site was clipped and aseptically prepared and the operator wore gloves. Samples were inspected immediately for colour, consistency and turbidity.

The cell count was performed using a haemocytometer. A differential cell count was determined following cytocentrifugation (cytospin). Cytospins were performed by centrifuging 0.5-0.75ml of CSF for 5 minutes at 750 rpm with a Cytospin3 R[7]; the supernatant was pipetted off and the pellet resuspended in a drop of serum. A smear of this was stained with Diff-Quick and examined.

Total protein concentration was determined colourmetrically by diluting the CSF sample in a ratio of 1:3 with 3% sulphosalicylic acid; after 5 minutes the absorption at 660nm was compared to that of the acid alone.

Anaesthetic protocols

Radiographic, CT examinations and CSF sampling were performed under general anaesthesia. Below is an anaesthetic technique that is currently in use at UGVS to anaesthetise dogs with suspected intracranial disease. Slightly variable anaesthetic regimens were used depending upon an individual patient's requirements. In patients with deteriorating cranial neurological status, the ideal anaesthetic agent should provide general anaesthesia while reducing cerebral metabolic rate, maintain cerebral perfusion and arterial oxygenation, and should not promote either cerebral vasodilation or seizures.

[7] Shandon Scientific Limited, Astmoor, Runcorn, Cheshire, WAT 1PR, England

Table 15. CT appearance of the most common intracranial tumours in the dog

	Meningioma	Choroid plexus papilloma	Pituitary tumours	Nasal adenocarcinoma	Astrocytoma	Oligodendroglioma
Occurrence	Singular rarely multiple	Singular may seed other areas	Singular	Singular	Singular	Singular
Anatomic site	At dura of calvarial floor, lateral convexities or falx, especially rostral fossa; occasionally within ventricular system or hypophyseal fossa or at cerebello-pontine and pontine regions	Associated with ventricular system: especially IV vent. but also III and lateral ventricles less commonly at interventricular foramen Relatively frequent at the cerebello-pontine angle	Hypophyseal fossa; macroadenomas extending into suprasellar or parasellar regions microadenomas usually not detected by CT	Caudal nasal passages with intracranial extension through the cribriform plate	Brain matter of rostral, middle or caudal fossa; (especially rostral fossa) Occasionally leptomeningeal	Brain matter of rostral, middle or caudal fossa (especially rostral fossa)
Margins	Smooth to irregular, varying from well to poorly defined	Distinct, lobulated to irregular	Distinct, smooth to irregular	Indistinct, smooth to irregular	Distinct to poorly defined and irregular	Indistinct, smooth to irregular
Shape	Spherical to ovoid, broad-based, lenticular or plaque-like; dura tail sign may be present	Spherical to ovoid	Spherical to ovoid (adenoma) Broad-based (adenocarcinoma)	Ovoid to amorphous	Ovoid to amorphous mass or focal to diffuse infiltrate	Ovoid
Pattern of growth	Displaces or compresses normal adjacent structures	Displaces or compresses ventricular anatomy	Displaces or compresses normal structures (especially hypothalamus and/or thalamus)	Invasive, thorough cribriform plate; possible displacement or compresses normal structures	Invasive	Invasive
Pre-contrast density	Isodense to hyperdense occasionally hypodense	Isodense to hyperdense	Isodense to hyperdense	Isodense, occasionally slightly hypo- or hyperdense	Extremely variable: hypodense to isodense to hyperdense	Hypodense to isodense
Enhancement	Strong and uniform, occasionally ring-like or non-uniform	Strong and uniform	Mild to strong, uniform (adenoma) or non-uniform (carcinoma)	Mild to strong, non-uniform	None to strong; uniform to non-uniform or ring enhancing	
Oedema	None to mild to extensive	None to mild	None to mild	Severe to extensive	Mild to extensive	None to mild
Other features	Occasionally cyst or less demarcated fluid accumulation Calcification Hyperostosis Hydrocephalus	Haemorrhages Calcification Hydrocephalus	Single or multiple cystic regions; Haemorrhages Hydrocephalus	Single or multiple cystic regions Calcification	Focally distorted, disrupted lateral ventricle(s) Haemorrhages Necrosis Calcification Hydrocephalus	Focally distorted, disrupted lateral ventricle(s) Haemorrhages

Kornegay 1990; Kraft 1990; Fike et al 1981; LeCouteur et al 1981; Turrel et al 1986; Moore et al 1991; Voges & Ackerman 1995; Wolf et al 1995; Thomas et al 1996

Patients were premedicated with pethidine (2 mg/kg IM) (Pethidine, Martindale); no premedicant was administered if the patient was obtunded and / or easy to handle. Prior to induction the animals were pre-oxygenated by facemask with 100% oxygen for 5 minutes and administered 1 mg/kg IV of lignocaine (Lignavet, C-Vet Veterinary Product). Lignocaine administration was followed by induction with diazepam (0.2-0.5 mg/kg IV) (Diazemuls, Dumex^{POM}) and thiopentone (Intraval sodium, Merial) or propofol (Rapinovet, Schering-Plough Animal Health) to effect. Maintenance was with low concentration of isoflurane (IsoFlo® vet, Schering-Plough Animal Health) in 100% oxygen. Patients were ventilated from immediately after induction until procedure completed. During the whole procedure, patients were carefully manipulated and positioned to avoid jugular compression, as this increases ICP.

Cerebral blood flow (CBF) is largely influenced by cerebral perfusion pressure (CPP), which is the difference between arterial blood pressure and ICP, and arterial blood gas tensions. Characteristic of cerebral blood vessels is the ability to alter their resistance in response to change in CPP. Via this mechanism of "autoregulation" CBF is maintained relatively constant within a wide range of arterial blood pressure values. Disease states and volatile anaesthetics affect cerebral autoregulation (Bedford 1991; Bagley 1996a).

In patients with progressively increasing ICP the most important sequel is the reduction in CPP that may lead to cerebral ischaemia. ICP may be manipulated by changing CBF and / or brain hydration (mannitol, frusemide). Mannitol (1.0 g/kg IV over 20 minutes) was administered prior to anaesthesia only in cases with strong evidence of increased ICP and / or deteriorating neurological status thought to be related to increasing ICP. Vomiting can increase ICP and drugs that are emetic are avoided. Pethidine was chosen as premedication agent because it does not induce vomit, does not depress respiratory function and is short-acting. Coughing and hypertension at intubation also increase ICP thus lignocaine administration was used to deepen anaesthesia and reduce these effects (Hamill et al 1981).

Diazepam was administered prior to thiopentone and propofol to reduce the dose of these two anaesthetic agents, as well as for its anti-epileptic properties. Thiopenthone and propofol (especially thiopentone) may in fact decrease arterial blood pressure by a larger extent than ICP thus increasing the risk of cerebral ischaemia. Benzodiazepines also decrease the incidence of propofol induced myoclonus (Golder 1999).

Thiopentone and propofol are chosen as induction agents in patients with increased ICP because they induce a marked reduction in cerebral metabolic rate while maintaining cerebral vascular responsiveness to changes in mean arterial blood pressure and PaCO2. Conversely, inhalation agents depress vascular autoregulation and this may result in a deleterious additional increase in ICP. This effect is much greater with halothane than isoflurane. Controlled ventilation of the patient from after induction, through the entire procedure reduces the effect of the inhalant agent on CBF (Nakaichi et al 1996). CBF, in fact, varies directly with PaCO2 and indirectly with PaO2; ICP falls within minutes of the onset of ventilation. However, PaCO2 does not have to be reduced below 25mmHg; at this point the vasoconstrictor effect of hypocarbia itself will cause hypoxia, and ischaemic cell damage (Golder 1999).

Close monitoring of the patient is required during and after contrast medium administration as haemodynamic changes occur and anaphylactoid reaction is possible. Reported haemodynamic effects include an initial increase followed by a decrease in arterial blood pressure, increased central venous pressure, increased cardiac output, and decreased systemic vascular resistance (Robertson 1999). A secondary effect of the increased plasma osmolarity is diuresis, leading to further alterations in fluid balance. During the whole procedure animals are administered intravenous fluids at maintenance rate. Lactated ringers may be used as a maintenance fluid, however it is hyponatremic relative to normal canine plasma, so isotonic saline is usually employed.

Management

From the history, clinical findings and results of further investigations, a diagnosis was made, a prognosis developed and treatment instigated as appropriate. The details are given for each case in the chapter Case Reports (page 55) and summarised in Table 17, page 119.

Therapeutic protocols

In all cases that were treated, therapy was instigated after discussion with the owner and modified if necessary in respect of their specific ambitions. At UGVS palliative therapy for intracranial neoplasia consists of anti-inflammatory doses of oral corticosteroids, with anticonvulsants as required.

The anti-inflammatory regimen used consists of oral prednisolone (Prednidale 5-Arnolds®, Arnolds Veterinary Products, Ltd) at a dose of 1 mg/kg/day for the first two weeks; the total daily dose divided in two doses separated by 12 hours. After this period, the dose was tapered to 0.5 mg/kg/day, administered once a day. However, this protocol was modified depending on patient response.

Anticonvulsant therapy consisted of phenobarbitone (Phenobarbitone tablets BP 15 or 60mg, Approved Prescription Services, Ltd) at initial dose of 4-6mg/kg/day, divided in two doses separated by 12 hours. Serum levels were measured as appropriate.

Post mortem

In five cases euthanasia was performed followed by post mortem examination. Gross post mortem examination was performed and the brain removed within 30 minutes of death. Brains were stored in a minimum of ~10x their volume of 4% buffered neutral formalin. Histological evaluation was initially made on routine haematoxylin and eosin preparations. Other special stains and immunostaining were undertaken as indicated to pursue definitive identification of tumour type.

Case reports

Index of cases

The clinical, ancillary and in some cases, pathological findings of sixteen selected canine clinical cases are detailed. Relevant information is reported in the description of each case; diagnostic investigation, management and outcome are summarised in Table 18 (page 122) and in more detail in Table 17 (page 119). In cases where precise indication of the medication the animal was on prior to referral is not reported is because this information was not available.

Table 16. Summary of patients' details

Case	*Breed*	*Age*	*Presenting sign(s)*	*Diagnosis*
1 (138470)	Border collie	14 yrs	Isolated, generalised, tonic-clonic seizures	Space-occupying lesion forebrain with nasal cavity involvement [C]*
2 (139044)	Collie-X	6 yrs	Clustered generalised, tonic-clonic seizures, behavioural changes	Space-occupying lesion forebrain with nasal cavity involvement[C]
3 (140763)	Lurcher	9.5 yrs	Clustered, generalised, tonic-clonic seizures	Space-occupying lesion forebrain [C]
4 (139076)	Collie-X	11 yrs	Seizure activity? unsteadiness, behavioural changes	Multiple space-occupying lesions: forebrain and rostral caudal fossa[C]
5 (140363)	Golden retriever	7 yrs	Clustered, generalised, tonic-clonic seizures, behavioural changes	Space-occupying lesion forebrain [C/P*]
6 (140354)	Boxer	6.5 yrs	Isolated, generalised, tonic-clonic seizures, behavioural changes	Space-occupying lesion forebrain with midbrain involvement [C/P]
7 (139916)	Labrador retriever	3.5 yrs	Clustered, generalised, tonic-clonic seizures, behavioural changes; mild ataxia	Space-occupying lesion hindbrain with forebrain metastasis [C/P]
8 (139452)	Golden retriever	11 yrs	Isolated, generalised, tonic-clonic seizures, behavioural changes	Hydrocephalus and intracranial arachnold cyst [C]
9 (138951)	Border collie	3.5 yrs	Isolated, generallsed, tonic-clonic seizures, behavioural changes	Idiopathic epilepsy [C]
10 (140277)	X-breed	7 yrs	Isolated, generalised, tonic-clonic seizures	Idiopathic epilepsy [C]
11 (139250)	Labrador retriever	5.5 yrs	Behavioural changes, ataxia, blindness?	Space-occupying lesion forebrain [C]
12 (139254)	Cairn terrier	9.5 yrs	Behavioural changes, ataxia, 'absence ' periods and absent pupillary light reflexes	Space-occupying lesion forebrain with midbrain involvement [C]
13 (139848)	Rough collie	8 yrs	Collapse, profound obtundation	Space-occupying lesion forebrain with midbrain involvement [C/P]
14 (138568)	Bullmastiff	2.5 yrs	Dysphagia, ataxia, vestibular signs	Hindbrain neoplasia and megaesophagus [C/P]
15 (139359)	Weimaraner	11 yrs	Ataxia, intermittent head tilt	Space-occupying lesion hindbrain [C]
16 (138763)	Boxer	7 yrs	Behavioural changes, weight loss, increased appetite, polydipsia/polyuria and enlarged extremities	Pituitary macroadenoma and acromegaly [C]

*[C] indicates clinical diagnosis; [P] indicates pathological diagnosis

Case 1: No. 138470

Signalment: Border collie, male entire, aged approximately 14 years, weight 27.5 kg

Diagnosis: mass lesion rostral forebrain, involving the right frontal lobe of the cerebrum and the right olfactory bulb, extending through the cribriform plate into the caudal aspect of the nasal cavity.

History

The dog was presented with a history of isolated, generalised, tonic-clonic seizures of approximately five months duration, occurring with a frequency of approximately one a month. The frequency of seizures had increased in the two weeks preceding referral. The case history did not give precise indication of the increased frequency of seizures. According to the owner the dog was otherwise normal between seizures. At the time of presentation the dog was on no anticonvulsant medication.

Physical examination

On physical examination the dog was bright and alert, with no significant clinical findings other than a bilaterally stiff hindlimb gait due to established and NSAIDs-responsive osteoarthritis (carprofen, Rimadyl™–Pfizer, Animal Health, Ltd). A full neurological examination failed to demonstrate any abnormalities. Based on the history, forebrain dysfunction was identified. Primary or secondary brain neoplasia, degenerative or inflammatory brain diseases were considered the most likely diagnoses.

Investigations and provisional diagnosis

The standard protocol for investigation of seizure disorders was performed.

The pre-contrast CT images of the skull and brain demonstrated the presence of a solitary, hypodense mass located in the right rostral cranial cavity, at the level of the frontal cortex, extending to the olfactory bulb and involving the cribriform plate (Figure 5a, b). The mass, grossly ovoid shaped, produced a midline shift with left displacement of the falx cerebri, and appeared to be eroding through the lamina temporalis laterally, and into the frontal sinus dorsally (Figure 5c). On the post-contrast images a thin, irregular, poorly defined rim of enhancement was seen (Figure 5d).

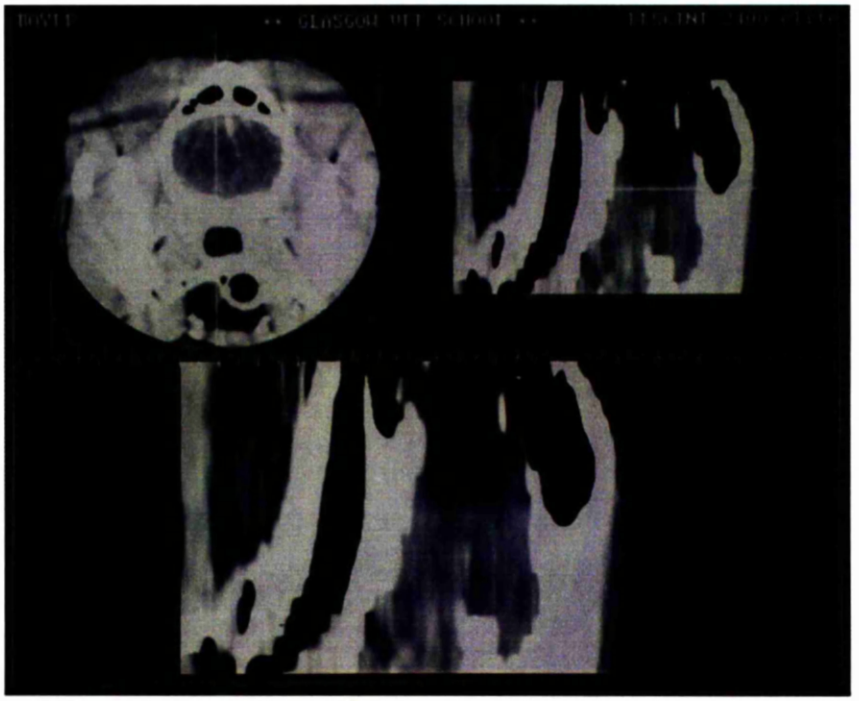
A diagnosis of an intracranial space-occupying lesion was made. Neoplasia was considered to be the most likely diagnosis because of the age of the patient and the evidence from the CT scan of bone lysis, suggesting an aggressive behaviour. Despite the apparent invasion of the nasal cavity, at the time of presentation, the dog did show neither nasal signs nor facial pain. The CT appearance was consistent with a meningioma or a primary nasal neoplasia extending caudally into the cranial vault. Oligodendroglioma and astrocytoma were also considered in the differential diagnosis.

Management and outcome

The size and erosive nature of the mass excluded the possibility of surgical excision. The position was such that radiation therapy carried the risk of significant acute ocular side effects[8], and the owner elected to manage the dog palliatively. The dog was discharged on anti-inflammatory doses of prednisolone (1 mg/kg/day), which resulted in control of seizure activity. No anticonvulsant therapy was initiated because the owner requested that they not be used.

The dog was seizure-free until the time of its death, which occurred suddenly 10 weeks after assessment at UGVS. The dog was found dead by the owner; neither seizure activity nor clinical signs of nasal cavity involvement had developed in the intervening period. No post mortem examination was performed.

[8] Dr J.M. Dobson, Department of Clinical Veterinary Medicine, The Queen's Veterinary Hospital, University of Cambridge Veterinary School



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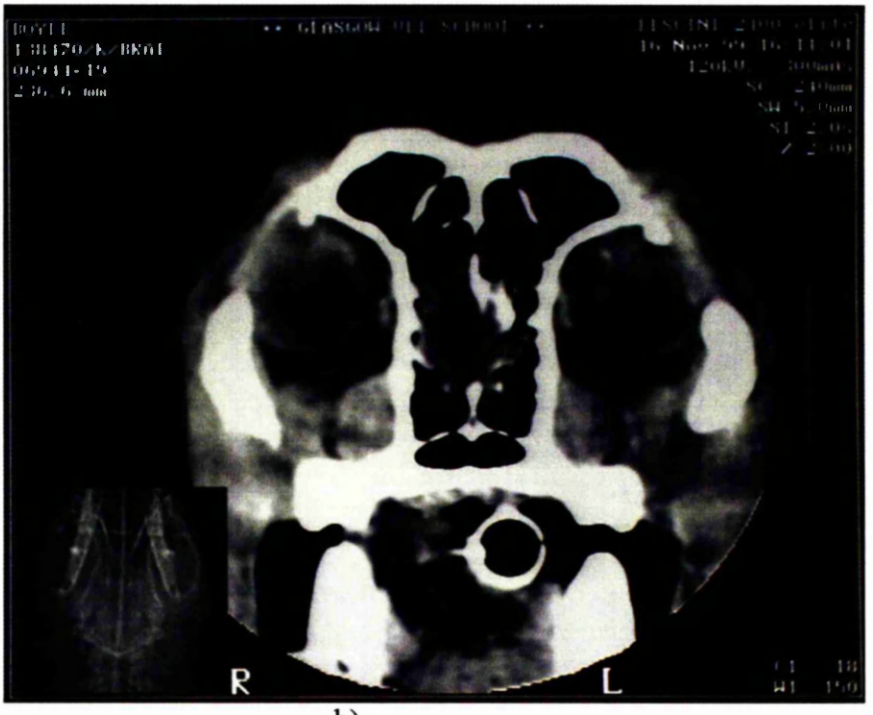
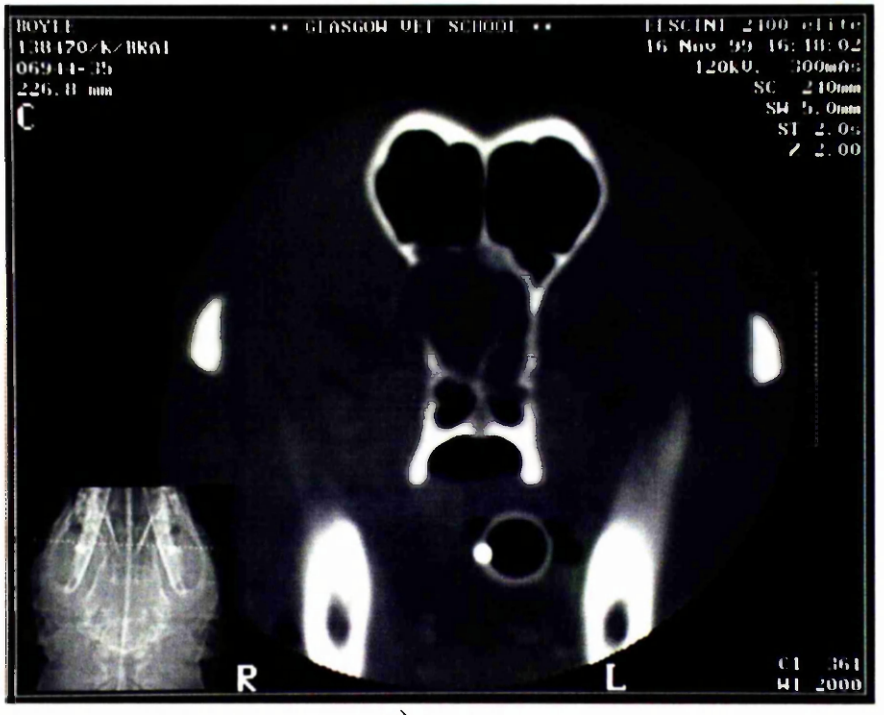


b)

Figure 5. Case 1, 138470. a) sagittal post-contrast image - note rostrally located hypodense mass with poorly defined enhancing peripheral rim and extension through the cribiform plate; b) transverse pre-contrast image at the level of the frontal sinuses - note soft tissue infiltration of the cribriform plate and displacement of the left olfactory bulb;



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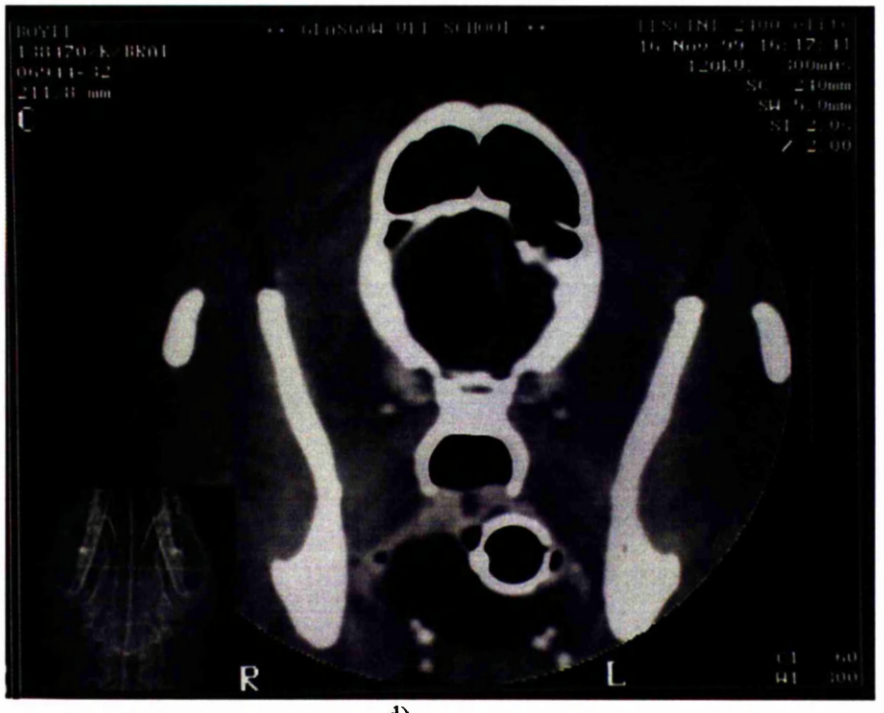


d)

Figure 5 (cont). Case 1, 138470. c) transverse post-contrast image at the level of the frontal sinuses - note osteolysis of the lamina temporalis laterally, the frontal sinuses dorsally and the displacement of the perpendicular lamina of the ethmoid; d) transverse post-contrast image at the level of the frontal lobe - a large, hypodense, non-enhancing mass lesion is present within the right frontal lobe; there is a poorly defined rim of enhancement and the presence of contrast in the falx cerebri emphasises the midline shift to the left.

Case 2: No. 139044

Signalment: Collie X, male entire, aged approximately 6 years, weight 17.5 kg

Diagnosis: mass lesion right frontal lobe and olfactory bulb extending through the cribriform plate into the caudal aspect of the right nasal cavity.

History

The dog was presented with a two-month history of generalised, tonic-clonic seizures, and behavioural changes consisting of lethargy, aggressiveness, and occasionally pacing, head pressing and circling. Initially the seizures were isolated in character and occurred with a frequency of once a week. Over the two weeks preceding referral, seizure activity had changed to cluster seizures occurring with a frequency of two to three episodes a week. In addition, the dog had a history of chronic sneezing and of apparent lumbar / caudal abdominal discomfort. The sneezing had lasted for approximately three months and had been unresponsive to antibacterial therapy. Ten weeks before presentation the dog had also been treated with delmadinone acetate (Tardak, Pfizer Ltd) for suspected prostatic hypertrophy.

Investigations prior to referral had concentrated on assessing potential extracranial causes of seizures. These investigations included routine haematology and biochemistry, bile acid stimulation test, plasma ammonia, serum phenobarbitone, plasma thyroxine, urinalysis, bacterial culture of the urine, radiology of the thorax, abdomen and spine, and abdominal ultrasound, all of which were unremarkable.

Treatment with phenobarbitone had been initiated about six weeks before referral to UGVS (3.5 mg/kg/day). Referral was precipitated by the increased frequency of seizures and the development of clusters, despite the increase of phenobarbitone to 8 mg/kg/day three weeks before presentation. Neurological assessment performed by the referring veterinary surgeon demonstrated multifocal central nervous system signs consisting of depressed mental status, pacing, circling to the right, absent consensual pupillary light reflex and decreased menace response on the right eye, reduced gag reflex and bilateral loss of nostril, ear and facial sensation.

Physical examination

At the time of presentation to UGVS there were no overt neurological deficits. The neurological impairment reported by the referring veterinary surgeon was most likely the manifestation of transient postictal effects. There was apparent lumbar / caudal abdominal pain and despite the dog sneezing several times in the consulting room, there was no evidence of nasal discharge, facial pain or swelling. Based on both history and physical examination findings a right-sided forebrain lesion was suspected. Primary and metastatic intracranial neoplasia were considered the most likely diagnoses.

Further investigation

On the basis of the history of suspected prostatic hypertrophy and the lumbar / caudal abdominal pain detected on examination, a rectal examination was performed and urine was taken for routine biochemistry and cytology, all of which were unremarkable. Lateral survey radiographs of the abdomen and of the spine were also unremarkable, as well as the CT of the lumbo-sacral joint. These results ruled out both secondary neoplastic CNS / lumbosacral area involvement and disease of the lumbosacral joint as the cause of the dog's abdominal and spinal hyperpathia.

On the basis of the history of chronic sneezing a ventral 20° rostral-dorsocaudal oblique open mouth (V20° Ro-DCd) view of the nasal cavity was taken. A subtle loss of ethmoid turbinate pattern and outline of the cribriform plate, next to a small area of soft tissue opacity in the caudolateral aspect of the right nasal cavity was detected (Figure 6e).

The pre-contrast CT images of the skull and brain demonstrated the presence of a singular, eccentric, isodense to hyperdense mass in the right olfactory bulb and frontal lobe and evidence of bony destruction involving the cribriform plate (Figure 6c). The mass was associated with displacement of the falx cerebri to the left and appeared to extend through the midline to the left frontal lobe. The mass was grossly ovoid in shape and the margins varied from well to poorly defined (Figure 6a). Brain tissue displacement to the left was detectable from the level of the olfactory bulbs to the pituitary region. A better appreciation of the extension of the mass was obtained by sagittal reconstruction (Figure 6d).

In the post-contrast study the mass enhanced intensely and relatively uniformly (Figure 6b) and a predominantly right-sided contrast enhancing mass became visible in the caudal aspect

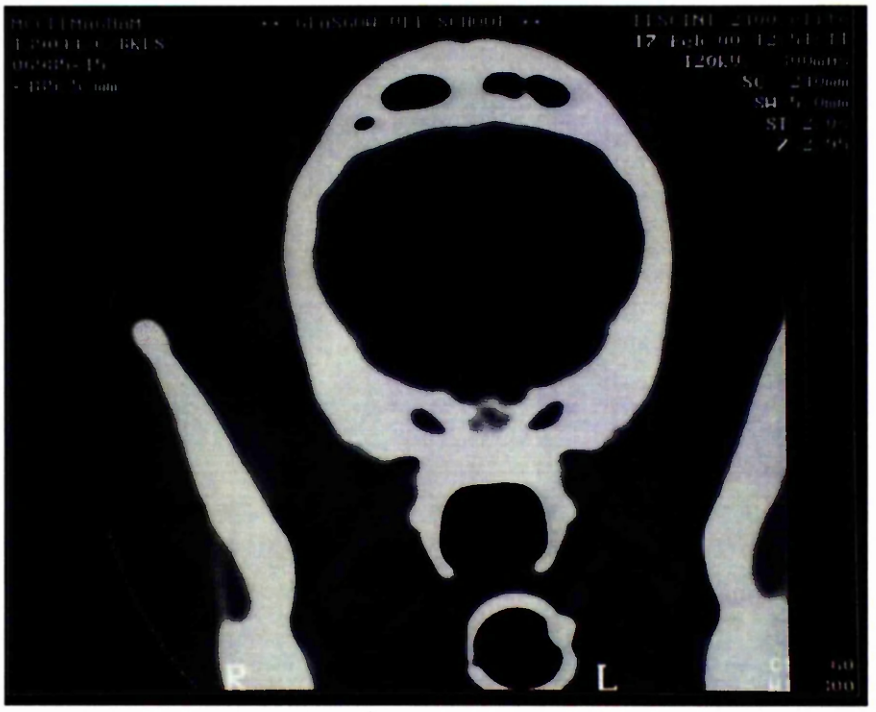
of the ethmoid turbinates. A diagnosis of a forebrain space-occupying lesion extending into the caudal portion of the right nasal cavity was made. Neoplasia was considered the most likely diagnosis. An attempt to obtain a biopsy specimen via the right nasal cavity was unsuccessful because of the position of the mass. Thus, it was not possible to establish if this was a primary brain tumour, which had secondarily involved the nasal passages or vice versa.

