Pakistan Veterinary Journal

ISSN: 0253-8318 (PRINT), 2074-7764 (ONLINE)
Accessible at: www.pvj.com.pk

CASE REPORT

Cognitive Dysfunction Syndrome with Lipofuscinosis in a Maltese Dog

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ARTICLE HISTORY (16-028)

Received:	February 04, 2016
Revised:	April 25, 2016
Accepted:	April 26, 2016
Published online:	July 02, 2016

Key words:
Brain atrophy
Cognitive dysfunction syndrome
Interthalamic adhesion thickness
Lipofuscin

ABSTRACT

A 16-year-old castrated Maltese was presented by its owner with a 6-month history of progressive cognition failure and behavioral changes. Based on a cognition and behavior evaluation and neurologic and blood examinations, cognitive dysfunction syndrome (CDS) was suspected. Magnetic resonance imaging revealed severe brain atrophy and reduced interthalamic adhesion thickness. A histopathologic examination in biopsied brain tissue revealed multifocal accumulation of lipofuscin in the hippocampus. Based on the cognition and behavior evaluation, diagnostic imaging, and histologic findings, the dog was diagnosed as having CDS with lipofuscin accumulation. To our knowledge, this is first case report of canine CDS induced by lipofuscinosis.

To Cite This Article: Park SG, Kang MH, Lee CM, Sur JH and Park HM, 2016. Cognitive dysfunction syndrome with lipofuscinosis in a Maltese dog. Pak Vet J, 36(4): 508-510.

INTRODUCTION

Cognitive dysfunction syndrome (CDS) is a progressive neurodegenerative disorder common in older dogs that leads to a diminishment of cognitive function (Osella *et al*., 2007). In one study, 68% of owners of 15- to 16-year-old dogs reported observing at least one behavior or condition category consistent with cognitive dysfunction (Nielson *et al*., 2001). Behavioral change associated with canine CDS are abundant, including changes in social interactions and general activity, becoming easily lost in previously familiar environments, experiencing disturbances in the sleep-wake cycle, and urinary and fecal incontinence (Rofina *et al*., 2006). A diagnosis of CDS in dogs is based on identifying age-related behavioral changes, excluding other disease processes, performing magnetic resonance imaging (MRI), and determining histochemical findings of the brain (Dewey, 2016). In this case report, we describe the behavioral, diagnostic imaging, and histochemical findings related to CDS in an elderly Maltese dog.

Case history and findings: A 16-year-old castrated Maltese was presented by its owner with a 6-month history of progressive behavioral changes, including loss of learned behaviors and inappropriate urination and defecation. Physical examination revealed an obtunded mental status, as well as severe abnormality in the cognition and behavior score (Table 1). However, the neurologic examination, complete blood count, serum biochemistry, and urine analysis showed no abnormalities. Based on the evidence of cognition and behavioral changes, CDS was highly suspected.

To rule out other intracranial disease, 1.5 Tesla MRI (Magnetom Essenza, Siemens Healthcare, Erlangen, Germany) was performed. The MRI scan revealed a severely enlarged subarachnoid space in the overall brain region, moderate ventriculomegaly of the lateral ventricle (right-side diameter: 13.16 mm, left-side diameter: 12.85 mm), and reduced interthalamic adhesion thickness (2.93 mm) using the method previously described by Hasegawa *et al*. (2005). The interthalamic adhesion was measured the linear distance between third ventricle in T1-weighted image (WI) and T2WI transverse images which contained the pituitary gland; (3.31+2.55)/2=2.93mm (Fig. 1). The CSF analysis showed no abnormality. Based on these findings, other possible causes of cognitive impairment were ruled out and a tentative diagnosis of CDS was made.

The dog was started on medical management with selegiline (1 mg/kg PO SID) (Jumex Tab, Han Dok Pharm, Korea) and a therapeutic diet (Prescription Diet® Canine b/d®, Hills Pet Nutrition). Environmental enrichment, such as increased exercise, novel toys, and continued education with previous cognitive experience, was also encouraged to enhance cognitive function. The cognitive and behavior score was re-evaluated 2 weeks after the initial presentation, but no improvement was noticed. Three weeks after the presentation, the dog

experienced a natural death during his sleep. Histochemical staining revealed a negative response to Congo red staining and multifocal plaque in Ziehl–Neelsen staining (Fig. 2).

