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Recognizing and Managing Cognitive Dysfunction in Dogs

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Abstract

With increasing age, some dogs develop a neurodegenerative disease that is commonly referred to as canine cognitive dysfunction syndrome (CDS). Diagnosis of CDS can be clinical or based on laboratory tests. The main behavioral changes associated with CDS are disorientation, altered interactions with people or other animals, sleep-wake cycle alterations, housesoiling, and changes in activity level. Ruling out medical conditions that can cause similar changes in behavior is important when performing a clinical diagnosis. Management of CDS includes dietary and pharmacological intervention. Dietary treatment of CDS has been based on the use of antioxidants and mitochondrial co-factors, and recent work has shown that long-term supplementation with medium-chain triglycerides can improve cognitive function in aged dogs. CDS must be considered an animal welfare issue, and the implications of this are discussed in this paper.

Glossary of Abbreviations
CDS: Cognitive Dysfunction Syndrome
CRF: Corticotropin-Releasing Factor
CRH: Corticotropin-Releasing Hormone
GAS: General Adaptation Syndrome
HPA: Hypothalamic-Pituitary-Adrenal Axis
SA: Sympatho-Adrenomedullary

Introduction

With increasing age, some dogs develop a neurodegenerative disease that is characterized by a gradual decline in cognitive function and is commonly referred to as canine cognitive dysfunction syndrome (CDS).[1] Interest in CDS has rapidly grown as it has been realized that CDS has many similarities with Alzheimer's disease in humans. Clinically, CDS may cause disorientation, altered interactions with people or other animals, alterations in the sleep-wake cycle, changes in activity level and housesoiling, among other signs.[2] The objectives of this paper are to: 1) briefly review the diagnosis as well as the dietary and pharmacological treatment of CDS, and 2) discuss the animal welfare implications of CDS.

Recognizing CDS

Diagnosis of CDS can be clinical or neuropsychological, e.g., based on laboratory tests. Apart from the clinical signs mentioned earlier, CDS may cause other signs, including an increase in anxiety, one of the main underlying factors of many behavioral problems in dogs.

Prevalence of CDS increases with age. According to one study[3] of 180 dogs, 28% of owners of 11- to 12-year-old dogs reported at least one clinical sign consistent with CDS, and this percentage increased up to 68% with owners of 15- to 16-year-old dogs.

Ruling out medical and behavioral conditions that can cause changes in behavior in geriatric dogs is important when performing a clinical diagnosis. For example, aging may lead to changes in the hierarchical relationship between dogs living in the same household, and this, in turn, may cause aggression. Also, animals that have impaired senses, physical debilitation or painful conditions may become more aggressive.[4] Other diseases that should be considered as differential diagnoses include renal and hepatic diseases, diabetes insipidus, Cushing's syndrome, diabetes mellitus, pancreatitis, cardiovascular and respiratory disease, and urinary incontinence.[4]

What is DISHA?
The acronym DISHA is frequently used to describe the main behavioral changes associated with CDS: disorientation, altered interactions with people or other animals, sleep-wake cycle alterations, housesoiling, and changes in activity level.[2]

Clinical diagnosis is based on the owners' report and therefore may be subjective and not very sensitive. A number of laboratory tests that measure the learning abilities and the spatial memory of dogs have been developed and provide valuable information on cognitive impairment and response to treatment, as recently reviewed.[5]

Managing CDS

Management of CDS includes dietary and pharmacological intervention. Additionally, changes in the environment may be extremely helpful and are dealt with in a different section of this paper.

Dietary Treatment

Dietary treatment of CDS has been based on the use of antioxidants and mitochondrial co-factors that may decrease the deleterious effects of free radicals. There is ample evidence suggesting that free radicals play an important role in aging; the brain is particularly susceptible to the effects of free radicals, as it has a high rate of oxidative metabolism, a high content of lipids and a limited ability for regeneration.[6] It has been shown that antioxidants improve the performance of aged rodents,[6] and several studies show that an antioxidant-enriched diet improves cognitive performance in senior dogs.[7]

Recent work has shown that long-term supplementation with medium-chain triglycerides can improve cognitive function in aged dogs. The underlying mechanism appears to be an increase in the circulating levels of ketones, which provide the brain with an alternative energy source.

