Behavioural and Medical Differentials of Cognitive Decline and Dementia in Dogs and Cats

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Cognitive dysfunction syndrome (CDS) is a diagnosis of exclusion given that there is no specific diagnostic test or tool and that medical disorders can cause the same set of signs. The veterinary surgeon must first identify that signs are present, collect a full history and then perform a full physical examination and relevant diagnostic tests to rule out medical causes for the signs including blood and urine analysis, radiographs and diagnostic imaging such as magnetic resonance imaging (MRI) where indicated.

It is important to remember that with increasing age, there will be further degenerative changes leading to new behavioural signs that must be differentiated from CDS (Landsberg and Denenberg 2009). Only after these medical changes are detected, treated and controlled can the veterinary surgeon determine which of the signs might be caused by CDS. On the other hand, in the senior pet, medical problems and CDS can be present concurrently.

In this chapter we provide the veterinary surgeon with a list of possible differential diagnoses for CDS including behavioural, medical and neurological abnormalities. In addition, we aim to provide the reader with an explanation as to how they might confound or complicate the diagnosis.

2.1 Differential Diagnosis of CDS

2.1.1 Behavioural Differentials of CDS in Dogs and Cats

Senior pets may suffer from ageing-related decline such as reduced vision and hearing, medical abnormalities such as renal disease and pain (Landsberg and Denenberg 2009). All these can affect the pet's ability to cope with different environments and

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situations. Reduced coping ability can later lead to behavioural changes such as the development or increase of fear, anxiety and aggression. Moreover, the pet may develop new strategies to cope. These can include avoidance, hiding and sleeping less to be better prepared.

2.1.1.1 Anxiety

Anxiety is the feeling of uneasiness or apprehension that a negative or dangerous situation may occur. Oftentimes anxiety is vague and not based on past experiences. Anxiety can occur in specific situations (e.g. owners are about to leave the house) or be more global where the pet is constantly anxious (Landsberg et al. 2001). Furthermore, anxiety can be mild where the pet may exhibit some anxiety-related behaviours or overwhelming where the pet outright refuses to interact, explore and learn. The behaviours and physiological signs of anxiety (Table 2.1) are modulated largely by serotonin and noradrenalin (both in the central nervous system (CNS) and peripherally).

Dogs and cats who are anxious may appear withdrawn to owners, leading to changes in interactions. Alternatively, increased anxiety may lead to more attention-seeking behaviours. Dogs may follow the owner around the home, show more separation distress and lie or rest only in areas where they can monitor the owner's presence. Cats may show attention-seeking behaviours as well. These may include following the owner, desire to sit on the owner's lap and even urine marking.

Pets may show more hypervigilant behaviours both at home and outside. This can include scanning the environment constantly, being easily aroused by minor triggers, disturbed sleep and high alertness (Ohl et al. 2008). The pet may eventually become exhausted and more irritable, leading to withdrawal from the environment and interactions.

At times these pets may eliminate inappropriately and lose interest in performing basic self-hygiene behaviours (mostly cats). The pet may be too anxious outside or near the litter box and begin to soil around the home or simply lose control over its sphincter at times of high anxiety (Landsberg et al. 2012). High and chronic anxiety can affect gastrointestinal (GI) motility, leading to diarrhoea. This in turn may lead to house soiling. Anxious cats may urine mark their environment trying to feel more secure.

Table 2.1 Behavioural and physiological aspects of anxiety

Behavioural changes	Physiological changes
Hypervigilance	Dilated pupils
High arousal	Tachycardia/tachypnoea
Attention-seeking behaviour	Excessive salivation
Monitoring of situation/owners	Panting
Changes in activity (increase of decrease)	Changes in GI motility leading to diarrhoea
Displacement behaviours	Muscle tremor/shaking
Behavioural inhibition (withdrawal)	Hypertension
Changes in sleep-wake cycles (light sleeping)	Increased Hypothalamic-pituitary-adrenal (HPA) axis activity

Anxious animals may have reduced appetite or avoid eating in different situations or environments, giving the impression of changes in appetite. For example, many dogs with separation distress will not eat from the time the owner is preparing to leave the house until the owner's return. They will, however, eat immediately upon the owner's return (Sherman and Mills 2008).

Chronic anxiety can lead to reduced production of several neurotransmitters that are required for effective learning and memory consolidation. Among these are serotonin, dopamine and brain-derived neurotrophic factor (BDNF). Serotonin and BDNF are particularly important for learning but also for inducing neurogenesis and synaptic plasticity (Gould 1999). Dopamine is important for memory consolidation in the hippocampus. Thus, pets with chronic anxiety may show deficits in memory or previously learnt behaviors during states of anxiety and will have difficulties acquiring new learning (Landsberg and Araujo 2005).

2.1.1.2 Fear

Fear is a basic survival response mechanism to a specific stimulus, an emotional response to a perceived threat and an innate response (Overall 2005). Fear is often adaptive, protecting the animal from harm. However, at times fear can become maladaptive; it may be overwhelming (panic attack), irrational (phobia) or out of context. Fear-related behaviours mostly originate in the amygdala and are modulated via the autonomic nerve system. The autonomic and somatic signs (Table 2.2) vary depending on the stimulus and its intensity; however, they can be grouped into defensive non-action (e.g. freezing, passiveness and hyper-attentiveness) or defensive action (e.g. flight or fight). The fear response is modulated primarily by noradrenalin both in the CNS and peripherally. In addition, the neurotransmitter gamma-aminobutyric acid (GABA) plays a role in fear-related behaviours in the amygdala.

Table 2.2 Behavioural and physiological signs of fear

Defensive action		Defensive non-action	
Behavioural	Physiological	Behavioural	Physiological
Vocalisation	Dilated pupils	Hiding	Dilated pupils
• Growling	Panting	Avoidance	Tachycardia or bradycardia later
• Barking	Tachycardia	Freezing	Changes in GI motility
• Whimpering	Tachypnoea	Muscle tremor	Pale mucous membranes
Cowering	Piloerection	Shaking	Hypertension
Lip curling	Hypertension	Submissive urination	HPA axis activation
Retracting lips	HPA axis activation	Rolling on side and exposing the abdomen	
Staring or gazing away		Whimpering	
Lunging or retreating		Closing eyes or gazing away	
Biting			

Ageing can lead to changes in fear responses in animals as a result of a decreased ability to cope with different triggers. For example, a dog with reduced hearing or vision and degenerative joint disease is not capable of avoiding a fearful situation as in the past and as a result may attack or freeze. This can easily be viewed as changes in interaction with the same trigger (Landsberg and Denenberg 2009).

Animals may be fearful of another pet in the house that controls access to resources such as food, sleeping areas and soiling areas. The fearful pet may eat less, soil inappropriately and even sleep less.

Sudden and intense fear may lead to loss of control over the bladder and anal sphincter. Dogs and cats that experience this may soil inappropriately. A dog who has fireworks phobia and in the past could have run away and hid may no longer be able to do that and may void its bladder as a result of intense fear (Sherman and Mills 2008).

Pets who learn that certain situations, environments or people cause fear may avoid the area or the interactions. These pets may also refuse to perform certain tasks when asked by the owner. This in turn can be viewed as forgetfulness.

2.1.1.3 Night-Time Waking

Dogs and cats tend to adopt their owners' routine and schedule. However, cats typically have dusk and dawn activity patterns (crepuscular species) related to their food acquisition needs and the activity of prey. Older pets may become more active at night-time when the owner is sleeping (Landsberg and Denenberg 2009). Younger pets may also wake their owners at night; however, the problem is more common in senior animals, because of many health issues (e.g. renal, gastrointestinal and joint diseases) that may contribute. They may seek food or attention or need to eliminate. In addition, the pet may wake up and walk around the house, and the owner's reaction (trying to stop or comfort the pet) may actually reinforce this behaviour by giving food or attention. Common reasons for night-time waking include not only CDS but also conditions that cause pain, discomfort, confusion or unsettled sleep including arthritis, gastrointestinal disease, organ-related dysfunction and endocrine disorders such as diabetes mellitus, hyperthyroidism and hypertension. Sensory decline (vision, hearing) may reduce the pet's awareness and ability to cope with darkness or its response to stimuli. Any disease process that might increase thirst or hunger or frequency or volume of urine or stool may also contribute to night waking. Changes in sleep-wake cycles are common CDS-presenting complaints (Landsberg et al. 2011, 2013).

A diagnosis is established by performing the physical examination, blood and urine tests, blood pressure measurements, pain assessment and thorough history collection and observing behaviour patterns. In addition, investigating other possible concurrent signs and problems must take place in order to rule out cognitive decline. These signs may include increased anxiety and fear; changes in appetite, elimination routine, and social interactions; and increased vocalisation (Denenberg and Landsberg 2016).

Changes in daily routine, including limiting cats from going outdoors or altering the dog's walk and play schedule or feeding routine, and household changes (e.g. adding new pets, loss of another companion pet or owners, moving and renovation) might lead to decreased sleep quality and duration. Inciting factors (e.g. disease, outside animals or routine changes) might be different from maintaining factors (e.g. owner's reinforcement). When the problem becomes chronic, it may be difficult to reverse the routine; therefore, prompt action is required (Landsberg et al. 2013).

Anxiety in senior pets (see above) may lead to development of displacement behaviours, one of which is repetitive pacing. While this can be throughout the day, it might only be noticeable to owners in the evening or nights when they are at home or trying to sleep (Landsberg et al., 2011; Landsberg and Denenberg 2009).

2.1.1.4 Excessive Vocalisation

Vocalisation becomes excessive or is considered to be a problem when it occurs at inappropriate times (e.g. nights, baby napping) or is particularly loud or long (Denenberg and Landsberg 2016). Duration, frequency and time of the day are some of the parameters that should be evaluated. Moreover, changes in health and other behaviours should be evaluated as well. Thorough history should be taken to evaluate any patterns or triggers (e.g. outdoor animals, being left alone, confined near feeding times or fearful situations).

Attention given by the owner might reinforce the behaviour. Punishment may reduce the behaviour for a short period of time; however, it is likely to increase anxiety and fear, leading to increased vocalisation in the long run, and does not address the underlying motivation to vocalise (Landsberg et al. 2011).

Painful conditions (e.g. arthritis, gastrointestinal, dental or neuropathic), organ dysfunction (e.g. chronic renal disease with uraemia or liver disease) and central nervous system disease including cognitive dysfunction, sensory decline and thirst or increased hunger might lead to increased vocalisation (Denenberg and Landsberg 2016). Anxiety can be coupled with increased vocalisation in the older pet, and this could be due to health issues, an increased dependency on the owner for comfort and safety, and sensitivity to changes in the environment.

2.1.1.5 House Soiling

Senior pets may soil inappropriately due to cognitive decline. However, there are many other reasons that should be considered first. The first question is whether the pet was housetrained in the past or the current soiling is a continuation of a pre-existing problem.

Many metabolic or organ dysfunction diseases such as diabetes mellitus or Cushing's disease, renal disease or cystitis can lead to inappropriate urination by both dogs and cats. Similarly, gastrointestinal dysfunction or irritable bowel syndrome, pancreatitis or infections can lead to defaecation inside the home (Bain 2016, Gruen and Sherman 2016).

Pain can be a leading contributor in inappropriate soiling in senior pets. The inability to reach the litter box in time or go out to eliminate or pain while soiling can lead to avoidance of the area or the box. The knowledge or memory of pain during soiling may last even after the successful resolution of the problem. Sensory decline may mean that the pet simply cannot reach a designated soiling area.

Anxiety and fear contribute to inappropriate soiling. The pet may be afraid to return to a familiar elimination area due to another pet or threatening situation. Moreover, anxious animals may mark their environment to feel more secure inside. Cats may start soiling along the perimeter of the home or on owners' personal possessions (e.g. clothing, shoes or bed).

Changes in household routine or environment can also lead to inappropriate soiling. Owners may change jobs or shifts and, as a result, alter their dog's schedule. Senior dogs may find it difficult to adapt to changes and may start soiling at home. Moving litter boxes inside the home, changing litter type or box structure, preventing cats from going outdoors or renovating can all lead to avoidance of the litter box.

The first step is a full physical examination, blood analysis and urinalysis. Tests such as faecal sampling should be considered as well. Once medical problems have been ruled out, the emphasis can be placed on behavioural problems. A detailed history is the next step. Type of soiling (urine, faeces or both), frequency of soiling, locations, vertical vs. horizontal surfaces, quantity and time of day are only some of the details that should be noted. In addition, the pet's body language while soiling, other behavioural changes, possible triggers and changes to environment or household should be considered. The goal is to identify patterns and possible triggers. Soiling can be divided into two distinct behaviours: (a) inappropriate elimination that is a result of changes in routine, environment and learning new behaviours, which all can lead to aversion or preference of a location or litter or box type, and (b) marking behaviour that is a result of anxiety and the pet is soiling in order to feel more secure in its own environment (Pryor et al. 2001).

