Gangliosidoses in cats

Latticha Pluemhathaikij1 Waruntip Bunyaputikul2 Katriya Chankow1,2 Benchaphorn Limcharoen3 Nardtiwa Chaivoravitsakul2 RampaiPat Penchome2 Sawang Kesdangsakonwut1 Kasem Rattanapinyopituk1 Wijit Banlunara1*

Abstract

Two 3-month-old, male, domestic short hair, cats of the same litter were presented to the small animal teaching hospital with the clinical sign of head tremor for 2 weeks. Three months later, the clinical sign had worsened. Both kittens had loss of balance and showed intention tremor. Physical examination revealed hypertelorism, depressed bridge of the nose and back pain. Radiography showed shortened cervicothoracic vertebral bodies. Both kittens died at 8 and 9 months of age, case no.1 and 2 respectively. Both carcasses were submitted for necropsy. Both brains were grossly normal. The costal cartilages of both cats were deformed into an ‘S’ shape with normal cartilage consistency. The histopathology showed swollen neurons with multiple intracytoplasmic fine eosinophilic granular substance, leading to the diagnosis of lysosomal storage disease. The periodic acid-Schiff’s (PAS) and Luxol fast blue (LFB) staining were positive and transmission electron microscopy revealed membranous cytoplasmic bodies and zebra bodies in the neurons. With the combination of clinical and pathological examination, gangliosidoses was diagnosed. This is the first report of Gangliosidoses in domestic short hair cats in Thailand.

Keywords: cat, electron microscopy, lysosomal storage disease, GM1 gangliosidosis, GM2 gangliosidosis

1Department of Pathology, Faculty of Veterinary Science, Chulalongkorn University, 39 Henri-Dunant Rd., Patumwan, Bangkok 10330, Thailand
2The Small Animal Teaching Hospital, Faculty of Veterinary Science, Chulalongkorn University, 39 Henri-Dunant Rd., Patumwan, Bangkok 10330, Thailand
3Department of Anatomy, Faculty of Veterinary Science, Chulalongkorn University, 39 Henri-Dunant Rd., Patumwan, Bangkok 10330, Thailand
*Correspondence: wijit.k@chula.ac.th (W. Banlunara)
Received: March 15, 2022
Accepted: May 4, 2022
https://doi.org/10.14456/tjvm.2022.49

**Introduction**

Lysosomal storage diseases are inherited diseases caused by a deficiency of enzyme, which leads to lysosomal catabolic pathway impairment (Skelly and Franklin, 2002). Lysosomal storage diseases are found in many species including humans, cats, dogs, horses, sheep, goats, cattle, mice, rats, guinea pigs, pigs, quail and emus (Haskins et al., 2006). Gangliosidoses are a group of lysosomal storage diseases which cause a defect in breaking down ganglioside and oligosaccharide, caused by autosomal recessive disorder. There are two major groups of gangliosidoses; GM1 and GM2 gangliosidosis. GM1 gangliosidosis is caused by a deficiency of β-galactosidase. GM2 gangliosidosis is caused by a deficiency of hexosaminidases A, B, AB or ganglioside activator protein (Summers et al., 1995; Kumar et al., 2021). GM1 gangliosidosis has been reported in Siamese cats (Baker et al., 1971), Korat cats (De Maria et al., 1998) and domestic short hair cats (Uddin et al., 2013) and GM2 gangliosidosis has been reported in domestic short hair cats (Cork et al., 1977), Japanese domestic cats (Neuwelt et al., 1985) and Korat cats (Yamato et al., 2004). At 3 to 6 months of age, the animal usually shows progressive central nervous system (CNS) signs, especially cerebellar medullary signs such as ataxia, balance loss, head tremor and abnormal nystagmus (Summers et al., 1995). Due to non-specific symptoms and the rareness of this disease, diagnosis may be difficult and could importantly be overlooked. The domestic short-hair breed is the most common breed in Thailand and is also frequently reported to have many lysosomal storage diseases (Skelly and Franklin, 2002). To date, there is still limited information about Gangliosidoses in cats. This is the first report of Gangliosidoses in domestic short hair cats in Thailand.