Pharmacological Treatment

Selegiline, which is a selective inhibitor of monoamine oxidase B, is the first therapeutic agent approved for the treatment of CDS in dogs. The mechanisms by which selegiline has a positive effect on dogs with CDS are not clear. However, at least the following effects may have a role: an increase in dopamine activity in the cortex and hippocampus, a decrease in free radical load in the brain, and a neuroprotective effect on dopaminergic, noradrenergic and cholinergic neurons. The recommended dose is 0.5-1 mg/Kg daily in the morning, and if there is no significant improvement after one month, the dose can be increased for another month.[5,8]

CDS as a Welfare Problem

What is Animal Welfare?

Before discussing whether and why CDS is an animal welfare problem, it is useful to provide a short overview of our current understanding of the basic principles of animal welfare. Definitions of animal welfare can be grouped into three main approaches: a "feeling-based" approach, a "functioning-based" approach, and a third set of approaches in which welfare is measured by assessing whether the animal can live according to its inherent "nature."[9]

According to the "feeling-based" approach, animal welfare involves the subjective feelings of animals, so that welfare will be reduced by negative subjective states, such as pain and fear, and improved by positive states. The task for science, therefore, is to study the subjective experiences of animals.[9] The main problem with this approach, however, is that subjective experiences cannot be measured directly. This raises a long-standing debate whether trying to study them falls within the realm of science. A thorough discussion of the arguments involved in this debate is beyond the scope of this paper, and the reader is referred to a review by Dawkins[10] and references therein for further information.

Many scientists agree that although an animal's experiences of suffering are the defining traits of its welfare, such experiences are difficult to assess, whereas measures based on biological functioning and the animal's ability to cope with the environment provide relevant information. Indeed, one of the most frequently cited definitions of animal welfare is that the welfare of an individual is its state as regards its attempts to cope with its environment.[11] This definition refers to both how much has to be done in order to cope with the environment and the extent to which coping attempts are succeeding. Impaired life expectancy and reduced ability to grow or reproduce are examples of indications of failure to cope. Attempts to cope include emergence physiological responses and a variety of behavioral changes. All these measures can be integrated in an assessment of welfare that is objective and independent of moral considerations.[12]

It is important to emphasize that although the different approaches to animal welfare do not always give rise to the same conclusions, very often they do. In particular, research indicates that the feeling-based and functioning-based interpretations often correspond.[9] Indeed, pleasant and unpleasant feelings — including suffering — are part of the experience of an animal when it attempts to cope with its environment.[12] According to Dawkins,[10] suffering occurs when the animal is unable to perform those behaviors that would allow it to cope with its environment.

In 1993, the United Kingdom Farm Animal Welfare Council proposed the so-called Five Freedoms,[13] which have become a widely used framework to define and assess welfare. Although primarily developed for farm animals, the five freedoms can also be used in companion animals. The five freedoms are:

1. Freedom from thirst, hunger and malnutrition — by ready access to fresh water and a diet to maintain full health and vigor.
2. Freedom from discomfort — by providing a suitable environment including shelter and a comfortable resting area.
3. Freedom from pain, injury and disease — by prevention or rapid diagnosis and treatment.
4. Freedom to express normal behavior — by providing sufficient space, proper facilities and company of the animals' own kind.
5. Freedom from fear and distress — by ensuring conditions that avoid mental suffering.

The five freedoms combine elements from the three approaches to welfare explained above and are a very useful framework to identify the main welfare problems in a given production system and also to use as a starting point to select the main welfare indicators.

Why Is CDS a Welfare Problem?

Many of the behavioral changes and medical conditions associated with aging may impair the welfare of the animal as defined by the five freedoms. For example, several diseases may result in pain and/or interfere with the expression of normal behavior. However, as for CDS in particular, its main effect on welfare is that, as already mentioned, it may cause an increase in anxiety and stress, particularly when animals are exposed to novelty.

