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Canine non-structural megaesophagus as a clinical sign of potential neurological disease: 99 cases

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the etiology and prognosis for canine megaesophagus (ME) is currently limited to small case series that may now be out-of-date in light of recent advances in the understanding of neurological syndromes and the availability of advanced diagnostic testing.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 non-structural ME were included. Congenital idiopathic ME was present in 10 cases, with complete resolution of clinical signs in only 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, whilst clinical signs persisted in around 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. Megaesophagus 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.

Introduction

Megaesophagus (ME) is a well-recognized disease manifestation, characterized by a dilated esophagus with impaired peristalsis.[1-7] Megaesophagus can be a transient incidental finding secondary to aerophagia, excitement, persistent vomiting or general anaesthesia.[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]

Megaesophagus 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 extra-luminal 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 'non-structural ME'. Normal esophageal function requires the coordination and correct response of both afferent and efferent functions of the vagus nerve, the nucleus ambiguous and 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, non-structural ME has been reported 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 non-structural ME, the majority – about 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 visco-elastic properties of the esophagus.[10,14-18] Studies have also described the presence of ME in cases with lower esophageal sphincter achalasia[19,20], 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.[21]

The prognosis of canine ME is currently thought to be poor, with a related mortality reported in approximately 74% of cases[1,22]; 57% for acquired cases and 94% in congenital idiopathic cases.[1] 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 more than 13 months.[8]

The majority of clinical studies investigating canine ME date from over 10 years ago[1,2,22,23], with only a single study reported regarding etiology, distribution and outcome of ME within a single subset of patients.[1] Two more recent studies focused on survival and risk factor analysis in ME[8,24] but no study to date has investigated the possible association between etiology and outcome for ME in dogs. Advances in knowledge and increasing availability of diagnostic equipment, such as

electrodiagnostics and MRI, could mean that some dogs with non-structural ME that 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 non-structural ME in a large case series of dogs, including its clinical presentation, associated neurological signs if present, etiological distribution, and outcome.

Material and methods

Medical records review

Electronic medical records of all dogs examined at two teaching hospitals (XXX and XXX) between 1st January 2001 and 31st December 2011, were searched to identify dogs and for which 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, (2) a 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, 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, magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis and/or post mortem

91 analysis were also retrieved. Electrodiagnostics included electromyography (EMG), nerve
92 conduction studies and repetitive nerve stimulation (RNS) tests.
93
94 **Etiological diagnosis**
95 The included dogs were divided in a congenital idiopathic ME or an acquired ME group,
96 depending on the age of onset of the clinical signs and concurrent pathologies, according to
97 previous definitions.[1] The congenital idiopathic ME group consisted of all dogs in which the
98 clinical signs were first observed before the age of 8 months and no underlying cause could be
99 found.[1] The acquired ME group consisted of all dogs in which the first clinical signs were
100 observed after the age of 8 months old, or cases with an onset less than 8 months old but for
101 which an acquired cause was identified. The acquired ME group was further divided into an
102 acquired idiopathic ME group when an underlying cause could not be found on further
103 investigations, and an acquired secondary ME group when a causative condition was found.
104 Within the acquired secondary ME group, pathologies were further separated into 4 different
105 groups: (1) myasthenia gravis, when diagnosed following recommendations described
106 elsewhere[25]; (2) polyneuropathies, when several nerves where found to be affected; (3)
107 myopathies, when evidence of muscle pathology was demonstrated, a category that included
108 endocrinopathies known to affect muscle function such as hypoadrenocorticism or
109 hyperadrenocorticism[26,27]; (4) central nervous system disease (CNS), when a primary or
110 secondary condition affecting the CNS was detected. When deemed of interest, specific cases or
111 diagnostic tests were described in more detail.
112
113 **Outcome & Survival**

Information regarding disease progression and outcome were retrieved from medical records and telephone interviews with referring veterinarians and/or owners. Outcome was divided into complete resolution of clinical signs, persistence of clinical signs, and related death. Clinical signs defining outcome 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, outcome of specific cases was described. Length of survival was defined as time from onset of clinical signs to death. Dogs which had not died were censored at last contact with the owner or the referring veterinarian.