DISCUSSION

It is important to distinguish severe behavioral changes that may be caused by pathological impairment which leads to functional impairment and eventually death from more mild age-related changes (Osella *et al*., 2007). According to a previous study (Rofina *et al*., 2006), the cognition and behavior evaluation index correlates with pathologic changes of the brain. In this case, the cognition and behavior evaluation score was 33 points (score range: 10 to 41, with scores above 10 representing an abnormality), which implies that the dog may have experienced pathologic brain changes.

Imaging findings using MRI revealed marked brain atrophy, generally enlarged subarachnoid space, and severe ventriculomegaly of the lateral ventricle. However, these findings are consistent with the normal aging process, and they may be found in older patients without evidence of CDS. Therefore, other criteria were needed to distinguish pathologic changes from normal aging. In one study, the interthalamic adhesion thickness measured on transaxial T1 and T2 MR images was found to be significantly smaller in dogs with CDS compared to dogs without CDS. An interthalamic adhesion thickness of 5.0 mm or less could be an indication of pathologic brain atrophy (Hasegawa *et al*., 2005). In this case, the interthalamic adhension thickness was 2.93 mm, which indicated that the brain atrophy in this dog should be associated with CDS.

Canine CDS is believed to be similar to human Alzheimer's disease (AD), particularly regarding pathological brain changes (Rofina *et al*., 2006). However, microscopic findings in the brains of human patients with AD, which include the presence of neurofibrillary tangles, hirano bodies, and granulovacuolar degeneration bodies in the parietal cortex and hippocampus, are not found in canine CDS (Yu *et al*., 2011). CDS has a complicated and interrelated pathophysiology that includes oxidative damage, inflammation, impairment of mitochondrial function, DNA damage, altered gene expression, and vascular compromise (Dewey, 2016). The deposition of amyloid protein and oxidative damage products might be important indicators for the pathologic brain change (Head *et al*., 2008). Lipofucin is a lipidic pigment composed of peroxidized lipids and proteins that is an age-related oxidative damage product (Head *et al*., 2008). In previous studies, oxidative damage was found to induce neuronal cell death, while amyloid plaque had no clear relation to neuron loss (Schmitz *et al*., 2004). In addition, a higher correlation between dementia score and lipofuscin than dementia score and the amyloid protein has been observed (Rofina *et al*., 2006). Oxidative damage may be a more important component than amyloid protein in the pathogenesis of CDS (Schmitz *et al*., 2004). In this case, a positive response to Ziehl–Neelsen staining and a negative response to Congo red staining was shown. These results represent an accumulation of lipofucin and an absence of the amyloid protein. We therefore concluded that a large accumulation of lipofuscin without amyloidosis as an age-related oxidative damage product may have impaired cognitive function in this case.

Selegiline is a selective and irreversible inhibitor of monoamine oxidase B (MAOB) that decreases levels of free radical load in the brain and improves neuronal impulse transmission (Landsberg *et al*., 2012). Cognitive improvement generally occurs within the first month of therapy. A therapeutic diet that consist of antioxidants, mitochondrial cofactors, and essential fatty acids improves cognitive function and delays cognitive decline in dogs with CDS (Landsberg *et al*., 2012). Also, environmental enrichment and continued education with previous cognitive experience improve cognitive function (Ikeda-Douglas *et al*., 2004). However, in this case study, we could not evaluate treatment response due to the death of the dog.

Table 1: Cognition and behavior score* in this case

Items	Point	Patient's condition	Score
Appetite			3
Normal	1		
Decreased	2		
Increased with diarrhea	3	X	
Increased without diarrhea	4		
Drinking			3
Normal	1		
Polydipsia	3	X	
Active incontinence			4
Not incontinent	1		
Urinates indoors	2		
Urinates and defecates in the house	4	X	
Day/night rhythm			2
Normal	1		
Sleeping increased	2	X	
Sleeps at day, restless at night	3		
Aimless behavior			4
No aimless behavior	1		
Star gazing	2		
Stereotyped walking	3		
Circling	4	X	
Activity/interaction			2
Normal	1		
Decreased	2	X	
No contact with the environment/owner	4		
Loss of perception			5
No loss of perception	1		
Collides into furniture	2		
Tries to pass through narrow spaces	5		
Tries to pass through the wrong side of the door	5	X	
Disorientation			5
No disorientation	1		
On new walks	2		
On daily walks	4		
At home	5	X	
Memory			4
Normal	1		
No recognition of acquaintance	2		
No recognition of the owner after a holiday	4	X	
No recognition of the owner on a daily basis	5		
Personality change			1
No change	1	X	
Aggressive towards other pets and/or children	3		
Aggressive towards the owner	4		
Total score (Minimum: 10, Maximum: 41)			33

*Scoring system was adapted from Rofina *et al.* (2006).

