Chapter 25

Cognitive Dysfunction Syndrome in Senior Dogs

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1. Introduction

Human history has been closely linked to some animal species, and very specifically to dog. This close relationship has endured, therefore the dog is considered the domestic specie closest to man, because for today plays socially important roles as a member of many families and / or as executor of activities that helps or facilitates human life. However, this closeness to man has promoted, either by love or not, that care provided to dogs is increasing, and therefore on the increase in life expectancy of these animals [1].

However, just as in humans, increased life expectancy of dogs, is often associated with behavioral disturbances and cognitive deficits related with clinical signs of disorientation, loss of social interaction, sleep disturbances, decreased general activity and progressive loss of acquired memories [2-3]. Initially, these behavioral changes have been assumed by some veterinarians, as evidence of senility [4]. It was recently proposed the term "Cognitive Dysfunction Syndrome of Geriatric Dogs" (CDS), to describe the cognitive deficits observed in some geriatric dogs [2,3,5,6], which seems being closely related with Alzheimer's disease (AD), therefore, it is likely that CDS can be known as Dog's Alzheimer's disease [7,8,9,10]

Cognition refers to mental processes such as perception, consciousness, learning, memory and making decisions, it allows obtaining information from the environment in order to interact normally with environment [11, 12, 13, 14]. Nevertheless, cognition alterations could be considered by some owners, as "normal" signs of aging, so these symptoms are always not informed to veterinarian. Other common modifications are inability to recognize the family members and to perform easy tasks such as eating and exercise, sleep-wake cycle changes are common too [15]. These behavioral modifications can cause limitation of social interaction of dogs; consequently can lead to rejection of certain owners to take care of these patients, so increasing the risk of some pets to be sacrificed.

To date it has been identified several similarities between CDS and AD, therefore it has been suggested that studies of geriatric canines that suffering CDS, could be a useful tool for recognizing clinicopathological aspects yet not clarified of AD, and thereby possibly give more effective management to disease [17-18]. However, despite the many similarities, there are also some important differences, such as the involvement factors that predispose to humans, but not dogs to diseases like EA. These factors including, gender [19] and background family [20].

Despite the large contribution that means owning a dog as the experimental model, which develops a disease with many similarities to that seen in humans [17], shall be taken into account that the results obtained from the use of this model is not always reflect a completely accurate information. Therefore, there are several voices that suggest that the results obtained in animals cannot always be extrapolated to humans because the techniques used to assess cognitive functions differ in their ability to describe functions such as perception, discrimination, storage and retrieval of cognitive flexibility [10]. However, after considering the possible similarities and differences in EA and SDC, this chapter is to describe in detail the clinical and patho-physiological characteristic of this canine dementia syndrome, likewise presents diagnostic and therapeutic tools that seek to stop the progression clinical signs of the disease, as well as discuss their clinic-pathologic similarities with the EA, and finally, discuss the facts that today are considered to CDS as a valid experimental model for human neurodegenerative diseases.

2. Clinical features

The behavioral abnormalities in geriatric dogs, are sometimes considered as traits of aging process, however, it is important to differentiate between those behavioral alterations that are related to serious damage of cognitive processes and slight decrease in psychomotor activity or "normal aging" [2,13,15,16]. The intensity which behavioral changes affect each animal, are characteristic of each patient and it is possible to identify a big variety of cognitive impairment, for example, some dogs are unable to distinguish to family's members, whereas others dogs, with lesser cognitive deficits, are able to remember instructions learned during training [17].

It is probably that altered urination habits, but not defecation habits, are the most frequent signs observed by owners in pets that suffering CSD [17], nevertheless, polyuria can occur without renal system diseases or without secondary environmental changes that prevent access to appropriate area of evacuation.

Other common signs reported are episodes of confusion and disorientation [18], in which pet gets lost in house or garden, going to wrong door or wrong side of the door. Clinical signs include reduced interaction with owners, slowness to obey orders, alterations in the sleep-wake cycle, excessive vocalization, exercise intolerance, difficulty climbing stairs, increased irritability and new fears or phobias. [17,18].