**Materials and methods**

**Case history:** A 3-month-old, male, domestic short hair cat (case no. 1), visited the Small Animal Teaching Hospital, Faculty of Veterinary Science, Chulalongkorn University with the clinical sign of head tremor for 2 weeks. The animal had normal appetite, urination and defecation, but had difficulty in bowing. During the next visit in 3 months, the cat had loss of balance and intention tremor. On physical examination, the cat had hypertelorism, a depressed bridge of the nose and back pain. Pupillary light, menace and palpebral reflexes were positive. On radiography, the cat had shortened cervicothoracic vertebral bodies and mucopolysaccharidosis was suspected. Complete blood count and blood chemistry analysis were performed on the first visit. The cat was treated with 10 mg/kg gabapentin and multivitamin, q 12 hr. The cat died at 8 months of age. Another male cat from the same litter (case no. 2) also visited the hospital on the same days, had the same clinical signs and treatment, and died at 9 months of age.

Both carcasses were submitted to the Pathology unit for necropsy. The tissue samples were collected and fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned in 4 μm thickness tissue sections and stained with hematoxylin and eosin (H&E) and Luxol fast blue (LFB) for histopathology (Luna, 1968). The brain tissue of case no.2 was stored at -20°C, embedded in OCT compound. The frozen tissue blocks were sectioned at 5 μm thickness. The frozen sections were stained with periodic acid–Schiff’s (PAS) reaction (Luna, 1968). The brain sample of case no. 2 was fixed in 2.5% glutaraldehyde in phosphate buffer, processed in resin blocks, cut and stained with uranyl acetate and osmium tetroxide and counterstained with lead citrate for transmission electron microscopy examination (TEM; JEM-2100, Japan) at the Scientific and Technological Research Equipment Centre, Chulalongkorn University (TEM-STREC).

**Results and Discussion**

**Complete blood count and blood chemistry:** Both cats had thrombocytopenia (84,000 and 114,000 cells/μL) and leukocytosis (28,950 and 27,230 cells/μL), Case No.1 and 2 respectively. Case no.1 had neutrophilia and lymphocytosis, 13,722 and 13,809 cells/μL respectively. Case no.2 had neutrophilia, 19,442 cells/μL. Case no.1 had elevated alkaline phosphatase (133 U/L) and case no.2 had mildly elevated alanine aminotransferase (90 U/L).

**Gross pathology:** Both cats were at a poor nutritional stage. Both cats had hypertelorism and depressed bridge of the nose (Fig. 1a&b). Both brains were grossly normal (Fig. 2a). The costal cartilages of both cats were deformed into an ‘S’ shape with normal cartilage consistency (Fig. 2b). Case no.1 had severe hypertrophic cardiomyopathy with mild multifocal petechial hemorrhage at the epicardium, hepatic lipidosis and mild splenomegaly. Case no.2 had a mildly swollen pancreas and mesenteric lymphadenopathy.

**Histopathology, histochemistry and TEM:** Both cats shared the same histopathological changes and histochemistry cellular component in the central and peripheral nervous system, liver and pancreas. The neurons of the cerebral, cerebellum and ganglionic neurons of the peripheral nervous system were swollen. There was eosinophilic fine granular substance in the cytoplasm of neurons (Fig. 3a&b). Multifocal axonal spheroids were observed. Special histochemistry using periodic acid–Schiff’s (PAS) reaction and Luxol fast blue (LFB) stain in the brain section was positive in intracytoplasmic granules in the neurons and gitter cells (Fig. 4a&b). The ultrastructural examination of the cerebral cortex showed numerous membranous cytoplasmic bodies in neurons (Fig. 5a). Zebra bodies were also observed in the cytoplasm (Fig. 5b). There were severe diffuse intracytoplasmic vacuoles in the hepatocytes. Diffusely decreased zymogen granules in the exocrine pancreatic acinar cells were observed. Case no.1 had severe suppurative myocarditis and mitral valvular endocarditis with intralobular bacterial colonies. The cause of death of case no.1 was Gangliosidoses and bacterial...
septicemia. Case no.2 had moderate multifocal pyogranulomatous nephritis with lymphoid depletion and necrosis. The cause of death of case no.2 was Gangliosidoses with underlying viral infection, most suggestive of feline infectious peritonitis. Based on the clinical signs, gross and histopathology, there was no significant inflammatory lesion within the nervous system. In case no.1 the cat had bacterial septicemia which was a concurrent lesion and was not related to Gangliosidoses. In case no.2, the cat had moderate multifocal pyogranulomatous nephritis with lymphoid depletion and necrosis which is most suggestive of feline infectious peritonitis. However, it was also a concurrent lesion and was, also, not related to Gangliosidoses. The lesion of lysosomal storage disease is quite specific and cannot differentiate with other diseases.

