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Behavioural Problems in Dogs and Cats Mini Series

Session 1: Canine Cognitive Dysfunction

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Canine Cognitive Dysfunction (CCD)

The signs of cognitive impairment will often precede other organic signs of ageing and are a good indicator of general health. Thus behavioural change may be the first indicator of the need to intervene more widely in the health of the geriatric dog. Owners should be made aware of the mildest signs of this condition so that they bring affected dogs for treatment at the earliest possible stage. It is vital that the signs of cognitive impairment are not taken for natural signs of old age.

Cognitive impairment is a serious problem, indeed it is a life threatening disease for many elderly dogs. Owners are not aware that in early cases the signs of impairment are treatable or temporarily reversible so they may not bring these cases to the clinic until they have progressed too far. Loss of activity and normal interaction with the owner impairs the human-animal bond, so that when the dog begins to disturb the owner's sleep, bark incessantly or soil in the house it more likely that owners will bring the animal to the clinic for euthanasia.

So, for the sake of the pet's health and welfare, we need to encourage owners to discuss subtle changes in the behaviour of their ageing pet.

Dementia of the Alzheimer's type is the commonest form of dementia in man. The pathology and pathophysiology are relatively well described, and broadly similar to that seen in CCD in dogs. A simplified description of the changes seen in both dog and man are listed below:

- Mitochondrial metabolism becomes defective: producing more metabolic waste (free radicals) per unit of energy.
- Antioxidant mechanisms that normally defend tissues against oxidative damage are overwhelmed by the excess production of free radicals.
- Repair processes are ineffective because there is insufficient energy production to fuel both maintenance and repair.
- The oxidation of lipid and protein components leads to cellular damage and increased production of beta-amyloid.
- Beta-amyloid and lipid peroxides are themselves neuro-toxic and so a spiral of cellular damage begins.
- Histologically there is deposition of beta-amyloid in microscopic plaques, beginning in the frontal cortex and sweeping rearwards throughout the cerebrum, leading to a characteristic progression of symptoms.
- Beta-amyloid is also deposited in vital structures such as the hippocampus (responsible for short-term memory formation).
- Beta-amyloid provokes an inflammatory response, which further interferes with local nerve function, and the histological changes extend to damage to the microcirculation of the brain so that oxygenation of tissues is reduced.
- There is also accompanying reduction in neurotransmitter production and recycling.

This process of degeneration can be divided into two phases. During the initiation phase (mild cognitive impairment) there is a general impairment of neurological functioning due to neurotransmitter depletion, cellular metabolic disturbance and oxidation but the amount of beta-amyloid is quite low. In the second phase, significant quantities of beta-amyloid have been deposited. The effects of oxidation and toxicity of oxidised cellular components creates a spiral of damage that is more rapid and irreversible.

Beta-amyloid and phosphorulated tau protein are seen in the plaques of feline, canine and human patients, but the organisation and distribution are different. In man, protein forms microscopically visible 'tangles'. In the dog, the beta-amyloid plaques are smaller and more diffusely distributed within the brain. Tau protein is chemically detectable but does not form large visible tangles.

It may be that the more diffuse beta-amyloid in the ageing dog causes less severe damage and allows for more gradual remodelling so that function is taken up by other nervous tissue. Alternatively the different role of Tau protein in human beta-amyloid plaques may be relevant.

Canine Cognitive Dysfunction
This form of dementia closely mirrors DAT in terms of clinical effects and pathology. Early diagnosis is critical. To treat these cases effectively, we must intervene during the earliest stages of the disease when damage is less critical; for example, during the first phase of mild cognitive impairment. Behavioural changes in early dementia are quite subtle and easily confused with depression, and the effects of age related health decline.

In the early stages of dementia we might typically see quite nondescript signs that are often hard to attribute to any specific cause:

- Lethargy & depression
- Reduced activity
- Reduced social interaction
- Loss of play
- Mild disturbance of sleep pattern
- Mild increases in fear and anxiety

There may be only mild cognitive impairment.