Pets with CDS will typically, but not always, soil without any particular pattern. Soiling will depend mostly on physiological need, for example, voiding urine when the bladder is full without relation to time of day or location (Landsberg and Araujo 2005).

2.1.1.6 Aggression

Aggression may appear in senior pets due to several reasons and indicate changes in relationships and interactions with owners and family, other pets at home and the environment. As with other problems, it is important to note if this aggression or predictors (behaviours that indicate pre-existence of covert aggression) existed in the past.

In most cases aggression is a result of fear or anxiety. While pets often prefer avoiding conflict, it may be that due to age-related changes they are limited and must choose to fight. Sensory reduction and reduced mobility are some of the reasons (see above).

Metabolic changes, organ dysfunction and neoplasia can all increase irritability, affect brain function and reduce the threshold for aggression. Therefore, a full physical exam and laboratory tests or diagnostic imaging (e.g. MRI) must be performed.

Learning may play a role in the development of aggression; the animal might be reinforced by the consequences of the behaviour. For example, aggression might be used to prevent children from approaching the pet; once successful in removing the threat, the animal may continue using aggression.

2.1.1.7 Repetitive Behaviours

Senior pets may start exhibiting repetitive behaviours such as pacing, licking themselves (usually one of the legs or flank) or rhythmic vocalisation (see above). These behaviours are usually ritualistic, excessive and evolve with time. This can lead to changes in activity levels and interactions with owners and the environment. In addition, avoidance of, or aggression towards, the owner may develop if the owner is trying to disrupt the pet from performing these behaviours.

Pain, neoplasia, organ dysfunction, metabolic diseases and hormonal abnormalities can all lead to the development of these behaviours. Anxiety and fear can also lead the pet to develop these behaviours initially as displacement behaviors, which may progress to stereotypic or compulsive behaviours (Luescher 2003).

Many owners believe that it is impossible to train and stimulate senior pets or that they should be left alone to rest due to joint disease or other painful conditions. While it is true that some adjustment might be required (reduced exercise, diet changes, rest, etc.), owners should still try engaging their pets. In some cases, lack of stimulation, or boredom, might be the cause of repetitive behaviours. Owners must ensure their pet has the possibility to practise normal species-specific behaviours even in old age.

The veterinary surgeon must first ensure the pet has normal outlets and a sufficient level of stimulation and interaction while considering possible limitations. Using feeding toys, chew toys, training and appropriate exercise all can help.

2.1.2 Medical Differentials of CDS in Dogs and Cats

Any disease process that can lead to signs of DISHAA (see Table 1.1) and other signs of cognitive dysfunction should be considered when assessing a senior pet. Diseases of the CNS can directly alter the pet's mentation, responsiveness and interactions. In addition, diseases outside the CNS can indirectly affect brain function (e.g. reduced oxygen perfusion, toxins and reduced glucose available for brain function) or cause other CDS-like signs. Moreover, chronic or debilitating disease can lead to increased anxiety, withdrawal or avoidance behaviour, increased irritability and aggression and house soiling (Table 2.3).

Table 2.3 Medical differentials of cognitive dysfunction in dogs and cats

System	Possible causes	Possible behavioural signs
Sensory	Cataracts/lenticular sclerosis	Fear/anxiety
	Loss of vision	Disorientation
	Loss of hearing	Decreased response to stimuli
		Reduced learning ability
		Aggression
		Avoidance
		Vocalisation
Pain/musculoskeletal	Degenerative diseases	Avoidance
	Arthritis	Reduced interest in exercise or play
	Muscular dystrophy	Altered response to stimuli; aggression
		Reduced self-hygiene
		Increased vocalisation
Cardiovascular	Mitral insufficiency	Disorientation
	Hypertension	Tiredness or reduced interest in play and activity
	Cardiomyopathy	Withdrawal/avoidance
		Irritability
		Fear/anxiety
		Changes in appetite
		Vocalisation
Endocrine	Diabetes mellitus	All signs of cognitive dysfunction
	Insulinoma	House soiling/urine marking
	Diabetes insipidus	Appetite—increased/decreased
	Hypothyroidism	Activity—increased/decreased/apathy
	Hyperthyroidism	Irritability
	Hyperadrenocorticism	Aggression
	Hypoadrenocorticism	Sleep-wake cycle
		Stereotypic—licking
		Restlessness—pacing
		Vocalisation
Digestive	Dental diseases	Reduced appetite
	Hepatic diseases	Aggression/irritability
	Infectious/inflammatory	Avoidance/withdrawal
	Constipation	House soiling
	Nutritional imbalances	Night-time waking
	Pain	Stereotypic—pacing/licking
		Coprophagia
Urinary	Renal diseases	House soiling/marking
	Urinary tract infection	Aggression
	Idiopathic cystitis	Withdrawal/avoidance
	Urolithiasis	Pacing
	Urinary incontinence	Sleep-wake changes

2.1.2.1 Sensory Decline

Age-related changes can affect hearing and vision of pets. Ageing of the lens may lead to nuclear sclerosis that may slightly affect the vision. In addition, age-related or other pathological causes, such as cataracts, can be partial or complete, leading to blindness. While dogs and cats rely mainly on olfaction, reduced vision and hearing can lead to changes in communication and interactions but not necessarily to increased aggression and anxiety (Farmer-Dougan et al. 2014). Reduced olfaction, while less common, is more difficult to cope with. Pets with sensory reduction are not able to appropriately evaluate the situation or environment in which they are found and have reduced ability to cope with it or with changes (Landsberg and Denenberg 2009).

2.1.2.2 Pain

Virtually any disease process that leads to pain will affect the pet's behaviour. Both acute and chronic pain will lead to increased irritability, withdrawal, changes in activity levels, reluctance to play and even aggression (Camps et al. 2012). Pain can also lead to increased anxiety and fear as the pet learns it cannot avoid threatening or painful triggers. The elimination of avoidance may lead to increased aggression.

While dogs are more likely to show overt signs of pain (e.g. limping, curling, rubbing or licking an area and vocalising), cats show more avoidance-related behaviour. For example, cats with degenerative joint disease may not show lameness but are more likely to avoid jumping on owners, playing or hunting (Landsberg and Denenberg 2009). Both dogs and cats with arthritis may refuse to interact with the owners or go for a walk. This may be viewed as changes in interactions. Animals with arthritis may develop a repetitive behaviour of licking the painful area (Frank 2014). The release of local endorphins, enkephalins and opioids may further reinforce and maintain this behaviour.

Oral or dental pain, as well as gastrointestinal pain, may lead to reduced appetite, lack of desire to interact or avoidance and possibly aggression when owners try petting the pet's head.

Pets with chronic pain may adjust to it by changing their habits and patterns of behaviour. These animals may eat less, have altered responses to various stimuli and withdraw from interactions. Pain can also reduce sleep duration and quality, and the animal may become more irritable.

Musculoskeletal diseases that lead to muscle weakness and wasting (e.g. muscular dystrophy, myositis and immune-mediated disease) can lead to pain, altered mobility and changes in interactions. Moreover, animals with these conditions may have altered responses to triggers, exhibit house soiling and be more irritable (Frank 2014).

2.1.2.3 Cardiovascular Disease

Compromised circulation and hypotension may lead to hypoxia in the brain. This in turn can lead to reduced awareness and social interactions and altered responses to stimuli. In addition, it can lead to tiredness, reduced activity and confusion.

Cats and dogs with cardiomyopathies have reduced appetite, exercise intolerance, tiredness and even increased irritability. These animals may appear more withdrawn and disoriented at times and have altered sleep-wake cycles (Landsberg 2005).

Advanced conditions such as chronic congestive heart failure and hypertension may lead to development of anxiety as a result of constant struggle with normal breathing, inability to exercise, taking frequent medications and a degree of hypoxia in the brain.

2.1.2.4 Endocrine Disease

Diabetes mellitus in both dogs and cats may lead first to an increase in appetite and later decrease. Animals with a ravenous appetite may show aggression over food and treats. Hyperglycaemia leads to excessive drinking and urination that in turn may lead to house soiling (Neilson 2004, Manteca 2011). Fatigue and lethargy are common signs of diabetes mellitus that can affect sleep-wake cycles. Advanced stages of diabetes can lead to hyperkalaemia, leading to withdrawal, reduced interactions, lethargy, disorientation and confusion.

Diabetes insipidus can lead to similar signs of house soiling, lethargy, irritability and aggression over water resources. Moreover, animals may have altered sleep-wake cycles, and night-time waking, searching for outlets to soil and drink.

Hyperadrenocorticism may mimic signs of chronic anxiety by inducing anxiety-like physical changes due to consistently high levels of cortisol in the body (activation of the hypothalamic–pituitary–adrenal axis). Animals may become more irritable and more aggressive. Increased appetite may be seen in early stages of the disease, together with polydipsia and polyuria. Many dogs with hyperadrenocorticism may exhibit exercise intolerance and avoid play, interactions and other physical activities (Bowen and Heath 2005).

Hypoadrenocorticism can lead to lethargy and apathy. In many patients hypoglycaemia can be noted as well as alterations of sodium and potassium. This will lead to withdrawal of the animal, reduced interactions, decreased appetite and changes in sleep-wake cycles. Exercise intolerance, disorientation and confusion are some of the signs seen during the low phase of the disease.

Hypothyroid, which is seen mostly in dogs (or iatrogenic in cats), will lead to slower metabolism. It can be seen as lethargy and changes in sleep-wake cycles, changes in appetite and reduced interactions with people and the environment. Dogs may refuse to go for a walk, avoid play and prefer to be left alone. Physical changes related to this condition (e.g. obesity, skin sensitivities and allergies and fatigue) may lead to increased irritability.

Hyperthyroid in cats (and iatrogenic in dogs) accelerates metabolism. Cats often appear to have a ravenous appetite, irritability and increased activity. This can lead to night-time waking, excessive vocalisation, aggression (over food or when interacting with other cats and people) and even repetitive behaviours (Neilson 2004).

While insulinoma is very infrequent in dogs and rare in cats, this tumour can certainly lead to behavioural changes also seen in CDS. The main result of oversecretion of insulin is hypoglycaemia. Dogs can be lethargic and withdrawn, avoiding interactions with people and the environment (Meleo and Peterson 2014). They may show more fear-related signs as they are not able to cope with changes. This will also lead to increased sleep and vocalisation and decreased activity. In advanced stages confusion and disorientation can be noted.

2.1.2.5 Gastrointestinal Disease

The feeling of nausea often accompanies many gastrointestinal diseases. Nauseous animals may show anxiety-related signs such as lip licking, excessive stretching and refusal to eat. Gastrointestinal pain can increase irritability, affect sleep leading to night-time waking and lead to avoidance of interactions.

Any disease that can increase intestinal motility and lead to diarrhoea (e.g. inflammatory bowel disease, infections and pancreatitis) may cause house soiling (Landsberg et al. 2013). In addition, pets that are well trained not to soil in the house may develop anxiety at times when the owners are not there to let them out. Moreover, these pets may pace repetitively, show night-time waking and excessive vocalisation and have increased irritability (Denenberg and Landsberg 2016).

Constipation may increase pain and irritability and lead to house soiling. Constipated pets may become more aggressive, avoid interactions and hide. If the need to soil exists overnight, sleep-wake cycles might be altered.

Hepatic diseases (e.g. hepatic insufficiency or failure, gall bladder inflammation or stones and hepatic neoplasias) may lead to pain and problems with digestion and absorption of nutrients. Dogs and cats may show avoidance and aggression and have reduced sleep. Furthermore, hepatic dysfunction may lead to toxaemia that affects the brain (hepatic encephalopathy) (Tisdall et al. 2000). This can have a direct effect on the animal's behaviour, including irritability, aggression, confusion and disorientation, and even seizures that may appear as displacement and repetitive behaviours (e.g. staring into mid-air, fly snapping and pacing).

Pancreatic diseases (such as pancreatitis, exocrine pancreatic insufficiency and tumours) can all cause pain, nausea and maldigestion. This, in turn, can lead to avoidance, increased irritability and displacement behaviours such as eating non-food objects (Becuwe-Bonnet et al. 2012). House soiling can occur as well.