Statistical analysis

Analysis was conducted using stata 13MP. 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 MO and acquired MO, as well as the acquired idiopathic MO and acquired secondary MO groups, significance was defined as $P \leq 0.05$

Results

Animals

One hundred and forty-four dogs presented with ME between 2001 and 2011 at both centres. Ninety-nine dogs with ME were included in this study with forty-five 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 diverticle (2), compressive neoplastic disease (2). Incidental findings accounted for 23 excluded cases, due to general anesthesia (10), multiple organ dysfunction syndrome (8) or brachycephalic obstructive syndrome (5).

Congenital idiopathic ME

Fourteen of the 99 dogs (14.1%) had an onset of signs of ME before 8 months 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. Onset of clinical signs occurred between 0 and 6 months (mean 2.2, median 2 months). Duration of clinical signs before presentation ranged from 0 to 22 months (mean 6.5, median 2 months). 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

158 Eighty-nine of the 99 dogs (89.9%) were classified as having acquired ME. Demographic
159 characteristics of this group, including gender and breed, are described in detail in Table 1. Onset
160 of clinical signs occurred between 4 to 160 months (mean, 78.8 months), and duration of clinical
161 signs before presentation ranged from 0 to 14 months (mean 2.2 months). Regurgitation was the
162 predominant clinical sign, being present in 79 cases (88.8%). In the 10 cases for which
163 regurgitation was not a presenting clinical sign, 6 cases presented a combination of both
164 respiratory and neurological signs, 3 only respiratory signs and 1 case only other neurological
165 deficits. Neurological deficits were identified on examination in 57 cases (64%) and respiratory
166 signs in 44 cases (49%) (Table 2). Neurological signs included generalized weakness (n=46/57,
167 80.7%), laryngeal paralysis (n=19/57,33.3%), dysphagia (n=9/57,15.8%), facial weakness
168 (n=6/57,10.5%), and altered mentation (n=3/57,5.2%). Aspiration pneumonia was identified in 52
169 cases (58.4%). Diagnostic tests performed included routine bloodwork in all cases, AChR-
170 antibody testing (n=73), thyroid function testing (n=31), adrenocorticotropic hormone (ACTH)
171 stimulation testing (n=25), edrophonium-response testing (n=20), laryngoscopy (n=13), CSF
172 analysis (n=7), brain MRI (n=3), and antinuclear antibody testing (n=2). Electrodiagnostics were
173 performed in 23 cases (25.84%). A cause for acquired ME was identified in 51 cases (57.3%). A
174 more detailed distribution on etiology can be found in Table 3.
175
176 **Overview of acquired ME**
177
178 **Idiopathic group**
179 A primary cause for acquired ME was not found in 38 cases. Neurological findings were
180 identified in 14 cases (36.8%) including generalized weakness (6), laryngeal paralysis (4), facial
181 weakness (2) and dysphagia (2); the remaining cases presented no accompanying neurological

signs. Diagnostic tests performed included AChR antibodies (23), T4/TSH (15), ACTH-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 focal and 2 presented with the acute fulminant form. Three out of these 34 dogs 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 which 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[28] 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. 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 7 dogs (Table 3). Three cases were diagnosed with idiopathic polyradiculoneuritis and 2 cases fitted 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 (n=7), laryngeal paralysis (4) and dysphagia (1). Electrodiagnostics were performed in 6 cases and revealed a mixed polyneuropathy, characterized by demyelination and axonal degeneration in 5 cases and an axonal neuropathy in one case. A polyneuropathy was confirmed by nerve biopsy in one case.

Myopathies

Seven dogs were diagnosed with an underlying primary or secondary polymyopathy (Table 3): hypoadrenocorticism (n=2), 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 4 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 due to severe regurgitation at presentation.

Central nervous system

Three dogs presented with 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. Magnetic resonance imaging 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 justifies the inclusion within the CNS group.

Outcome & 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 to 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 which 36 were euthanized or died of causes related with ME (20 of which 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 differences between the groups in survival time ($p=0.817$ and 0.957). Overall survival ranged from 0 to 26 months (median 4 months).

