

Cognitive Dysfunction Syndrome in Companion Animals: Diagnosis and Treatment

Amy L. Pike, DVM, DACVB

Introduction:

Dogs and cats are living much longer these days, thanks to improvements in nutrition, disease prevention and outstanding veterinary care. With this advanced age, however, comes similar problems encountered in human medicine, including certain cancers, osteoarthritis, organ decline and neuropathologic degeneration. All mammals experience a version of degeneration of the nervous system, with Alzheimer's disease being the most commonly encountered in humans.

Our companion animals also experience cognitive changes as they age. These cognitive changes seen in dogs and cats are similar in both manifestation and pathophysiology to humans with Alzheimer's disease or dementia, and the condition is termed cognitive dysfunction syndrome (CDS). The symptoms associated with CDS, especially early in onset, can be very subtle. Often owners fail to even mention them to their veterinarian, deeming them a normal part of the aging process. In a survey of 250 veterinarians, only 7% of owners of older dogs spontaneously report such problems to their veterinarians. However, just like with Alzheimer's disease, the changes seen with CDS are not "normal" and veterinarians should be proactive and ask owners if their pet is experiencing any signs consistent with CDS. In a study looking at owner reported symptoms and prevalence, 28% of dogs aged 11-12 showed signs consistent with cognitive decline which then rose to 68% by age 15-16¹. In a study on cats 11 years of age and older, 35% had at least one clinical sign consistent with cognitive decline with no detectable health concerns.

Pathophysiology of CDS

There are numerous changes that occur in the brain due to aging. Whether these changes truly cause the behaviors associated with CDS is still unclear. Changes seen include cerebrocortical and basal ganglia atrophy; increase in ventricle size; narrowing of the gyri and widening of the sulci; leptomeningal thickening in the cerebral hemispheres; meningeal calcification; demyelination; an increase in the size and number of glial cells; and a reduction in neurons, especially in the cortical regions over the hippocampus. There can also be an increase in lipofuscin, apoptotic bodies, neuroaxonal degeneration, accumulation of ubiquitin granules, and an accumulation of beta-amyloid plaques and perivascular infiltrates.

There are vascular and perivascular changes that occur including microhemorrhage and infarcts in periventricular vessels. Non-lipid arteriosclerosis may be seen due to fibrosis of the vessel walls, endothelial proliferation, hyalinization, mineralization, and beta amyloid deposition. This angiopathy may impair blood flow and decrease glucose utilization. The brain in elderly animals may also suffer from hypoxia secondary to decreased cardiac output, anemia, blood hyperviscosity and platelet hypercoagulability and diseases that lead to hypertension, such as diabetes, hyperthyroidism, renal disease and respiratory insufficiency. There may be an overall vasoconstrictive effect due to cholinergic depletion and increase in noradrenergic tone, thus compromising blood flow.

Aging mitochondria become less efficient and produce relatively more free radicals such as hydrogen peroxide, superoxide and nitric oxide. Neutrophils and macrophages respond to

infections and inflammation with increasing amounts of free radicals as well. Exogenous sources of free radical damage include ionizing radiation, carcinogens and air pollutants. If free radicals escape the normal physiologic defenses, they may react with DNA, lipids and proteins and lead to cellular damage, dysfunction, mutation, neoplasia and cell death. The brain is the most susceptible to the effects of free radicals because of its high lipid content, high demand for oxygen and limited ability for antioxidant defense and repair.

Diagnosis

CDS is currently diagnosed by ruling out other possibilities for the presenting symptoms. Although MRI and PET scans are available, their use is currently not widespread for the diagnosis of CDS because of financial and anesthetic concerns. Because the diagnosis of CDS is one of exclusion of other problems, symptoms may be falsely attributed to a medical disease process or other behavioral disorder. It is important to remember that a senior dog can have a primary behavioral problem like separation anxiety that has been exacerbated by age, concurrent disease or the mere fact that owners may no longer be willing to put up with it.

Unfortunately, despite its prevalence, it still appears to be severely underdiagnosed by clinicians in general practice¹¹.

A standard minimum database should begin with a basic physical examination, orthopedic and neurologic examination and laboratory analysis including CBC, Chemistry, total T4, free T4 by ED, and urinalysis. Further diagnostics including ACTH stimulation may be warranted.

The symptoms associated with CDS can be remembered using the acronym "DISHA"; **D**isorientation, **S**ocial Interaction changes, **S**leep/wake cycle disturbance, **H**ouse soiling, and changes in **A**ctivity² and increased **A**nxiety. Other symptoms may include decrease in hygiene and grooming, changes in appetite, decreased response to external stimuli and decline in memory or learning capabilities².

