

**REVIEW**

# Classification of myasthenia gravis and congenital myasthenic syndromes in dogs and cats

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**Abstract**

Myasthenia, a syndrome of impaired neuromuscular transmission, occurs as either an acquired or congenital condition. Myasthenia gravis (MG) is an acquired autoimmune disorder with autoantibodies against the neuromuscular junction (NMJ) of skeletal muscle whereas congenital myasthenic syndromes (CMSs) are a clinically heterogeneous group of genetic disorders affecting the NMJ with a young age of onset. Both conditions are diseases for which recognition is important with regard to treatment and outcome. We review the published literature on MG and CMSs in dogs and cats, and by comparison with published classification used in humans, propose a classification system for MG and CMSs in dogs and cats. Myasthenia gravis is first classified based on focal, generalized, or acute fulminating presentation. It then is subclassified according to the autoimmune disease mechanism or seronegativity. Autoimmune disease mechanism relates to the presence or absence of a thymoma, or administration of thiourylene medication in cats. Congenital myasthenic syndromes are classified according to the affected NMJ component, the mechanism of the defect of neuromuscular transmission, the affected protein, and ultimately the mutated gene responsible. In proposing this categorization of MG and CMSs, we hope to aid recognition of the disease groups for both conditions, as well as guide treatment, refine prognosis, and provide a framework for additional studies of these conditions.

**KEYWORDS**

canine, feline, megaesophagus, thymoma, weakness

## 1 | INTRODUCTION

Myasthenia gravis (MG) is a disorder of neuromuscular transmission affecting dogs and cats that has historically encompassed an acquired

or autoimmune form, characterized by autoantibodies against the neuromuscular junction (NMJ),<sup>1,2</sup> with a reported onset from 6 months of age onwards,<sup>3,4</sup> and a congenital form in which no autoimmunity against the NMJ is present,<sup>1-3</sup> with reported onset in the first weeks to months of life.<sup>1-3,5</sup>

Historically, the congenital form of MG originally was thought to solely be the result of a postsynaptic deficiency of acetylcholine receptors (AChRs) in the absence of autoantibodies directed against them.<sup>2,6,7</sup> However, it is now clear that it is only 1 of several clinically heterogeneous congenital syndromes affecting the NMJ, resulting in skeletal muscle weakness and fatigability.<sup>5,8-17</sup> These syndromes now

**Abbreviations:** 3,4-DAP, 3,4-diaminopyridine; ACh, acetylcholine; AChE, acetylcholinesterase; AChE-I, acetylcholinesterase inhibitor; AChE-Is, acetylcholinesterase inhibitors; AChR, acetylcholine receptor; AChRs, acetylcholine receptors; CHAT, choline acetyltransferase; CHRNE, cholinergic receptor nicotinic  $\epsilon$  subunit; CMS, congenital myasthenic syndrome; CMSs, congenital myasthenic syndromes; COLQ, collagen-like tail subunit of asymmetric acetylcholinesterase; EMG, electromyography; LRP4, low-density lipoprotein receptor-related protein 4; MG, myasthenia gravis; MUSK, muscle specific kinase; NMJ, neuromuscular junction; RNS, repetitive nerve stimulation.

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collectively are referred to as congenital myasthenic syndromes (CMSs), and considered as a separate disease entity, meaning that the term MG now solely refers to autoimmunity against the NMJ.<sup>5,17</sup> There is currently no established classification system for CMSs in dogs and cats.

Myasthenia gravis currently is classified in dogs and cats according to generalization, progression, and severity of skeletal muscle weakness and fatigability.<sup>1,2,18,19</sup> However, factors such as the presence or absence of a thymoma, or administration of thiourylene medication in cats, can influence treatment, outcome, or both, frequently leading to the division of affected dogs and cats into separate disease groups based on these factors.<sup>1,2,4,18,20-26</sup>

Our goal was to review the published literature on MG and CMSs in dogs and cats, and by comparison with published classifications for humans of these 2 conditions, propose a classification system for MG and CMSs in dogs and cats to facilitate their recognition, as well as guide treatment, refine prognosis, and provide a framework for additional studies of these conditions (Figure 1).

