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A Review of Canine Cognitive Dysfunction Syndrome and its Similarity to Human Alzheimer's Disease

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ABSTRACT

As dogs age, they become more prone to a variety of medical conditions. In particular, canine cognitive dysfunction syndrome (CCDS), a neurodegenerative disease, can have a profound impact on both pets and their owners because it can drastically alter quality of life. However, there is a lack of awareness of this disease in Korea, with a scarcity of clinical studies and reported effects. The present study investigated the occurrence and characteristics of this disease based on reports of neurodegenerative diseases in dogs and studies of canine animal models of human neurodegenerative diseases. The ensuing discussion addresses the importance of disease recognition and the need for appropriate management.

CCDS typically causes cognitive dysfunction in elderly dogs, with cognitive deficits similar to symptoms of neurodegenerative disease in humans, including disorientation, memory loss, and behavioral changes. CCDS manifests as changes in behavioral patterns and routines, and clinical features characterized according to "DISHA" signs (disorientation, interactions, sleep-wake cycles, house soiling, and activity levels) have been associated with neurodegenerative changes including cortical atrophy and amyloid-beta (Aβ) deposition. Furthermore, previous studies using canine animal models to investigate human Alzheimer's disease have yielded similar results, including the accumulation of Aβ, decline in learning and memory, and cognitive domain-specific vulnerabilities.

As the number of elderly dogs increase, the number of senior-age-related diseases will also increase; as such, it is important to be aware and prepared. Notably, CCDS is a neurodegenerative disease in animals that requires careful attention and observation to recognize. In addition, more active clinical research is needed to effectively inform management and treatment strategies tailored to the domestic pet population and environment.

1. Introduction

As dogs live longer with improved care, the number of elderly dogs is increasing. Aging is characterized by increased morbidity and a decline in the body's ability to function, which eventually

leads to death (Mitchell et al., 2015). In the same way that individuals are becoming increasingly interested in healthy aging, the aging of pets has also become a major concern, with the intention of maintaining and improving their health through effective management (Bellows et al., 2015).

Nevertheless, as dogs age, many age-related changes occur, and they become vulnerable to a variety of diseases, including infectious diseases, immune disorders, and tumors (Pereira et al., 2019). In particular, the development of canine cognitive dysfunction syndrome (CCDS), a neurodegenerative disease, can have a profound impact on both pets and their owners because it can significantly alter their quality of life. Such outcomes can be observed in dogs with CCDS and in similar neurodegenerative diseases in humans, such as Alzheimer's and Parkinson's disease.

CCDS is an age-dependent neurodegenerative disease characterized by changes in behavioral patterns, which primarily affects elderly dogs and exhibits features similar to Alzheimer's disease in humans (Fast et al., 2013; Schutt et al., 2015). Currently more than 55 million people have dementia worldwide. Alzheimer disease is the most common form of dementia and may contribute to 60−70% of cases (WHO, 2023). The two hallmark pathological lesions of Alzheimer's disease include the deposition of extracellular amyloid-beta (Aβ) plaques surrounded by dystrophic neurites, and the presence of intraneuronal neurofibrillary tangles (NFTs) in the hippocampus, cerebral cortex, and other areas of the brain associated with cognition (Iqbal et al., 2002; Serrano-Pozo et al., 2011).

Neurodegenerative diseases in humans have become more widespread worldwide and continue to increase and contribute to the social burden. Despite the increasing prevalence of neurodegenerative diseases due to aging populations, there are no effective treatments. Alzheimer's disease is one of the most common neurodegenerative diseases, and its pathogenesis remains largely unclear. CCDS, a neurodegenerative disease in dogs, is similar to Alzheimer's disease in humans, and has been used as an animal model to study the disease (Mihevc et al., 2019).

However, there is a general lack of awareness of CCDS in Korea, with no clinical studies, effects, or outcomes reported. To raise awareness of the disease, it is necessary to provide information about it to enable pet owners to recognize and manage it. In addition, veterinary hospitals should be prepared for the increasing number of cognitively impaired domestic pets by reporting disease outbreaks and initiating clinical studies investigating management and treatment strategies. The present article provides an overview of the relevant literature investigating neurodegenerative disease(s) in dogs, pathological features, and characteristic signs to encourage clinical research in veterinary hospitals with the aim of providing disease-related information to pet owners.

2. Methods

The present study searched and analyzed the relevant literature addressing canine aging, CCDS, and canine models of human Alzheimer's disease in order to conduct the method of narrative review on the topic. For this, the available literature was searched using keywords including "aging of pets", "diseases of elderly dogs", "CCDS", "Alzheimer's disease", and "Alzheimer's dog model" (Table 1). The contents were examined focusing on data from more recent studies, published since 2000.