2.1.2.6 Urinary System Disease

Renal insufficiency or failure is a common disease in senior cats and dogs. One of the earlier signs is polyuria and polydipsia. This can lead to house soiling in senior pets. In advanced stages uraemia can lead to nausea, pain and lethargy. These pets may appear anxious, irritable and disoriented. Reduced appetite, changes in interactions, sleep-wake cycle alterations and avoidance are all common signs of advanced renal disease (Landsberg and Denenberg 2009).

Urinary tract infection, idiopathic cystitis and feline urinary syndrome are all common reasons for house soiling, night-time waking and changes in interactions. Urinary stones (kidneys and bladder) can cause pain, irritability and aggression (Neilson 2004, Landsberg et al. 2013).

Urinary incontinence is not an infrequent problem in senior pets, especially neutered female dogs. It can lead to house soiling, increased irritability and problems with self-hygiene. Increased anxiety can be a consequence of the disease and a result of the owner's reactions.

Renal or bladder tumours can lead to house soiling, pain and avoidance, reduced activity, night-time waking, pacing and excessive vocalisation. In later stages confusion and disorientation may also be seen.

2.1.3 Neurological Differentials of CDS in Dogs and Cats

A systematic diagnostic approach is of paramount importance in the face of non-specific clinical signs. As seen in the first part of this chapter, there is a large overlap in the clinical signs seen with CDS and behavioural, metabolic, neurological or painful conditions. One cannot stress enough the importance of the signalment, history taking, physical and neurological examinations to form a problem and then differential list before pursuing advanced laboratory or imaging testing. Here is the step-by-step approach the authors use in patients presented for signs that could be suggestive of CDS.

2.2 Diagnostic Approach to Reach a Presumptive Diagnosis of CDS

2.2.1 Signalment

Signalment will have an important impact on the organisation of the differential diagnosis list. Cats or dogs younger than 6 years of age are very unlikely to be affected by CDS—at least not at a clinically detectable level. While the individual's breed seems less relevant, it should be incorporated in the clinical reasoning (Head et al. 2009a, b). The clinician should be familiar with breed predispositions (Table 2.4) as these could have an impact on the suspicion of a non-infectious inflammatory brain disease, a neoplastic process, an infectious process or a metabolic condition. Some databases are available online or in veterinary textbooks to inform the clinician about disease prevalence for specific breeds.

2.2.2 History Taking

Thorough history serves to identify indicators of any neurological or metabolic diseases that would lead you to reject CDS as your suspected diagnosis (e.g. the presence of polyuria or polydipsia (PU/PD), recurrent urinary tract infection, seizures, circling and head pressing). Focus the questions around the DISHAA questionnaire (see Table 1.1).

Table 2.4 Suspected breed predisposition

Conditions	Breeds
Gliomas	Boxer, French bulldog, Boston terrier
Choroid plexus tumours	Golden retriever, Dalmatian, Irish setter
Meningiomas	Golden retriever, miniature schnauzer, rat terrier
Non-infectious meningoencephalitis	Pug, maltese, Yorkshire terrier, West Highland white terrier, rottweiler
Ceroid lipofuscinosis	Tibetan terrier, dachshund
L2-HGA	Yorkshire terrier, Staffordshire bull terrier, West Highland white terrier
Vitamin E deficiency	English cocker spaniel
Congenital PSS	Yorkshire terrier
Ischaemic strokes	Greyhound, Cavalier King Charles spaniel
FIP infection	Purebred cats

L2-HGA L2-hydroxyglutaric aciduria, *PSS* Portosystemic shunt, *FIP* Feline infectious peritonitis

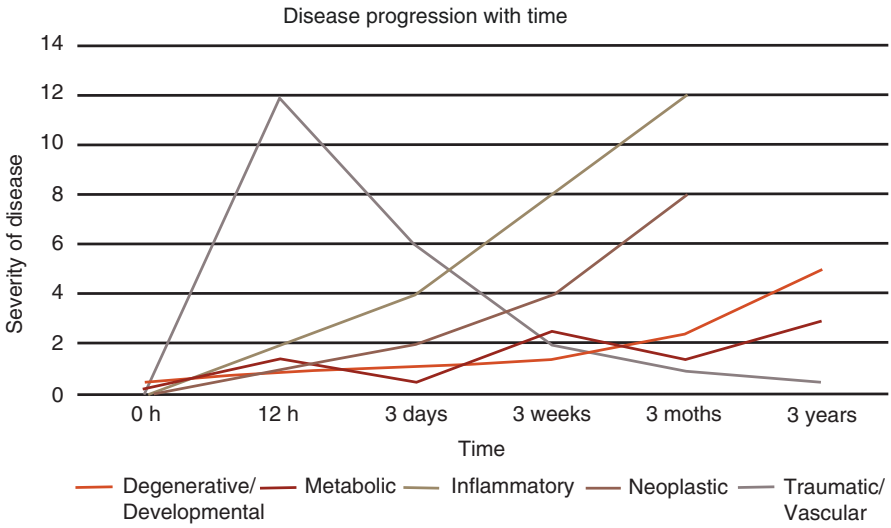


Fig. 2.1 Temporal progression of neurological diseases

Another important consideration is the onset and progression of clinical signs, which is useful in forming different lists (Fig. 2.1). As mentioned, CDS should have an insidious onset and is slowly progressive in nature; if the animal history suggests differently, the diagnosis of CDS is not likely.

2.2.2.1 Disorientation

Is this occurring at any particular time of the day? Is it happening during exercise, in the middle of the day or immediately after feeding? The former could raise the suspicion towards hypoglycaemia, while the latter can be seen in animals with

hepatic insufficiency following a large protein intake. If disorientation occurs mainly or solely later in the evenings or in dim lighting conditions, then the clinician should be suspicious of an altered sense of vision (e.g. nyctalopia seen with progressive retinal atrophy or with retinal degeneration in patients suffering from neuronal ceroid lipofuscinosis).

2.2.2.2 Alterations in Interactions with Owners, Other Pets and the Environment

This could occur in specific situations: a pet who growls, hisses or bites when woken could have reduced hearing, while an animal reluctant to play with other animals or to go for walks could be in pain or weak. Clinical signs that include compulsive pacing, circling to the same side, head pressing against walls or objects, hemineglect syndrome, episodes of opisthotonus or seizures would suggest a metabolic disorder or intracranial lesion.

2.2.2.3 House Soiling

House soiling can be seen in a variety of situations, but history will provide invaluable information to guide the clinician in their diagnostic approach. The presence of polyuria, polydipsia (water intake >100 mL/kg/day), pollakiuria, periuria or dysuria should be documented and will require further, more specific investigation. The diagnostic approach for an animal with polyuria and polydipsia would certainly be different from that for an animal accidentally passing faeces inside the house. Intestinal parasites control should also be documented as well as the presence of chronic gastrointestinal signs (vomiting, diarrhoea, dyschezia, regurgitation, melaena, weight loss, etc.) (Head et al. 2009a, b). The clinician should also ask whether the animal seems to be conscious of the fact they are passing faeces or urine and the frequency and nature of the faeces/urine. For example, being aware of urination and the urine being passed with pollakiuria and haematuria would suggest a lower urinary tract disease.

Differential diagnosis for house soiling: polyuria, polydipsia, urinary tract infection, urinary incontinence, faecal incontinence and loss of training, and painful conditions.

2.2.2.4 Changes in Activity

Again the clinician should focus the questioning on the possibility of the presence of a hypometabolic state or hypermetabolic state. Any recent weight loss or gain should be documented as well as the presence of excessive panting (hypertension, cardiorespiratory disease) or polyphagia (diabetes mellitus, hyperadrenocorticism, hyperthyroidism, acromegaly).

2.2.2.5 Establishment of the Most Relevant Complaint(s)

This step ensures the clinician lists specific and less specific complaints but also attends to the needs and expectations of the pet's owner, irrespective of the animal's problem. Managing the owner's expectations means taking into account the

historical and clinical findings but also addressing the owners' concerns. CDS could be the main disease or could be concomitant with other conditions.

The greater the number of DISHAA signs (see Table 1.1) present, the stronger the suspicion for CDS, although concurrent or alternative differentials remain possible.

2.2.3 Patient Examination

2.2.3.1 Physical Examination

The physical examination should be thorough and systematic (Table 2.5). An in-depth description of the physical examination is beyond the scope of this chapter but should focus on the detection of painful body areas or signs suggestive of an underlying metabolic disease (ulcerative tongue lesions and small irregular kidneys could be part of a uremic syndrome, organomegaly could suggest acromegaly, etc.). A cat's neck should be thoroughly palpated for the presence of a thyroid slip that could be indicative of an enlarged thyroid gland.

2.2.3.2 Orthopaedic Examination

Due to the aged population being considered, concomitant orthopaedic issues are likely. The clinician will then be faced with the dilemma of determining whether the abnormalities found on orthopaedic examination are concomitant/incidental or the primary cause for the presenting complaint. In particular, osteoarthritis is common in ageing cats and dogs and could be a plausible reason for reduced activity, fearful behaviour or altered interactions. It is worth noting that generally speaking scuffing of the nails is associated with a neurological rather than an orthopaedic complaint.

Joint or orthopaedic conditions seen in older patients include osteoarthritis, cranial cruciate ligament injury, intervertebral disc disease, bone neoplasia and discospondylitis.

Table 2.5 Physical examination findings suggestive of a neurological dysfunction

Clinical signs	Potential significance
Head tilt	Brainstem lesion, otitis, idiopathic vestibular syndrome, ear neoplasia
Head turn	Contralateral forebrain lesion
Scuffed nails	Proprioceptive deficits
Facial twitching	Partial seizures, myokymia
Self-mutilation	Neuropathy
Anisocoria	Ocular lesion, Central or peripheral nervous system lesion
Circling	Contralateral forebrain lesion
Head pressing	Raised intracranial pressure

2.2.3.3 Ophthalmological Examination

The goal of a thorough ophthalmological examination is to detect any vision loss but also to document further clues for the diagnostic puzzle. The clinician should assess the presence of cataracts, retinal haemorrhage, retinal degeneration, retinal detachment or chorioretinitis. Retinal haemorrhage and chorioretinitis are more specific findings and would warrant further investigation that may lead to the more efficient diagnosis of a primary underlying process. The optic nerve will be visible in most animals and should be assessed for the presence of optic neuritis or papilloedema. Abnormal vision in the absence of ophthalmological abnormality will be strongly suggestive of a central nervous system lesion.

2.2.3.4 Neurological Examination

The neurological examination allows you to assess if the patient has a neurological problem and to localise the lesion. Localisation in turn, when used in combination with signalment and history, allows the creation of a differential list which will guide your diagnostic plan and let you know if CDS should be considered a differential.

The neurological exam is completed by (a) observing the neurological patient and (b) performing specific hands-on tests. The patient is assessed in five major areas (Table 2.6)

Following this, an assimilation of the information allows you to localise to one (or more) of eight major anatomical regions: forebrain, brainstem, vestibular-cerebellar system, spinal cord C1-C5, C6-T2, T3-L3 and L4-S3, and neuromuscular system.

It is important to perform a full neurological exam in a patient you suspect with CDS as any abnormality outside changes of behaviour or mentation may suggest an alternative diagnosis. This could be changes suggestive of a forebrain disease or a multifocal exam which could suggest raised intracranial pressure resulting in CNS herniation, diffuse degenerative process, a multifocal inflammatory/infectious disease or neoplasia.

It is worth considering that some older dogs could have concurrent diseases (such as some signs of an L4-S3 localisation associated with lumbosacral disease) alongside forebrain signs of CDS, but a multifocal exam with a progressive history could also be highly suggestive of neoplastic and inflammatory/infectious diseases, so it is worth trying to exclude these as possibilities both clinically and with diagnostics testing when felt appropriate (Head 2009a, b).

Table 2.6 Areas being tested and methods of assessment

Area of testing	Method of testing
Behaviour and consciousness	Observation
Cranial nerves	Observation and the hands-on examination
Gait and posture	Observation
Postural reactions	Hands-on examination
Spinal reflexes	Hands-on examination

Describing how to perform a full neurological exam is beyond the scope of this article and can be found in dedicated textbooks. We will now discuss changes that, when found, would lead you away from considering CDS as a diagnosis. Doing a full neurological examination takes time so ensure you leave more than the 5–15 minutes of a general consultation.

