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One-health approach to canine cognitive decline: Dogs Overcoming Geriatric Memory and Aging Initiative for early detection of cognitive decline

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ABSTRACT

Treatment options for human dementia remain limited, and additional research is needed to develop and validate translational models. Canine cognitive decline (CCD) is common in older dogs and a major source of morbidity. The decline includes physiological and behavioral changes comparable to those in humans diagnosed with dementia. There are also corresponding changes in plasma neurodegenerative biomarkers and neuropathology. Biomarkers for both human and canine cognitive decline can be used to identify and quantify the onset of behavioral data suggestive of CCD. Successful correlations would provide reference values for the early identification of neurodegeneration in canine patients. This could allow for the subsequent testing of interventions directed at ameliorating CCD and offer translational value leading to safe and effective treatment of dementia in people. Research can help exploit, track, and provide benefits from the rapid progression of spontaneous naturally occurring CCD in a large heterogenous community of companion dogs. Research efforts should work to deliver information using blood biomarkers, comorbidities, and wearable technologies to track and evaluate biometric data associated with neurodegeneration and cognitive decline that can be used by both human and companion animal researchers. The synergistic approach between human and veterinary medicine epitomized in one health underscores the interconnectedness of the well-being of both species. Leveraging the insights gained from studying CCD can not only lead to innovative interventions for pets but will also shed light on the complex mechanisms of human dementia.

Keywords: canine cognitive decline, one health, dementia, p-glycoprotein, DOGMA

Health care has improved as the world's population ages, but the incidence of chronic, progressive neurodegenerative disease has increased. A critical challenge to dementia drug development has been the absence of translational models to drive human clinical studies. While transgenic mice are valuable in unraveling the mechanistic changes, rodents do not develop spontaneous neurodegeneration or the hallmark pathology of dementia, amyloid plaque, and neurofibrillary tangles.[1] Therefore, they have limited utility as platforms for testing interventions' potential safety and efficacy.

Canine cognitive decline (CCD) is a chronic, progressive neurodegenerative condition with behavioral and pathological symptoms resembling aspects of dementia: disorientation, memory loss, behavior changes, and neuropathology that includes brain atrophy, with β-amyloid deposits in both extracellular spaces and around blood vessels. In addition, there are demonstrated increases in phosphorylated tau (τ) in the canine brain, oligomeric species of both τ and amyloid are evident, and declining β42 in the cerebrospinal fluid are inversely correlated with brain amyloid load, similar to humans. There are also changes in the cholinergic system of dogs, including reduced muscarinic receptors and increased sensitivity to the cognitive impairing effects of anticholinergics.[2] The prevalence of CCD does not

differ between breeds, and there are no breed-specific differences in clinical signs or pathology of the disease.[3] Similarities to dementia in etiology, clinical presentation, histopathology, and shared environment make companion dogs with CCD a practical and appropriate research model for human dementia research. Few, if any, research organizations (ie, clinical research organizations, pharmaceutical companies, or breeders) maintain dogs until they reach senior status (typically 6–7 years for large dogs, 10 years for small breeds). By contrast, pet dogs are kept through old age and represent a global source of canines experiencing CCD. Pet owners almost universally show high engagement with veterinarians and researchers and welcome options to ameliorate CCD. The American Animal Hospital Association recently reported[4] that 44% of the companion pet population falls into the senior category, reflecting an alignment with the aging "baby-boomer" generation in the human population. While current guidelines offer valuable recommendations for senior pet care, the broader One Health Initiative calls attention to a significant opportunity. By narrowing the gap between human and animal researchers, we can foster collaborations that will enhance the diagnostic methods and therapeutic options, benefitting both humans and animals.

Why the Dogs Overcoming Geriatric Memory and Aging Initiative?

