



The Canine Cognitive Dysfunction Syndrome: epidemiology, pathophysiology and diagnosis

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Abstract: Canine Cognitive Dysfunction Syndrome (CDS) represents a progressive neurodegenerative disease primarily studied in elderly dogs. CDS manifests various clinical signs within the behavioural realm, ranging from alterations in social interaction to disorientation and anxiety. This paper provides an in-depth exploration of CDS, encompassing its epidemiology, pathophysiology, and diagnosis. The diagnosis and management of CDS in ageing dogs present a significant challenge due to the wide array of nonspecific clinical symptoms and pathological signs associated with the condition. Recognising CDS as a neurobehavioral disease, where neurological signs and behavioural symptoms are intricately linked, is imperative, and early detection of cognitive impairment is crucial for successful treatment. Various screening questionnaires could play a pivotal role in objectively assessing cognitive decline, aiding in the identification and management of CDS. Further studies should investigate deeper the results of such tools, comparing the methods and reliability in both research and clinical environment.

Key Words: Canine Cognitive Dysfunction Syndrome; ageing; dog.

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Introduction

Canine Cognitive Dysfunction Syndrome (CDS), also referred to as Canine Cognitive Deficiency Syndrome, represents a progressive neurodegenerative disease primarily studied in elderly dogs, commonly known as ‘canine dementia.’ Some authors, like Salvin et al. (2011), characterise it as a neurobehavioral syndrome, emphasising the intimate connection between the pathology of the Nervous System and its impact on the animal’s behaviour. CDS manifests various clinical signs within the behavioural realm, ranging from alterations in social interaction to disorientation and anxiety. It’s noteworthy that many of these symptoms are shared with unafflicted, ill dogs, necessitating further investigation to discern the root cause. It’s crucial to distinguish CDS as a distinct disease rather than a typical geriatric condition experienced by all animals. While most mammals undergo age-related changes, not all succumb to CDS. For instance, Schutt et al. (2015) observed that only 33% of dogs aged eight years and older developed mild cognitive impairment, with a subsequent 22% progressing to CDS. Conversely, not all age-related behavioural symptoms can be attributed to CDS, as Landsberg et al. (2010) reported that among dogs over seven years exhibiting CDS-related symptoms, merely 12% were brought to the attention of a veterinarian by their owners. The pathological and clinical manifestations of CDS bear a striking resemblance to human Alzheimer’s Disease (AD) (Mihevc & Majdic, 2019):

- Both conditions are associated with the widening of cerebral sulci and ventricular enlargement (Toepper, 2017).
- They share characteristics such as neuronal loss and cortical atrophy in the cortex, hippocampus, and limbic system (West et al., 2000; Siwak-Tapp et al., 2008).

- Both CDS and AD exhibit a gradual onset, marked by a preclinical stage with pathological signs but devoid of clinical symptoms, progressing to mild cognitive impairment and culminating in dementia in both humans and canines (Bature, 2017).

This paper provides an in-depth exploration of CDS, encompassing its epidemiology, pathophysiology, and diagnosis.

Epidemiology of Canine CDS

Describing an accurate epidemiological profile of CDS poses significant challenges. As highlighted by Landsberg & Malamed (2017), the reporting rate by owners can introduce bias in the prevalence of the disease and its clinical signs. This bias is often influenced by the severity of symptoms, where mild clinical signs, of minimal concern or unnoticed by owners, may go unreported to the veterinarian. Salvin et al. (2010) illustrated this phenomenon through owners' interviews, where, among 957 respondents, 497 questionnaires were randomly selected. CDS was estimated in 14.2% of cases (68/479), but only 1.9% of cases (9/479) were brought to the attention of veterinary surgeons. Madari et al. (2015) further emphasised that pet owners tend to overlook signs of mild cognitive impairment until prompted by the veterinarian. This behaviour highlights two critical issues:

1. Owners may not be aware of symptoms in their ageing pets.
2. Veterinarians may not routinely inquire about potential behavioural concerns in ageing pets.