Symptoms

Disorientation

Disorientation can manifest in numerous ways. One of the most common signs reported is the dog standing at the wrong side of the door when asking to go out. Owners may witness their pets walking towards solid objects such as furniture or tables, and appearing not to know how to maneuver around the object. Some dogs and cats will walk into a corner and then are unable to turn around. Owners often describe this as "head-pressing" since the pet cannot seemingly turn and will press their head against the wall or in the corner since they cannot figure out what else to do. Head-pressing can be a symptom of other neurologic syndromes and processes so it is important for the clinician to first rule out any medical disease processes which may be causing this. If unsure based on the clients description, a video may show the problem more clearly. Another common owner complaint is the pet who asks to go outside, once allowed out, turns right back around and wants to come back in, almost as if to say "I have no idea what I was out there for". This confusion can also lead to the pet soiling in the house, since normal elimination is not achieved when allowed outdoors.

Changes in social interactions

Many pets experience changes in their social interactions with other pets or people. There can be aggression towards another animal member of the household, whereas the pets

were seemingly friendly prior to the onset of disease. Or vice versa, where once the pets were antagonistic towards one another, with the onset of CDS we see amicable or at least benign interactions between them. Dogs often do not get up to greet familiar people, may walk away when petted, or no longer solicit social attention from their owners. Dogs who were over-exuberant when familiar people come to the home, may not even make attempts to greet visitors or may even become aggressive towards people they were previously friendly with.

Changes in sleep/wake cycle

Owners may complain that their older dogs and cats sleep all day and are then awake during the night. Most of the time, the awake period in the night is not a relaxed state of wakefulness, but is often characterized by panting, pacing and vocalization in both dogs and cats. This is thought to be analogous to "sundowners syndrome" seen in humans with Alzheimer's dementia. Owners will often complain of attention seeking behaviors in both dogs and cats. Dogs may pace and pant all night long and nudge and bother the owner to awaken, while cats may pace and loudly vocalize.

House soiling

A common symptom in companion animals with CDS is house soiling, or urinating and defecating in an inappropriate location. There are many reasons why an older dog or cat might suddenly eliminate in the home and a thorough medical workup must be performed to rule out hormonal incontinence, neurologic dysfunction, renal disease, thyroid dysfunction, and endocrinopathies that may be causing this behavior. A thorough behavioral evaluation must be performed as well to rule out separation anxiety, noise phobia and generalized anxiety as a cause for the inappropriate elimination. However, once all medical and other behavioral reasons have been sufficiently ruled out, the house soiling can be attributed to CDS. Dogs with CDS often just urinate in front of their owners and perhaps right after coming back inside.

Activity level

Changes in activity level are often misinterpreted by owners as being a normal part of the aging process. Even healthy dogs and cats will show a decline in activity as they age, but there may be many medical reasons for this change. Osteoarthritis, obesity, and thyroid dysfunction are common medical problems of aged pets and may decrease their activity levels. Laboratory studies have actually shown the opposite to be true in CDS, where the pet experiences increased locomotor activity and decreased immobile time³ although some owners still self-report a decrease in activity associated with the onset of CDS.

Anxiety

Anxiety is a common sequelae of CDS. It may be either an exacerbation of anxiety disorders that the dog or cat previously had prior to diagnosis or brand new anxieties that appeared with the onset of the dementia. Noise phobias (fear of thunderstorms and fireworks), separation anxiety and fear-based aggression are frequent manifestations of the anxiety component of CDS. Part of the goal of medical intervention revolves around relieving the anxiety associated with the disease process. These phobias and anxieties are likely analogous to the agitation and anxiety that many humans with dementia and Alzheimer's disease experience³.

Treatment:

Treatment of CDS in dogs and cats is difficult at best. Just like with human cognitive decline, the process cannot be reversed or cured. However, the goal is to improve the welfare of the pet by intervention focused on relieving the anxiety, slowing the disease process if possible, and supporting cognitive function. If other underlying medical or behavioral problems are also present, those must be treated concurrently with treatment for CDS.

Diet:

The first stage of intervention in dogs often involves a dietary change to a prescription diet containing high levels of anti-oxidants like vitamins C and E. The anti-oxidants help to scavenge free radicals in the body, decreasing the amount of oxidative damage to healthy brain tissue, an organ which is highly susceptible to oxidative stress⁴. There is one prescription diet labeled for CDS, Hills Science Diet b/d (the "brain diet") which is currently only formulated for dogs. Not only does it contain increased level of vitamins E and C, but also beta carotene, selenium, flavonoids and carotenoids from vegetables and fruits, L-carnitine to enhance mitochondrial function, and high levels of Omega-3 fatty acids which enhance cell membrane health and are anti-inflammatory⁴. Dodd et. al. performed a double blind placebo controlled study on the diet using 142 dogs and demonstrated a significantly higher level of improvement of cognitive signs in the dogs on b/d⁵. Purina recently came out with their version, Purina One Vibrant Maturity, an over-the-counter diet for Senior dogs and cats which contains high levels of similar anti-oxidants and medium chain triglycerides.

