Canine Nonstructural Megaesophagus as a Clinical Sign of Potential Neurological Disease: 99 Cases

Sergio A. Gomes, DVM, Luc Van Ham, DVM, PhD, Anouk Van Ham, DVM, Edward J. Ives, MA, VetMB, An Vanhaesebrouck, DVM, PhD

Downloaded from jaaha.org by University of Saskatchewan on 11/16/19. For personal use only.
Journal of the American Animal Hospital Association

ABSTRACT

Knowledge regarding the etiology and prognosis for canine megaesophagus (ME) is currently limited to small case series that may now be out of date in light of recent advances in the understanding of neurological syndromes and the availability of advanced diagnostic testing. Ninety-nine dogs diagnosed with nonstructural ME were included. Congenital idiopathic ME was present in 10 cases, with complete resolution of clinical signs in a single case. Eighty-nine cases were considered acquired, with most cases being either idiopathic (42.7%) or associated with myasthenia gravis (38.2%). Idiopathic cases represented a smaller percentage of acquired ME than previously reported. Death or euthanasia directly related to ME occurred in almost 50% of acquired cases, whereas clinical signs persisted in ~20% of cases and resolved in 30% of cases. A diagnosis of an underlying etiology, in particular myasthenia gravis, was associated with a better outcome in acquired ME. ME continues to be a challenging condition to manage, with a guarded-to-poor prognosis, particularly when an underlying etiology is not identified. Thorough diagnostic testing for an underlying neurological disorder is important in cases with ME as this may allow institution of appropriate treatment and the potential for a better prognosis. (*J Am Anim Hosp Assoc* 2020; 56:■■■–■■■. DOI 10.5326/JAAHA-MS-6955)

Introduction

Megaesophagus (ME) is a well-recognized disease manifestation characterized by a dilated esophagus with impaired peristalsis.[1–7] ME can be a transient incidental finding secondary to aerophagia, excitement, persistent vomiting, or general anesthesia.[6,7] However, clinical signs associated with persistent ME can result in significant morbidity and include regurgitation, with or without secondary aspiration pneumonia and associated respiratory signs (coughing, dyspnea), weight loss, and lethargy. Findings compatible with concurrent laryngeal and pharyngeal weakness may also be observed.[1,2,4,6]

ME is usually classified as either an idiopathic congenital form or an acquired form, with the latter further described as either primary (idiopathic) or secondary.[3,4,6] Considering the esophageal path within the neck and thoracic cavity, any structural intra- or extraluminal compression, such as tumors, strictures, hiatal hernias, or vascular ring anomalies, can result in esophageal dilation.[6,8] However, ME is widely reported in the absence of gross structural disease, termed "nonstructural ME." Normal esophageal function requires the coordination and correct response of both afferent and efferent functions of the vagus nerve, the nucleus ambiguus and

From Dovecote Veterinary Hospital, Derby, United Kingdom (S.A.G.); Department of Medicine and Clinical Biology of Small Animals, Faculty of Veterinary Medicine, University of Ghent, Ghent, Belgium (L.V.H., A.V.H.); Anderson Moores Veterinary Specialists, Winchester, United Kingdom (E.J.I.); and Department of Veterinary Medicine, The Queen's Veterinary School, University of Cambridge, Cambridge, United Kingdom (A.V.).

Correspondence: sergio.gomes@dovecoteveterinaryhospital.co.uk (S.A.G.)

AChR (acetylcholine receptor); CK (creatinine kinase); CNS (central nervous system); CSF (cerebrospinal fluid); ME (megaesophagus); MUO (meningoencephalitis of unknown origin); RNS (repetitive nerve stimulation)

Accepted for publication: May 6, 2019.

© 2020 by American Animal Hospital Association

nucleus of the solitary tract in the brain stem, and the esophageal musculature.[9–12] In the dog, the esophageal musculature consists almost entirely of striated muscle.[13] Dysfunction of any of these elements can therefore result in clinical ME, and acquired, secondary, nonstructural ME has been reported to be associated with immune-mediated, endocrine, toxic, and paraneoplastic conditions affecting the neuromuscular control of esophageal function.[4,6] The presence of peripheral neuropathies, laryngeal paralysis, acquired myasthenia gravis, esophagitis, and chronic or recurrent gastric dilatation, with or without volvulus, have been reported as risk factors associated with the development of acquired secondary ME.[2] However, in previous studies reporting the etiology of acquired nonstructural ME, the majority (~70% of cases) were reported to be idiopathic.[1,8]

Idiopathic acquired ME is a diagnosis of exclusion, only achieved following extensive investigations.[2] Pathogenesis of idiopathic ME is still not fully understood, despite several experimental and histopathological studies.[10,14,16] Possible etiologies include a defective afferent neural pathway, more precisely an impaired vagal response to intraluminal esophageal distension, and altered viscoelastic properties of the esophagus.[10,14–18] Studies have also described the presence of ME in cases with lower esophageal sphincter achalasia; however, this does not appear to be a common finding in the majority of idiopathic ME cases, as manometric studies have demonstrated retained peristalsis of the lower portion of the esophagus and a functional lower esophageal sphincter in some dogs with idiopathic ME.[19–21]

The prognosis of canine ME is currently thought to be poor, with a related mortality reported in ~74% of cases—57% for acquired cases and 94% in congenital idiopathic cases.[1,22] Risk factors associated with death before discharge in cases of ME were the presence of aspiration pneumonia on surveys radiographs and age at onset of clinical signs of >13 mo.[8]

The majority of clinical studies investigating canine ME date from over 10 yr ago, with only a single study reported regarding etiology, distribution, and outcome of ME within a single subset of patients.[1,2,22,23] Two more recent studies focused on survival and risk factor analysis in ME, but no study to date has investigated the possible association between etiology and outcome for ME in dogs.[8,24] Advances in knowledge and increasing availability of diagnostic equipment, such as electrodiagnostics and MRI, could mean that some dogs with nonstructural ME who would have previously been classified as idiopathic may be diagnosed with an underlying causative disorder, which may impact on treatment options and prognosis. The aim of this study was to describe nonstructural ME in a large case series of dogs, including its clinical presentation, associated neurological signs if present, etiological distribution, and outcome.