As a consequence, addressing owner awareness can be challenging, but refining veterinarians' anamnesis questionnaires could offer a valuable solution.

In the majority of CDS cases, dogs are over 8 years old and exhibit progressive cognitive impairment over several months. Dewey (2019) pointed out that current information on predisposition and risk factors is controversial. While some studies suggest a correlation between CDS and female gender, smaller size, others refute this association. Katina et al. (2017) observed in a group of 215 dogs (8-11 years old) that CDS onset was linked to diet, supporting the idea that providing high-quality commercial food tailored to the breed and size of the pet could mitigate cognitive damage. Another noteworthy correlation is between idiopathic epilepsy and the early onset of CDS (Packer et al., 2018; Vrinda et al., 2018), a finding of particular interest given its similarity to human Alzheimer's Disease.

Neilson et al. (2001) reported a prevalence of CDS ranging from 28% in dogs aged 11-12 years to 68% in dogs aged 15-16 years.

Osella et al. (2006) conducted a study on 124 dogs over 7 years old, not referred for behavioural consultation. Of these, 22 were excluded for non-CDS-related clinical issues. Among the remaining 102, 75 were suspected of CDS, but only 35 owners pursued a diagnosis.

Azkona et al. (2009) and Salvin et al. (2010) reported lower prevalence rates, ranging from 14.2-22.5% in dogs older than 8 years to 50% in dogs over 15 years old.

In a study in Thailand (Benjanirut et al., 2018), CDS prevalence ranged from 43% to 68% in dogs aged 7 to 12 years, increasing with age.

In conclusion, Benzal et Rodriguez (2016) reported an overall prevalence of 14.2% for CDS in dogs older than 8 years, potentially reaching 4% in subjects older than 14 years.

Pathophysiology of Canine CDS

While various pathological changes occur in the ageing brains of dogs, not all of these signs necessarily indicate Canine CDS. For instance, oxidative damage and ventricular enlargement,

as noted by Head et al. (2008), are associated with old age in dogs but are not directly linked to cognitive decline.

The accumulation of beta-amyloid presents conflicting findings. While many studies have linked senile plaque formation and neurofibrillary tangles to cognitive impairment, and consequently to CDS in dogs and AD in humans (Cummings et al., 1996; Head et al., 2008; Yamada, 2015), others offer different perspectives. According to Schutt et al. (2016), although beta-amyloid plaques were similar to those in early stages of AD, their load was proportional to age rather than the severity of cognitive impairment. Ozawa et al. (2016) suggested that CDS is associated with an increasing number and functionality of astrocytes and microglial cells rather than beta-amyloid levels. Two separate studies (Colle et al., 2000; Rofina et al., 2006) reported a correlation between senile plaques and the severity of CDS, but no link was found between senile plaques and the onset of CDS. In dogs older than 13 years, there was no statistical difference in senile plaque amount between those affected by CDS and those not affected.

As of now, the pathogenetic process of CDS has not been conclusively identified. According to Ozawa et al. (2016), the increasing level of ubiquitin in the brains of dogs affected by CDS could suggest a failure in protein homeostasis as the primary cause. This hypothesis is supported by the decreasing activity of the glymphatic system with increasing age (Toriello et al., 2020), the involvement of aquaporin-4 protein in the foot of astrocytes in protein homeostasis in the human brain, and its discovery in the canine species (Alvarez et al., 2021).

Despite the development of various theories over the last decade, further research is needed to clarify the main pathogenetic process and explain why, in a population of elderly dogs with similar neuropathological signs, only a portion of them are affected by CDS.

Clinical signs in Canine CDS

Cognitive impairment in dogs can manifest through various symptoms, many of which are not specific to CDS. According to Fast (2013), the four main owner-reported problems related to cognitive impairment are apparent confusion, anxiety, sleep-wake cycle disturbance, and alteration in pet-owner interaction. These findings, consistent with similar studies (Nielson et al., 2001; Salvin et al., 2010; Landsberg et al., 2012; Vite et al., 2014; Schutt et al., 2016; Chapagain et al., 2018), led to the development of the acronym DISH, representing Disorientation, Interaction with owner alteration, Sleep-wake disturbance, and Housesoiling. This acronym has been expanded to DISHA and further to DISHAA, adding Activity changes and Anxiety. In elderly dogs affected by CDS, similar to humans with AD, an increase in locomotor activity and a decrease in immobile time have been observed (Siwak et al., 2001; Rosado et al., 2011), along with memory impairment leading to learning and memory deficits (Studzinski et al., 2006; Milgram et al., 2011).

