

A Retrospective Histopathological Survey on Canine and Feline Liver Diseases at the University of Tokyo between 2006 and 2012

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ABSTRACT. To determine the incidence of hepatic diseases in dogs and cats in Japan, a retrospective study was performed using data of 463 canine and 71 feline liver biopsies at the Veterinary Medical Center of the University of Tokyo. The most common canine hepatic disease was microvascular dysplasia (MVD) and occupied 29.4% of all diagnoses. This terminology might contain “real” MVD and primary portal vein hypoplasia, because these two conditions were difficult to be clearly distinguished histopathologically. Parenchymal and interstitial hepatitis and primary hepatic tumors accounted for 23.5% and 21.0% of the diagnoses, respectively. Parenchymal and interstitial hepatitis occupied 34.1% of non-proliferative canine hepatic diseases, while hepatocellular adenoma and carcinoma were 26.6% and 24.5% of proliferative hepatic diseases, respectively. Breed-specificity was seen in MVD for Yorkshire terrier, Papillon and Toy poodle, in hepatitis for Doberman pinscher and Labrador retriever, in cholangiohepatitis for American cocker spaniel, Miniature schnauzer and Pomeranian, in hepatocellular adenoma for Golden retriever and Shiba and in hepatocellular carcinoma for Shih Tzu. The most common feline liver disease was parenchymal and interstitial hepatitis (45.1% of all diagnoses). Among feline hepatitis, neutrophilic cholangiohepatitis (23.9%), lymphocytic cholangiohepatitis (14.1%) and chronic hepatitis (5.6%) were recorded. Adult polycystic liver disease was 5.6%. Among proliferative diseases in the feline liver (11.3% of the all), lymphoma (4.2%) and primary epithelial tumors (4.2%) including hepatocellular carcinoma, cholangiocellular adenoma and cholangiocellular carcinoma were observed. Hepatic degeneration was 14.1%, and MVD was 12.7%, respectively.

KEY WORDS: canine, epidemiology, feline, liver disease, pathology.

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Most of previous reports on canine liver diseases were concerned with chronic hepatitis [3, 5, 11, 29], some reported hepatocellular carcinoma and adenoma [10, 21, 23, 24] and microvascular dysplasia (MVD) [1, 18]. Regarding an incidence survey on feline liver diseases, only the one in the United States has been published [12], but there have been no data in Japan. There are many case reports concerning feline liver diseases, such as cholangitis/cholangiohepatitis [12, 13, 16, 20, 26] and hepatic lipidosis [2, 7, 8, 14], but was only a review article [30]. In 2006, the World Small Animal Veterinary Association (WSAVA) Liver Standardization Group proposed criteria for histological diagnosis of canine and feline hepatic diseases in order to unite interpretations by veterinary pathologists. After the WSAVA proposal, some reports [3, 25, 28] included retrospective reviews on diagnoses of canine liver diseases, in particular, hepatitis. Epidemiological reports on feline liver disease have never been made even after the proposal.

The aim of the present study is to reveal the incidence of hepatic diseases in dogs and cats in Tokyo area, Japan, through histopathological data.

MATERIALS AND METHODS

The pathological database at the Department of Veterinary Pathology, the University of Tokyo (UT) was used in the present study. The database consists of basic data of patients (age, breed and gender), clinical information and histopathological features of biopsy cases sampled at the Veterinary Medical Center (VMC) at UT. We searched the database using key words of “liver biopsy” or “liver”. Totally, 4,755 cases of dogs and 1,016 cases of cats were chosen, which had been biopsied during 6 years and 2 months, between November 2006 and December 2012.

