



Clinical features and prognosis of canine megaesophagus in Japan

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ABSTRACT. Megaesophagus (ME) is a common esophageal disease in dogs and the prognosis is generally poor, especially with aspiration pneumonia (AP). We retrospectively investigated the clinical features and prognosis of canine ME in Japan. Twenty-eight dogs were included in this study, with the Miniature Dachshund breed being significantly overrepresented (odds ratio: 4.33). Most cases (21 of 28) were diagnosed as idiopathic ME and Myasthenia gravis was the most common cause of secondary ME. The overall median survival time (MST) was not reached and the 3-month survival rate was 85.7%. Ten dogs were diagnosed with AP, at least once during the study period, and the MST of ME dogs with AP was 114 days. The survival time overall and even with AP, was notably more prolonged compared to the previous studies. We hypothesized that treatment for canine ME could prolong the survival time, even in those with both ME and AP.

KEY WORDS: aspiration pneumonia, megaesophagus, miniature dachshund

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Megaesophagus (ME) is a common cause of regurgitation in dogs and it is characterized by diffuse esophageal dilation and concurrent esophageal dysmotility. ME is categorized into congenital and acquired forms [14]. Congenital ME is attributed to vagal afferent dysfunction [9, 10]. Acquired ME is either idiopathic, or secondary to another disease, such as myasthenia gravis (MG) [8, 15, 20], hypoadrenocorticism [2, 24], dysautonomia [5, 16], polyradiculoneuritis [3], hypothyroidism [7], polymyopathies [6], and esophageal cancer [1, 12]. MG is the most common cause of the secondary ME and it has been reported that positive anti-acetylcholine receptor antibody titers were found in 26% of ME dogs without generalized muscle weakness. [15, 20]. Most cases, however, of canine ME are of unknown cause and are therefore considered to be idiopathic [15].

Although there have been few reports about the prognosis of canine ME, the prognosis is generally considered guarded. Boudrieau *et al.* reported that the 3-month survival rate of canine ME, after the onset of clinical signs was 38% [3]. Secondary ME may recover with successful treatment of the underlying disease [2, 20, 24]. Meanwhile, the idiopathic form is difficult to treat, and the prognosis is generally considered poor [3, 14, 15]. Mcbreaty *et al.* reported that 76% of ME had no underlying disease and the median survival time (MST) was 90 days [15]. Aspiration pneumonia (AP) is one of the most common causes of death in canine ME and related to a significantly shorter survival time [3, 15]. In one study [15], the MST of ME dogs with and without AP was 16 days and 589 days, respectively. In the study, however, 80% of the ME cases that died were euthanatized, therefore the actual prognosis and the effect of treatments remain unknown.

Elevated feeding, which involves feeding from a high position, or keeping dogs in a standing posture after feeding, is a common palliative treatment of canine ME [14]. Elevated feeding is not easy to perform with large breed dogs, therefore the population of affected breeds may resultantly skewed, in relation to the treatment and survival times in canine ME. Clinical features of canine ME in the Japanese population of dogs have not been previously reported. The purpose of this study is to clarify the clinical features and the prognosis of canine ME in Japan.

MATERIALS AND METHODS

Case records from dogs with ME, diagnosed at the Veterinary Medical Center at the University of Tokyo (VMC-UT) from January 2012 to August 2017, were included in this study. Clinical data were collected from the clinical database and investigated retrospectively. The following clinical data parameters were collected: breed; age; sex; body weight; clinical signs; treatments undertaken; and case outcome. All dogs were diagnosed with ME by plane or contrast thoracic radiography, as they had evidence of generalized esophageal dilation. Cases were excluded from the study if they had no evidence of apparent esophageal dilation on

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radiography. Anti-acetylcholine receptor titer was measured to diagnose ME caused by MG and cases without measurement of anti-acetylcholine receptor antibody titer were excluded. All dogs included in the study were categorized as having idiopathic (primary) or secondary ME based on the clinical findings and laboratory data. Idiopathic ME is defined as having no evidence of diseases that are associated with secondary ME. Dogs who neither underwent ACTH stimulation test nor measurement of total thyroxine concentration were included in this study. AP was defined as evidence of clinical signs relating to pneumonia (cough, dyspnea, and fever) and/or thoracic radiographic abnormalities (pulmonary alveolar pattern or lung consolidation) during the study period.