In 1929, Cannon described stress as the sympatho-adrenomedullary (SA) system's attempt to regulate homeostasis when threatened by a variety of aversive stimuli.[14] Later, Selye conducted some of his classic studies on the response of the hypothalamic-pituitary-adrenal (HPA) axis to noxious stimuli; Selye suggested that the organism reacted in a nonspecific manner to a wide variety of aversive stimuli, and this stress reaction was termed "general adaptation syndrome."[14] More recently, Mason[15] suggested that the psychological component of the aversive stimuli is the main determinant of the stress response. For example, animals that could control and/or predict the occurrence of an electric shock showed less pronounced stress responses than counterparts with no control or warning signals.[16,17] Most researchers agree that the animal's appraisal of the situation is a major determinant of the stress response.[18]

Current research on stress biology has addressed the role of the brain.[19] Several areas of the brain are involved in the organization of responses to aversive or threatening stimuli, and these areas interact extensively. Neurons in the hypothalamus, for example, are sensitive to internal physicochemical stimuli and to external physical and psychosocial stimuli.[20] To a great extent the stress response is mediated by the hormone CRF (corticotrophin-releasing factor) that is secreted mainly by the paraventricular nucleus of the hypothalamus.[21] For example, behavioral stressors have the potential to severely reduce feed intake in animals. Although the mechanisms underlying the effect of stress on feed intake are not completely understood, corticotrophin-releasing hormone, which plays a key role in the stress response, appears to have a significant effect on appetite. It has been shown that intracerebroventricular administration of CRH reduces feed intake in a variety of animals.[22]

Managing CDS as a Welfare Problem

When considering CDS as a welfare problem, two main issues arise. First, it is important to provide animals that suffer cognitive impairment with an environment that does not lead to unnecessary stress. In particular, avoiding sudden changes in the animal's routine and allowing it to have control over its environment seem particularly important.

Second, the possibility to express normal behavior patterns has positive effects on the health and welfare of animals. Environmental enrichment is widely used in both captive wild animals and domestic animals to improve their welfare. Environmental enrichment techniques for animals in captivity follow one or more of the following guiding principles: (a) increasing control or contingency between animal action and environmental reaction; (b) presenting cognitive challenges such as learning what a trainer is requesting or solving a problem; (c) meeting specific behavioral needs such as need for shelter/hiding or foraging; (d) providing an environment in which exploration is stimulated and rewarded; and (e) stimulating social interaction.[23] There is ample evidence showing that environmental enrichment has positive effects on welfare, and in most cases, it causes a decrease in stress, either in baseline level responses or in responsiveness to acute stressors.[24] In aged dogs, environmental enrichment has positive effects on cognitive performance, and these are more pronounced when dietary treatment and environmental enrichment are combined.[7]

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Q&A Discussion

Q: Dr. Stan Marks, University of California-Davis: Can you expound on the topic of hearing impairment in geriatric dogs that may contribute to cognitive dysfunction? When working these patients up, we talk about the medical approach to ruling out organic disease, liver, kidney, etc. However no mention was made of hearing impairment that we see so commonly in our geriatric patient population, and as it is in people, this is an important aspect of the senile dementia deterioration/depression that we see in human patients. So, I was wondering if you could comment further on the role of hearing impairment and how that should be evaluated in these patients.

A: Dr. Manteca: You are absolutely right. As I said, we have to think about behavior as something that results from the function of the brain, but the brain is responding to a variety of stimuli in the environment, and obviously the dog responds to olfactory, visual, auditory stimuli and many others. So any impairment in the senses, including in sight or in hearing, may lead to behavioral changes that may contribute to that pattern of altered behavior in the geriatric dog. The other thing that I think is very important is that any sense impairment may contribute very much to a perceived sense of lacking control and predictability. So, I think that checking whether the dog

is hearing well, checking whether the dog is seeing well, must be a fundamental part of the medical workup. And when that it not the case, when there is a hearing impairment, we have to try to provide mechanisms that may replace sound stimulus, for example, by olfactory or tactile stimulus so that the dog may somehow recover that sense of control.

Q: Dr. Dottie Laflamme, Nestlé Purina Research: I have heard that as hearing loss progresses in senior dogs, the lower frequencies are lost first and the higher frequencies are retained. And I've heard suggestions from trainers and behaviorists that using whistles and so forth is a way to work with the senior dog and provide appropriate stimuli in a way to train them during the phase when their hearing is going down but is not quite gone. And I'd like to ask you and maybe others in the audience who have experience in that regard to comment.