Discussion

This retrospective case series evaluated the etiology, neurological signs, outcome and survival in a large cohort of dogs affected with non-structural ME. Megaesophagus 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 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 to 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, Labradors, Crossbreeds 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%), being the second most common presenting sign and surpassing 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

277 acquired ME also presented with dysphagia, inspiratory stridor and/or dysphonia, suggesting
278 concurrent pharyngeal and laryngeal weakness. This finding is not entirely surprising as the
279 larynx, pharynx and esophagus are innervated by branches of the vagus nerve. A potential
280 parallel could be made with other disease processes such as idiopathic laryngeal paralysis, where
281 a larger proportion of dogs than previously reported were found to have an underlying
282 generalized neurological disorder.[29,31]
283 A few reports have described the etiology of acquired non-structural ME, with around 67-70% of
284 cases found idiopathic.[1,8,23] In this study, less than half of acquired non-structural ME cases were
285 found to be idiopathic (42.6%). The increased proportion of dogs with ME being diagnosed with
286 an underlying disorder than previously reported possibly relates to more extensive investigation
287 and advances in both diagnostic tools and knowledge since previously reported case-series.[1,2,22] It
288 is also important to note that 39.5% of the cases identified as idiopathic in this study were not
289 tested for AChR-antibodies. Therefore, an undiagnosed myasthenia gravis remains possible in
290 cases, meaning that an even smaller proportion of acquired non-structural ME may be truly
291 'idiopathic' than that reported in this study. Twenty-six percent of cases previously identified to
292 have idiopathic acquired ME tested positive for AChR-antibodies in a previous study.[32] Further
293 to this, electrodiagnostics was not extensively performed on this group of patients; considering its
294 prevalence of neurological signs (36.8%), perhaps even more cases could have had been
295 identified with an underlying neurological cause.
296
297 In previous studies reporting ME, outcome was reported in 2 reports of 79 (22) and 42 cases (1).
298 The overall ME-related mortality rate was reported to be 74% in these cases[1,22]; 57% for acquired
299 ME and almost 94% for congenital idiopathic ME.[1] A lower ME-related mortality rate was found
300 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 are suspected to be the main mechanism underlying congenital idiopathic ME according to several studies,[10,15,17,33] and esophageal maturity was shown to be an important recovery mechanism of esophageal function.[18,34] Congenital idiopathic ME can resolve with age in some cases, such as reported in the Miniature Schnauzer where 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 megaesophagus in about 90% of cases.[37] In accordance with previous studies, myasthenia gravis was an important cause of acquired ME in this study, being the second most prevalent presentation comprising 38.2% of acquired ME cases. This was the group in which a better outcome was achieved, emphasizing the importance of performing electrodiagnostics, namely repetitive nerve stimulation, 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, since seroconversion may occur later in the course of the disease, AChR antibody titers could have been repeated 1-2 months 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,[1] complete resolution of clinical signs was identified in two idiopathic polyradiculoneuritis cases. 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 18-61% of cases [42,43]and it can be a relevant differential diagnosis in certain geographical areas, namely in Midwestern United States where most cases have been reported.[42-44]

An underlying myopathy was identified in 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 creatinine kinase 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[2] but in agreement with a more recent study.[8]

Conditions affecting the central nervous system, either primary or secondary, were identified in 3 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 ablongata,[9,11,12] esophageal dysfunction and ME could arise from a compressive or invasive lesion at this level. In the case with a suspected pulmonary malignant histiocytosis and 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 months (median 4 months), which could not be directly comparable to previous reports as inclusion criteria and survival time definitions differed – these were reported as 0-81 months (median 1 month)[22], 0-96.5 months (median 3 months)[8] and as a median of 3 months.[24]

This study is limited by its retrospective nature, which meant that information gathered might have been incomplete. Diagnostic work-up 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 to previous literature. Inclusion criteria meant that structural cases were excluded, making comparison of results more difficult with previous studies.[1,8] Outcome was many times 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 to 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. Megaesophagus

continues to be a challenging condition to manage, with a guarded to poor prognosis, particularly when an underlying etiological process is not found.