Clinical response was described as either complete response (CR: complete resolution of regurgitation), partial response (PR: improvement but not complete resolution of regurgitation), and uncontrolled (UC: no improvement or worsening of regurgitation). Overall survival was calculated from the time of diagnosis to the time of death. Clinical data, if not available from medical records, was collected from owners and referring veterinarians by telephone interviews or questionnaire. Dogs still alive at the time of statistical analysis were censored from analysis. Kaplan-Meier method was used to estimate the overall survival. Wilcoxon test was used to compare survival between two groups classified by the categories. The Fisher's exact test was used to compare the 3-month survival. A *P* value of less than 0.05 was considered statistically significant.

To evaluate the predisposition of ME in each breed, all cases presenting to VMC-UT during the study period were used as the reference population. The odds ratio and 95% confidence interval (CI) were calculated. A lower limit of the 95% CI was >1 was considered to represent a significantly higher risk of ME in the breed ($P < 0.05$). All statistical analyses were performed using commercially available software (JMP Pro version 13.0.0, SAS Institute, Cary, NC, U.S.A.).

RESULTS

A diagnosis of ME was made in 37 dogs during the study period. Of these dogs, 9 dogs were excluded from the study because 6 of these dogs were not examined anti-acetylcholine receptor antibody titers and the other 3 dogs did not exhibit esophageal dilation by thoracic radiography, at the time of diagnosis. A total of 28 dogs met the inclusion criteria. Of the 28 dogs, 12 were male (6 castrated) and 16 were female (9 spayed). The median age of the dogs was 98.5 months (range: 7–170). Median body weight was 5.5 kg (range: 1.8–36) and 20 were small (body weight <10 kg) breed dogs. In total, 13 breeds were represented, and one dog was crossbreed. The most common breed was Miniature Dachshund ($n=13$). Other breeds included the American Cocker Spaniel ($n=2$), Chihuahua ($n=2$), Yorkshire Terrier ($n=2$). One case presented in each of the French Bulldog, Standard Poodle, Shih Tzu, Border Collie, Welsh Corgi Pembroke, Doberman, Wire Fox Terrier, and Labrador Retriever breed. Miniature Dachshund was overrepresented, and the odds ratio was 4.33 (95% CI: 2.06–9.13). Clinical signs at the time of diagnosis were regurgitation ($n=28$), body weight loss ($n=14$), coughing ($n=8$), anorexia ($n=6$) and fever ($n=1$).

Secondary ME was diagnosed in 7 dogs, of which 5 dogs were diagnosed with MG, shown by an elevation of anti-acetylcholine receptor antibody titers. Other diseases diagnosed included atypical hypoadrenocorticism ($n=1$) and esophagitis ($n=1$). The cause of ME was not recognized in 21 cases, which were then given a diagnosis of idiopathic ME. AP was diagnosed in 10 dogs, at least one time during the study period. Of 10 dogs with AP, 4 dogs were diagnosed with AP at the first examination and 6 dogs were diagnosed further into the study period. Of the 10 dogs with AP, 7 dogs were idiopathic ME and 2 dogs were MG, and a dog was esophagitis.

In cases of secondary ME, the underlying disease process was treated. Pyridostigmine bromide was used for MG ($n=4$) and idiopathic ME ($n=1$). Other treatments for MG were azathioprine ($n=3$), prednisolone ($n=2$). An atypical hypoadrenocorticism dog was treated with hydrocortisone initially. Three months after the diagnosis of atypical hypoadrenocorticism, the dog developed hyperkalemia and hyponatremia, and prednisolone and fludrocortisone acetate were substituted for hydrocortisone. Elevated feeding was indicated for all idiopathic ME dogs, to prevent regurgitation and AP. Other therapies administered to cases of idiopathic ME were mosapride citrate ($n=9$), bethanechol ($n=1$), gastrostomy tube placement ($n=1$), and esophagostomy tube and esophagogastric tube placement ($n=1$). Nine dogs were treated solely with elevated feeding.