Materials and Methods

Medical Records Review

Electronic medical records of all dogs examined at two teaching hospitals (Veterinary Clinic of the University of Ghent and The Queen's Veterinary School Hospital of the University of Cambridge) between January 1, 2001, and December 31, 2011, were searched to identify dogs for whom the term "megaesophagus" or "dilated esophagus" appeared in the medical records. In this study, dogs were included based on the presence of ME on thoracic radiographs. Dogs were excluded if (1) a structural cause of ME was present, including esophageal and gastrointestinal disease or obstruction, or (2) an ME was considered an incidental finding on radiographs for an unrelated condition (i.e., observed during general anesthesia, or secondary to brachycephalic obstructive syndrome, without related clinical signs and resolving with the disappearance of the stated inciting factor). Information retrieved from the medical records included signalment, clinical presentation, and onset and duration of clinical signs. Results of further diagnostic testing, including thoracic radiographs, esophageal fluoroscopy, hemogram and extensive biochemistry, adrenal and thyroid hormone function testing, acetylcholine receptor (AChR) antibody levels, results of edrophonium-response testing, laryngoscopy, electrodiagnostics, muscle/nerve biopsies, MRI and cerebrospinal fluid (CSF) analysis, and/or postmortem analysis were also retrieved. Electrodiagnostics included electromyography, nerve conduction studies, and repetitive nerve stimulation (RNS) tests.

Etiological Diagnosis

The included dogs were divided in a congenital idiopathic ME or an acquired ME group, depending on the age of onset of the clinical signs and concurrent pathologies, according to previous definitions.[1] The congenital idiopathic ME group consisted of all dogs in whom the clinical signs were first observed before the age of 8 mo and no underlying cause could be found.[1] The acquired ME group consisted of all dogs in whom the first clinical signs were observed after the age of 8 mo as well as those with an onset before the age of 8 mo but for whom an acquired cause was identified. The acquired ME group was further divided into an acquired idiopathic ME group when an underlying cause could not be found on further investigations and an acquired secondary ME group when a causative condition was found. Within the acquired secondary ME group, pathologies were further separated into the following four different groups: (1) myasthenia gravis, when diagnosed following recommendations described elsewhere; (2) polyneuropathies, when several nerves were found to be affected; (3) myopathies, when evidence of muscle pathology was demonstrated, a category that included endocrinopathies

Journal of the American Animal Hospital Association
Downloaded from jaaha.org by University of Saskatchewan on 11/16/19. For personal use only.

known to affect muscle function such as hypoadrenocorticism or hyperadrenocorticism; and (4) central nervous system (CNS) disease, when a primary or secondary condition affecting the CNS was detected. When deemed of interest, specific cases or diagnostic tests were described in more detail.[25–27]

Outcome and Survival

Information regarding disease progression and outcome were retrieved from medical records and telephone interviews with referring veterinarians and/or owners. The outcomes were divided into complete resolution of clinical signs, persistence of clinical signs, and related death. Clinical signs defining outcomes included the ones identified at initial presentation relating to ME, namely and most frequently, regurgitation (e.g., if treatment reduced but did not completely control regurgitation episodes, then the animal was included in the persistence category). When deemed of interest, outcomes of specific cases were described. Length of survival was defined as time from onset of clinical signs to death. Dogs who had not died were censored at last contact with the owner or the referring veterinarian.

Statistical Analysis

Analysis was conducted using Stata 13MP[a]. Categorical data were summarized as frequency (percentage) and continuous data as mean and range. Qualitative comparisons were made between the congenital idiopathic and acquired ME groups as well as between the acquired idiopathic ME and acquired secondary ME groups. A Kaplan-Meier curve was created comparing survival of the congenital ME and acquired ME, as well as the acquired idiopathic ME and acquired secondary ME groups; significance was defined as $P \leq .05$

Results

Animals

One hundred forty-four dogs presented with ME between 2001 and 2011 at both centers. Ninety-nine dogs with ME were included in this study, with 45 cases being excluded. Morphological causes accounted for 22 of the excluded cases—gastrointestinal disease (6), stomach torsion (5), vascular ring anomalies (4), esophagitis (3), congenital esophageal diverticula (2), and compressive neoplastic disease (2). Incidental findings accounted for 23 excluded cases, as a result of general anesthesia (10), multiple organ dysfunction syndrome (8), or brachycephalic obstructive syndrome (5).

Congenital Idiopathic ME

Of the 99 dogs, 14 (14.1%) had an onset of signs of ME before 8 mo of age. Ten dogs (10.1%) were subsequently classified as congenital idiopathic cases, with the other 4 cases diagnosed with an acquired underlying disorder (3 cases of myasthenia gravis and 1 case with degenerative polyneuropathy, see further under "Acquired ME"). Demographic characteristics including gender and breed of this group are described in detail in **Table 1**. The onset of clinical signs occurred between 0 and 6 mo (mean 2.2, median 2 mo). Duration of clinical signs before presentation ranged from 0 to 22 mo (mean 6.5, median 2 mo). Regurgitation was the main clinical sign, being present in 9 of 10 cases (90%), followed by respiratory signs, identified in 5 cases (50%). More details relating to clinical signs are presented in **Table 2**. Aspiration pneumonia was identified in 6 out of 10 cases (60%). Diagnostic tests performed included routine bloodwork in all cases, thyroid function testing (n = 2) and AChR antibody testing (n = 1). These were all considered within normal limits.