Of the 4,755 cases of dogs and of 1,016 cases of cats, 463 and 71 were hepatic diseases, respectively. Among them, 414 and 68 cases were histopathologically available, respectively. These cases were reviewed histologically according to the WSAVA’s criteria by the pathologists. If there had been more than two diagnoses for one case, only a main diagnosis could be adopted. The diagnoses were basically based on the WSAVA criteria, but we adopted other diagnoses not within the criteria: the diagnosis “MVD” in the present study included primary portal vein hypoplasia, because these two diagnoses are difficult to be distinguished

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Table 1. Incidence of non-proliferative liver diseases in dogs

Diagnosis	Number of cases
Inflammatory responses	
Cholangiohepatitis	60
Canine chronic hepatitis	25
Liver fibrosis	13
Cholangitis	8
Liver cirrhosis	5
Acute hepatitis	3
Hepatic capsulitis	2
Periangitis	1
Liver abscess	1
Regressive changes	
Microvascular dysplasia	136
Hepatic degeneration	49
Hepatic necrosis	6
Hepatocyte atrophy	1
Dysplasia	1
Hemochromatosis	1
Progressive changes	
Granuloma	2
Extramedullary hematopoiesis	1
Hepatocyte swelling	1
Bile duct proliferation	1
Circulatory disturbance	
Congestive hepatopathy	2
Hematoma	1

histopathologically. In addition, we used the terms "hepatic degeneration" and "hepatic necrosis" for the diagnoses of cases otherwise we could not diagnose.

Statistical analysis was performed using a commercially available statistical software (JMP Pro 10). The χ^2 test was done to determine a breed predisposition in canine liver diseases. We then calculated odd ratios (ORs) and the 95% confidence intervals (CIs) for each breed. The ORs are defined to be significantly increased only when the OR and 95% CI were both more than 1. The Mann-Whitney *U* test was performed to know whether there was a significant age difference between the groups of MVD with or without portosystemic shunt (PSS) in dogs and to determine the significance of age difference between neutrophilic cholangiohepatitis and lymphocytic cholangiohepatitis in cats. $P < 0.05$ was considered to be statistically significant.

RESULTS

Canine liver biopsies: Of 4,755 canine biopsy cases, 463 (9.7%) were liver biopsies, including 320 (69.1%) non-proliferative and 139 (30.0%) proliferative liver diseases. In the remaining 4 cases, there were no significant lesions. The results are summarized in Tables 1–4.

Canine non-proliferative liver diseases: MVD occupied 42.5% (136 of 320) of non-proliferative diseases. The ratio

of MVD with PSS was 87.0% (114 of 131), and that without PSS was 13.0% (17 of 131). The data on PSS of the other 5 MVD cases were not available. Parenchymal and/or interstitial hepatitis accounted for 34.1% (109 of 320, 23.5% of all diagnoses), being the second popular non-proliferative liver disease in the dog. Parenchymal hepatitis included canine chronic hepatitis (22.9%, 25 of 109) and liver fibrosis (11.9%, 13 of 109), and interstitial hepatitis included cholangiohepatitis (55.0%, 60 of 109) and cholangitis (7.3%, 8 of 109). The hepatitis mentioned above was all chronic hepatitis. The third most often encountered liver disease was hepatic degeneration (15.3%, 49 of 320).

Each major non-proliferative disease had a breed-specific tendency. Among 136 cases of MVD, Yorkshire terriers ranked first (27 cases, 19.9%), toy poodles second (16 cases, 11.8%) and papillons third (13 cases, 9.6%). Female Yorkshire terriers were more susceptible than male ones (male/female=9:18), while males were more susceptible in toy poodles and papillons (male/female=11:5 and 12:1, respectively). The median age of MVD was 1 year and 9 months old, and the mean age was 3 years and 2 months old.

Among 60 cases of cholangiohepatitis, miniature dachshunds ranked the first (11 cases, 18.3%), and American cocker spaniels (5 cases, 8.3%), miniature Schnauzers (5 cases, 8.3%) and Pomeranians (5 cases, 8.3%) second. Male miniature dachshunds were more susceptible than females (male/female=9:2). The median age of the disease was 9 years and 7 months old.