## 2 | MYASTHENIA GRAVIS

Myasthenia gravis is an autoimmune disorder that impairs neuromuscular transmission by the production of autoantibodies against the NMJ.<sup>5</sup> In dogs, these autoantibodies most frequently target the acetylcholine receptor (AChR)<sup>1,2,5,18</sup> but autoantibodies targeting a protein called muscle specific kinase (MUSK) also are reported.<sup>27</sup> In cats, however, autoantibodies are exclusively reported against the AChR, with no reports of autoantibodies against other components of the NMJ.<sup>2,24</sup> Myasthenia gravis can present focally, in a generalized fashion, or in an acute fulminating manner.<sup>19</sup> Myasthenia gravis also can occur with or without a thymoma in dogs and cats,<sup>1,2,4,18-26</sup> or after administration of thiourylene medication in cats,<sup>1,2,20-23</sup> and the autoimmune disease mechanism differs based on these factors,<sup>1,2,18,20,22,23</sup> as can treatment, outcome, or both.<sup>1,2,18-26</sup>

### 2.1 | Terminology and definition used in humans

Myasthenia gravis is defined in humans as skeletal muscle weakness and fatigability caused by autoantibodies against components of the NMJ of

skeletal muscle.<sup>28-30</sup> This definition is used because autoantibodies are not limited to the AChR, but instead can be directed against MUSK, or low-density lipoprotein receptor-related protein 4 (LRP4).<sup>28-30</sup>

### 2.2 | Classification used in humans

Because clinical presentation, diagnosis, optimal treatment, and outcome vary among human MG patients, subgrouping is necessary.<sup>28-30</sup> It is performed according to the autoimmune disease mechanism, protein or proteins targeted, status of the thymus gland, genetic characteristics, response to treatment, and whether skeletal muscle involvement is focal or generalized.<sup>28-30</sup> Subgroups include AChR autoantibody positive ocular, early onset, late onset, or thymoma-associated MG, AChR autoantibody negative MUSK or LRP4 autoantibody positive MG, and seronegative MG (see Table 1).<sup>28-30</sup>

### 2.3 | Terminology and definition in dogs and cats

Myasthenia gravis classification historically has included both acquired and congenital forms of the disease.<sup>1,2</sup> In recent years, the term CMS has replaced the term congenital MG in dogs and cats, and the term MG now refers only to autoimmunity against the NMJ.<sup>5,17</sup>

### 2.4 | Classification in dogs and cats

Current classification of MG includes focal, generalized and acute fulminating presentations based on a previous classification system used in humans.<sup>19,31</sup> Focal MG is defined as weakness in  $\geq 1$  focal skeletal muscle group that does not involve the appendicular skeletal muscles.<sup>1,2,19,31,32</sup> These focal skeletal muscle groups are the facial, esophageal, pharyngeal, and laryngeal skeletal muscles.<sup>1,2,19,31,32</sup> Generalized MG is defined as appendicular skeletal muscle weakness, which can range from mild to severe, with or without facial, esophageal, pharyngeal, or laryngeal skeletal muscle involvement.<sup>1,2,18,19,31</sup> Acute fulminant MG is defined as an acute, rapidly progressive and very severe form of generalized MG frequently but not necessarily causing respiratory failure and death.<sup>1,2,18,19,31,33,34</sup> This classification is widely accepted, and will therefore be retained. However we believe that differentiation between

**TABLE 1** Classification of myasthenia gravis subgroups in humans as previously described<sup>29</sup>

MG subgroups	Autoantibody target	Age of onset	Sex	Haplotype associations	Thymic status
Early onset	AChR	<50 years	Female predisposition	Various	Hyperplasia common
Late onset	AChR (titin, ryanodine receptor)	>50 years	Male predisposition	Various	Atrophy common
Thymoma	AChR (titin, ryanodine receptor)	Any age	...	...	Lymphoepithelioma
MUSK	MUSK	Any age	Female predisposition	DRB1:14, DRB1:16, DQB1:5	Normal
LRP4	LRP4	Any age	...	...	Normal
Ocular	Variable	Any age	...	...	Normal
Seronegative	Unknown	Any age	...	...	Normal or hyperplasia

Abbreviations: AChR, acetylcholine receptor; LRP4, low-density lipoprotein receptor-related protein 4; MG, myasthenia gravis; MUSK, muscle specific kinase.

