



# Cognitive Dysfunction Syndrome in old dogs

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*Abstract:* Cognitive Dysfunction Syndrome in old dogs is a pathology from which dogs will more easily suffer, and whose symptoms dogs' owners will have to learn to recognize because dogs' average life is increasing more and more thanks to the considerable improvements in terms of nutrition and of lifestyle. Cognitive Dysfunction Syndrome is a multi-factorial pathology: genetic, environmental and food causes play a determinant role in creating the conditions for the onset of the symptoms; in fact, prevention passes through the improvement of these aspects. Different brain areas are affected and the mechanisms with which the brain tissue is damaged are several. Cognitive Dysfunction Syndrome is characterized by the fact that it is similar to Alzheimer's disease in man, both for what concerns the causes, the pathogenic mechanisms, the affected brain areas and prevention, so much to be used as respective study model.

*Key Words:* dog, ageing, cognitive dysfunction

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## Introduction

Ageing is a process which regards each living species; since it has been studied, ageing has been defined in a lot of different ways: physiological rather than pathological process (Wright et al., 1996); process characterized not only by a loss of functions (senescence), but also by an acquisition of functions (development and growth) (Bowen & Atwood, 2004); process determined by specific genes, which influence the activity of the nervous, endocrine and immune systems (genetic theory) or process mainly influenced by the environment (error theory), to which the random damage of the molecules would add (Weinert & Timiras, 2003).

Ferrara et al. (2005) have summed up the theories that would explain ageing in man: the "redundance" phenomenon, the gene-regulation theory, the theory of evolution, the free-radical theory, the neuroendocrine theory, the theory of the ageing of dismissible bodies, the immune theory.

The dog's ageing could be explained starting from the hypothesis already seen for man, but other factors are involved: size, breed, weight, food as well as lifestyle. Careau et al. (2010) have found a correlation between breed and metabolism, due to which the most "docile" breeds have a longer life expectancy than more "aggressive" breeds: in the first ones metabolism is slower and energy needs are lower. Artificial selection in dogs carried out by man has fostered the appearance of recessive genetic mutations, this is the reason why purebred dogs live less than mixed-breed dogs of the same size (Patronek et al., 1997). The insulin-like growth factor (IGF1) would foster the selection of bigger-sized specimens but with shorter life expectancy because these entities are characterized by a high growth speed, which predisposes to a higher rate of chromosome alterations and, as a result, to a higher probability to develop cancer (Szabò et al., 2016).

From this quick examination it is possible to infer that ageing must be considered as a multifactorial complex process, in which a lot of mechanisms are relevant and interact (Kowald & Kirkwood, 1996).

Despite the processes determining or influencing it, ageing can be differentiated into: “successful ageing” (absence of pathologies and absence of any minimal functional cognitive loss); “physiological ageing” (absence of pathologies with presence of functional decline); “pathological ageing” (presence of organic diseases and of physical and cognitive disabilities). It is obvious that each species aims at reaching the successful ageing, because in that the organism maintains the ability to respond to environmental stimuli in a proper way managing to live longer and in a healthy way (Waters, 2005).

## Anatomical lesions

Cognitive Dysfunction Syndrome in old dogs is caused by the damage to the brain tissue. Different brain areas are affected: the prefrontal cortex, the temporal cortex, the occipital one, the fascia dentata hippocampi are affected by degenerative processes which lead to the death of neurons and reduce neurotransmitter-system function (Siwak-Tapp et al., 2008; Josephs et al., 2011; Mad’Ari et al., 2017). The affected tissues undergo metabolic, neurotropic, structural and vascular modifications. The following modifications occur:

