



# Physical signs of canine cognitive dysfunction

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**ABSTRACT.** Physical disturbances are common in dogs with canine cognitive dysfunction (CCD). However, the relation between these physical disturbances and CCD has not been clarified. The aim of this study was to clarify the physical disturbances in CCD by questionnaire survey. The questionnaire consisted of items of general information, physical disturbances (gait and posture abnormalities, and deteriorating perception) and a CCD assessment scale named the CCD rating scale (CCDR). The survey was conducted toward owners of dogs aged 10 years or older in two ways: A web-based (Web survey) and a paper-based (Paper survey) survey. To determine which physical disturbances were associated with CCD, ordinal logistic regression analyzes were performed. Through the Web survey, 726 valid responses were obtained, and the test results revealed that vision impairment, smell disturbance, tremor, swaying or falling and head ptosis were significantly associated with CCD. These items, except for head ptosis, were also significantly associated with, or tended to be associated with, CCD in 103 valid responses to the Paper survey. The prevalence of CCD was increased in the elderly dog population, especially in dogs aged 16 years or older. In contrast, physical signs gradually increased from 10 years of age. These results suggest that physical disturbances may appear in the early stages of CCD. In conclusion, the present study revealed new clinical signs of CCD linked to physical disturbances and suggested that these signs could be useful for detecting early stage of CCD.

**KEY WORDS:** canine cognitive dysfunction, clinical sign, dog, physical disturbance, questionnaire

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Canine cognitive dysfunction (CCD) is a behavioral syndrome that affects old dogs. Dogs with CCD show behavioral alterations such as disorientation, altered interactions with owners, other pets and the environment, sleep-wake cycle disturbance, house-soiling and changes in activity [14]. Such dogs may have severely impaired cognitive function that is considered to be similar to dementia in humans.

A number of questionnaires have been proposed to assess CCD syndrome [6, 8, 20–22]. Among them, the CCD rating scale (CCDR), which is a questionnaire consisting of 13 behavioral items that is significantly associated with CCD, is considered to have a high diagnostic accuracy of 98.9% [25]. However, the questionnaires were filled in by owners and as a result are less objective. Therefore, clinical signs regarding CCD that veterinarians can directly observe are needed for more objective assessments.

In humans, a number of clinical signs have been used to detect and diagnose the dementia and related diseases. For example, motoric disorder, rigidity, gegenhalten and stooped posture are observed in the middle stages of Alzheimer's disease. Moreover, recent reports have demonstrated that mild cognitive impairment (MCI) syndrome, which is the intermediate stage between normal ageing with a slight cognitive decline and dementia, is associated with gait abnormalities [16]. Recently, motoric cognitive risk (MCR) syndrome that is characterized by a slow gait and cognitive impairment has been newly described as a prodementia syndrome [7].

Physical disturbances such as gait, posture disorders and decline in perception are also common in dogs with CCD. A report mentioned a non-significant trend toward an increased prevalence of blindness among dogs with CCD [22]. The CCD assessment

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questionnaire proposed by Kiatipattanasakul *et al.* [12] included items related to posture abnormalities. However, normal old dogs often present with various physical abnormalities, and the relation between such physical disturbances and CCD has not yet been fully clarified. Therefore, we conducted a large questionnaire survey and evaluated the relation between physical disturbances and CCD.

## MATERIALS AND METHODS

### Questionnaire

The questionnaire consisted of three sections; namely, general information, physical disturbances and CCDR. The general information included age, breed, sex, neutered state, body weight, housing (inside, outside or both), history of epilepsy (yes/no), vestibular disorder (yes/no) and diseases that influence gait and posture (yes/no, and if yes, write the name of the disease). The physical disturbances consisted of eight questions concerning gait and posture (circle the relevant ones, multiple answers are allowed) and three questions concerning perception (normal, impaired or complete loss) (Supplementary Table 1). The dog's sense of smell was difficult for owners to evaluate, so we asked questions concerning sniffing behavior (normal, decreased or complete loss). Supplementary Fig. 1a and 1b demonstrate the head ptosis and head tilt. The CCDR proposed by Salvin *et al.* [22] is a clinical assessment tool for CCD, and comprises 13 items related to CCD-related behaviors. We used the CCDR with a slight modification (Supplementary Table 2). Each item is scored with a five-point or three-point scale. The CCDR score was expressed as the sum of the scores of each question with the score of two items that contribute to CCD severity being weighted ( $Q 9 \times 2$ ,  $Q 11 \times 3$ ), and the addition of 14 points to adjust the highest total score to 80. Dogs with no behavioural changes scored 34, and the threshold for CCD was set at 50.

