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The association between gall bladder mucoceles and hyperlipidaemia in dogs: A retrospective case control study

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ABSTRACT

The diagnosis of gall bladder mucoceles (GM) in dogs has become increasingly frequent in veterinary medicine. Primary breed-specific hyperlipidaemia is reported in Shetland Sheepdogs and Miniature Schnauzers, breeds in which GM are known to occur more frequently than in other breeds. The objective of this study was to evaluate the association between GM and hyperlipidaemia in dogs. The study design was a retrospective case control study. Medical records of dogs diagnosed with GM at the Veterinary Medical Centre of The University of Tokyo between 1 April 2007 and 31 March 2012, were reviewed.

Fifty-eight dogs with GM and a record of either serum cholesterol, triglyceride, or glucose concentrations were included in the study. Hypercholesterolaemia (15/37 cases; odds ratio [OR]: 2.92; 95% confidence interval [CI]: 1.02–8.36) and hypertriglyceridaemia (13/24 cases; OR: 3.55; 95% CI:1.12–15.91) showed significant association with GM. Pomeranians (OR: 10.69), American Cocker Spaniels (OR: 8.94), Shetland Sheepdogs (OR: 6.21), Miniature Schnauzers (OR: 5.23), and Chihuahuas (OR: 3.06) were significantly predisposed to GM. Thirty-nine out of 58 cases had at least one concurrent disease, including pancreatitis (five cases), hyperadrenocorticism (two cases), and hypothyroidism (two cases). A significant association between GM and hyperlipidaemia was confirmed, suggesting that hyperlipidaemia may play a role in the pathogenesis of GM.

Introduction

Gall bladder mucoceles (GM) in dogs appear to be increasingly frequently diagnosed in veterinary medicine (Besso et al., 2000; Pike et al., 2004; Agguirre et al., 2007). The basic definition of GM is an inappropriate accumulation of intraluminal, inspissated bile, and/or mucus in the distended gall bladder (Besso et al., 2000; Mehler and Bennett, 2006). Mucosal cystic hyperplasia of the gall bladder is commonly found in dogs with GM (Kovatch et al., 1965; Pike et al., 2004; Worley et al., 2004). Although GM is becoming one of the major gall bladder diseases in dogs, little is known about its pathogenesis.

There are several reports regarding risk factors for GM. It is more commonly diagnosed in older than in young dogs; it has been reported to occur more frequently in Shetland Sheepdogs, American Cocker Spaniels and Miniature Schnauzers (Newell et al., 1995; Besso et al., 2000; Pike et al., 2004; Worley et al., 2004); it is also associated with hyperadrenocorticism and hypothyroidism, but not with diabetes mellitus (Mesich et al., 2009). A recent study reported that a 1-base insertion mutation on the *ABCB4* transporter gene, which is involved in phospholipid transport, was significantly associated with GM (Mealey et al., 2010).

Primary breed-specific hypercholesterolaemia (HC) has been reported in Shetland Sheepdogs (Sato et al., 2000; Mori et al., 2010), and hyperlipidaemia was found to be a common finding dogs of that breed with GM (Agguirre et al., 2007). Primary hyperlipidaemia, especially hypertriglyceridaemia (HTG), is also common in Miniature Schnauzers (Whitney et al., 1993; Xenoulis et al., 2007; Mori et al., 2010). Furthermore, hyperlipidaemia such as HC or HTG is a common finding in dogs with hyperadrenocorticism and hypothyroidism. These observations led to the hypothesis that hyperlipidaemia may be a risk factor for canine GM. Some studies have implied a relationship between GM and hyperlipidaemia in dogs, although not in a very detailed manner (Agguirre et al., 2007).

In humans, gall bladder dysmotility is frequently observed in HTG patients, which improves with appropriate HTG treatment (Jonkers et al., 2003). However, the relationship between gall bladder dysmotility and hyperlipidaemia in dogs is unclear. Gall bladder dysmotility is thought to be associated with insulin resistance and diabetes mellitus in humans (Nakeeb et al., 2006). In humans, one report showed that the gall bladder motility response to low-dose cholecystokinin (CCK) was decreased in hyperglycaemic patients and those with hyperinsulinaemia

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(Gielkens et al., 1998). However, the relationship between gall bladder dysmotility and diabetes mellitus or insulin resistance has not been elucidated.