The authors, as a group, support the Dogs Overcoming Geriatric Memory and Aging (DOGMA) Initiative as a reflection of the AVMA's one-health goals, emphasizing the shared challenges of aging and cognitive decline across species. By fostering collaboration between veterinarians, medical doctors, and researchers from various fields, the proposed CCD study aims to enhance our understanding of these processes and to devise cross-species solutions. This alignment underscores the vital concept that improving the health and well-being of our pets may also pave the way for advancements in human health.

CCD highlights the shared health challenges faced by both humans and canines, particularly in the context of geriatric cognitive decline, and underscores the importance of interdisciplinary collaborations in addressing these challenges, which is a key tenet of the one-health approach. CCD offers a clear and engaging introduction of the one-health approach to veterinarians, whether they are familiar with the concept or approaching interdisciplinary collaborations and communications in all aspects of health care for humans, animals, and the environment for the first time. The authors propose to reframe CCD from the perspective of the DOGMA acronym **(Table 1)** to put this condition into a broader framework of issues.

Research Needs

In humans, a diagnosis of dementia is determined by a multidisciplinary approach, embracing medical history, physical examination, neurological tests, brain scans, blood tests, genetic tests, and mental health evaluation. These parameters assess balance, sensory responses, reflexes, memory, and thinking skills. The ultimate gold standard for confirmatory diagnosis is universally agreed to be neuropathological assessment, postmortem. In canines, the presumptive diagnosis of CCD is made through medical history, physical examination, and blood tests are primarily used to exclude systemic or metabolic conditions and are similar to the evaluation and diagnosis done for humans. The most important determinant for the presence of CCD, changes in the pet's behavior, must be interpolated through the filter of owner observations, which can be and are highly subjective and indirectly influenced by the owner. There is a clear need for more unbiased assessment parameters, ideally measures that can be reliably quantified. There is a demonstrated link between owner behavior and their dog during a veterinary office visit/consult. The results of Helsly et al[5] support that it is beneficial to canine welfare when owners interact positively with their pets during veterinary consultations. This also supports the idea that advances in wearable technology offer quantitative ways to address this need without influence from the pet owner or other environmental cues or to assist with differentiation due to owner or environmental influence.

The diagnosis of CCD is a diagnosis of elimination. The illness exacerbating symptoms commonly observed in CCD must be excluded, such as CNS

Table 1—Dogs Overcoming Geriatric Memory and Aging (DOGMA) Initiative.

DOGMA

D – Dogs: Dogs share our homes and lifestyles, leading to shared health risks. Studying cognitive decline and aging in dogs can yield comparative insights into similar human conditions, benefiting both canine and human health.

O – Overcoming: This term encapsulates the proactive goal of the One Health Initiative to improve health and well-being across species. It underscores our shared aim of finding solutions to health issues affecting all living beings and their environments.

G – Geriatric: As life expectancies increase, age-related health issues are a growing concern in both human and veterinary medicine. By focusing on geriatric health, we address a significant challenge shared across species.

M – Memory: Cognitive decline, especially memory loss, significantly impacts aging in both humans and dogs. By studying and addressing memory impairment in dogs, we might uncover findings applicable to human medicine, particularly conditions like Alzheimer disease.

A – Aging: Aging is a universal biological process impacting all living organisms. Research into systemic changes that occur with aging can provide insights applicable across species, leading to potential interventions that can improve health and lifespan.

tumors, hypertension, other neurological conditions, metabolic and hormonal imbalances, etc. Screening and diagnosis of CCD are primarily based on observation of clinical signs, which can be summarized by the acronym DISHAA, which refers to disorientation, altered social interactions, altered sleep-wake cycles, house soiling, and loss of other learned behaviors, altered activity levels, and increasing anxiety.[3]

As with early human dementia, the subtle changes present at the onset of CCD are difficult to identify or quantify. The ability to, at least presumptively, identify the initial and elusive behavioral changes instigated by CCD would be instrumental in defining early diagnosis. Wearable sensors, with remote reporting, offer robust markers for behavioral change. This would offer CCD and dementia researchers a robust, quantitative platform to develop new prevention and treatment strategies.