As the disorder progresses more severe signs emerge that are linked to five underlying degenerative processes:

- Generalised and localised cortical impairment (frontal cortex, motor cortex etc):
  - Changes of 'personality'
  - Confusion and failure to interpret sensory information correctly (Staring into space or at inanimate objects)

- Loss of learned behaviours:
  - Housetraining
  - Control commands
  - Social inhibition (ignorance of the restraining influence of the presence of other individuals, including the owner).
    - Food snatching & stealing in front of the owner
    - Elimination in front of owner

- Changes in emotionality:
  - Worsening of existing fear and phobia problems
  - Increased anxiety
  - Depression
  - Irritability

- Impaired ability to form new short-term memory:
  - Repetition of behaviour (e.g. requests for attention, food, or to go outside)
  - Difficulty acquiring new learning (for example, being housetrained again)

- Specific neurological impairments:
  Loss of proprioception
  Sensory impairment (central blindness, central deafness)

Each case will have a different mix of these signs.

A large proportion of the animal's consistent pattern of responses that we might call 'personality' is learned during life. In particular, this includes patterns of social inhibition in which the animal learns to suppress highly motivated behaviour according to the social context.

For example, many young dogs will try to snatch food from the plate of a person or another animal, but they rapidly learn that this is unacceptable. Likewise, an attention-seeking dog learns not to pester its owner. Dogs with dementia lose these inhibitions and may return to acting purely on current motivation. Punishment, including ignoring behaviour, has little or no effect other than to distress the animal and create conflict with it.

Despite the fact that a decline in interaction is often cited as an indication of dementia, this is not always the case. In some individuals the level of attention seeking increases. There are many reasons for this, for example if the animal's level of anxiety forces it to demand more reassurance from its owner or because it still feels hungry and cannot remember when it last asked for food. So it is best to remember the underlying factors in dementia-related behavioural change and then to use them to interpret the animal's current behaviour.

As the condition progresses further, there is an accumulation of damage in specific areas leading to discrete neurological signs such as ataxia, central blindness or deafness. These sensory losses are often confused with actual primary sensory loss, especially in dogs with already limited vision. Usually an examination will reveal that the animal's actual hearing or vision loss is not enough to account for the overall sensory impairment. In these cases it is damage to the CNS, which is leading to the loss of functional vision or hearing because the animal is not able to process and interpret the sensory information it is getting. Even at this advanced stage there is some value in treatment.

It is relatively easy to pick up moderately severe cases, but early and severe ones are more difficult. The former because owners may assume that what they are seeing is the effect of normal ageing, the latter because the more obvious signs of cognitive dementia are obscured by severe neurological signs.

Case detection

There are currently no biological tests for CCD. Changes can be detected on MRI, including increases in fluid spaces and a reduction in the thickness fo grey and white matter. Interthalamic adhesion thickness has been found to be a good MRI indicator of CCD. Circulating levels of beta-amyloid are detectable in dogs, but are not associated with severity of signs; levels are high in dogs with moderate CCD but not severe. Elevated plasma beta-amyloid may therefore be an early indicator of CCD onset, but this has not been validated.

Questionnaires are often used in experimental studies of CCD, to evaluate the presence or severity of disease, and to monitor response to treatment. However, caution shudl be applied to using these questionnaires as none have been validated for retest reliability; any changes in scores may be due to repeated use of the questionnaire rather than due to changes in the condition. Also, the questionnaires used in experimental studies have not been validated for use by clinicians or the general public to assess the clinical status of pet dogs.

The DISHA acronym is a good aide memoire for the main signs of CCD, as a basis for questioning owners on their dog's behaviour, but many aspects of it are non-specific. For example, changes in activity can result from many age related health problems.

The only questionnaire which has been specifically developed and validated to aid detection of CCD, and to differentiate between it and other ailments that can cause behavioural changes in older dogs, is the Canine Cognitive Dysfunction Rating Scale (CCDR scale). It is

suitable for clinicians and owners to use, and provides a score and classification of presence/absence of CCD and its severity. The CCDR scale has not been validated for retest rliability, and due to its structure it may not be effectve for monitoring change over time. It is reliable for discriminating between moderate and severe cases, but less reliable for discriminating between healthy and mild/moderate cases. This makes it less suitable for the detection of the first onset of CCD.