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Figures

Figure 1. Kaplan Meier curve of survival in congenital idiopathic and acquired megaesophagus (ME) cases. Differences in survival between these groups were not statistically significant (P=0.817)

Figure 2. Kaplan Meier curve of survival in idiopathic acquired megaesophagus (Idiopathic Acq ME), acquired secondary megaesophagus (Secondary Acq MO) cases. Differences in survival between these groups were not statistically significant (P=0.957)

523 **Tables**

	Total N (%)	**Congenital idiopathic ME N (%)**	**Acquired ME N (%)**
Total	**(n=99)**	**(n=10)**	**(n=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	11 (11.1%)	1 (10%)	10 (8.9%)
Crossbred	9 (9.1%)	2 (20%)	7 (7.9%)
German Shepherd	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	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%)
Long-Haired Collie	1 (1%)	0	1 (1.1%)
German Pointer	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%)
Schnauzer	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%)

524

525 **Table 1.** Demographic distribution of congenital and acquired megaesophagus (gender and

526 breeds).

527

	All, n=99	Congenital idiopathic ME, n=10	Acquired ME, n=89	Idiopathic Acq ME, n=38	Secondary Acq ME, n=51
Gender – Male, n(%)	57(57.6)	4(40.0)	53(59.6)	25(65.8)	24(54.9)
Age at presentation (months), median (range)	72(25-114)	4(3-14)	84(43-119)	94.5(65-120)	66(34-114)
Age at onset (months), median (range)	71(24.8-107.5)	2(2-4)	83.8(42-114)	92.3(64-117)	65(30-114)
Clinical signs					
Regurgitation, n(%)	88(88.9)	9(90.0)	79(88.8)	34(89.5)	45(88.2)
Hypersalivation, n(%)	23(23.2)	0	23(25.8)	0.111	6(15.8)
Respiratory signs, n(%)	49(49.5)	5(50.0)	44(49.4)	22(57.9)	22(43.1)
Neurological signs					
General weakness, n(%)	43(43.4)	0	37(72.6)	0	37(72.6)
Facial weakness, n(%)	6(6.1)	0	6(6.7)	2(5.3)	4(7.8)
Pharyngeal weakness (dysphagia), n(%)	9(9.1)	0	9(9.1)	2(5.3)	7(13.7)
Laryngeal weakness (dysphonia, stridor), n(%)	19(19.2)	0	19(21.4)	4(10.5)	15(29.4)
Generalized lower motor neuron, n(%)				3 (7.9)	
Mentation, n(%)	3(3.0)	0	3(3.4)	0	3(5.9)
None (normal) , n(%)	42(42.4)	10(1000)	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)

Table 2. Gender prevalence, age at presentation, age at onset and selected clinical and neurological signs. Congenital idiopathic megaesophagus (Congenital idiopathic ME), acquired megaesophagus (Acquired ME), idiopathic acquired megaesophagus (Idiopathic Acq ME), acquired secondary megaesophagus (Secondary Acq ME).

Acquired megaesophagus (number of cases)	Diagnosis	Number of cases (% of acquired cases)
Idiopathic (n=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)	Meningoencephalitis of unknown origin	2 (2.2%)
	Malignant histiocytosis	1 (1.1%)
Total		89 (100%)

Table 3. Acquired megaesophagus group etiology distribution.

	Congenital idiopathic ME n=9 (%)	Acquired ME n=72 (%)	Idiopathic Acq ME n=26 (%)	Secondary Acq 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 in literature (1)	Resolution 0% Persistence 6% Related death 94%	Resolution 22% Persistence 14% Related death 57%	NA	NA	NA	NA	NA	NA	Resolution 10% Persistence 16% Related death 74%

Table 4. Distribution of outcome: resolution of clinical signs, persistence of clinical signs, related death and euthanasia at presentation. Congenital idiopathic megaesophagus (Congenital idiopathic ME), acquired megaesophagus (Acquired ME), idiopathic acquired megaesophagus (Idiopathic Acq ME), acquired secondary megaesophagus (Secondary Acq ME), myasthenia gravis (MG), central nervous system conditions (CNS), not available (NA).