Supplementation:

There are many supplements purported to slow the progression of the disease process offer neuronal support and perhaps buy some more quality time in the life of the pet. One such product is Novifit, which is the tosylated form of S-adenosyl methionine (SAME) (Virbac Animal Health). The tosylated form may do a better job of crossing the blood/brain barrier than other SAME products. SAME products have been used for years in both human and veterinary medicine as support for both brain and liver function, treatment for acute and chronic hepatopathies, osteoarthritis and even ADHD, AIDS-related myopathy, depression and fibromyalgia⁶. SAME is naturally found in our bodies and is a key component in three biochemical pathways. It helps cell membranes retain their structure and function, has anti-inflammatory effects, and detoxifies cells⁶. In humans with depression, although the mechanism is poorly understood, it is theorized that SAME increases serotonin turnover and increases dopamine and norepinephrine levels⁶. In this way, SAME not only helps to delay the progression of CDS, but likely decreases the anxiety component of the disease as well. In a study done by Gary Landsberg and colleagues, SAME was shown to improve executive function in dogs and cats, but not in short and long-term memory, and only in the top performing animals versus the bottom performers⁷. This indicates that the need for early intervention for better outcomes.

Senilife, by Ceva Animal Health, is another nutraceutical supplement which shows promising results with cognitive decline. It contains phosphatidylserine, *Ginkgo biloba*, vitamin E and pyridoxine. Aruajo and colleagues performed testing on laboratory beagles using a short-term visuospatial memory test, the delayed-non-matching-to-position task, and found supplemented dogs had significantly higher levels of performance accuracy than non-supplemented dogs⁸.

Neutricks, by Quincy Animal Health, is a rather recent addition to the veterinary supplement market. The product contains Apoaequorin, a protein isolated from a particular

species of jellyfish. There is currently only one veterinary study on the product which did show improvements on learning and attention⁹. A placebo controlled study done on the original human version of the product, Prevagen by Quincy Bioscience, demonstrated increase in scores of executive function using the Groton Maze Learning task, and improved short-term memory and recall performance using the One Card Learning task and International Shopping List test¹⁰.

Environmental enrichment:

The adage of "use it or lose it" is often touted to humans in an attempt to arrest the onset of age-related dementia, and it appears to apply to dogs and cats as well³. In companion animals, we recommend environmental enrichment and mental stimulation through the use of feeder toys, puzzle toys, climbing and agility, opportunities for hunt and chase games, on-going task and obedience training, and general exercise.

Medication:

There is currently only one FDA- approved medication for the treatment of Cognitive Dysfunction Syndrome in dogs, Anipryl by Zoetis (formerly Pfizer Animal Health). Anipryl is the brand name of the drug Selegiline, an irreversible monamine oxidase inhibitor (MAO-i) that acts to increase dopamine production in the brain⁶. The recommended dose is 0.5 mg/kg once daily in the morning for four weeks. If there is no perceived response, increase to 1.0 mg/kg once daily thereafter. It is not labeled for cats, but has been used off-label in the treatment of cats with cognitive decline and is endorsed by the American Association of Feline Practitioners for use in CDS. The dose range for cats is 0.25 mg/kg- 1.0 mg/kg once daily. Although the exact mechanism of action is largely unknown, it is thought that the dopamine enhancing effects, the catecholamine enhancement and the increase of 2-phenylethylamine causes an increase in cognitive function and neuronal impulse transmission⁴. It is possible that it also acts as a free radical scavenger by increasing the scavenging enzymes catalase and superoxide dismutase and decreasing the production of the toxic free radicals themselves⁴. It may take 4-6 weeks to see appreciable response to therapy. Appropriate dosing essential because selegiline usage is contraindicated with other commonly prescribed medications, including tick preventives, pain medications like tramadol, SSRIs and TCAs possibly resulting in overdose and serotonin syndrome⁶. A 4-6 week wash-out period is needed prior to using Anipryl in dogs and cats that were previously on serotonin enhancing medications.

Conclusion:

Cognitive Dysfunction Syndrome is common in the aging companion animal population now that they live longer due to the advances of veterinary medicine. However, CDS still remains under-diagnosed by general practitioners³. Veterinarians need to focus on earlier screening and education of owners that the symptoms seen in their aged pets are not "normal" signs of aging. This allows for early intervention that while not curative appears to help improve longevity and quality of life for our patients. More and more studies are being done on dogs and cats with cognitive decline in the hopes of finding better treatments modalities to enhance the well-being and prolong the quantity and quality of life in our companion animals. Since dogs with CDS provide a very comparable model to human patients with Alzheimer's disease, especially in the earliest stages of that disease, continued study in this field is imperative for finding better treatment options for them as well.

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