Clinical response was evaluated in all dogs. Three dogs were CR: idiopathic ME ($n=1$); MG ($n=1$); atypical hypoadrenocorticism ($n=1$). PR was recognized in 10 dogs: idiopathic ME ($n=7$); and MG ($n=3$). The remaining 15 dogs were UC: idiopathic ME ($n=13$); MG ($n=1$); esophagitis ($n=1$).

During the study period, 12 dogs died while 16 dogs were alive at the study conclusion. The MST was not reached (NR) and the mean survival time for all dogs was 648 days (Fig. 1). The cause of death included AP ($n=4$), gastric ulcer induced by contact of the esophagogastric tube to the stomach ($n=1$), renal carcinoma ($n=1$), oral melanoma ($n=1$), mammary gland carcinoma ($n=1$) and chronic kidney disease ($n=1$). In three dogs, the cause of death was not apparent. Four dogs had died within three months of diagnosis, and the overall 3-month survival rate was 85.7%.

The relationship between variables and survival dates is shown in Table 1. The survival time of ME dogs, with or without AP, was significantly different between the two groups with the MST being 114 days and NR, respectively (Fig. 2). Three months after diagnosis, four dogs with AP died, while all dogs without AP were alive, showing that the 3-month survival rate was significantly different between dogs with or without AP ($P=0.03$, Table 2). Other variables including age, sex, breed, body weight, prokinetics administration and diagnosis (idiopathic or secondary) were not of significance to the overall survival time or 3-month survival rate (Table 2).

In the group of idiopathic ME, nine dogs were treated exclusively with elevated feeding, while another 12 dogs were given combination therapy (elevated feeding with other medications). The difference in survival time between dogs treated exclusively with elevated feeding or with combination therapy, was not significant. The MST was NR and 951 days, respectively ($P=0.49$).

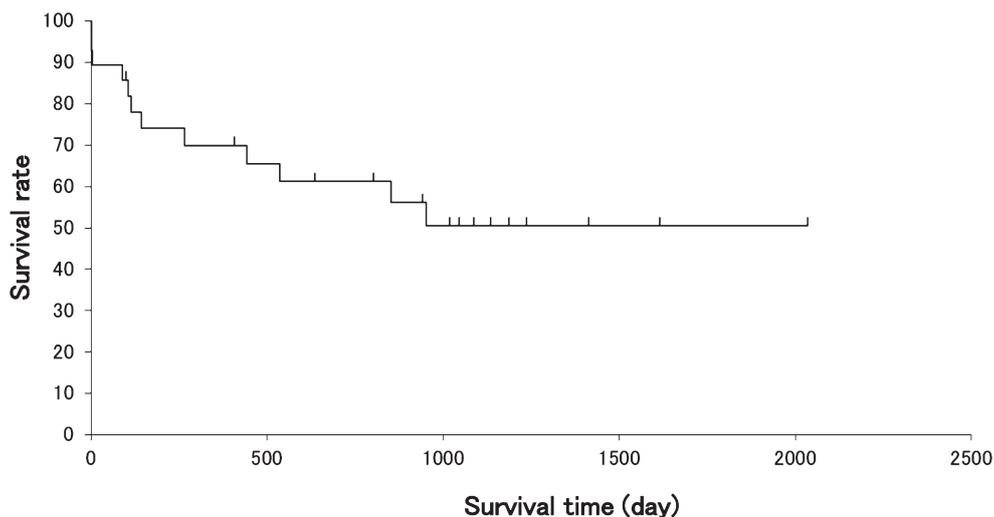


Fig. 1. Kaplan-Meier survival curve for 28 dogs with ME. Vertical marks represent censored data.

Table 1. Relationship between survival time and clinical variables

Variable	Level	n	Median Survival Time (days)	P value
Age	<24 month	4	NR	0.10
	>24 month	24	852	
Sex	Male	12	NR	0.43
	Female	16	536	
Breed	MD	14	NR	0.84
	Other breed	14	951	
Body weight	<10 kg	20	NR	0.94
	>10 kg	8	951	
Prokinetic administration	Absent	10	NR	0.74
	Present	18	536	
Aspiration Pneumonia	Absent	18	NR	0.03
	Present	10	114	
Diagnosis	Idiopathic	21	951	0.79
	Secondary	7	NR	

NR: Not Reached, MD: Miniature Dachshund.