2.2.3.5 Changes on Neurological Examination that Would Not Be Expected with CDS

Items in bold are in the authors' experience the most common changes seen in cases with a purely forebrain (FB) localisation that would suggest CDS is not a differential. Although all items of the neurological exam are to be checked, we have tried to place them in order of preference/importance to screen the neurological system for disease. For example, looking for nystagmus (in particular a positional nystagmus) is a good screen of brainstem function given the extensive nature of the vestibular nuclei in this region of the brain. This is obviously important if inflammatory diseases are a differential or if you are worried about raised intracranial pressure where nystagmus may be encountered secondary to brain herniation. Items with a FB in brackets are tests that may be abnormal with a purely FB lesion.

Behaviour and consciousness:

- **Seizures (FB)**
- **Persistent circling (FB)**
- **Head pressing (FB)**
- Stuporous mentation (FB)
- Comatose mentation
- Hemineglect syndrome (FB)

Notes: Persistent circling can be both secondary to a forebrain lesion and a vestibular-cerebellar disturbance, so you would want to perform tests on the vestibular-cerebellar system to differentiate the two. Circling due to a forebrain lesion tends to be in less tight circles. Stuporous and comatose mentation is rarely seen with forebrain diseases in the absence of numerous other forebrain deficits on exam as they would need to affect such diffuse areas of brain tissue. As a result, it is more common to see these with brainstem disease. The exception would be a disease affecting the diencephalon of the forebrain (e.g. a pituitary neoplasm).

Cranial nerves testing:

- **Reduced/absent menace response (FB)**
- **Reduced/absent visual tracking (FB)**
- **Reduced/absent facial sensation usually found with reduced/absent nasal mucosal response (FB)**
- Nystagmus-spontaneous or positional
- Anisocoria (FB)
- Facial droop/paresis (FB)
- Reduced palpebral light reflex

- Strabismus
- Absent/reduced vestibulo-ocular reflex
- Reduced gag reflex
- Reduced/absent corneal reflex
- Reduced/absent dazzle reflex
- Masticatory muscle wastage
- Inability to close the jaw

Notes: The menace response and positional nystagmus are considered by the authors the most important cranial nerve tests to screen the forebrain and brainstem, respectively. A head tilt and facial paresis are both very rare with forebrain disease but remain possible. It is worth noting that finding these signs in isolation without other changes suggestive of a forebrain localisation would point towards alternative localisations in the neurological system.

Gait and posture:

- **Deficits in postural reactions (FB)**
- **A head turn (FB)**
- **Circling (FB)**
- Paresis/ataxia (FB)
- A head tilt (FB)
- Decerebrate posture
- Decerebellate posture

Notes: Deficits in postural reactions can be detected through paw placement, hopping, tactile placement, visual placement, wheelbarrowing and hemi-walking. A head tilt is very rarely seen secondary to a purely forebrain disease and usually only occurs secondary to vascular lesions affecting the thalamus.

Relevant spinal reflexes:

- Patellar reflex
- Withdrawal reflex (thoracic and pelvic limbs)
- Perianal reflex/anal tone
- Cutaneous trunci

Notes: No spinal reflexes should be abnormal with CDS or any other forebrain, cerebellar-vestibular or brainstem disease. I have only included the spinal reflexes that are reliable, but others do exist. When assessing these, we would also consider muscle wastage, tone, a crossed extensor and evidence of spinal pain.

2.2.4 Problem List and Differential Diagnosis

2.2.4.1 Problem List

After the history has been taken and after the patient's examination has been performed, a problem list is established. The clinical suspicion of CDS will increase with each addition of the DISHAA (see Table 1.1) clinical sign. The problem list will

also help the clinician by listing problems that are more specific (PU/PD vs. lethargy, neurological deficits vs. lethargy) or that are more likely to lead to the diagnosis of an underlying alternative pathology (seizures vs. increased fearful behaviour).

2.2.4.2 Differential List

Using the problem list and then considering the signalment, history, and physical and neurological examinations will allow formation of a differential list. We have compiled a differential list below based on conditions with overlapping signs with CDS in patients over the age of 6 years.

2.2.4.3 Differential Diagnosis: DAMNITV

Here is a non-exhaustive list of the conditions that may enter the differential diagnosis list of a clinician faced with a patient suffering from clinical signs that could be due to a metabolic disease, neurological disease or CDS. The authors use the DAMNITV (degenerative, anomalous, metabolic, nutritional or neoplastic, inflammatory or infectious, traumatic or toxic, vascular) or VITAMIND algorithm.

2.2.4.4 Degenerative Differentials

Ceroid Lipofuscinosis

Aetiopathogenesis Ceroid lipofuscinosis is a neurodegenerative disease characterised by the accumulation of autofluorescent lipopigments (ceroid- or lipofuscin-like lipopigments) in neurons and other cells within the body. While most affected dogs and cats will present with signs early in life (within the first 2 years), ceroid lipofuscinosis is one of the few storage diseases that can present in adulthood. This is particularly true in the Tibetan terrier and dachshund breeds who may develop obvious signs when 6 years or older and can survive past 10 years of age. The pathophysiology of the disease is yet to be elucidated as it is unclear whether the mechanism of injury is a direct consequence of the pigment accumulation in cells or if it involves an abnormal mitochondrial function. The advances of molecular genetics have permitted the identification of multiple gene defects causing enzymatic dysfunction, leading to ceroid lipofuscinosis in specific dog breeds.

Clinical Signs The clinical signs reflect the organ dysfunction where the pigment accumulates. The two main systems affected are the visual system and the forebrain. The owners may report a progressive decline in vision with a tendency to bump into objects, especially at night (nyctalopia). Behavioural changes include loss of training, development of unprovoked aggression, progressive clumsiness, pacing, difficulty recognising the owners and house soiling. Affected dogs can also be easily startled and can develop overwhelming anxiety. Neurological deficits are usually symmetrical and may be initially subtle or absent. Vestibular signs with an intermittent loss of balance, decreased vision and mild proprioceptive deficits in all limbs despite normal spinal reflexes can progress later in the disease to signs of head pressing or severe ataxia. Ophthalmological examination may reveal changes

consistent with retinal degeneration (tapetal hyperreflectivity, thinning and paucity of the retinal arteries).

Clinical signs that overlap with CDS:

- Loss of training
- Unprovoked aggression
- Progressive clumsiness
- Pacing
- Difficulty recognising the owners and house soiling

Clinical signs that would not overlap with CDS:

- Loss of vision
- Ataxia
- Neurological deficits

Diagnosis/Exclusion For breeds in which a known causative mutation has been identified, a diagnosis can be reached with genetic tests performed on DNA samples (EDTA blood sample or buccal swab). The diagnosis can also be supported by advanced imaging, with MRI changes of generalised brain atrophy despite normal spinal fluid results being suggestive of a neurodegenerative disease. Sometimes EEG changes will support this disease process too. Contrast enhancement of the meninges has also been reported in a cohort of affected chihuahuas.

Treatment Unfortunately, there is no known treatment for this condition. The progression is variable, but some dogs will survive for years before euthanasia is elected based on welfare or security grounds (in the case of unprovoked aggression unresponsive to treatment).

L-2-Hydroxyglutaric Aciduria

Aetiopathogenesis L-2-hydroxyglutaric aciduria (L2-HGA) is a neurometabolic disease with an unknown pathogenesis. It is suggested that L2-HGA may act as a direct toxin on the central nervous system or act through oxidative stress or mitochondrial dysfunction.

Clinical Signs This disease has only been reported in the Staffordshire bull terrier (SBT), West Highland white terrier and Yorkshire terrier to date. While L2-HGA is usually reported in younger animals, some dogs have first presented with the disease after 7 years of age.

Clinical signs are progressive and include behavioural changes (including inability to learn new tasks and forgetting learned tasks, getting stuck under tables and chairs/corners, etc.), changes in mentation (e.g. obtundation), head pressing as well as psychomotor retardation, dysmetria, cerebellar signs (including dysmetria, head tremors and reduced menace response in the presence of normal vision), muscular stiffness after exercise, ataxia, tremors and seizures.

Clinical signs that overlap with CDS:

- Obtundation and behaviour changes

Clinical signs that would not overlap with CDS:

- Head pressing
- Seizures
- Ataxia
- Dysmetria
- Cerebellar signs
- Muscular stiffness after exercise and tremors

Diagnosis/Exclusion Diagnosis is made based on consistent clinical signs in combination with consistent laboratory findings, with or without imaging studies and genetic testing. In particular, demonstrating the presence of increased levels of L2-HGA in urine or serum with metabolic testing is diagnostic. In SBT there is a genetic test available, and MRI imaging of the central nervous system is characteristic.

Treatment There is no specific treatment. In people, various dietary supplements have shown anecdotal improvements.

Other Neurodegenerative Diseases

Most neurodegenerative disease will present early in life and will be considered as unlikely differentials for CDS.

Lafora disease can affect older dogs, in particular wire-haired dachshunds, beagles and basset hounds, but most dogs will present with myoclonic seizures, although some behavioural changes may be reported. The diagnosis is made by exclusion of metabolic and intracranial lesions and identification of the known mutation causing Lafora disease, when available. Tissue biopsy may allow the identification of polyglucosan bodies within the brain, muscles, skin or liver. Treatment is symptomatic to control the seizures.

Neuroaxonal dystrophy is another neurodegenerative disease for which the chief complaint could be behavioural changes, although the neurological examination will almost invariably reveal neurological deficits suggestive of a cerebellovestibular dysfunction. The aetiopathogenesis is poorly understood, but an abnormal metabolism of vitamin E is often cited as a possible cause. Diagnosis can be supported by an abnormal MRI scan, although post-mortem examination is often necessary to reach a definitive diagnosis. The benefit of vitamin E supplementation is yet to be proven.

2.2.4.5 Anomalous: Brain Malformations

Aetiopathogenesis Brain malformations occur due to a failure of development of normal brain tissue or its destruction during foetal or embryonic life. The latter can be seen secondary to infectious, traumatic or vascular injury to the developing brain. While most malformations would be expected to cause problems in young animals,

some malformations may remain silent and may manifest only later as the malformation gets bigger (e.g. quadrigeminal cysts, hydrocephalus) or causes obstruction of the spinal fluid pathways (e.g. fourth ventricle arachnoid cysts). The injury results from direct pressure on the brain tissue or due to secondary increased intracranial pressure following the development of obstructive hydrocephalus.

Clinical Signs The clinical signs reflect the localisation of the lesion. With quadrigeminal cysts and fourth ventricle cysts, compression of the brainstem may lead to signs of central vestibular syndrome, including an obtunded mental status, lethargy, and neurological deficits such as a head tilt, nystagmus and proprioceptive deficits. An animal with increased intracranial pressure can manifest signs of neck pain and, as a consequence, may become aggressive and withdrawn.

Clinical signs that overlap with CDS:

- Altered mental status
- Aggression

Clinical signs that would not overlap with CDS:

- Head tilt
- Nystagmus
- Proprioceptive deficits
- Ataxia, circling
- Seizures
- Pain

Diagnosis/Exclusion The diagnosis is made by advanced imaging, with an MRI scan of the brain characterising the lesions and their potential consequences as oedema, mass effect, brain herniation or syringohydromyelia. One dilemma resides in the fact that some animals can have incidental cystic lesions as quadrigeminal cyst not causing clinical signs but diagnosed later in life for the investigation of a clinical complaint of lethargy or abnormal behaviour. In this instance the clinician has to use his judgement to decide whether or not the cyst can explain the clinical complaint and the clinical signs of the animal and whether or not the cyst should be treated. One retrospective paper has suggested that the relative size and compression of quadrigeminal cysts may relate to incidence of clinical signs.

Treatment The treatment of brain malformations, in particular cystic lesions, can be medical, with drugs used to reduce oedema or Cerebrospinal fluid (CSF) production, or surgical, to remove the lesion or restore a CSF pathway to resolve obstructive hydrocephalus.

2.2.4.6 Metabolic Differentials

Hypoglycaemia

Aetiopathogenesis Hypoglycaemia can be caused by hyperinsulinaemia (e.g. insulinomas), Addison's disease, hepatic failure, sepsis, neoplasia, repeated inappropriate

medication dosing and rarely hunting dog hypoglycaemia or starvation. Other general causes of hypoglycaemia include toy breed hypoglycaemia and xylitol or ethylene glycol toxicity. The lack of glucose results in abnormal neuronal function and activation of the sympathetic nervous system, resulting in clinical signs.

Clinical Signs Any value lower than the reference interval should be considered suspicious for hypoglycaemia, but signs do not usually become apparent until <2.5 mmol/L. Hypoglycaemia can be seen in any age and breed of dog, but xylitol or ethylene glycol toxicity should have a peracute/acute onset of signs, and toy breed hypoglycaemia would be seen in the young.