For early detection, a brief questionnaire is currently being developed for CEVA Animal Health. It is based on findings from a study using the CCDR, and on owner reports of the first signs of CCD that were noticable.

Thie questionnaire is presented at the end of the notes, and links will be provided during the lecture to online versions of this and the CCDR.

High risk periods for the geriatric pet

Certain events are known to place additional stress on patients, and represent a unique risk to the cognitively impaired pet.

Veterinary Procedures	Anaesthesia /sedation	Hypoxia, hypovolaemia, low blood pressure, after effects of drugs
	Surgery	Blood loss
	Medication	e.g. Steroids, tranquillisers,
	Examination	Emotional and physical stress, fear, anxiety
Move to a new environment	Hospitalisation	Loss of familiar cues that enable animal to comprehend environment Emotional stress
	Kennelling	
	House move	
Alterations to current environment	Building work or redecoration	Loss of familiar cues and layout, causing a reduction in coping.
	New pets of children	Loss of owner attention, unfamiliar noises/activities
	Change of owner routine	Loss of reassuring presence of owner

Preparations can be made for these events so that their impact is minimised. For example using dietary modification and psychoactive/antioxidant/neuroprotective drugs may be given in advance of planned events such as general anaesthesia. Pre-operative blood screening, together with continuous intra-operative and recovery blood pressure and oximetry measurement are essential for proper anaesthetic management.

Wherever possible peri-operative pain relief should be used to reduce the uncomfortable after effects of prolonged recumbency, and reversible or short acting sedatives and induction agents should be used so that anaesthetic duration is minimised. The animal should be returned to a familiar environment as soon as safely possible after recovery.

Medical factors

Table 1
Medical causes of behavioral signs

Medical Condition/Medical Presentation	Examples of Behavioral Signs
Neurologic: central (intracranial/ extracranial), particularly if affecting forebrain, limbic/temporal, and hypothalamic; REM sleep disorders	Altered awareness, response to stimuli, loss of learned behaviors, house soiling, disorientation, confusion, altered activity levels, temporal disorientation, vocalization, soiling, change in temperament (fear, anxiety), altered appetite, altered sleep cycles, interrupted sleep
Partial seizures: temporal lobe epilepsy	Repetitive behaviors, self-traumatic disorders, chomping, staring, alterations in temperament (eg, intermittent states of fear or aggression), tremors, shaking, interrupted sleep
Sensory dysfunction	Altered response to stimuli, confusion, disorientation, irritability/aggression, vocalization, house soiling, altered sleep cycles
Endocrine: hyperthyroid or hypothyroid, hyperadrenocorticism or hypoadrenocorticism, insulinoma, diabetes, testicular or adrenal tumors	Altered emotional state, irritability/aggression, lethargy, decreased response to stimuli, anxiety, house soiling/marking, night waking, decreased or increased activity, altered appetite, mounting
Metabolic disorders: hepatic/renal	Signs associated with organ affected: may be anxiety, irritability, aggression, altered sleep, house soiling, mental dullness, decreased activity, restlessness, increase sleep, confusion
Pain	Altered response to stimuli, decreased activity, restless/unsettled, vocalization, house soiling, aggression/irritability, self-trauma, waking at night
Peripheral neuropathy	Self-mutilation, irritability/aggression, circling, hyperesthesia
Gastrointestinal	Licking, polyphagia, pica, coprophagia, fecal house soiling, wind sucking, tongue rolling, unsettled sleep, restlessness
Urogenital	House soiling (urine), polydypsia, waking at night
Dermatologic	Psychogenic alopecia (cats), acral lick dermatitis (dogs), nail biting, hyperesthesia, other self-trauma (chewing/biting/sucking/scratching)

Clinical Signs and Management of Anxiety, Sleeplessness, and Cognitive Dysfunction in the Senior Pet

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All medical problems should be resolved or managed as effectively as possible before a behavioural assessment is carried out.

