Canine cognitive dysfunction syndrome: Prevalence, clinical signs and treatment with a neuroprotective nutraceutical

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Abstract

Cognitive dysfunction syndrome (CDS) is a progressive neurodegenerative disorder of senior dogs. Since age-related behavioural changes may be useful indicators for early diagnosis and treatment, the first purpose of the present study was to investigate the prevalence of clinical signs of CDS in a general population of aged dogs. The second aim was to evaluate the use of a neuroprotective nutraceutical (Senilife®, Innovet Italia srl, Rubano, Italy) using an open-label clinical pilot trial.

Dogs were recruited from a geriatric population not referred for behavioural consultations. A questionnaire with a checklist of behaviours was filled out to evaluate behavioural items grouped in the following categories: disorientation (D), socio-environmental interaction (I), sleep–wake cycles (S), house soiling (H), general activity (A)—(DISHA). Each owner was asked to rate the frequency of the behavioural signs: never, rarely, often, or always.

One hundred and twenty-four dogs were assessed in the first survey; 22 of the 124 dogs tested in the survey were ruled out based on exclusion criteria (clinically and/or sensory severe impairment), 42 dogs had alterations in one category and 33 dogs had signs in 2 or more categories. Consequently 75 dogs had signs consistent with CDS.

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Among this population eight dogs affected by CDS were enrolled for the second step of the project, an open-label clinical pilot trial with the neuroprotective nutraceutical Senilife®. Senilife® contains 25 mg phosphatidylserine, 50 mg of standardized Ginkgo biloba extract, 33.5 mg/d-alpha tocopherol and 20.5 mg pyridoxine per capsule and is dosed at one capsule per 5 kg body weight. The investigator asked the owners to rate the frequency of behaviours referring to DISHA using a four point frequency scale (never, rarely, often, always). Post-treatment, the owners were asked to evaluate all the signs in each category on a five point scale (much better, slightly better, the same, slightly worse, much worse). At the time of the first visit \( V_0 \) the owners were briefed verbally about the procedure; no behavioural advice was given throughout the study time and whenever appropriate therapy with Senilife® was started. At \( V_0 \), \( V_1 \) (28 ± 3 days), \( V_2 \) (56 ± 3 days) and \( V_3 \) (84 ± 3 days) a control visit was performed and the owners were interviewed. Dogs treated with Senilife® showed a highly significant difference at \( V_3 \) compared to \( V_0 \) (\( p < 0.001 \)).

Preliminary results from dogs on Senilife® showed a marked improvement of CDS related signs, even if the dogs failed to show a complete remission of symptoms.

Keywords: Ageing; Cognitive dysfunction; Dementia; Dog; Neuroprotection; Nutraceutical

1. Introduction

Ageing represents a complex biological process characterized by a progressive modification of tissues and cells (Kiatipattanasakul et al., 1996) with a gradual loss of adaptive capacity. Ageing animals can show a decrease in their learning and memory performance (Milgram et al., 1994; Landsberg and Ruehl, 1997; Adams et al., 2000; Chan et al., 2002). The behavioural signs shown by ageing animals might be referred to as “aged dog syndrome” or, when severe, of “senile impairment”. Sometimes, they are considered as features of “normal ageing”. A serious impairment of cognitive processes must be distinguished from a simple and mild decrease in psychomotor activity and may be considered “pathological ageing” (Ruehl and Hart, 1998).

In aged dogs behavioural problems are often related to organic and functional disorders. Although a change in behaviour could have an entirely medical or behavioural cause, it is actually the combined effects of disease and ageing on the pet’s mental and physical health that cause geriatric behavioural disorders in the dog (Landsberg and Ruehl, 1997; Landsberg and Araujo, 2005). Sometimes complications may develop in animals with pre-existing behaviour problems that have been tolerated by the owners until the consequences are exacerbated by a clinical geriatric problem (Houpt and Beaver, 1981; Chapman and Voith, 1990; Dodman, 1998). More recently a specific “Cognitive dysfunction syndrome” (CDS) of senior dogs has been described (Ruehl et al., 1995; Ruehl and Hart, 1998). Other specific age-related disorders such as involutive depression, confusional syndrome of the ageing dog and dysthymia of the ageing dog have also been suggested by Pageat (2001), as affective and cognitive dysfunctions.