### Study setting

The owners of dogs that were 10 years old or older were asked to participate in two types of surveys: A web-based questionnaire survey (Web survey) and a paper-based questionnaire survey (Paper survey). In the Web survey, we prepared a questionnaire on the home page of the Laboratory of Veterinary Pathology, the University of Tokyo (<http://www.v.m.a.u-tokyo.ac.jp/byouri/>) between November 2013 and March 2014, and announced this to the owners of the dogs through Anicom Insurance Inc. by e-mail. In the Paper survey, we collected responses to questionnaire papers distributed to veterinary hospitals in Japan between December 2013 and April 2014. The data from the Web and Paper surveys were then analyzed, respectively.

### Statistical analyzes

All statistical analyzes were performed using JMP 11.0 software (SAS Institute, Cary, NC, U.S.A.) with a  $P < 0.05$  accepted as the priori significance level. To examine which factors were related to CCD, ordinal logistic regression analysis was adopted using the following explanatory variables: age, body weight (<5 kg, 5–10 kg, 10–15 kg, 15–20 kg, >20 kg), sex (male-intact, male-neutered, female-intact, female-neutered), housing, history of seizure, history of vestibular disorder, and history of diseases that influence gait and posture (yes/no), gait and posture abnormalities (awkwardness, swaying or falling, head ptosis, abasia, bedridden, head tilt and tremor), perception abnormalities (vision, hearing and smell).

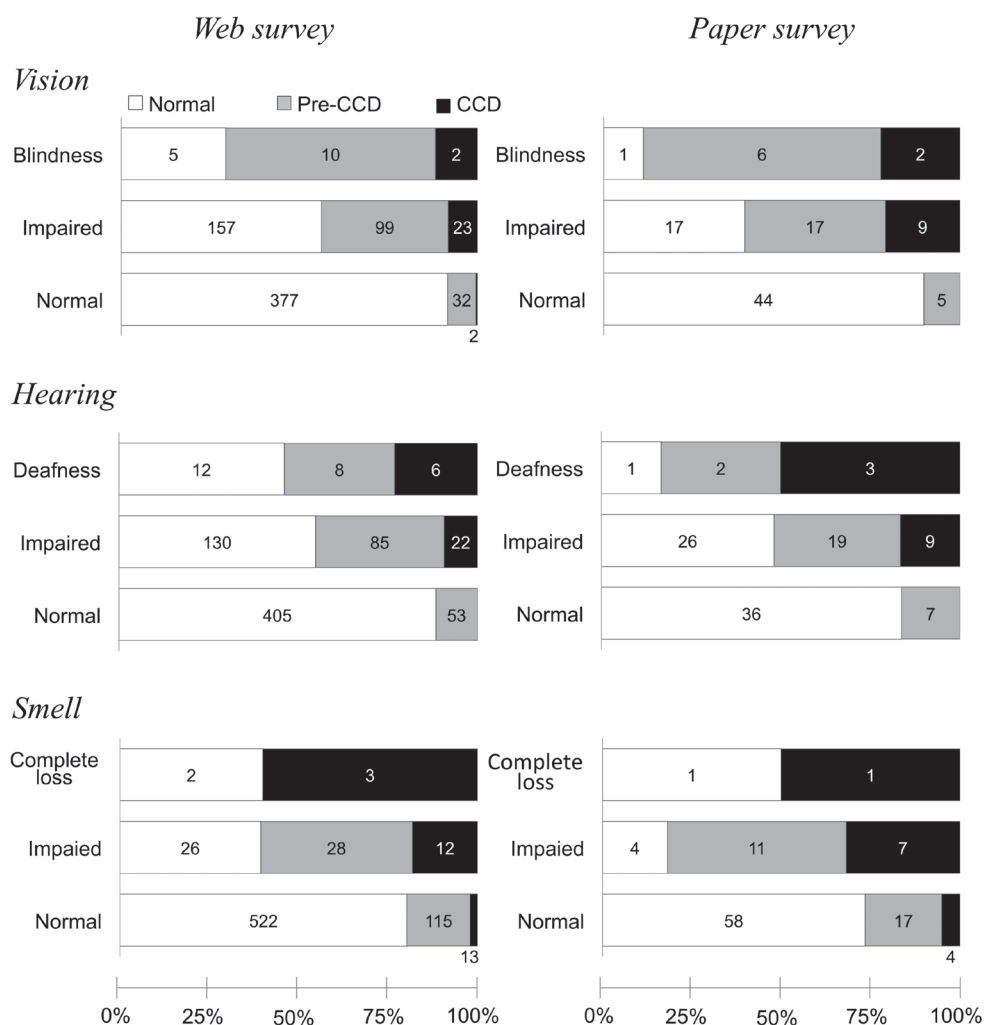
The severity of CCD was used as an ordinal dependent variable with three categories as follows: the dog was given a score of '3' and placed in the 'CCD' group if the CCDR score was 50 or above; the dog was given a score of '2' and placed in the 'Pre-CCD' group if the CCDR score was 40–49; the dog was given a score of '1' and placed in the 'Normal' group if the CCDR score was 39 or below. Likelihood ratio tests were used to test the significance of individual variables in the model.