Research Goals

To provide researchers with a powerful experimental database large enough to account for regional variabilities and multivariate statistical modeling, including sex, age, breed, and body weight (given the generally longer lifespan and later onset in smaller breeds), DOGMA anticipates a global registry of 10,000+ dogs. Data management and algorithms will identify those animals with the earliest signs of developing CCD, which will be matched against concomitant biomarker findings to allow for a validated diagnostic determination of the onset time. Additional research is needed to support and demonstrate the link between behavior and cognitive decline in dogs.[2,6] The goals are as follows:

- To deliver data correlating biomarker levels with the biometric wearable collar tracking of key behaviors associated with CCD, including disorientation, changes to sleep/wake cycle, and repetitive or restless activity. These are currently reported using subjective owner observations.
- Assess and correlate expression changes in p-glycoprotein (p-gp) observed in human dementia patients to CCD patients.
- To plot and quantify the longitudinal progression of behavioral deviations and biomarker values that pinpoint the onset of CCD.

Achieving these goals in full will require appropriately powered studies that initiate tracking as early as practicable but before the onset of biomarker changes that lead to the expression of altered behaviors. Successful outcomes will allow researchers access to patients with naturally occurring CCD and the ability to investigate the potential of treatment interventions under real-world conditions.

Behavior

The Canine Dementia Scale (CADES) questionnaire[6] aims at identifying the onset, severity, and progression of behavioral and cognitive impairment in dogs with mild cognitive declines through observation of changes in social interaction and alterations of spatial orientation. Using CADES, dogs are classified as "mild," "moderate," or "severe" based on the level of behavioral change exhibited. Physical impairment, including visual and smell, has been linked to CCD progression.[6]

Innovative 24/7 wearable smart collars (ie, PetPace.com) can identify and track a number of physiological signs and behavioral changes that are consistent with CCD. The devices continuously monitor, collect, and report a dog's vital signs using noninvasive sensors for body temperature, heart rate, respiration rate, degree of physical activity, body positioning, heart rate variability, and physical location as well as movement within the home. The activity sensor can identify, record, and report minute changes in activity patterns. Collected data are sent to a cloud-based monitoring platform that analyzes the information and issues an alert if deviations from routine exist.[7]

The proprietary algorithms for these devices recognize the behavior, position, and biometric data representing an animal's pattern of life, ie, that individual's physiological values, behaviors, and routines. Data collection from individuals will continue to the end of life. If pattern of life findings are consistent with CCD onset diagnostics and one can rule out any concomitant issues, that individual could be viable for potential enrollment in a CCD research study.

In addition to biometric data, routine laboratory diagnostics would monitor for comorbidities that could result in CCD-like symptoms. Routine and specialized tests should include blood/serum analysis such as CBC, blood chemistry profile, C-reactive protein, amyloid-β proteins, phosphorylated τ proteins, neurofilament light chain protein, and glial fibrillary acidic protein. Additional evaluations should include routine ophthalmoscopic exams for hypertensive retinopathy and interstitial fluid evaluation. Samples could be cryobanked for later access and further CCD investigations.

P-glycoprotein and Drug Transport

The potential role of P-gp expression and its role in CNS transport underscores the connection between CCD and human dementia. By delving into the function of P-gp and its implications in both species, this area of study reveals promising insights into the shared mechanisms governing cognitive decline. The similarities between CCD and human dementia extend to the molecular level, offering the following valuable insights:

1. Amyloid accumulation: Both CCD and Alzheimer disease show an accumulation of amyloid plaques in the brain.[8,9]
2. Neuroinflammation: Similar inflammatory responses are observed in both human and canine brains.
3. P-gp functionality and ivermectin sensitivity: P-gp, an efflux pump highly expressed at the endothelial cells of the blood-brain barrier, is involved in transporting amyloid-β in humans. Its

decreased function has been linked to β-amyloid accumulation in AD. Similarly, in canine medicine, a subpopulation is genetically deficient in P-gp, including "ivermectin-sensitive" dogs found in some breeds of herding dogs and hounds. This compromised transporter function is demonstrated by specific drug toxicity, reflecting the mutation in the multidrug resistance-1 gene.[10,11] While the degree of homology of the multidrug resistance-1 gene is high across species (> 90%), the sequence similarity of intron 1 is substantially lower (< 50%).[12]