Management and outcome

The position of the mass was such that surgical excision was not possible and radiation therapy would have been likely to produce significant acute ocular side effects (Harris et al 1997). The owner elected to manage the dog palliatively. The dog was discharged on anti-inflammatory doses of prednisolone (1 mg/kg/day) in addition to the phenobarbitone (8 mg/kg/day).

On steroid medication the demeanour of the dog progressively improved over the following month, to the point where the dog was as active as before the seizures started and no longer aggressive, head pressing or pacing; the intensity and frequency of the sneezing had also decreased. The dog was seizure-free for eight weeks. Seizure activity recurred two weeks after the dose of corticosteroids had been tapered to 0.5 mg/kg/day. Despite increasing the prednisolone dose to the previous regimen (1mg/kg/day) seizure activity increased and other clinical signs such as lethargy, pacing and intense sneezing recurred suggesting that the palliative effects of the corticosteroids were waning, and that the mass was reaching a critical size.

The dog was euthanased approximately two weeks later (10 weeks after first assessment at UGVS) because of the development of status epilepticus; no post mortem examination was performed.



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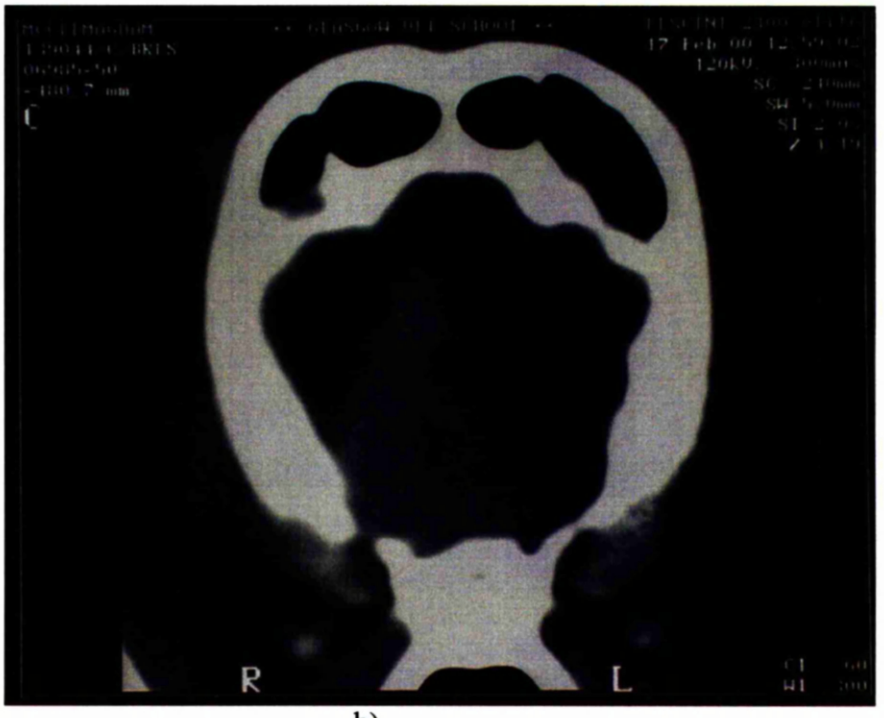
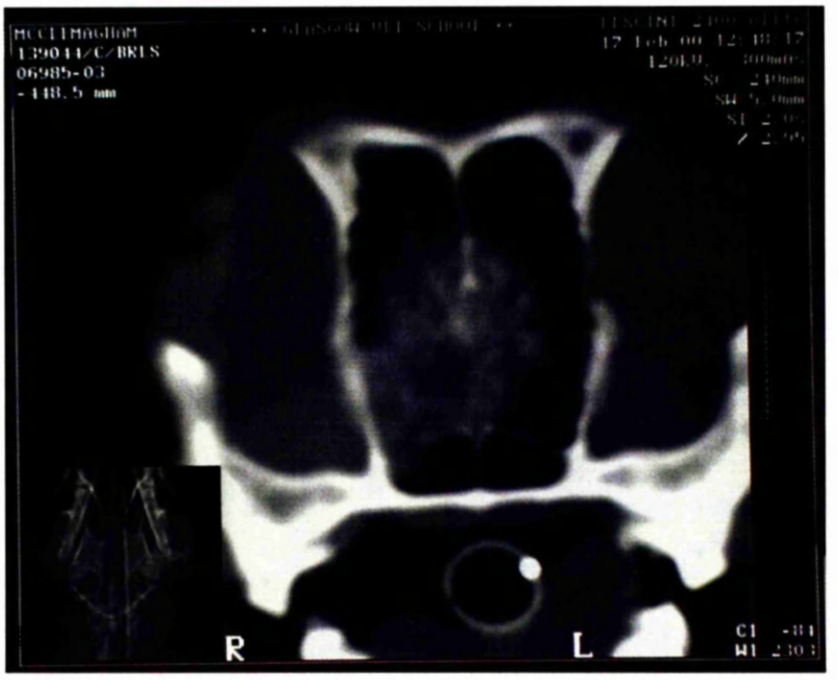


b)

Figure 6. Case 2, 139044. a) Transverse pre-contrast image at the level of the frontal cortex, an iso- to mildly hyperdense broad-based eccentric mass may be seen within the right olfactory and frontal lobe with displacement to the left of the falx cerebri; b) Transverse post-contrast image at similar level to a) uptake of contrast is intensive and uniform and emphasises the abnormalities present on the pre-contrast image;



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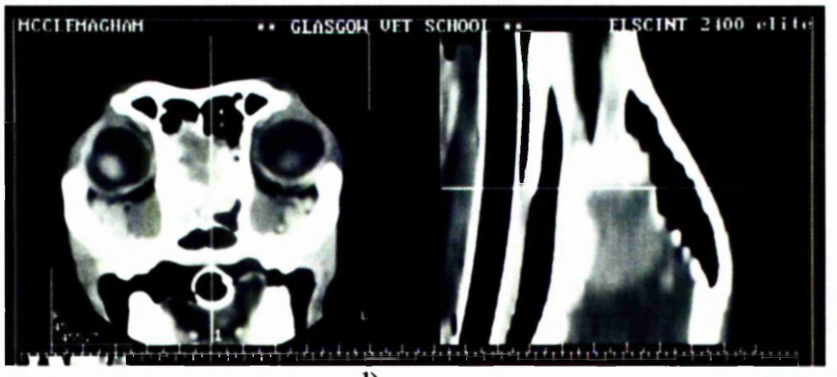

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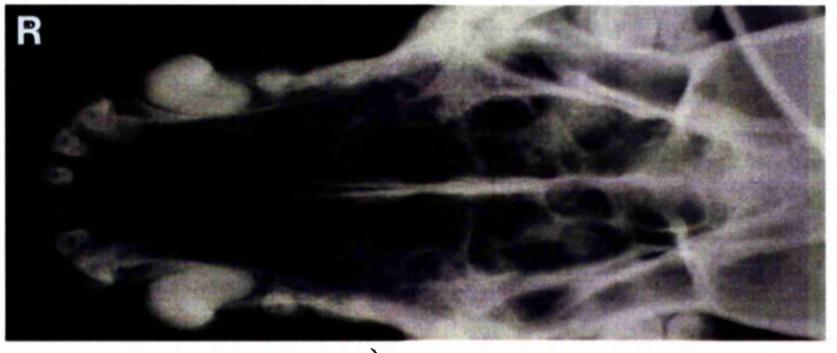


e)

Figure 6 (cont). Case 2, 139044. c) Transverse pre-contrast image at the level of the cribriform plate, abnormal soft tissue infiltrates through the right side of the cribriform plate destroying the turbinate pattern and partially the horizontal wing of the vomer; d) contrast enhanced sagittal image confirms involvement of caudal nasal and rostral cerebral structures; e) V20° Ro-DCd radiograph showing soft tissue opacity in the caudolateral aspect of the right nasal cavity, in addition to a subtle loss of ethmoid turbinate pattern and outline of the cribriform plate.

Case 3: No. 140736

Signalment: Lurcher, female entire, aged 9 years and 5 months, weight 18.0 kg

Diagnosis: mass lesion, right forebrain involving the frontal and olfactory cortex.

History

The dog was presented with approximately a two-month history of isolated, generalised, tonic-clonic seizures, the frequency of which had increased in the week preceding referral. The first two seizure episodes had been separated by an interictal period of seven weeks; a third seizure had occurred two weeks after the second. Referral was precipitated by the development of cluster seizures. Postictal signs consisting of disorientation and attention seeking characterised all seizure events, and lasted 10 to 15 minutes; the dog was otherwise normal between seizures. Routine biochemistry performed by the referring veterinary surgeon was unremarkable. At the time of presentation the dog was on no anticonvulsant therapy.

Physical examination

On physical examination the dog was bright and alert with no significant clinical findings. Based on the history a forebrain lesion was suspected. The most likely diagnoses were considered primary and secondary intracranial neoplasia; inflammatory or degenerative brain diseases.

Investigations and diagnosis

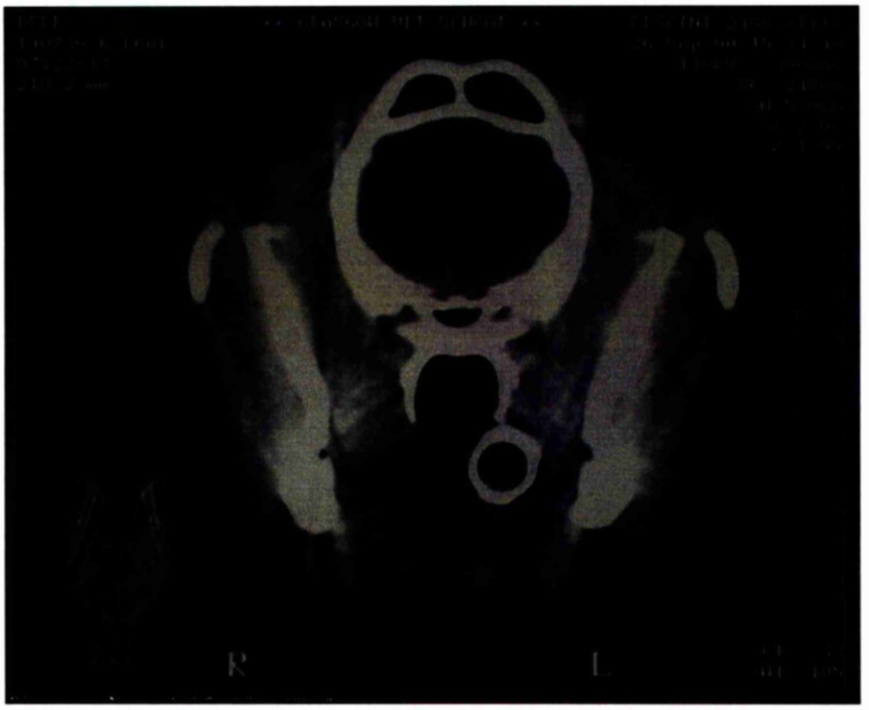
The standard protocol for investigation of intracranial disease and seizure disorders was performed.

The pre-contrast CT images of the brain and skull identified a deeply located area of hypodensity within the right frontal and olfactory lobes. This area was ovoid in shape, had poorly defined margins and appeared to extend cranially into the olfactory bulb. Mild displacement to the left of the falx cerebri was also detected (Figure 7a). On the post-contrast images a thin, poorly defined rim of enhancement was seen; contrast enhancement of the falx cerebri emphasised the midline shift to the left (Figure 7b).

A diagnosis of an intracranial space-occupying lesion was made. This mass was thought to be most likely neoplastic in nature; oligodendroglioma and astrocytoma were considered the main differential diagnoses.

Management and outcome

Surgical excision was not possible because of the deep location of the mass. The owner did not consider radiation therapy a viable option. The dog was discharged on anti-inflammatory doses of prednisolone (1 mg/kg/day) and phenobarbitone (7 mg/kg/day). The dog was seizure-free for seven weeks, except for one seizure episode, which had occurred 10 days after reducing the dose of corticosteroids to 0.5 mg/kg/day. On that occasion, increasing the prednisolone dose to the previous regimen (1 mg/kg/day), regained the control of seizures activity. The dog was euthanased approximately three weeks later because of the development of severe clusters of seizures. No post mortem examination was performed.



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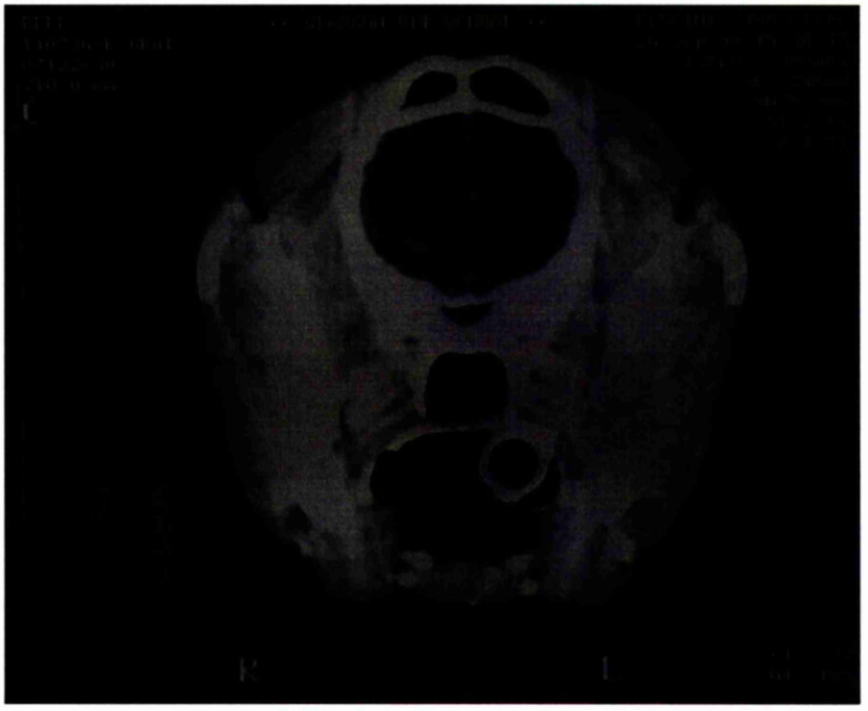


b)

Figure 7. Case 3, 140736. a) Transverse pre-contrast image at the level of the frontal lobe showing a deeply located area of hypodensity with poorly defined margins to the right of midline; b) Transverse post-contrast image at the same level as a), the area of hypodensity identified in the pre-contrast studies is surrounded by a thin, irregular rim of enhancement and the midline shift to the left is emphasised by enhancement of the falx cerebri.

Case 4: No. 139076

Signalment: Collie X, male neutered, aged approximately 10 years and 9 months, weight 21 kg

Diagnosis: multiple mass lesions forebrain and rostral aspect of caudal fossa, and mass effect not associated with visible mass / masses in the right hemisphere at the level of the midbrain. 1) space-occupying lesion involving the right frontal lobe and olfactory bulb, and eroding through the cribriform plate; 2) midline mass lesion ventral to the tentorium cerebelli.

History

The dog was presented with a one-month history of ataxia, which had deteriorated over the week preceding referral. The history was also suggestive of recent, subtle but progressive mental status / behavioural changes, mainly consisting of lethargy, and occasionally vacant staring, and possible seizure activity.

Physical examination

At the time of examination the dog appeared "vacant" and obtunded, though there were no overt neurological deficits. Based on the history and clinical examination findings a forebrain lesion was suspected. Primary and secondary brain neoplasia was thought to be the most likely diagnosis. Degenerative and inflammatory brain diseases were also considered a possibility.

Investigations and provisional diagnosis

The standard protocol for investigation of intracranial diseases and seizure disorders was performed.

Plain radiographs of the thorax and abdomen were unremarkable.

On the pre-contrast CT images of the brain and skull morphological abnormalities were detected on the ventral aspect of the brain, extending from the cribriform plate to the midbrain. A midline shift to the left of the falx cerebri (imaged due to partial mineralisation) and both lateral ventricles was evident. Both lateral ventricles appeared misshapen with the right smaller than the left; the temporal horn of the left lateral ventricle also appeared enlarged (Figure 8a, b). These findings were suggestive of the presence of a right-sided mass lesion causing CSF flow obstruction at the level of interventricular foramina. Areas of hypodensity

surrounding an eccentric, hypo- to isodense mass lesion were seen at the level of the ventral right frontal lobe (Figure 8b). These areas of hypodensity were suggestive of cerebral oedema and appeared to follow the so-called corona radiata pattern. Invasion through the cribriform plate was apparent.

On the post-contrast CT images a non-homogeneously enhancing mass was seen in the rostral portion of the brain, with the most intense enhancement in the right olfactory bulb and frontal lobe regions. Contrast enhancement of the falx cerebri indicated a marked midline shift to the left at the level of the frontal lobe (Figure 8c).

Midline shift to the left was also present at the level of the midbrain, not caused by a visible mass in both pre- and post-contrast studies. Post-contrast transverse CT images detected a second contrast enhancing smaller mass, located along the midline, ventrally to the rostral aspect of the tentorium cerebelli at approximately the level of the tectum. A mass in this location is likely to interfere with CSF flow through the mesencephalic aqueduct. CT findings indicating the presence of CSF flow obstruction and cerebral oedema, in addition to the size of the mass suggest that ICP was likely to be elevated (North & Reilly 1990). Increased ICP might have accounted for the depressed mental status of the animal upon examination.

A diagnosis of multiple intracranial space-occupying lesions, most likely neoplastic in character, was made. However, multiple primary brain tumours, including meningioma, have been rarely reported in dogs (LeCouteur et al 1981; LeCouteur 1990).

For the mass involving the right frontal lobe of the cerebrum and olfactory bulb, meningioma and a primary nasal neoplasia, which had extended caudally into the cranial vault, were considered the main differential diagnoses. The second, more caudal lesion was considered most likely to be a pathologic process independent from the cranial one. However, the possibility this second mass represented a single metastasis and / or the focal extension of the forebrain mass lesion could not be excluded. The second mass could also have represented a single intracranial metastasis of an extracranial neoplasia, despite no abnormalities being detected on physical examination and on survey radiographs of chest and abdomen.

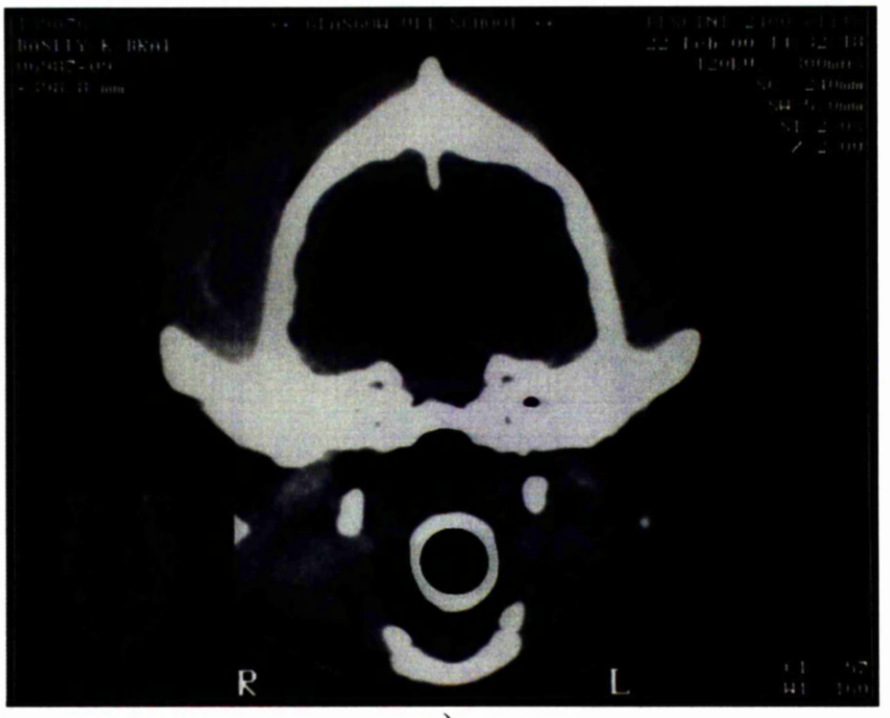
The midbrain midline shift was probably a secondary consequence of the severe cerebral oedema associated with the frontal lobe mass. Moore *et al* (1991) describes the CT and MRI features of a case of primary nasal adenocarcinoma involving the left frontal lobe and

olfactory bulb in which the intense peritumoural oedema extended caudal to the tumour mass as far as the midbrain producing at this level, displacement of the brain to the right.

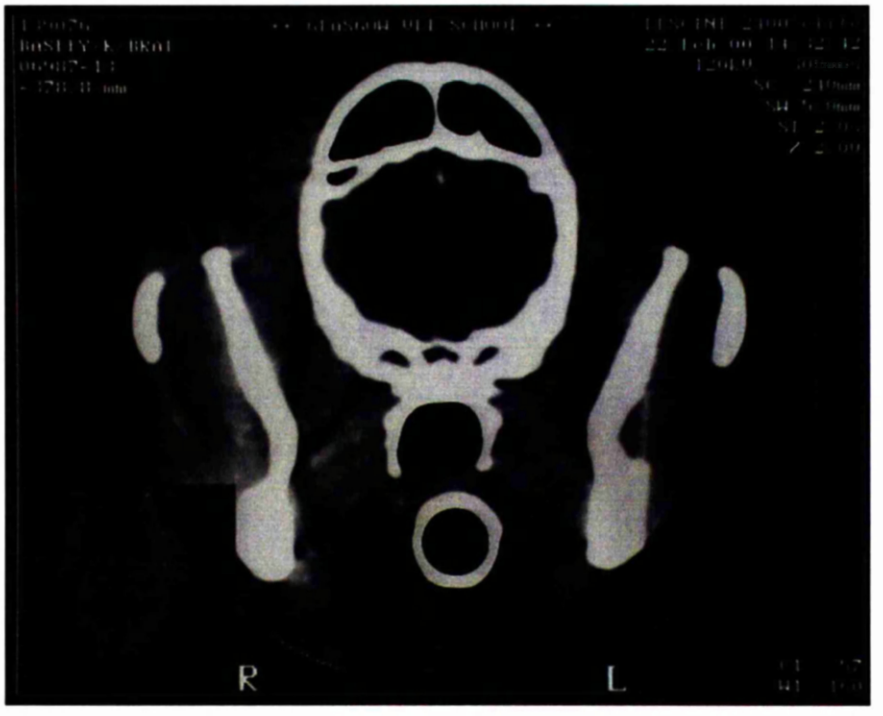
Management and outcome

Patients with multiple and deeply located lesions are poor candidates for surgery. Radiation therapy was likely to result in severe acute ocular side effects, and was not considered a viable option by the owner. In addition, the nature of the lesion causing the major displacement of the brain in the right hemisphere was uncertain. Thus, it was elected to manage the dog palliatively. The dog was discharged on anti-inflammatory doses of prednisolone (1 mg/kg/day).

After starting corticosteroid medication the dog showed a temporary improvement, being more alert and less unsteady. Cluster seizures were observed after twenty days; at that point the owner elected euthanasia. No post mortem examination was performed.

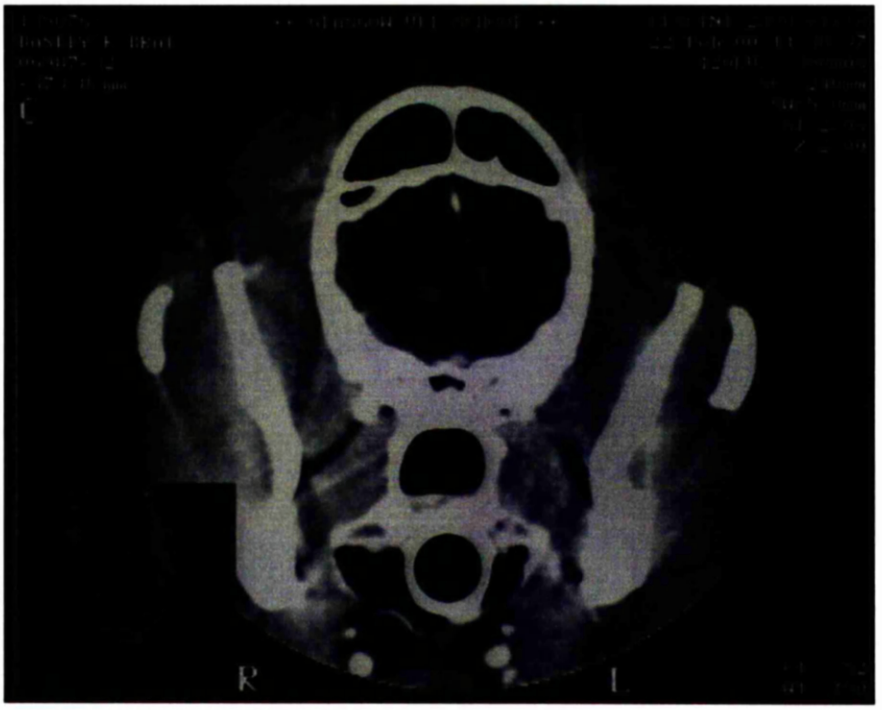


a)



b)

Figure 8. Case 4. 139076. a) Transverse pre-contrast image at the level of the cranial aspect of the tympanic bulla - note the asymmetrical distorted lateral ventricles, enlarged left ventricle, and shift to the left of both falx cerebri and ventricular system suggesting the presence of a right sided mass; b) transverse pre-contrast image at the level of the frontal lobe. An iso- to hypodense mass is present in the ventrolateral aspect of the right frontal lobe surrounded by an extensive area of hypodensity. A shift to the left of a partially mineralised falx cerebri is also evident;



c)

Figure 8 (cont). Case 4, 139076. c) Transverse post-contrast image at a similar level to b) – note the strong peripheral rim of enhancement and the contrast enhancement of the falx cerebri.

Case 5: No. 140363

Signalment: Golden retriever, female entire, aged 7 years, weight 32.3 kg

Diagnosis: mass lesion forebrain located on the lateral convexity of the left cerebral hemisphere at the level of the fronto-parietal cortex junction; meningioma.

History

The dog was presented with a history of two episodes of clustered, generalised, tonic-clonic seizures occurring approximately three months apart. Phenobarbitone medication had been initiated after the second episode (4 mg/kg/day), which had occurred a week before examination at UGVS. The history was also indicative of recent development of behavioural changes consisting of aggression and attention seeking.

Physical examination

At the time of presentation no abnormalities were detected. The history was suggestive of forebrain dysfunction. Primary or secondary brain neoplasia, degenerative or inflammatory brain diseases, as well as idiopathic epilepsy were considered possible differential diagnoses.

Investigations and diagnosis

The standard protocol for investigation of intracranial disease and seizure disorders was performed.

The pre-contrast CT images of the brain and skull identified a focal area of thickening on the left dorsolateral calvarium, extending from the level of the choanae to the rostral end of the tympanic bullae, caused by hyperostosis of the frontal / parietal bones (Figure 9a). An irregular, thin, hypodense rim of brain tissue suggestive of white matter oedema was seen within the left cerebral hemisphere at the junction of the parietal / frontal lobes. Mild enlargement of the left lateral ventricle was also detected (Figure 9b).

On post-contrast CT images a single extra-axial intensely and uniformly enhancing mass lesion could be detected on the lateral convexity of the left cerebral hemisphere at the level of the parietal cortex. The mass was broad-based and plaque-like with well-defined margins and a pedunculated portion extending medially (Figure 9c). A diagnosis of a forebrain space-

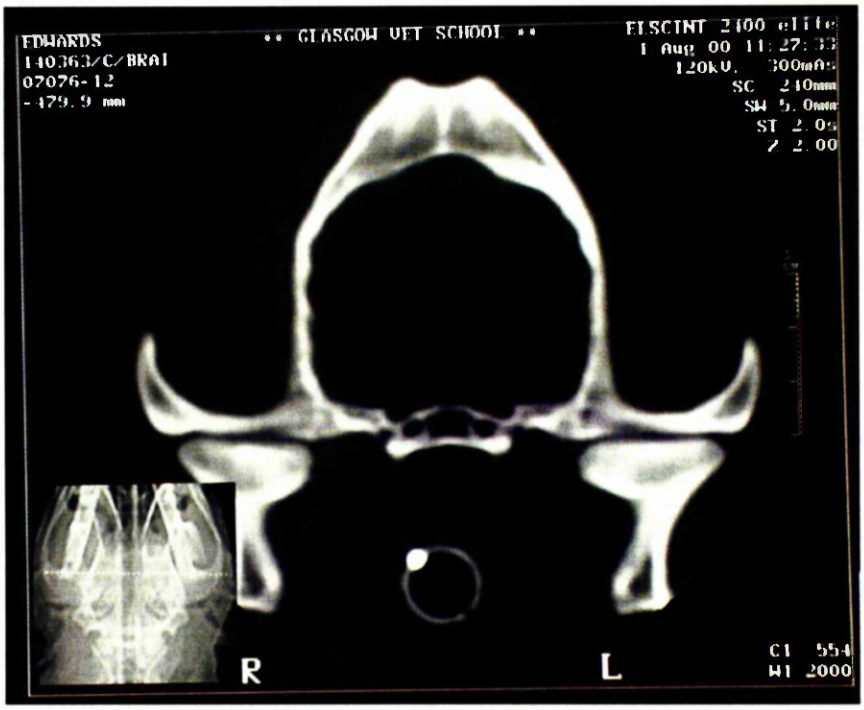
occupying lesion was made. Neoplasia was considered the most likely diagnosis, with the CT appearance being consistent with meningioma.