The aim of this retrospective case control study was to identify possible factors associated with GM, especially metabolic disorders such as hyperlipidaemia and hyperglycaemia, in order to gain insight into the pathogenesis of GM in dogs.

Materials and methods

Study design

A retrospective breed-and age-matched case control study in dogs was carried out in the Veterinary Medical Centre of the University of Tokyo (VMC-UT) from 1 April 2007 to 31 March 2012.

Cases

GM cases were identified by ultrasonography or gross findings and/or histopathology following cholecystectomy. Those identified by ultrasonography had a finely striated and/or stellate bile pattern, inside or outside the gall bladder, which did not move with changes in the dog's position (Besso et al., 2000).

For both clinical cases and controls, the following information was obtained from medical records: breed, age, sex, bodyweight, body conditioning score (BCS), concurrent diseases, serum total cholesterol (T-Cho), triglyceride (TG), and glucose (Glu) concentrations. For the cases, it was not possible to know clearly how long the dogs had fasted before they came to the hospital although we were able to confirm fasting on the day they came to the hospital. In most cases, it was not clear how long the dogs had fasted.

Controls

To examine breed predisposition to GM, all cases that came to VMC-UT during the study period were used as the reference population. The control group consisted of breed- and age-matched (each within ±3 years) cases in which serum TG, T-Cho or Glu concentrations were measured. Serum T-Cho, TG, and Glu concentrations were measured using a Fuji drychem 7000 V (Fujifilm) with the following reference ranges: T-Cho (111–312 mg/dL), TG (30–133 mg/dL), and Glu (75–128 mg/dL). Dogs were considered to have HC, HTG, or hyperglycaemia if serum T-Cho, TG, or Glu concentrations were above the reference ranges.

Statistical analysis

The mean ± SD age of each group was calculated. Data for age, T-Cho, TG, and Glu were analysed using unpaired Student's t test or Welch's t test. The univariate odds ratios (OR) and 95% confidence interval (CI) for GM associated with HC, HTG, or hyperglycaemia were estimated using Fisher's exact test. Breed predisposition was also analysed using Fisher's exact test. Multiplicity of the data was corrected using the Bonferroni method and the breeds were considered to be statistically significantly different when $P < 0.0033$. Sex data for cases and controls were analysed by a chi-square test. Pearson's correlation coefficient and corresponding P values were calculated to assess the relationship between HC and HTG. Statistical analyses were performed using the R free statistical software (R Development Core Team, 2011).

Results

Fifty-eight dogs with GM were enrolled in the study. The mean ± SD age was 10.2 ± 2.3 years in GM group and 8.9 ± 3.6 years in the control group. There were no significant differences in age between the GM group and the control group ($P = 0.101$). The mean BCS score was determined in 50 dogs of the GM group and was 3.0/5. The GM group included 12 sexually intact females, 14 spayed females, 26 sexually intact males, and 6 castrated males. The number of castrated males was significantly less in the GM group than in the control group ($P = 0.0002$). When we compared each sex category with the castrated males, the OR were as follows: 1.75 (95% CI: 0.66–4.67; $P = 0.258$) for intact females, 3.32 (95% CI: 1.27–8.67; $P = 0.009$) for spayed females, and 2.89 (95% CI: 1.19–7.04; $P = 0.015$) for intact males.