Acquired ME

Of the 99 dogs, 89 (89.9%) were classified as having acquired ME. Demographic characteristics of this group including gender and breed are described in detail in Table 1. Onset of clinical signs occurred between 4 and 160 mo (mean 78.8 mo), and duration of clinical signs before presentation ranged from 0 to 14 mo (mean 2.2 mo). Regurgitation was the predominant clinical sign, being present in 79 cases (88.8%). In the 10 cases for which regurgitation was not a presenting clinical sign, 6 cases presented a combination of both respiratory and neurological signs, 3 cases presented with only respiratory signs, and 1 case presented with only other neurological deficits. Neurological deficits were identified on examination in 57 cases (64%) and respiratory signs in 44 cases (49%; Table 2). Neurological signs included generalized weakness (n = 46/57, 80.7%), laryngeal paralysis (n = 19/57, 33.3%), dysphagia (n = 9/57, 15.8%), facial weakness (n = 6/57, 10.5%), and altered mentation (n = 3/57, 5.2%). Aspiration pneumonia was identified in 52 cases (58.4%). Diagnostic tests performed included routine bloodwork in all cases, AChR antibody testing (n = 73), thyroid function testing ($n = 31$), adrenocorticotropic hormone–stimulation testing ($n = 25$), edrophonium-response testing ($n = 20$), laryngoscopy (n = 13), CSF analysis ($n = 7$), brain MRI (n = 3), and antinuclear antibody testing (n = 2). Electrodiagnostics were performed in 23 cases (25.84%). A cause for acquired ME was identified in 51 cases (57.3%). A more detailed distribution on etiology can be found in **Table 3**.

Overview of Acquired ME

Idiopathic Group

A primary cause for acquired ME was not found in 38 cases. Neurological findings were identified in 14 cases (36.8%) including generalized weakness (6), laryngeal paralysis (4), facial weakness (2),

Journal of the American Animal Hospital Association
Downloaded from jaaha.org by University of Saskatchewan on 11/16/19. For personal use only.

TABLE 1

Demographic Distribution of Congenital and Acquired ME (Gender and Breeds)

	Total, n (%)	Congenital Idiopathic ME, n (%)	Acquired ME, n (%)
Total	99	10	89
Gender			
Female	57 (57.6)	4 (40)	53 (59.6)
Male	42 (42.4)	6 (60)	36 (40.4)
Affected breeds			
Golden retriever	17 (17.2)	1 (10)	16 (18)
Labrador retriever	11 (11.1)	1 (10)	10 (8.9)
Mixed-breed dog	9 (9.1)	2 (20)	7 (7.9)
German shepherd dog	9 (9.1)	3 (30)	6 (6.7)
Great Dane	5 (5.1)	0	5 (5.6)
Jack Russell terrier	5 (5.1)	0	5 (5.6)
Irish setter	4 (4)	0	4 (4.5)
Dachshund	3 (3)	0	3 (3.4)
Bordeaux dog	2 (2)	0	2 (2.2)
Dalmatian	2 (2)	0	2 (2.2)
Fox terrier	2 (2)	0	2 (2.2)
Maltese	2 (2)	0	2 (2.2)
Pyrenean mountain dog	2 (2)	0	2 (2.2)
Border collie	2 (2)	1 (10)	1 (1.1)
Cavalier King Charles spaniel	1 (1)	1 (10)	0
Irish wolfhound	1 (1)	1 (10)	0
Airedale terrier	1 (1)	0	1 (1.1)
American Staffordshire terrier	1 (1)	0	1 (1.1)
Bearded collie	1 (1)	0	1 (1.1)
Bernese mountain dog	1 (1)	0	1 (1.1)
Bouvier des Flanders	1 (1)	0	1 (1.1)
Boxer	1 (1)	0	1 (1.1)
Chihuahua	1 (1)	0	1 (1.1)
German pointer	1 (1)	0	1 (1.1)
Long-haired collie	1 (1)	0	1 (1.1)
Miniature schnauzer	1 (1)	0	1 (1.1)
Neapolitan Mastiff	1 (1)	0	1 (1.1)
Newfoundland	1 (1)	0	1 (1.1)
Patterdale terrier	1 (1)	0	1 (1.1)
Pekingese	1 (1)	0	1 (1.1)
Pointer	1 (1)	0	1 (1.1)
Poodle	1 (1)	0	1 (1.1)
Scottish collie	1 (1)	0	1 (1.1)
Scottish terrier	1 (1)	0	1 (1.1)
Shiba Inu	1 (1)	0	1 (1.1)
Shih tzu	1 (1)	0	1 (1.1)
Vizsla	1 (1)	0	1 (1.1)

ME, megaesophagus.

Journal of the American Animal Hospital Association
Downloaded from jaaha.org by University of Saskatchewan on 11/16/19. For personal use only.

TABLE 2

Gender Prevalence, Age at Presentation, Age at Onset, and Selected Clinical and Neurological Signs