Signs of hypoglycaemia include lethargy, tremors/muscle facilitations, weakness, changes in behaviour (nervousness, vocalisation, irritability, forgetting learned behaviours), tachycardia, visual disturbances, hypothermia, changes in mentation (obtundation, stupor or comatose state) and seizures. Given the list of differentials above, some cases may show other systemic signs such as polyphagia and vomiting.

Clinical signs that overlap with CDS:

- Lethargy
- Obtundation and behaviour changes

Clinical signs that would not overlap with CDS:

- Seizures
- Blindness
- Hypothermia and tachycardia
- Weakness or tremors

Diagnosis/Exclusion Diagnosis is made based on consistent clinical signs in the presence of recorded hypoglycaemia. It is necessary to perform a starved glucose measurement to exclude the disease, while inclusion would be any signs of hypoglycaemia (defined as <3.3 mmol/L). The authors perform serial blood glucose levels over a 24-hour starvation period and may consider a serum fructosamine to exclude hypoglycaemia as a cause for encephalopathy.

Treatment In the acute setting, this revolves around feeding, intravenous dextrose and glucose-infused fluid therapy. The underlying cause should then be investigated and treated appropriately.

Hepatic Encephalopathy

Aetiopathogenesis Hepatic encephalopathy (HE) can occur due to portosystemic shunting (PSS), which can be acquired or congenital, and due to acute or chronic hepatopathies, for example, feline hepatic lipidosis. Cases with PSS or microvascular dysplasia may present later in life with signs of HE secondary to a trigger such as infection, constipation, diarrhoea, increased dietary protein, gastrointestinal haemorrhage, electrolyte imbalances and arginine deficiency in cats with hepatic lipidosis (Holt et al. 2002).

A number of proposed mechanisms have emerged to explain the pathogenesis of hepatic encephalopathy. These revolve around increased levels of ammonia (which may be worsened by inflammation), increased levels of neurosteroids, increased manganese, increased oxidative stress through upregulated reactive oxygen and nitrogen species, and decreased aromatic amino acids. Ultimately, a dysfunction in neurotransmitters, neurotransmitter receptors and transporters, alteration in blood-brain barrier and electrolytes and alterations in neuronal and glial cell function or survival result in encephalopathic clinical signs (Wolschrijn et al. 2011).

Clinical Signs HE can be seen in dogs of any age and any breed. PSS tends to be seen in younger dogs, while acquired hepatopathies tend to be seen in older patients.

HE signs range from mild (e.g. mild obtundation) to more severe (e.g. seizures or comatose state) and often have an episodic nature in history often worsened by a meal. In a study of 80 dogs with hepatic encephalopathy, the most common historical signs were obtundation (33%), altered behaviour (29%), head pressing (28%), ataxia (26%), seizures (24%), vomiting (24%), lethargy (24%), ptyalism (23%) and blindness (19%). Other signs include anorexia, weight loss, diarrhoea, polydipsia and polyuria or poor weight gain. On neurological examination the most common findings were obtundation (31%), ataxia (20%), weakness (10%), proprioceptive deficits (9%), seizures (8%), circling (6%), cranial nerve deficits (5%), stupor (5%) and tremors (4%).

Clinical signs that overlap with CDS:

- Lethargy
- Obtundation and behaviour changes

Clinical signs that would not overlap with CDS:

- Head pressing
- Seizures
- Vomiting
- Diarrhoea
- Weight loss
- Icterus
- Organomegaly
- Ptyalism
- Blindness
- Circling
- Ataxia
- Neurological deficits
- Tremors
- Stupor

Diagnosis/Exclusion Diagnosis is made on consistent clinical signs, laboratory findings and imaging studies followed by response to treatment (in the exclusion of other causes of encephalopathy).

A complete blood count and biochemistry profile (including urinalysis) may be normal or may show a non-regenerative, microcytic anaemia, hypoglycaemia, hypoalbuminaemia, hypocholestrolaemia, increased Alkaline phosphatase (ALP) or Alanine aminotransferase (ALT), hyperbilirubinaemia, decreased urea and decreased urine concentrating ability with ammonium biurate crystals on cytology of urine.

Other laboratory tests for liver dysfunction include analysis of ammonia, resting bile acids or more importantly a dynamic bile acid stimulation test. Fasting ammonia levels have been shown to be relatively sensitive for detecting PSS with 91% in dogs (>59 μmol/L) and 83% (>94 μmol/L) in cats, with fasting bile acids being 78% for dogs (>58 μmol/L) and 100% in cats (>34 μmol/L). Although the sensitivity and specificity are not known for dynamic bile acids for hepatic dysfunction, this is proposed to be the superior test compared to a resting bile acid.

A definitive diagnosis of hepatic dysfunction causing encephalopathy must come from either demonstrating a shunting vessel with CT with IV contrast, mesenteric portography and abdominal ultrasound or less commonly scintigraphy for a PSS, or through imaging and liver biopsy for other hepatopathies.

Treatment This revolves around medical and surgical therapy. Medical therapy includes enemas in the acute setting alongside non-absorbable disaccharides (e.g. lactulose), antibiosis and high-quality protein diets. Anticonvulsants should be used if seizures are occurring. Other proposed supportive drug therapies include flumazenil (as an antagonist of benzodiazepines), probiotics and prebiotics, L-carnitine supplementation and L-ornithine-L-aspartate. Addressing and treating the underlying cause for the hepatic disease should also be undertaken.

Renal Encephalopathy

Aetiopathogenesis Renal encephalopathy (RE) comes secondary to renal failure. Renal failure can be caused by many differing disease processes—the scope of which is beyond this book chapter. These can be referenced in various medical textbooks (Holt et al. 2002).

There are many proposed mechanisms by which RE may come about and include increased parathyroid hormone levels, ionic imbalances with associated hyperosmolality, hypertension, uraemia and acidosis. These cause alterations in neuronal and glial cell function or survival by altering neurotransmitters, neurotransmitter receptors and transporters, the blood-brain barrier, cell membrane stability and ischaemia by various means.

Clinical Signs RE can be seen in any age or breed but is very rare in the author's experience. First and foremost these patients will present with signs of renal failure—polydipsia, polyuria, inappetence, weight loss, vomiting, lethargy, etc. In addition to the above signs, RE can cause changes in mentation (obtundation progressing to coma), seizures, muscle tremors, generalised weakness and irregular patterns of respiration.

Clinical signs that overlap with CDS:

- Lethargy
- Obtundation
- House soiling

Clinical signs that would not overlap with CDS:

- Stupor or comatose state
- Seizures
- Irregular patterns of respiration
- Muscle tremors
- Polydipsia
- Polyuria
- Weight loss
- Vomiting
- Inappetence

Diagnosis/Exclusion Diagnosis is made through consistent clinical signs and supporting laboratory findings. A complete blood count and biochemistry panel include full urinalysis and blood pressure evaluation.

Electrolytes Disturbances

Aetiopathogenesis Electrolytes are indispensable for the normal function of living cells by allowing the creation of electric potentials and message transduction. Potassium, sodium, calcium and magnesium are the most common ions inside or outside cells, and their disturbances will affect cell and organ function, with the central or peripheral nervous system being particularly affected. In older animals, the two electrolytes disturbances of interest are sodium or calcium abnormalities (Attems 2005).

Clinical Signs Hypernatraemia can cause systemic hypertension with the clinical signs mentioned earlier in this chapter. As an acute change, it can cause a marked demyelination (as below) and in a chronic state when corrected quickly can lead to cytotoxic oedema secondary to the formation of idiogenic osmoles within the neurons. Chronic hyponatraemia is unlikely to cause clinical signs on its own, but rapid correction of hyponatraemia (more rapidly than 0.5 mmol/L/h) can lead to signs of pontine and extrapontine demyelination including altered mental status, disorientation, seizure and proprioceptive deficits suggestive of a brainstem or forebrain lesion.

These signs can persist despite resolution of the electrolyte imbalance (Yoshino et al. 1996). Hypocalcaemia will mainly cause tremors, cramping, facial rubbing, panting, behavioural changes (disorientation, restlessness, excitation, aggression, hypersensitivity to stimuli), lethargy and cardiac arrhythmias. Hypercalcaemia can cause polyuria, polydipsia (which can lead to house soiling), anorexia, lethargy, weakness, dehydration, seizures, arrhythmias, constipation and renal failure.

Clinical signs that overlap with CDS:

- Behavioural changes
- Disorientation
- Lethargy
- House soiling

Clinical signs that would not overlap with CDS:

- Muscle cramps
- Arrhythmia
- Neurological deficits
- Seizures
- Arrhythmias

Differential diagnosis for hypercalcaemia:

- Hyperparathyroidism
- Hypercalcaemia of malignancy
- Hypervitaminosis D
- Hypoadrenocorticism
- Renal insufficiency
- Osteolytic lesions
- Granulomatous diseases
- Sepsis
- Laboratory error
- Idiopathic (cats)

Differential diagnosis for hypocalcaemia:

- Hypoparathyroidism
- Eclampsia
- Hypovitaminosis D
- Hyperadrenocorticism
- Renal insufficiency
- Pancreatitis
- Laboratory error

Differential diagnosis for hypernatraemia:

- Pure water deficit: hypodipsia, diabetes, insipidus fever
- Hypotonic fluid loss: gastrointestinal loss, renal losses, third space losses, burns
- Impermeant solute gain: salt poisoning, hypertonic fluid administration, hyperaldosteronism, hyperadrenocorticism

Differential diagnosis for hyponatraemia:

- With hypervolemia: cardiac failure, advanced renal failure, severe liver disease
- With normovolaemia: psychogenic polydipsia, syndrome of inappropriate antidiuretic hormone secretion, myxoedema coma of hypothyroidism
- With hypovolemia: gastrointestinal losses, third space losses, burns, hypoadrenocorticism

Diagnosis/Exclusion The diagnosis is made by measuring blood electrolytes. Total calcium being dependent on blood pH, protein concentration and other parameters, it is not a reliable marker of the available body calcium; ionised calcium should be performed to rule out hypo- or hypercalcaemia.

Treatment The treatment will aim at correcting the electrolytes disorder but most importantly its underlying cause. The correction of hypernatraemia or hyponatraemia should be done slowly, with the sodium being decreased or increased by no more than 0.5 mmol/L/h to avoid the development of brain oedema or pontine and extrapontine demyelination syndrome, respectively. Calcium correction should be done while the ECG of the animal is monitored for arrhythmias.

2.2.4.7 Nutritional

The origin of vitamin deficiency in dogs and cats is an inappropriate dietary intake, a lack of absorption or the presence of molecules that inhibits or destroys the vitamins in the food. The two vitamins of interest to us are vitamin E and vitamin B1 (thiamine) (Head et al. 2009a, b).

Vitamin B1 Deficiency

Aetiopathogenesis Vitamin B1 (thiamine) is a coenzyme in the Krebs cycle and additional enzymatic pathways involved in energy production. The absence of thiamine may lead to damage of high-energy structures, in particular brainstem nuclei in dogs and cats but also the heart and retina.

Clinical Signs The clinical signs seen in dogs or cats suffering from thiamine deficiency include abnormal mentation, ventro-flexion of the neck/head, blindness, vestibular ataxia, head tilt, nystagmus, mydriasis, facial paralysis and seizures (Gold et al. 2015).

Clinical signs that overlap with CDS:

- Abnormal mentation

Clinical signs that would not overlap with CDS:

- Ventro-flexion of the neck/head
- Ataxia, head tilt, nystagmus
- Facial paresis, blindness
- Seizures (Head et al. 2009a, b)

Diagnosis/Exclusion Thiamine deficiency is diagnosed by measuring total thiamine level in blood, but the diagnosis can also be strengthened by the presence of characteristic bilaterally symmetrical lesions in brainstem nuclei on MRI and by an abnormal organic acid profile in urine.

Treatment The treatment involves oral or parenteral supplementation of the deficient vitamin and correction of the underlying cause. Animals suffering from thiamine deficiency can recover fully.

Vitamin E Deficiency

Aetiopathogenesis Vitamin E is a potent antioxidant whose deficiency leads to oxidative stress injury, this being pronounced in the muscles, CNS and retinas. Vitamin E deficiency is suspected to have a genetic basis in English cocker spaniels (Norton et al. 2016).

Clinical Signs The clinical signs associated with vitamin E deficiency include progressive vision loss (retinal epithelial pigment dystrophy), reduced activity and reluctance to walk, muscle weakness and neurological deficits consistent with a myopathy or a cerebello-vestibular localisation.