Among 25 cases of canine chronic hepatitis, Labrador retrievers and Doberman Pinschers ranked the first (8 cases, 32.0%) and the second (3 cases, 12.0%), respectively. Females were more susceptible than males in both breeds [Labrador retrievers (male/female=1:7) and Doberman pinschers (male/female=1:2)]. The median age of the hepatitis cases was 8 years and 7 months old. Eight of the 25 canine chronic hepatitis cases had copper deposition. Two of the 8 cases were Doberman pinschers, and 1 was Labrador retriever, Bedlington terrier, Welsh corgi, Cavalier King Charles spaniel or a mixed breed.

Canine proliferative liver diseases: Of 139 cases of canine proliferative liver diseases, primary epithelial tumors were 74 cases [53.2%, including hepatocellular adenoma (26.6%) and hepatocellular carcinoma (24.5%)], followed by nodular hyperplasia (26 cases, 18.7%), primary non-epithelial tumors (23 cases, 16.5%) and metastatic tumors (16 cases, 11.5%). That is, primary hepatic tumors were 97 cases (21.0% of the all). Among the 113 neoplastic cases excluding nodular hyperplasia, hepatocellular adenoma was in the first place (37 cases, 32.7%) and hepatocellular carcinoma in the second (34 cases, 30.1%). There was no breed predilection in nodular hyperplasia. The median age of the lesion was 11 years and 9 months old, and no sex difference in the occurrence was observed. As for hepatocellular adenoma, Golden retrievers, Shibas and mixed breeds were of the highest incidence (13.5%, 5 of 37), respectively. The median age was 12 years and 1 month old, and there was no sex differences in each breed (16:21). In hepatocellular carcinoma, Shih Tzu was the breed of the highest incidence

Table 2. Breed, median age and male-to-female ratio of non-proliferative liver diseases in dogs

Diagnosis	Breed	Nm	Median age	Male:female	% ^{a)}	% ^{b)}	P value ^{c)}	OR	95% CI of OR
Cholangiohepatitis		60	9 y 7 m	28:32					
	Miniature Dachshund	11	10 y 9 m	9:2	18.3	15.62	0.455	1.21	0.63–2.34
	American Cocker Spaniel	5	9 y 6 m	2:3	8.3	1.65	<0.001	5.52	2.19–13.92
	Miniature Schnauzer	5	10 y 10 m	0:5	8.3	2.54	<0.001	3.52	1.40–8.84
	Pomeranian	5	9 y 1 m	2:3	8.3	3.17	0.003	2.80	1.11–7.01
Canine chronic hepatitis		25	8 y 7 m	7:17 (ND1)					
	Labrador Retriever	8	10 y 2 m	1:7	32.0	4.00	<0.001	11.44	4.92–26.62
	Doberman Pinscher	3	6 y 3 m	1:2	12.0	0.29	<0.001	50.93	14.64–177.16
Liver cirrhosis		5	10 y 2 m	0:5					
	Labrador Retriever	3	10 y 2 m	0:3	60.0	4.00	<0.001	36.20	6.04–217.04
	American Cocker Spaniel	2	9 y 6 m	0:2	40.0	1.65	<0.001	40.13	6.68–241.27
Microvascular dysplasia		136	1 y 9 m	67:69					
	Yorkshire Terrier	27	3 y	9:18	19.9	4.49	<0.001	5.45	3.55–8.37
	Toy Poodle	16	1 y 5 m	11:5	11.8	5.85	0.011	2.17	1.28–3.67
	Papillon	13	2 y 6 m	12:1	9.6	2.48	<0.001	4.27	2.39–7.64

Nm, number of cases; OR, odds ratio; CI, confidence interval; ND, no data available; y, year (s); m, month (s). a) The number of cases of a breed / the total number of cases with the diagnosis X 100. b) The number of cases of a breed / the total number of cases of the breed including all breeds X 100. c) P value from the χ^2 test between % of a breed in total liver biopsy samples and % of the breed in total biopsy samples.