	All (n = 99)	Congenital Idiopathic ME (n = 10)	Acquired ME (n = 89)	Idiopathic Acquired ME (n = 38)	Secondary Acquired ME (n = 51)
Gender: male, n (%)	57 (57.6)	4 (40.0)	53 (59.6)	25 (65.8)	24 (54.9)
Age at presentation, median (range), mo	72 (25–114)	4 (3–14)	84 (43–119)	94.5 (65–120)	66 (34–114)
Age at onset, median (range), mo	71 (24.8–107.5)	2 (2–4)	83.8 (42–114)	92.3 (64–117)	65 (30–114)
Clinical signs, n (%)					
Regurgitation	88 (88.9)	9 (90.0)	79 (88.8)	34 (89.5)	45 (88.2)
Hypersalivation	23 (23.2)	0	23 (25.8)	0.111	6 (15.8)
Respiratory signs	49 (49.5)	5 (50.0)	44 (49.4)	22 (57.9)	22 (43.1)
Neurological signs, n (%)					
General weakness	43 (43.4)	0	37 (72.6)	0	37 (72.6)
Facial weakness	6 (6.1)	0	6 (6.7)	2 (5.3)	4 (7.8)
Pharyngeal weakness (dysphagia)	9 (9.1)	0	9 (9.1)	2 (5.3)	7 (13.7)
Laryngeal weakness (dysphonia, stridor) Generalized lower motor neuron	19 (19.2)	0	19 (21.4)	4 (10.5) 3 (7.9)	15 (29.4)
Mentation	3 (3.0)	0	3 (3.4)	0	3 (5.9)
None (normal)	42 (42.4)	10 (100)	32 (36.0)	26 (68.4)	6 (11.8)
Aspiration pneumonia, n (%)	58 (58.6)	6 (60)	52 (58.4)	24 (63.2)	28 (54.9)

ME, megaesophagus.

Journal of the American Animal Hospital Association
Downloaded from jaaha.org by University of Saskatchewan on 11/16/19. For personal use only.

and dysphagia (2); the remaining cases presented no accompanying neurological signs. Diagnostic tests performed included AChR antibodies (23), T4/TSH (15), adrenocorticotropic hormone–stimulation test (14), edrophonium-response test (1), and CSF analysis (1); all these tests were unremarkable. Electrodiagnostic testing was performed in one case and was unremarkable.

Myasthenia Gravis

Myasthenia gravis was diagnosed in a total of 34 cases, of which 24 were generalized, 8 were focal, and 2 presented with the acute fulminant form. Of the 34 dogs, 3 had an associated thymoma identified. Neurological examination findings included generalized weakness (n = 27, 79.4%), laryngeal paralysis (n = 8, 23.5%), facial weakness (4), and dysphagia (3). Five cases had an unremarkable neurological examination. An edrophonium-response test was carried out in 18 dogs, of whom 16 were considered positive. Electrophysiological studies were performed in 15 cases and revealed decrement of the compound muscle action potentials on RNS testing in 8 cases. AChR antibody titers were assessed in 33 cases, of which 28 (85%) were elevated. The remaining 5 cases were diagnosed with seronegative myasthenia gravis according to previously reported criteria including the presence of exercise-induced limb weakness, decrement of the compound muscle action potentials on RNS, positive edrophonium-response testing, and/or improvement following anticholinesterase therapy.[28] None of the seronegative cases presented with facial weakness, and AChR antibody titers were not measured a second time in cases classified as seronegative.

Polyneuropathies

A generalized polyneuropathy as a cause for acquired ME was diagnosed in seven dogs (Table 3). Three cases were diagnosed with idiopathic polyradiculoneuritis, and two cases fit the criteria of geriatric polyneuropathy-laryngeal paralysis complex.[29] One case of acquired ME was suspected to represent a paraneoplastic polyneuropathy, with a splenic hemangiosarcoma identified following ultrasound-guided, fine-needle aspiration of a splenic mass. An additional case, a Pyrenean mountain dog, was diagnosed with hereditary polyneuropathy-laryngeal paralysis.[30] Neurological deficits were present in all cases and included generalized reduced spinal reflexes (7), laryngeal paralysis (4), and dysphagia (1). Electrodiagnostics were performed in six cases and revealed a mixed polyneuropathy, characterized by demyelination and axonal degeneration in five cases and an axonal neuropathy in one case. A polyneuropathy was confirmed by nerve biopsy in one case.

Myopathies

Seven dogs were diagnosed with the following underlying primary or secondary polymyopathy (Table 3): two hypoadrenocorticism,

TABLE 3

Acquired ME Group Etiology Distribution

Acquired ME (n)	Diagnosis	Cases, n (%)
Idiopathic (38)	Idiopathic megaesophagus	38 (42.6)
Myasthenia gravis (34)	Generalized	24 (26.9)
	Focal	8 (9)
	Acute fulminant	2 (2.2)
Polyneuropathy (7)	Idiopathic polyradiculoneuritis	3 (3.3)
	Geriatric polyneuropathy-laryngeal paralysis complex	2 (2.2)
	Laryngeal paralysis-polyneuropathy complex (Pyrenean mountain dog)	1 (1.1)
	Paraneoplastic polyneuropathy (splenic hemangiosarcoma)	1 (1.1)
Myopathies (7)	Immune-mediated polymyositis	2 (2.2)
	Necrotizing myopathy	1 (1.1)
	Systemic Lupus Erythematous	1 (1.1)
	Hypoadrenocorticism	2 (2.2)
	Iatrogenic hyperadrenocorticism (secondary polymyopathy)	1 (1.1)
	Hypoadrenocorticism (secondary polymyopathy)	1 (1.1)
Brain disease (3)	MUO	2 (2.2)
	Malignant histiocytosis	1 (1.1)
Total		89 (100)

ME, megaesophagus; MUO, meningoencephalitis of unknown origin.

Journal of the American Animal Hospital Association
Downloaded from jaaha.org by University of Saskatchewan on 11/16/19. For personal use only.

and one each of immune-mediated polymyositis, necrotizing polymyopathy, systemic lupus, erythematosus syndrome, and iatrogenic hyperadrenocorticism. Neurological deficits were identified in all but one case of hypoadrenocorticism and included generalized weakness (4), laryngeal paralysis (2), and dysphagia (1). Electrodiagnostics were performed in four cases and revealed generalized abnormal spontaneous muscle activity in all cases. Muscle biopsy was performed in a single patient and revealed a necrotizing myopathy. Both hypoadrenocorticism cases were euthanized owing to severe regurgitation at presentation.