The dog represents a suitable animal model to study cognitive impairment observed in human ageing (Ruehl et al., 1995; Cummings et al., 1996; Overall, 2000; Adams et al., 2000; Cotman et al., 2002; Studzinski et al., 2005). Dogs normally share environmental conditions with humans and present a sophisticated repertoire of complex cognitive behaviours. Furthermore, the brain in aged dogs shows many pathological changes common to humans and the neuropathological patterns are significantly associated with cognitive decline (Head et al., 2000). CDS shares some analogies with Alzheimer’s disease (AD) in humans and is characterized by brain pathology that
negatively affects the interaction of dogs with their own environment (Cummings et al., 1996). In fact the term canine CDS is used in veterinary literature to describe the progressive neurodegenerative disorder of senior dogs that is a result of a gradual decline in cognitive function (Landsberg, 2005). Typical behavioural changes in affected animals include signs of disorientation, a decrease in or alteration of social interaction, impairment of normal housetraining, and changes in both the usual sleep–wake cycle and general activity (Milgram et al., 1994; Cummings et al., 1996; Ruehl and Hart, 1998); traditionally the clinical signs are described by the acronym DISHA (disorientation, interaction changes, sleep/wake disturbances, housetraining and activity changes) (Landsberg et al., 2003).

CDS is a common disorder among senior dogs but a great number of owners fail to discuss geriatric-onset behaviour changes with their veterinarian because they incorrectly assume that these problems are an unfortunate and untreatable aspect of ageing (Neilson et al., 2001; Bain et al., 2001). Furthermore, differentiating normal from pathological ageing is a challenge since the progressive decline of canine CDS, leading to functional impairment and eventually death, may be greatly underestimated. Age-related neurodegenerative changes and associated behavioural signs that characterize pathological brain ageing are progressive in nature; the sooner they are detected the more effectively they can be corrected or at least slowed down (Head et al., 2000).

Since age-related behavioural changes may be useful indicators for early diagnosis and treatment, the first purpose of this study was to investigate the prevalence of clinical signs of CDS in a general population of aged dogs, through a questionnaire designed by the authors. The assessment scale sought to facilitate the earliest possible detection of pathology and to accurately follow the changes in behaviour over the time. The second part of this study was to use this scale to make a preliminary evaluation of the effectiveness of a nutraceutical for the treatment of CDS (Senilife®, Innovet Italia s.r.l., Rubano, Italy) through a pilot prospective open-label clinical trial. Senilife® contains a combination of phosphatidylserine (PS), a standardized extract of Ginkgo biloba (EGb), d-alpha-tocopherol and pyridoxine. These components have been reported to have potentially neuroprotective properties on age-related brain neurodegenerative changes (Landsberg, 2005).

2. Materials and methods

2.1. Animals

One hundred and twenty-four male and female dogs not referred for behavioural consultations were used for the initial study. Inclusive criteria were the age (>7 years old), exclusive criteria were primary organ failure and/or neurological signs and living with the owner for less than 1 year.

2.2. Procedure

First visit ($V_0$). In order to determine prevalence of CDS signs a screening interview assessed if the dog was suffering from any major medical problem that might have behavioural effects. Furthermore a questionnaire adapted from other authors (Kiatipattanasakul et al., 1996; Colle et al., 2000; Pageat, 2001; Landsberg et al., 2003; Pugliese et al., 2005) was used to evaluate cognitive status (Table 1). It has been reported that the requirements for CDS diagnosis in dogs include the presence of one or more of the following signs: spatial disorientation and confusion, learning and memory disorders, ranging from inappropriate elimination to inability to recall previously learned commands; modified activity levels (general, pointless, repetitive) to hypoactivity; deterioration in social interaction; modified sleeping-wake patterns; state of anxiety or restlessness; change in appetite (increase or decrease); decline in personal
### Table 1