Table 1. Number of related literature by keyword

Keywords	Number of related literature
Aging	15
Diseases of elderly dogs	12
CCDS	13
Alzheimer's disease	10
Alzheimer's dog model	5

3. Results

3.1 Reports documenting the incidence and characteristics of CCDS

CCDS causes impairment of canine cognitive function, typically in elderly dogs and, in many ways, similar to human Alzheimer's disease. The disease manifests as changes in behavioral patterns and routines, and clinical signs are associated with neurodegenerative changes including cortical atrophy and Aβ deposition. Similar to human symptoms, cognitive deficits observed in dogs include disorientation, memory loss, and behavioral changes; moreover, Aβ plaques observed in the brain are typically found in both the extracellular space and around blood vessels (Mihevc et al., 2019; Fast et al., 2013).

Many cases presumed to be in the precursor stage of CCDS have been observed to develop into CCDS over time. Abnormalities that are apparent through observation of aging dogs include aimless wandering, staring into space, avoidance of petting, difficulty retrieving dropped food, and anxiety. The diagnosis of CCDS does not necessarily affect survival; however, signs of cognitive dysfunction increase over time in dogs diagnosed with the disease, although they do not exhibit significant differences in survival based on breed, size, or sex (Schutt et al., 2015; Fast et al., 2013).

The major clinical features of dogs with CCDS can be categorized according to "DISHA" signs, which refer to "disorientation, interactions, sleep-wake cycles, house soiling, and activity levels". Disorientation refers to getting lost in a familiar place(s) or going to the wrong door. Interactions refer to changes in social interactions between pets and their owners or between pets and other pets. Some pets may become more "clingy", while others may become indifferent or dislike being petted or approached. Sleep-wake cycles can be irregular, with affected pets sleeping more during the day or awakening at night and becoming restless. House soiling refers to pets randomly soiling indoor or outdoor areas, or are unable to cover up urine or feces, in contrast to pre-disease behaviors. Overall activity levels may initially decrease or interest in play may subside; nevertheless, over time, some pets may become restless, wander aimlessly, or exhibit repetitive behaviors such as licking. Anxiety may also occur, in which the pets become more anxious when separated from their owners, react more strongly to visual or auditory stimuli, and/or become fearful of new environments or venturing outdoors (Vikartovska et al., 2021; Benzal et al., 2016; Fast et al., 2013).

The main signs of CCDS can be identified using the Canine Cognitive Dysfunction Rating Scale

(CCDR) (Table 2) (Salvin et al., 2011). Salvin et al. (2011) used data from a large cross-sectional survey of 957 elderly dogs (mean age, 11 years 9 months) to develop a clinical scale to assess CCDS. Through data-driven analysis techniques, 27 important behavioral items were identified to establish an assessment tool with a wide cognitive-behavioral breadth. As a result, the CCDR consists of 13 behavioral items, 3 of which are sensitive to the severity of disease stage: “avoidance of touch or petting” are characteristic of mild disease; “changes in difficulty retrieving dropped food” are characteristic of moderate disease; and “changes in recognizing the owner” are characteristic of severe disease. The assessment sums the scores for each of the 13 items, with a range of 0-39 defined as normal, 40-49 as at risk, and ≥ 50 as cognitively impaired. These rating scales can be useful tools in research and clinical settings to assess cognitive changes and follow-up, in addition to veterinary evaluations.

Table 2. Canine cognitive dysfunction rating (CCDR) scale

	Never	Once a month	Once a week	Once a day	> Once a day	Score
How often does your dog pace up and down, walk in circles and/or wander with no direction or purpose?	□ =1	□ =2	□ =3	□ =4	□ =5	=
How often does your dog stare blankly at the walls or floor?	□ =1	□ =2	□ =3	□ =4	□ =5	=
How often does your dog get stuck behind objects and is unable to get around?	□ =1	□ =2	□ =3	□ =4	□ =5	=
How often does your dog fail to recognise familiar people or pets?	□ =1	□ =2	□ =3	□ =4	□ =5	=
How often does your dog walk into walls or doors?	□ =1	□ =2	□ =3	□ =4	□ =5	=
How often does your dog walk away while, or avoid, being patted?	□ =1	□ =2	□ =3	□ =4	□ =5	=
	Never	1-30% times	31-60% times	61-99% times	Always	
How often does your dog have difficulty finding food dropped on the floor?	□ =1	□ =2	□ =3	□ =4	□ =5	=
	Much less	Slightly less	The same	Slightly more	Much more	
Compared with 6 months ago, does your dog now pace up and down, walk in circles and/or wander with no direction or purpose?	□ =1	□ =2	□ =3	□ =4	□ =5	=
Compared with 6 months ago, does your dog now stare blankly at the walls or floor?	□ =1	□ =2	□ =3	□ =4	□ =5	=
Compared with 6 months ago, does your dog urinate or defecate in an area it has previously kept clean (if your dog has never house-soiled, tick ‘the same’)?	□ =1	□ =2	□ =3	□ =4	□ =5	=
Compared with 6 months ago, does your dog have difficulty finding food dropped on the floor?	□ =1	□ =2	□ =3	□ =4	□ =5	**Multiply by 2 =**
Compared with 6 months ago, does your dog fail to recognise familiar people or pets?	□ =1	□ =2	□ =3	□ =4	□ =5	**Multiply by 3 =**
	Much more	Slightly more	The same	Slightly less	Much less	
Compared with 6 months ago, is the amount of time your dog spends active?	□ =1	□ =2	□ =3	□ =4	□ =5	=
0-39 = Normal / 40-49 = At risk / 50+ = CCD				Total		=