Figure 1  Hypertelorism and depressed bridge of nose, case no. 1 (a), case no. 2 (b).

Figure 2  Grossly normal brain, case no. 2 (a). Deformed ‘S’ shape costal cartilages with normal cartilage consistency, case no. 1 (b).
The clinical signs of balance loss and intention tremor correlated with clinical signs described in Gangliosidoses (Summers et al., 1995). However, the symptoms were not specific to lysosomal storage disease. The combination of signalment, clinical signs, radiographs, histopathology, histochemistry and ultrastructure examination (Summers et al., 1995; Skelly and Franklin, 2002) led to a differential diagnosis of lysosomal storage disease; mucopolysaccharidosis. The transmission electron micrographs showing numerous membranous cytoplasmic bodies and zebra bodies in the neurons led to the differential diagnosis of Gangliosidoses and Sphingomyelinosis, and mucopolysaccharidosis.
could be ruled out. The PAS and LFB stains highlighted the intracytoplasmic granules. This could rule out Sphingomyelinosis. The definitive diagnosis in this cat was made based on transmission electron micrographs, together with PAS and LFB staining. The histopathology findings of swollen neurons were similar to a previous report of Gangliosidoses (Müller et al., 2001 and Porter et al., 2010). The genetic background of both cats also confirms the genetic etiology for Gangliosidoses. The intracytoplasmic vacuolization in the hepatocytes had been previously described in Gangliosidoses (Summers et al., 1995). There was no related data about decreased zymogen granules in pancreatic tissue and bone deformity in Gangliosidoses. These findings might be related to the poor nutritional stage in this cat. The blood result was done on the first visit which was 5 and 6 months apart from the death date, therefore it cannot be used for discussion.

In antemortem cases, Gangliosidoses and other lysosomal storage diseases can be diagnosed by lysosomal enzyme analysis. This method can identify the deficient enzyme by evaluating the activities of selected lysosomal enzymes. The appropriate samples will include whole blood leukocytes, liver and kidneys biopsy samples and cultured skin fibroblasts. In dogs and cats, the analysis technique and artificial substrates are similar to humans (Skelly and Franklin, 2002). Unfortunately, there is no available laboratory for lysosomal enzyme analysis in cats in Thailand. Another diagnostic method is molecular genetic testing (Skelly and Franklin, 2002). There are reports of the mutation of β-galactosidase (GLB1) gene in GM1 gangliosidosis cats (Uddin et al., 2013; Ueno et al., 2001 and 2005), GM2 activator protein (Martin et al., 2005) in GM2 gangliosidosis of cats.

Diagnosing lysosomal storage diseases is a challenge for veterinarians due to limited incidence and information about these diseases. Hopefully, this report may aid veterinarians’ awareness on neurological patients by considering these diseases as one of the differential diagnoses, which can definitely lead to developing more precise diagnostic techniques and treatment. There have been several reports about Gangliosidoses in humans in Thailand but there are no reports in animals. These cases are the first report with a complete pathological confirmation of Gangliosidoses in domestic short hair cats in Thailand.

Acknowledgements

This case study was financially supported by Veterinary Science Graduate Studies, Chulalongkorn University for electron microscopy work.

References