Criteria for evaluation of cognitive status in dogs

<table>
<thead>
<tr>
<th>Category</th>
<th>Description of the category</th>
<th>No. of items</th>
<th>Description of items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorientation (D)</td>
<td>Confusion, altered spatial orientation, failure in recognizing familiar people, surroundings and routines</td>
<td>9</td>
<td>Gets lost in familiar location outdoors; gets lost in familiar location indoors; decreased recognition of familiar people outdoors; decreased recognition of familiar people indoors; goes to wrong side of door; goes to wrong door in the house; restless, agitation, wandering in the house; gets stuck, Cannot navigate around or over obstacles; abnormal reaction to well known objects</td>
</tr>
<tr>
<td>Socio-environmental interaction (I)</td>
<td>Altered interaction with people or other dogs, late or no answer to learnt commands</td>
<td>13</td>
<td>Decreased interest in greetings; decreased interest in petting; decreased interest in play with the owners; decreased interest in play with toys; decreased interest in play with other dogs; decreased responsiveness to commands; decreased ability to perform tasks; in need of constant contact; increased irritability; increased aggressiveness toward other dogs outdoors; increased aggressiveness toward household dogs; increased aggressiveness shown by the other dogs</td>
</tr>
<tr>
<td>Sleep–wake cycles (S)</td>
<td>Increased daytime sleep, decreased and altered sleep at night</td>
<td>4</td>
<td>Restless at bedtime; switches between insomnia and hypersomnia; restless sleep, waking at nights, pacing and/or vocalizing, without any need to go outside; increased daytime sleep</td>
</tr>
<tr>
<td>House soiling (H)</td>
<td>Accidents indoors, loss of urination and/or defecation control with or without incontinence</td>
<td>6</td>
<td>Indoor elimination random sites or in view of owners; elimination in crate or sleeping area; decrease of signaling; indoor elimination on return after going outside; change of substrates for elimination; incontinence</td>
</tr>
<tr>
<td>Activity (A)</td>
<td>Decreased purpose activities and increased repetitive aimless activities</td>
<td>7</td>
<td>Decreased responsiveness to familiar stimuli; decreased exploration and activity, apathy; staring, fixation, snaps at air or objects; excessive licking owners, household objects; pacing, wandering, vocalization aimlessly; increased appetite; decreased appetite</td>
</tr>
</tbody>
</table>

The 39 items of the questionnaire were grouped in five categories: disorientation (9 items), socio-environmental interaction (13 items), sleep–wake cycles (4 items), house soiling (6 items) and general activity (7 items).
cleanliness; reduced perception of and/or response to stimuli. Thirty-nine items were identified which were grouped as disorientation (9 items), socio-environmental interaction (13 items), sleep–wake cycles (4 items), house soiling (6 items) and general activity (7 items), as described in Table 1. Each owner provided the required information rating the frequency of the behavioural signs as: never, rarely, often, or always, scored 0–3 accordingly in subsequent analysis. At V₀ a standard physical examination and a laboratory assessment (complete blood count, basic biochemical profile, urinalysis, basic endocrine screen) were performed to determine whether there were underlying medical problems. Further diagnostic tests or specific consultations, such as a neurological examination were recommended when necessary. Sensory evaluation (vision and hearing impairment) was assessed clinically by the investigator.

From all of the animals assessed, 75 showed potential clinical signs of CDS and these owners were advised to seek a behavioural consultation. From this referral population 18 dogs were diagnosed as having CDS. One of the criteria for impairment in each category was that dogs had two or more distinct signs in that category which had not been observed when they were younger, comparing the pet’s present cognitive status to his or her behaviour prior to 7 years of age; additionally the dog had to have dysfunction signs in that category at least once a week for at least the previous month (Neilson et al., 2001). Since an analysis of pilot data showed that the prevalence of each category of signs did not vary with age group, all the categories were treated in the same way. It was then determined whether each dog had impairment in 0, 1 or 2 or more categories. As a result of the investigator’s assessment and the owners’ agreement, eight dogs were enrolled on the Senilife trial.

At V₀ the owners were briefed verbally about the procedure. No behavioural advice was given throughout the study time. The owners were requested to administer Senilife* at the dosage of 1 capsule per 5 kg body weight per day Per Os (each capsule contains 25 mg phosphatidylserine, 50 mg Ginkgo biloba extracts, 33.5 mg/d-alpha tocopherol, 20.5 mg pyridoxine) for 3 months.

2.2.1. Further visits (V₁, V₂, V₃)

After V₀, dogs were checked in three control visits V₁ (28 ± 3 days after V₀), V₂ (56 ± 3 days) and V₃ (84 ± 3 days). At V₁, V₂ and V₃ the investigator referred to the aforementioned questionnaire (Table 1) and asked the dog owners the frequency of each item and to rate the signs of each category on a five point change scale (much better, slightly better, the same, slightly worse, much worse).

2.3. Data analysis

To assess the prevalence of clinical signs associated with CDS a descriptive analysis was conducted in relation to age, sex and castration status, and the weight for all dog groups was considered (Wells and Hepper, 2000).