Management and outcome

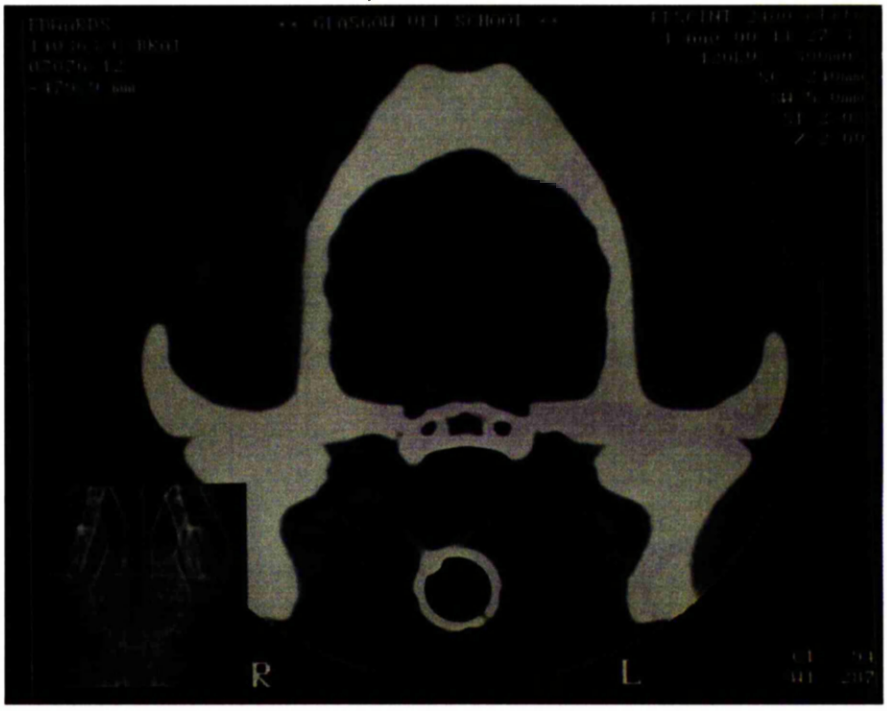
Although the mass would have been amenable to surgical excision, because of its superficial location, the owner decided to have the dog euthanased.

Post mortem examination

Gross post mortem examination confirmed the presence of a slightly brownish plaque shaped mass lesion in the region of the parietal / frontal lobe junction (Figure 9d). The mass was strictly adherent to the dura mater. Histopathology confirmed the nature of the mass as a meningioma and local infiltration into the brain parenchyma.

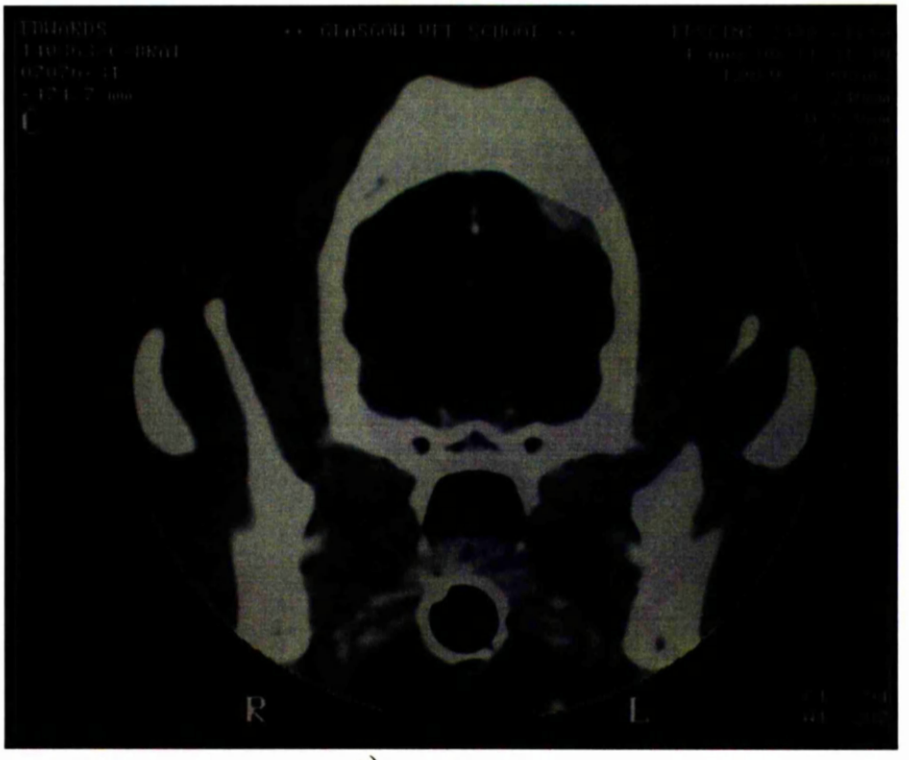


a)



b)

Figure 9. Case 5, 140363. a) Transverse pre-contrast -image at the level of the temporomandibular joint (bone window) where a focal area of hyperdensity is seen in the left dorsolateral calvarium at the junction of the parietal / frontal bones indicating hyperostosis; b) Transverse pre-contrast image at the same level as a) (brain window) in which the increased density of the parietal / frontal bones cannot be seen;



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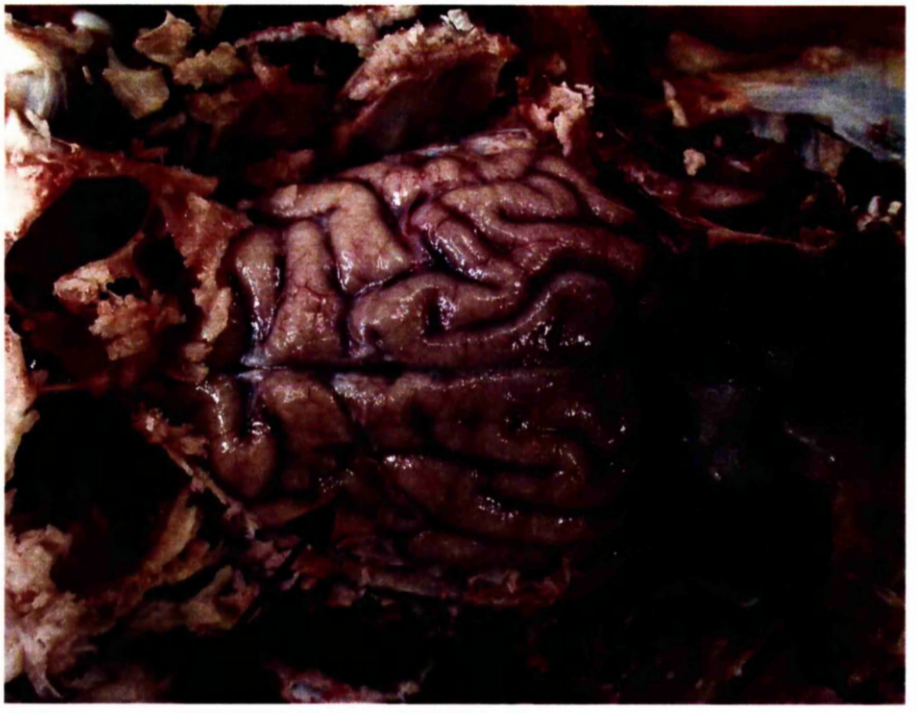


d)

Figure 9 (Cont). Case 5, 140363. c) Transverse post-contrast image at a similar level to a) and b). showing an extra-axial, intensively enhancing mass lesion involving the frontal / parietal lobes, which is plaque shaped and has a broad base of contact with the bone; d) post mortem appearance of the mass (arrow).

Case 6: No. 140354

Signalment: Boxer, male entire, aged ~ 6 years and 6 months, weight 25 kg

Diagnosis: mass lesion right forebrain affecting the frontal, temporal and parietal lobes of the cerebrum, and the thalamic area, and extending caudally to involve the midbrain; anaplastic oligodendroglioma.

History

The dog was presented with a history of a single generalised, tonic-clonic seizure, which had occurred two weeks previous to referral. The seizure episode had been followed by the development of blindness in the left eye and ataxia. The ataxia had progressively deteriorated, with the dog stumbling, staggering to the left and occasionally falling to the side. The history was also indicative of changes in mentation and behaviour, consisting of lethargy, bumping into objects, getting stuck into corners and occasional head pressing. Five days prior to referral, steroid medication had been initiated, which had resulted in improvement of the clinical signs.

Physical examination

On examination the dog was found to be severely obtunded and staggering to the left; it had severe left-sided proprioceptive deficits and decreased menace response in the left eye. In addition the dog occasionally exhibited head pressing behaviour. Based on these findings a right-sided forebrain lesion was suspected. Primary and secondary brain neoplasia was considered the most likely diagnoses. Vascular accidents, inflammatory brain diseases, or degenerative CNS diseases were also considered a possibility.

Investigations and diagnosis

The standard protocol for investigation of intracranial disease and seizure disorders was performed.

CT of the brain and skull detected morphological abnormalities extending from the level of the fronto-parietal junction, to approximately the level of the tentorium cerebelli.

On the pre-contrast CT images a shift to the left of the falx cerebri and a markedly compressed, distorted right lateral ventricle with a dilated left lateral ventricle were seen. The

temporal horn of both lateral ventricles also appeared enlarged (Figure 10a). Distortion of the ventricular system was detected from the level of the frontal cortex to the region of the midbrain. Poorly marginated areas of hypodensity suggestive of cerebral oedema were seen within the right cerebral hemisphere and followed the typical telencephalic white matter pattern (corona radiata pattern) (Figure 10a). These areas were particularly evident within the parietal lobe and extended caudally to involve the occipital cortex. These findings were suggestive of the presence of a right-sided mass lesion.

On the post-contrast CT images a single, irregularly shaped mass lesion was detected in the right cerebral hemisphere at the level of the frontal lobe. The mass appeared to involve the ventral portion of the corona radiata, the internal capsule, the caudate nucleus area, and extended dorsally into the parieto-temporal region. It also appeared to impinge on the thalamus and third ventricle, causing obstructive hydrocephalus. The mass enhanced with a ring-like pattern and had a wide central hypodense area, suggestive of a necrotic core (Figure 10b).

On a post-contrast sagittal image (slightly to the right of midline) the markedly hypodense, deeply located mass, appeared to extend from approximately the level of the optic chiasm to the rostral aspect of the tentorium cerebelli. The ring-like enhancement and the hypodense areas detected on the transverse images were extensive and obvious on the sagittal reconstruction. Sagittal reconstruction emphasised the rostral extension of the mass to involve the frontal area of the cerebrum (Figure 10c).

A diagnosis of an intracranial space-occupying lesion was made. Neoplasia was considered the most likely diagnosis with oligodendroglioma and astrocytoma being the main differential diagnoses. Rapidly growing, malignant variants, such as glioblastoma multiforme were considered a possibility on the basis of history, clinical (acute onset and rapid deterioration of neurological deficits) and CT findings (widespread cerebral oedema and necrotic core).

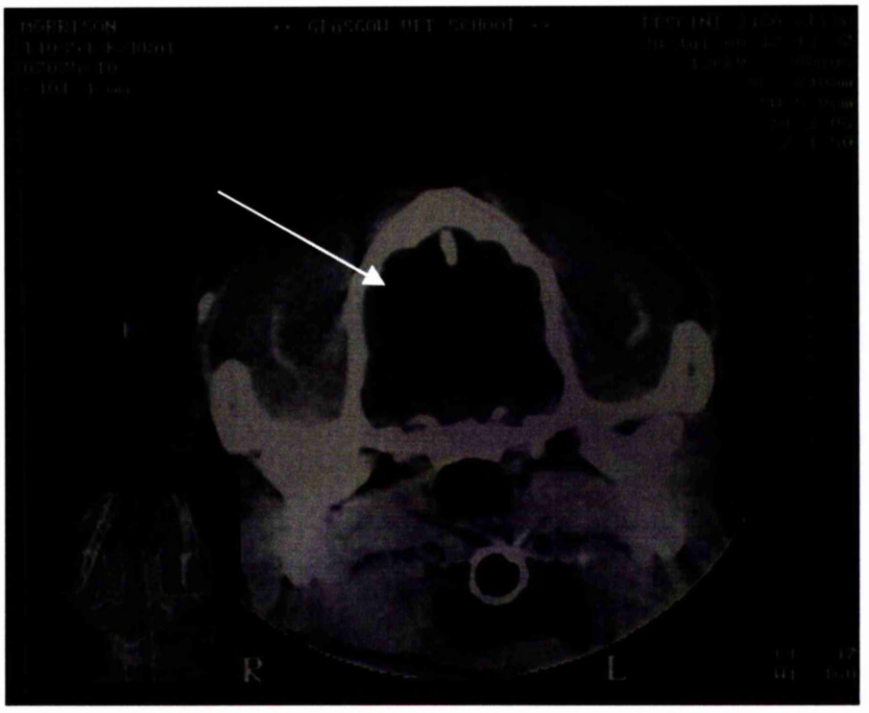
Management and outcome

The size and location of the mass excluded the possibility of surgical excision and/or radiation therapy. The prognosis was considered grave and the dog was started on anti-inflammatory doses of prednisolone (1 mg/kg/day). During the first twelve hours following recovery from

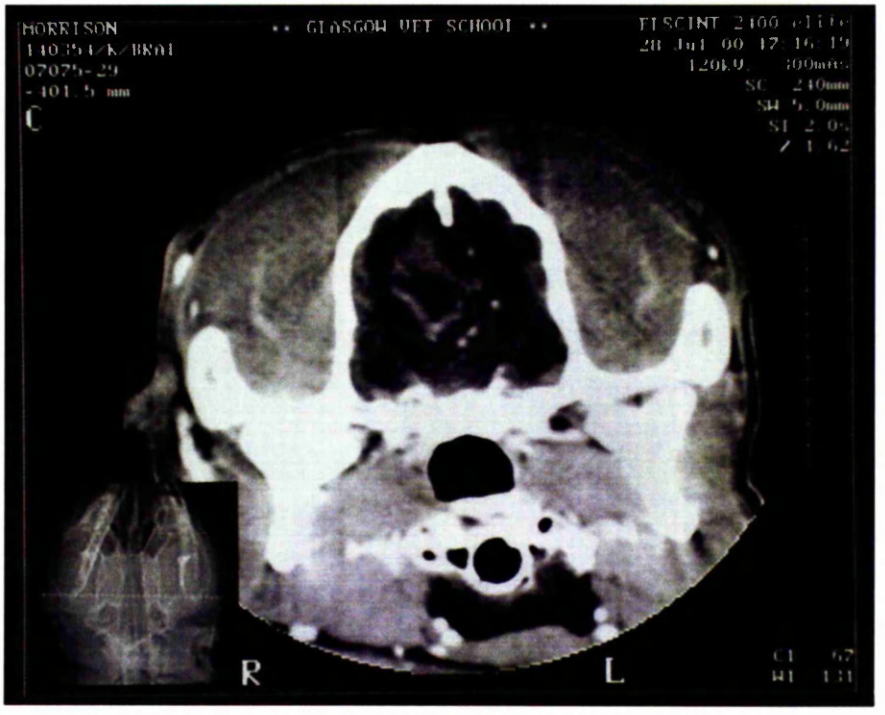
anaesthesia, the neurological status of the dog dramatically deteriorated, and the owner elected euthanasia.

Post mortem examination

Gross post mortem examination (Figure 10d) confirmed the presence of a fairly well circumscribed, unencapsulated mass involving the cerebral hemispheres (predominately on the right) at the level of the thalamus. Histopathology confirmed the nature of the mass as an anaplastic oligodendroglioma. Infiltration into the adjacent lateral ventricles was apparent.

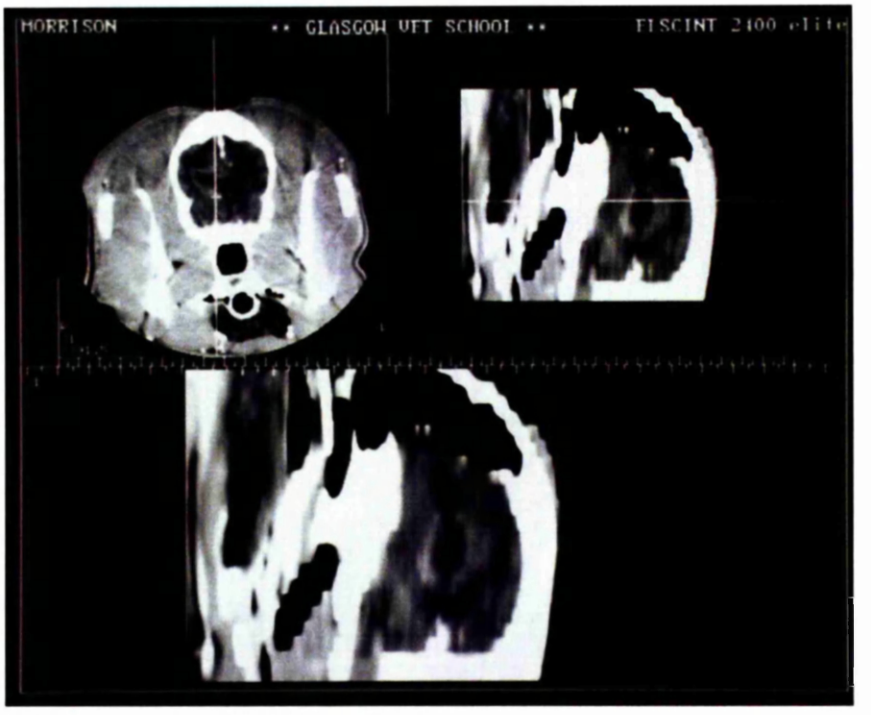


a)



b)

Figure 10. Case 6, 140354. a) Transverse pre-contrast image at the level of the midbrain showing changes in the lateral ventricles with distortion of the right and enlargement of the left and evidence of white matter oedema (arrow); b) Transverse post-contrast image at the same level as a) revealing a hypodense mass with an irregular rim of enhancement involving the right temporal and parietal lobes, as well as the corona radiata, caudate nucleus, internal capsule and thalamus;



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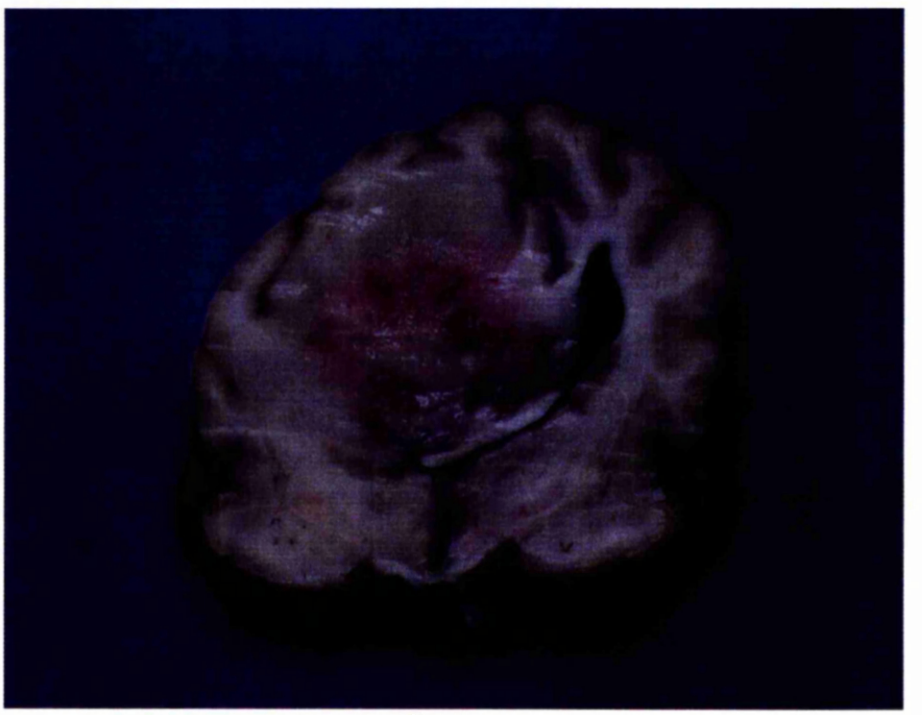


d)

Figure 10 (Cont). Case 6, 140354. c) sagittal post-contrast image confirming the deep location of the mass and extensive associated oedema d) post mortem preparation at similar level to images a) and b).

Case 7: No. 139916

Signalment: Labrador retriever, male neutered, aged 3 years and 7 months, weight 36 kg

Diagnosis: mass lesion, right hindbrain next to the fourth ventricle, with a broad base of attachment to the petrous bone; choroid plexus papilloma.

History

The dog was presented with a one-month history of severe generalised, tonic-clonic seizures. The seizures had the tendency to occur as clusters.

The referring veterinary surgeon had diagnosed idiopathic epilepsy given the dog's breed and age, the absence of interictal neurological deficits and abnormalities on routine haematology and biochemistry panels. Treatment with phenobarbitone (2.5 mg/kg/day) had been initiated, initially resulting in a degree of improvement. Referral was precipitated by the increased frequency of seizures despite the increased dosage of medication (3.3 mg/kg/day). Over the two weeks preceding referral, the dog developed changes in mentation consisting mainly of decreased awareness and slight ataxia.

Physical examination

At the time of presentation no significant clinical and neurological abnormalities were detected. Based on the historical picture forebrain dysfunction was identified. Idiopathic epilepsy was thought to be the most likely diagnosis, although inflammatory, degenerative and neoplastic brain diseases were also considered a possibility.

Investigations and diagnosis

The standard protocol for investigation of seizure disorders was performed.

Computed tomographic study of the brain and skull revealed the presence of a mass lesion within the caudal fossa, extending from the petrosal crest to the occipital bone.

On the pre-contrast CT images a right-sided singular, large, hyperdense, eccentric mass was seen located near the fourth ventricle. The mass was ovoid in shape, had distinct, smooth margins, and an iso- to hyperdense centre. It had a broad base of attachment to the right petrous bone and involved the cerebellopontine angle area (Figure 11a, c). Displacement of the brainstem and cerebellum, as well as compression of the fourth ventricle was evident. On

the post-contrast CT images the mass enhanced intensely and uniformly and was surrounded by a hypodense rim, suggestive of cerebral oedema (Figure 11b). A ring-like pattern of hypodensity was seen within the caudal portion of the mass, suggestive of a necrotic centre. On the post-contrast study a second smaller enhancing area could be seen just left of midline at approximately the level of the fourth ventricle. CT images resolution was not sufficient to establish whether or not this mass was connected to the first one.

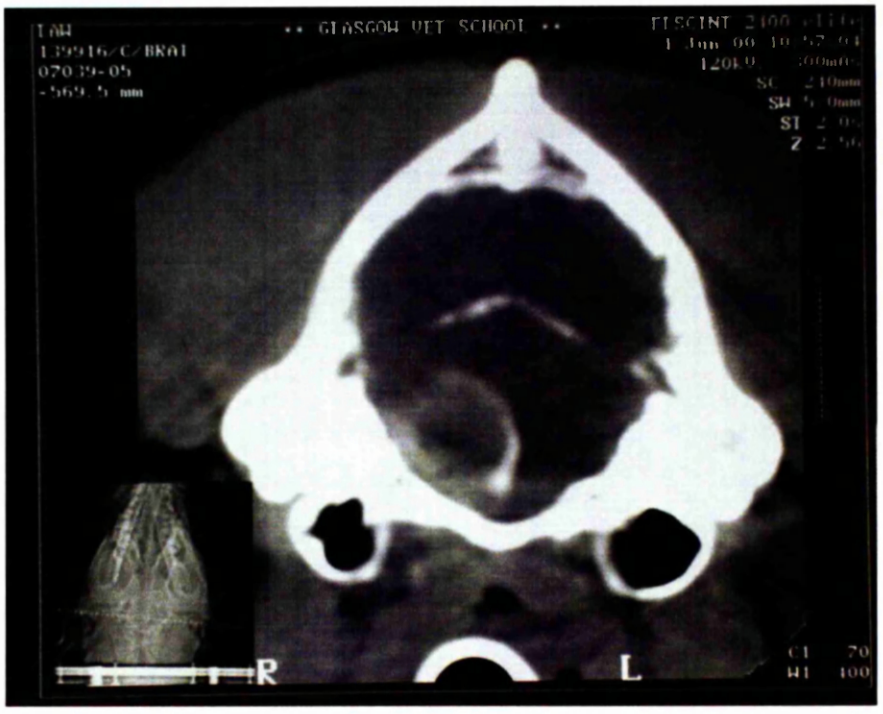
A diagnosis of caudal fossa space-occupying lesions was made. These masses were thought to be most likely neoplastic in nature; meningioma and choroid plexus papilloma were considered the main differential diagnosis. Ependymoma was also considered a possibility.

Management and outcome

The size and location of the masses excluded the possibility to elect for surgical excision. The owner did not consider radiation therapy a viable management option. However, in this case radiation therapy would have carried the risk of severe otitis externa (Spugnini et al 1995). In addition, radiation therapy is poorly effective with highly vascularised tumours, and in this case choroid plexus papilloma was one of the main differential diagnosis. The owner was given a poor prognosis and the dog was euthanased.

Post mortem examination

Post mortem examination revealed an off-white / yellow erosive friable mass in the region of the right hindbrain. Several smaller lesions of similar colour were seen over the ventral surface of the cerebrum and in the region of the optic chiasm (Figure 11d). Histopathology confirmed the nature of the mass as a choroid plexus papilloma.



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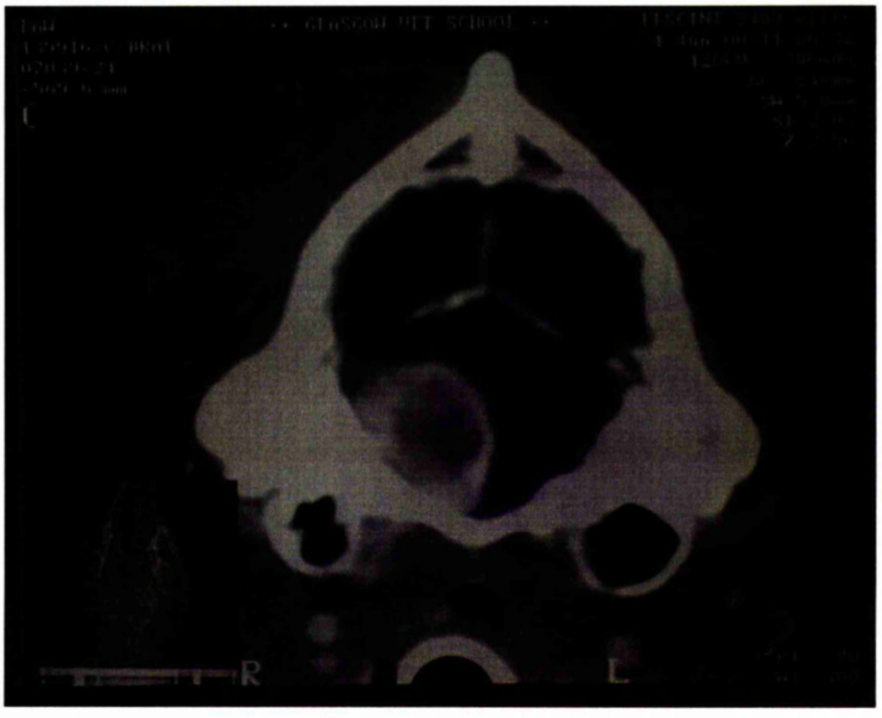
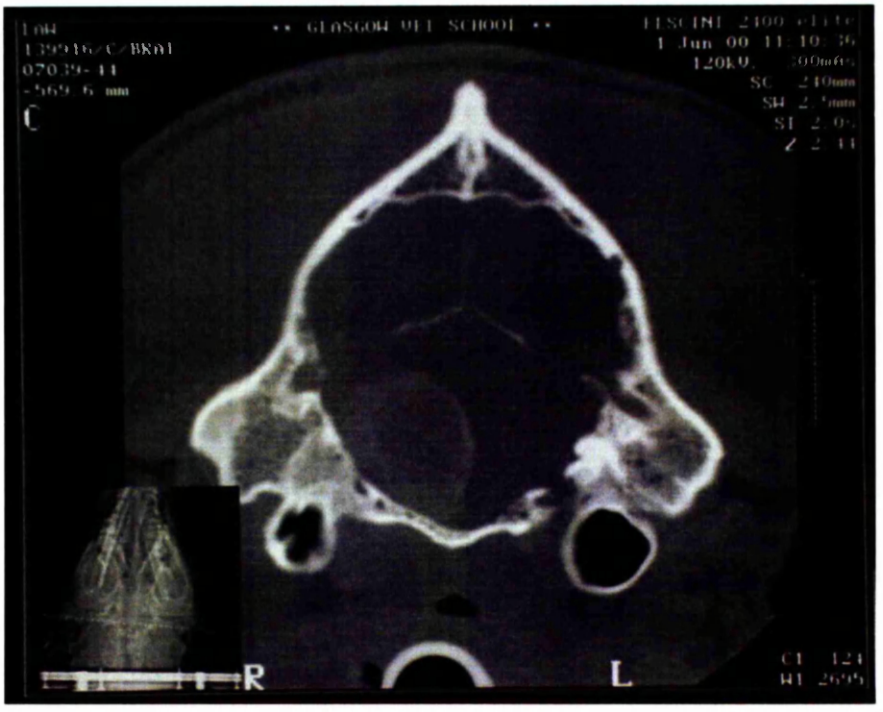


b)

Figure 11. Case 7, 139916. a) Transverse pre-contrast image at the level of the caudal fossa showing an extra-axial, ovoid-shaped, hyperdense mass in the ventrolateral aspect of the right hindbrain and involving the cerebellopontine angle – note the broad-base of attachment to the petrous bone; b) Transverse post-contrast image at the same level as a) showing the mass to enhance intensively and uniformly, with the strongest enhancement occurring at its periphery;



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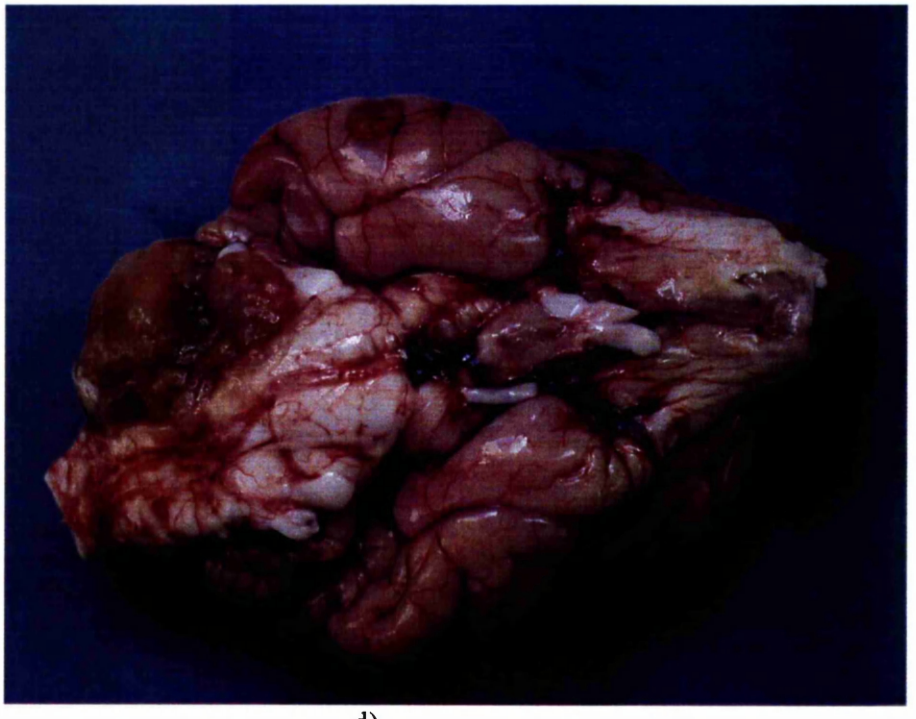


d)

Figure 11. Case 7, 139916 (Cont). c) Transverse post-contrast image at the same level as a) and b) viewed with a bone window showing no apparent bony involvement; d) post mortem appearance of the brain.