Table 3. Incidence of proliferative liver diseases in dogs

Diagnosis	Number of cases
Primary epithelial tumors	
Hepatocellular carcinoma	34
Hepatocellular adenoma	37
Cholangiocellular carcinoma	2
Cholangiocellular adenoma	1
Primary nonepithelial tumors	
Carcinoid tumor	5
Lymphoma	5
Sarcoma (not otherwise specified)	5
Hemangiosarcoma	4
Malignant peripheral nerve sheath tumor	1
Lymphangiosarcoma	1
Fibrosarcoma	1
Histiocytic sarcoma	1
Metastatic tumors	
Hemangiosarcoma	3
Mammary gland carcinoma	3
Lymphoma	2
Sarcoma (not otherwise specified)	2
Gastrointestinal stromal tumor	1
Mast cell tumor	1
Islet cell adenocarcinoma	1
Lung adenocarcinoma	1
Peripheral nerve sheath tumor	1
Smooth muscle sarcoma	1
Other proliferative diseases	
Nodular hyperplasia	26

(35.3%, 12 of 34), followed by Yorkshire terriers (11.8%, 4 of 34). The median age was 11 years and 6 months old, and

no sex difference was observed.

Feline liver biopsies: Of 1,016 feline biopsy cases, 71 (7.0%) were liver biopsies. In the data, non-proliferative liver diseases were 56 (78.9% of all diagnoses), and proliferative diseases were 8 (11.3% of the all). In the remaining 7 cases, there were no significant lesions. The results are summarized in Tables 5–7.

Feline non-proliferative liver diseases: Parenchymal and interstitial hepatitis occupied 57.1% (32 of 56) of non-proliferative liver diseases (45.1% of the all diagnoses), including neutrophilic cholangiohepatitis (53.1%, 23.9% of the all), lymphocytic cholangiohepatitis (31.3%, 14.1% of the all), chronic hepatitis (12.5%, 5.6% of the all) and neutrophilic cholangitis (3.1%, 1.4% of the all). There was one case of giant cell hepatitis. Copper deposition in chronic hepatitis and in cholangiohepatitis was seen in one case, respectively. The second popular non-proliferative liver disease was hepatic degeneration (17.9%, 10 of 56, 14.1% of the all), including 3 cases of lipidosis. The third most often encountered disease was MVD (16.1%, 9 of 56, 12.7% of the all). The fourth was adult polycystic liver disease (7.1%, 4 of 56, 5.6% of the all). One of the 4 cases was accompanied with polycystic kidney disease.

More than half cases (57.7%, 41 of 71) in this survey were Japanese domestic cats. Although the difference was not significant ($P=0.052$), the median age of neutrophilic cholangiohepatitis was 10 years and 11 months, being elder than that of lymphocytic cholangiohepatitis (5 years and 1 month). The male/female ratio of neutrophilic cholangiohepatitis was 9:7, while that of lymphocytic cholangiohepatitis was 1:1. The median age of lipidosis was 11 years and 11 months, and its male/female ratio was 1:2. The median age of MVD was 8 months, and its male/female ratio was 7:2. Six of 9 MVD cases were accompanied with PSS, while 2 of 9 were not and the remaining one case was unknown. The median age of adult polycystic liver disease was 7 years and

Table 4. Breed, median age and male-to-female ratio of neoplastic liver diseases in dogs

Diagnosis	Breed	Nm	Median age	Male:female	% ^{a)}	% ^{b)}	P value ^{c)}	OR	95% CI of OR
Hepatocellular carcinoma		34	11 y 6 m	14:20					
	Shih Tzu	12	12 y 5 m	5:7	35.3	5.85	<0.001	8.89	4.38–18.02
	Yorkshire Terrier	4	12 y 11 m	2:2	11.8	4.49	<0.001	2.85	1.00–8.11
Hepatocellular adenoma		37	12 y 1 m	16:21					
	Golden Retriever	5	12 y	2:3	13.5	3.86	<0.001	3.92	1.52–10.09
	Mixed-breed	5	12 y 6 m	3:2	13.5	8.13	0.049	1.77	0.69–4.55
	Shiba	5	13 y 5 m	2:3	13.5	3.29	<0.001	4.63	1.80–11.95

Nm, number of cases; OR, odds ratio; CI, confidence interval; ND, no data available; y, year (s); m, month (s). a) The number of cases of a breed / the total number of cases with the diagnosis X 100. b) The number of cases of a breed / the total number of cases of the breed including all breeds X 100. c) P value from the χ^2 test between % of a breed in total liver biopsy samples and % of the breed in total biopsy samples.