In the assessment of the therapeutic effects of the nutraceutical, an exact percentage confidence interval test (SAS System, Version 8) was used to investigate the changes after treatment with Senilife between V₃ and V₀.

3. Results

3.1. Demographic information

Twenty-two of the 124 dogs tested in the survey were removed based on exclusion criteria clinical concerns and/or severe sensory impairment. Twenty-seven of the 102 dogs included in the study expressed ageing without any signs of CDS, 42 dogs had alterations in one category and 33 dogs had signs in 2 or more categories. Consequently 75 dogs had signs referring to CDS.

The general activity category has been scored separately in order to compare the results with other existing data as discussed below.
3.1.1. Dogs with alterations in one category (n = 42)

Among the 42 dogs, 15 were females, 10 neutered females, 15 males, and 2 were castrated males. The age range was 8–17 years (mean: 12.61), whereas weight ranged from 21 to 30 kg (mean: 25.69). Mix breeds and pure breeds were equally represented. Twenty-one dogs (50%) had mild clinical complications, 22 (52.38%) were undergoing some form of therapy and 10 dogs (23.81%) required further clinical evaluation.

Twenty-five dogs had alterations in socio-environmental interaction (59.52%), 16 in sleep–wake cycles (38.10%) and 1 in house soiling (2.38%). Eighteen dogs (42.86%) had general activity changes with 12 dogs being hypoactive.

3.1.2. Dogs with alterations in two categories (n = 26)

Females and males were equally represented (50% of each), 8 females were spayed and all the males were entire. Age range was 9–19 years (mean: 12.61). Mix breeds were most prevalent with 15 dogs. Weight range was 3.5–62 kg (mean: 21.03). Fifteen dogs had mild clinical complications, 18 were undergoing some form of therapy and 6 required further clinical evaluation.

Thirteen dogs had alterations in socio-environmental interaction (50%), 16 in sleep–wake cycles (61.53%) and 2 in house soiling (7.69%), 20 dogs (76.92%) had general activity changes, with 8 dogs (30.76%) being hypoactive.

3.1.3. Dogs with alterations in three categories (n = 5)

All the dogs in this group were females; four of them were spayed. Two dogs were 12 years old and the others were each 13, 14 and 15 years old, respectively. Weights ranged from 4 to 40 kg (mean: 16.60). One dog had a mild clinical complication and one dog was undergoing some form of therapy. About 33.33% had alterations in socio-environmental interactions, 33.33% in sleep–wake cycles, 20% disorientation and 13.34% in house soiling. All the dogs showed marked hypoactivity.

Table 2

For each animal and item, the variation was calculated between score at $V_0$ and $V_3$

<table>
<thead>
<tr>
<th>Subset (no. of items)</th>
<th>Observed answers</th>
<th>Score</th>
<th>Variation ($V_0 - V_3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Average</td>
<td>Maximum</td>
</tr>
<tr>
<td>A (13)</td>
<td>39</td>
<td>$V_0$ 2.2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$V_3$ 0.3</td>
<td>3</td>
</tr>
<tr>
<td>B (9)</td>
<td>36</td>
<td>$V_0$ 1.6</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$V_3$ 0.6</td>
<td>3</td>
</tr>
<tr>
<td>C (4)</td>
<td>18</td>
<td>$V_0$ 2.2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$V_3$ 1.0</td>
<td>3</td>
</tr>
<tr>
<td>D (6)</td>
<td>14</td>
<td>$V_0$ 1.9</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$V_3$ 0.6</td>
<td>1</td>
</tr>
<tr>
<td>E (7)</td>
<td>30</td>
<td>$V_0$ 2.2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$V_3$ 0.6</td>
<td>3</td>
</tr>
</tbody>
</table>

This variation was classified as positive, unchanged and negative according to an improvement or worsening of animal behaviour.

A: socio-environmental interaction (13 items), B: disorientation (9 items), C: sleep–wake cycles (4 items), D: house soiling (6 items), and E: general activity (7 items).
3.1.4. Dogs with alterations in four categories \((n = 2)\)

Two dogs were included, an 18 years old female Yorkshire Terrier weighing 5 kg and a 16 years old male mix breed weighing 6 kg. The dogs showed neither clinical signs of organic disorders nor were they undergoing therapy and further examinations were unnecessary.

The dogs had impairment in all categories and they had a severe impairment in activity (hypoactivity, repetitive activities).