Figure 01

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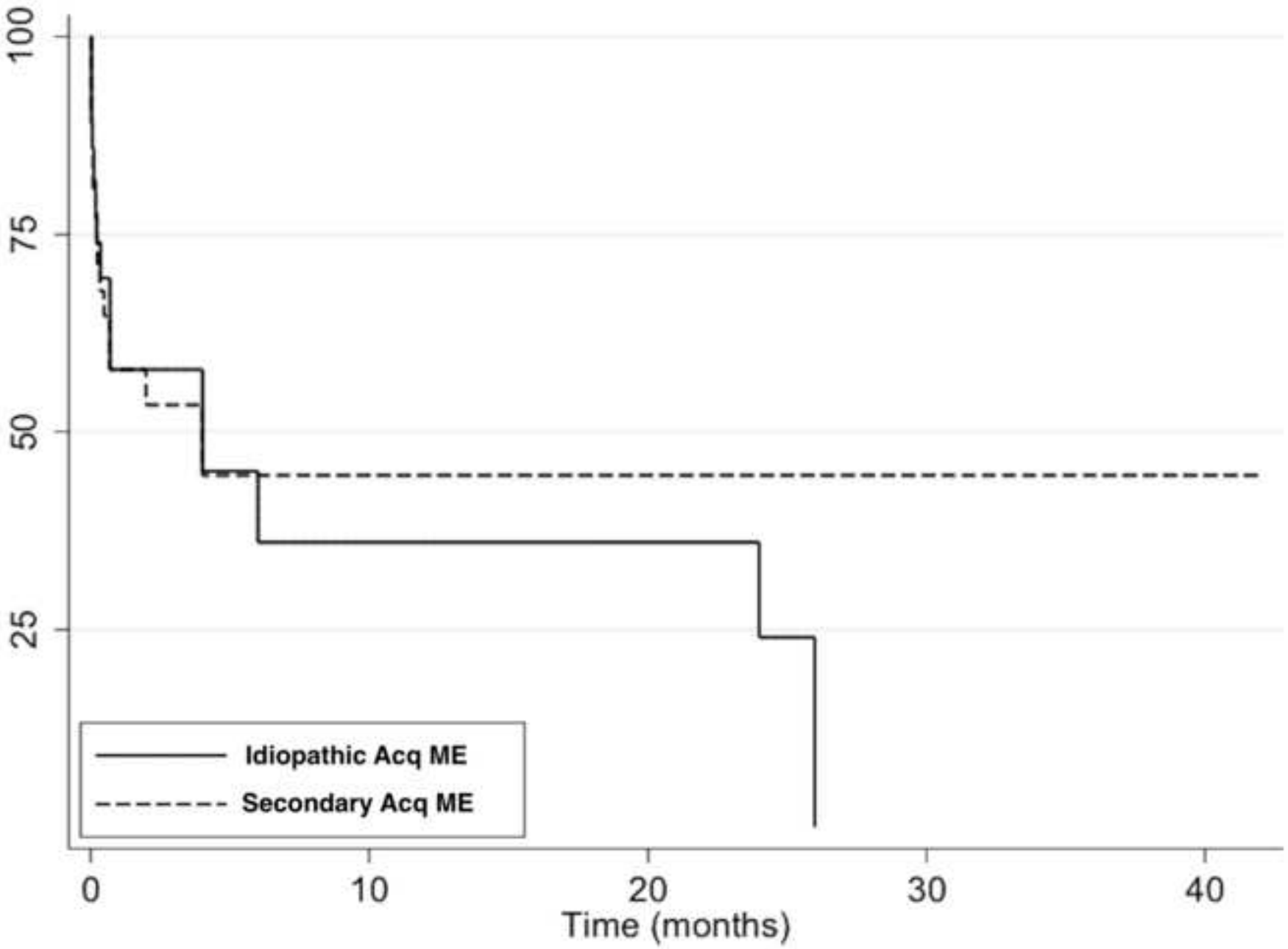


Figure 02

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