## RESULTS

Seven hundred and twenty-six valid responses were obtained from the Web survey. Male dogs (53%) slightly outnumbered female dogs (47%). The median age of the dogs was 12 years old, and the majority were neutered, housed inside and less than 10 kg. On the other hand, 103 valid responses were obtained from the Paper survey. Female dogs (52%) outnumbered male dogs (41%), and 7% were unknown. The median age of the dogs was 13 years old, and the numbers for the neutered state, housing and body weight were similar to those of the Web survey. Diseases that influenced gait and posture changes reported by the owners were arthritis, spondylosis deformans, intervertebral disk displacement, cauda equina syndrome, hip dysplasia, patella dislocation, anterior ligament cruciate injury, fracture, encephalitis and generalized tremor syndrome. Detailed characteristics of each group, Pre-CCD, CCD and Normal, are described in Supplementary Table 3. Results of the physical disturbances for each group, Pre-CCD, CCD and Normal, are summarized in Fig. 1 and Supplementary Table 4.

Table 1 shows the results of ordinal logistic regression. 'Vision' ( $\chi^2=30.21$ ,  $P < 0.0001$ ) was strongly associated with CCD in the Web survey, followed by 'smell' ( $\chi^2=12.97$ ,  $P=0.0015$ ), 'tremor' ( $\chi^2=10.97$ ,  $P=0.0009$ ), 'age' ( $\chi^2=9.57$ ,  $P < 0.0020$ ), 'swaying or falling' ( $\chi^2=5.55$ ,  $P=0.0185$ ) and 'head ptosis' ( $\chi^2=4.91$ ,  $P=0.0266$ ). 'Hearing' showed only a tendency towards significance ( $\chi^2=4.61$ ,  $P=0.10$ ). 'Swaying or falling' ( $\chi^2=8.20$ ,  $P=0.0042$ ), 'smell' ( $\chi^2=6.20$ ,  $P=0.0451$ ) and 'tremor' ( $\chi^2=4.40$ ,  $P=0.0359$ ), were also significantly associated with CCD in the Paper survey, and 'vision' ( $\chi^2=5.73$ ,  $P=0.057$ ) and 'age' ( $\chi^2=3.13$ ,  $P=0.0769$ ) showed a tendency towards significance. 'Head ptosis' was not associated with CCD in the Paper survey.