Central Nervous System

Three dogs presented with the following clinical signs relating to a primary or secondary CNS disease: meningoencephalitis of unknown origin (MUO; 2) and suspected pulmonary malignant histiocytosis (1). Neurological signs were present in all cases and included reduced mentation (3) and dysphagia (2). Cerebrospinal fluid changes were identified in both cases diagnosed with MUO. MRI was performed for both cases with MUO and revealed hyperintense lesions affecting the thalamic region in one dog. Malignant histiocytosis was identified through cytology of a lung mass although it was not confirmed histologically; however, neurological findings including obtundation justify the inclusion within the CNS group.

Outcome and Survival

Outcome data was available in 81 dogs (81.8%) and is detailed in **Table 4**. Outcome in congenital idiopathic ME was found to be poor, with only a single case achieving complete resolution of clinical signs (11.1%). Within the acquired ME group, a complete recovery was reported in 33% of all cases, including 56% of the cases diagnosed with myasthenia gravis. A worse outcome was found for idiopathic acquired cases (7.7% achieving complete resolution), with a higher related mortality, compared with secondary acquired cases. In the polyneuropathies group, full recovery occurred in two polyradiculoneuritis cases, and in the myopathies group, full recovery was obtained in one case of immune-mediated polymyositis. In the CNS group, full recovery was found in one of the MUO cases. Time of death or last contact was available in 74 dogs, of whom 36 were euthanized or died of causes related to ME (20 of whom were euthanized at the time of presentation). Kaplan-Meier survival analysis illustrated a worse prognosis for congenital idiopathic ME when compared with acquired ME (**Figure 1**) and acquired idiopathic ME when compared with acquired secondary ME (**Figure 2**); however, there were no significant

Journal of the American Animal Hospital Association
Downloaded from jaaha.org by University of Saskatchewan on 11/16/19. For personal use only.

TABLE 4

Distribution of Outcome: Resolution of Clinical Signs, Persistence of Clinical Signs, Related Death, and Euthanasia at Presentation

	Congenital Idiopathic ME (n = 9)	Acquired ME (n = 72)	Idiopathic Acquired ME (n = 26)	Secondary Acquired ME (n = 46)	MG (n = 32)	Polyneuropathies (n = 6)	Myopathies (n = 5)	CNS (n = 3)	Total
Resolution	1 (11.1)	24 (33.3)	2 (7.7)	22 (47.8)	18 (56.3)	2 (33.3)	1 (20)	1 (33.3)	25 (30.9)
Persistence	1 (11.1)	15 (20.8)	10 (38.5)	5 (10.9)	4 (12.5)	0	1 (20)	0	16 (19.8)
Related death	7 (77.8)	33 (45.8)	14 (53.9)	19 (41.3)	10 (31.2)	4 (66.7)	3 (60)	2 (66.7)	40 (49.4)
Euthanized at presentation	2 (2.0)	18 (20.2)	7 (18.4)	11 (21.6)	NA	NA	NA	NA	20 (20.2)
Comparison with previous reports, %[1]									
Resolution	0	22	NA	NA	NA	NA	NA	NA	10
Persistence	6	14							16
Related death	94	57							74

Data are presented as n (%) unless otherwise noted.
CNS, central nervous system; ME, megaesophagus; MG, myasthenia gravis; NA, not available.

FIGURE 1 *Kaplan-Meier curve of survival in congenital idiopathic and acquired megaesophagus cases. Differences in survival between these groups were not statistically significant (P = .817). ME, megaesophagus.*

differences between the groups in survival time ($P = .817$ and .957). Overall survival ranged from 0 to 26 mo (median 4 mo).

Discussion

This retrospective case series evaluated the etiology, neurological signs, outcome, and survival in a large cohort of dogs affected with nonstructural ME. ME has been previously associated with a guarded-to-poor prognosis, with high morbidity and mortality reported.[1,2,3,8,22] However, it is important to note that these studies

FIGURE 2 *Kaplan-Meier curve of survival in idiopathic acquired megaesophagus and secondary acquired megaesophagus cases. Differences in survival between these groups were not statistically significant (P = .957). Acq, acquired; ME, megaesophagus.*

have looked at different aspects of ME with different inclusion criteria to this study, particularly in terms of inclusion of structural ME and the age group distribution. In light of these differences, unless stated otherwise, comparisons with other studies have been performed by adapting the available information to ensure a fair comparison to this present study.

Previous reports indicated that German shepherd dogs, Golden retrievers, and Irish setters were at greater risk of developing acquired secondary ME[2], with several accounts of Great Danes also being affected.[1,22] In this study, the main affected breeds in the acquired ME group were Golden retrievers, Labrador retrievers, mixed-breed dogs, and German shepherd dogs, which is mostly compatible with the previous literature.[1,2,23] However, no comparison with the hospital population has been performed, precluding any conclusions on breed predilection for ME in this study.

In agreement with the previous literature, regurgitation was also found to be the primary presenting clinical sign of ME.[1,2,22] Interestingly, a large proportion of cases in this study presented with other signs of neurological dysfunction (64.04%), which was the second most common presenting sign and surpassed respiratory signs (49.3%). Although the exclusion of structural diseases could have contributed to this finding, this supports the importance of diagnostic investigations for neurological disease in ME cases. In the acquired ME group, generalized weakness was the most common finding in secondary cases, likely reflecting the high incidence of underlying neuromuscular disorders in acquired cases. Interestingly, a proportion of dogs with acquired ME also presented with dysphagia, inspiratory stridor, and/or dysphonia, suggesting concurrent pharyngeal and laryngeal weakness. This finding is not entirely surprising as the larynx, pharynx, and esophagus are innervated by branches of the vagus nerve. A potential parallel could be made with other disease processes such as idiopathic laryngeal paralysis, in which a larger proportion of dogs than previously reported were found to have an underlying generalized neurological disorder.[29,31]