Details of the dog breeds are shown in Table 1. The GM group included 11 Pomeranians (19%), 11 Chihuahuas (19%), 6 Miniature Schnauzers (10%), 5 Shetland Sheepdogs (9%), 4 American Cocker Spaniels (7%), 4 Miniature Dachshunds (7%), 3 Yorkshire Terriers (5%), and 3 Shibas (5%). The number of all cases without GM that came to VMC-UT during the study period was 6812, and the proportion of each breed was as follows: 146 Pomeranians (2%), 732 Chihuahuas (11%), 147 Miniature Schnauzers (2%), 102 Shetland Sheepdogs (1%), 56 American Cocker Spaniels (1%), 739 Miniature Dachshunds (11%), 255 Yorkshire Terriers (4%), and 175 Shibas (3%). A significant breed predisposition to GM was observed in Pomeranians (OR: 10.69; 95% CI: 5.43–21.03; $P < 0.001$), American Cocker Spaniels (OR: 8.94; 95% CI: 3.13–25.53; $P = 0.002$), Shetland Sheepdogs (OR: 6.21; 95% CI: 2.43–15.86; $P = 0.002$), Miniature Schnauzers (OR: 5.23; 95% CI: 2.21–12.37; $P = 0.002$), and Chihuahuas (OR: 3.06; 95% CI: 1.58–5.94; $P = 0.002$).

Thirty–eight out of 58 dogs (65.5%) in the GM group had one or more concurrent diseases (Table 2). The most frequent concurrent disease with GM was pancreatitis (5 cases). Hyperadrenocorticism and hypothyroidism were found in only two GM cases each. One case with GM had diabetes mellitus. In contrast, the control group included 64 diseases. The most frequent disease was epilepsy (10 cases). Hyperadrenocorticism was diagnosed in four controls, and hypothyroidism was diagnosed in three controls. No case of diabetes mellitus was included in the control group.

Serum T-Cho, TG, and Glu concentrations were measured in 37, 24, and 23 dogs, respectively, in each group. HC and HTG were present in 15 (41%) and 13 dogs (54%) in the GM group (Table 3) and in 7 (19%) and 6 dogs (25%) in the control group, respectively. Four dogs (17%) in the GM group and two dogs (9%) in the control group were diagnosed with hyperglycaemia. Fisher's exact test revealed that the odds of GM in dogs with HC were 2.92 times that of dogs without HC (95% CI: 1.02–8.36; $P = 0.043$) and the odds of GM in dogs with HTG were 3.55 times that of dogs without HTG (95% CI: 1.12–15.91; $P = 0.039$). There was no significant association between the presence of GM and the presence of hyperglycaemia (OR: 2.21, 95% CI: 0.36–13.47, $P = 0.381$). Serum TG concentrations were found to be significantly ($P = 0.028$) higher in the GM group (median: 140 mg/dL; range: 48–2075 mg/dL) compared to the control group (median: 71 mg/dL; range: 1–380 mg/dL). Serum T-Cho concentrations also had a tendency to be increased in the GM group (median: 309 mg/dL; range: 58–1215 mg/dL) compared with the control group (median: 211 mg/dL; range: 53–885 mg/dL), but this did not reach statistical significance ($P = 0.067$). No significant difference in serum Glu concentrations were observed between the GM group (median: 108 mg/dL; range: 68–391 mg/dL) and the controls (median: 108.5 mg/dL; range: 84–161 mg/dL). There was no significant correlation between serum TG and T-Cho concentrations ($r = 0.119$; $P = 0.531$) in the GM group.

Discussion

In this study, we found that both HTG and HC were significantly associated with the occurrence of canine GM. However, the rationale for the relationship between hyperlipidaemia and GM remains unknown. Previously, postprandial- and CCK-stimulated gall bladder motility were reported to be decreased in HTG humans, with improvements in gall bladder motility observed following successful TG-lowering therapy (Jonkers et al., 2003). It is possible that HTG may reduce gall bladder motility in dogs owing to prolonged exposure to concentrated bile-containing cytotoxic hydrophobic bile acids, which may be associated with the pathogenesis of GM. The relationship between GM and HC appears to be directly due to excessive excretion of cholesterol in the bile with subsequent oversaturation of the bile leading to the formation of biliary sludge. We have previously reported that biliary sludge reduces gall bladder motility in dogs (Tsukagoshi et al., 2012) and we consider that it may lead to GM.