Common signs of CDS, as outlined by Dewey (2019), include inattentiveness, inactivity, compulsive wandering and pacing (especially at night), demented behaviour, urinary and/or faecal incontinence, difficulty navigating stairs, attempting to pass through inappropriately narrow spaces, inability to locate dropped food, getting lost in familiar environments, failure to recognize familiar people or animals, decreased interaction with family, apparent hearing loss, excessive vocalisation (especially at night), and acting senile. The latter is specific to demented subjects who exhibit abnormal mentation and respond inappropriately to their environment. Similar problems have been reported by Osella et al. (2006), Madari et al. (2015), Schutt et al. (2015), Landsberg et al. (2012 and 2017), and have also been incorporated into the Canine Dementia Scale (CADES), which will be discussed further.

In addition to behavioural signs, physical symptoms have been linked to CDS, with gait, posture disorders, and blindness being the main focus of studies (Kiatipattanasakul et al., 1996; Salvin et al., 2011; Montero-Odass et al., 2014). Through a web survey, Ozawa (2019) identified vision

impairment, smell disturbance, tremors, and falling as physical symptoms related to CCD. The wide range of behavioural and physical signs contributes to the challenge of diagnosing CDS accurately, leading to potential false positives and false negatives. Therefore, the development of a reliable diagnostic instrument is imperative.

Diagnose CDS

Given the wide array of nonspecific clinical symptoms and pathological signs associated with Canine CDS, diagnosing this condition can be challenging. The initial step involves ruling out potential medical differentials that may present similar behavioural symptoms, such as neurological diseases, musculoskeletal diseases, and endocrine or metabolic disorders (Landsberg et al., 2010; Salvin et al., 2011). A comprehensive diagnostic approach includes a complete blood count, serum biochemistry profile, thyroid level assessment, and urinalysis, with further investigations possibly including endocrine testing, radiographs, ultrasound, and advanced imaging (Landsberg, 2017).

According to Dewey (2019), magnetic resonance imaging (MRI) stands out as the most useful imaging test for diagnosing CDS. Despite owner reluctance due to perceived risks for geriatric pets and the associated costs, MRI results have proven promising. Measurements of the thickness of the interthalamic adhesion and its ratio with the height of the brain and lateral ventricle serve as predictors of CDS (Hasegawa et al., 2005; Noh et al., 2017).

Behavioural tests, while accurate in measuring canine cognitive impairment based on the dog's signal and history, may not always be practical for clinical use. The Delayed Nonmatching to Position (DNMP) memory task is an example of such a test. It assesses short-term visuospatial working memory and involves two stages:

1. the sample stage, where the subject displaces one out of three objects to receive a reward
2. the test stage, where the subject must displace one out of two objects, now located over the position of one of the two previously incorrect objects, to receive a reward.

Between the two stages, there is a small delay (generally starting from 5 seconds) that increases every time the subject completes the task correctly, once it learns to choose the non matching object. The DNMP test has been observed to assess cognitive impairment in dogs as young as 6 years old and is associated with altered sleep-wake cycles, increased stereotypy, and changes in interaction with humans, similar to CDS (Cretin, 2018; Katina, 2017; Vrinda, 2018). Another behavioural test, the Food Searching task, has shown promising results, especially for clinical use (Gonzalez-Martinez et al., 2013).