Clinical signs that overlap with CDS:

- Reluctance to exercise or walk

Clinical signs that would not overlap with CDS:

- Neurological deficits, blindness

Diagnosis/Exclusion The diagnosis of vitamin E deficiency is made by measuring serum vitamin E concentration and by ruling out other extracranial and intracranial causes. MRI and CSF analysis have been reported as normal in dogs for which it has been performed.

Treatment Cocker spaniels affected by vitamin E deficiency supplemented orally did not experience an improvement in their visual function, but their neurological function improved or stabilised, in some cases for years (Johnson et al. 2015).

2.2.4.8 Neoplastic Brain Disease

Aetiopathogenesis Intracranial neoplasia can be primary if originating from the brain structures themselves, secondary if invading the brain by local extension (e.g. from a nasal, ocular or skull origin) or metastatic if affecting the brain by vascular spread of a distant neoplastic process. In dogs and cats, primary intracranial tumours are more common, while metastatic neoplasias (hemangiosarcoma, carcinomas or multicentric lymphoma) remain on the differential diagnosis list. Brain tumours are often classified according to the cell lineage they originate from (meninges, glial cells, choroid plexus cells, lymphocytes, ependymal cells, etc.) or based on the

circumferential location of the tumour in relation to the brain (extra-axial, intra-axial or intraventricular). In both dogs and cats, the most common intracranial tumours are meningiomas and typically present as single extra-axial masses, while the most common intra-axial tumours are gliomas (astrocytomas, oligodendrogliomas, glioblastoma). Round cell tumours such as lymphoma or histiocytic sarcoma can present with an intra-axial, intraventricular or extra-axial localisation (Dickinson 2014). The mechanisms of injury to the brain are multiple and depend on the size, growth and location of the tumour: direct invasion of the brain tissue and loss of function, ischaemia, focal compression, oedema formation and increased intracranial pressure, alteration of the balance of neurotransmitters, but also biochemical and immunological derangements. The strong breed predisposition seen for some tumours as gliomas in some dog breeds such as boxers, bulldogs and Boston terriers suggests a genetic susceptibility in specific breeds (Truvé et al. 2016).

Clinical Signs The clinical signs depend not only on the location of the neoplasm but also on the rate of its growth and the local biochemical changes as mentioned above. It is not uncommon to diagnose a sizeable mass in the light of relatively subtle signs, as the brain is able to compensate for substantial changes in pressure and volume before the compensation mechanisms are exhausted. Behavioural changes are common and do not infrequently precede the development of neurological deficits that will make a forebrain neurolocalisation more obvious. As an example, the most common clinical signs in a study of pituitary macroadenoma were mentation (depression, stupor) and behavioural changes (pacing, disorientation, circling, head pressing, aggression). Behavioural changes can also be the only clinical complaint. Masses affecting the limbic system, association areas (such as the frontal lobe and parieto-temporal junction) or the ascending reticular activating system are likely to produce behavioural changes with or without any obvious neurological deficits (Berns et al. 2015). The changes that can be seen include the development of fearful or aggressive behaviour or conversely the development of an attention-seeking behaviour in a previously fearful animal. Cats can be seen hiding more in unusual places or can be found stuck in a corner of a room. Head pressing or compulsively circling to one side only will raise the suspicion towards a significant intracranial lesion, with the former signs being suggestive of raised intracranial pressure. House soiling can also precede the development of more worrisome neurological signs and could be exacerbated by the presence of a concurrent endocrinopathy causing PU/PD (hyperadrenocorticism, central diabetes insipidus or acromegaly due to a secreting pituitary tumour). Raised intracranial pressure can also lead to clinical signs of pain including vocalisation, aggression, lethargy and head pressing behaviours (Madison et al. 2015).

A history of seizure is a specific sign for a forebrain lesion and can be seen in the absence of neurological deficits despite the presence of a substantial lesion. Neurological deficits will vary depending on the location and size of the mass and can suggest a focal or multifocal pathology. Due to the crossover of the sensory and motor pathways, a lateralised forebrain lesion will manifest as neurological deficits

on the contralateral side of the body (absent vision, abnormal proprioception or nasal sensation).

Clinical signs that overlap with CDS:

- Depression
- Pacing
- House soiling
- Altered interactions

Clinical signs that would not overlap with CDS:

- Neurological deficits
- Seizures
- Signs of raised intracranial pressure

Diagnosis The cornerstone of the diagnosis of intracranial neoplasia remains advanced imaging (with MRI being preferred to CT). This is performed after having ruled out extracranial causes of forebrain or brainstem dysfunction. A presumptive diagnosis of a brain tumour is often reached after considering the history, signalment and imaging findings along with the cerebrospinal fluid results. Occasionally, repeated imaging or brain biopsies may be necessary to reach a more definitive diagnosis or to rule out other non-neoplastic neoplastic differentials (Fig. 2.2).

Treatment Treatment options include surgery, chemotherapy, radiation therapy, palliative therapy or a combination of these depending on the clinical presentation, location, size and nature of the tumour. While the prognosis is guarded at best, remarkable results can be achieved in selected patients following surgery (extra-axial meningiomas in cats, pituitary tumours) or following a combination of surgery and radiation therapy (extra-axial meningiomas in dogs) or with chemotherapy (lymphoma) (Madison et al. 2015).

2.2.4.9 Inflammatory Non-infectious Brain Disease

Aetiopathogenesis The pathophysiology of non-infectious inflammatory brain disease is still poorly understood. An immune-mediated mechanism following an overreaction of the immune system due to antigen mimicry is often postulated, but a multifactorial process is likely. The fact that a strong breed predisposition is present in dogs makes a genetic basis a very popular theory (supported by the identification of a gene locus associated with an increased risk of developing necrotising meningoencephalitis in pug dogs). Non-infectious inflammatory brain diseases are less common in cats but are likely under-reported or underdiagnosed (Zeira et al. 2015).

The non-infectious meningoencephalitis is often described under the umbrella "meningoencephalitis of unknown aetiology/origin = MUE/MUO". This covers a number of pathological lesions, for example, necrotising meningoencephalitis, necrotising leucoencephalitis, eosinophilic meningoencephalitis and granulomatous meningoencephalitis.

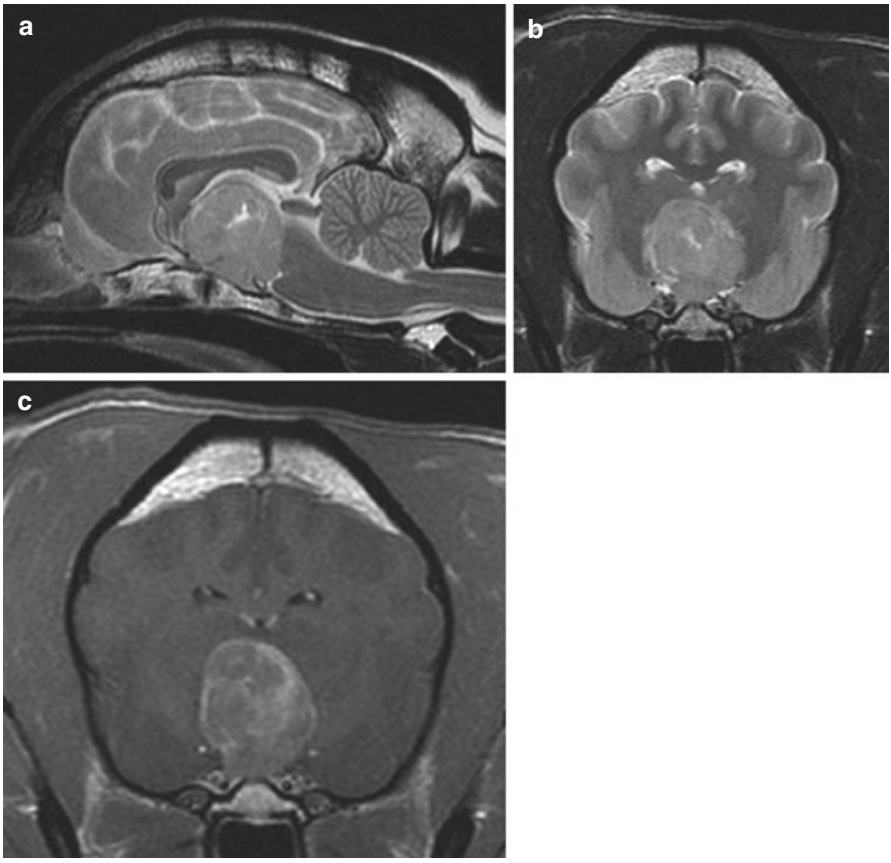


Fig. 2.2 Sagittal T2 (**a**), transverse T2 (**b**) and transverse T1 post-contrast (**c**) images of a 9.5-year-old border terrier presenting with progressive behavioural changes alone showing a large mass in the pituitary region

Clinical Signs The clinical signs again reflect the anatomical location of the lesion(s) and are often a combination of neurological signs (neurological deficits, seizures, signs of raised intracranial pressure) and behavioural changes. While typically the presentation involves a middle-aged patient with clinical signs that can progress rapidly, some animals will present later in age with insidious and non-specific clinical signs as being less responsive, pacing, lethargic or unwilling to move. Many of the inflammatory diseases seem to have a predisposition for the brainstem and cerebellum, so cerebello-vestibular signs are relatively common with this diagnosis (Han et al. 2015).

Clinical signs that overlap with CDS:

- Lethargy
- Pacing
- Loss of trained behaviours

Clinical signs that would not overlap with CDS:

- Neurological deficits
- Seizures
- Signs of raised intracranial pressure

Diagnosis/Exclusion The diagnosis is based on exclusion of extracranial causes of forebrain or brainstem dysfunction supported by advanced imaging and CSF analysis and after ruling out the common infectious pathogens present in the geographical area. Ante-mortem diagnosis is often speculative after exclusion of infectious causes. However, the advances of stereotactic brain biopsy techniques have recently permitted the gain of more definitive ante-mortem diagnosis in carefully selected patients.

Treatment The treatment of MUE/MUO is centred on immunosuppression with prednisolone as the first-line drug. The use of adjunctive immunosuppressives and which drug to use is a more debated topic. Following treatment, the clinician is often presented with three case scenarios: one population of patients will be well controlled and weaned off medications over the course of 3–6 months, one population of animals will require lifelong or adjunctive immunosuppression, and one population may fail and deteriorate despite treatment.

2.2.4.10 Infectious Brain Disease

Aetiopathogenesis Infectious agents involved can be bacterial, viral, protozoal or even fungal or algal depending on the geographical region involved. The route of entry of the pathogen can be by local extension from a nearby infection (ocular, nasal, penetrating wound) or could be secondary to systemic circulation of the agents and penetration through the blood CSF or blood-brain barrier (Ebani et al. 2014).

When a pathogen is present, the tissue injury is not only the consequence of the pathogen's direct insult but almost more importantly reflects a detrimental response of the immune system to this pathogen. The inflammatory reaction may lead to the creation of abscess or empyema (bacterial diseases), granulomas (*Toxoplasma* infection, fungal diseases, mycobacterial infection), brain atrophy or necrosis (*Neospora* infection), vasculitis (FIP virus) or demyelination (distemper) (Ebani et al. 2014).

While young unvaccinated animals are more at risk, cats or dogs of any age can be affected, and a latent infection can reactivate later in life (e.g. old dog distemper).

Pathogens involved in infectious meningoencephalitis in dogs and cats.

Cats:

- Bacterial: rods, cocci, mycobacteria
- Viral: FeLV, FIV, FIP, bornavirus
- Protozoal: *Toxoplasma gondii*
- Fungal: *Blastomyces*, *Cryptococcus*, *Coccidioidomycosis*
- Parasitic: *Taenia serialis*, *Cuterebra*, *Dirofilaria immitis*

Dogs:

- Bacterial: rods, cocci, mycobacteria, rickettsia
- Viral: distemper
- Protozoal: *Toxoplasma gondii*, *Neospora caninum*, *Leishmania*, *Toxoplasma gondii*
- Fungal: *Aspergillus*, *Cryptococcus*, *Blastomyces*, *Coccidioidomycosis*
- Parasitic: *Angiostrongylus vasorum*, *Baylisascaris procyonis, Dirofilaria immitis*

Clinical Signs The clinical signs are variable and reflect the anatomical location of the lesion(s) present. The neurolocalisation can indeed reflect focal or multifocal pathology. Neurological deficits are commonly noticed but could be mild and can be overshadowed by more conspicuous neurological signs such as seizures or behavioural changes. Behavioural changes can manifest as an altered mental status, reduced activity or lethargy, especially if the ascending activating reticular formation is involved either in the brainstem or in both cerebral hemispheres. Circling, pacing, head pressing and excessive panting or restlessness are also not uncommon.