Case 8: No. 139452

Signalment: Golden retriever, female neutered, aged ~ 11 years, weight 36.5 kg

Diagnosis: hydrocephalus and intracranial arachnoid cyst (IAC).

History

The dog was presented with a three-month history of generalised, tonic-clonic seizures, with an inter-ictal period of fourteen to seventeen days. Seizures were isolated in character with the exception of one incident of cluster seizures. Interictal abnormalities were limited to increased vocalisation for no apparent reason and a poorly defined change in behaviour. The latest seizure occurred the evening before examination at UGVS.

Physical examination

Physical and neurological examination was unremarkable. Based on the history a forebrain lesion was suspected. Primary or secondary brain neoplasia was thought to be the most likely diagnosis; degenerative or inflammatory brain diseases, as well as idiopathic epilepsy, were considered in the differential diagnosis.

Investigations and diagnosis

The standard protocol for investigation of intracranial disease and seizure disorders was performed.

Pre-contrast CT images of the brain and skull revealed an extreme hydrocephalus extending thorough the entire telencephalon (Figure 12a, b, c, d). The lateral and third ventricles were remarkably dilated; a fluid filled cyst-like structure with sharply defined margins was evident in the region of the quadrigeminal cistern (Figure 12b). On post-contrast study no other morphological abnormalities were detected and the cyst-like structure did not enhance.

The otherwise relatively normal features of the cranium, and the mild clinical signs despite the dramatic distension of the ventricular system, suggested that the hydrocephalus was acquired. A diagnosis of hydrocephalus and possible intracranial arachnoid cyst (IAC) was made.

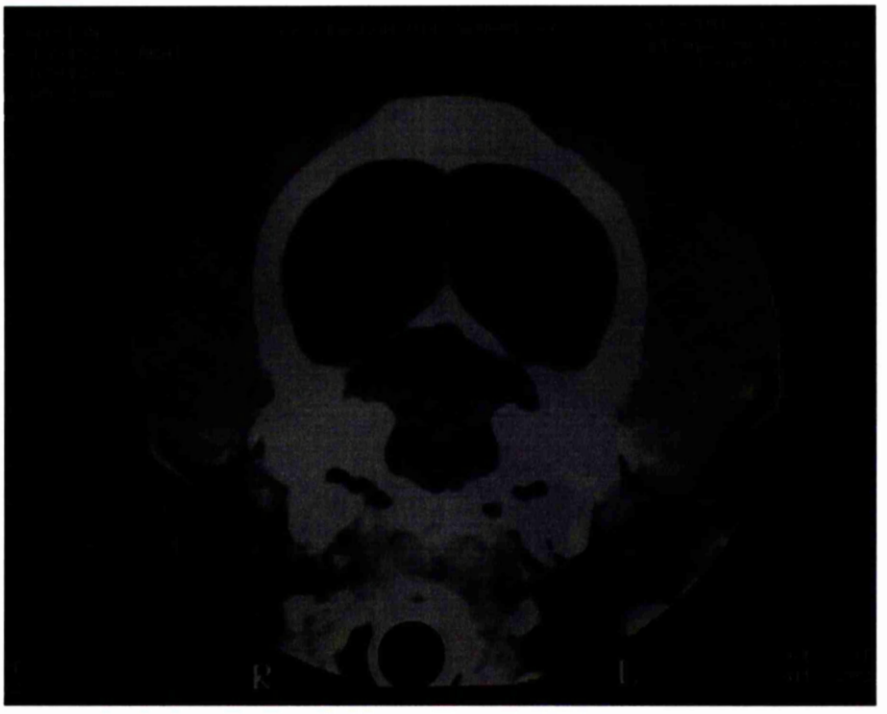
Management and outcome

Both hydrocephalus and intracranial arachnoid cysts are reported in association with seizures and behavioural changes in dogs (Harrington et al 1996; Vernau et al 1997; Thomas 1999).

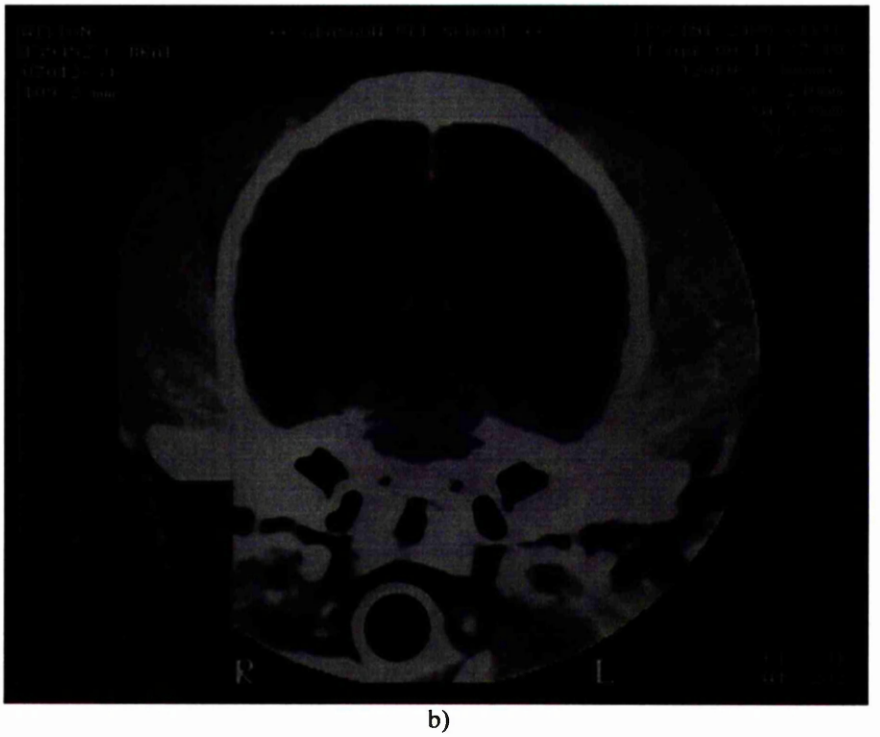
Whether in this case seizure activity related to the hydrocephalus and / or the IAC is not established. However, for both conditions the literature suggests that shunting may improve the clinical status of the patient (Thomas 1998; Anderson et al 2000). In human patients fenestration is also used for the surgical treatment of IAC and this has also been reported in the dog (Vernau et al 1997). The most appropriate surgical approach (fenestration *vs* shunting) has not been established. In this case, a ventriculoperitoneal shunt was considered a viable method of achieving long-term drainage of the ventricular system and thus ameliorating the neurological abnormalities.

Whilst the owner considered this option the patient was managed with 4 mg/kg/day of phenobarbitone and prednisolone (1 mg/kg/day). During the three weeks preceding surgery the patient did not seizure. A medium pressure (opening pressure 5-9 cm H_2O) ventriculoperitoneal shunt (Shunt kit, contour-flex valve, Radionics) with reservoir was placed, with the ventricular catheter in the right lateral ventricle. The patient was discharged on an unchanged phenobarbitone dosage regime. The steroids were withdrawn.

During the three weeks following surgery the dog remained seizure-free and its demeanour improved remarkably. At 7 weeks following surgery there was a sustained improvement in demeanour, in particular the reappearance of behavioural traits that had been lost prior to surgery. A CT scan at this point showed that there had been some relaxation of the cortex and an unsuspected collapse of the right hemisphere. Only one seizure occurred during the first twelve weeks following surgery. Telephone follow up at ten months following surgery confirmed a normal demeanour and behaviour of the dog, as well as a good control of seizure activity, with episodes of isolated, generalised tonic-clonic seizures occurring with a frequency of one every six to ten weeks. The phenobarbitone dosage regime has not been modified (4 mg/kg/day). Monitoring of the anticonvulsants therapy has been performed by the referring veterinary surgeon.

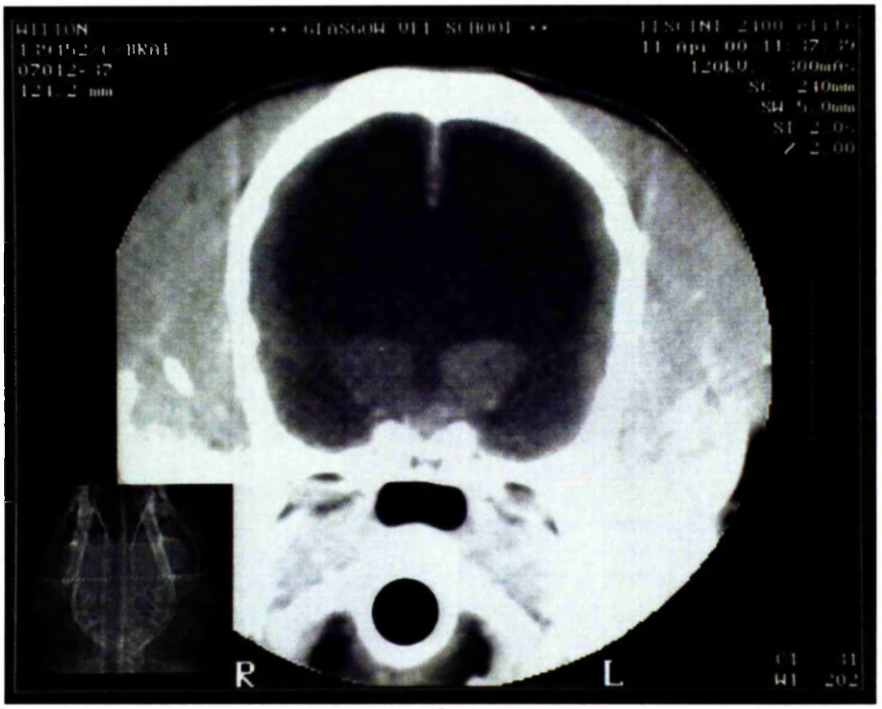


a)



b)

Figure 12. Case 8, 139452. Transverse post-contrast images showing abnormal dilation of the ventricular system, which was present in the entire telencephalon: a) Transverse post-contrast image at the level of the caudal telencephalon, showing the caudal extension of the hydrocephalus; b) Transverse post-contrast image at the level of the rostral colliculi in the midbrain region - note the presence in addition to the abnormal dilated lateral ventricles of a non-enhancing fluid filled cyst like structure in the region of the quadrigeminal cistern;



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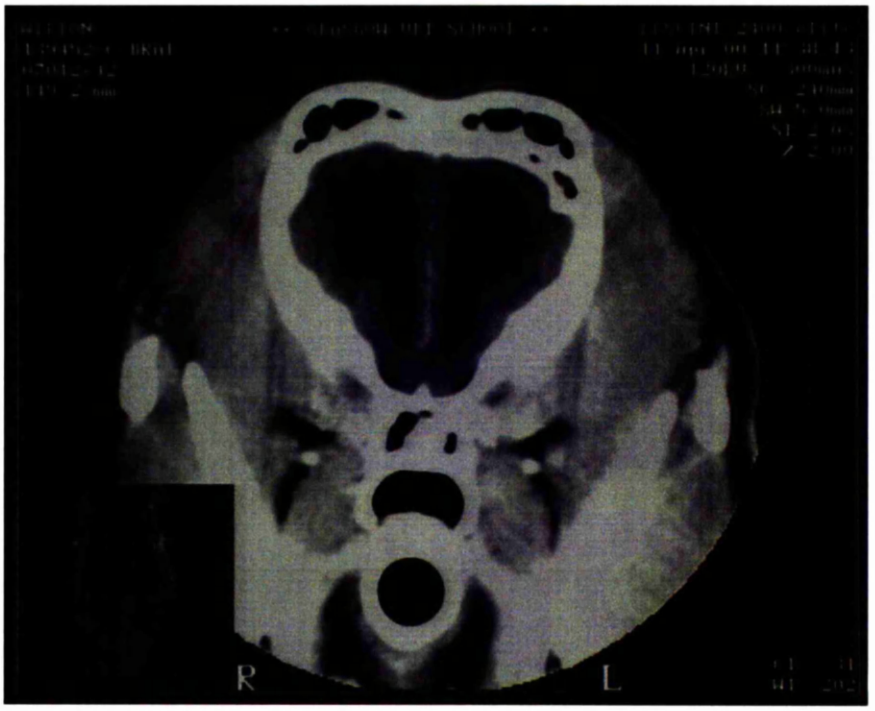


d)

Figure 12 (Cont). Case 8, 139452. c) Transverse post-contrast image at the level of the thalamus; d) transverse post-contrast image at the level of the frontal lobe, showing the rostral extension of the hydrocephalus.

Case 9: No. 138951

Signalment: Border collie, female neutered, aged 3 years and 6 months, weight 14.7 kg

Diagnosis: idiopathic epilepsy.

History

The dog was presented with a thirteen-month history of isolated, generalised, tonic-clonic seizures lasting two to three minutes and occurring approximately every three to four weeks. According to the owner, the dog was showing no other signs of illness, was eating well, and appeared to be perfectly normal between seizures. No pre- and postictal neurological abnormalities were reported. The history was not indicative of the dog having been involved in any trauma or exposure to toxins. Treatment with phenobarbitone (2 mg/kg/day) had been initiated two months prior to referral; this had not resulted in control of seizure activity.

Physical examination

On examination the dog was bright and alert, with no significant clinical findings. A full neurological examination failed to demonstrate any abnormalities. Based on the history, forebrain dysfunction was identified. Idiopathic epilepsy was thought to be the most likely diagnosis. Inflammatory, neoplastic and degenerative diseases were also considered in the differential diagnosis.

Investigations and provisional diagnosis

The standard protocol for investigation of seizure disorders was performed. Routine haematology and biochemistry panels were within normal limits, as well as toxoplasma titres and neospora neutralisation dilutions. On both pre- and post-contrast CT images of the brain and skull, no structural abnormalities were detected. The CSF tap and fluid analysis were unremarkable. Based on elimination of metabolic causes of seizures, normal appearance of the brain on CT, and unremarkable CSF analysis, a diagnosis of idiopathic epilepsy was made.

Management and outcome

The dog was discharged on phenobarbitone at a dosage regime of 4 mg/kg/day; a blood sample taken after two weeks showed the serum phenobarbitone level (15.2 mg/l) being in the therapeutic range (15-45 mg/l), although close to the lowest limit. Clinical biochemistry and

serum phenobarbitone level were re-evaluated six months after first assessment at UGVS. The results indicated adequate phenobarbitone serum concentration (21.6 mg/l peak; 18.6 mg/l trough); there were no evidence of phenobarbitone-induced bone marrow toxicity, but the SAP was raised (850 U/l). However, the transaminases, bilirubin, and serum bile acids, the latter evaluated at the referring veterinary practice, were within normal limits, suggesting that this represented enzyme induction rather than hepatic pathology. During the following five months routine biochemistry and serum bile acids evaluation performed in two occasions by the referring veterinary surgeon did not suggest the development of liver disease.

Telephone follow up at twelve months after first assessment at UGVS confirmed that phenobarbitone medication at the dose of 4 mg/kg/day has resulted in acceptable control of seizure activity with only four seizures during this period.

Case 10: No. 140277

Signalment: X breed, male entire, aged approximately 7 years, weight 29 kg

Diagnosis: idiopathic epilepsy

History

The dog was presented with an approximately four-month history of isolated, generalised, tonic-clonic seizures, occurring with a frequency of once a week. Jaw snapping and rhythmic turning of the head toward the right shoulder were described to precede the tonic-clonic phase in each seizure event. Duration of the ictus was two to three minutes; postictal disorientation usually lasted five to ten minutes. No interictal abnormalities were reported. The history was not indicative of the dog having been involved in any trauma or exposure to toxins. In addition the dog had a history of chronic sneezing; more recently a clear nasal discharge had appeared. Three months prior to referral, phenobarbitone medication had been initiated (4 mg/kg/day). This had not resulted in control of seizure activity. The dose of phenobarbitone had been increased from 4 to 5 mg/kg/day, four days before presentation. Referral was precipitated by the increased frequency of seizures over the previous two weeks (two and three episodes per week, respectively).

Physical examination

At the time of presentation no significant clinical and neurological abnormalities were detected, with the only remarkable abnormality consisting of corneal opacity, secondary to oedema, in the left eye. Based on the history, forebrain dysfunction was identified. Seizure activity was thought to be most likely the result of a structural brain disease. Primary or secondary brain neoplasia was considered the most likely diagnosis. Inflammatory or degenerative brain diseases, as well as idiopathic epilepsy were included in the differential diagnosis.

Investigations and diagnosis

The standard protocol for investigation of seizure disorders was performed.

Routine haematology showed a mildly inflammatory leukogram with neutrophilia, most likely related to the recently developed rhinitis. (WBC 18.300 x $10^{\Lambda 9}$/l; neutrophils 12.810 x 10^{Λ}

^{9}/l). Routine biochemistry panels revealed increased SAP (307 U/l); Toxoplasma titres and Neospora neutralisation dilutions were within normal limits. On both pre- and post-contrast CT images of the brain and skull no structural abnormalities were detected. The CSF analysis was unremarkable. Based on elimination of metabolic causes of seizures, normal appearance of the brain on CT, and unremarkable CSF analysis, a presumptive diagnosis of idiopathic epilepsy was made.

Management and outcome

The patient was discharged on an unchanged phenobarbitone dosage regimen; a blood sample taken two weeks after showed the phenobarbitone level to be within therapeutic range (18.58 mg/l). During the following month, seizure frequency decreased approximately to one episode every four weeks; at that point the referring veterinary surgeon initiated potassium bromide medication (25 mg/kg/day). Telephone follow up at seven months after assessment at UGVS confirmed improvement in seizure activity control, with seizures occurring every 6 to 7 weeks, and being less severe than when the dog was first presented.

Case 11: No. 139250

Signalment: Labrador retriever, male entire, aged ~ 5 years and 6 months, weight 37 kg

Diagnosis: mass lesion in the forebrain involving the mid-parietal lobe of the dorsal cerebrum, at the level of the midbrain.

History

The dog was presented with an approximately one-month history of behavioural change, mainly consisting of aggression, intermittent ataxia and visual dysfunction. The ataxia had suddenly deteriorated two weeks preceding referral, with the dog staggering and falling over; in addition it had become anorexic, extremely anxious and occasionally had been seen bumping into objects. Subsequent progress had been variable, with the dog having "good" days and "bad" days.

Physical examination

On examination the dog was found to be mildly obtunded and withdrawn, with proprioceptive deficits in all four limbs and occasional hypermetria in the hindlimbs. Based on these findings a forebrain and / or a multifocal lesion involving also the brainstem / cerebellum was suspected. Primary and secondary brain neoplasia, inflammatory or degenerative brain diseases were considered the most likely diagnostic possibilities.

Investigations and diagnosis

The standard protocol for investigation of intracranial disease was performed.

The pre-contrast CT images of the skull and brain demonstrated the presence of a large, singular, midline located, mildly hyperdense mass, in the midparietal lobe of the dorsal cerebrum (Figure 13a). The mass extended from just rostral to the thalamus caudally as far as the midbrain. The mass was ovoid in shape and had poorly defined margins. It was associated with a mass effect consisting of mild enlargement of both lateral ventricles (with the left larger then the right) and right displacement of the falx cerebri. On the post-contrast images the mass enhanced intensely and relatively uniformly. A hypodense ring-like area surrounded the mass, suggestive of perilesional oedema; (Figure 13b). Post-contrast sagittal CT images

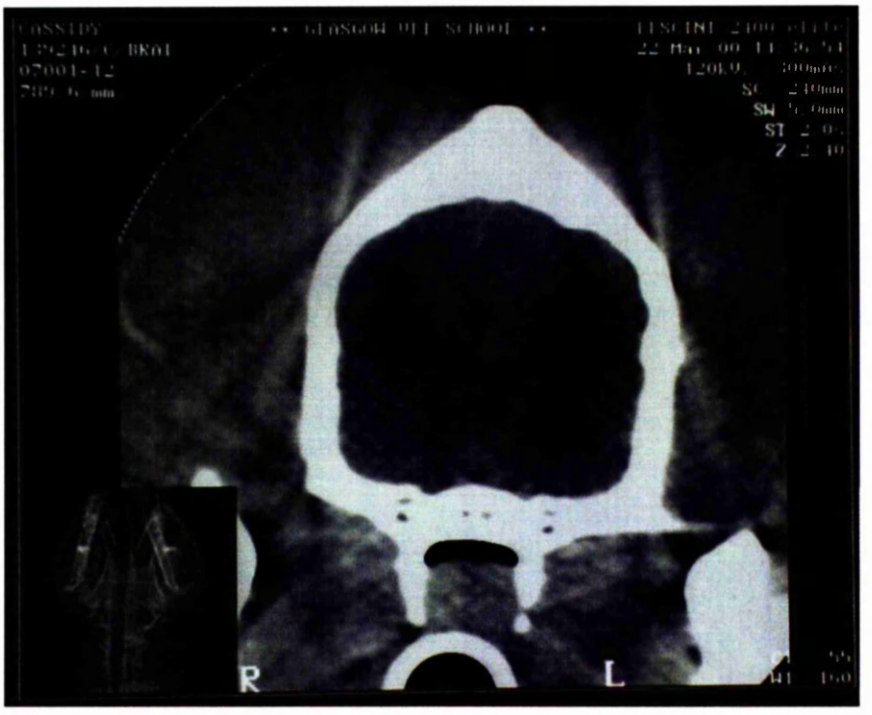
emphasised that the mass extended cranially to involve the caudal portion of the dorsal frontal lobe (Figure 13c).

A diagnosis of a forebrain space-occupying lesion was made. This mass was thought to be most likely neoplastic in nature; meningioma, astrocytoma and oligodendroglioma were considered the main differential diagnoses.

Management and outcome

The size and location of the mass excluded the possibility of surgical excision and / or radiation therapy. The owner elected to manage the dog palliatively. The dog was discharged on anti-inflammatory doses of prednisolone (1 mg/kg/day).

After starting steroid medication the demeanour of the dog improved, it became more active, was no longer anorexic or aggressive and no longer bumped into objects. The staggering and falling episodes stopped, although the dog remained mildly ataxic. Nine weeks after discharge clinical signs of aggressiveness and falling recurred, suggesting that the palliative effects of the corticosteroids were waning, and that the mass was reaching a critical size. These signs worsened over the following week and the dog was euthanased. No post mortem was performed.



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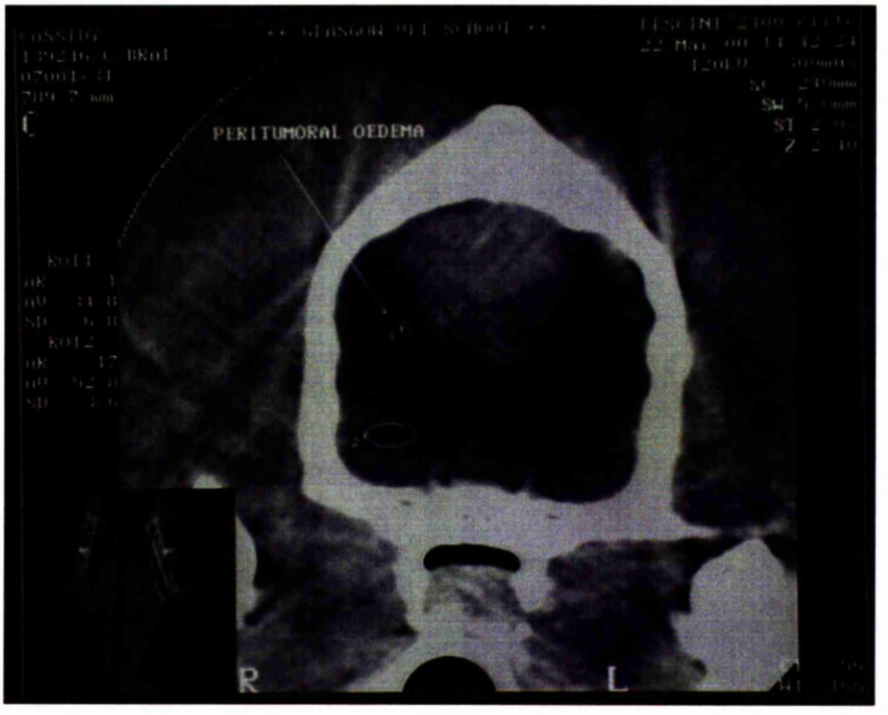
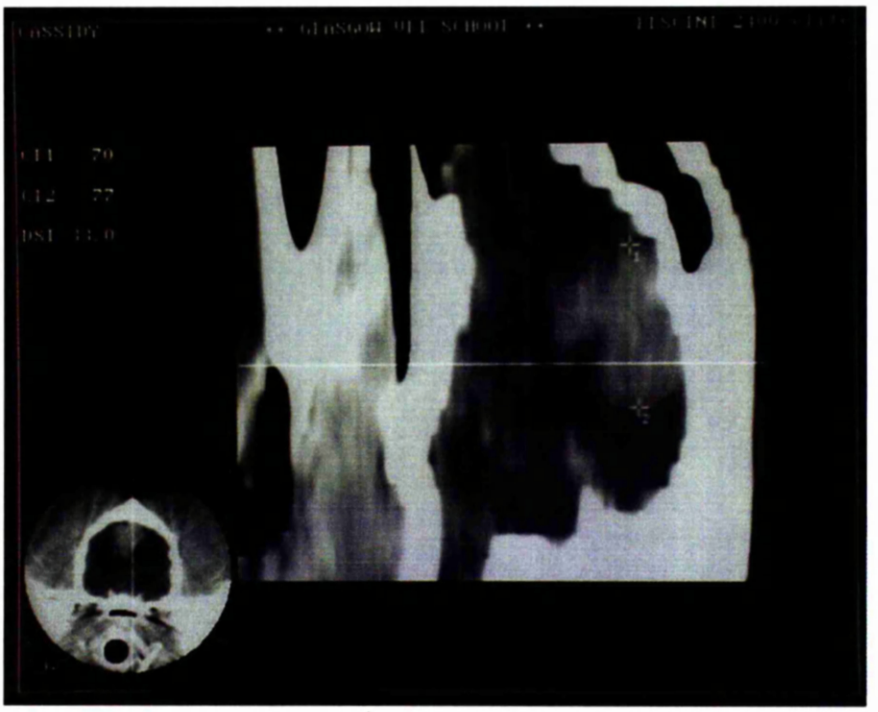


b)

Figure 13. Case 11, 139250[a]. a) Transverse pre-contrast image at the level of the midbrain showing a hyperdense, ovoid-shaped mass in the dorsal cerebrum surrounded by an irregular area of hypodensity, suggestive of cerebral oedema; b) Transverse post-contrast image at the same level as a) - the mass enhances intensely and uniformly and the margins vary from well to poorly defined; the displacement of the focally enhanced falx cerebri suggests a midline shift to the right;

[a] CT images are marked 139246 due to a technical error.



c)

Figure 13. Case 11, 139250 (Cont). c) In the post-contrast sagittal image the mass extends rostrally and appears to also involve the frontal lobe.

Case 12: No. 139254

Signalment: Cairn terrier, female neutered, aged 9 years and 6 months, weight 9.5 kg

Diagnosis: mass lesion forebrain in the left cerebral hemisphere involving the ventricular system and extending through the olfactory, frontal, and temporal lobes, the thalamic area and the midbrain.

History

The dog was presented with an approximately two-week history of sudden onset of ataxia, behavioural changes, consisting mainly of aggression, 'absence' periods and absent pupillary light reflexes. Occasionally, the dog had also been seen to fall to either side. Three days prior to referral treatment with carprofen (Rimadyl, Pfizer Animal Health Ltd) (4.2 mg/kg/day) had been initiated, with no improvement.