Besides in wide variety of behavioral alterations reported, some authors have suggested to use rating scales for diagnosing CDS in dogs, as proposed by Landsberg [3]. Landsberg's method

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sorts clinical signs in following topics: 1. Spatial disorientation and / or confusion, 2. Impaired learning abilities and memory (loss of home grooming habits, incompetence to obey certain orders or previously learned tasks), 3.Decreased activity or repetitive activities, 4.Alteration and reduction of social interactions, 5.Decreased perception and / or responsiveness, 6.Increased anxiety or restlessness, 7.Alteration of appetite associated with confusional states that could prevent to find their food, 8.Alteration of day-night cycles (sleep-wake) [19, 20].

3. Prevalence

The life expectancy of humans and dogs has increased steadily over the past decades, due to improved medical and health conditions available [21]. However, this increase in life expectancy has increased the prevalence of certain diseases related to aging, such as AD and CDS.

Therefore, after considering reports that suggest world presence of 52 million dogs around 7 years old [22], and taking into account that dogs over 7 years old could be considerate in geriatric condition, it is possible to suppose that these both conditions could generate a big population with great risk to suffer CDS [20. 23]. Some regional studies, have designed and implemented various observational questionnaires, for the geriatric canine pet owners, that try to identify behavioral changes in their pets and achieving determine CDS prevalence in animals evaluated. Recently, an Italian study that included 124 geriatric dogs, revealed prevalence about 50% of CDS, 75 dogs older than 7 years showed signs consistent with CDS [13]. Similarly, another study [1] conducted with 180 dogs between 11 and 16 years old, reported that 28% of dogs between 11 and 12 years showed some degree of cognitive impairment, while those individuals between 15 and 16 years had a probability close to 68% to develop CDS, these data suggests a close relationship between the aging process and likelihood of developing SDC.

However, although researches mentioned above are obviously important, it is worth noting that their impact is restricted to local areas where researches were develop and, therefore, data on the global prevalence of CDS have not yet been achieved, in part, due to tendency of pet owners to not report to veterinarian the possible behavioral changes in geriatric pets [13], which probably has limited accurate data to estimate the prevalence of CDS to worldwide.

4. Patho-physiological basis of CDS

To date have been identified several pathophysiological changes that matching for diseases such as AD and CDS. Neurodegeneration defines pathological neural death observed in several neurodegenerative diseases such as CDS, which is characterized morphologically by a decrease in the number of cholinergic neurons in hippocampus and cerebral cortex (areas especially related with changes in behavior and cognitive memory) [3.24]. Although the causes of neuronal death is unknown, some authors have suggested to oxidative

stress and accumulation of beta-amilode peptide (βA) as possible causal factors of clinical signs observed in CDS [2].

βA peptide, which plays an important role in pathophysiology of canine dementia [2,8,25-26] and AD [2], generates its neurotoxic effects by intra-neuronal accumulation [6], hence, it induces degeneration of cholinergic neurons and it seems that quantity of accumulated βA is associated with severity of clinical signs [1,10, 23,25,27, 28]. Reactive oxygen species (ROS), which are recognized as inductors of oxidative stress, has been involved in presentation of CDS and other demential syndromes as AD. Oxidative stress induces its deleterious effects on neuronal cells and their effects are similar in dogs and older adults [2]. Mitochondria is the first organelle involved in production of ROS due to its aerobic metabolism [29], nevertheless, other sources could be also considerating as metabolic sources of ROS generation, such as peroxisomes and release of oxidants by neutrophils. Similarly, exogenous influence such as ionizing radiation, pollution and carcinogens, can contribute to production of free radicals in mammalian systems [30].