CDS Scales

The challenges presented by CDS in ageing dogs underscore the need for reliable assessment tools to facilitate early diagnosis and effective management. CDS Scales refer to standardised tools designed for the assessment and quantification of cognitive dysfunction in ageing dogs (Madari et al., 2015). These scales aim to provide an objective and comprehensive evaluation of various behavioural changes associated with canine cognitive decline. CDS scales comprise a set of easily administered tests, including assessments of spatial orientation, social interaction, and response to specific stimuli. These scales allow veterinary surgeons to efficiently evaluate cognitive function during routine examinations, enabling early detection and intervention in dogs experiencing cognitive decline. Various screening questionnaires have been developed for assessing canine cognitive decline.

- Pugliese et al. (2005) introduced a rapid behavioural test assessing CDS severity, correlating each disease stage with modifications in cerebral energy metabolism.

- Rofina et al. (2006) analysed previous questionnaires, investigating correlations between scores and various cerebral parameters in geriatric dogs.
- Osella et al. (2007) amalgamated previous questionnaires to explore CDS clinical sign prevalence in an elderly dog population.
- Salvin et al. (2011) developed the Canine Cognitive Dysfunction Rating scale (CCDR), identifying key behavioural signs based on a survey of over 900 dogs aged 8 years or older.
- Madari et al. (2015) devised the CADES for objective cognitive impairment assessment in 215 dogs aged 8 years and older, aiming to create a tool free from owner bias, in contrast to CCDR.

These rating scales play a crucial role in providing a standardised and objective means of assessing cognitive function in ageing dogs, aiding in the identification and management of CDS.

Conclusions

The enduring companionship between dogs and humans over millennia has fostered the development of a profound bond between them (Pörtl et al., 2017; Jung et al., 2018). As demonstrated by numerous studies (Carlone et al., 2019; Mariti et al., 2013a; Mariti et al., 2013b; Mariti et al., 2014; Mariti et al., 2017; Mariti et al., 2018; Mariti et al., 2020; Riggio et al., 2021; Riggio et al., 2021a; Riggio et al., 2021b; Riggio et al., 2021c), this attachment underscores the unique and enduring nature of the human-dog relationship, adding a layer of complexity and emotional significance to the understanding and management of cognitive decline in our canine companions. The diagnosis and management of CDS in ageing dogs present a significant challenge due to the wide array of nonspecific clinical symptoms and pathological signs associated with the condition. Recognising CDS as a neurobehavioral disease, where neurological signs and behavioural symptoms are intricately linked, is imperative, and early detection of cognitive impairment is crucial for successful treatment (Osella et al., 2007). Various screening questionnaires, such as the CCDR by Salvin et al. (2011) and the CADES by Madari et al. (2015), could play a pivotal role in objectively assessing cognitive decline, aiding in the identification and management of CDS. Further studies should investigate deeper the results of such tools, comparing the methods and reliability in both research and clinical environment.

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La Sindrome di Disfunzione Cognitiva nel cane: epidemiologia, patofisiologia e diagnosi

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Sintesi

La sindrome da disfunzione cognitiva canina (CDS) rappresenta una malattia neurodegenerativa progressiva studiata principalmente nei cani anziani. La CDS manifesta vari segni clinici nell'ambito comportamentale, che vanno dalle alterazioni nell'interazione sociale al disorientamento e all'ansia. Questo articolo fornisce un'esplorazione approfondita della CDS, comprendendone l'epidemiologia, la fisiopatologia e la diagnosi. La diagnosi e la gestione della CDS nei cani anziani rappresentano una sfida significativa a causa dell'ampia gamma di sintomi clinici e segni patologici non specifici associati alla condizione. Riconoscere la CDS come una malattia neurocomportamentale, in cui i segni neurologici e i sintomi comportamentali sono strettamente collegati, è imperativo e la diagnosi precoce del deterioramento cognitivo è cruciale per il successo del trattamento. Vari questionari di screening potrebbero svolgere un ruolo fondamentale nella valutazione oggettiva del declino cognitivo, aiutando nell'identificazione e nella gestione della CDS. Ulteriori studi dovrebbero indagare più approfonditamente i risultati di tali strumenti, confrontando i metodi e l'affidabilità sia nella ricerca che nell'ambiente clinico.