Physical examination

On neurological examination the dog was found to be mildly obtunded, ataxic on all four limbs, with bilaterally absent pupillary light reflexes and absent menace response in both eyes, despite having no obvious visual deficits. In the consulting room the dog spent most of the time lying in sternal recumbency. When walking, it was ataxic with a crouched forelimb gait and fell on two occasions. The dog also showed discomfort on manipulation of the neck. Based on these findings a forebrain and / or a multifocal lesion involving also the brainstem was suspected. Intracranial neoplasia and inflammatory brain disease were considered the most likely diagnoses.

Investigations and provisional diagnosis

The standard protocol for investigation of intracranial diseases was performed.

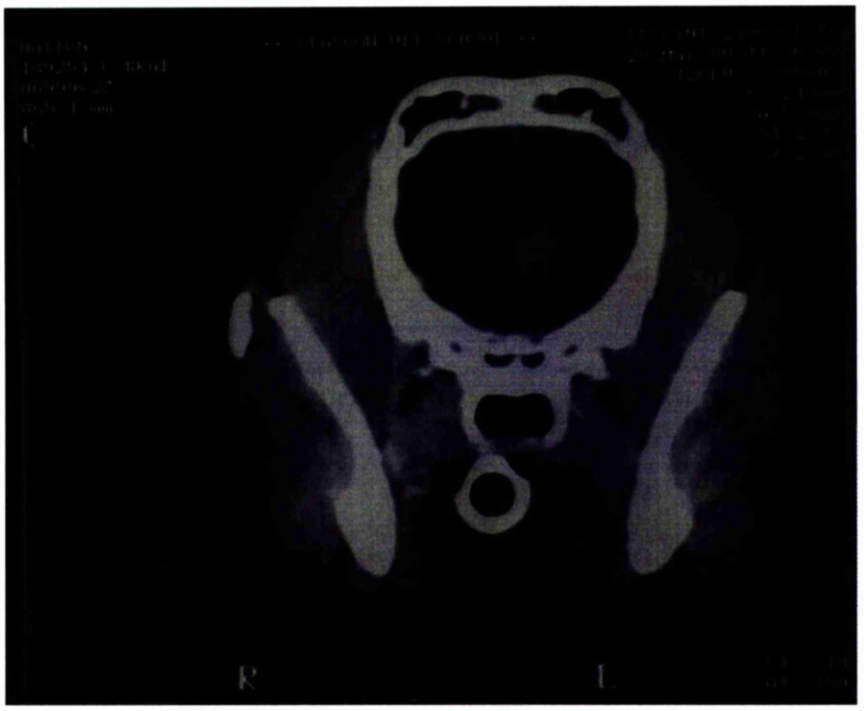
On the pre-contrast CT images of the brain and skull a poorly marginated, predominately ovoid, hyperdense mass was seen to the left of the midline and ventral to the left lateral ventricle, extending from the level of the frontal / olfactory cortex to the level of the midbrain. The mass produced compression and distortion of the left lateral ventricle, as well as enlargement of the right lateral and third ventricles and appeared to impinge on the thalamic

and caudate nucleus regions. After contrast injection the mass enhanced intensely and uniformly, with fairly distinct margins (Figure 14a, b).

A diagnosis of intracranial space-occupying lesion was made. This mass was thought to be most likely neoplastic in nature. On the basis of CT appearance and location, choroid plexus papilloma and ependymoma were considered the main differential diagnoses. However, oligodendroglioma can also be associated with a similar CT pattern. In addition, focal GME was also considered in the differential diagnosis, on the basis of signalment, history and CT findings (Braund 1985; Muñana & Luttgen 1998). Focal GME is characterised by hyperdense appearance on pre-contrast images and by a strong, in most cases uniform and well marginated enhancement on post-contrast studies (Sorjonen 1990; Speciale et al 1992; Gibbons et al 1999).

Management and outcome

The owner declined any treatment. Over the three days following discharge the dog deteriorated very quickly. The ataxia and falling worsened and severe mental status / behavioural changes developed, to the point where the dog was restless, unable to sleep and eat, and continuously vocalising. At that point the dog was euthanased; no post mortem examination was performed.



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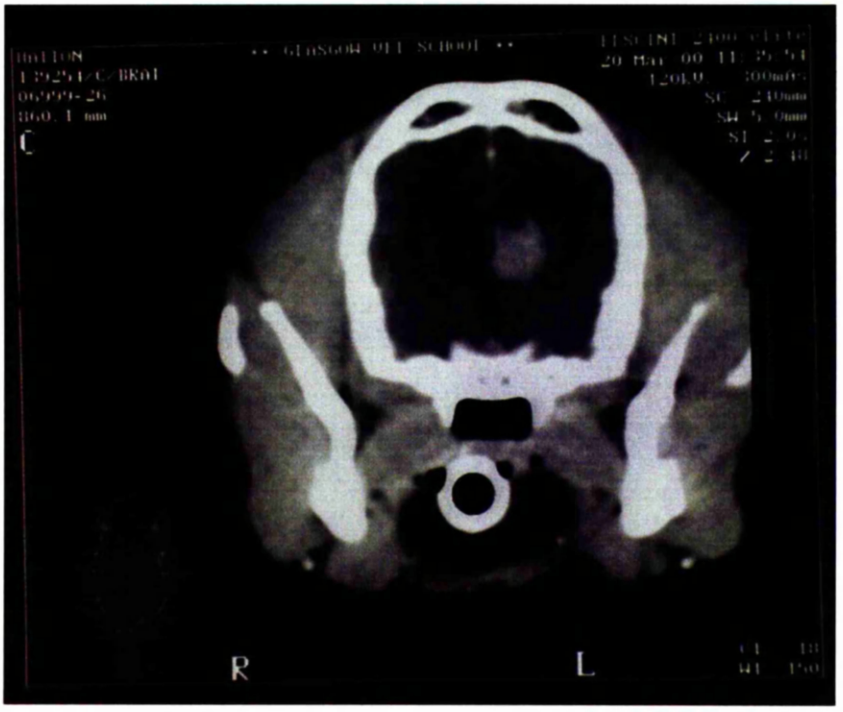


b)

Figure 14. Case 12, 139254. a) Transverse pre-contrast image at the level of the frontal sinuses showing a discrete region of hyperdensity near the midline, ventral to the left lateral ventricle, resulting in distortion and enlargement of both lateral ventricles; b) Transverse post-contrast image at a similar level to a) - the mass enhances intensely and uniformly and has fairly distinct margins; distension of the third ventricle is evident.

Case 13: No. 139848

Signalment: Rough collie, male entire, aged 8 years, weight 27 kg

Diagnosis: mass lesion forebrain located on the floor of the calvarium at the level of the thalamus and extending caudally into the midbrain region; meningioma.

History

The dog was presented with a twenty-four hour history of collapse and profound obtundation. Investigations prior to referral included routine haematology, routine biochemistry, and plain radiographs of the thorax, all of which were unremarkable. The dog had been treated with intravenous fluid-therapy and diazepam, in addition to antibiotic (amoxycillin-clavulanic acid) and corticosteroid (dexamethasone) injections, with no improvement.

Physical examination

On clinical and neurological examination the dog was severely obtunded, had proprioceptive deficits in all four limbs and mild papilloedema in both eyes. Based on these findings a forebrain and / or brainstem lesion was suspected. Intracranial neoplasia, vascular accidents, and inflammatory brain diseases were considered the most likely diagnoses.

Investigations and diagnosis

The standard protocol for investigation of intracranial diseases was performed. Prior to anaesthesia the patient was administered mannitol at the dose of 1 g/kg with the aim of reducing ICP.

The pre-contrast CT images of the brain and skull demonstrated the presence of an isodense to mildly hyperdense large mass on the floor of the calvarium in the region of the thalamus, which extended caudally as far as the midbrain. The mass was relatively broad-based and attached to the meninges. Mass effects consisting of enlarged left lateral ventricle, distorted and slightly enlarged right lateral ventricle, and enlarged and distorted third and fourth ventricles were detected on the plain scans (Figure 15a). Distortion of the ventricular system was detected from the level of the frontal cortex to the midbrain region in both transverse and sagittal images. An irregular pattern of enhancement occurred after injection of contrast agent (Figure 15b,c). A diagnosis of an intracranial space-occupying lesion was made. This mass

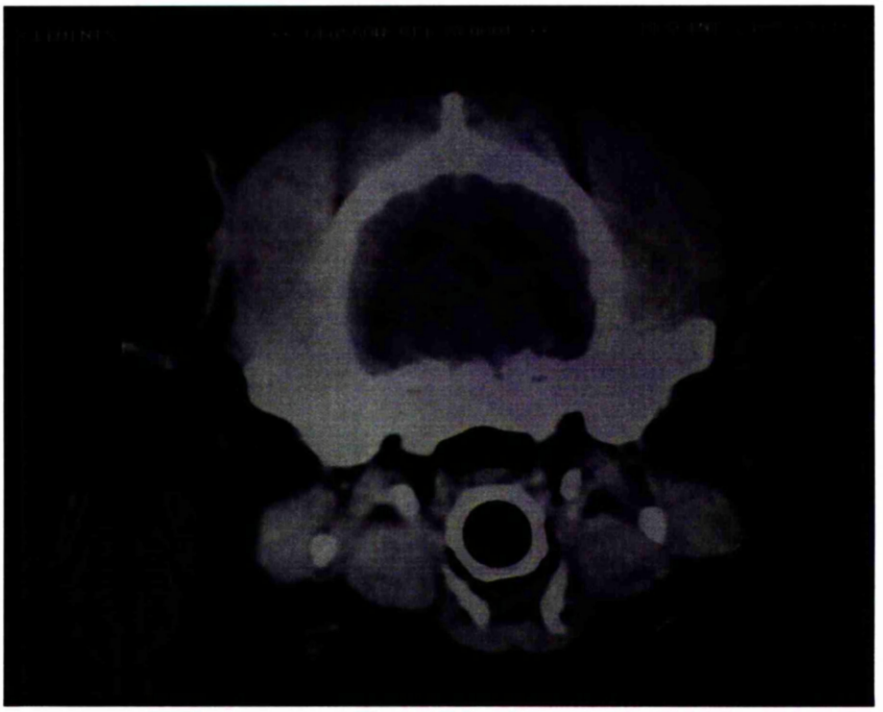
was thought to be most likely neoplastic in nature; meningioma was the main differential diagnosis.

Management and outcome

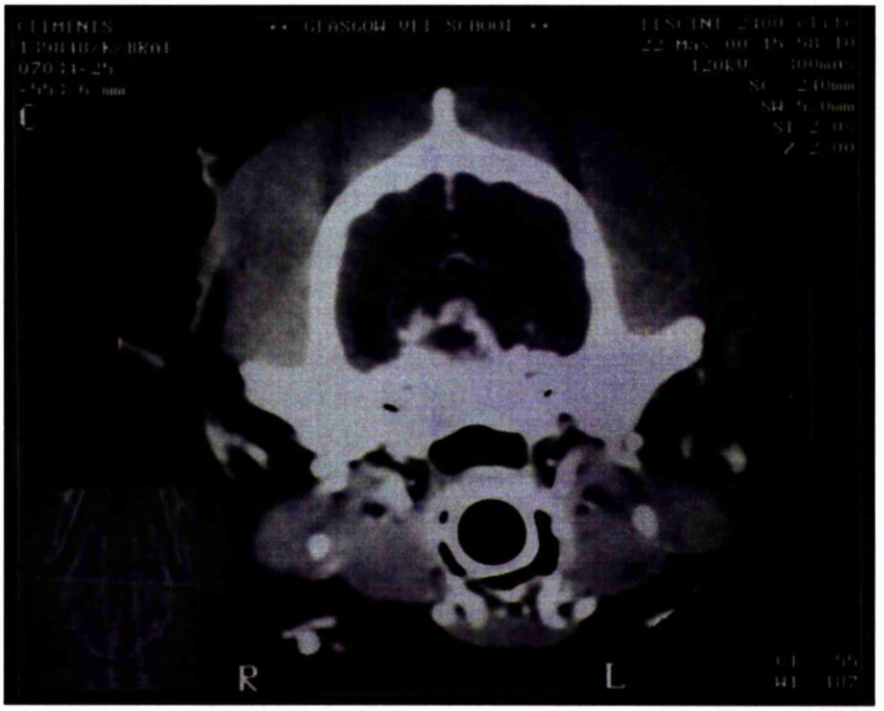
Because of its location and size, the mass was considered unsuited to surgical excision and / or radiation therapy. As they were given a poor prognosis the owners elected for euthanasia.

Post mortem examination

Gross post mortem confirmed the presence of a mass on the ventral aspect of the brainstem at the level of the hippocampus. Histology identified the nature of the mass as a meningioma.

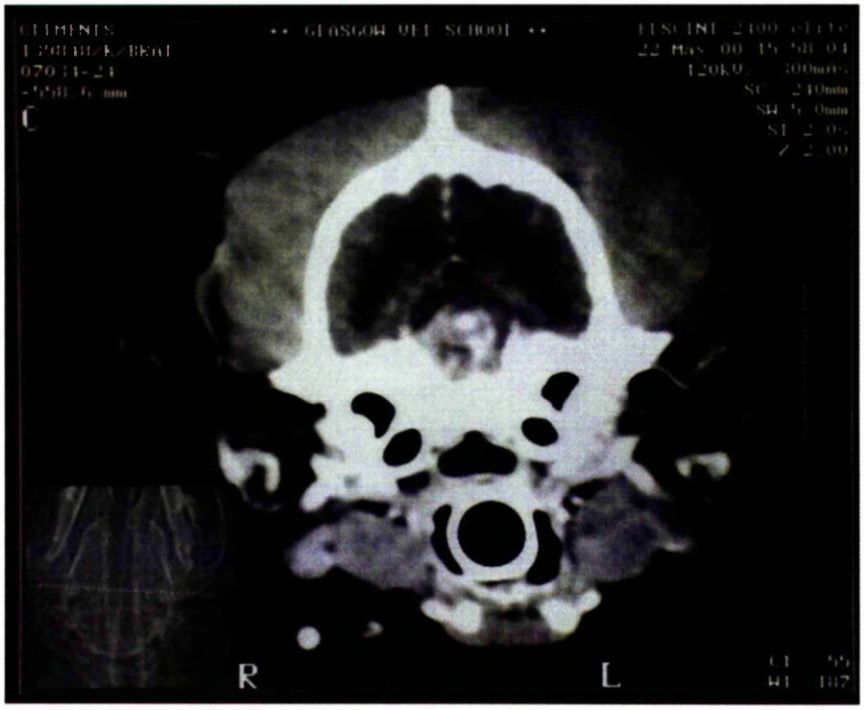


a)



b)

Figure 15. Case 13, 139848. a) Transverse pre-contrast image at the level of the thalamus showing enlarged left lateral ventricle, distorted right lateral ventricle and enlarged and distorted third ventricle. A mildly hyperdense mass may be seen on the floor of the calvarium; b) Transverse post-contrast image at a similar level to a) - note the intense enhancement at the periphery of the mass;



c)

Figure 15 (Cont). Case 13, 139848. c) Transverse post-contrast image approximately at the level of the rostral aspect of the tentorium cerebelli - note the different pattern of enhancement from figure b).

Case 14: No. 138568

Signalment: Bullmastiff, male entire, aged 2 years and 6 months, weight 37 kg

Diagnosis: brainstem neoplasia; histopathology remains unclassified.

History

The dog was presented with a ten-day history of dysphagia, ataxia, vestibular signs and occasional head pressing. Prior to referral the dog had been diagnosed with bilateral otitis media / externa and started on systemic corticosteroids and antibiotic medication in conjunction with topical application of ears drops, with no improvement.

Physical examination

On physical and neurological examination the dog was found to be severely obtunded (Figure 16a), weak and ataxic on all four limbs, with a left head tilt, intermittent positional nystagmus, ventrolateral strabismus of the left eye, absent gag reflex and depressed tongue movements. In addition, the dog occasionally circled to the left. There were increased chest sounds in the ventral lung fields and a mucopurulent nasal discharge. No evidence of otitis was detected.

The multiple cranial nerve deficits (VIII, IX, X and XII) along with the severe depression were consistent with a hindbrain lesion involving the pons and medulla oblongata; mental dullness may be observed as a consequence of disruption of the ascending reticular activating system. Inflammatory brain diseases, neoplasia and hypothyroidism were considered the main differential diagnosis.

Mental dullness, otitis externa, circling and vestibular signs are possible clinical manifestation of hypothyroidism in dogs. Certain primary brain tumours, such as medulloblastoma, choroid plexus papilloma and epidermoid cyst, as well as some inflammatory diseases, including distemper encephalitis and the disseminated form of GME, have a predilection for the pontomedullary area of the brain (Braund 1999). All the above, mentioned tumour types have been reported to occur in dogs younger than 5 years of age (LeCouteur 1999; Moore et al 1996).

Investigations and provisional diagnosis

The standard protocol for investigation of intracranial diseases was performed.

No abnormalities were detected on routine haematology and biochemistry except for increased hepatic enzymes considered secondary to the administration of prednisolone prior to referral (SAP 847 U/l, AST 51 U/l, ALT 161 U/l). T4 and TSH serum concentration was within normal limits.

A megaoesophagus was identified on plain radiographs of the chest along with a diffuse increased opacity of the lungfields consistent with aspiration pneumonia. No discrete masses were identified.

In both pre- and post-contrast CT images of the brain a mild, bilateral enlargement of the lateral ventricles was detected. CSF analysis was within normal limits, as well as Toxoplasma titres, Neospora and Distemper neutralisation dilutions. Myasthenia gravis might have accounted for clinical signs of weakness, megaoesophagus and cranial nerves IX, X and XII dysfunction. However, myasthenic animals are not ataxic and / or obtunded, and the condition was not further investigated. Thymoma, a possible cause of myasthenia gravis, was ruled out with the plain radiographs of the chest (Taylor 2000).

Management and outcome

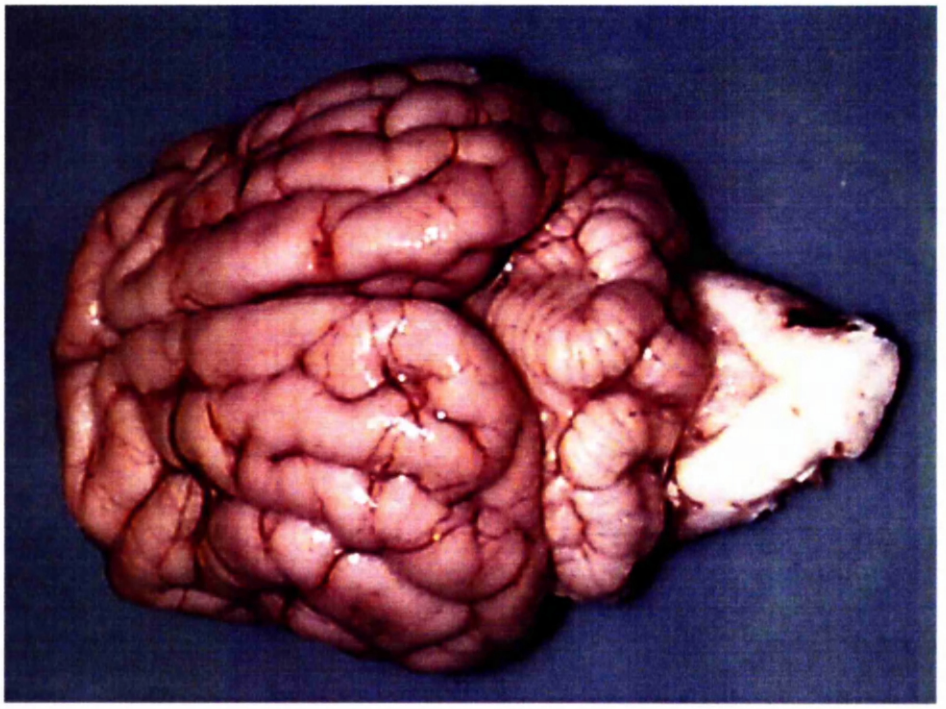
During the period of hospitalisation the dog received parenteral fluid therapy (Compound sodium lactate intravenous infusion BP (Vet), Ivex Pharmaceuticals), intravenous antibiosis (40mg/kg/day amoxycillin/clavulanate; Augmentin Intravenous, Smith Kline Beecham) and was started on immuno-suppressive doses of corticosteroids (prednisolone 4 mg/kg/day) with no improvement.

The prognosis for recovery was considered grave and the owner elected for euthanasia.

Post mortem examination

Gross post mortem (Figure 16b) of the brain revealed a diffuse swelling affecting the medulla and the presence of a pale homogenous mass disrupting the normal brain architecture. Sectioning of the brain at the level of the optic chiasma confirmed the presence of hydrocephalus. Histopathological analysis has not, so far, definitively identified the tumour type, although, the cytological appearance was suggestive of a glial origin.

a)



b)

Figure 16. Case 14, 138568. a) Photograph of the patient to show profound obtundation and weakness; b) gross post mortem appearance of the dorsal surface of the brain – note the generalised swelling of the brain stem and the distortion of the fourth ventricle.

Case 15: No. 139359

Signalment: Weimaraner, male entire, aged 10 years and 8 months, weight 40.5 kg

Diagnosis: mass lesion left hindbrain involving the caudal pole of the cerebellum and the brainstem.

History

The dog was presented with a four-month history of ataxia that had deteriorated over the previous few days. Two weeks before presentation to the Neurology Service the dog had been diagnosed with laryngeal paralysis by the UGVS Soft Tissue Surgery service. This was corrected with an arytenoid lateralisation procedure and the dog was recovering well. At that time plain radiographs of the chest revealed, in addition to aortic calcification and moderate bronchial mineralisation, the presence of a cavitating lesion in the periphery of the right middle lung lobe. The nature of this lesion was not established. Over the two weeks preceding referral the dog developed an intermittent right head tilt and occasionally was seen leaning to the right.

Physical examination

On examination the dog was found to have a mild, but persistent right head tilt, ataxia, mild proprioceptive deficits in all four limbs and an occasional ventral strabismus in both eyes. The reflexes in all four limbs and the function of the cranial nerves were within normal limits. These findings of vestibular disease with upper motor neuron signs in all four limbs were consistent with a lesion in either the caudal fossa or two lesions, one in the spinal cord (most probably C1-C5 segments) and a separate lesion in either the hindbrain or in the middle ear. For an intracranial localisation, primary and secondary neoplasia was considered the main differential diagnosis.

Investigations and diagnosis

The standard protocol for investigation of intracranial diseases was performed.

No abnormalities were detected on the pre-contrast study of the brain and skull (Figure 17a). On the post-contrast CT images a large, ovoid, intensely enhancing paraxial mass, was seen between the caudal pole of the cerebellum and the brainstem. The mass had well defined

margins, extended predominantly left to the midline, and appeared to involve the cerebellopontine angle area (Figure 17b). Post-contrast dorsal images confirmed the location and extent of the mass (Figure 17c).

A diagnosis of an intracranial space-occupying lesion of the caudal fossa was made. The mass was thought to be most likely neoplastic in nature, and the main differential diagnoses included meningioma and choroid plexus papilloma; oligodendroglioma and astrocytoma were also considered in the differential diagnoses.

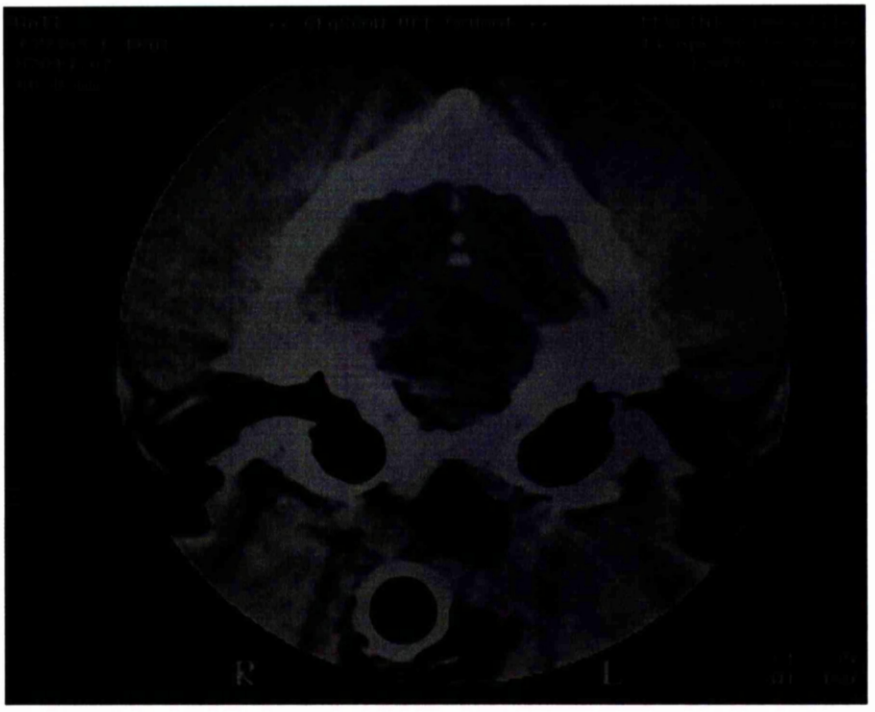
Management and outcome

The location and size of the mass excluded the possibility of surgical excision. The owner elected for palliative management and the dog was discharged on anti-inflammatory doses of prednisolone (1 mg/kg/day).

After starting steroid medication the dog improved markedly, becoming significantly less ataxic; the head tilt also improved. Three weeks after the dog had been diagnosed with intracranial neoplasia, two skin masses appeared, one located on the plantar surface of the left stifle and one on the right side of the prepuce. Fine needle-aspirate and smear examination showed these masses to be mast cell tumours. These masses had most likely arisen independently of the brain tumour; mast cell tumours do not commonly metastasise to the nervous system (Paterson 1998).

No further treatment was instigated as the dog was already on prednisolone, the use of which alone or in combination with other chemotherapeutic agents (Thamm et al 1999) is recommended for disseminated mast cell tumours. In addition the owner did not consider a viable option to start the dog on chemotherapy. The dog at the time of the diagnosis of the mast cell tumour was on 1 mg/kg/day of prednisolone, which almost equates to the chemotherapeutic dose for mast cell tumours (Thamm et al 1999)

During the following seven weeks the patient remained stable although the mast cell tumours became progressively larger. At this point the dog deteriorated acutely, was unable to stand and / or to walk, and developed haematuria with uncontrollable bleeding from the skin tumours. These symptoms were thought to relate to the mast cell tumours and not to intracranial neoplasia. At that point the dog was euthanased; no post mortem examination was performed.



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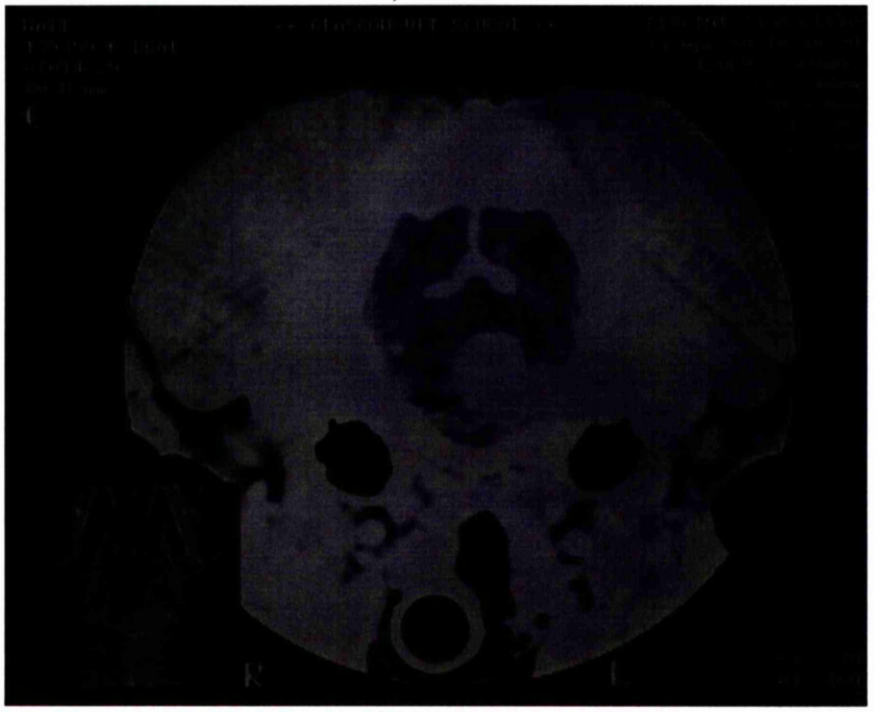
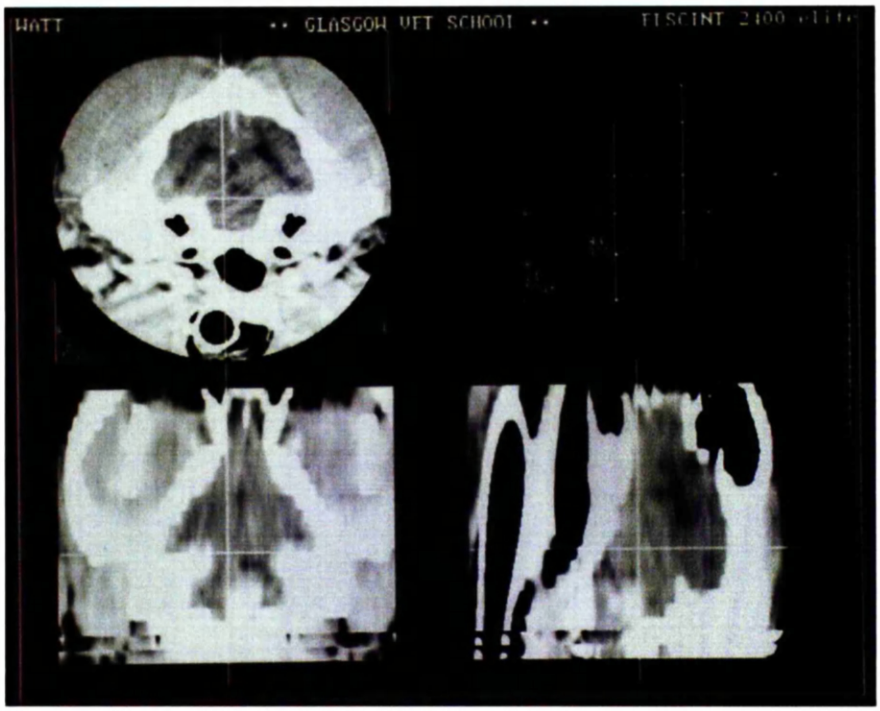


b)

Figure 17. Case 15, 139359. a) Transverse pre-contrast image at the level of the rostral aspect of the tentorium cerebelli- note the absence of morphological abnormalities suggesting a mass; b) Post-contrast study at the level of the caudal fossa, showing the presence of a para-axial, mainly left sided, intensely enhancing mass involving both brainstem and cerebellum - note the involvement of the cerebellopontine angle;



c)

Figure 17 (Cont). Case 15, 139359. c) Post-contrast dorsal and sagittal images highlighting the caudal fossa location of the mass.

