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Canine cognitive decline and Alzheimer disease: clinical insights to solve a shared one-health problem

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ABSTRACT

Alzheimer disease (AD) is the leading cause of dementia among older adults. Current AD treatment options are limited, and the absence of appropriate research animals has significantly hindered the development of new AD therapies. Canine cognitive decline (CCD) is a major determinant of morbidity in older animals, with alterations in blood biomarkers, neuropathology, physiology, and behavior comparable to those seen in humans diagnosed with dementia and AD.

The one-health goal of achieving optimal health is supported by academics, researchers, and governments. Veterinarians' ability to identify patients in the early stages of CCD is crucial to the successful implementation of interventions that can improve the quality of life of affected dogs. Timely identification of CCD also opens opportunities for innovative interdisciplinary research that will contribute to a better understanding of the underlying mechanisms, early detection, and effective treatments for AD, ultimately benefiting human health as well.

Until now, veterinary practitioners have played limited roles as interdisciplinary leaders in the One Health initiative to combat disease. The authors discuss how client-owned animals with spontaneous, naturally occurring CCD can play a significant role as disease-relevant surrogates for translational AD research. The proposed Dogs Overcoming Geriatric Memory and Aging (DOGMA) Study to be conducted in veterinary practices will analyze the relationship between blood biomarkers and biometric behavior in mature and older dogs, with the aim of establishing benchmark CCD data. The DOGMA Study is addressed in the companion Currents in One Health by Hunter et al, *AJVR*, November 2023.

Keywords: one health, canine cognitive dysfunction, canine cognitive decline, dementia, Alzheimer disease

Background

"As the world's population ages, overall health care has improved, yet the incidence of chronic, progressive neurodegenerative diseases has increased."[1] Alzheimer disease (AD) is a progressive neurodegenerative disorder characterized by memory loss and cognitive decline. It is the most common form of dementia and a leading cause of death in people over the age of 65, affecting as many as half of those aged 85 or older.[2] In the US alone, the estimated costs for AD treatment were $305 billion, a figure expected to rise to over $1 trillion as population aging continues.[3]

One significant obstacle in the development of a safe and efficacious AD drug is the lack of translational animal surrogates that accurately reflect the etiology, pathogenesis, and heterogeneity of the ailment in humans. These models are crucial for research studies.[4]

There are substantial similarities in clinical features between AD and canine cognitive decline (CCD). These shared features include the progression of neurodegeneration, neuropathy, and behavioral changes such as disorientation, memory loss, and disrupted sleep cycles **(Table 1)**. Both conditions exhibit similar etiology, clinical presentation, and histopathology. The shared living environment of companion dogs with CCD and humans offers an advantageous one-health perspective for examination of the influence of environmental factors on disease manifestation. Importantly, due to their pivotal role as first responders in the diagnosis and management of CCD, veterinary practitioners are well positioned to become significant contributors to this interdisciplinary research approach. This is particularly relevant as the animals exhibiting traits similar to AD are commonly first discussed and identified during routine veterinary care visits.

Table 1—The progressive cognitive decline associated with both canine cognitive decline (CCD) and Alzheimer disease (AD) is classified into several stages.[5]

Stage	AD/Dementia	CCD
Early/Mild	People in the early stage of AD exhibit mild memory loss and have increased difficulty managing involved tasks.	Dogs exhibit increased anxiety, a decrease in interactions, with owners, altered sleep patterns, and frequently forget familiar routes or objects.
Mid/Moderate	There is significant memory loss, disorientation, and changes in behavior and/or personality.	Exhibit increased confusion and disorientation, a reduced response to commands, changes in appetite or elimination. habits, and may forget familiar people or places.
Late/Severe	Patients suffer from a complete loss of cognitive function, are unable to recognize familiar people or objects, and require assistance with activities of daily living.	Demonstrate aimless wandering, restlessness, agitation, vocalization, incontinence, and an inability to recognize familiar people or objects.

While few research organizations maintain dogs until they reach senior status (typically 6 to 7 years old for large dogs and 10 years old for small breeds),[6] CCD is present in 28% of dogs aged 11 to 12 years, with a prevalence that increases to 68% at 15 to 16 years old.[7] Companion animals that are kept through old age represent a virtually unlimited global source of canines experiencing CCD. These dogs are cared for by pet owners who almost universally support research engagement and welcome options that might ameliorate the CCD-related decline that is experienced by these animals in their care.

The authors posit in this Currents in One Health article that the similarities between the progressive neurodegeneration, neuropathy, and behavioral signs seen in CCD resemble aspects of AD: disorientation, memory loss, and changes in sleep cycles make them suitable and practical surrogates for human dementia and AD research.

The Challenge

AD is the predominant cause of dementia in older people. Even though the FDA recently approved Leqembi (manufactured by Eisai and Biogen), the first AD drug that has shown clinical benefit, its efficacy is limited, serving only to modestly slow cognitive decline. Moreover, its yearly cost of $26,500 will make it inaccessible for many. There remains a pressing need for the development of more effective and affordable translational research models that can improve efficiency, reduce failure rates, and foster more strategic collaborations. Ultimately, CCD translational research models identified by veterinary practitioners have the potential to significantly reduce the high costs associated with drug development, thereby addressing the problem of prohibitively priced medications.

CCD is common in older dogs and a major determinant of morbidity in companion animals. It mirrors many of the physiological and behavioral changes observed in humans diagnosed with dementia and AD, including disorientation, memory deficits, altered social interactions, disruptions in sleep-wake cycles, changes in activity levels, and pathologies such as brain atrophy **(Figure 1)**. Similarities also exist in neuropathology, specifically with the presence of amyloid-β deposits in both extracellular spaces and around blood vessels (cerebral amyloid angiopathy) and increased phosphorylated tau in the brain.[8]

Despite the well-recognized similarities between AD and CCD, leveraging these parallels for effective treatments has proved to be challenging. Identifying and assessing the early onset of behavioral alterations is difficult in both humans and dogs. Additionally, achieving consensus of the diagnostic value of neurodegenerative biomarkers remains a significant hurdle.[9]

Diagnosing CCD

Diagnosing AD in humans involves a comprehensive multidisciplinary approach, including the evaluation of balance, sensory responses, and reflexes as well as patient and family interviews, memory, and cognitive skills.[10] While a probable diagnosis of AD can be made using a combination of symptomatology and biomarkers, the confirmation of an AD diagnosis is universally agreed to be postmortem neuropathological verification of specific brain changes, including senile plaques and neurofibrillary tangles.[11] Similarly, diagnosing CCD is multifaceted and presents unique considerations **(Table 2)**.

In veterinary practice, careful physical and neurological examinations, blood tests, and imaging studies (eg, CT scans or MRI, if available) are essential to exclude other conditions with similar symptoms. Tools like wearable sensors are robust markers for CCD-related changes. Any illnesses with symptoms like CCD must be excluded, including brain tumors, osteoarthritis, and metabolic imbalances. Diagnosis relies primarily on observation of clinical science, summarized by the acronym DISHAA.

A thorough understanding of both CCD and AD is crucial for achieving early diagnosis and effective treatment. The growing convergence of technology and research holds promise for novel analytical strategies that can reshape the landscape of cognitive health for both humans and animals. Veterinarians' ability to identify initial and elusive behavioral changes linked to CCD is vital for early diagnosis. Wearable sensors with remote reporting offer robust markers for these changes, including alterations in sleep patterns and restlessness.