3.2. **Senilife\textsuperscript{[1]}** treated dogs \((n = 8)\)

Eight dogs among the 75 with CDS signs were enrolled in the second step of the project and treated with Senilife\textsuperscript{[1]}. The dogs showed mild impairment and they had impairment in two or more categories. Four dogs belonged to the group of dogs with alterations in two categories; two dogs were included in the group of dogs with three alterations and the other two dogs were among the animals showing alterations in four categories.

### Table 3

<table>
<thead>
<tr>
<th>Set</th>
<th>Items, obs. (%)</th>
<th>Improvement</th>
<th>Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No.</td>
<td>II</td>
</tr>
<tr>
<td>A</td>
<td>39 (37.5)</td>
<td>37</td>
<td>0.949</td>
</tr>
<tr>
<td>B</td>
<td>36 (50.0)</td>
<td>32</td>
<td>0.889</td>
</tr>
<tr>
<td>C</td>
<td>18 (56.3)</td>
<td>16</td>
<td>0.889</td>
</tr>
<tr>
<td>D</td>
<td>14 (29.2)</td>
<td>14</td>
<td>1.000</td>
</tr>
<tr>
<td>E</td>
<td>30 (53.6)</td>
<td>27</td>
<td>0.900</td>
</tr>
<tr>
<td>All</td>
<td>137 (43.9)</td>
<td>126</td>
<td>0.920</td>
</tr>
</tbody>
</table>

A: socio-environmental interaction (13 items), B: disorientation (9 items), C: sleep–wake cycles (4 items), D: house soiling (6 items), and E: general activity (7 items).

### Table 4

Distribution of score variations for question subsets as at \(V_3\)

#### Distribution of score variations for question subsets

![Image](image.png)

A: socio-environmental interaction (13 items), B: disorientation (9 items), C: sleep–wake cycles (4 items), D: house soiling (6 items), and E: general activity (7 items).
For each animal and item, the variation between score at $V_0$ and $V_3$ was calculated. This variation was classified as Positive, Unchanged and Negative depending on improvement or worsening of the behaviour. Only items with scores different from zero were considered. Data are reported in Table 2.

Except for the subset D where it was not possible to perform any statistical analysis, the hypothesis that changes are due to a random effect ($p = 0.5$) is rejected with a $p$-value $< 0.001$, as showed in Table 3.

The eight dogs showed a highly significant difference at $V_3$ versus $V_0$, in all the categories as well as the overall assessment ($p < 0.001$), even if some items did not significantly differ when analysed individually (Table 4).

4. Discussion

Data on the prevalence of CDS suggest that the phenomenon is underestimated in veterinary medicine. In this study of 124 geriatric dogs not referred for behavioural consultation, the questionnaire detected 75 dogs with signs of suspected CDS, but only 35 clients followed up on the advice to seek a behavioural consultation. In fact pet owners supposed their animals not to have behavioural changes connected with senility, even if the most practical means of early detection of CDS is actually the owners’ observation and reporting of clinical signs (Landsberg, 2005).

In human medicine, early general screening for detection of dementia involves the administration of a standardized and validated neuro-psycho-physiological evaluation scale such as MMSE (Mini-Mental Status Examination). A dementia evaluation index in dogs which discriminates among normal, predementia and dementia has been proposed (Kiatipattanasakul et al., 1996), and Pageat has presented the ARCAD scale (Colle et al., 2000; Pageat, 2001) where the dogs’ behaviour was indirectly assessed by a formal ‘questionnaire (evaluation of age-related cognitive and affective disorders–ARCAD). By contrast, Pugliese et al. (2005) have taken a neurophysiological approach and correlated severe cognitive impairment with higher cerebrospinal fluid levels of lactate and pyruvate in a canine model of senile dementia. It should be noted that the questionnaire used in the first part of this project is not a validated scale for a specific diagnosis of the disease but it might be used as part of a preliminary global geriatric screen for CDS by practitioners. The questionnaire has been developed on the basis of the geriatric signs already reported in literature (Kiatipattanasakul et al., 1996; Colle et al., 2000; Pageat, 2001; Landsberg et al., 2003; Pugliese et al., 2005), but the checklists of the items following DISHA as applied by the Authors in the present paper actually proved to be easy and quick to complete, and the veterinarian could readily realize if further examinations were necessary.