Case 16: No. 138763

Signalment: Boxer, female neutered, aged approximately 7 years, weight 23 kg

Diagnosis: pituitary macroadenoma and acromegaly.

History

The dog was presented with a five to six month history of progressive weight loss in addition to vague endocrine and neurological abnormalities. The owner reported that progressive enlargement of the distal part of all four limbs had occurred in addition to the development of behaviour abnormalities consisting of lethargy, wandering, occasionally pacing, head pressing, and circling, the latter often compulsive in character. The history was also suggestive of mild polyuria / polydipsia (PUPD) and increased appetite.

Investigation prior to referral included routine haematology and biochemistry, thyroid function evaluation, urinalysis, radiology of the chest and abdomen, and abdomenal ultrasound, all of which were unremarkable except for mild increase in SAP, ALT and cholesterol.

Physical examination

On examination the dog was found to be thin, obtunded, and to have a strong tendency to circle to the right. The distal part of all four limbs was noticeably enlarged, although neither painful nor oedematous. This enlargement was more pronounced on the forelimbs and on palpation was thought to represent soft tissue enlargement (Figure 18a). Mild hypertrichosis was noted, especially on the hindquarters. The dog also had a broad face with prominent jowls, a protruding mandible, and increased interdental spacing (Figure 18a). Though these features were characteristic of the breed, in this case they were remarkable and the owner, when questioned, reported that they had become more evident over the last few months.

Based on these findings a tumour in the region of the pituitary gland was suspected. Hypertrichosis, enlargement of the head and extremities, increased soft tissue in the oropharyngeal area and PUPD are clinical signs reported in dogs with acromegaly (Feldman & Nelson 1996).

Investigations and provisional diagnosis

Routine biochemistry analysis confirmed the mild abnormalities in SAP (243 U/l), ALT (121.00 U/l) and cholesterol (11.59) reported by the referring veterinary surgeon. These abnormalities are common findings in both hyperadrenocorticism and acromegaly, due to increased secretion of growth hormone. Thus an ACTH stimulation test was performed along with the measurement of basal IGF-I levels. The results of the ACTH stimulation test were unremarkable, whereas the increased levels of IGF-I substantiated a diagnosis of acromegaly (IGF-I > 1,000 nmol/l).

Plain radiographs of the skull identified a slightly thickened calvarium; however, the degree of thickening was considered unremarkable in a dog of this breed. Survey radiographs of the distal part of the forelimbs identified that the enlargement was due to development of the soft tissues.

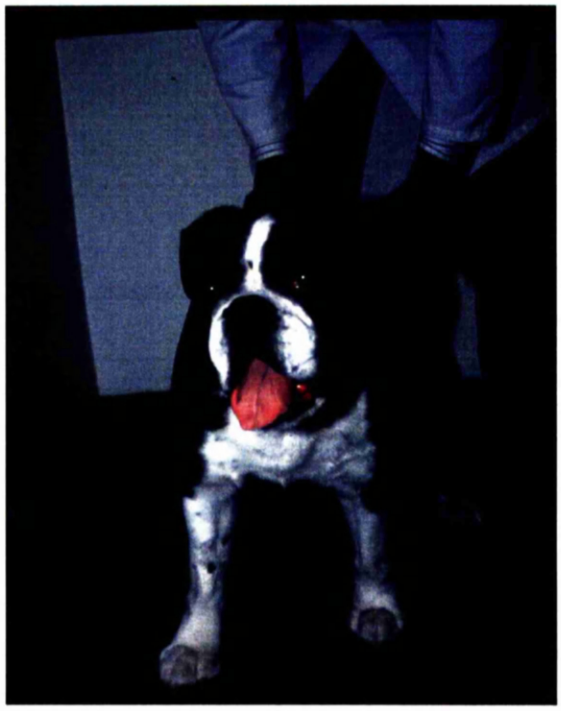
The pre-contrast CT images of the brain and skull demonstrated the presence of a singular, large, ovoid, hyperdense mass at the level of the pituitary fossa. The mass was located on the midline and extended dorsally beyond the sella turcica into the thalamic / hypothalamic area. The mass had distinct and smooth margins and was associated with enlargement of both lateral ventricles (Figure 18b). On the post-contrast study the mass enhanced intensely and uniformly (Figure 18c).

A diagnosis of intracranial neoplasia was made. In conjunction with clinical signs of acromegaly and diencephalic syndrome it was thought the mass was likely to represent an endocrinologically active pituitary macroadenoma, arising from the somatotropic cells. Acromegaly as the result of a pituitary tumour has not previously been reported in the dog (Herrtage 1998a,b). As meningioma in the hypophyseal fossa mimicking the clinical and CT features of pituitary macroadenomas has been described, meningioma was considered in the differential diagnosis, though this would not give an increase in IGF-I.

Management and outcome

The owner elected for palliative management, and the dog was discharged on anti-inflammatory doses of prednisolone (1 mg/kg/day).

After starting steroid medication the demeanour of the dog and the neurological signs improved; the referring veterinary surgeon reported that the behavioural abnormalities were still present but less severe than when the dog was first presented to UGVS. The dog remained stable for the nine months following assessment at UGVS, except for a transient deterioration of behaviour, which occurred approximately 30 weeks after assessment. Nine months after assessment at UGVS a mild recrudescence of neurological abnormalities occurred, with the dog becoming lethargic and occasionally pacing and head pressing. The dog was euthanased approximately nine weeks later because of further deterioration of neurological status in addition to the development of severe dermatitis, which was unresponsive to antibacterial therapy. During the 11 months following assessment at UGVS, the dog had been kept on an unchanged prednisolone dosage regimen. No post mortem examination was performed.



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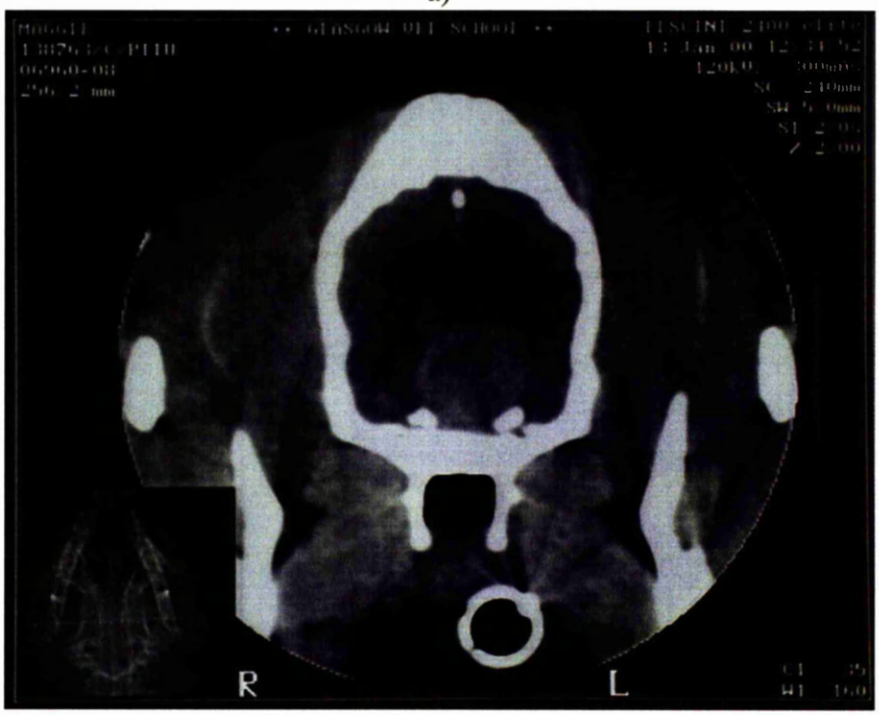
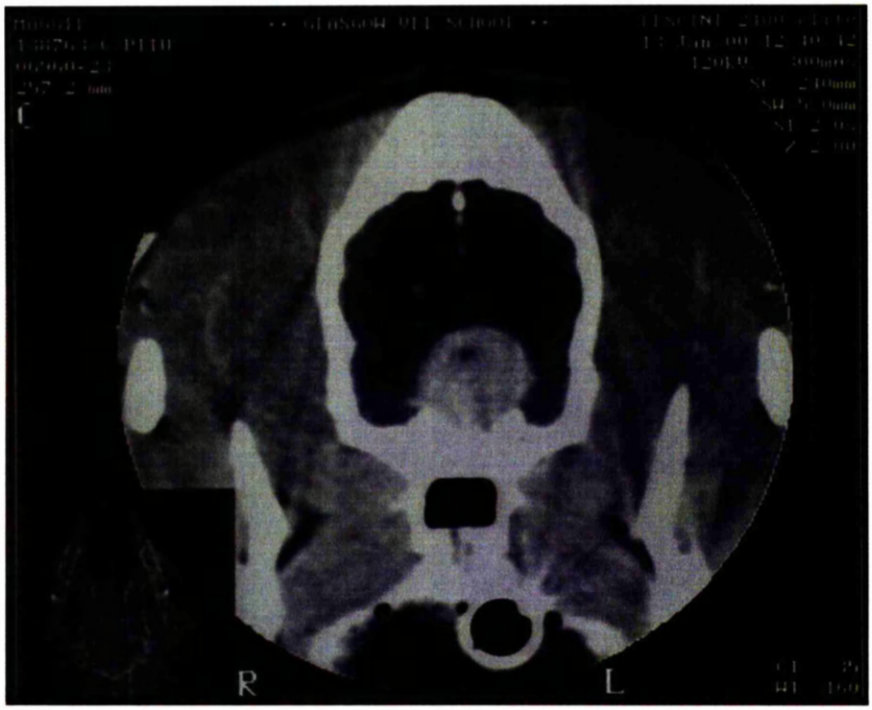


b)

Figure 18. Case 16, 138763. a) Note the broad face and enlargement of the forelimbs; b) Transverse pre-contrast image at the level of the pituitary gland showing the presence of a hyperdense large, ovoid-shaped, midline located mass at the level of the pituitary fossa - note dorsal extension into the thalamic / hypothalamic area and dilation of both lateral ventricles;



c)

Figure 18 (Cont). Case 16, 138763. c) Transverse post-contrast image at the same level as c) showing the intense and uniform enhancement.

Summary of case reports

The aim of this dissertation is to emphasise the need for a systematic diagnostic approach to intracranial disease, with particular regard to the investigation of seizure disorders, which may occur in association with intracranial neoplasia.

The cases presented here highlight the wide variety of clinical presentations associated with brain tumours and illustrate the features of signalment, history and physical examination that are useful in making the clinician suspicious that a brain tumour may be present.

Cases useful in highlighting exceptions from the general guidelines have also been included (cases 7, 8, and 10). Cases have been grouped according to the presenting complaint into four categories: a) animals in which seizure activity was part of the presenting complaint (cases 1 to 10); b) dogs in which seizures were not part of the admitting complaint but whose history and physical examination findings localised the lesion to the forebrain and / or were suggestive of a multifocal / diffuse lesion with forebrain involvement (cases 11, 12 and 13); c) dogs with brainstem signs (cases 14 and 15); and d) dogs with hypothalamic syndrome (case 16).

The investigative protocol in all cases concentrated, initially on assessing potential extracranial causes for the signs of intracranial dysfunction observed. Additional investigations were undertaken as thought appropriate. These included canine distemper virus, Toxoplasma and *Neospora caninum* status, serum lead and phenobarbitone levels, endocrinological function tests, urinalysis and plain radiographs. In some cases, economical restrictions had to be taken into consideration in planning the diagnostic work-up.

All cases involved underwent a CT evaluation of the brain and skull. CSF analysis was only performed if felt to be essential for diagnosis in cases with CT evidence of a mass lesion or overt clinical signs of raised ICP.

Table 17. Summary of case reports

Case identification				Presentation		Diagnosis	Management	Outcome
Case No	age	breed	sex	Signs	Duration			
1 (138470)	14 ys	Border collie	M	• Seizures: isolated, generalised, tonic-clonic	• 5 months	Mass lesion right rostral forebrain (frontal lobe and olfactory bulb) with involvement of the caudal right nasal cavity	Prednisolone 1 mg/kg/day	Full control of seizure activity Sudden death 10 weeks after first assessment at UGVS
2 (139044)	6 ys	Collie-X	M	• Seizures: a) isolated, generalised, tonic-clonic b) clustered, generalised, tonic-clonic • Behavioural changes • Chronic sneezing	• 2 months • 2 weeks • 2 months • 3 months	Mass lesion right rostral forebrain (frontal lobe and olfactory bulb) with involvement of the caudal right nasal cavity	Prednisolone 1 mg/kg/day Phenobarbitone 8 mg/kg/day	Full control of seizure activity for 8 weeks Development of status epilepticus 10 weeks after first assessment at UGVS → euthanasia
3 (140763)	9.5 ys	Lurcher	FN	• Seizures: b) isolated, generalised, tonic-clonic c) clustered, generalised, tonic-clonic	• 2 months • 1 week	Mass lesion right rostral forebrain (frontal and olfactory lobe)	Prednisolone 1 mg/kg/day Phenobarbitone 6.67 mg/kg/day	Full control of seizure activity for 7 weeks Development of severe clusters of seizures 10 weeks after first assessment at UGVS → euthanasia
4 (139076)	11 ys	Collie-X	MN	• Seizures ? • Unsteadiness • Behavioural / mental status changes	• 1 month (all signs)	Multiple mass lesions: a) right rostral forebrain (frontal lobe and olfactory bulb); b) midline mass ventral to the tentorium cerebelli	Prednisolone 1 mg/kg/day	Decreased unsteadiness and improved alertness Development of clustered seizures 3 weeks after assessment at UGVS → euthanasia
5 (140363)	7ys	Golden retriever	F	• Seizures: clustered, generalised, tonic-clonic • Behavioural changes	• 3 months • 1 week	Mass lesion forebrain at the lateral convexity of the left cerebral hemisphere (fronto-parietal cortex junction)	Prednisolone 1 mg/kg/day	Euthanasia at UGVS

6 (140354)	6.5 ys	Boxer	M	• Seizures: isolated, generalised, tonic-clonic • Behavioural / mental status changes	• 2 weeks (all signs)	Mass lesion right forebrain (frontal, temporal, parietal lobes and thalamus) with midbrain involvement		Dramatic deterioration of neurological condition during the 12 hours following admission → Euthanasia at UGVS
7 (139916)	3.5 ys	Labrador retriever	MN	• Seizures: clustered, generalised, tonic-clonic • Changes in mentation • mild gait/balance abnormalities	• 1 month • 2 weeks • 2 weeks	Mass lesion right hindbrain next to the IV th ventricle		Euthanasia at UGVS
8 (139452)	11 ys	Golden retriever	FN	• Seizures: isolated, generalised, tonic-clonic • Behavioural changes	• 3 months (all signs)	Hydrocephalus and intracranial arachnoid cyst	Prednisolone 0.5 mg/kg/day for 3 weeks Phenobarbitone 4 mg/kg/day Ventriculo-peritoneal shunt	Telephone follow up at 10 months following surgery confirmed good seizure control (1 isolated, generalised, tonic-clonic seizure every 6 to 10 weeks) and normal behaviour
9 (138951)	3.5 ys	Border collie	FN	• Seizures: isolated, generalised, tonic-clonic	• 13 months	Idiopathic epilepsy	Phenobarbitone 4 mg/kg/day	Telephone follow up at 12 months after first assessment at UGVS confirmed good seizures control (4 seizures during 12 months)
10 (140277)	7 ys	X-breed	M	• Seizures: isolated, generalised, tonic-clonic	• 4 months	Idiopathic epilepsy	Phenobarbitone 4 mg/kg/day Potassium bromide 25 mg/kg/day*	Progressive improvement of seizures control → at 7 months following assessment at UGVS seizures were reported to occur with a frequency of one every 6 to 7 weeks

Table 17 (cont). Summary of case reports

11 (139250)	5.5 ys	Labrador retriever	M	• Behavioural changes • Ataxia • Blindness ?	• 1 month (all signs)	Mass lesion forebrain (midparietal lobe of the dorsal cerebrum)	Prednisolone 1 mg/kg/day	Remarkable improvement Recurrence of clinical signs 9 weeks after assessment at UGVS → euthanasia 1 week later
12 (139254)	9.5	Cairn terrier	FN	• Behavioural changes • Changes in mentation • Ataxia • 'absence' periods • absent PLRs	• 2 weeks (all signs)	Mass lesion left forebrain (olfactory, frontal and temporal lobes) with ventricular system, thalamic area and midbrain involvement		Dramatic deterioration over the 3 days following assessment at UGVS → euthanasia
13 (139848)	8 ys	Rough collie	M	• Collapse • Profound obtundation	• 24 hours (all signs)	Mass lesion forebrain on the floor of the calvarium at the level of the thalamus with midbrain involvement		Euthanasia at UGVS
14 (138568)	2.5 ys	Bullmastiff	M	• Dysphagia • Ataxia • Vestibular signs • Profound obtundation	• 7-10 days (all signs)	Hindbrain neoplasia and megaesophagus	Prednisolone 4 mg/kg/day I/V fluid-therapy I/V antibiosis	No improvement → Euthanasia at UGVS 24 hours after admission
15 (139359)	11 ys	Weimaraner	M	• Ataxia • Head tilt – right (intermittent) • leaning - right	• 4 months • 2 weeks • 2 weeks	Predominantly left-sided mass lesion hindbrain (caudal pole of the cerebellum and brainstem)	Prednisolone 1 mg/kg/day	Remarkable improvement of neurological signs but acute deterioration mast cells tumour related 10 weeks after first assessment by the neurology service at UGVS → euthanasia
16 (138763))	7 ys	Boxer	FN	• Behavioural / mental status changes • Weight loss • Enlarged extremities • PUPD • Increased appetite	• 5-6 months (all signs)	Pituitary macroadenoma and acromegaly	Prednisolone 1 mg/kg/day	Improvement Deterioration of neurological signs and development of severe dermatitis 11 months after assessment at UGVS → euthanasia

*(introduced by the referring veterinary surgeon 1 month after assessment at UGVS)

Table 17 (cont). Summary of case reports

Tab 18. Summary of diagnostic evaluation

Case identification		Routine clinical pathology			Serology		CT brain & skull	CSF	Other	PME*
Case	Hospital No	Haematology	Biochemistry	Urinalysis	Toxoplasma	Neospora				
1	138470	◦	◦	NE	NE	NE	◦	NE		NP
2	139044	•	•	◦	NE	NE	◦	NE	CT lumbosacral joint: ◦ Plain radiographs abdomen and spine: ◦ Plain radiographs nasal cavity: ♦	NP
3	140763	◦	◦	NE	◦	◦	◦	NE	Serum phenobarbitone level: ◦	NP
4	139076	◦	◦	NE	NE	NE	◦	NE	Plain radiographs chest and abdomen: ◦	NP
5	140363	◦	◦	NE	◦	◦	◦	NE		◦
6	140354	◦	◦	NE	◦	◦	◦	NE	Serum lead concentration: ◦	◦
7	139916	◦	◦	NE	◦	◦	◦	NE	Serum lead concentration: ◦	◦
8	139452	◦	◦	NE	◦	◦	◦	NE	Serum phenobarbitone level: •	alive
9	138951	◦	◦	NE	◦	◦	◦	◦	Serum phenobarbitone level: ◦ / •	alive
10	140277	♦	♦	NE	◦	◦	◦	◦	Ophthalmologic examination: ◦ Serum phenobarbitone level: •	alive
11	139250	◦	◦	NE	◦	◦	◦	NE		NP
12	139254	◦	◦	NE	NE	NE	◦	NE	Ophthalmologic examination: ◦	NP
13	139848	◦	◦	NE	NE	NE	◦	NE	Ophthalmologic examination: ◦	◦
14	138568	◦	♦	NE	◦	◦	◦	◦	T4 and TSH serum concentration: ◦ Serum and CSF distemper titres: ◦ Plain radiographs chest: ◦	◦
15	139359	◦	◦	NE	NE	NE	◦	NE	Fine needle aspirate (skin mass lesions): ◦ (Mast cells tumour)	NP
16	138763	◦	♦	NE	NE	NE	◦	NE	ACTH stimulation test: ◦ Basal IGF-I serum concentration: ◦ Plain radiographs skull and forelimbs: ◦	NP

(◦) unremarkable; (•) unremarkable – performed by the referring veterinary surgeon; (◦) space-occupying lesion or other morphological abnormalities; (♦) mild abnormalities

NE: not evaluated; NP: not performed. *(PME) post-mortem examination.

Tab 19. Summary of CT findings in reported cases

Case identification		Pre-contrast			Post-contrast	Differential diagnoses
Case	Hospital No	Location of the mass	Features of the mass	Mass effect		
1	138470	R rostral forebrain (FL, OL, OB) + R caudal nasal cavity; eccentric	Singular, ovoid poorly defined margins Hypodense	Midline shift: L displacement falx cerebri Bone erosion (cribriform plate + others)	Thin, irregular, poorly defined rim of enhancement	*Mengioma* *Nasal neoplasia* Astrocytoma Oligodendroglioma
2	139044	R rostral forebrain (FL, OL, OB); eccentric	Singular, ovoid well to poorly defined margins Isodense to hyperdense	Midline shift: L displacement falx cerebri and brain tissue Bone erosion (cribriform plate)	Intense and mostly uniform enhancement Second mass visible within the R caudal ethmoid turbinates	*Mengioma* *Nasal neoplasia*
3	140763	R forebrain (FL, OL, OB); deeply located	Singular, ovoid, poorly defined margins Hypodense	Midline shift: L displacement falx cerebri	Thin, irregular, poorly defined rim of enhancement	*Oligodendroglioma* *Astrocytoma*
4	139076	R forebrain (FL); eccentric	Singular, ovoid, poorly defined margins, Hypodense	Midline shift (from olfactory area to the midbrain region): L displacement falx cerebri and both LVs) Abnormal morphology V.S. distorted R and L LVs enlarged L LV Cerebral oedema perilesional hypodensity and corona radiata patter Bone erosion (cribriform plate) Mineralisation falx cerebri	Non-homogeneous enhancement Second mass lesion: midline; ventral to the tentorium cerebelli	Forebrain lesion: *Meningioma* *Nasal neoplasia* Midbrain lesion: Meningioma Metastasis / focal extension forebrain lesion Metastasis from a primary extracranial neoplasia

5	140363			Hyperostosis Cerebral oedema: irregular, thin, area of hypodensity (L cerebral hemisphere: parietal/frontal lobes junction)	Intense and strong enhancement of a solitary, broad-based, plaque-like, extra-axial mass Lateral convexity L cerebral hemisphere: fronto-parietal cortical junction	*Meningioma*
6	140354			Midline shift (from frontal cortex area to the midbrain region): L displac. falx cerebri and R LV Abnormal morphology V.S. Enlarged R and L LV Compressed and distorted R LV Cerebral oedema corona radiata pattern (R cerebral hemisphere)	Intense non-homogeneous rim of enhancement; R forebrain (FL, TL, PL, thalamic area, M); deeply located Necrosis wide central area of hypodensity	*Oligodendroglioma* *Astrocytoma*
7	139916	R hindbrain (next to the fourth V); eccentric	Singular, ovoid distinct, smooth margins broad base of attachment to the petrous bone Hyperdense	Midline shift: L displacement brainstem and cerebellum Abnormal morphology V.S compressed fourth V	Intense and uniform enhancement Cerebral oedema (peripheral rim of hypodensity) Second smaller enhancing mass at the level of IVth V	*Meningioma* *Choroid plexus papilloma* Ependimoma
8	139252	entire telencephalon		Extreme dilation of both LVs and third V Fluid filled cyst-like structure with sharp margins in the region of the quadrigeminal cistern	unremarkable	*Hydrocephalus and ICA cyst*
9	138951					No abnormalities detected
10	140277					No abnormalities detected

Table 19 (cont). Summary of CT findings in reported cases

11	139250	Forebrain midline located mass (mid-parietal lobe of the dorsal cerebrum); eccentric	Solitary, large, ovoid poorly defined margins mildly hyperdense	Midline shift (from thalamic area to the midbrain region): R displacement falx cerebri Abnormal morphology V.S. enlarged L and R LVs	Intense and relatively uniform enhancement Cerebral oedema: perilesional rim of hypodensity	*Meningiomas* *Oligodendroglioma* *Astrocytoma*
12	139254	L Forebrain (ventricular system, OL, FL, TL, thalamic area and M); deeply located	Solitary, mostly ovoid poorly defined margins Hyperdense	Abnormal morphology V.S. compressed and distorted L LV enlarged R LV and third V	Intense and uniform enhancement with fairly distinct margins	*Choroid plexus papilloma* Ependymomas Oligodendroglioma GME
13	139848	Forebrain (floor of the calvarium from the level of the thalamus to the M region); extra-axial	Solitary, mostly ovoid, well defined margins broad-based Isodense to mildly hyperdense	Abnormal morphology V.S. distorted and slightly enlarged R LV enlarged L LV enlarged and distorted third and fourth Vs	Intense enhancement; irregular pattern	*Meningioma*
14	138568			Abnormal morphology V.S. slightly enlarged R and L LVs	unremarkable	No space-occupying lesion/s detected
15	139359				Solitary, ovoid, intensely enhancing, mass; well defined margins L hindbrain: caudal pole cerebellum and brainstem; paraxial	*Meningioma* *Choroid plexus papilloma* Oligodendroglioma Astrocytoma
16	138763	Pituitary fossa (dorsal extension into the thalamic / hypothalamic area); midline	Solitary, ovoid distinct, smooth margins Hyperdense	Abnormal morphology V.S. enlarged R and L LVs	Intense and uniform enhancement	*Pituitary macroadenoma* meningioma

(FL) frontal lobe; (L) left; (L LV/s) left lateral ventricle/s; (M) midbrain; (OB) olfactory bulb; (OL) olfactory lobe; (R) right; (R LV/s) right lateral ventricle/s; (TL) temporal lobe; (V.S.) ventricular system;

Table 19 (cont). Summary of CT findings in reported cases

Tab 20. Summary of clinical pathology results in reported cases

Clinical pathology report[1]												
a) Biochemistry panels												
analyte	range	units	Case 1 (138470)	Case 2[2] (139044)	Case 3 (140736)	Case 4 (139076)	Case 5 (140363)	Case 6 (140354)	Case 7 (139916)	Case 8 (139452)		
Sodium (Na)	136-159	mmol/l	149.00	147.00 (139-154)	143.00	146.00	140.00	143.00	142.00	143.00	127.00	132.00
Potassium (K)	3.4-5.8	mmol/l	4.40	4.50 (3.6-5.6)	4.50	4.50	4.30	4.40	4.50	3.90	4.20	4.20
Na/K ratio	> 27		33.90	32.70	31.80	32.40	32.60	32.50	31.60	36.70	30.20	31.40
Chloride (Cl)	95-115	mmol/l	113.00		114.00	116.00	113.00	108.00	119.00	110.00	93.00	95.00
Calcium (Ca)	2.34-3.00	mmol/l	2.56	2.47 (2.30-3.00)	2.50	2.67	2.40	2.47	2.63	2.67	2.49	2.30
SAP	< 230	U/l	66.0	75.0 (20-60)	91.00	322.00	101.00	158.00	114.00	85.00	988.00	783.00
AST	< 40	U/l	17.0		41.00	11.00	25.00	15.00	25.00	23.00	36.00	38.00
ALT	< 90	U/l	37.00	40 (15-60)	48.00	23.00	40.00	69.00	66.00	48.00	228.00	123.00
GGT	< 20	U/l	5.00		5.00	7.00	6.00	14.00	4.00	6.00	38.00	19.00
Cholesterol	2.0-7.0	mmol/l	6.22		7.73	8.73	7.49	5.05	10.37	9.12	3.75	3.97
Glucose	3.3-5.5	mmol/l	5.50	4.90 (3.00-5.00)	6.40	4.80	4.80	6.30	5.50	5.80	6.70	ne
Triglyceride	< 0.6	mmol/l	0.27		0.93	0.70	0.58	0.43	3.06	0.79	1.74	0.93
Urea	2.5-8.5	mmol/l	5.80	6.60 (1.70-7.4)	5.00	4.30	4.90	8.50	5.40	4.10	4.90	9.60
Creatinine	45-155	µmol/l	95.00	103 (0.00-106)	97.00	103.00	94.00	114.00	111.0	109.00	103.00	80.00
Phosphate	1.29-2.90	mmol/l	1.21	1.08 (0.90-2.0)	0.57	1.46	1.31	1.76	1.28	0.70	1.71	1.71
Bilirubin	< 10	µmol/l	2.00		3.00	2.00	3.00	0.00	2.00	4.00	2.00	1.00