According to some authors, oxidative damage is a key mechanism for development of diseases associated with age that cause cognitive dysfunction [31]. Brain is highly predisposing to suffer lesions induced by oxidative stress because it is common accumulation of oxidants substances and because it is probably that protective mechanisms, such as superoxide dismutase and vitamin E, can be less efficient to prevent alterations induced by oxidative stress [32], and thus FR could potentially damage neuronal function causing cell death [2]. Neuronal death leads to uncontrolled release of excitatory neurotransmitters such as acetylcholine, involved in practically all cognitive functions especially in the memory, dopamine, which is associated with control of movement (motor); norepinephrine, associated with wakefulness, attention and serotonin, which is related to mood and sleep control [23,24,33,34]. In this sense, it is possible suggest that neurochemical changes which occurring in brain of aged patients, are the responsible of severity and clinical manifestation in patients with CDS.

5. Pathological lesions

Many morphological features which occur in brains of old dogs are similar to those observed in the brains of aged humans [34]. These changes, which are related to age, include cortical atrophy and increased ventricular spaces, morphological changes in meninges and choroid plexus, changes in cerebral and meningeal vasculature; it is also evident degraded protein accumulation and DNA damage [43 - 44.16]. Other lesions in dogs include inflammation of meninges, gliosis, amyloid deposits, degeneration of myelin in white matter and accumulation of oxidative stress products which have a close relationship with apoptotic processes. Apoptotic cell death has been described in brains from AD patients and in geriatric dogs affected with CDS. Neuronal death by apoptosis processes is related to amyloid accumulation, and according to various authors, may be the main responsible factor for age-related dementia [1]. These morphological changes are related to the characteristic signs of dementia in dogs [2,37, 41,42,45], therefore these has received much attention from researchers who have considered dog as a model for studying human neurodegenerative diseases [29].

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In contrast, brains of patients with AD show neurofibrillary plaques and intra-neuronal formation of tau protein products. Tau protein normally is a essential constituent of cytoskeleton in neurons [46], however, in people with AD, protein is hyper-phosphorylated, then it starts a process which induces formation of paired helical filaments which saturate the cytoplasm and induce destruction of microtubules and neurodegeneracion [47-49]. Neurofibrillary plaques are rare in other species and their presence is a major difference between CDS and AD, especially because dogs not develop these structures, because tau's protein sequence is different in dogs and human beings, it could affect formation of neurofibrillary plaques. However, recent studies suggest presence of immature nascent plaques in brains of aged dogs [2,5].

6. Pathological lesions

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Neurochemical changes such as low levels of dopamine, norepinephrine, serotonin, acetylcholine, choline acetyl-transferase and decreased number of D2 receptors, are characteristics that are commonly observed in CDS and AD [34]. However, there are disease-specific changes as decrease of muscarinic receptor number [46] and increase of activity of enzyme acetylcholinesterase, which are factors present only in AD [47]. In

contrast, in affected dogs have been detected increased MAO activity and increased sensitivity to glutamate neurotransmitter, which is capable of initiating processes neurotoxicity [23]. However, the most consistent alteration in brains of dogs and humans with AD is βA peptide accumulation in hippocampus and frontal cortex (areas especially related cognitive behavioral changes) [10, 48]. In neuron, βA is initially concentrated in microdomains of plasma membrane in neurons of the prefrontal cortex and subsequently affects other brain regions such as the parietal and entorhinal cortices [49].

7. Diagnosis

Veterinarians commonly faced with behavioral disturbances in older dogs, however, although it is true that CDS may be the main responsible for these changes, it is also true that behavioral disturbances could be induced by other multifactorial causes [6,10,28]. Therefore, considering the variety and inspecificity of clinical signs associated with CDS, it is important to use clinical history for obtain patient-specific data, which ensures that owners had provided a complete list of all medical and behavioral signs observed in their pets. This information could provide a solid support in finding potential medical problems that may be responsible for the development or exacerbation of clinical signs [3], furthermore this information along with clinical and neurological examination, which can be developed using assessment tests cognitive, may let to veterinarian obtain an early diagnosis [23].