Table 5. Incidence of non-proliferative liver diseases in cats

Diagnosis	Number of cases
Inflammatory responses	
Neutrophilic cholangiohepatitis	17
Lymphocytic cholangiohepatitis	10
Neutrophilic cholangitis	1
Chronic hepatitis	4
Regressive changes	
Hepatic degeneration	10
Microvascular dysplasia	9
Biliary disorders	
Adult polycystic liver disease	4
Others	
Anomalous artery	1

Table 6. Incidence of proliferative liver diseases in cats

Diagnosis	Number of cases
Primary epithelial tumors	
Hepatocellular carcinoma	1
Cystic cholangiocellular adenoma	1
Cholangiocellular carcinoma	1
Primary nonepithelial tumors	
Lymphoma	3
Plasmacytoma	1
Sarcoma (not otherwise specified)	1

5 months, and the male/female ratio was 1:3.

Feline proliferative liver diseases: The most popular proliferative liver disease was lymphoma (37.5%, 3 of 8, 4.2% of the all). Hepatocellular carcinoma, cystic cholangiocellular adenoma and cholangiocellular carcinoma were 12.5% (1 of 8), respectively. That is, primary epithelial tumors were 4.2% of the all.

The median age of lymphoma was 11 years and 9 months old, and all of the cases were female.

DISCUSSION

The present study was the first incidence survey on canine and feline liver diseases in Japan. We demonstrated here that the most popular canine liver disease was MVD (29.4%), followed by hepatitis (23.5%) including cholangiohepatitis and cholangitis and by primary hepatic tumors (21.0%) including hepatocellular carcinoma and adenoma. We propose that the term of "MVD" is more appropriate rather than "primary portal vein hypoplasia", which is used in the WSAVA's criteria, to represent the lesion histopathologically, because the lesion includes not only hypoplasia of the portal vein but also microvascular proliferation.

Labrador retrievers, American Cocker spaniels and Doberman pinschers were known to be the breeds prone to chronic hepatitis [3]. There were histological differences

among hepatitis of these three breeds. The hepatitis in Labrador retrievers was characterized by severe infiltration of inflammatory cells into the parenchyma. That of American Cocker spaniels was by less infiltration of inflammatory cells and severer liver fibrosis. Besides, the hepatitis of Doberman pinschers was often characterized by severe copper deposition. The result of the present study partly supported the previous description [3].

According to the reports by Patnaik *et al.* [23, 24], the incidence of hepatocellular carcinoma was 52% of total primary hepatic neoplasms. The mean age of hepatocellular carcinoma was 11 years old. There was a male predominance (male/female=1.7:1) and no breed predisposition. In the present study, the incidence of hepatocellular carcinoma was 35.1% of total primary hepatic neoplasms. The mean age was 13 years and 1 month old in the present study. There was no sex predisposition, whereas Shih Tzu was the breed with highest incidence. The ratio of hepatocellular carcinoma versus hepatocellular adenoma was approximately equal (34:37), indicating no predominant incidence between malignant and benign tumors. These results were inconsistent with the previous study in the United States [21], reflecting the difference in a breed-popularity between Japan and the United States. The ratio of nodular hyperplasia to total proliferative hepatic diseases was 18.7% in the present study. This indicated that approximately one-fifth of hepatic masses sampled from patients through biopsy were with completely benign prognosis, because nodular hyperplasia neither causes any significant hepatic dysfunctions nor expresses any clinical symptoms.