[1] Diagnostic services, UGVS, Bearsden Road, Bearsden, Glasgow G61 1QH

[2] Diagnostic service (internal), Department of Veterinary Clinical Studies, R .(D). S.V.S., Easter Bush, Roslin, Midlothian EH25 9RG

Total protein	50-78	g/l	65.00	58.40 (58-73)	63.00	69.00	60.00	66.00	72.00	68.00	62.00	57.00
Albumin (A)	29-36	g/l	37.00	25.80 (26-35)	38.00	39.00	33.00	34.00	38.00	39.00	34.00	29.00
Globulin (G)	28-42	g/l	28.00	32.60 (18-37)	25.00	30.00	27.00	32.00	34.00	29.00	28.00	28.00
A/G ratio			1.32		1.52	1.30	1.22	1.06	1.12	1.34	1.21	1.04
Bile acids (fasting)				51.10 (0.00-7.00)								
b) Haematology panels												
WBC	6.0-12.0	X10^9/l	6.660	8.200 (6.000-15.000)	5.610	6.320	7.210	8.100	10.100	7.820	10.500	17.300
neutrophils	3.0-11.8	X10^9/l	4.330	5.986 (3.6-12.000)	4.710	3.920	4.250	6.160	4.550	6.410	8.400	13.670
lymphocytes	0-4.8	X10^9/l	1.470	1.722 (0.700-4.800)	0.450	1.640	2.310	1.050	3.840	0.860	1.160	1.210
monocytes	0.15-1.35	X10^9/l	0.270	0.410 (0.00-1.500)	0.220	0.320	0.290	0.730	0.710	0.470	0.630	1.210
eosinophils	0.1-1.25	X10^9/l	0.600	0.082 (0.00-1.000)	0.170	0.440	0.360	0.080	0.910	0.080	0.000	0.000
basophils	0.00-0.20	X10^9/l	0.000	0.000 (0.00-0.200)	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
RBC	5.5-8.5	X10^12/l	7.980	5.970 (5.5-8.5)	7.970	8.000	6.180	6.640	6.990	6.400	6.020	4.240
HB	12.0-18.0	g/dl	19.0	14.5 (12.0-18.0)	19.4	19.3	15.4	16.0	17.0	15.7	14.8	10.4
HT	37-55	%	50.9	38.9 (39-55)	56.2	53.2	42.4	43.6	45.6	42.0	39.4	27.9
MCV	60.0-77.0	fl	63.7	65.1 (60.0-77.0)	70.5	66.5	68.7	65.7	65.3	65.7	65.4	65.9
MCH	32.0-36.0	g/dl	23.8		24.3	24.1	25.0	24.1	24.3	24.6	24.6	24.7
MCHC	32.0-36.0	g/dl	37.3	37.3 (32.0-36.0)	34.4	36.2	36.4	36.7	37.2	37.4	37.6	37.5

Tab 20 (cont). Summary of clinical pathology results in reported cases

RDW		%	16.0		15.4	14.8	14.2	15.4	15.4	15.2	16.4	15.4
PLT	200-500	X10^9/l	387	238 (200-500)	210	316	245	9.00[3]	161[4]	426	338	286
MPV		fl	6.010		11.600	5.530	6.920			6.210	6.150	8.380
PCT		%	0.230		0.240	0.180	0.170			0.270	0.210	0.240
PDW		%	16.600		19.800	16.900	17.400			17.400	18.100	18.200
c) Serology												
Toxoplasma[5] (Dye test titre)	negative ≤ 30	iu/ml			15		< 8	15	30	< 8		
Neospora[6] (IFAT titres)	negative ≤ @ 1 : 50				1 : 50		1 : 50	1 : 50	1 : 50	1 : 50		
d) Lead[7]												
(plasma level)	0.5-2.4	µmol/l						0.1	< 0.01			
f) Endocrinological function tests												
Thyroxine (T4)	15-45	nmol/l		24.00 (15.00-48.00)								
TSH	0.01-0.69	ng/ml										
g) Serum phenobarbitone (PB) level[8]												
PB	15-45	mg/l			17.90							
h) Urinalysis												
qualit. protein				trace								
qualit. glucose				-Ve								
qualit. ketone				-Ve								
qualit. blood				-Ve								

[3] the low platelet count was likely an artefact: fibrin clots / platelet aggregates with degranulation were present in the sample
[4] small platelet aggregates were present - platelet number was normal
[5] Scottish Toxoplasma Reference Laboratory, Raigmore Hospital NHS Trust, Inverness
[6] Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA.
[7] Capitol Diagnostics, Bush Estate, Penicuik EH26 0QE
[8] Capitol Diagnostics, Cleeve Gardens, Perth PH1 1HF

Tab 20 (cont). Summary of clinical pathology results in reported cases

qualit. pH				6.0								
qualit. SG				1.034								
RBC				-Ve								
WBC				-Ve								
E.C. Small				+Ve								
E.C. Medium				-Ve								
E.C. Large				-Ve								
Sperm				+++Ve								
Organism				-Ve								
Cell debris				+Ve								
Yeast				-Ve								
Casts - Hyaline				-Ve								
Casts - Granular				-Ve								
Casts epithelial				-Ve								
Casts - RBC				-Ve								
Casts - WBC				-Ve								
Crystals				none found								

Clinical pathology report (Cont.)											
a) Biochemistry panels											
analyte	range	units	Case 9 (138951)		Case 10 (140277)	Case 11 (139254)	Case 12 (139254)	Case 13 (139848)	Case 14 (138568)	Case 15 (139359)	Case 16 (138763)
Sodium (Na)	136-159	mmol/l	144.00	140.00	139.00	144.00	147.00	151.00	146.00	144.0	146.00
Potassium (K)	3.4-5.8	mmol/l	4.20	4.00	3.80	3.90	3.80	3.30	3.90	4.10	3.90
Na/K ratio	> 27		34.30	35.00	36.60	36.90	38.70	45.80	37.40	35.10	37.40
Chloride (Cl)	95-115	mmol/l	113.00	113.00	113.00	109.00	106.00	121.00	104.00	108.00	108.00
Calcium (Ca)	2.34-3.00	mmol/l	2.31	2.28	2.47	2.46	2.44	2.80	2.51	2.66	2.48
SAP	< 230	U/l	220.0	850.0	307.00	112.00	106.00	88.00	847.00	62.00	243.00
AST	< 40	U/l	32.0	35.00	18.00	20.00	71.00	28.00	51.00	26.00	20.00
ALT	< 90	U/l	30.00	59.00	34.00	38.00	17.00	96.00	161.00	77.0	121.00
GGT	< 20	U/l	9.00	7.00	7.00	4.00	16.00	7.00	0.48	1.06	3.00

Tab 20 (cont). Summary of clinical pathology results in reported cases

Cholesterol	2.0-7.0	mmol/l	3.55	3.52	4.92	6.48	3.88	8.31	7.45	6.12	11.59
Glucose	3.3-5.5	mmol/l	5.20	6.10	5.50		5.10	6.90	6.00	5.70	5.60
Triglyceride	< 0.6	mmol/l	0.46	0.32	0.49	0.41	0.27	0.53	0.48	1.06	0.60
Urea	2.5-8.5	mmol/l	7.50	4.80	4.60	4.00	4.20	6.30	6.00	11.00	3.50
Creatinine	45-155	µmol/l	96.00	90.00	92.00	103.00	79.00	122.00	118.0	134.00	78.00
Phosphate	1.29-2.90	mmol/l	1.12	1.07	1.12	1.39	1.89	1.15	1.66	1.11	1.79
Bilirubin	< 10	µmol/l	3.00	1.00	3.00	2.00	1.00	3.00	1.00	4.00	3.00
Total protein	50-78	g/l	56.00	56.00	69.00	62.00	65.00	76.00	73.00	70.00	65.00
Albumin (A)	29-36	g/l	34.00	32.00	39.00	40.00	37.00	45.00	45.00	37.00	34.00
Globulin (G)	28-42	g/l	22.00	24.00	30.00	22.00	28.00	31.00	28.00	33.00	31.00
A/G ratio			1.55	1.33	1.30	1.82	1.32	1.45	1.61	1.12	1.10
b) Haematology panels											
WBC	6.0-12.0	X10^9/l	6.660	8.760	18.300	8.260	13.300	18.300	8.550	10.000	6.630
neutrophils	3.0-11.8	X10^9/l	5.000	6.750	12.810	5.530	11.700	14.820	7.520	8.300	4.240
lymphocytes	0-4.8	X10^9/l	0.730	0.880	2.560	1.320	0.800	0.730	0.680	1.200	1.660
monocytes	0.15-1.35	X10^9/l	0.330	0.610	1.650	0.580	0.800	0.730	0.340	0.500	0.530
eosinophils	0.1-1.25	X10^9/l	0.600	0.530	1.280	0.740	0.000	0.000	0.000	0.000	0.130
basophils	0.00-0.20	X10^9/l	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
RBC	5.5-8.5	X10^12/l	6.890	6.750	5.800	6.790	6.190	7.610	6.960	6.900	5.390
HB	12.0-18.0	g/dl	16.500	16.3	14.900	16.200	16.0	18.2	16.8	15.3	13.9
HT	37-55	%	44.8	45.6	39.0	42.700	42.4	51.0	46.9	41.9	37.4
MCV	60.0-77.0	fl	65.0	67.5	67.1	62.8	68.5	67.1	67.4	60.8	69.3
MCH	32.0-36.0	g/dl	24.0	24.2	25.7	23.9	25.9	14.0	24.1	22.1	25.7
MCHC	32.0-36.0	g/dl	36.9	35.9	38.2	38.1	37.7	35.7	35.8	36.4	37.1
RDW		%	15.2	15.6	15.2	15.3	13.5	15.0	14.6	15.9	13.0
PLT	200-500	X10^9/l	297	337	255	258	566	283	162	400	531
MPV		fl	7.570	10.200	9.020	5.920	5.140	6.870	7.760	5.700	5.600
PCT		%	0.230	0.340	0.230	0.150	0.290	0.190	0.130	0.230	0.300
PDW		%	17.800	18.900	18.400	16.300	16.900	17.600	18.500	16.500	16.900

Tab 20 (cont). Summary of clinical pathology results in reported cases

c) Serology											
Toxoplasma (Dye test titre)	negative ≤ 30	iu/ml			30	< 8			15		
Neospora (IFAT titres)	negative ≤ @ 1 : 50		1 : 50		1 : 50	1 : 50			1 : 50		
Distemper[9] (neutralization dilution titres)									No significant titres in both serum and CSF		
e) Endocrinological function tests[10]											
Thyroxine (T4)	15-45	nmol/l		24.00 (15.00-48.00)					16.90		
TSH	0.01-0.69	ng/ml							0.10		
IGF-I	< 1,000	ng/ml									1,092
Cortisol Pre ACTH Post ACTH	 > 600	 nmol/l nmol/l									 64.5 483.50
f) Serum phenobarbitone (PB) level											
PB	15-45	mg/l	Two weeks after first assessment at UGVS[11] 15.2	21.2	Two weeks after first assessment at UGVS[11] 18.6 trough 21.6 peak						
h) CSF analysis											
cell count	0-5	cells/µl	2		1				2		
total protein	< 250	mg/l	112		78.0				130		
cytospin			unremarkable		unremarkable				unremarkable		

[9] Canine Infectious Disease Research Unit, UGVS
[10] Cambridge Specialist Laboratory Services, Stapleford, Cambridge CB2 5XY
[11] performed at the referring veterinary practice

Tab 20 (cont). Summary of clinical pathology results in reported cases

Discussion

Seizures are the reflection of a state of increased neuronal excitability and / or synchronisation (Heinemann & Eder 1997; March 1998). Increased neuronal excitability and / or synchronisation may occur in association with a wide spectrum of conditions capable of disrupting, temporarily and / or permanently, normal cerebrocortical function. A detailed history and a carefully conducted physical and neurological examination are fundamental to rationally elaborate a list of differential diagnoses, and hence planning the diagnostic work-up accordingly.

Lesion localisation

Signs of forebrain disease

Though not indicative of a specific aetiology seizures, by definition, always localise the lesion to the forebrain if toxic and metabolic causes can be ruled out (Kraus & McDonnell 1996). Animals with forebrain lesions, which have the potential to promote seizures activity, can also manifest other neurological deficits indicative of forebrain dysfunction (Bagley et al 1999a). Close observation and evaluation of consciousness, behaviour, posture of head, trunk and limbs, as well as gait, are necessary (Schwartz-Porsche 1999). This is the reason why all cases presented for evaluation of seizure disorders, undergo a neurological examination as detailed as that reported in Figure 3 (page 44) and Figure 4 (page 45).

Seizures in animals that exhibit interictal neurological deficits are indicative of an underlying, structural brain disease (symptomatic epilepsy) (March 1998). However, in two (cases 1 and 3) of the eight cases (cases 1-8) reviewed here for which a structural brain abnormality was identified (seven space-occupying lesion and one case of hydrocephalus-IAC) the history and physical examination findings did not suggest / detect interictal neurological abnormalities (Tab 21, page 133). This observation suggests that whereas animals with interictal abnormalities always have a structural brain disease, a normal interictal period does not rule out that a structural brain disease is the cause of the observed seizure activity.

Primary idiopathic epilepsy is thought to be the result of multifocal or diffuse unrecognised morphological and / or functional abnormalities of the cerebral cortex (March 1998;

Table 21. Summary of case reports exhibiting signs of forebrain dysfunction at presentation

No of cases with seizures		No of cases without seizures
10 (Cases 1 - 10)		**3** (Cases 11 - 13)
with interictal neurological a/n	**6**	3/3 → structural brain disease***
6/6 → structural brain disease (Cases 2, 4, 5, 6, 7 and 8)		
without interictal neurological a/n	**4**	
2/4* → structural brain disease 2/4** → idiopathic epilepsy *(Cases 1 and 3) **(Cases 9 and 10)		*** 3/3 had neurological abnormalities

a/n: abnormalities

Westbrook 2000). Diagnosis of idiopathic epilepsy is reached via exclusion of other possible extracranial and intracranial causes of seizures. Lack of interictal abnormalities and typical age at onset are the two clinical features most useful in making the clinician consider IE as a possible diagnosis (Knowles 1998). In the two cases of idiopathic epilepsy included in this series (cases 9 and 10) neither showed interictal neurological abnormalities (Tab 21, page 133). As I have described above the lack of interictal abnormalities does not rule out symptomatic epilepsy and such findings must be put in the context of other features of the case.

Although seizures are one of the most common clinical signs in animals with forebrain disease (Braund 1999), all pathologic processes capable of resulting in seizure activity may also occur without being accompanied by seizures. Thus, neurological deficits indicative of forebrain dysfunction other than seizures may be the only clinical signs detectable in patients with intracranial disease (e.g., case 12).

Deranged mental status and behavioural changes as a indicator of forebrain disease

Animals with forebrain disease frequently manifest mental status and / or behavioural changes such as: apathy, disorientation, obtundation, stupor, failure to recognise the owner and familiar people, lack of recognition of environment, loss of trained habits and, occasionally hyperexcitability or aggression. Abnormal propulsive movements such as pacing, circling (usually toward the side of the lesion) and head pressing are also common (Braund 1999; de Lahunta 2000a).

Changes in mental status and / or behaviour are likely to be in the history. Conversely, these abnormalities are often not recognised / detected by the veterinary surgeon during examination. In six (cases 4, 6, 11-13 and 16) of the nine cases (2, 4-6, 8, 11-13, and 16) exhibiting derangement of mental status / behavioural changes as part of the presenting complaint, which had a diagnosis of a structural lesion affecting the forebrain, such changes could be detected at the time of examination. In three other cases with structural brain disease (cases 2, 5 and 8) neurological examination was unremarkable. This emphases the need in all cases of suspected intracranial disease, for careful questioning the client regarding behaviour and personality (see History and physical examination, page 40). This is particularly true for brain tumour patients, which often suffer a slow progression (over months) of early, non-

specific signs such as dulling of personality. These signs are commonly initially attributed to "old age" and may not be recognised by both owners and veterinary surgeons (Dewey et al 2000). Between the six cases above mentioned with forebrain disease and detectable mental status / behavioural change at the time of presentation, a more severe obtundation was observed in patients with extensive involvement of the thalamic and midbrain regions (cases 6, 12 and 13). The thalamus and midbrain contribute to the reticular activating system (RAS). The function of the RAS is to diffusely alert the entire cerebral cortex; lesions of each of its components may result in stupor and coma (Chrisman 1990).

Proprioceptive deficits and gait abnormalities

Proprioception depends on the successful integration and performance of many components of the CNS and PNS. Postural reactions are frequently abnormal in animals with brain disease. They may occur in combination with cranial nerve deficits, especially with brainstem lesions caudal to the midbrain, or may be the only sign of intracranial disease. The finding of postural reaction deficits in combination with cranial nerve dysfunction is especially significant, since it provides evidence that a lesion lies within the CNS, rather than the PNS (Jeffery 2001).

Abnormalities in the gait are often apparent in animals that have lesions in the spinal cord or parts of the brain caudal to the midbrain; the induced deficit is ipsilateral to the lesion (Jeffery 2001). Gait abnormalities, if present, consist of sensory (general proprioceptive) ataxia accompanied by UMN hemi/ or tetraparesis depending upon location and extension of the lesion; patients adduct / abduct the limbs while walking and occasionally "knuckle". A delayed onset (long stride) and prolonged protraction of limbs movements is noticed (de Lahunta 2000a). Conversely, forebrain lesions will often cause no deficits in the gait (although there may be abnormalities in control of the direction that the dog walks), but there are frequently deficits in postural reactions controlateral to the lesion (Braund 1999; Dewey at al 2000; Jeffery 2001). Animals with unilateral thalamic or cerebral cortical disease usually exhibit contralateral postural deficits, whereas in animals with multifocal or diffuse thalamic and cerebral cortex lesions postural reaction deficits may be present in all four limbs (Chrisman 1990; de Lahunta 2000a).

Careful evaluation of the postural reactions and spinal reflexes in patients with depressed postural reactions is important in differentiating between intracranial and spinal cord disease

(Braund 1999; de Lahunta 2000a). Results of muscle tone and muscle bulk evaluation contribute to further substantiate a postural deficit that is UMN in origin. The neurological deficits in limb coordination associated with disease in the rostral spinal cord (C1-C5) may be very similar to those found in association with intracranial disease affecting structures caudal to the midbrain (e.g., case 15). This emphasises the need for carefully examining of cranial structures whenever disease in the rostral spinal cord is suspected (Braund 1999; Dewey 2000; Jeffery 2001).

Cranial nerve deficits arising from forebrain dysfunction

Impairment of vision (e.g., bumping into objects, depressed menace response) on the contralateral side may be seen with lesions of the occipital cortex (cortical blindness); in this circumstance pupil size and pupillary light reflexes are normal (Braund 1999; de Lahunta 2000a). Vision is frequently impaired if the lesion extends to involve the optic chiasma, optic tract and the lateral geniculate nuclei. Whereas in case 16 only visual deficits were observed, with lesions involving the optic chiasma pupils may be dilated and weakly or not responsive to light stimulation (Braund 1999). Ocular and optic nerve lesions may also results in PLR deficits, but the lesion has to be extremely severe (de Lahunta 2000a). Acute vision loss may be the only or the predominant neurological deficit with tumours affecting the optic chiasma region (Davidson et al 1991). Lesions of the somatosensory cortex and / or thalamus may also result in contralateral facial hypoalgesia (Braund 1999; de Lahunta 2000a; Jeffery 2001). Anosmia / hyposmia may occur with forebrain lesions affecting the second or higher order neurons of the olfactory system (King 1987; Myers at al 1988). Cranial nerves deficits other than those above reported are not a feature of forebrain disease. Evaluation of cranial nerves reflex function is therefore essential in lesion localisation.

Signs of forebrain dysfunction and pituitary tumours

Signs of forebrain dysfunction, primarily consisting of behaviour and / or mental status changes may be associated with a pituitary tumour. In most cases patients with pituitary neoplasia develop clinical signs of endocrine dysfunction (most commonly hyperadrenocorticism and / or diabetes insipidus) prior to the onset of signs of CNS dysfunction (Sarfaty et al 1988; Nafe 1990). However, as many canine pituitary tumours are non-functional, neurological abnormalities may be the only clinical signs manifested by the

patients (Davidson et al 1991; Kipperman et al 1992). In case 16, progression of signs of adversive syndrome (deLahunta 2000b) in a patient with a relatively long-term (five to six months) history of vague endocrine and neurological abnormalities was suggestive that a pituitary macroadenoma might have been causative. In this case serum IGF-I concentrations were only marginally elevated and the time elapsed might not have been sufficient for the development of more severe clinical abnormalities secondary to the endocrine dysfunction (Feldman & Nelson 1996).

Pituitary tumours in dogs tend to expand dorsally causing compression of and encroaching on the diencephalic structures (Nafe 1990). The extent and severity of the diencephalic involvement correlate to the severity of the behavioural / mental status changes (Bertoy et al 1996; Sarfaty et al 1988). Visual impairment is rare; however, deficits in the optic nerve at the level of the optic chiasma including dilated, poorly responsive pupils and visual impairment may occur (Braund 1999). Seizures have been reported in association with pituitary tumours, but are rare (Sarfaty et al 1988; Bagley & Gavin 1998).

Signs of brainstem disease

Although seizures are a specific sign of forebrain dysfunction, seizure activity and / or other neurological abnormalities localising the lesion to the rostrotentorial structures may occur as result of multifocal and / or diffuse intracranial disease. In these circumstances, neurological deficits suggestive of brainstem, less commonly cerebellar involvement, may be seen. In cases 11 and 13 the historical picture and physical examination findings were consistent with a forebrain lesion but also exhibited abnormalities consistent with disease of the caudal fossa.

In addition, neurological deficits arising from brainstem / cerebellar impairment may be the only clinical signs detectable in patients with multifocal / diffuse intracranial disease also involving the forebrain. Not all forebrain lesions result in detectable neurological abnormalities (Foster et al 1988) (see Silent areas of the cerebral cortex, page 145).

Dysfunction of one or more cranial nerves (other than cranial nerves I and II) in an animal with obvious gait and proprioceptive abnormalities and / or altered mental status (often severely), localise the lesion to the brainstem and, sometimes, to specific areas within the brainstem (case 14). Signs of vestibulocochlear nerve dysfunction localise the lesion to the brainstem only if neurological examination findings rule out a peripheral lesion (Braund 1999;

Kraus & McDonnell1996). Clinical signs related to cranial nerve nuclei include jaw paralysis, masticatory muscle atrophy, facial paralysis, depressed corneal / palpebral reflex and menace response, strabismus, altered pupillary light reflexes, pharyngeal paralysis resulting in dysphagia and diminished gag reflex, dysphonia and inspiratory distress from laryngeal paralysis, tongue paralysis and signs of central vestibular disease (Braund 1999). Cranial nerve deficits may be mono- or bilateral depending upon extension of the lesion. Detection of multiple cranial nerve deficits in an animal with postural reactions deficits ipsilateral to cranial nerve involvement, and intact spinal reflex function, suggests a brainstem lesion (Kraus & McDonnell 1996).

Dogs with brainstem tumours frequently are presented with vestibular signs, such as ataxia and head tilt, but signs commonly useful in differentiating central from peripheral vestibular disease (positional / vertical and / or variable nystagmus and conscious proprioceptive deficits in the limbs) are not consistently detected. Nevertheless, peripheral disease should never cause changes in animal's state of consciousness. It would seem justified that dogs older than 5 years of age with vestibular signs of unknown cause be evaluated with advanced imaging techniques to exclude intracranial space-occupying lesions (Harrington et al 1995; Kraus & McDonnell 1996; Bagley 1999; Bagley et al 1999a).

Signs of cerebellar disease

Whereas both forebrain and brainstem lesions may result in disturbances of the sensorium of the animal and cranial nerves dysfunction, in general, this is not true for cerebellar disease (Jeffery 2001). Signs of cerebellar dysfunction include dysmetria (usually hypermetria), head or body intention tremors, a broad-based stance at rest, and truncal ataxia. There may be a delay in initiation of movements that are often accompanied by tremors. There may be menace deficits with normal vision (Braund 1999). However, pure cerebellar signs are rarely encountered (e.g., cerebellar malformation, white hair shaking syndrome).

Paradoxical vestibular disease and neurological signs associated with cerebellopontine angle lesions

Cerebellar lesions that affect the vestibular pathway in the flocculonodular lobes and / or the caudal cerebellar peduncles may cause paradoxical vestibular syndrome. In this syndrome the head and body tilt are toward the side opposite the lesion. Usually the general proprioceptive

system afferent to the cerebellum is involved as well. This produces a mild ipsilateral ataxia and a postural reaction deficit, on the same side as the lesion. There is an associated nystagmus with the fast phase toward the lesion (Adamo & Clinkscales 1991; Braund 1999). Mass lesions are the most common cause of paradoxical vestibular diseases. Neoplasia, especially choroid plexus tumours and meningiomas, and the focal form of GME are the main differential diagnoses for lesions at this site (Adamo & Clinkscales 1991; Braund 1999).

When the cerebellopontine angle is involved, the clinical signs observed include ipsilateral head tilt, asymmetrical tetraparesis, positional nystagmus, and facial and trigeminal nerve palsies. Lesions of the cerebellopontine angle may also result in the above, mentioned paradoxical vestibular syndrome (Nafe 1990). For space-occupying lesions affecting the cerebellopontine angle, neoplasia is the most likely diagnosis. The differential diagnoses for tumours arising in this location include choroid plexus tumours, neurofibromas (most commonly affecting the VIIIth cranial nerve), meningiomas and occasionally ependymomas or glial tumours as well as GME. Vestibular disease and facial paresis have been reported with meningioma of the cerebellopontine angle (Fischer 1994). In case 7, in which CT study revealed a hindbrain space-occupying lesion that involved the right cerebellopontine angle, post mortem examination demonstrated this lesion to be a choroid plexus papilloma.

Diagnostic approach to seizure disorders

The ultimate goal of the diagnostic evaluation of seizure disorders is to identify the cause of the seizure activity. Only then a reliable prognosis may be given and a rational treatment plan instituted (Schwartz-Porsche 1999). Reactive seizures carry the possibility of being eliminated if the underlying cause is detected and corrected (Cuddon 1996; O'Brien 1998). Idiopathic epilepsy generally carries a better prognosis than symptomatic epilepsy due to progressive and active brain disease; however in large-breeds of dogs seizures are usually more severe and difficult to control with anticonvulsants than in small-breeds of dogs (Shell 1993b).

The first step in the diagnostic approach to seizure disorders is to ascertain that seizure activity has occurred.

Seizure-like paroxysmal events associated with a transient alteration in neurological function may represent a diagnostic problem. The only diagnostic test, which distinguishes definitively between seizures and seizure-like paroxysmal disorders, is the EEG recording at the time of

the episode. The practical difficulties in achieving this means that such tests are not undertaken in veterinary clinical work. Additionally, difficulties related to both the recording and interpretation of interictal EEGs in dogs has resulted in a low take up of this technique in the veterinary world (Srenk & Jaggy 1996; Holliday & Williams 1998; Jaggy & Bernardini 1998)

Therefore careful history taking remains the corner stone in the identification of seizures in most dogs. In practically all instances, dogs with seizure-like paroxysmal events do not exhibit post-ictal effects. Possible exceptions are dogs that exhibit autonomic release phenomena after a syncopal episode and dogs with vestibular disease that continue to appear disorientated from their vertigo. Tab 22 (page 142) summarises the major historical and physical examinations findings used to distinguish seizures from seizure-like paroxysmal events.

History

The history is the cornerstone of the diagnostic approach to seizure disorders.

Signalment

The breed and age are of aetiological significance. Developmental and congenital brain diseases may present with seizures – e.g., the congenital hydrocephalus of certain miniature breeds such as Maltese, Chihuahuas and Yorkshire terrier (Harrington et al 1996; Podell 1996; Thomas 1999)[9]. This is also true for dogs of brachycephalic breeds which, with increasing age, show a disposition for brain tumours and, therefore, for epileptic seizures (Podell 1996). Miniature schnauzers can suffer from a massive, genetically caused hyperlipidaemia, which can cause seizures (Schwartz-Porsche 1999). Age-dependence can signify both extracerebral and cerebral causes of seizures. For example, in puppies and young animals, especially from miniature and toy breeds, hypoglycaemia is caused by anorexia and gastrointestinal disturbances, but rarely by storage diseases (Schwartz-Porsche 1999). In dogs older than five years the cause is often an insulinoma (Podell 1996).

Age-dependence is evident in idiopathic epilepsy in that it generally manifests itself between the ages of six months and five years. Related dogs with epilepsy, an increasing number of

[9] A causative relation between hydrocephalus and seizures has not been definitely proved.

epileptics in the breeding-line or in the breed itself confirm or suggest a hereditary origin. (Knowles 1998).

Seizure history

Clients' observations are fundamental in defining seizure type and pattern. Historical details that we found to be useful in patients with seizures have been reported in the section case assessment protocols – History and physical examination (page 40).

However, many dogs are unobserved for long period of time and many owners do not accurately know the number of unobserved seizures, or they genuinely may never have observed their dog to seizure. In this case the suspicion of seizure activity may arise from the clients' observations regarding changes in behaviour and / or attitude, and or patterns of elimination in previously housetrained individuals. For example in case 4 the recent development of lethargy and attention seeking in a dog, which in one occasion had been found lying in lateral recumbency and completely disorientated in the garage, were the historical details which suggested the possibility of seizure activity.

Historical findings and idiopathic epilepsy

Idiopathic epilepsy usually begins with a single generalised tonic-clonic seizure and the initial interictal periods can extend for weeks or months (Podell 1996). In most cases the frequency of seizures gradually increases, although this can vary widely between individuals (Schwartz-Porsche 1999). However, although generalised tonic-clonic seizures are the most common seizure type in dogs with idiopathic epilepsy, simple or complex partial seizures or partial seizure with secondary generalisation also occur, and some individuals have more than one type of seizure (Heynold et al 1997; Jaggy et al 1998; Knowles 1998; Thomas 2000). In case 9, seizure type (isolated, generalised, tonic-clonic), seizure frequency (one episode every 3-4 weeks), and the absence of interictal neurological abnormalities (see forward) were highly suggestive of idiopathic epilepsy in an individual with a supportive signalment.