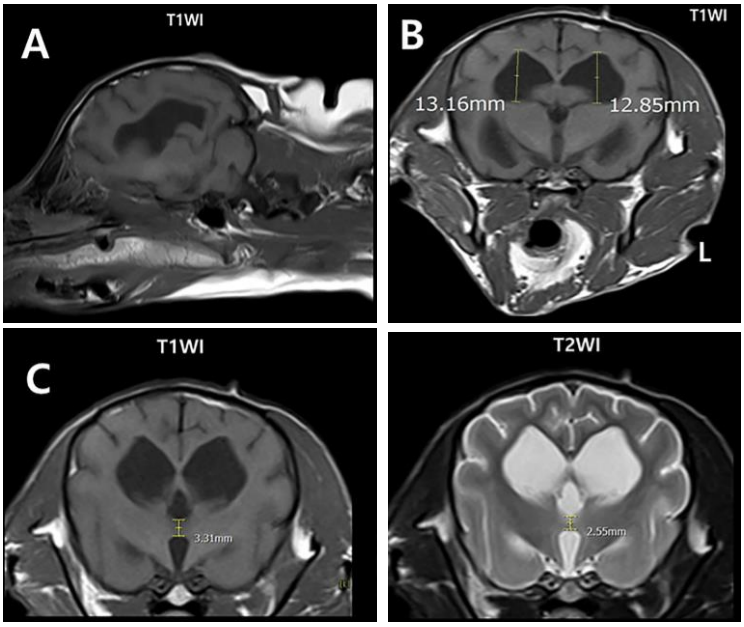

Fig. 1: Magnetic resonance images of a dog in this case. (A) Generally enlarged subarachnoid space and (B) ventriculomegaly of lateral ventricle (Right side diameter: 13.16mm, Left side diameter: 12.85mm) were observed. (C) Reduced mean interthalamic adhension thickness (2.93 mm) was also detected on transverse images.

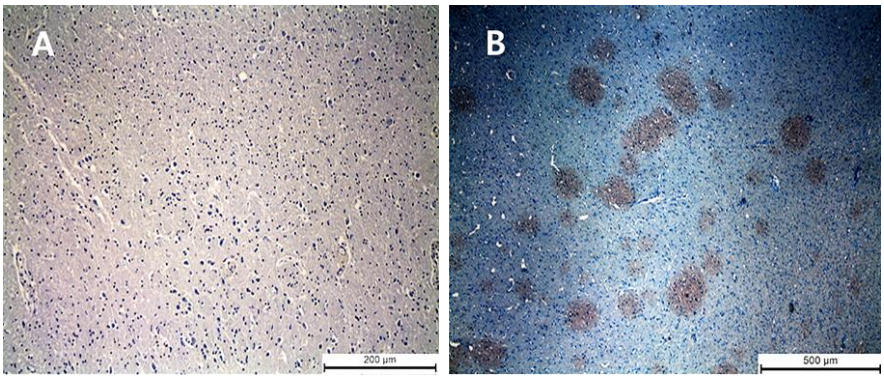

Fig. 2: Histopathologic examination of biopsied frontal lobe of brain revealed negative response to Congo red staining (A, Bar=200 μm) and multifocal plaque in Ziehl–Neelsen staining (B, Bar=500 μm).

Conclusions: This case has demonstrated canine CDS with lipofuscin accumulation in the hippocampus of the brain. To our knowledge, this is the first case report of CDS induced by lipofuscinosis in the canine species.

Authors' contributions: PSG took part in the care of the patient and contributed in preparation of the manuscript. The manuscript was prepared by PSG under the supervision of KMH, LCM and PHM. SJH analyzed tissue sample. All authors critically revised the manuscript and approved the final manuscript.

Acknowledgements: This work was supported by Konkuk University in 2015.

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