- loss of neurons (due to necrotic and apoptotic processes), together with the reduction of neurogenesis (Head, 2011), with consequent brain atrophy (Youssef et al., 2016);
- accumulation of pathologic proteins (hyperphosphorylated and insoluble tau protein) in cell cytoplasm of neurons (Youssef et al., 2016) and reduced efficiency of “Ubiquitin Proteasome System” of the Hippocampus, which cause the alteration of the normal physiology of the nerve cell, with consequent decrease of cognitive abilities of the old dog (Ghi et al., 2009);
- deposition of  $\beta$ -amyloid plaques in prefrontal, temporal and occipital cortex with consequent cognitive and behavioral changes of the affected dog: appetite, memory, orientation, social interaction, house-soiling are the most involved behavioral aspects (Rofina et al., 2006). The deposition of  $\beta$ -amyloid plaques and the hyperphosphorylation of the tau protein are processes which can co-occur simultaneously during ageing, but they are independent from each other (Pugliese et al., 2006);
- brain-tissue vascular pathologies (deposition of  $\beta$ -amyloid plaques in perivascular area and calcification of capillaries, arterioles and venules), which cause loss of myelin (Colle et al., 2000; Youssef et al., 2016), decrease of blood-brain barrier function and microhaemorrhages (Nichol et al., 2017);
- oxidation processes caused by the production of free radicals inside the neuronal cell, which involve damages of proteins, lipids and of cell nucleotides. A decreased efficiency of antioxidant enzyme systems worsens the cell damage causing nerve demyelination and white-matter damage (Head et al., 2008). A research by Skoumalova et al. (2011), states that, in man, from the interaction between free radicals and cell proteins and lipids Lipofuscin-Like Pigments are generated and that these pigments concentrate also in erythrocytes of people suffering from Alzheimer’s disease. This discovery has enabled to use LFPs as biomarkers of Alzheimer’s disease. This is not possible in dogs, even if LFPs have been found also in erythrocytes of patients suffering from Cognitive Dysfunction Syndrome and their toxicity for erythrocytes has been proved: it is not sure that these pigments are responsible for the oxidative damage of dog brain tissue (Skoumalova, 2003);
- the old dog’s brain tissue can also be affected by inflammatory processes, from whose severity, measured from the astrocytosis level, may depend the intensity of the dog’s cognitive deficit (Pugliese et al., 2006);

- neurotransmitter systems can be damaged too: in particular a loss of serotonergic neurons is observed, above all in dogs in which the deposition of  $\beta$ -amyloid plaques in the prefrontal cortex takes place (Bernedo et al., 2009). A loss of noradrenergic neurons has been observed in old dogs suffering from cognitive dysfunction (Insua et al., 2010). Consistent losses of neurons occurs also in the GABAergic and cholinergic systems (Arajuet et al., 2005), these are linked to decreases of attention and memory capacities, responsible, in turn, of the lower ability of old dogs to elaborate new information.

## Behavioral signs

All these pathologic processes characterize, in a more or less intense measure, the Cognitive Dysfunction Syndrome in old dogs determining a series of behavioral symptoms, whose severity depends on the intensity of the same processes as well as on the extent of the affected brain areas. It is important to underline that a lot of the symptoms characterizing the Cognitive Dysfunction Syndrome can be caused also by other organ pathologies (Rofina et al., 2001), a pain caused by otitis or a pain of neuro-musculoskeletal origin can trigger aggressive responses as a reaction to a stroke; an important decrease of the auditory and visual functionalities can alter the dogs' usual perception of their environment and thus lead them to show fears, anxieties, aggression and other adjusting strategies, which had never been shown before (Table 1).

**Table 1.** Behavioral issues linkable with medical problems according Landsberg et al. (2017).

System	Possible causes	Possible behavioral signs
<b>Sensory</b>	Cataracts/lenticular sclerosis	Fear/anxiety
	Loss of vision	Disorientation
	Loss of hearing	Decreased response to stimuli
		Reduced learning ability
		Aggression
		Avoidance
Vocalisation		
<b>Pain/musculoskeletal</b>	Degenerative diseases	Avoidance
	Arthritis	Reduced interest in exercise or play
	Muscular dystrophy	Altered response to stimuli; aggression
		Reduced self-hygiene
Increased vocalisation		
<b>Cardiovascular</b>	Mitral insufficiency	Disorientation
	Hypertension	Tiredness or reduced interest in play and activity
	Cardiomyopathy	Withdrawal/avoidance
		Irritability
		Vocalisation
		Changes in appetite
Fear/anxiety		

<b>Endocrine</b>	Diabetes mellitus	All signs of cognitive dysfunction
	Insulinoma	House soiling/urine marking
	Diabetes insipidus	Appetite—increased/decreased
	Hypothyroidism	Activity—increased/decreased/apathy
	Hyperthyroidism	Irritability
	Hyperadrenocorticism	Aggression
	Hypoadrenocorticism	Sleep-wake cycle Stereotypic—licking Restlessness—pacing Vocalisation
<b>Digestive</b>	Dental diseases	Reduced appetite
	Hepatic diseases	Aggression/irritability
	Infectious/inflammatory	Avoidance/withdrawal
	Constipation	House soiling
	Nutritional imbalances	Night-time waking
	Pain	Stereotypic—pacing/licking Coprophagia
<b>Urinary</b>	Urinary tract infection	House soiling/markings
	Idiopathic cystitis	Withdrawal/avoidance
	Urolithiasis	Pacing
	Urinary incontinence	Sleep-wake changes
	Urinary tract infection	Aggression

In old dogs the behavioral modification can remain even when the medical cause has been solved. This is due to the fact that the dog has learnt that the new behavior (above all the aggressive one) represents a winning social strategy. The medical therapy is thus useful also for the diagnosis of the Cognitive Dysfunction Syndrome: if the behavioral problem disappears, it means it was determined by the medical cause. If it persists, there is the learning of a new behavioral strategy or there may be two problems: a medical one and a behavioral one, which are not interconnected (Landsberg et al., 2013). In light of these considerations, it is of vital importance to submit the old dog with suspect of Cognitive Dysfunction to medical examinations in order to rule out other possible causes not due to ageing.