However, we must emphasize difficulty for obtaining accurate information, because in many cases information obtained from pet owners could be little objective, possibly leading to false diagnosis. Thus, shortage of reliable diagnostic tests to ensure presence or absence of disease, gives to early identification of clinical signs a crucial role in establishment of effective treatment, capable of improvement the quality of life of affected patients. In this sense, and according to some authors, the most effective way to detect the condition is through the routinely establishment of behavioral questionnaires in geriatric dogs [2.10]. These questionnaires that ask to owners about your pet's behavior, which have been obtained from various researches [15.35], pretend classifying the behavior of affected patients. Within these cognitive evaluation questionnaires, neuropsychological tests are looking classify systematic cognitive impairment through methods such as modified apparatus of Wisconsin General Test (University of Toronto), in which the dogs are rewarded for each correct answer they obtain. Overall, in this test the dogs have access to a removable tray containing three food wells built in, which can be covered to test visual learning and memory [50, 51].

These neurophysiological tests allow assessment objective and quantitative of deficits in learning and memory, without relying on questionnaires applied to owners. These evaluation tests look for three specific objectives: 1. Identification of non-subjective cognitive changes that are characteristic of aging in dogs, 2. Characterization of the neurobiological basis of decline in cognitive abilities due to aging, and 3. Preparation of potential interventions in order to eliminate or minimize the adverse effects on quality of life [2, 50, 51].

Although learning and memory are quite susceptible to decline with aging, it is necessary evaluating too the spatial memory (the ability to remember the location of food, for example) and the object recognition memory (the ability to recall objects seen with 10-120 seconds ahead) [10], because it is well accepted that these both two memory types are affected in neurodegenerative processes, therefore several studies have developed scales that evaluate the spatial memory and the recognition abilities for indirect evaluation of dementia in dogs [52]. For example, it has been proposed a dementia evaluation index that discriminates between normal, pre-dementia and dementia states [17]. ARCAD scale (assessing cognitive and affective disorders associated with age), where dog's behavior is assessed indirectly through a questionnaire applied to owner, in order to assess the deficit by a scale evaluation of 1 to 5 [53].

Although various tests have shown be able to diagnose the cognitive dysfunction syndrome, we must consider that the results obtained with each test, can vary according to the test, it is possible that cognitive skills, may have a different meaning on the outcome of the test [11.13]. Moreover, besides the possibility to compare results obtained in each test, it is necessary to correlate the results of behavior modifications in dogs examined with paraclinical test results, such as electroencephalography. This relationship could establish whether the test results are able to correlate disturbances in learning, memory and cognitive with disorders of brain circuits that are involved in CDS. It is possible that paraclinical tests can predict dysfunctional brain diseases in dogs?

Finally, it is worth mentioning that several cognitive domains that are affected during the CDS (language, memory, visuospatial skills) and observation of a sign, is not sufficient for beginning a treatment. However, the onset of cognitive impairment in some specific domain could be related into a worsening of other existing signs, therefore it is important following up clinical evaluations routinely [10].

In conclusion, to determine if a dog shows signs of cognitive dysfunction, the veterinarian must rely on information provided by the owner in the medical record, however, the design and implementation of a questionnaire, and possibly paraclinical tests, are necessary to detected signs of CDS during the early stages of development, especially if it comes from animals that have previously had a high level of training [3].

8. Therapeutic alternatives for the treatment of CDS

Currently there are several therapeutic strategies that have been developed along different studies in geriatric dogs affected by CDS.

9. Behavioral type therapy

One consequence of age-associated diseases in dogs is loss of memories acquired during professional or home training, therefore dog may lose its ability to perform simple tasks or to

answer previously learned commands. Faced with this kind of behavioral changes, which may be observed in patients with CDS, the establishment of behavioral therapy, in the early stages of the disease, has been suggested as appropriate, when it is accompanied with additional therapeutic tools like drug treatment. Re-training dogs with cognitive dysfunction requires patience and it is necessary to use simple commands with a clear reward and it is important that re-training begins as soon as possible to prevent the development of unwanted behaviors in the dog [2.6].