A few reports have described the etiology of acquired nonstructural ME, with ~67–70% of cases found to be idiopathic.[1,8,23] In this study, less than half of acquired nonstructural ME cases were found to be idiopathic (42.6%). The increased proportion of dogs with ME being diagnosed with an underlying disorder than previously reported possibly relates to more extensive investigation and advances in both diagnostic tools and knowledge since previously reported case series.[1,2,22] It is also important to note that 39.5% of the cases identified as idiopathic in this study were not tested for AChR antibodies. Therefore, an undiagnosed myasthenia gravis remains possible in cases, meaning that an even smaller proportion of acquired nonstructural ME may be truly "idiopathic" than that reported in this study. Twenty-six percent of cases previously identified to have idiopathic acquired ME tested positive for AChR antibodies in a previous study.[32] Furthermore, electrodiagnostics was not extensively performed on this group of patients; considering its prevalence of neurological signs (36.8%), perhaps even more cases could have had been identified with an underlying neurological cause.

In previous studies reporting ME, outcome was reported in two reports in 50[22] and 42 cases.[1] The overall ME-related mortality rate was reported to be 74% in these cases—57% for acquired ME and almost 94% for congenital idiopathic ME.[1,22] A lower ME-related mortality rate was found in this study (overall 49.4%, acquired 45.8%, congenital 77.8%), but the results remained consistent with a generally poor prognosis for dogs diagnosed with ME, particularly when presenting with the congenital form. Several studies looking into congenital idiopathic ME mainly reported no significant abnormalities on histopathological examination of both the esophageal musculature and the vagus nerve.[10,14] Dysfunction of the afferent pathways is suspected to be the main mechanism underlying congenital idiopathic ME according to several studies, and esophageal maturity was shown to be an important recovery mechanism of esophageal function.[10,14,15,17,18,33,34] Congenital idiopathic ME can resolve with age in some cases, such as reported in the miniature schnauzer, in which this has been related with an immaturity of nerve myelination.[35] This breed was not represented in this study.

It is worth noticing that within the subset of congenital idiopathic ME cases, investigations did not include electrodiagnostics or AChR antibody. More extensive testing in these suspected congenital idiopathic ME cases may have also subsequently identified an acquired cause. Recently, promising results were published for congenital idiopathic ME treated with sildenafil, in terms of reduction of regurgitation frequency and increased weight gain; however, outcome was not described for those patients.[36]

When looking in more detail at the outcome of the different etiological groups within acquired ME cases, idiopathic cases presented a higher mortality rate (53.9%) and reduced resolution rate (7.7%) when compared with the animals diagnosed with myasthenia gravis (mortality rate 31.2%, resolution rate 56.3%) or acquired secondary causes in general (mortality rate 41.3%, resolution rate 48.8%). These results seem to indicate that within acquired ME, idiopathic cases have a poorer prognosis, confirming a clinical suspicion raised in several other reviews of ME.[5–7] This reinforces the suggestion that extensive investigations should ideally be performed in all ME cases, particularly focusing on myasthenia gravis, which has a specific treatment and presented the best outcome within the different groups analyzed. Myasthenia gravis cases are reported to present with ME in ~90% of cases.[37] In accordance with previous

Journal of the American Animal Hospital Association
Downloaded from jaaha.org by University of Saskatchewan on 11/16/19. For personal use only.

Journal of the American Animal Hospital Association
Downloaded from jaaha.org by University of Saskatchewan on 11/16/19. For personal use only.

studies, myasthenia gravis was an important cause of acquired ME in this study, being the second most prevalent presentation, making up 38.2% of acquired ME cases. This was the group in which a better outcome was achieved, emphasizing the importance of performing electrodiagnostics, namely, RNS, in conjunction with AChR antibody testing.[25,38] However, electrodiagnostics should only be performed in clinically stable patients as it requires a sometimes lengthy general anesthetic that could worsen the clinical condition in dogs, particularly when aspiration pneumonia is present. The reported mortality for myasthenia gravis cases in this study is in line with previous reports of 33–40%.[39,40] The mortality rate for myasthenia gravis may be decreased even further with early diagnosis, as spontaneous remission is possible in cases treated with anticholinesterase therapy.[41] Five cases of myasthenia gravis were considered seronegative following a negative AChR antibody titer, as they had consistent findings such as decrement of the compound muscle action potentials on RNS or a positive response to anticholinesterase therapy, according to previously reported criteria.[28] However, because seroconversion may occur later in the course of the disease, AChR antibody titers could have been repeated 1–2 mo following an initially negative AChR antibody titer in order to further strengthen the diagnosis of myasthenia gravis in these cases.[28]

Polyneuropathy was also found to represent 7.9% of acquired ME cases in this study. In agreement with a previous report, complete resolution of clinical signs was identified in two idiopathic polyradiculoneuritis cases.[1] However, the prognosis was poor for polyneuropathy cases in general, with a 66.7% related mortality rate. The limited number of polyneuropathy cases identified in this study complicates interpretation of this finding. Canine dysautonomia, although not found in this subset of patients, can present with ME in between 18 and 61% of cases, and it can be a relevant differential diagnosis in certain geographical areas, namely, in the Midwestern United States, where most cases have been reported.[42–44]

An underlying myopathy was identified as a cause of acquired ME in 7.8% of cases. Although detailed description of creatinine kinase (CK) measurement results were outside the scope of this study, CK was measured in all patients as part of our standard biochemistry panel investigations. An elevated CK could be suggestive of myocyte injury and when persistently elevated could be an indicator of an underlying inflammatory, necrotizing, or dystrophic myopathy, guiding the clinician's differential diagnosis list and required investigations, which should include muscle biopsies in some cases.[45] Hypoadrenocorticism was diagnosed in two cases. Both of these dogs were euthanized at presentation, emphasizing the clinical importance of ME in a condition that is normally associated with a favorable response to treatment.[46–48] In this study, no dog was found to suffer from hypothyroidism of the 31 tested dogs. This is in contrast to studies in which hypothyroidism was cited with concurrent ME but in agreement with a more recent study.[2,8]