3.2 Animal models of CCDS

Aging of the brain is not only associated with molecular and morphological changes but also results in varying degrees of behavioral and cognitive dysfunction. The most common neurodegenerative disorder among aging humans is Alzheimer's disease, which progressively impairs cognition, behavior, and quality of life. There is a lack of research investigating the clinical significance and outcomes of cognitive function in animals; as such, pathological changes corresponding to lesions in Alzheimer's disease can be described in several other animal species (Youssef et al., 2016). Researchers have used numerous experimental animal models to understand the biological and environmental factors that influence aging, morbidity, and longevity. However, laboratory mice and rats, the most commonly studied animal species, do not experience environmental conditions similar to those humans are exposed to, and are not diagnosed with many of the naturally occurring diseases affecting humans. As such, dogs have recently been proposed as a powerful model to better understand the genetic and environmental factors that determine disease morbidity and mortality in humans (Hoffman et al., 2018).

Hoffman et al. (2018) reported a large-scale comparison of human and canine patterns of age-specific morbidity and mortality. Many common chronic human conditions, such as obesity, arthritis, hypothyroidism, and diabetes, were found to have a high degree of similarity to those in dogs. Significant similarities were observed in age effects on disease risk in humans and dogs, confirming that tumors and congenital and metabolic causes of death had similar age-related associations between the two species (Hoffman et al., 2018).

Dogs exhibit a pattern of cognitively impaired learning ability and memory decline similar to humans, and also develop amyloid plaques and cerebral amyloid angiopathy, but not NFTs (Bosch et al., 2018; Yu et al., 2011). Similar to humans, Aβ plaques are observed in normal aging dogs, and their accumulation has been strongly associated with cognitive impairment (Youssef et al., 2016; Colle et al., 2000).

There are significant individual variations in cognitive domain-specific vulnerability and severity of cognitive decline in aging dogs. Elderly dogs exhibit deficits in both reversal learning and visuospatial working memory, which are believed to be measures of declining frontal lobe function with age, in laboratory assessments using visual stimuli such as size discrimination. The dog's ability to remember and select the object that is closest or furthest to them was also found to be sensitive to age. However, not all cognitive functions decline with age, with older dogs performing similarly to younger dogs on simple visual discrimination or sequential learning tasks (Studzinski et al., 2006; Colle et al., 2000; Milgram et al., 1994).

The task that provides the most useful evidence for detecting age-associated dysfunction in laboratory procedures is spatial memory. Spatial memory requires the animal to first learn the location of a stimulus object and, after a period of time, whether it chooses the same object placed in a different location can be tested. By increasing the time interval between the original presentation of the target and the subsequent selection phase, elderly dogs require more prompting to remember and have difficulty with long-term delays (Chan et al., 2002).

Thus, elderly dogs exhibit a characteristic age-related decline in only some cognitive domains,

such as memory and executive functioning, and even among elderly dogs, some domains remained intact. This is similar to findings among elderly human subjects and those who develop Alzheimer's disease (Youssef et al., 2016).

Results of laboratory-based studies can be difficult to apply in real-world veterinary hospital settings. However, in several studies, veterinarians have used rating scale questionnaires and reported measurements of animals that were verified by pet owners by information gained from observations made at home. Based on previous studies using cognitive and behavioral aging assessment instruments in dogs, each appears to have promising potential in distinguishing between normal aging in dogs and abnormal behavioral changes indicative of cognitive dysfunction. Several behaviors have been identified as useful in diagnosing cognitive dysfunction in dogs, including walking, emotional expression, elimination behavior, daily rhythms, play behavior, exploratory behavior, learned specific behaviors, adaptive abilities, and interactions with other animals or pet owners (Bosch et al., 2012; Landsberg et al., 2012; Landsberg et al., 2005).

4. Conclusion

Improved levels of dog care have led to an increase in the number of older dogs, which in turn has led to an increase in age-related disease(s). Among these diseases, CCDS is similar to human Alzheimer's disease, and can significantly impact the lives of both dogs and owners. Much is known about Alzheimer's disease, not only from animal model studies, but also from real-world cases, which can be helpful in recognizing and managing CCDS. Due to the nature of the disease, CCDS can be difficult to recognize quickly without close attention and care. Although this disease is common, it is also severely underdiagnosed (Salvin et al., 2011).

The present article discussed the reported characteristics of CCDS, as well as the CCDR, used to assess characteristic clinical features and behavioral items according to the DISHA signs. In addition, studies investigating canine animal models of Alzheimer's disease—the most common neurodegenerative disorder in humans—have reported pathological similarities to CCDS.

As the number of elderly dogs increases, the number of senior-age diseases will only continue to increase, and it is important to be aware and prepared. If a pet exhibits suspected clinical DISHA signs, it is necessary to consult with a veterinarian to initiate active management. Furthermore, active clinical research is needed to inform the development of management and treatment strategies tailored to the domestic pet population and environment.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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