The estimated prevalence of CCD detected by the CCDR was 18% (18/101) in the dogs 14 years or older based on the Web survey. It was less than 5% in dogs 13 years old or younger, and increased in the older dogs, especially those aged 16 years or older (7% of 14 years old, 6% of 15 years old, 36% of 16 years old, and 80% of 17 years old or older) (Fig. 2). In contrast,

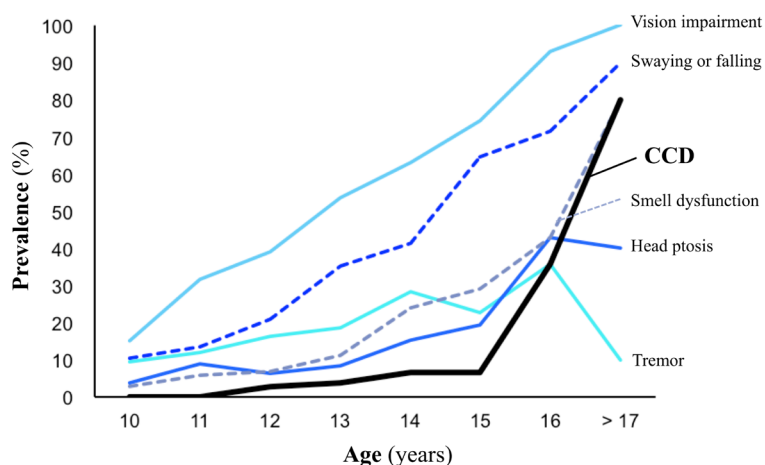


**Fig. 1.** Percentages of the three groups: Pre-CCD, CCD and Normal in dogs with impaired, complete loss (blindness, deafness) and normal vision, hearing and smell, respectively. CCD; dogs with a score of 50 or above, Pre-CCD; dogs with a score of 40-49, and Normal; dogs with a score of 39 or below on the canine cognitive dysfunction rating scale (CCDR). The numbers inside the bars indicate the number of dogs.

**Table 1.** Results of ordinal logistic regression analyses on 726 dogs from the Web survey and 103 dogs from the Paper survey

Variables	Web survey		Paper survey	
	Estimate	P	Estimate	P
Age	0.256	0.002	0.318	0.086
Tremor	0.453	0.0007	1.026	0.047
Swaying or falling	0.303	0.017	1.517	0.008
Head ptosis	0.379	0.021	0.007	ns
Awkwardness	0.211	0.075	0.374	ns
Vision				
Impaired (v.s. normal)	1.307	<0.0001	2.08	0.061
Blind (v.s. impaired)	0.772	ns	1.281	ns
Hearing				
Impaired (v.s. normal)	0.532	0.048	0.66	ns
Deaf (v.s. impaired)	0.261	ns	0.963	ns
Smell				
Impaired (v.s. normal)	0.819	0.01	2.017	0.031
Complete loss (v.s. impaired)	2.387	0.058	1.317	ns

ns, Not significant.



**Fig. 2.** The Prevalence of canine cognitive dysfunction (CCD) [canine cognitive dysfunction rating scale (CCDR)  $\geq 50$ ] and physical signs.

physical signs, especially vision impairment and swaying or falling, gradually increased from 10 years old (Fig. 2).

## DISCUSSION

In the present study, we obtained 726 responses to the questionnaire through the Web survey. The results of the analysis demonstrated that physical disturbances such as vision impairment, smell disturbance, tremor, swaying or falling and head ptosis were related to CCD. The Paper survey showed similar results in which vision impairment, smell disturbance, tremor and swaying or falling were related to CCD (Table 1). Head ptosis was not, however, associated with CCD. The small sample size of the Paper survey may have failed to detect head ptosis.