Clinical signs that overlap with CDS:

- Altered mental status
- Reduced activity or lethargy

Clinical signs that would not overlap with CDS:

- Neurological deficits
- Seizures
- Signs of raised intracranial pressure

Diagnosis/Exclusion The diagnosis is reached after exclusion of metabolic causes of forebrain and/or forebrain dysfunction and ideally following advanced imaging. MRI is the modality of choice and should ideally be performed before spinal fluid collection or analysis is performed. Blood serology, CSF culture and PCRs for specific agents can be performed to try to identify the causative pathogen. This should take into consideration the geographical area of residence of the pet but also the relevant travel history.

Treatment The treatment is based on the pathological agent identified and the presence or not of a discrete lesion. Surgery can be indicated in the presence of a focal abscess or granuloma for both diagnostic and therapeutic purposes. A specific medical therapeutic plan can be instaured once the pathogens have been identified and, ideally, when culture and sensitivity results are available.

2.2.4.11 Traumatic Differential: Chronic Repetitive Traumatic Brain Injury

Aetiopathogenesis Chronic repetitive traumatic brain injury occurs in professional sports such as American football or boxing (called chronic traumatic encephalopathy) but remains exceedingly rare in small animal patients when it

almost invariably results from animal abuse. The brain damage usually occurs following the development of subarachnoid haemorrhage, lacerations of the brain tissue and secondary vasogenic oedema.

Clinical Signs While only one case report described the clinical signs of a dog with repetitive brain trauma due to physical abuse, people may show mainly behavioural signs, potentially years after the injuries stopped, with signs of progressive dementia and depression. The dog in the published report showed signs of decreased mentation, disorientation, absence of response to sound and acoustic stimuli, generalised proprioceptive ataxia, neurological deficits pointing towards a forebrain neurolocalisation and tremors (Plessas et al. 2013).

Clinical signs that overlap with CDS:

- Behavioural changes
- Disorientation
- Decreased mentation

Clinical signs that would not overlap with CDS:

- Tremors
- Generalised proprioceptive ataxia
- Neurological deficits

Diagnosis/Exclusion The diagnosis is supported by the history, physical examination with evidence of repetitive trauma, and evidence of brain atrophy on CT or MRI. Spinal fluid results may reveal a neutrophilic pleocytosis.

Treatment There is no specific treatment.

2.2.4.12 Toxic Differential: Lead Poisoning

Aetiopathogenesis The heavy metal causes direct damage to blood vessels leading to haemorrhage ischaemia (with subsequent necrosis) and oedema of the central nervous system. It is also postulated that lead or other secondary metabolic substances may cause neuronal damage (Pauli and Buskirk 2007).

Clinical Signs Dogs usually present with GI signs (vomiting and diarrhoea), and these are usually seen in combination with CNS disease, but rarely the CNS signs will be the only ones present. In this case seizures are common, but behavioural/mentation changes with hysteria can occur in isolation alongside other signs of tremors, ataxia, hypersensitivity, champing of the jaws and tics.

Clinical signs that overlap with CDS:

- Mentation/behaviour changes with hysteria

Clinical signs that would not overlap with CDS:

- Seizures
- GI signs
- Tremors
- Ataxia
- Champing of the jaws and tics (which in the author's opinion are interpreted as a myoclonus)

Diagnosis/Exclusion Appropriate clinical signs alongside increased levels of lead in the blood.

Treatment Chelation therapy using calcium EDTA or penicillamine and antiepileptics where seizures are present is preferred.

2.2.4.13 Vascular

Cerebrovascular disease defines any brain pathology that results from pathology of its blood supply. The major pathological processes include blood vessel disruption (leading to haemorrhage), blood vessel obstruction (leading to ischaemia or infarction), blood vessel malformation and vasculitis.

Hypertensive Encephalopathy

Aetiopathogenesis Hypertensive encephalopathy is due to blood vessel damage following sustained or acute periods of hypertension. The blood vessels under stress may narrow or become harder (atherosclerosis) or thinner, leading to blood vessel obstruction, rupture or leakage. This can ultimately lead to the development of haemorrhagic or ischaemic strokes which are peracute manifestations or neurological signs following damage to the brain blood vessels. Other proposed mechanisms of injury include the failure of the normal autoregulation of the vasculature leading to hyperperfusion and secondary vasogenic oedema. Target organ damage is possible when the systolic blood pressure exceeds 150–160 mmHg, but some authors suggest that a systolic blood pressure over 180 mmHg may be more relevant to the brain (Panciera 2000).

Clinical Signs The clinical signs can initially be vague. Animals can present for non-specific lethargy, altered mentation, decreased vision or decreased ability to find their food. Neurological deficits (localising the problem to the forebrain and or brainstem) may ensue, with some animals developing signs suggestive of raised intracranial pressure (head pressing, decerebrate posture, opisthotonus). Retinal haemorrhages, tortuous blood vessels, multifocal retinal oedema or retinal detachment may be detected on ophthalmological examination of the fundus. Some patients may present with peracute episodes against a background of more insidious illness. Ischaemic or haemorrhagic strokes can also cause an acute onset of neurological signs that may be witnessed or missed by the owners. Neurological

signs such as circling, pacing or decreased vision could be residual signs perceived by the owners as a decline in cognitive function. Most clinical signs attributable to a stroke would be expected to improve with time, although recurrent or multiple cerebrovascular accidents (CVAs) are possible and can complicate the clinical picture (Cain and Khalil 2002).

Clinical signs that overlap with CDS:

- Lethargy
- Altered mentation
- Inability to find food

Clinical signs that would not overlap with CDS:

- Neurological deficits
- Signs of raised intracranial pressure

Diagnosis/Exclusion The diagnosis of hypertensive encephalopathy is based on the identification of a systolic blood pressure over 160–180 mmHg in the presence of neurological deficits suggestive of brain dysfunction together with other clinical signs (hypertensive retinopathy) or imaging findings (white matter oedema, ischaemic or haemorrhagic stroke) suggestive of hypertension in the absence of other pathological processes. After a clinical suspicion of hypertensive encephalopathy due to systemic hypertension is established, the clinician should focus on the diagnosis of the underlying primary pathological process. Indeed, in dogs and cats, systemic hypertension is seldom idiopathic (although possibly seen in up to 20% of cats) and often reflects endocrinopathy (hyperthyroidism, hyperadrenocorticism, diabetes mellitus, hyperaldosteronism, acromegaly, phaeochromocytoma), cardiomyopathy (hypertrophic cardiomyopathy in cats), renal insufficiency or obesity (Stepien et al. 2003).

Treatment The treatment of hypertensive encephalopathy should be focused on the treatment of the underlying primary cause. While angiotensin-converting enzyme (ACE) inhibitor forms the first-line treatment of hypertension in dogs, calcium channel blockers as amlodipine are often necessary to bring the blood pressure within physiological ranges in cats.

Cerebrovascular Accidents

Aetiopathogenesis As mentioned above, CVAs are the peracute clinical manifestation of neurological signs due to a non-traumatic blood vessel rupture (haemorrhagic stroke) or blood vessel occlusion (ischaemic stroke). Causes of blood vessel disruption include coagulopathies, hypertension, neoplasia, and inflammatory or infectious processes. Blood vessels can get occluded by a thrombus formed in situ or at a distant site (thromboembolism), a neoplastic or septic emboli or fat embolisation. Some of the common diseases implicated in the pathogenesis of ischaemic or haemorrhagic strokes in dogs and cats are listed below. However, in a significant number of cases, no underlying cause can be identified (Jensen et al. 1997).

Causes of ischaemic stroke in dogs and cats:

- Chronic kidney disease
- Hypertension
- Diabetes mellitus
- Neoplasia
- Protein-losing nephropathy or enteropathy
- Cushing's disease
- Cardiomyopathy
- Hypothyroidism (dogs)

Common causes of haemorrhagic stroke in dogs and cats:

- Angiostrongylus vasorum infection (dogs)
- Neoplasia
- Hypertension
- Coagulopathy
- Bacterial infections
- Brain atrophy

Clinical Signs The clinical signs will reflect the localisation of the lesion(s) present. The neurolocalisation can therefore be focal or multifocal. The thalamus and cerebellum are two regions of predilection for ischaemic stroke. Clinical signs present can include an altered mentation, pacing, compulsive circling, vocalising, hemineglecting or bumping into things. The onset tends to be peracute with a progressive improvement of the signs. However, in the case of multiple CVAs, the signs can be persistent waxing and waning. Moreover, the onset can be missed and the neurological deficits can persist, leaving the pet debilitated. The owner may bring their pet to the clinician with the complaint of an altered mentation or recent-onset dementia.

Diagnosis/Exclusion The diagnosis is based on the identification of ischaemic or haemorrhagic lesion(s) on MRI. CT can be valuable in the identification of intracranial haemorrhage, but MRI will be superior as it allows the identification of neoplastic processes that can cause secondary intracranial haemorrhage (e.g. some gliomas or meningiomas). The identification of a stroke warrants further investigation to rule out an underlying cause. This may involve blood pressure monitoring, additional blood testing, endocrine testing, urinalysis (including a Urine Protein Creatinine Ratio (UPC) and imaging of the thorax and abdomen. In a substantial number of cases, no underlying cause can be identified. This subset of patients seems to be at a decreased risk for suffering further episodes in the future (Kraft and Egner 2003).

Treatment The treatment should be aimed at the underlying pathological process present and is otherwise supportive. Most of the current research is trying to identify treatment options to reduce the secondary injury occurring in the brain, but to date no effective treatment is available (Jensen 1997; Kraft and Egner 2003).

2.2.5 Diagnostic Testing

2.2.5.1 Laboratory Testing

The following step is the investigation of possible underlying metabolic conditions (Table 2.7). Most metabolic conditions will cause symmetrical neurological deficits if any, but this is not a hard and fast rule. Asymmetrical signs, including circling or vestibular signs (including positional nystagmus), can be seen with metabolic diseases as hepatic encephalopathy (although vestibular signs alone are not usually expected with hepatic encephalopathy). The minimum initial database should include a blood haematology with differential and cytology to investigate the presence of anaemia (congenital portosystemic shunt, hypothyroidism, anaemia of chronic disease, lead poisoning, etc.), an abnormal white blood cell count (inflammatory or neoplastic process) or abnormal platelet count (e.g. paraneoplastic thrombocytopenia, thrombocytosis associated with hyperadrenocorticism) (Ettinger and Feldman 2009).

A serum biochemistry is recommended to evaluate renal (urea, creatinine) and liver (ALT, ALP) parameters but should also include blood electrolytes, serum albumin, globulin and serum cholesterol. Repeated fasting blood glucose measurements are performed (at least twice in a 24–48 h period) after at least 12 h of fasting in animals presenting with intermittent or persistent alteration of consciousness (especially if the neurological examination is normal) to rule out hypoglycaemia. Serum ammonia and pre- and post-prandial bile acid are performed in animals with raised liver enzymes or in the presence of forebrain or brainstem signs or altered mental

Table 2.7 Metabolic conditions to rule out

Condition	Common causes	Testing suggested
Hypoglycaemia	Insulinoma (dogs), neoplasia, Addison	Repeated fasting blood glucose, fructosamine
Hyperglycaemia	Diabetes mellitus, hyperadrenocorticism	Blood glucose
Hepatic encephalopathy	Congenital portosystemic shunt, chronic hepatopathies and acquired portosystemic shunt	Fasting blood ammonia, dynamic bile acid stimulation test
Hyperthyroidism	Thyroid adenoma (cats)	Total T4
Uremic encephalopathy	Renal insufficiency	Serum urea, creatinine, SDMA, USG
Hypothyroidism	Lymphoplasmacytic adenitis, idiopathic atrophy (dogs)	Total T4, TSH
Hypernatraemia	Hyperaldosteronism (cats), adipsia, diabetes insipidus	Serum sodium
Hyponatraemia	Hyperadrenocorticism, GI or renal losses, cardiac or hepatic insufficiency	Serum sodium
Hypercalcaemia	Paraneoplastic, osteolytic lesions, hyperparathyroidism, renal insufficiency	Ionised calcium
Hypocalcaemia	Hypoparathyroidism, nutritional secondary hyperparathyroidism, renal insufficiency	Ionised calcium

status (hyper or hypo). Serum thyroid level (total T4) is assessed in patients with altered mental statuses and accompanying relevant clinical signs to investigate the presence of hypothyroidism (dogs) or hyperthyroidism (cats). It is worth noting that clinical signs of forebrain disease are only reported in dogs with myxoedema coma and multiple vascular events.