generalized and fulminant presentations can be difficult because of lack of objective criteria to differentiate a fulminant presentation from a severe generalized presentation, and that they might represent a continuous spectrum of disease. A separately classified acute fulminant MG form no longer exists in people, rather it is accepted that the disease spectrum of generalized MG ranges from mild to extreme weakness with some patients initially presenting in a myasthenic crisis, which is objectively defined as onset or exacerbation of skeletal muscle weakness to the point that intubation and mechanical ventilation are required.<sup>28-30,35</sup> In people, a myasthenic crisis can occur at any time point in the disease including as the initial presentation of the disease.<sup>35</sup>

As in humans, the autoimmune disease mechanism can affect treatment, outcome, or both, and relates to the presence or absence of a thymoma, or administration of thiourylene medication in cats.<sup>1,2,18,20-26</sup> We therefore introduce subgroup classification according to the autoimmune disease mechanism. Lastly, as in humans, NMJ autoantibody testing can be negative in some dogs with generalized MG.<sup>1,27</sup> Such cases must fulfill specific criteria to be referred to as seronegative, including serum AChR autoantibody testing to have been negative at least twice.<sup>1,27</sup> A seronegative subgroup was not included in the previous classification of MG in dogs because of a lack of defining criteria.<sup>19</sup> Such criteria are now available, and classification based on seronegativity is therefore possible in dogs.<sup>1,27</sup> A summary of our proposed classification of MG in dogs and cats is presented in Table 2.

Additional characteristics of the disease that are used in humans to further classify patients, such as protein or proteins targeted, thymus gland status, and genetic characteristics cannot be used at this time for classification of MG in dogs and cats. The underlying reasons are discussed below.

Regardless of the subgroup, certain dogs and cats can present with associated coexisting diseases.<sup>1,31,36-43</sup> The implications of the presence of these coexisting diseases on patients with MG are currently unknown.<sup>1</sup> Although such affected dogs and cats are classified into specific subgroups, we recognize that treatment, outcome, or both might differ from the remainder of their respective subgroup depending on the concurrent condition or conditions. However the decision to include such cases into a specific subgroup appears reasonable given that all other aspects of their MG are consistent with the subgroup in which they are categorized.

**TABLE 2** Classification of myasthenia gravis in dogs and cats

Focal myasthenia gravis	Nonthymoma associated subgroup
	Thymoma associated subgroup
Generalized myasthenia gravis	Nonthymoma associated subgroup
	Thymoma associated subgroup
	Thiourylene medication associated subgroup (cats only)
	Seronegative subgroup (dogs only)
Acute fulminant myasthenia gravis	Nonthymoma associated subgroup
	Thymoma associated subgroup