Conditions affecting the CNS, either primary or secondary, were identified in three cases. Considering that the striated muscles of the esophagus are innervated by axons with cell bodies that reside in the nucleus ambiguus, a long ill-defined nucleus located in the medulla oblongata, esophageal dysfunction and ME could arise from a compressive or invasive lesion at this level.[9,11,12] In the case with a suspected pulmonary malignant histiocytosis, its relation with ME could be that of an invasion into the esophagus leading to an impaired motor activity.[49]

Overall survival for dogs with ME in this study ranged from 0 to 26 mo (median 4 mo), which could not be directly comparable with previous reports as inclusion criteria and survival time definitions differed—these were reported as 0–81 mo (median 1 mo), 0–96.5 mo (median 3 mo), and as a median of 3 mo.[8,22,24]

This study is limited by its retrospective nature, which meant that information gathered might have been incomplete. Diagnostic workup differed from patient to patient, particularly as cases from two different institutions were included. Despite this, investigative protocols and procedures were found to be very similar. Limited diagnostic investigations mean that more cases of acquired ME may have been missed, further reducing the number of idiopathic cases compared with previous literature. Inclusion criteria meant that structural cases were excluded, making comparison of results with previous studies more difficult.[1,8] The outcome was oftentimes assessed through telephonic interviews, which are prone to caregiver placebo effect.

Conclusion

Overall, the results of this study support the importance of trying to ascertain a definitive diagnosis for cases with ME in terms of planning a treatment protocol and optimizing the prognosis. A lesser proportion of cases within the acquired ME group were classified as idiopathic compared with previous studies, potentially indicating that as knowledge increases and more cases are thoroughly investigated, an underlying cause may be identified and a better outcome can be achieved through a more targeted treatment strategy. The authors therefore advocate further testing in dogs with ME to determine if a more generalized neurological disorder is present, particularly using electrodiagnostics and AChR antibody testing. ME continues to be a challenging condition to manage, with a guarded-to-poor prognosis, particularly when an underlying etiological process is not found.

FOOTNOTES

[a] StataCorp, College Station, Texas

Downloaded from jaaha.org by University of Saskatchewan on 11/16/19. For personal use only.
Journal of the American Animal Hospital Association