Any animal with polyuria, polydipsia, periuria, dysuria or house soiling with inappropriate urination should have a complete urinalysis with urine cytology, UPC and urine culture performed to document the presence of crystalluria, urinary tract infection or proteinuria. Animals with gastrointestinal signs or passing faeces in the house should have a rectal examination performed as well as a faecal analysis.

2.2.5.2 Blood Pressure

Non-invasive blood pressure is recommended in older animals presenting with vague, non-specific or waxing and waning signs of altered consciousness or behaviour. This is often repeated in a quiet environment to increase the accuracy of the readings. Consistently elevated blood pressure should warrant further investigation to rule out the underlying cause, provided the readings are not due to the so-called white coat effect. If the latter is suspected, the measurements should be performed if possible at home while the animal is most relaxed (Nelson and Couto 2014).

Causes of hypertension in older animals:

- Chronic renal insufficiency
- Hyperthyroidism (cats)
- Hyperadrenocorticism (dogs)
- Diabetes mellitus
- Cardiomyopathy
- Phaeochromocytoma
- Hyperaldosteronism (cats)
- Idiopathic
- Raised intracranial pressure

2.2.5.3 Advanced Imaging

Whether or not the neurological examination is normal, in the presence of behavioural signs, an MRI scan of the brain should be considered before establishing a presumptive diagnosis of CDS. Advanced imaging is performed after having ruled out the potential metabolic causes mentioned in the previous two paragraphs. MRI is the modality of choice to assess the brain and will be superior to CT due to its better soft tissue resolution. The results of the MRI scan need to be interpreted in conjunction with the index of suspicion and additional tests. If the MRI scan is normal, then CSF is collected. Patients affected by CDS can have a normal brain MRI or evidence of brain atrophy and ventricular enlargement. However, MRI changes of brain atrophy are not pathognomonic and can be seen with some chronic metabolic (chronic hypoglycaemia, congenital PSS), inflammatory (eosinophilic meningoencephalitis), neurodegenerative (e.g. ceroid lipofuscinosis) or even infectious diseases (*Neospora*

caninum infection). Consequently, MRI findings of brain atrophy are not diagnostic of CDS but are compatible with it (Ettinger and Feldman 2009).

Differential diagnosis for brain atrophy on MRI includes CDS; degenerative storage diseases, in particular ceroid lipofuscinosis; congenital portosystemic shunt; chronic or repeated metabolic/toxic disturbances, for example, chronic hypoglycaemia; eosinophilic meningoencephalitis; *Neospora* infection; and chronic repetitive traumatic brain injury (Fig. 2.3).

MRI changes compatible with CDS:

- Normal MRI
- Ventricular system dilation
- Cortical atrophy—prominent sulci
- Narrowing of the interthalamic adhesion

2.2.5.4 CSF Analysis

The next step consists in performing a CSF analysis to rule out neoplastic or inflammatory conditions. If judged safe, the CSF analysis should be performed irrespective of the MRI findings as an inflammatory or neoplastic process can be present despite a normal MRI scan. An elevated cell count or protein level will be suggestive of an inflammatory process, although vascular, neoplastic or degenerative diseases can also cause such elevations. Cytological analysis may allow the identification of infectious agents, abnormal inclusions (e.g. viral) or neoplastic cells (e.g. lymphoma) (Nelson and Couto 2014).

2.2.5.5 Additional Testing

If the neurological examination, MRI scan and CSF analysis are normal, then an underlying pathological process such as inflammation, infection or neurodegenerative disease will be considered very unlikely. A presumptive diagnosis of CDS could be established at this stage. If in the neurological examination the MRI scan and/or the CSF results are abnormal, then an underlying pathological process other than CDS is suspected, and further testing is warranted.

In the presence of brain atrophy alone (despite a normal CSF analysis), the clinician should focus again on ruling out chronic hypoglycaemia by repeating dome fasting blood glucose sampling, being sure a dynamic bile acid stimulation test was correctly performed and was normal, and by ruling out neurodegenerative causes such as ceroid lipofuscinosis (Ettinger and Feldman 2009).

Blood serology against infectious agents or PCRs looking for DNA for such agents (e.g. feline coronavirus, canine distemper virus, *Neospora caninum*, etc.) are performed when the MRI scan or spinal fluid results suggest that an inflammatory process is present. PARR testing (PCR for lymphocyte antigen receptor rearrangement) or flow cytometry can also be valuable for the diagnosis of lymphoma in the presence of an atypical population of lymphocytes, while genetic testing for a known mutation associated with degenerative diseases (e.g. identification of one of the known breed-specific mutations identified for ceroid lipofuscinosis or L2-HGA) may offer a definitive diagnosis (Nelson and Couto 2014).

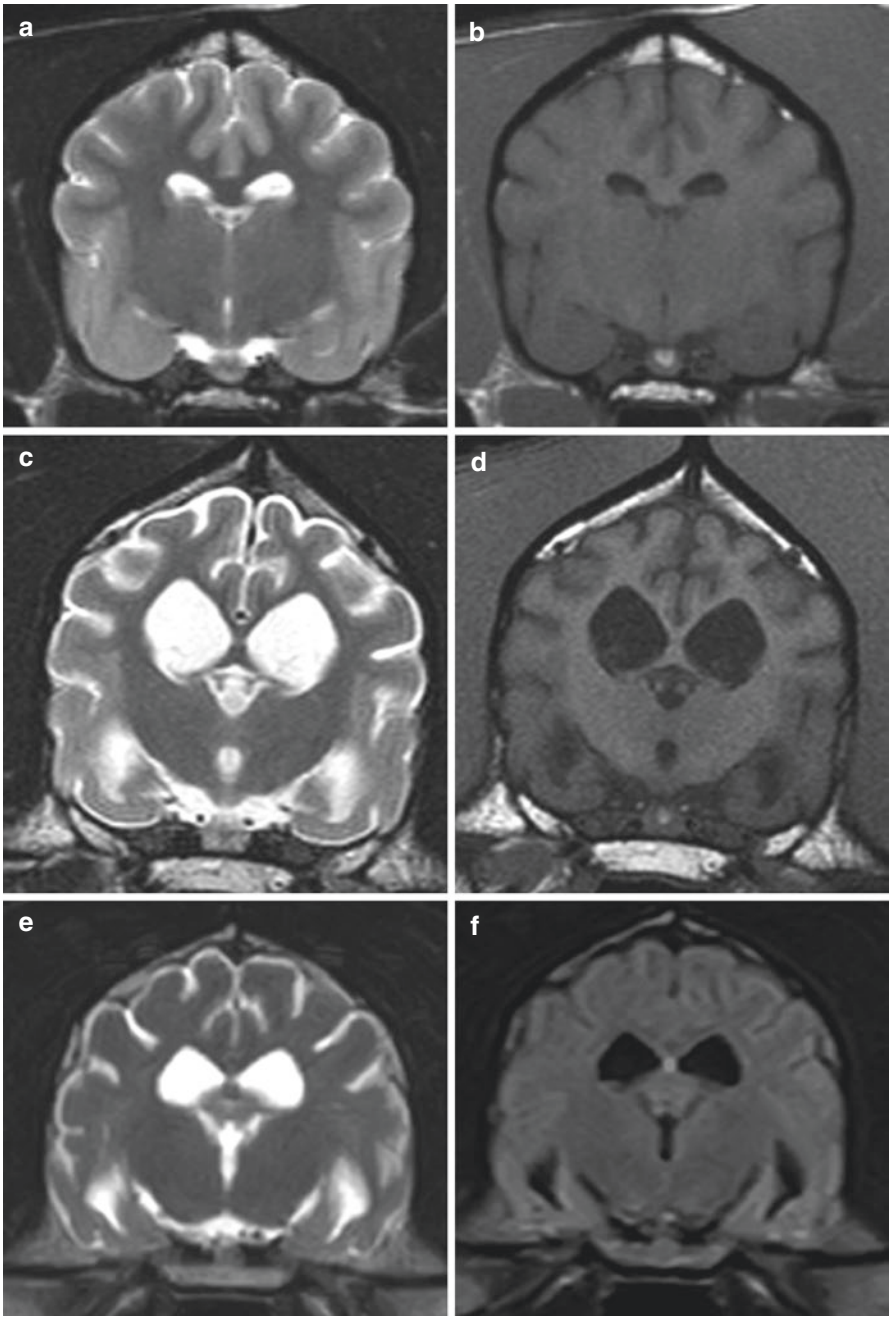
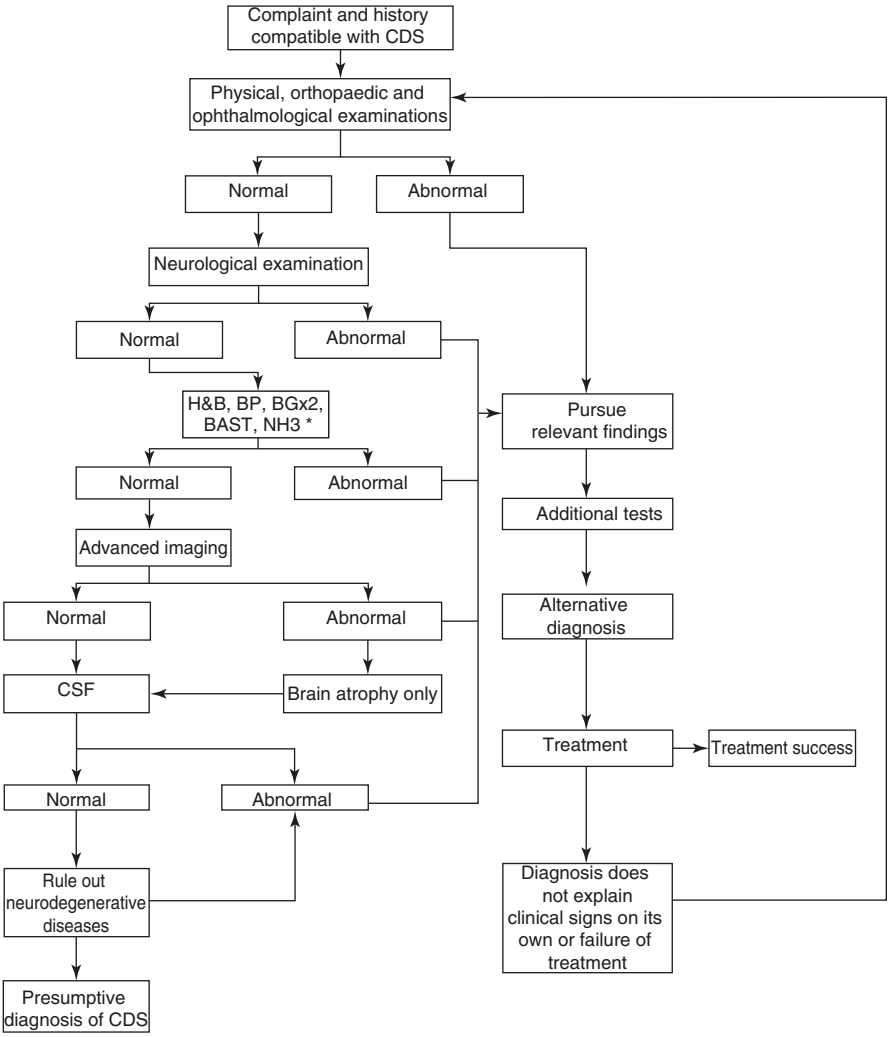


Fig. 2.3 Transverse T2 (**a**)- and T1 (**b**)-weighted images of a normal dog. Transverse T2 (**c**)- and T1 (**d**)-weighted images of a dog suffering from ceroid lipofuscinosis. Transverse T2 (**e**)- and FLAIR (**f**)-weighted images of a dog affected by CDS. All sections are at the level of the interthalamic adhesion

Urine screening for metabolic diseases will allow the identification of organic acidurias (e.g. L2-HGA) and some other storage diseases, as will biopsy of other organs (e.g. liver, skin, etc., depending on the storage disease).

2.2.6 Summary

The following chart summarises the clinical approach taken to rule out the differential diagnosis for CDS in dogs and cats. As mentioned above, a strong suspicion for CDS exists when all the diagnostic testing rules out other differentials (Nelson and Couto 2014).



* *H&B* Hematology and Biochemisty, *BP* Blood pressure, *BGx2* blood glucose X 2, *BAST* Bile acid stimulation test, *NH3* Ammonia

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