## 2.4.1 | Non-thymoma-associated myasthenia gravis

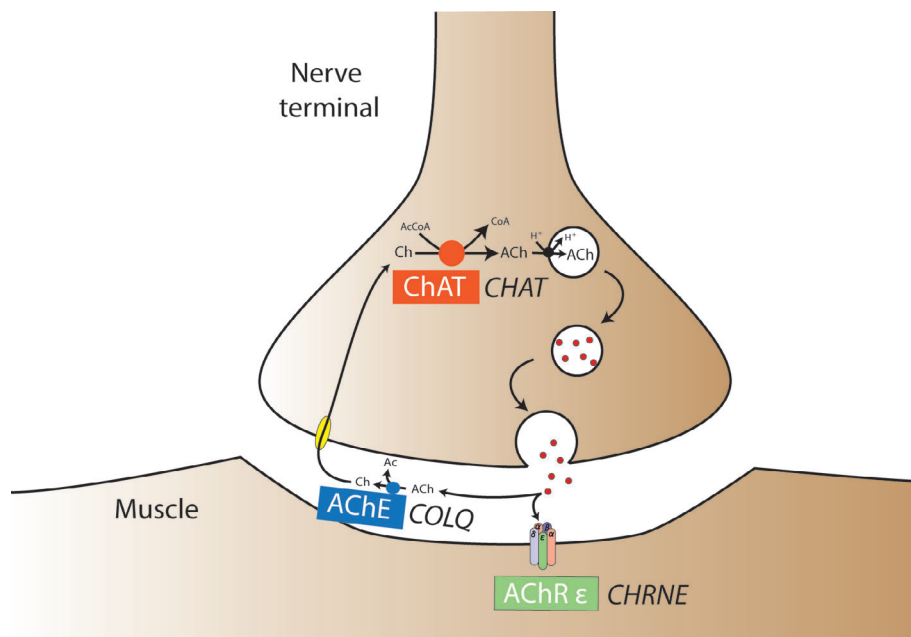
Dogs and cats in the focal, generalized, and acute fulminating categories that do not have a thymoma are referred to by this designation. The targeted protein is the AChR,<sup>1,2,18-21,24</sup> although striational autoantibodies against titin and the ryanodine receptor are reported in some dogs.<sup>1,44</sup> These striational autoantibodies are typically accompanied by AChR autoantibodies when clinical signs of skeletal muscle weakness and fatigability are present, and are thought not to be pathogenic, hence they are not classified separately, although they might serve as markers of disease severity.<sup>29,30,44</sup> Attempts at categorizing some dogs and cats into early or late onset non-thymoma-associated MG subgroups, as in humans, are reported.<sup>41,44,45</sup> These range from being based on severity of clinical signs alone,<sup>41</sup> to using the bimodal age of onset alongside either demonstration of an association with the *DLA-DQB1* haplotype,<sup>45</sup> itself frequently observed in humans with early onset MG, or by identification of striational autoantibodies,<sup>44</sup> which are predominantly but not exclusively reported in late onset MG in humans.<sup>30</sup> However, the frequency of thymic hyperplasia or atrophy is unknown in dog and cats,<sup>19,21,46</sup> as is the benefit of removing the thymus in those cases.<sup>19,21</sup> The presence of an age-related sex predisposition as seen in humans is not clear in dogs and cats,<sup>19,31</sup> and despite a bimodal age of onset, no cut-off value permits separation into early and late onset MG subgroups.<sup>19,31</sup> Because of this lack of necessary information, it is prudent not to subgroup dogs and cats into early and late onset non-thymoma-associated MG subgroups at this time.

## 2.4.2 | Thymoma-associated myasthenia gravis

Dogs and cats in the focal, generalized, and acute fulminating categories that have a thymoma are referred to by this designation. In these dogs and cats, MG is the result of a paraneoplastic syndrome.<sup>1,2,18,19,21</sup> The targeted protein is the AChR,<sup>1,2,19,21</sup> and striational autoantibodies against titin and the ryanodine receptor also are reported in some dogs.<sup>1,44</sup> In creating a thymoma-associated MG subgroup, we recognize that classification of dogs or cats with any concurrent neoplasia, but specifically those with cranial mediastinal neoplasia, might be difficult because it could be argued that such tumors also might induce MG as part of a paraneoplastic syndrome.<sup>1</sup> However, aside from individual reports, no neoplasia is repeatedly identified in conjunction with MG in dogs,<sup>1,47-49</sup> cats,<sup>21</sup> or even humans,<sup>30</sup> suggesting that the presence of concurrent neoplasia that is not a thymoma might be coincidental.

## 2.4.3 | Thiourylene medication-associated myasthenia gravis

Myasthenia gravis occurs secondarily to the administration of thiourylene medication in some cats as a consequence of a reversible break in tolerance to self-AChRs.<sup>1,2,20,22,23</sup> Myasthenia gravis appears



**FIGURE 1** Schematic illustration of currently reported CMSs in dogs and cats including the affected neuromuscular compartment, the mechanism of failure of neuromuscular transmission, the affected protein, and the underlying mutated gene. Ac, acetyl; AcCoa, acetyl-coenzyme A; ACh, acetylcholine; AChE, acetylcholinesterase; AChR  $\epsilon$ , acetylcholine receptor  $\epsilon$  subunit; Ch, choline; ChAT, choline acetyltransferase protein; CHAT, choline acetyltransferase gene; CHRNE, cholinergic receptor nicotinic  $\epsilon$  subunit gene; CoA, coenzyme A; COLQ, collagen-like tail subunit of asymmetric acetylcholinesterase gene; CMS, congenital myasthenic syndrome; H<sup>+</sup>, hydrogen ion

drug-induced and reversible in this subgroup because clinical signs often resolve after discontinuation of the medication.<sup>2</sup> This subgroup is only present in the generalized category of MG, because all cats with thiourylene medication-associated MG to date have been reported to have generalized clinical signs.<sup>1,2,20,22,23</sup>