The present survey showed that the most popular feline

Table 7. Breed, median age and male-to-female ratio of liver diseases in cats

Diagnosis	Breed	Nm	Median age	Male:female
Neutrophilic cholangiohepatitis		17	10 y 11 m	9:7 (ND1)
	Japanese Domestic Cat	9	11 y 1m	4:4 (ND1)
	American Shorthair	2		
	Maine Coon	2		
Lymphocytic cholangiohepatitis		10	5 y 1 m	5:5
	Japanese Domestic Cat	4		2:2
Chronic hepatitis		4	5 y 7 m	2:2
	Japanese Domestic Cat	4		
Lipidosis		3	11 y 11 m	1:2
	Japanese Domestic Cat	3		
Microvascular dysplasia		9	8 m	7:2
	Japanese Domestic Cat	9		
Lymphoma		3	11 y 9 m	0:3
	Japanese Domestic Cat	1		
Adult polycystic disease		4	7 y 5 m	1:3
	Japanese Domestic Cat	2		

Nm, number of cases; y, year (s); m, month (s); ND, no data available.

hepatic disease in Japan was neutrophilic cholangiohepatitis (23.9%, 17 of 71). The second ones were lymphocytic cholangiohepatitis and hepatic degeneration including lipidosis (each 14.1%, 10 of 71), respectively. MVD, the most popular canine liver disease in Japan, was the fourth (12.7%, 9 of 71). The present results showed that neutrophilic cholangiohepatitis was a disease of older cats in comparison with lymphocytic cholangiohepatitis, consistent with those of previous reports in other countries [16, 20, 26]. Neutrophilic cholangiohepatitis in the chronic stage was associated with the infiltration of mixed inflammatory cells consisting of neutrophils, lymphocytes and plasma cells [19]. However, neutrophilic cholangiohepatitis can be distinguished from lymphocytic cholangiohepatitis that is often characterized by distinct lymphoid follicle formation around the bile ducts and/or portal areas.

Hepatic copper deposition was reported in a European shorthair cat with chronic hepatitis and cirrhosis [22] and in a Siamese cat with hepatopathy [15]. In the present survey, two Japanese domestic cats with chronic hepatitis and neutrophilic cholangiohepatitis had moderate hepatic copper deposition. Although hepatic lipidosis is one of the most common liver diseases in cats in North America [2, 8, 12, 14, 30], it occupied only 4.2% (3 of 71) of liver diseases in Japan. The difference in the prevalence of feline hepatic lipidosis between Japan and North America might reflect the difference in breeds kept or foods.

We propose that “MVD” is more suitable than “primary portal vein hypoplasia” also for feline cases, because the lesion includes not only portal vein hypoplasia but also microvascular proliferation as in canine cases. MVD in cats has been seldom reported up to the present [17]. In the present study, however, the disease accounted for 12.7% (9 of 71) of liver diseases. The ratio of MVD with PSS in cats was less than that in dogs both in the present result and a previous report [27]. This may indicate that cats are less susceptible to PSS than dogs [4, 27].

In Japan, feline adult polycystic liver disease was 5.6% (4 of 71). Among 4 cases of adult polycystic liver disease, a case was accompanied with polycystic kidney disease; consistent with a previous report [6] in which cats with single- or multiple-cysts in the liver also had polycystic kidney disease. As for proliferative diseases, the number of primary epithelial tumors was less than that of primary nonepithelial tumors, and the most common neoplasm was lymphoma (4.2%, 3 of 71). In the present study, lymphoma accounted for 37.5% of feline hepatic tumors (n=8). This is consistent with the results of a previous report [9]; the incidence of feline lymphoma was higher than that of other malignant hepatic neoplasms.

There is, however, a limitation and a bias in this study, because the sampling itself is strongly influenced by some clinical matters, such as the difficulty of biopsy, according to the balance between advantages and disadvantages. If a diagnosis can be obtained by other imaging devices, such as CT and MRI, liver biopsy is not always needed. However, there have been no incidence surveys of canine and feline liver diseases previously in Japan. The present data will be a reference standard for histopathological studies of liver diseases.

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