This connection emphasizes the importance of further research needed to understand changes in p-gp expression in CCD and to explore potential clinical implications.[11,12] Innovative diagnostics to assess p-gp expression in aging dogs and those with CCD can be equated to corresponding changes in the aging human, facilitating a one-health understanding of intertwined biological connections to form a robust foundation for a unified approach to understanding, diagnosing, and treating cognitive disorders in both humans and animals. The exploration of these commonalities could lead to breakthroughs in therapeutic intervention, highlighting the vital importance of a collaborative one-health approach.[13]

Laboratory Diagnostics

A novel blood test, the soluble oligomer binding assay, has been developed that can identify toxic β-amyloid oligomer compounds associated with Alzheimer disease in patients' blood even before any symptoms are manifested.[14] This groundbreaking work indicates the potential for early diagnostic tests for neurodegenerative conditions, including CCD.[14,15] Current clinical veterinary diagnostics are discussed in the companion Currents in One Health by Ehrenzweig et al, *JAVMA*, November 2023.

Imaging

While various imaging techniques are used in human medicine, more work is needed to establish the correlation between human and canine imaging. MRI can identify brain atrophy, which in addition to clinical signs of behavioral changes in dogs over 10 years old, is diagnostic for CCD. MRI is important for confirming brain atrophy and eliminating other causes of symptoms (ie, brain tumor, stroke, ischemia, etc). CT may also be employed to identify other conditions like subdural hematomas or aneurysms. PET imaging can help reveal the atypical metabolism of diseases even before the disease shows up on CT and MRI.[16]

Histopathology

Postmortem histopathological changes that are characteristic of CCD include amyloid plaques of mainly diffuse and dense types. These are seen in the brain parenchyma and around larger blood vessels (resembling cerebral amyloid angiopathy, seen in some human dementia patients). Formation and maturation of amyloid deposits were observed by immunostaining throughout the canine cortical gray matter layers in a 4-stage distribution, which is also characteristic of human dementia, and this, according to some studies, correlates with the severity of cognitive deficit in the dog and varies as a function of age and size (weight) in companion dogs.[2,3,6,16,17] The β-amyloid load was higher in small- and medium-sized dogs, which can be explained by the longer life span of smaller dogs and thus longer time necessary to accumulate these deposits.[2] Activated microglia are CD68-positive and exhibit morphological changes characteristic of a phagocytic phenotype, such as amoeboid body and dystrophic processes, some with spheroidal and bulbous swellings. It is of note that canines with CCD can develop hyperphosphorylated τ pathology or neurofibrillary tangles.

Conclusion

The advances in science and medicine have enabled people and pets to live longer and healthier lives. This achievement has also resulted in an increased incidence of chronic conditions associated with advanced age and a dramatic surge in neurodegenerative diseases like Alzheimer disease and CCD. Treatments aimed at slowing or stopping the progression of neuropathic conditions have been hindered by the lack of suitable animal surrogates emulating the natural progression of people with the disease. The ability to recognize early behavioral manifestations of CCD and concurrent deviations in neurodegenerative biomarkers will allow for the identification of clinical study candidates for the treatment of CCD and comparative data that could ultimately lead to the diagnosis of early onset and the successful management of dementia.