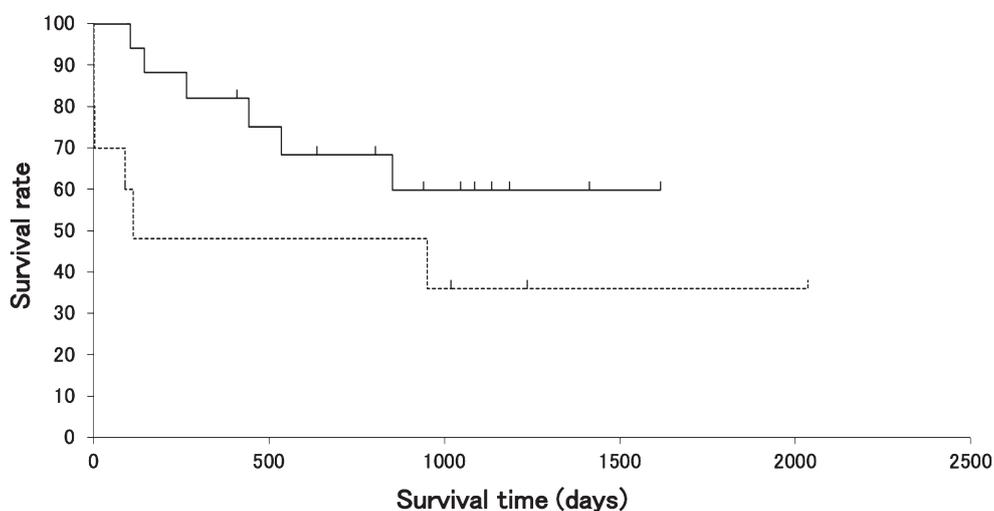


Fig. 2. Kaplan-Meier survival curve for ME dogs with AP (dashed line) and those without AP (solid line). Vertical marks represent censored data.

Table 2. Relationship between the three-month survival rate and clinical variables

Variable	Level	n	3-month survival rate	P value
Age	<24 month	4	4/4 (100.0%)	1.00
	>24 month	24	20/24 (83.3%)	
Sex	Male	12	11/12 (91.6%)	0.61
	Female	16	13/16 (81.2%)	
Breed	MD	14	12/14 (85.7%)	1.00
	Other breed	14	12/14 (85.7%)	
Body weight	<10 kg	20	17/20 (85.0%)	1.00
	>10 kg	8	7/8 (87.5%)	
Mosapride administration	Absent	10	10/10 (100.0%)	0.26
	Present	18	14/18 (77.7%)	
Aspiration Pneumonia	Absent	18	18/18 (100.0%)	0.01
	Present	10	6/10 (60.0%)	
Diagnosis	Idiopathic	21	18/21 (85.7%)	1.00
	Secondary	7	6/7 (85.7%)	

MD: Miniature Dachshund.

DISCUSSION

Previous studies have shown that cases of canine ME had only short survival times [3, 15]. However, the present study suggests that canine ME can have a more favorable prognosis. The MST of ME was NR and the 3-month survival rate was 85.7%. The result is substantially better than the previous studies, in which MST was 90 days [15] and the 3-month survival rate was 38% [3]. One of the possible explanations for the discrepancy is the rate of euthanasia. In the previous study [15], 37% of dogs died within 1 month of diagnosis, 79% of these patients were euthanized because of factors related to either ME or AP [15]. In this study, in contrast, no dogs were euthanized. From the high euthanasia rate, it was inferred that many dogs died without treatment in the previous study [15]. Meanwhile, many dogs in our study were performed several treatments and nine dogs were treated with elevated feeding only. The efficacy of elevated feeding alone is unknown, however, the dogs treated with elevated feeding only had a good prognosis, comparable to the combination therapy in the present study. Therefore, treatment involving elevated feeding and medications, resulted in a better prognosis in the present study.