The behavioral symptoms can be distinguished into two groups. In the first one there are the ones that have a big impact on the dog's health and, as a result, on the dog – owner relationship (they are less frequent, but they are more reported: aggressions, change of the sleep-wake cycle, house soiling). The second group includes minor behavioral modifications and which have a lower impact on the dog – owner relationship (they are reported less even if they are more frequent: decrease of physical and exploration activity, less search of social contacts) (Landsberg et al., 2017).

The behavioral patterns more reported by owners of old dogs suffering from Cognitive Dysfunction Syndrome are:

- spatial disorientation
- hyperaggression
- decrease of physical and exploration activity (Rosado et al., 2012)
- variation of the sleep-wake cycle
- loss of acquired habits (house soiling)
- less interest for social interactions: about this a research by Mongillo et al. (2013) has pointed

out that the decline of the sensory abilities together with the physical and psychic weakness make the old dog less able to adapt to emotional stress. A consequence would also be anxious behavioral modifications such as separation anxiety.

## Diagnosis

Once excluded the medical cause of behavioral modifications, the diagnosis is defined by means of specific questionnaires filled in by the owners. Some problems have been pointed out about the questionnaires. One of the problems is that there are different versions, with different items, which are classified and evaluated differently (Szabò et al., 2016).

Another problem is about the cooperation given by the owners: they are prone to fill in questionnaires with fewer items, even if the longer ones are more accurate and give more precise results. Owners are also prone not to tell their veterinarian about the problem (Mad'Ari et al., 2015), because they do not notice the behavioral modification, or because they consider it physiological for the dog's age, or because they think there is no therapy. This situation has been confirmed also by a research by Landsberg et al. (2013), according to which on a sample of 255 owners of dogs over 8 years old, only 17% of those who recognized at least one behavioral symptom has informed their veterinarian. The problem gets worse if you think that only a minor part of those who refer the symptoms to their veterinarian accept to see a behavioral veterinarian (Osella et al., 2007): from all this you can say that Cognitive Dysfunction Syndrome cases are most likely underestimated.

The categorization of the behavioral symptoms taken into account is done by using three acronyms:

- DISH (Disorientation, alteration of social Interactions, alteration of the normal Sleep-wake cycles, loss of acquired habits (House soiling; Landsberg et al., 2017);
- DISHA (behavioral alterations of DISH and behavioral patterns related to ACTIVITY, such as alteration of appetite, of personal hygiene, of activities in general (Osella et al., 2007);
- DISHAL (previous alterations and behavior modifications related to states of anxiety, as well as to the reduced cognitive and memory abilities (Landsberg et al., 2012).

After the questionnaire has been filled in by the owner, the practitioner assigns a score to each item according to three scales:

- 1) ARCAD Scale (Age Related Cognitive and Affective Disorders), developed by Pageat (1998), according to which the behavioral disorders of old dogs are divided into three groups: social-behavior disorders (Hyper aggression of old dogs), cognitive-ability disorders (Confusion Syndrome of old dogs), thymic disorders of old dogs (Depression from involution).
- 2) EDED Scale (Evaluation of Dogs' Emotional and cognitive Disorders), this takes into account emotional-related disorders of dogs of any age, and not only of old dogs, like the ARCAD scale; the final score allows to tell whether the dog is normal or affected from phobias, anxiety or other emotional disorders (Mills et al., 2013).
- 3) CADES scale (Canine Dementia Scale), proposed by Mad'Ari et al. (2015), it takes into account 17 items divided into 4 groups. The final evaluations are 4: normal ageing (occasional behavioral modifications), ageing with light cognitive handicap (reduction both of contacts with owners and of daily activity), ageing with moderate cognitive handicap (the dog's night activity and inappropriate elimination reach annoying levels for the owner), ageing with severe cognitive handicap (the behavior worsens so much that the owners do not feel like keeping on living together with their dog).

## Therapy

The therapy for the Cognitive Dysfunction Syndrome includes the use of drugs and of nutraceutical products. The first ones include PROPENTOFILLYNE (this is able to improve blood perfusion and to inhibit the formation of microthrombi (Donenberg & Landsberg, 2010)); DIAZEPAM and FLUOXETINE (which are able to reduce the effects of stress and depression (Cory, 2013)); SELEGILINE (thanks to its antioxidant property and to its dopaminergic and catecholaminergic activity (Landsberg et al., 2010)); PHOSPHATIDYL SERINE (with neuroprotective properties, able to improve neurotransmission and synaptic functioning (Osella et al., 2007)).