REFERENCES

1. Boudrieau RJ, Rogers, WA. Megaoesophagus in the dog: A review of 50 cases. *J Am Anim Hosp Assoc* 1985;21:33–40.
2. Gaynor AR, Shofer FS, Washabau RJ. Risk factors for acquired megaoesophagus in dogs. *J Am Vet Med Assoc* 1997:211:1406–12.
3. Guilford, WG. Megaoesophagus in the dog and cat. *Semin Vet Med Surg (Small Anim)* 1990;5:37–45.
4. Washabau R. Gastrointestinal motility disorders and gastrointestinal prokinetic therapy. *Vet Clin North Am Small Anim Pract* 2003;33:1007–28.
5. Johnson BM, DeNovo RC, Mears EA. Canine Megaesophagus. In: Bonagura JD, Twedt DC, eds. *Kirk's Current Vet Therapy XIV.* Philadelphia: WB Saunders; 2008:486–92.
6. Mace S, Shelton G, Eddlestone S. *Megaoesophagus.* Compend Contin Educ Vet 2012;34:E1–8.
7. Van Ham A, Vanhaesebrouck A, Polis I, et al. Megaoesofagus bij hond en kat [Megaoesophagus in the dog and cat]. *Vlaams Diergeneeskd Tijdschr* 2009;78:388–99.
8. McBrearty AR, Ramsey IK, Courcier EA, et al. Clinical factors associated with death before discharge and overall survival time in dogs with generalized megaesophagus. *J Am Vet Med Assoc* 2011;238:1622–28.
9. Hudson L, Cummings J. The origins of innervation of the oesophagus of the dog. *Brain Res* 1985;326:125–36.
10. Holland C, Satchell P, Farrow B. Vagal esophagomotor nerve function and esophageal motor performance in dogs with congenital idiopathic megaoesophagus. *Am J Vet Res* 1996;57:906–13.
11. Fletcher TF, Beitz AJ. The brain. In: Evans HE, de Lahunta A, eds. *Miller's Anatomy of the Dog.* 4th ed. St. Louis: Saunders; 2013:658–707.
12. Thomson CE, Hahn CN. Cranial nerves. In: *Veterinary Neuroanatomy.* 1st ed. Edinburgh (UK): Elsevier-Saunders; 2012:91–108.
13. Mann C, Shorter R. Structure of the canine oesophagus and its sphincters. *J Surg Res* 1964;4:160–3.
14. Strombeck DR, Troya L. Evaluation of lower motor neuron function in two dogs with megaoesophagus. *J Am Vet Med Assoc* 1976;169:411–4.
15. Tan B, Diamant N. Assessment of the neural defect in a dog with idiopathic megaoesophagus. *Dig Dis Sci* 1987;32:76–85.
16. Holland C, Satchell P, Farrow B. Selective vagal afferent dysfunction in dogs with congenital idiopathic megaooesophagus. *Auton Neurosci* 2002;99:18–23.
17. Holland C, Satchell P, Farrow B. Oesophageal compliance in naturally occurring canine megaooesophagus. *Aust Vet J* 1993;370:414–20.
18. Bexfield N, Watson P, Herrtage, M. Esophageal Dysmotility in Young Dogs. *J Vet Intern Med* 2006;20:1314–8.
19. Boria PA, Webster CRL, Berg J. Esophageal achalasia and secondary megaesophagus in a dog. *Can Vet J* 2003;44:232–4.
20. Kempf J, Beckmann K, Kook PH. Achalasia-like disease with esophageal pressurization in a myasthenic dog. *J Vet Intern Med* 2014;28:661–5.
21. Diamant N, Szczepanski M, Mui H. Manometric characteristics of idiopathic megaesophagus in the dog: An unsuitable animal model for Achalasia in man. *Gastroenterol* 1973;65:216–23.
22. Harvey, CE, O'Brien, JA, Durie, VR, et al. Megaoesophagus in the dog: A clinical survey of 79 cases. *J Am Vet Med Assoc* 1974;165:443–6.
23. Wray J, Sparkes A. Use of radiographic measurements in distinguishing myasthenia gravis from other causes of canine megaooesophagus. *J Small Anim Pract* 2006;47:256–63.
24. Schönfelder J, Schönfelder A, Neiger R. Überlebensdauer bei verschiedenen Formen des kaninen Megaösophagus [Survival duration for different forms of canine megaesophagus]. *Schweiz Arch Tierheilkd* 2011;153:236–8.
25. Shelton GD. Myasthenia gravis and disorders of neuromuscular transmission. *Vet Clin North Am Small Anim Pract* 2002;32:189–206
26. Greene CE, Lorenz MD, Munnell JF, et al. Myopathy associated with hyperadrenocorticism in the dog. *J Am Vet Med Assoc* 1979;174:1310.
27. Platt SR. Neuromuscular complications in endocrine and metabolic disorders. *Vet Clin North Am Small Anim Pract* 2002;32:125–46.
28. Shelton GD. Acquired myasthenia gravis: what we have learned from experimental and spontaneous animal models. *Vet Immunol Immunopathol* 1999;69:239–49.
29. Jeffery N, Talbot C, Smith P, et al. Acquired idiopathic laryngeal paralysis as a prominent feature of generalized neuromuscular disease in 39 dogs. *Vet Rec* 2006;158:17–21.
30. Gabriel A, Poncelet L, Van Ham L, et al. Laryngeal paralysis-polyneuropathy complex in young related Pyrenean mountain dogs. *J Small Anim Pract* 2006; 47:144–9.
31. Stanley B, Hauptman J, Fritz M, et al. Esophageal Dysfunction in Dogs with Idiopathic Laryngeal Paralysis: A Controlled Cohort Study. *Vet Surg* 2010; 39:139–49.
32. Shelton GD, Willard MD, Cardinet GH III, et al. Acquired myasthenia gravis. Selective involvement of esophageal, pharyngeal and facial muscles. *J Vet Intern Med* 1990;4:2814.
33. Satchell P. The neuropathic oesophagus. A radiographic and manometric study on the evolution of megaoesophagus in dogs with developing axonal neuropathy. *Res Vet Sci* 1990;48:249–55.
34. Diamant N, Szczepanski M, Mui H. Idiopathic megaoesophagus in the dog: reasons for spontaneous improvement and a possible method of medical therapy. *Can Vet J* 1974;15:66–71.
35. Cox VS, Wallace LJ, Anderson VE, et al. Hereditary esophageal dysfunction in the Miniature Schnauzer dog. *Am J Vet Res* 1980;41:326–30.
36. Quintavalla F, Menozzia A, Pozzoli C, et al. Sildenafil improves clinical signs and radiographic features in dogs with congenital idiopathic megaesophagus: a randomized controlled trial. *Vet Rec* 2017;180:404.
37. Shelton GD, Schule A, Kass PH. Risk factors for acquired myasthenia gravis in dogs: 1154 cases (1991–1995). *J Am Vet Med Assoc* 1997;211:1428–31.
38. Cuddon, PA. Electrophysiology in neuromuscular disease. *Vet Clin North Am Small Anim Pract* 2002;32:31–62.
39. Dewey, C, Bailey, C, Shelton, et al. Clinical forms of acquired myasthenia gravis in dogs: 25 cases (1988–1995). *J Vet Intern Med* 1997;11:50–7.
40. Dewey C, Cerda-Gonzalez S, Fletcher D, et al. Mycophenolate mofetil treatment in dogs with serologically diagnosed acquired myasthenia gravis: 27 cases (1999–2008). *J Am Vet Med Assoc* 2010;236:664–8.
41. Shelton GD, Lindstrom JM. Spontaneous remission in canine myasthenia gravis: Implications for assessing human MG therapies. *Neurology* 2001;57:2139–41.
42. Detweiler DA, Biller DS, Hoskinson JJ, Harkin KR. Radiographic findings of canine dysautonomia in twenty-four dogs. *Vet Radiol Ultrasound* 2001;42:108–12.
43. Harkin KR, Andrews GA, Nietfeld JC. Dysautonomia in dogs: 65 cases (1993–2000). *J Am Vet Med Assoc* 2002;220:633–9.
44. O'Brien DP, Johnson GC. Dysautonomia and autonomic neuropathies. *Vet Clin North Am Small Anim Pract* 2002;32:251–65.
45. Shelton GD, Engvall E. Muscular dystrophies and other inherited myopathies. *Vet Clin North Am Small Anim Pract* 2002;32:103–24.
46. Bartges JW, Nielson DL. Reversible megaoesophagus associated with atypical primary hypoadrenocorticism in a dog. *J Am Vet Med Assoc* 1992;201:889-91.
47. Burrows C. Reversible mega-oesophagus in a dog with hypoadrenocorticism. *J Small Anim Pract* 1987;28:1073–8.
48. Whitley N. Megaooesophagus and glucocorticoid-deficient hypoadrenocorticism in a dog. *J Small Anim Pract* 1995;36:132–5.
49. Moore P, Rosin A. Malignant histiocytosis of Bernese mountain dogs. *Vet Pathol* 1986;23:1–10.