#### 2.4.4 | Seronegative myasthenia gravis

Acetylcholine receptor autoantibody testing by radioimmunoassay is negative in approximately 2% of dogs with generalized MG and they are referred to as seronegative.<sup>1</sup> To be classified as such, dogs are required to have general and neurological examination, pharmacologic, and electrophysiologic findings consistent with MG, as well as normalization of clinical signs after acetylcholinesterase inhibitor (AChE-I) treatment and for serum AChR autoantibody testing by radioimmunoassay to have been negative at least twice.<sup>1</sup> Because AChR autoantibody testing can be negative early in the course of the disease and because many patients subsequently can seroconvert, measurement of serum AChR should be repeated 1 to 2 months after a negative AChR test.<sup>1</sup> Prior treatment with immunosuppressive medication can result in a negative result,<sup>1,37</sup> and should therefore be ruled out. Possible explanations as to why AChR autoantibody radioimmunoassay testing can be negative in dogs with MG include damage to the antigenic epitopes during the process of solubilization thereby preventing recognition of autoreactive AChR autoantibodies, the majority of autoantibodies being bound in the skeletal muscle thereby causing circulating AChR autoantibody concentration to be within normal limits, or autoantibodies being directed against the toxin binding site.<sup>1</sup> Additionally, autoantibodies can be directed against other components of the postsynaptic NMJ.<sup>27</sup> This has been demonstrated in 1 dog seronegative for the AChR in which

autoantibodies were detected against MUSK.<sup>27</sup> Availability of MUSK autoantibody testing is limited and no established reference range is available in dogs.<sup>27</sup> The percentage of dogs with focal MG, and cats with focal or generalized MG, that are seronegative is unknown.<sup>1,37</sup> Such cases might exist,<sup>19</sup> however because they have not been reported and no criteria are available to define them, such subgroups are not included in our classification.

## 2.5 | DIAGNOSIS

The gold standard for the diagnosis of MG in dogs and cats is positive NMJ autoantibody testing by measurement of AChR autoantibody concentration using radioimmunoassay.<sup>1,2,18</sup> The presence of skeletal muscle weakness and fatigability supports the diagnosis.<sup>1,2,18</sup> Ancillary tests such as pharmacological testing and electrophysiology continue to play a key role in the diagnostic approach to MG in dogs and cats.<sup>1,2,18</sup> They can support the clinical suspicion of MG while NMJ autoantibody testing is pending, but they lack the combined sensitivity and specificity required to permit a definitive diagnosis.<sup>1,2,18</sup> For instance, although dramatic improvement in skeletal muscle weakness and fatigability usually is expected after administration of acetylcholinesterase inhibitors (AChE-Is) in dogs and cats with MG, subjective improvement also can be observed in other myopathic or neuropathic disorders, hence mimicking MG.<sup>1</sup> Furthermore, pharmacological testing can be negative in dogs and cats with MG and primarily is observed in those with focal MG as opposed to generalized MG.<sup>1</sup> Evaluation for the presence or absence of a cranial mediastinal mass, which in most cases is a thymoma, is important in dogs and cats.<sup>1,2,4,19,21</sup> This evaluation should be done using thoracic imaging, either thoracic radiography or ideally computed tomography.<sup>24</sup> The incidence of a concurrent cranial mediastinal mass in dogs and cats is

3.4% and 52%, respectively.<sup>4,21,37</sup> In addition to evaluation for the presence or absence of a thymoma, inquiring about the administration of any thiourylene medication in cats is necessary to permit adequate subgrouping. Lastly, given that MG can be associated with certain coexisting diseases in dogs and cats, investigations should evaluate for their presence or absence.<sup>1,18,37</sup>

## 2.6 | Treatment and outcome

Currently, limited evidence is available to guide treatment, and hence controlled studies are needed.<sup>1</sup> Treatment of MG can be divided into that which is beneficial for all subgroups and that which is specific for a given subgroup or subgroups in dogs and cats.<sup>1,2,18</sup> Symptomatic treatment using AChE-Is, immunosuppression, and supportive treatment are all successfully reported in the management of all subgroups in dogs and cats.<sup>1,2,18</sup>

Supportive care is an important aspect of management.<sup>1</sup> Unlike the situation in people, megaesophagus and associated aspiration pneumonia require particular attention in dogs and cats.<sup>1</sup> Aspiration pneumonia is the most frequent cause of death, and its management therefore represents a cornerstone of treatment.<sup>1</sup>