Two nutraceutical products have resulted particularly effective: one containing antioxidant principles and mitochondrial co-factors, able to protect the brain tissue from the action of free radicals (Landsberg et al., 2010). The other one made up of phosphatidyl serine, Ginkgobiloba, pyridoxine and dl- $\alpha$ -tocopherol, in addition to antioxidant substances and mitochondrial co-factors; this product has proven able to increase the old dog's memory and learning ability (Colangeli et al., 2005).

## Prevention

Several predisposing factors have been into account; concerning sex, breed, size and neutering opinions are different (Azkona et al., 2009; Katina et al., 2016; Mad'Ari et al., 2017). Opinions are the same, instead, for what concerns food and the environment. Regarding food, it has been discovered that dogs fed on uncontrolled diets have 2.8 times higher probability to develop the Cognitive Dysfunction Syndrome than dogs fed on controlled diets (Katina et al., 2016). Araujo et al. (2005) have shown that supplementation of the diet with antioxidant factors (Vitamins A, E, C, selenium) and with mitochondrial cofactors (lipoic acid, carnitine, Coenzyme Q<sub>10</sub>) can have beneficial effects on the dog's cognitive abilities in both the short and long term, both by protecting the brain tissue from oxidative damage and by increasing the percentage of free polyunsaturated fats (arachidonic acid) inside the neuronal cell, with consequent improvement of neurotransmission and of synaptic function (Bazinet & Layé, 2014).

Regarding the environment, understood as proper relationship with the owner, regular contacts with other dogs, as well as regular physical and mental exercise (problem solving and sniffing practice), it has been shown how it can postpone the onset of the first symptoms of the Cognitive Dysfunction Syndrome, as well as slow down its course, in case it has already started (Mad'Ari et al., 2017). These results have been confirmed also by a research by Chapagain et al., (2017), which showed that, even if the ability of concentration and of keeping attention decreases with ageing, physical and mental exercises carried out during the dog's whole life prevent the clinical symptoms of cognitive decline.

## Conclusions

Dogs live longer and longer thanks to the advances made both in Veterinary Medicine and in studies about animals' nutrition and food.

Of course, this involves a price to pay: AGEING. As any other part of the organism also the nervous system undergoes some modifications as time goes by: it is important that the onset of behavioral and cognitive symptoms typical of the brain malfunction takes place as late as possible and, in case, that the symptoms are as light as possible, in order to ensure a good quality life to old dogs and to their owners. In this regard the knowledge of the risk factors and the

therapeutic and prevention measures of the Cognitive Dysfunction become essential. A very important role will be more and more played by an early diagnosis: biochemical diagnostics is already being studied, which aims at identifying the markers that can be more linked to animals' dementia. The cerebrospinal fluid and blood are the fluids who can better serve this research because the first one contains the higher concentrations of them, while the second one is easier to use. The identifying technique of these markers is represented by the immunologic dosage, thanks to which it is possible to identify the protein elements that typically appear in case of a pathology of the nervous system; unluckily the standard procedures necessary to avoid diagnostic errors have not been validated yet (Kovacek et al., 2017).

Considerable advances have been recorded also in therapy these latest years; the effectiveness of new methods is already being studied, such as vaccination against  $\beta$ -amyloid proteins and the use of stem cells obtained from the olfactory mucosa and implanted in the cisterna magna (Veron et al., 2014).

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## Sindrome di disfunzione cognitiva nei cani anziani

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### *Sintesi*

La Sindrome di Disfunzione Cognitiva nei cani anziani è una patologia di cui i cani soffriranno sempre più facilmente e i cui sintomi i proprietari dei cani dovranno imparare a riconoscere perché la vita media dei cani sta aumentando, grazie ai notevoli miglioramenti in termini di nutrizione e di stile di vita. La Sindrome di Disfunzione Cognitiva è una patologia multi fattoriale: le cause genetiche, ambientali e alimentari giocano un ruolo determinante nel creare le condizioni per l'insorgenza dei sintomi; infatti la prevenzione passa attraverso il miglioramento di questi aspetti. Diverse aree del cervello sono interessate e i meccanismi con cui il tessuto cerebrale è danneggiato sono diversi. La Sindrome di Disfunzione Cognitiva è caratterizzata dal fatto che è simile al morbo di Alzheimer nell'uomo, sia per quanto riguarda le cause, i meccanismi patogenetici, le aree cerebrali interessate e la prevenzione, tanto da essere utilizzato come rispettivo modello di studio.