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References

1. Joel Z, Izquierdo P, Salih, DA, Richardson JC, Cummings DM, Edwards FA. Improving mouse models for dementia. Are all the effects in tau mouse models due to overexpression? *Cold Spring Harb Symp Quant Biol.* 2018;83:151–161. doi:10.1101/sqb.2018.83.037531
2. Ozawa M, Inoue M, Uchida K, Chambers JK, Takeuch Y, Nakayama H. Physical signs of canine cognitive dysfunction. *J Vet Med Sci.* 2019;81(12):1829–1834. doi:10.1292/jvms.19-0458

3. Mihevc SP, Majdič G. Canine cognitive dysfunction and Alzheimer's disease – two facets of the same disease? *Front Neurosci.* 2019;13:604. doi:10.3389/fnins.2019.00604

4. Dhaliwal R, Boynton E, Carrera-Justiz S, et al. 2023 AAHA senior care guidelines for dogs and cats. *J Am Anim Hosp Assoc.* 2023;59(1):1–21. doi:10.5326/JAAHA-MS-7343

5. Helsly M, Priymenko N, Girault C, Duranton C, Gaunet F. Dog behaviours in veterinary consultations: part II. The relationship between the behaviours of dogs and their owners. *Vet J.* 2022;281:105789. doi:10.1016/j.tvjl.2022.105789

6. Vikartovska Z, Farbakova J, Smolek T, et al. Novel diagnostic tools for identifying cognitive impairment in dogs: behavior, biomarkers, and pathology. *Front Vet Sci.* 2021;7:551895. doi:10.3389/fvets.2020.551895

7. Rowlison de Ortiz A, Belda B, Hash J, Enomoto M, Robertson J, Lascelles BDX. Initial exploration of the discriminatory ability of the PetPace collar to detect differences in activity and physiological variables between healthy and osteoarthritic dogs. *Front Pain Res.* 2022;3:949877. doi:10.3389/fpain.2022.949877

8. van Assema DME, Lubberink M, Bauer M, et al. Blood–brain barrier P-glycoprotein function in Alzheimer's disease. *Brain.* 2012;135(1):181–189. doi:10.1093/brain/awr298

9. Deo AK, Borson S, Link JM, et al. Activity of P-glycoprotein, a β-amyloid transporter at the blood–brain barrier, is compromised in patients with mild Alzheimer disease. *J Nuclear Med.* 2014;55(7):1106–1111. doi:10.2967/jnumed.113.130161

10. Mealey KL, Bentjen SA, Gay JM, Cantor GH. Ivermectin sensitivity in collies is associated with a deletion mutation of the mdr1 gene. *Pharmacogenetics.* 2001;11(8):727–733. doi:10.1097/00008571-200111000-00012

11. Mealey KL. Therapeutic implications of the MDR-1 gene. *J Vet Pharmacol Therap.* 2004;27(5):257–264. doi:10.1111/j.1365-2885.2004.00607.x

12. Mealey KL. Adverse drug reactions in herding-breed dogs: the role of P-gp. *Compendium.* 2006;28:23–33.

13. Martinez M, Modric S, Sharkey M, Troutman L, Walker L, Mealey K. The pharmacogenomics of P-glycoprotein and its role in veterinary medicine. *J Vet Pharmacol Therap.* 2008;31(4):285–300. doi:10.1111/j.1365-2885.2008.00964.x

14. Shea D, Colasurdo E, Smith A, et al. SOBA: development and testing of a soluble oligomer binding assay for detection of amyloidogenic toxic oligomers. *Proc Natl Acad Sci USA.* 2022;119(50):e2213157119. doi:10.1073/pnas.2213157119

15. Habiba U, Ozawa M, Chambers JK, et al. Neuronal deposition of amyloid-β oligomers and hyperphosphorylated tau is closely connected with cognitive dysfunction in aged dogs. *J Alzheimers Dis Rep.* 2021;5(1):749–760. doi:10.3233/ADR-210035

16. Maschio C, Ni R. Amyloid and tau positron emission tomography imaging in Alzheimer's disease and other tauopathies. *Front Aging Neurosci.* 2022;14:838034. doi:10.3389/fnagi.2022.838034

17. Denenberg S, Liebel FX, Rose, J. Behavioural and medical differentials of cognitive decline and dementia in dogs and cats. *Canine Feline Dementia.* 2017;21:13–58.