Data collected are in accordance with results obtained in other studies and provide estimates of various degrees of age-related behavioural changes associated with CDS (Ruehl and Hart, 1998; Neilson et al., 2001; Bain et al., 2001). However, the relationship between the number of signs in the categories and cognitive impairment should not be assumed arbitrarily; i.e. dogs with impairment in 1 category did not necessarily have mild impairment, nor dogs with impairment in 2 or more categories severe impairment. For instance, there were dogs in the group with cognitive impairment in more than two categories that were actually presenting only mild cognitive impairment which was confirmed by later behavioural evaluation (Pugliese et al., 2005). Consequently, the traditional distinction used in humans for dementia might not be directly applicable to animals without further experimentation aimed at correlating behavioural,
emotional and cognitive signs with biological markers and post-mortem brain lesion analysis. Moreover, in dogs it seems suitable to perform visual-spatial tests instead of the human batteries of neuropsychological tests. Adams et al. (2000) have demonstrated that in aged dogs, on the basis of cognitive test performance it is possible to identify the following categories of cognitive impairment: successful ageing, mildly impaired dogs and severely impaired dogs. These categories are analogous to the human groups: successful ageing, mild cognitive impairment and dementia. Another important question is whether the experimental method designed to test learning ability and memory in ageing dogs correlates with clinical behavioural observation. In the laboratory studies have shown some correlation between levels of impairment in learning ability and memory and clinical signs such as exploration and social interaction. (Milgram et al., 1994; Siwak et al., 2001, 2002, 2003; Tapp et al., 2003). Even if findings suggest that the dog shows age-dependent deterioration in cognitive function there may be differences related to breed and previous experience (Head et al., 1997). In the present study, the dog population did not provide an opportunity to investigate these factors, not least because a variety of breeds were represented including a large number of mixed breed dogs, so further research is necessary.

It has been suggested that it is necessary to know exactly the main patho-genetic mechanisms of ageing to formulate a precise diagnosis and establish successful treatment protocols in order to manage geriatric behavioural problems (Overall, 2001). In human and canine senile brains the main neurodegenerative changes are both grossly neuropathological (e.g. thickening of the meninges, gliosis and diffuse plaques) (Borras et al., 1999; Gonzalez-Soriano et al., 2001; Fukuoka et al., 2004) and neurochemical (e.g. neuronal apoptosis, beta-amyloid deposits) (Anderson et al., 2000; Papaioannou et al., 2001; Dimakopoulos and Mayer, 2002; Head et al., 2002). In humans, a variety of neurotransmitter abnormalities have been described in patients affected by age-related dementia and even aged animals may show modifications of neurotransmitter levels and/or their receptor concentrations. In patients with Alzheimers Disease (AD), a decrease in muscarinic receptor (Araujo et al., 2005) and acetylcholinesterase activity occurs (Rinne, 1987). A decrease in catecholamines, especially dopamine, has been reported to correlate with cognitive and degenerative changes (Kalaria et al., 1989; Kalaria and Andorn, 1991; Meana et al., 1992; Arnsten, 1993; Palmer, 1996; Sastre et al., 2001). The serotonergic system also seems to be involved in ageing and in pathogenesis of AD in humans (Baker and Reynolds, 1989; Reinkainen et al., 1990; Tohgi et al., 1992; Kumar et al., 1995; Lai et al., 2002). Oxidative stress plays a pivotal role in the neurodegenerative processes associated with age-related dementia (Anderson et al., 2001; Milgram et al., 2002; Cotman et al., 2002; Skoumalova et al., 2003; Rofina et al., 2004). A decline in NMDA glutamate receptors, mainly affecting the cortex and hippocampus areas, has also been demonstrated in aged dogs (Magnusson et al., 2000). Advanced research has also demonstrated significant quantitative reductions in neurotrophic factors such as BDNF (Brain Derived Neurotrophic Factor) and NGF (Nerve Growth Factor) (Head et al., 2000).

The first therapeutic agent approved for use in dogs based on the results of both neuropsychological testing including reversal and spatial memory as well as clinical trials was selegiline (Milgram et al., 1995; Ruehl et al., 1995; Head et al., 1996; Campbell et al., 2001), a selective and irreversible inhibitor of monoamino-oxidase B (MAO B). Drugs for enhancing cerebral perfusion and/or alertness in aged dogs, antidepressants and anxiolytics, cholinergic agonists have also been considered (Landsberg, 2005). Complementary products have also been suggested as useful in improving or preventing cognitive decline, but so far data to validate their efficacy is very limited (Overall, 2001).
The results of this preliminary trial on Senilife® showed a marked improvement in CDS related signs even but it should be noted that the average score at $V_0$ and percentage of observed items were very low, which means the status of animals at baseline was not very severe. Furthermore dogs did not show complete remission of symptoms, but their signs became less severe. In human medicine mild cognitive impairment is considered a transitory state between normal ageing and dementia; patients in this category may represent a potential clinical population cohort targeted for early intervention (Lockhart and Lestage, 2003), due to the better prognosis.