- Full clinical examination
- Comprehensive haematology and biochemistry
- Complete review of the effectiveness of current medical treatments
- Assessment of effectiveness of current pain management

If anything it should be assumed that the elderly dog has medical issues that will affect its behaviour unless it is proven to the contrary.

Management and treatment

Treatment should have several aims:

- Delay progression of disease (if possible).
- Return mental function to a level at which normal behaviour may be re-established.
- Retrain lost behaviour.
- Re-establish relationships with people and other animals in the house so that social support helps to maintain improvement

The treatable underlying mechanisms of cognitive dementia are:

- Depletion of neurotransmitter function.
- Localised inflammation around beta-amyloid plaques.
- Mitochondrial inefficiency (producing more free radicals per unit of useable energy).
- Depletion of cytochemicals needed for cell repair.
- Ongoing oxidative damage.

There are several approaches to correcting these faults which may be used in combination with each other.

Dietary modification

There is considerable evidence that dietary supplementation can be used to improve mitochondrial metabolic function and assist oxygen free radical scavenging mechanisms.

Trials also suggest that these supplements are equally effective in-vivo, improving neuronal metabolic function and boosting CNS anti-oxidant reserve. Supplements with demonstrable efficacy include vitamin E, n-acetyl-l-carnitine and alpha-lipoic acid, which have been trialled in a number of species, but most specialist diets also include a range of other antioxidant chemicals and additives.

The diet should also include increased levels of cellular repair materials such as essential fatty acids. Such diets must also be compatible with other medical problems the animal is also experiencing, but most senior and disease specific diets can be easily and safely modified to give benefits to the cognitively impaired animal.

Dietary modification of this kind should be the mainstay therapy to delay progression of dementia and should be instituted in dogs with the earliest signs of dementia. Owners can expect to see improvements within 4-6 weeks of dietary change.

Cerebral hypometabolism has been identified as a target for therapy in DAT and CCD. A recently identified approach is to supplement with beta-hydroxy-butyrate, which can act as a supplementary energy source for CNS metabolism. Medium chain triglycerides, which are a dietary precursor of beta-hydroxy-butyrate, are found in some specialised diets and also in coconut oil. MCTs are cheaper, more palatable and easier to add to the diet than beta-hydroxy-butyrate and have been shown to have beneficial effects on cognition in dogs and people.

Drug therapy

In behavioural medicine psychoactive drugs are primarily used to correct neurotransmitter abnormalities, but some of these drugs have specific properties that may be useful for the cognitively impaired dog or cat. Drugs like propentofylline (Vivitonin) have specific effects on cerebral circulation in the dog.

Effect	Drug types
Improve cerebral circulation	Propentofylline
Antioxidant effects	Selegiline Propentofylline
Improve neurotransmitter function Dopamine Serotonin	 Selegiline Clomipramine, fluoxetine
Neuroprotective effects	Selegiline Propentofylline (cholinergic neurons)

Drugs should be carefully selected to compliment dietary modification, in line with anticipated neurotransmitter problems or cerebral oxygenation/perfusion problems.
Where cerebral oxygenation is an issue all efforts should be made to correct any cardiovascular or pulmonary problems that may be the root cause.

The dopaminergic drug Selegiline is useful for cases where there is behavioural inhibition and impaired learning, because this drug increases exploratory behaviour and the intensity of the experience of reinforcement. In particular this assists with the retraining of learned behaviours. Selegiline is also useful for cognitively impaired dogs that have fear related problems, especially if fearfulness has increased as a result of cognitive changes.

Serotonergic drugs such as clomipramine and fluoxetine are useful for animals that suffer from chronic anxiety, attachment problems and sleep disturbance. They should not be used in combination with dopaminergic drugs such as selegiline. When switching between serotonin reuptake inhibitor and monoamine oxidase inhibitor drugs there must be a minimum 14 day washout period when neither drug is given, to prevent the occurrence of potentially fatal serotonin syndrome.

It is important to remember that these while these drugs may be used in the cat, they are not licensed for this species and dose rates must be checked with current references.

Changes in behaviour may be slow with psychoactive drug treatment, with a partial response seen after 4-6 weeks, sometimes waiting until 8-10 weeks for a significant response.