Vision impairment was observed in more than 90% CCD dogs in the Web survey, and most strongly involved physical disturbance in the CCD. Vision impairment has also been suggested to relate to dementia and neurodegenerative diseases in humans [3, 5, 9, 15, 24]. For example, vision impairment is common among the earliest in Alzheimer's disease, and some of ocular tests are thought to be potential biomarkers to detect early stage of this disease [5]. Pathological changes in the eyes, such as retinal nerve fiber layer thinning, senile plaques and neurofibrillary tangles in the retina, optic nerve head cupping, and changes within the lens and blood vessels have been noted in these human diseases [5]. Pathological changes in the central nervous system have also been suggested to relate to vision impairment in dementia. Alzheimer's disease patients have often impaired motion sensitivity, and this has thought to due to selective damage to the magnocellular pathway that is involved in the processing of motion and critical for the projection of visual signal from the primary visual cortex area 17 and 18 [5]. Considering these facts in human, dogs with CCD thought to have some pathological changes in the visual perception route associated with behavioral changes. Besides, human age-related eye diseases are suggested to aggravate cognitive decline. It is hypothesized that the loss of vision at older ages results in adverse effects on brain functions because the visual loss leads to a decrease in physical, cognitive, and social stimulation over time [9]. Vision impairment itself may also aggravate the CCD condition in old dogs.

Smell disturbance is thought to be caused by pathological changes in the olfactory perception route, including the olfactory epithelium, olfactory bulb, piriform cortex, amygdala and entorhinal cortex. In humans, smell dysfunction is associated with neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, as well as MCI [17, 19]. In the Alzheimer's disease the olfactory bulb is affected at the late stages and in the Parkinson's disease the olfactory bulb and piriform cortex are affected from the early stages, and these pathological changes in the brain have been thought to relate to smell dysfunction in these two disease. Dogs with CCD may also undergo similar pathological changes in the olfactory perception route.

Tremor, swaying or falling, and head ptosis may be induced by changes in the nervous, muscular or skeletal systems concerning motor function. Tremor, swaying or falling and head ptosis are all involved in extrapyramidal symptoms in humans. The extrapyramidal symptoms are caused by impairment of extrapyramidal pathway of the central nervous system that comprises various basal ganglia, thalamus, cerebellum and cerebral cortex, and induce characteristic movement and posture disorders. The representative extrapyramidal disease in humans is Parkinson's disease; it is caused by loss of neurons in the substantia nigra and the patients present with extrapyramidal symptoms such as tremor, bradykinesia, rigidity and postural instability. Some of the symptoms are also common in Alzheimer's disease patients in the late stages [11]. Other pathological changes in the brain that may be associated with gait and posture disturbances are an age-related cerebral white matter decrease and micro-vascular lesions. These changes are reported to be associated with gait dysfunction, falling and imbalance in human patients [1, 13, 23, 25]. Neuronal loss in the basal ganglia [2, 10], a decrease in cerebral white matter and an increase in cerebral amyloid angiopathy (CAA) have been reported in old dogs [4]. These pathological changes might develop with CCD.

As described above, all of the physical disturbances observed in the present study are similar to those of human dementia

diseases. Our results may suggest that CCD have similarities in physical changes, as well as behavioral and pathological changes, to human dementia.

The present study revealed some physical signs associated with CCD. These signs are easily detectable for veterinarians even if the owners do not complain about any behavioral changes of their animals. Therefore, the physical signs extracted in the present study are useful predictive tools to determine CCD.

Based on the Web survey, the prevalence of CCD determined by CCDD was 18% in dogs of 14 years of age or older. This result was similar to a previous cross-sectional study which reported the prevalence of CCD as 14.4% in dogs of 14 years of age or older using CCDD [18]. In both the present and the previous studies, the prevalence rate was less than 5% in dogs under 13 years old, but sharply increased in older dogs [18]. However, CCD condition is thought to progress gradually. The early stages in CCD condition may be difficult to detect using the questionnaire about behavioral changes. On the other hand, some physical disturbances gradually increased even in dogs aged less than 13 years in present study. Therefore, the physical disturbances that we extracted in this study are considered to be useful for the early detection of CCD.

In conclusion, the results of the present study suggested that physical disturbances such as vision impairment, smell disturbance, tremor, swaying or falling and head ptosis are physical signs of CCD. In addition, these clinical signs are possibly evident even in the preclinical or early stages of CCD, and may be useful for early detection of the syndrome. The present findings also suggest that CCD has similarities to the physical signs, as well as behavioral and pathological changes, of human dementia.

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