Historical findings and symptomatic epilepsy

Symptomatic epilepsy should be suspected when: a) seizures start before 1 or after 5 years of age (see forward); b) the patient suffers partial seizures or partial seizures with secondary generalisation, or when the first seizure had been a focal seizure; c) there is a sudden onset of

multiple seizures; and / or d) interictal abnormalities are detected on history, examination, or laboratory tests (Podell et al 1995; Podell 1996; March 1998; Thomas 2000).

Table 22. Clinical features of the most common seizure-like paroxysmal disorders in dogs

Syncope	Often associated with exercise or excitement (may be induced by changes in posture) Partial or complete loss of consciousness Lack of violent motor activity Short duration and rapid recovery Lack of postictal signs Presence of underlying cardiac (cardiac arrhythmias) or respiratory disease
Narcolepsy / Cataplexy	Attacks often induced by excitement or feeding attacks reversed by external stimulation Flaccid paralysis and loss of consciousness Lack of postictal and autonomic signs
Myasthenia gravis	Precipitated by exercise; often gradual onset and gradual recovery stiffness, tremors, weakness No impairment of consciousness Lack of postictal signs
Vestibular dysfunction	Nystagmus, head tilt, ataxia with prolonged duration of signs (days) Usually no impairment of consciousness Lack of postictal signs
Sleep disorder	Occurs only during sleep attacks can be interrupted by awakening Abnormal movements during sleep (twitching, vocalisation, paddling) Lack of postictal and autonomic signs
Obsessive compulsive behaviour	Stereotypic pattern of abnormal behaviour prolonged duration of signs (hours, days) Event can usually be interrupted Normal consciousness Lack of postictal signs
Scotty cramp	Breed specific Exercise or stress-induced Lack of postictal signs
Canine distemper myoclonus	Continuous abnormal movements No impairment of consciousness (if disease inactive) Lack of postictal or autonomic signs
Tremor disorders	Often exacerbated by exercise or excitement prolonged duration of signs Usually no impairment of consciousness Lack of postictal signs

Parker 1990; Speciale & Dayrell-Hart 1996; Knowles 1998; Thomas 2000

Clinically it is essential to distinguish between progressive and non-progressive brain disease because this influences both treatment options and prognosis (Schwartz-Porsche 1999). The presence of active structural brain disease is suggested by a short first interictal period (Podell et al 1995), a rapid increase in seizure frequency (LeCouteur 1995) and changes in seizure type and duration of the events (Schwartz-Porsche 1999). Conversely, the longer the duration of the period during which the patient has had seizures without any other abnormalities, the less likely an underlying progressive brain disease is present (Thomas 1998).

In cases of progressive brain disease the seizures frequently manifest themselves as cluster seizures or as status epilepticus (Schwartz-Porsche 1999). In cases 2 and 3 the dramatic

increase of seizure frequency over a short period of time (approximately two weeks) and the development of cluster seizures were highly suggestive of a progressive brain disease. In case 5, a progressive structural brain disease was considered likely to be the cause of the seizure activity, despite an interictal period of three months, because of the development of cluster seizures in an elderly patient and the appearance, shortly prior to referral, of behavioural changes. A progressive morphological brain disease was thought to be most likely the cause of the seizures also in case 10, but in this case all diagnostic testing was unremarkable leading to a diagnosis of idiopathic epilepsy. Despite the age at onset for idiopathic epilepsy clusters between six months and 5 years, reports in the veterinary literature suggests that it may develop in dogs younger than six months as well as older than ten years of age (Knowles 1998). However, the intrinsic limits of the neurodiagnostic investigative techniques currently available may not allow in some cases a confident diagnosis of idiopathic epilepsy. In case 10, signalment and history were highly suggestive of a progressive structural brain disease. In such a case, despite the results of all the diagnostic investigations performed being unremarkable, the clinician may still suspect that an underlying undetected morphological brain disease is present and he / she might consider a diagnosis of cryptogenic epilepsy more appropriate than a diagnosis of idiopathic epilepsy (Berendt & Gram 1999; Thomas 2000).

Inflammatory, degenerative and neoplastic brain diseases are typical examples of progressive brain disease. Inflammatory brain disease should be strongly suspected in any patient with neurological deficits referable to multifocal lesions, and with persistent neurological deficits in addition to seizures, or evidence of systemic illness (Koblik 1995; Thomas 1998). Moreover, inflammatory disorders should be considered in any dog with a very short duration (less than several weeks) of seizures even in the absence of other abnormalities, because seizures may be the preliminary sign of a progressive inflammatory disease (Tipold 1995; Thomas 1998) (e.g., case 3). However, inflammatory brain diseases may not result in seizures and thus they should be suspected whenever progressive deterioration of neurological deficits is observed (e.g., cases 11, 12 and 14).

Historical findings and reactive seizures

Although in seizure disorders of extracerebral aetiology the seizure event can vary greatly, there are some features that tend to be consistent. As extracranial causes of seizures affect the brain symmetrically, most reactive seizures are generalised, tonic-clonic in character. Toxicity

is usually characterised by sudden onset of cluster seizures or status epilepticus in previously healthy animals, whereas, in most cases by the time metabolic diseases produces seizures, historical, physical, and laboratory findings are highly suggestive of the underlying disease (O'Brien 1998). However, even dogs with idiopathic epilepsy may be presented to a veterinarian for their first seizure in status epilepticus whilst dogs with intracranial neoplasia may only present after a mild, complex, partial seizure (Podell 1996).

Other historical details

Association of the seizures with specific activity (e.g., feeding, exercise) and / or time of the day are of diagnostic importance. In idiopathic epilepsy many seizures occur while the animal is sleeping or resting, and usually when it is at home. This association is less frequent in symptomatic epilepsy, and it is usually absent with seizures resulting from progressive brain disease (Shell 1993b). Pre- and post-prandial seizures may be an indication of metabolic disorder, especially hepatic encephalopathy and hypoglycaemia resulting from insulinoma. Seizures that occur on excitement or physical exertion may also be hypoglycaemic in origin, but they can also point to cardiac causes (Podell 1996; Schwartz-Porsche 1999). In none of the clinical cases presented in this dissertation did seizure activity appeare to be correlated to specific circumstances.

Interictal neurological abnormalities

While many dogs have seizures where a morphologic or metabolic cause is not found (idiopathic epilepsy) in patients with structural brain disease seizures are an expression of this and thus, such patients are more likely to develop interictal neurological abnormalities (Bagley & Gavin 1998). Whereas the presence of interictal neurological abnormalities is always indicative of an underlying structural brain disease, a normal interictal neurological examination does not exclude the possibility that a structural brain abnormality is the cause of the observed seizure activity. Idiopathic epilepsy, reactive seizures as well as structural lesions affecting the so-called "quite" areas of the cerebral cortex (see Silent areas of the cerebral cortex, page 145) are often characterised by a normal interictal neurological examination (de Lahunta 2000a).

Particular care must be taken when examining dogs during the immediate postictal period as neurological impairment may simply be a manifestation of transient ictal or postictal

disturbances and thus not the result of a permanent structural damage. Repeated neurological examinations of postictal animals in 24 to 48 hours are needed to determine whether the deficits remain consistent (Nafe 1990; Knowles 1998). Case 2 at the time of presentation to UGVS did not have any overt neurological deficits; the profound neurological abnormalities observed by the referring veterinary surgeon probably reflected transient postictal disturbances in cerebrocortical function.

Silent areas of the cerebral cortex

Seizure activity is a frequent clinical manifestation of intracranial neoplasia in the canine species. Although, in many cases by the time owners seek the attention of a veterinary surgeon overt motor and / or sensory neurological deficits are detectable, seizures may be the only clinical manifestation of an intracranial neoplasm. This is especially true for lesions affecting the rostral cerebrum (Foster et al 1988; Nafe 1990). The presence in the rostral cerebrum of the "silent / quiet" areas of the brain is likely to contribute to this trend (Muñana & Luttgen 1998).

"Silent / quiet areas" of the cerebral cortex represent regions which can be stimulated mechanically, chemically, or electrically without producing an obvious motor or sensory response. These areas are also referred to as the association cortex. They are not involved in processing sensory and motor information *per se* but the integration of more than one sensory modality may take place (Hogg 1987; Chrisman 1990). The frontal and prefrontal areas of the human cerebral cortex are specifically involved with cognitive behaviour, motor planning, thought, and perception. The frontal lobes may allow humans to weigh the consequences of future actions and plan accordingly. Disease within these areas frequently produces vague symptoms of transient personality disturbances, temperament changes, memory loss, or convulsions. As disease progresses additional symptoms consistent with motor or sensory dysfunction, or both, develop. This observation has been attributed to spread of involvement to "non-silent" areas of the brain (Saper et al 2000).

Although the association area is much smaller in dogs than in man, and dysfunction in such areas is difficult to evaluate in dogs, a parallel between neoplasia in man and animals may be reasonably made. In domestic animals, the association cortex consists of the cognitive association area of the parietal and occipital lobes, the interpretative association area of the

temporal lobe, and the premotor association area of the frontal lobe (Hogg 1987; Chrisman 1990).

In the dog, experimentally produced lesions of the frontal lobes have been reported to cause no signs, seizures alone, or behavioural changes such as uncontrolled rage or apathy. Frontal lobotomy may result in reduced proficiency in tests requiring memory. In this study, integrative frontoparietal function (vision, intellect, proprioception, movement initiation, and sensation) was initially unimpaired in most dogs. Seizures or behavioural abnormalities, or both, preceded detectable abnormalities in the neurological examination. This is consistent with the natural progression of disease in dogs: rapid deterioration of neurological status follows development of persistent neurological deficits (Foster et al 1988; Bagley & Gavin 1998; Bagley 1999).

Lesions of the olfactory lobe and rostral portion of the frontal lobe are more commonly associated with seizure activity and normal interictal neurological function (Patnaik et al 1986; Foster et al 1988; Patnaik 1989; Smith et al 1989; Moore et al 1991; Voges & Ackerman 1995). Nasal / paranasal tumours that invade the brain causing CNS dysfunction with minimal or no signs of nasal cavity involvement (e.g., swelling at the site of origin of the neoplasm, epistaxis, etc) can represent a diagnostic challenge (e.g., case 2) (Sackman et al 1989; Thrall et al 1989; Park et al 1992).

Epidemiological issues

In the canine species symptomatic epilepsy is said to be less common than idiopathic epilepsy but objective data is not available. Idiopathic epilepsy is a clinical diagnosis based on the typical age at onset, lack of interictal abnormalities and exclusion of other causes (Knowles 1998; Thomas 2000). Idiopathic epilepsy is statistically more probable when the dog experiences its first seizure between 1 and 5 years of age. Conversely, symptomatic epilepsy is more likely in dogs that have their first seizure at less than 1 or greater than 5 years of age, have an initial interictal period less than 4 weeks, or have a partial seizure as the first observed seizure (Podell et al 1995). Overall, dogs older than 7 years have the highest prevalence of symptomatic epilepsy, with primary intracranial neoplasia as the most common diagnosis (Podell et al 1995). However, more recent reports suggest that despite brain tumours being the

most frequent cause of late-onset seizures in the geriatric dog, they should be considered in the differential diagnosis for dogs that start seizuring from 5 years of age (Bagley et al 1999a).

In dogs younger than 1 year of age, congenital / development brain diseases (e.g., lissencephaly, hydrocephalus), inflammatory and degenerative diseases (e.g., storage diseases) are the most common cause of seizures. However, a significant proportion of dogs between 1 and 5 years of age can also suffer from a congenital brain disorder that may be progressive in nature, such as storage disease and hydrocephalus (Podell 1996).

All the above considerations indicate that in dogs presented for the evaluation of seizure disorders, signalment, history and initial physical and neurological examination findings provide essential information for the rational planning of the diagnostic approach.

Diagnostic evaluation

A minimum database should be collected for all dogs including a complete blood count, serum chemistry profile, and urinalysis though these tests have in themselves a low yield of a positive diagnosis for seizures (Podell 1996). However, in conjunction with a thorough physical examination the results of these tests allow the clinician to confidently rule out, or conversely diagnose, most causes of extracerebral seizure disorders (Podell 1996). Additional metabolic and / or endocrinological diagnostic testing, plasma lead concentration, and specific serum antibody titres for infectious diseases may be performed according to the history and clinical suspicion for each case. At UGVS dogs presented for evaluation of seizure disorders are routinely tested for serum Toxoplasma titres and Neospora neutralisation dilution titres, unless other causes of symptomatic epilepsy are considered more likely and / or economic restriction are a consideration.

In animals that at the time of presentation are on anticonvulsant therapy, evaluation of serum anticonvulsant agent(s) concentration is also recommended as this may underlie perceived problems with seizures control. Serum anticonvulsant levels are routinely measured at UGVS unless: a) anticonvulsant therapy has been initiated or the dosage regimen has been modified at a time prior to referral such that immediate assessment is inappropriate (e.g., cases 5 and 7); b) this evaluation had been performed at the referring veterinary practices (e.g., cases 2, 8 and 9); c) the development of interictal neurological abnormalities suggests that failure in control of

seizure activity is unlikely to be due to inappropriate serum anticonvulsant concentrations (case 7).

Advanced diagnostic imaging study of the brain should be performed in all dogs less than 1 or greater than 5 years of age because they have the highest probability for symptomatic epilepsy. Advanced neuroimaging techniques offer the best opportunity to detect morphological abnormalities resulting from an intracranial anomaly or neoplasia, the most prevalent causes of seizures in dogs less than 1 and greater than 7 years old, respectively (Podell et al 1995; Podell 1996). In addition, as general rule, advanced imaging techniques studies should be performed in all animals with persistent interictal neurological abnormalities, determined via either history or examination, regardless of the age of the patient: permanent interictal neurological abnormalities always indicate the presence of structural brain abnormalities. In the light of an unremarkable scan a CSF tap is justified.

Seizures and brain tumours

Epidemiological issues

While seizures are often reported to be a clinical manifestation of brain tumours in dogs, the actual incidence of seizures associated with intracranial tumours is not well established. In a series of 21 dogs with brain tumour, 8 had seizures (Palmer et al 1974). Foster *et al* (1988) described the clinical features of 43 dogs with forebrain tumours, 51% of which had seizures. In a more recent series of 95 dogs with brain tumours, 46 had seizures as admitting complaint (Bagley 1999; Bagley et al 1999a). As seizures were more often a presenting complaint in dogs older than 9 years of age, the possibility that the recent development of seizure activity in dogs of this group of age is due to a brain tumour should strongly be considered, and advanced imaging testing would be mandatory for diagnosis. In the brain tumour case series presented by Bagley (1999) 95% of the dogs were 5 years or older at the time of the diagnosis. The cases reviewed here are in accordance with this observation: in all but two (cases 7 and 14) of the fourteen cases which were diagnosed with intracranial neoplasia (six known – cases 5, 6, 7, 13, 14 and 16 - and seven suspected - cases 1, 2, 3, 4, 11, 12 and 15), the patient was 5 years or older at the time of diagnosis.

The relationship between brain tumours and seizure activity

The historical and clinical findings in patients with intracranial neoplasia are variable and reflect the location, size and associated pathologic effects of the tumour (LeCouteur 1999; Dewey et al 2000).

Location

Tumour location appears to be the most important factor associated with the development of seizures. The literature suggests that the majority of brain tumours associated with seizures affect the rostrotentorial structures, especially the frontal, olfactory and parietal lobes (Foster et al 1988; Bagley 1999; Bagley et al 1999a). The cases reviewed here are in accordance with this observation: of the nine cases of forebrain neoplasia (three known – cases 5, 6 and 13 – and six suspected – cases 1-4, 11 and 12), six had seizures as admitting complaint (cases 1-6). Only one dog with seizure activity and interictal signs, which localised the lesion to the forebrain, was diagnosed with a caudal fossa tumour following computed tomographic study (case 7). The mild gait / balance abnormalities reported by the owner might have made the clinician suspicious of brainstem / hindbrain involvement, but no apparent neurological deficits were found at the time of examination. Bagley and Gavin (1998) also report a case of brainstem neoplasia associated with seizure activity; on post mortem examination the diagnosis was choroid plexus papilloma and no apparent metastasis were found in the rostrotentorial structures. In case 7 the histopathological diagnosis was also choroid plexus papilloma but multiple metastases were found in the diencephalon and cerebral hemispheres.

Mass lesions may not be identified on CT study if isodense to normal brain parenchymal tissue in the pre-contrast study, non-enhancing on the post-contrast one, not associated with other noticeable pathology(ies) and / or because of small size (Kraft & Gavin 1999). In addition, small metastatic foci may also go undetected on post mortem evaluation.

Thus, a direct causative relation between seizure activity and brainstem tumours can neither be claimed nor excluded. Interestingly, seizures can be experimentally produced from brainstem stimulation. However, the seizure activity observed in human patients with brainstem tumours is thought to originate from cortical tissue that is distant from the tumour (Pilcher et al 1993). Currently seizures in animals with brainstem tumours are thought most likely to result from

secondary pathophysiological alterations (e.g., vasogenic oedema, hydrocephalus, alterations in blood flow) affecting forebrain structures (Bagley & Gavin 1998).

Tumours of the frontal, olfactory and parietal lobes are reported to be more often associated with seizures (Smith et al 1989; Bagley & Gavin 1998; Bagley 1999; Bagley et al 1999a). In four of the six dogs with forebrain tumours and seizure activity, the lesion involved the frontal and / or olfactory lobes (cases 1 to 4); in cases 5 and 6 involvement of the parietal lobe was apparent.

Tumours of the diencephalon are also reported as frequently associated with seizure activity (Bagley & Gavin 1998). Thalamocortical circuits are in fact essential in generalisation of seizures activity within the cerebral cortex (Coulter 1997). In the experience here presented, three dogs (cases 6, 12 and 13) had had findings suggestive of involvement of the thalamic area but only one had seizures as part of the presenting complaint (case 6). In this dog the simultaneous presence of cortical and thalamic lesions, might have enhanced both antidromic and orthodromic activity in the thalamocortical axons. Antidromic and orthodromic are proved to lead to a "reverberating circuit" of excitation, thus facilitating spread of electrical activity and the development of seizure activity (Coulter 1997; March 1998). Development of seizure activity might have also been facilitated by the midbrain involvement. A role for the midbrain reticular formation in generalisation of electrical activity has in fact also been proposed, because of its diffuse projection to the cortex. As seizures frequently occur while the animal is asleep, it is thought that changes in the reticular formation during sleeping affect the spread of the seizure activity (Shell 1993a; Proctor & Gale 1997).

One dog (case 12) with involvement of the thalamic area exhibited "absence periods". In human patients dysfunction of specific thalamic nuclei has been proved to be responsible for the appearance of generalised, absence seizure (MacDonald 1997; Stefan & Carter Snead III 1997). In case 12 the absence periods apparently experienced by the dog might have represented true absence seizures.

Other features potentially related to whether a tumour is related to seizures

Other features have been identified that are associated with increased incidence of seizures in humans with brain tumours. These include a young age, slow growth rate, and a benign nature (Recht & Glantz 1997). The latter two features may also be relevant in dogs. In the studies of

Foster *et al* (1988) and Bagley (1999) the majority of dogs exhibiting seizures had meningioma, which tends to grow slowly and to be histologically benign (Moore et al 1996).

Other tumour types affecting the rostrotentorial structures, which had been reported in dogs with seizures include: astrocytomas, oligodendrogliomas, choroid plexus papillomas, pituitary tumours, and nasal adenocarcinoma extending caudally into the olfactory areas, as well as unclassified types of tumours (Bagley & Gavin 1998; Bagley 1999).

Interestingly, the incidence of seizures in humans with cerebral metastases is lower compared with those patients with primary brain tumour (Recht & Glantz 1997). No data is available in the veterinary literature to state if a similar trend occurs in animals as well.

Pathophysiological mechanisms of seizure generation in brain tumour patients

As previously stated in this dissertation, the pathophysiological mechanisms of seizure generation are still not completely understood. Brain tumours probably result in seizures either because of direct alteration in neuronal function and inter-neuronal connectivity or because of secondary changes induced by the tumour such as changes in blood flow, cerebral oedema, haemorrhages and hydrocephalus (Bagley 1996a; Bagley 1996b; Bagley & Gavin 1998).

Normal CNS function relies on the initiation and transmission of excitatory impulses between neurons and groups of neurons. The morphological and functional organisation of the cerebral cortex is such that excitatory activity is prevalent (Martin 1991; Connors 1997). Under normal circumstances local and regional inhibitory circuits modulate the electrical activity within the cerebral cortex and prevent abnormal spread of excitatory activity to both cortical and subcortical areas (Prince 1997; March 1998). During a seizure the normal balance of excitation and inhibition is altered, favouring excitation. Seizure activity may develop because of increased inherent neuronal excitability, increased recurrent excitation and / or decreased recurrent inhibition (March 1998). Any of these factors, alone or in combination, may result in a paroxysmal hypersynchronous discharge of neurons within a seizure focus (Connors 1984; Selcer & Selcer 1990). However, a clinical seizure occurs only if the number of neurons in the seizure focus reaches a "critical mass" (Lane & Bunch 1990). Unsuccessful local and regional inhibition has also to occur, to allow the electrical activity to be carried to other parts of the brain. If unsuccessful inhibition occurs, then other neuronal aggregates are excited; successful

recruitment of a critical number of areas with synchronised depolarisation, ultimately, leads to a seizure (Podell 1996; Westbrook 2000).

Brain tumours may increase inherent neuronal excitability by inducing morphological and / or functional changes such as changes in dendritic structures, receptor density and / or receptor sensitivity as well as dysfunction of cellular ion pumps (During et al 1995; Connors 1997; Heinemann & Eder 1997; March 1998). Similar changes may also occur in inhibitory interneurons, leading to a decreased efficacy of inhibitory mechanisms (Kandel & Schwartz 1991; Connors 1997; Shumate & Jin 1998). Compression, distortion and shift of brain parenchyma may physically disrupt inhibitory circuits resulting in decreased recurrent inhibition (feed-forward and feedback inhibition) and increased recurrent excitation (Bagley 1996b; March 1998). True loss of brain parenchyma occurs only with slow growing tumours as a compensatory mechanism to a progressively increasing ICP (North & Reilly 1990; Bagley 1996a).

Tumour-associated inflammation of surrounding normal brain tissue, in conjunction with immune-mediated events, contributes significantly to regional tissue damage and creates a condition of neuronal hyperirritability, which in turn may enhance seizure activity (Bagley 1996b). Focal or multifocal / diffuse cerebral ischaemia secondary to decreased cerebral pressure perfusion results in ischaemic necrosis (Bedford 1991). Areas of ischaemic necrosis also contribute to brain inflammation, thus facilitating generation and spread of abnormal electrical activity. In turn, vasogenic and inflammatory oedema increase ICP further. Increased ICP results in further deterioration of cerebral blood flow; thus a vicious cycle can develop, in which oedema and brain ischaemia become progressive (North & Reilly 1990). Haemorrhages are likely to facilitate seizure generation via ischaemic necrosis secondary to increased ICP, and via the inflammatory reaction of surrounding brain tissue (Bagley 1996b). However, despite the evidence that brain tumour associated pathologies might play a role in the generation of seizures in brain tumour patients, no correlation has been proved between their severity or extension and the presence and severity of seizures.

In brain tumour patients, neuronal death occurs through a wide variety of mechanisms ranging from direct disruption of cerebral blood circulation to ischaemic necrosis secondary to increased ICP. Neuronal death results in loss of inhibitory circuits and increased recurrent

excitation. The axons of deranged excitatory neurons that have lost their target connections undergo sprouting and make aberrant connections with other excitatory neurons. The net result is a hyperexcitable neuronal network (Au Louis et al 1997; McNamara & Wada 1997; McKinney et al 1997; Prince 1997).

Neuronal swelling, hyperirritability, and increased neuronal discharge may facilitate generation and maintenance of synchronised neuronal firing also via potentiation of non-synaptic mechanisms of synchronisation such as ephaptic transmission and electrotonic coupling (McNamara 1994; Gibson et al 1999; Velazquez & Carlen 2000).

Kindling and mirror focus (Lane & Bunch 1990; Shell 1993a; March 1998) may contribute to the progressive increase in seizure frequency observed in brain tumour patients, as well as to explain why seizure activity, in humans, usually does not originate in tumour-involved brain tissue, and why in some instances seizure activity may originate in cortical tissue relatively distant from the tumour itself (Pilcher et al 1993). Cerebral ischaemia and associated oedema are likely to play an important role in creating a condition of neuronal hyperirritability in areas of the brain distant from the tumour.

Axonal sprouting, kindling, mirror focus and most of the cellular changes described are chronic in character; this may account for the apparent higher incidence of seizures in patients with slow growing tumours (e.g., meningiomas). However, to date, in both human and veterinary medicine the information available regarding the pathophysiological mechanisms of seizure generation, the biological behaviour of brain tumours and the mechanisms by which brain tumours interfere with normal brain function, are not sufficient to elucidate the pathogenesis of seizure activity in brain tumour patients. This also means that further work is necessary to be able to identify the properties of brain tumours that correlate with the potential for seizure generation, as well as the severity of seizure activity.

Conclusions

Seizures are one of the most common clinical signs in dogs with intracranial neoplasia, together with signs of vestibular dysfunction and ataxia. With the advent of advanced imaging modalities the ability to diagnose brain tumours in-vivo has increased. However, as these diagnostic modalities are costly and access to them is not universal, it is important to

determine, on the basis of historical and physical examination findings, which patients are likely to benefit from advanced imaging as part of their diagnostic evaluation.

At the time of presentation, seizures may be the only clinical manifestation of an intracranial tumour, although they are frequently accompanied by changes in mental status and / or behavioural derangement. In domestic animals, the bulk of neuronal integration occurs in the brainstem and spinal cord. Thus, even relatively large tumours in some areas of the cerebrum may not result in detectable deficits in either motor or sensory function. Rapid deterioration of neurological status usually occurs following development of persistent abnormalities detectable upon neurological examination. Poor seizure control is the reason why most canine brain tumour patients are euthanased, making this clinical problem an important determinant of morbidity and mortality.

The case material presented here, in conjunction with a broad review of the literature, indicates that brain tumours are likely to be the cause of the neurological dysfunction more often, and in younger dogs, than was believed in the past. Advanced imaging modalities are a relatively new acquisition in veterinary medicine and their utilisation in the diagnostic evaluation of seizure patients has provided clinicians with information regarding intracranial disease which was not available in the past. The consequent changes in our understanding of the epidemiology of brain tumours, has driven and represents a major impetus to their further investigation.

In such a dynamic scenario the ultimate goal of clinicians everywhere is to identify those clinical features which will enable us to recognise patients with suspect intracranial neoplasia at earlier stages of the disease. Currently, it is still fair to regard the treatment of canine brain tumours as palliative. Earlier identification is likely to be one of the factors contributing to an improvement in outcome in the future.

Abbreviations

A	albumin
ACTH	adrenocorticotropic hormone
ALT	alanine aminotransferase
AP	alkaline phosphatase
AST	aspartate aminotransferase
BBB	blood-brain barrier
BCNU	carmustine
Ca	calcium
CBF	cerebral blood flow
CPP	cerebral perfusion pressure
Cl	chloride
CSF	cerebrospinal fluid
CNS	central nervous system
CP	complex partial
CT	computed tomography / tomographic
E.C.	epithelial cells
EEG	electroencephalographic / electroencephalogram/s
e.g.	for example
EMA	epithelial membrane antigen
et al	and others
FL	frontal lobe
g	gram
G	globulin
GFAP	glial fibrillary acidic protein
GH	growth hormone
GME	granulomatous meningoencephalitis / -encephalomyelitis
HB	haemoglobin
H&E	haematoxylin and eosin
HT	haematocrit
IAC	intracranial arachnoid cyst
ICP	intracranial pressure
IE	idiopathic epilepsy
IFAT	indirect fluorescent antibody test
IGF-I	insulin-like growth hormone
III / IIIrd	third
IM	intramuscular
IV	intravenous / fourth
IVth	fourth
K	potassium
KBr	potassium bromide
l	litre
L	left
LV/s	lateral ventricle/s

M	midbrain
MAG	myelin-associated glycoprotein
MBP	myelin basic protein
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
mmol	millimole/s
MPV	mean platelet volume
MRI	magnetic resonance imaging
Na	sodium
n	nanogram/s
NE	not evaluated
nmol	nanomole/s
NP	not performed
NSAID	nonsteroidal anti-inflammatory drug
OB	olfactory bulb
OL	olfactory lobe
PaCO2	arterial carbon dioxide tension
PaO2	arterial oxygen tension
PB	phenobarbitone
PDH	pituitary dependent hyperadrenocorticism
PE	primary epilepsies
PLT	platelet count
PME	post mortem examination
PNS	peripheral nervous system
PUPD	polyuria / polydipsia
qualit.	Qualitative
R	right
RAS	reticular activating system
RBC	red blood cells
RDW	red cell size distribution width
RS	reactive seizures
SAP	serum alkaline posphatase
SE	symptomatic epilepsies
SG	specific gravity
SP	simple partial
T4	thyroxin
TL	temporal lobe
TSH	thyroid-stimulating hormone
U	unit/s
UGVS	University of Glasgow Veterinary School
UMN	upper motor neuron
V20° Ro-DCd	ventral 20° rostral-dorsocaudal oblique open mouth
V.S.	ventricular system
WBC	white blood cell
WHO	World Health Organisation
XPT	X-ray phototherapy

°	degree	>	greater than
α	alpha	<	less than
β	beta	≥	greater than or equal to
g	gram		
μ	micro	≤	less than or equal to
n	nano		
%	percentage		

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