Short-term drug treatments may be used to deal with problems of sleep disturbance, which can be very difficult for owners to cope with. Dogs with cognitive dementia will often find it hard to get to sleep or may wake up at a specific time in the night. Chronic anxiety is linked to waking in the first third of the sleep period. In other cases the dog wakes an hour or two before the owner is up, which creates insecurity and anxiety. The aim if using short term sedatives is to help the dog to sleep through the periods when it might awake and cause a disturbance, but leave it fully awake during the day so that the owner can exercise it more and try to return the animal's pattern of activity to normal. The choice of drug should be

appropriate to the type of sleep disturbance, with short acting drugs being suitable for early night time wakefulness. Strongly sedative drugs, such as Acepromazine, should be avoided where possible because they produce hangover effects that affect cognition during the daytime.

Benzodiazepine drugs such as diazepam may produce a short-term sedative effect, but they too should be avoided because the memory impairment they produce will interfere with retraining and may exacerbate some of the behavioural problems. Benzodiazepines are toxic when given orally to cats. Caution should be exercised over the prescribing of benzodiazepines due to their abuse potential in the human population.

Sedative antihistamines such as chlorphenamine maleate (Piriton) can be useful useful because they produce short-term sedation without any after effects. This drug works well in combination with behavioural therapy to alter sleep patterns. In most cases sedation should be needed for only 1-2 weeks if other behavioural therapy is used to alter the sleep pattern.

Melatonin has recently been introduced to the veterinary market (under the trade name Melacutin). In DAT, melatonin secretion is reduced, and this is thought to be connected with sleep disturbance and the phenomenon of "sundowning" in which patients show a significant worsening of dementia signs around nightfall. Melatonin has also been shown to interact with beta amyloid, reduing its ability to bind to cell membranes and thereby reducing its impact on membrane function. This may help to explain the positive effects that melatonin supplementation can have on cognitive function. Melatonin can be used in dogs to reduce sleep disturbance.

Managing sleep disturbance in CCD
Make the resting place more comfortable and familiar: • Install a dim night-light next to the dog's resting place. • Add a piece of the owner's unwashed clothing. • Make it well padded with high sides so that the dog can get comfortable and feels safe. • Keep windows closed to avoid ingress of sound. • Use heavy curtains to stop light and external stimuli from waking the dog up. Increase daytime activity levels: • Short walks and lots of play throughout the day. • Activity feeding. • Wake the dog regularly during the day, don't allow it to sleep all the time. Melatonin • This may be used to faciliate sleep, and it may have beneficial effects on cognition. Use a short term sedative to improve sleep: • Chlorphenamine maleate (Piroton).

Behavioural therapy
This can be divided into three components:

- Making the environment more accessible to the geriatric pet.

- Re-training the behaviours that the animal has lost through cognitive impairment.

- Providing environmental enrichment to stimulate and maintain mental processes, and to improve quality of life.

Environmental modification to improve accessibility
The two main problems for these dogs are locating, and then getting to, the resources they need. Pain or frustration experienced when using stairs or climbing onto furniture, for example, can make dogs irritable and aggressive. Many older dogs with back problems will object to being removed from furniture simply due to back pain. Not being able to find or easily access a water bowl is a potential cause of mild dehydration, especially for any animal fed on a dried diet.

Certain simple changes will make resources more useable for the less mobile pet, and help to reduce competition with other animals in a multi-pet household:

- Additional water bowls, close to resting areas.

- Additional resting sites

- Steps/ramps to get on and off furniture (if desired)

Pets with defective vision may need to be given extra cues that enable them to navigate the home:

- Carpets and rugs to give a tactile identification of central floor spaces and corridors so that the animal can move about confidently without bumping into things.

- Quiet radios placed at the animal's level in different rooms close to resources so that the animal can use sound to locate them.

- Different scents to identify specific rooms so that the pet can locate them.

These changes also benefit anxious or confused pets, by giving them additional cues to navigate by. Confused animals also benefit from having properly designed bed areas, with a well padded wrap around basket, nearby night light and a piece of the owner's recently worn clothing to aid familiarity. Large dogs may benefit from a raised bed that is easier to get in and out of.