The effects observed in treated dogs may be related to the neuroprotective activities exerted by its active constituents. Senilife® contains phosphatidylserine (PS), a standardized Gingko biloba extract (EGb), pyridoxine and d-alpha-tocopherol. PS is a phospholipid associated with membrane proteins that regulate the fluidity of neural membranes (Tsakiris and Deliconstantinos, 1984) which may be severely compromised in aged brains (Samson, 1987). Administration of PS both to human patients and laboratory animals with cognitive decline has produced excellent results in terms of improved learning and memory (Crook et al., 1992; Cenacchi et al., 1993; Blokland et al., 1999; Suzuki et al., 2001). Such results are also considered to be related to other neuroprotective activities of PS (Milan et al., 1988; Suzuki et al., 1999). Furthermore PS stimulates acetylcholine release in the cerebral cortex of elderly animals (Vannucchi et al., 1990; Yamatoya et al., 2000), modulates acetylcholinesterase activity in the synaptosome of the canine brain (Tsakiris and Deliconstantinos, 1984, 1985) and activates the synthesis and release of dopamine (Raitieri et al., 1988). PS also inhibits the age-related loss of NMDA receptors, cholinergic muscarinic receptors and hippocampus NGF receptors (Cohen and Mueller, 1992; Gellmann and Muller, 1992; Nunzi et al., 1992). The safety of its use has been confirmed through a toxicological study conducted on dogs (Heywood et al., 1987) and through clinical trials conducted in humans (Cenacchi et al., 1987).

EGb has a PS co-adjuvant activity, since it stimulates the cholinergic, serotonergic, noradrenergic and glutaminergic systems in aged animals (Taylor, 1986; Chopin and Briley, 1992; Huguet and Tarrade, 1992; Huguet et al., 1994; Nathan, 2000; Lee et al., 2004). EGb reversibly inhibits MAO A and B in the brains of laboratory animals thus increasing the levels of dopamine (White et al., 1996). Interestingly, EGb also protects the neurons against apoptosis induced by beta-amyloid protein (Yao et al., 2001), one of the main pathogenic processes of cognitive age-related decline in dogs (Colle et al., 2000; Le Bars et al., 2002). This effect seems to be primarily mediated by the marked antioxidant properties possessed by the active constituents of EGb (Sastre et al., 1998; Bastianetto and Quirion, 2002). Finally, EGb has been demonstrated to increase brain metabolism (DeFeudis and Drieu, 2000; McKenna et al., 2001), to promote short-term retention of spatial memory (Hoffman et al., 2004), and to exert reproducible effects on cognitive functions in Alzheimer’s disease (Gertz and Kiefer, 2004).

Pyridoxine is synergistic with the neurotransmission restoring effects of both PS and EGb, since it is an essential co-factor in the biosynthesis of many neurotransmitters (dopamine, noradrenaline and serotonin) (Dakshinamurti et al., 1995). As oxidative stress is considered to be one of the main pathogenic factors in the age-related cognitive decline in dogs (Head et al., 2002; Skoumalova et al., 2003; Rofina et al., 2004), compounds that prevent free radical production or scavenge them, have been suggested to augment cognitive function (Overall, 2002; Head and Zicker, 2004). The marked antioxidant properties of d-alpha-tocopherol make the compound an excellent candidate for controlling pathological brain ageing in the dog. Clinical and experimental evidence have demonstrated its neuroprotective potential (Behl and Moosmann, 2002) and beneficial cognitive effect (Guerriero et al., 1999). In particular, tocopherol slows the functional deterioration clinically observable in patients with pathological brain ageing (Sano et al., 1997).
In conclusion, further studies are necessary to validate the screen used in this study, but it appears to be a simple and practical tool for initial assessment of geriatric subjects. Results of treatment with Senilife suggest further studies investigating the effects of complementary therapy in canine cognition should be encouraged as the quality of life of senior dogs has the potential to be improved.

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References