Recommendations in humans are to start symptomatic treatment, usually with pyridostigmine and then add immunosuppression, usually with prednisolone if clinical remission is not achieved with symptomatic treatment alone.<sup>29,30</sup> A similar approach is suggested in dogs given the high incidence of megaesophagus and therefore risk of aspiration pneumonia, although AChE-Is can themselves cause serious adverse effects manifested as cholinergic crises.<sup>1</sup> No recommendations currently exist in cats.<sup>1,2</sup> Although the incidence of megaesophagus, and therefore risk of aspiration pneumonia is also high, cats are suggested to be more prone to the adverse effects of AChE-Is.<sup>20,50</sup> Furthermore, immunosuppression with corticosteroids is thought to be more beneficial, and cats appear more tolerant to the adverse effects of corticosteroids, unlike dogs, which often experience exacerbation of their skeletal muscle weakness.<sup>1,2</sup>

Dogs and cats with acute fulminant MG, with deterioration of their skeletal muscle weakness because of surgery or general anesthesia, or with aspiration pneumonia causing respiratory distress, often require intensive care including intubation and mechanical ventilation.<sup>1,2,37</sup> Plasmapheresis has been reported as a treatment in addition to prednisolone in a dog with MG, resulting in clinical remission.<sup>51</sup> Additionally, human IV immunoglobulin also has been reported as a treatment in 2 dogs with MG resulting in transient clinical remission.<sup>37</sup> In humans, plasmapheresis and IV immunoglobulins are used for the management of myasthenic crises for all subgroups.<sup>29,30</sup> Perhaps all MG subgroups in dogs and cats might similarly benefit from these treatments in an emergency situation. Most dogs and cats with acute fulminating MG are reported to die either because of respiratory failure or severe aspiration pneumonia.<sup>1,2,19,31</sup>

Although some aspects of treatment are common to all subgroups, the presence or absence of a thymoma or the administration of thiourylene medication in cats can affect treatment, outcome, or both.<sup>1,2,18,20-26</sup>

Clinical remission is defined by the resolution of clinical signs of MG, whereas immune remission is defined by the resolution of clinical signs in conjunction with discontinuation of treatment and normalization of serum AChR autoantibody concentration.<sup>24</sup> A peculiarity of generalized non-thymoma-associated MG in cats is that spontaneous immune remission, as defined as resolution of the clinical signs and normalization of serum AChR autoantibody concentration without any treatment, can occur, suggesting that treatment is not always necessary.<sup>24</sup> Furthermore, immune remission is frequent in dogs with focal and generalized non-thymoma-associated MG, and hence treatment often can be discontinued, and long-term outcome is usually excellent if the dog does not succumb to aspiration pneumonia or respiratory failure before achieving immune remission.<sup>26</sup> This is not as clear in cats with focal and generalized non-thymoma-associated MG, although in 1 study immune remission was achieved with excellent long-term outcome in 8/8 cats without the need for continued treatment.<sup>24</sup> In the absence of immunosuppression, serial measurement of AChR autoantibody concentration is useful to monitor the course of the disease in affected dogs and cats.<sup>1,2</sup>

In focal and generalized thymoma-associated MG in dogs, anecdotal evidence suggests that a complete thymectomy is necessary for these patients to achieve immune remission.<sup>1</sup> However the percentage of dogs that achieve immune remission after a complete thymectomy is unknown.<sup>1</sup> In cats with focal and generalized thymoma-associated MG, no difference in outcome was reported whether thymectomy was performed or not in 1 study, but the completeness of the resection of the thymomas was not known.<sup>21</sup> To date, the only reported cat with thymoma-associated MG to have achieved immune remission underwent thymectomy.<sup>21</sup> Aside from these dogs and cat reported to have achieved immune remission after thymectomy, the long-term outcome of dogs and cats with focal and generalized thymoma-associated MG does not appear as favorable as that of dogs and cats in the focal or generalized non-thymoma subgroups because immune remission is not reported and therefore continued treatment with medication is required if they do not succumb to aspiration pneumonia or respiratory failure, but clinical remission can be achieved.<sup>1,2,21,24,52,53</sup> Furthermore, thymomas can occupy a large amount of space in the thorax, invade local tissues, metastasize to other organs, or induce hemothorax which might result in death.<sup>1,54-57</sup> Hence for this reason alone, thymectomy generally is recommended.<sup>1,37</sup> A major caveat to thymectomy however is the requirement for general anesthesia which is a substantial risk for dogs and cats with MG, and the surgery itself can cause a clinically relevant postoperative exacerbation of skeletal muscle weakness and fatigability, which is thought to be the result of surgical stress.<sup>1,37</sup>