10. Pharmacological treatment alternatives

Drug therapy is aimed, on the one hand, restoring neurotransmitter concentrations and, on other hand, preventing too rapid advancement of neurodegenerative process [54, 55]. Most treatments used for people affected with AD, have not yet been tested in dogs, nevertheless it is necessary perform clinical studies which be able to clarify which treatments work and which do not. However, there are some options available as selegiline, this was the first therapeutic agent approved by the FDA in 1998 for use in dogs [5.56], this is a selective irreversible inhibitor of the enzyme monoamine oxidase B (MAO B) which increases the concentration of dopamine in brain and it seems to prevent oxidative stress, therefore it could decrease neuronal death. The therapeutical efficacy of selegiline has been shown by studies that verify a decrease in the progression of degenerative changes in AD patients and a significant improvement in dogs with CDS [1]. Therefore, regulating the concentration of neurotransmitters has been considered the main therapeutic alternative for treatment of CDS in dogs, nevertheless, it is possible that new studies could verify a major efficiency of other drugs, for example drugs with anticholinenterase activity or NMDA blockers drugs, which have been effective for treatment of AD, could be could be effective for dogs.

11. Nutritional therapies

After recognizing the role of ROS (reactive oxygen species) in neurodegenerative diseases, some researchers have recommended reduce the amount of free radicals formed from exogenous influences or include in habitual diet nutritional supplements capable to scavenge ROS, nowadays it is well accepted which these supplements can maximize the benefits of psychopharmacological therapy, improving quality of life promoting positive changes in behavior of canines that suffering CDS [5, 57].

Within the beneficial effects attributed to the antioxidant products, could be considered potentiating of mitochondrial function during aging, which resulting in decreased production of ROS [2-3,8,58]. As a result of these effects, some authors have suggested that dogs suffering CDS, and have received a supplement of antioxidants in diet, show an improvement in cognitive ability [59]. Besides, a variety of studies have shown that intake of fruits and vegetables may decrease the risk of cognitive declines associated with age in rodents, dogs,

and even humans, attributing this property to its antioxidant and anti-inflammatory capabilities [3,5,58].

There are several compounds which have been described their antioxidant activity, among them we can mention the vitamins E and C, beta-carotene, selenium, L-carnitine and alpha lipoic acid, all them have shown to improve mitochondrial function and likely by some neuroprotective effect it is explains the improvement of memory. Similarly, some authors suggest that GingkoBiloba, besides possessing antioxidant effect, has a variety of properties such as anti-inflammatory, cerebral vasodilator, mitochondrial function enhancer and MAO enzyme inhibitor [3,13,60], therefore, it has been suggested that GingkoBiloba could reduce the severity of clinical symptoms observed in patients with CSD. Additionally, natural compounds of animal origin, such as propolis, which our research group studies its neuroprotective properties, currently are valued for their antioxidant and neuroprotective qualities [61], however, there are still no studies describing the positive effects of this compound on CDS.

Other group of compounds with ROS activity is composed of certain molecules classified as mitochondrial cofactors (acidolipoico, L-carnitine) which can potentiate the function of mitochondria, resulting in a lower production of ROS during aerobic respiration. Nutritional supplementation with these mitochondrial cofactors induces their cell acumulation where they restore mitochondrial efficiency and reduces oxidative damage to RNA [62]. It has also been suggested the use of mitochondrial cofactors along with antioxidants, in order to cause an improvement in learning processes and memory, through a synergistic action [19].

It is probably the best evidence of positive effect of dietary supplementation on cognitive impairment in dogs, was found after applying neuropsychological tests for a period exceeding two years. The study aimed to supplement diet of dogs with mitochondrial cofactors and antioxidants of broad spectrum to enhance antioxidant defenses and reduce ROS accumulation. Results indicated that these products slowed the age associated cognitive decline [3]. However, to develop a diet supplemented with antioxidants, it should be noted that the selection of components, the ranges of dosage and route of administration, vary considerably between species. Also, some antioxidants are absorbed more quickly than others, species-specific factors, metabolic differences due to inherent bioavailability: thus, different species may benefit from different types of antioxidants, but not all species may benefit from the same antioxidants [2].

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