Retraining behaviour
Some behaviour, such as housetraining, may be completely lost, but in many cases there is a residue of original learning that simply needs to be reactivated.

It is essential to avoid using positive punishment to retrain new behaviour, because this will simply cause fear and stress. Cues and reinforcement need to be clear and intelligible to the animal. Conditioned secondary reinforcers are useful because they may be tailored to the individual animal's perceptual abilities. For example, although clicker training is often very valuable, touch or light flashes may be used as alternative conditioned reinforcers once associated with a suitably motivating reward (e.g. food).

It may also be necessary to retrain the animal to reduce its attention-seeking behaviour once it is not showing signs of anxiety or confusion and will not suffer distress at being ignored.

Environmental Enrichment
There is no point in giving medication and a specialist diet in order to improve cognitive ability if we do nothing to stimulate the animal. Indeed a mentally functional animal with nothing to do is a potential welfare problem.

There are some simple things that can be used to exercise the animal's mental abilities, none of which require a lot of effort from the owner:

- Activity feeding
  This can be as simple as scattering dried food for the pet to find, but can include homemade or manufactured feeders (Havaball, activity ball, buster cube, miniature activity balls for cats). It is best to start with very simple and undemanding exercises that replace only a small proportion of the animal's daily food intake, and then to increase the range and complexity of feeders and food finding opportunities as the pet seems able to cope.

- Exposure to stimulating environments
  Debilitated dogs may not be able to walk far, but they should still be taken daily to interesting places so that they can sniff around, meet other dogs and people (if this is

something they have previously enjoyed). Even a couple of short (5-10 minute) periods are beneficial to an otherwise housebound dog.

Low or zero load exercise, such as swimming, is a good way to improve strength and stamina in older dogs that have become sedentary and unfit. It is also a good opportunity for fitter animals to enjoy more vigorous play and social contact with less risk of pain.

- Play
  Owners should make a list of the games that the animal used to enjoy when it was younger. Some of these may be beyond its abilities, but others may be safely adapted to suit an older animal. It is also good to create new games based on reliable motivators like food. For example, teaching a dog to play a food finding game on command.

- Social contact
  Geriatric and cognitively impaired pets often become socially isolated because they become less demanding. Owners should be encouraged to interact with their pet more often, and less often on-demand from the pet. This may include invitations to play or have contact. For dogs this should also involve group play and contact with other dogs that the animal has previously got on well with.

Prognosis
Cognitive dementia is always progressive. It has been shown that dogs with one major sign of dementia will progress to have at least one further sign within 12-18 months. The course of the disease is very variable, and in some cases dogs will show severe signs within only a few months.

However, the animal's current level of disease is composed of both reversible and irreversible brain changes:

- Reversible/treatable
  - Inflammatory responses around beta-amyloid plaques
  - Neurotransmitter system deficits
  - Mitochondrial metabolic defects
  - Oxidative damage

- Irreversible
  - Cellular death
  - Deposition of beta-amyloid

So in fact many of the processes underlying dementia in dogs are treatable, although a combination of approaches is needed in many cases. In any given individual it is hard to assess whether signs are (*temporarily*) reversible or not, so it is difficult to prognosticate.

However, severely affected cases with neurological impairment have a poor prognosis.

Brief questionnaire for dog owners

Does your dog *ever* show any of the following behaviours at home?
(answer “yes” or “no” to each question):

- Pace or wander aimlessly, finding it hard to settle.
- Stare blankly, or into space, as if unaware of its surroundings.
- Fail to recognise or respond to familiar people such as family and friends.
- Appear lost or confused when moving around the home or garden.
- Appear forgetful about things. For example forgetting to go to the toilet when let outside, or repeatedly asking for attention, food, or a walk.
- Vocalise repeatedly for no reason (e.g. barking or whining).

This test only applies to older dogs (typically 8 or more years old).

If you answered “yes” to one or more of these statements then your dog may have cognitive dysfunction, particularly if these signs have become worse over recent months.