Given that MG is caused by administration of thiourylene medication in cats with thiourylene medication-associated MG, this medication should be discontinued if possible.<sup>1,2</sup> Furthermore, immune remission has only been reported with discontinuation of the thiourylene medication being administered.<sup>20,23</sup> In these cats, treatment eventually was discontinued, and long-term outcome was excellent.<sup>20,23</sup> Comparatively, although anecdotally, the outcome of cases in which thiourylene medication administration was not discontinued

does not appear to be as favorable, because immune remission is not reported and therefore continued treatment with medication is required although clinical remission can be achieved.<sup>20-23</sup>

Aspiration pneumonia and respiratory failure remain frequent causes of death from MG in dogs and cats, regardless of the subgroup.<sup>1,2,18,58</sup> The 1-year mortality rate for the disease including all subgroups together is 40% to 60% in dogs<sup>4,18,19,37</sup> and 15% in cats.<sup>31</sup> A high rate of euthanasia (58%) also was reported in cats with MG, but it is not known whether their disease was the reason for euthanasia.<sup>21</sup> The mortality rate for each subgroup currently is undetermined other than for cats with generalized non-thymoma-associated MG in the absence of megaesophagus, in which no fatalities occurred in 1 study, although sample size was small.<sup>24</sup>

### 3 | CONGENITAL MYASTHENIC SYNDROMES

Many syndromes resembling but distinct from MG have been recognized in dogs and cats since 1974.<sup>1,2,5-17,59-71</sup> Affected dogs and cats also manifest skeletal muscle weakness and fatigability, but NMJ autoantibody testing for AChRs is negative.<sup>1,2,5-17,59-71</sup> A notable feature of these syndromes is that onset is no older than a few weeks to months of age and a genetic basis is generally identified or suspected.<sup>5,8-17,59-64,66-71</sup> When determined, the pathogenesis of these syndromes invariably involves deficient neuromuscular transmission although the location and mechanism of this failure vary, as do their clinical features including response to a given treatment.<sup>5,8-14,17,68</sup>

#### 3.1 | Terminology and definition used in humans

In humans, the term CMSs is used to refer to a clinically heterogeneous group of genetic disorders causing aberrant neuromuscular transmission.<sup>72-75</sup>

#### 3.2 | Classification used in humans

Although CMSs share the common features of skeletal muscle weakness and fatigability associated with inadequate neuromuscular transmission, their clinical presentation (ie, age of onset, presenting signs, distribution of skeletal muscle weakness and fatigability, and response to treatment) varies according to the mutation.<sup>72-77</sup> Over 30 mutations have been identified in humans, and affect proteins involved in NMJ structure, function, or repair.<sup>70-75</sup> Numerous criteria can be used to classify these CMSs although the most frequently used classification system is based on the affected NMJ component or components, thereby organizing them into presynaptic, synaptic, postsynaptic, and concurrent presynaptic- and postsynaptic CMSs (see Table 3).<sup>72,74,75</sup> These CMSs then are categorized further according to the mechanism of the defect of neuromuscular transmission, the affected protein, and ultimately the mutated gene (see Table 3).<sup>72-75</sup> For some mutations,

however, the location of the affected protein or proteins is unknown, meaning that these CMSs cannot presently be classified, and are referred to as "other".<sup>72,74</sup>

#### 3.3 | Terminology and definition in dogs and cats

Previous terminology frequently has referred to these syndromes as congenital MG, but more recent publications follow the terminology used in humans and use the term CMS<sup>5,8,17</sup> because it more appropriately characterizes the genetic and clinical heterogeneity of these syndromes. Similar to humans, CMSs also are defined in dogs and cats as a clinically heterogeneous group of genetic disorders causing aberrant neuromuscular transmission.<sup>5,17</sup>