Regarding AP, the prevalence was 35.7% in this study, and dogs with AP had significantly shorter survival times, with a lower 3-month survival rate than dogs without AP. This result was similar to the previous report that the prevalence of AP was 45% and that AP was a negative prognostic factor for canine ME [15]. In the present study, however, the MST of ME with AP was 114 days, substantially longer than the previous study, which reported the MST of canine ME with AP as 16 days [15]. As mentioned above, euthanasia of cases without treatment, in the previous study is likely to alter the study outcome. Several studies reported that the prognosis for AP was favorable and the presence of ME did not adversely impact the survival rate [13, 21]. This suggests that appropriate treatment for concurrent AP would likely prolong the survival time of ME. In our study, patients diagnosed with AP at least once during the study period were included. In the previous study, in contrast, AP was diagnosed at the initial presentation [15]. Therefore, the prevalence and survival time of the dogs with AP may be overestimated in the present study.

We hypothesized that it is difficult to keep a large breed dog in an elevated position appropriately, resulting in a negative effect on the prognosis of canine ME. However, body weight (>10 kg vs <10 kg) was found to have no significant influence on the survival time in this study. The previous study showed that higher body weight dogs (>25 kg) were prone to worse prognosis [15]. In this study, only four dogs were of a bodyweight more than 25 kg, and further investigation is therefore needed to clarify the effect of elevated feeding and body weight on the prognosis of canine ME.

Some dogs in our study were prescribed prokinetics, of which mosapride citrate is most frequently used. Although Mosapride citrate is 5-HT₄ receptor agonist, serotonin does not have prominent effect on canine esophageal contraction and 5-HT₄ receptor agonist are not considered to be effective to the canine ME [4, 14]. Moreover, prokinetics may prolong the esophageal transportation time, due to an increase in the tone of the lower esophageal sphincter, and are therefore not proven to be beneficial in the management of idiopathic megaesophagus in dogs [4, 11, 14, 22]. In the present study, there was no significant difference in survival between groups with or without mosapride citrate administration. Therefore, the efficacy of prokinetics remains unclear.

In the present study, the Miniature Dachshund was at a significantly higher risk of developing acquired ME. A predisposition of congenital ME has been reported in some dog breeds such as the Irish Setter, Great Dane, German Shepherd, Labrador Retriever, Newfoundland, and Chinese Shar-Pei. Autosomal dominant inheritance has been demonstrated in the Miniature Schnauzer and Fox Terrier breeds [23]. Conversely, no predisposition has been reported in canine acquired ME. The underlying causes of acquired idiopathic ME can be challenging. Vagal afferent dysfunction has been demonstrated to relate with the congenital idiopathic form of ME [9, 10], while the cause of acquired idiopathic ME is unknown. Previous studies suggested that the Miniature Dachshund

in Japan was predisposed to some immunological diseases, such as inflammatory colorectal polyps, idiopathic polyarthritis, and sterile panniculitis [17–19, 25]. Immunological dysfunction against the esophagus may play a role in the development of acquired idiopathic ME in the Miniature Dachshund, but this remains unclear as cases of idiopathic ME dogs were not treated with immunosuppressive drugs in this study. Further examination is warranted regarding the pathogenesis of ME in the Miniature Dachshund.

A limitation of this study is its retrospective nature and therefore, the diagnostic approach and treatment are naturally inconsistent. Idiopathic ME is a diagnosis of exclusion; however, the panel of diagnostic tests was incomplete in some dogs and therefore, secondary ME may be underestimated in this study. Furthermore, the treatment was not standardized and the detail of the elevated feeding procedure was unclear. Therefore, inconsistency in the treatment regime may affect the clinical response and the prognosis in the present study.

In conclusion, the present study revealed the clinical features and prognosis of canine ME in Japan. Small breed dogs are predominantly affected with the Miniature Dachshund having a high odds ratio, therefore being considered a predisposition to acquired ME. The prognosis overall, and even with AP, was notably improved compared to the previous studies. Therefore, we hypothesized that treatment for canine ME could prolong the survival time, even in those with both ME and AP.

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