A: Dr. Manteca: What I can contribute to that is that the hearing ability of the dog is very different from ours in the sense that the dog is more sensitive to higher frequencies than we are. So when we compare the two audiograms, the human and the dog, the dog would be toward the right-handed side of the diagram in the sense that they hear higher frequency sounds better than we. So if we assume that when the animals partially lose their hearing ability, it is logical to assume that since they are more sensible to higher frequency sounds, they may still retain the ability to respond to some of those sounds. So, I am not convinced that this has been explored in a scientifically controlled way, how the aging dogs respond to different types of sounds, but considering that they are more receptive to high frequency sounds, I think that would be worth exploring.

Dr. Gary Landsberg, Moderator: One element that I would comment on is that in some cases of cognitive dysfunction, you will sometimes notice that the hearing and visual response to stimuli sometimes seem to actually improve with the treatment of cognitive dysfunction, meaning it's more of a central or cortical problem. These animals that apparently couldn't hear before, after treatment of the cognitive components sometimes seem to start "beginning to hear again" or beginning to respond to stimuli again. So remember that hearing also can be central or cortical rather than just the specific sensory organ itself.

Dr. Karen Overall, University of Pennsylvania: In addition to what Gary just said about animals beginning to show the behavioral effects of being able to hear after they're not distressed, I think that we have to realize how distress factors into how they process all sorts of information, whether it's visual or olfactory or auditory. Once they become distressed, they can't learn about their environment. I'll explain why when I give my talk after lunch. Once that happens, they begin to lose parts of the information chain that gives them the predictability. So if you can both treat that anxiety and treat the cause of the dysfunction, you see a whole host of effects including, oddly enough, increased olfactory ability. And it's interesting to see that happen. As far as the range of the spectrum, because they hear at the frequency that Xavier said so much better than we do, they actually lose the very end of that relatively early on. And I have to tell you, our ability to assess hearing in dogs is pathetic. We really need to be concentrating on not only how well they hear but also how well they process information, and measure it instead of measuring deafness. Our work has shown that the reactivity and the kind of reactivity you have to noise is heritable. All the genes that we've so far got localized that are overrepresented in dogs that have noise reactivity are all involved, with one exception, in how well you process information. So this is a cognitive issue. And when we look at them losing that first end, when they realize that other dogs in the house are hearing things they don't hear, they become distressed and then they also clip off that other end. And one of the things we can do to ameliorate this early is not just whistles, but there are now vibrating collars, that vibrate in a variety of ways, so that a dog gets to be included in things and gets told to attend to something. I believe this is important because they are so social and so cognitive, I believe that as in humans, deafness is far more isolating than blindness. It's your early warning system that keeps you alive.

Dr. Richard Hill, University of Florida: I guess as an internist I'm a little bit uncomfortable about a diagnosis of exclusion that your approach seems to be. The clinical approach is really to rule out everything else and then, if we have these signs, therefore it must be cognitive dysfunction. In a diagnosis of exclusion you're really depending on your ability as a diagnostician in many, many fields. I always get a little worried that maybe we're not picking up that they are in pain, that they've got hearing impairment, whatever. So my question is whether there is any test we can run that really shows that they do have cognitive dysfunction?

Dr. Manteca: Yes, I think you are absolutely right. I am as uncomfortable as you with any diagnostic approach that is based on ruling out everything else because we never rule out everything else. So, this approach is fraught with difficulties. Dr. Milgram has explained some tests that can be used in a clinical setting. The portable equipment he has been referring is being developed and those tests will show that the dog has a cognitive deficit. But, as far as I know, we don't have any practical test that would tell us that those cognitive changes are due to the sort of brain pathological changes that we associate with cognitive dysfunction syndrome. So I would say that this is the best we have for the moment.

Dr. Bill Milgram, CanCog: The situation in dogs, by the way, isn't necessarily that different from the situation with humans. In human subjects the classification of dementia and different kinds of dementia is sort of an ongoing area. And I think from a critical perspective, the one thing that you can probably be confident in, based upon the work we've done, is if your dog is beyond a certain age, it's going to be showing cognitive impairment. But to be able to get it more refined, as in humans where we try to distinguish between people who are demented and people who show mild cognitive impairment, that involves a lot of work and there's often an invisible line. It is probably the case with dogs as well. There may be other diagnostics in the future that would be useful. There might be, for example, an analysis of certain types of metabolites in cerebrospinal fluid. I think it is something that will require more than just behavior to come up with a more confident diagnosis. And you can be confident that all dogs show cognitive impairment, but the extent of the impairment is, at this stage, something I think is very, very difficult to quantify.