#### 3.4 | Classification in dogs and cats

Given the shared genetic basis of CMSs in humans, dogs, and cats, a similar classification system of CMSs in dogs and cats to that used in humans appears appropriate. Following the classification system used in humans, we propose to classify CMSs in dogs and cats according to the affected NMJ component, the mechanism of the defect of neuromuscular transmission, the affected protein, and ultimately the mutated gene (see Table 4).<sup>75</sup> A concurrent presynaptic and postsynaptic category is not included in this classification of CMSs in dogs and cats because at the present time such CMSs are not reported in these species.<sup>5,10</sup> This situation might change as new CMSs are discovered. Despite efforts to classify CMSs in dogs and cats, many suspected CMSs presently cannot be classified because of a lack of identification of an underlying genetic mutation.<sup>7,15,16,60,61,64,65,67</sup> Among these suspected CMSs, many are suspected to be postsynaptic because of a lack of postsynaptic AChRs,<sup>7,15,16,64</sup> but these suspected CMSs still cannot be classified, because concurrent presynaptic involvement cannot be excluded because of a lack of knowledge of the suspected underlying genetic mutation,<sup>7,15,16,64</sup> and as such a deficiency although marginal also is reported in some synaptic CMSs in dogs.<sup>8,10</sup>

##### 3.4.1 | Presynaptic CMSs

###### *Defect in the synthesis of acetylcholine*

A presynaptic CMS is reported in Old Danish Pointing dogs.<sup>11,63,66,71</sup> It involves a missense mutation in exon 6 of the choline acetyltransferase (*CHAT*) gene the normal function of which is the synthesis of acetylcholine (ACh), and is inherited in an autosomal recessive manner.<sup>11</sup> Reported onset is 12 to 16 weeks of age, and a period of exercise is required before observation of skeletal muscle weakness and fatigability, at which time palpation of the affected skeletal muscles can identify hypertonicity.<sup>11,66,71</sup> A decremental response is observed upon repetitive nerve stimulation (RNS), but a preceding high frequency conditioning train is required, and

**TABLE 3** Classification of congenital myasthenic syndromes in humans as previously described<sup>75</sup>

Site of defect	Mechanism	Gene	Protein
Presynaptic	Defect in ACh recycling	<i>SLC5A7</i> (solute carrier family 5 member 7)	ChT (choline transporter)
	Defect in ACh synthesis	<i>CHAT</i>	ChAT (choline acetyltransferase)
	Defects in loading of ACh in synaptic vesicles	<i>SLC18A3</i> (solute carrier family 18 member A3)	VAcHT (vesicular acetylcholine transporter)
	Defect in synaptic vesicle docking, priming, fusing and exocytosis	<i>SNAP25B</i> (synaptosomal nerve-associated protein 25)	Soluble N-ethylmaleimide-sensitive factor attachment protein receptor 25
		<i>UNC13A</i> (unc-13 Homolog A)	Munc 13 (mammalian uncoordinated-13)
		<i>SYB1</i> (Synaptobrevin-1)/ <i>VAMP1</i> (vesicle associated membrane Protein 1)	SYB1/VAMP1
		<i>SYT2</i> (synaptotagmin 2)	SYT2
<i>PREPL</i> (prolyl-endopeptidase Like)	PREPL		
Defect in axonal transport of proteins	<i>MYO9A</i> (myosin IXA)	MYO9A	
Synaptic	Acetylcholinesterase deficiency	<i>COLQ</i>	COLQ
	Synaptic basement membrane defects	<i>COL13A1</i> (collagen type 13 $\alpha$ 1)	COL13A1
		<i>LAMA5</i> (laminin $\alpha$ 5)	LAMA5
		<i>LAMB2</i> (laminin $\beta$ 2)	LAMB2
	Defects in AChR clustering pathway	<i>AGRN</i> (agrin)	AGRN
Postsynaptic	Reduced numbers of AChR (AChR deficiency)	<i>CHRNE</i> , <i>CHRNA1</i> (cholinergic receptor nicotinic $\alpha$ 1 subunit), <i>CHRNB1</i> (cholinergic receptor nicotinic $\beta$ 1 subunit), <i>CHRND</i> (cholinergic receptor nicotinic $\delta$ subunit)	AChR subunits
	Kinetic changes in AChR function (slow channel syndromes)	<i>CHRNA1</i> , <i>CHRNB1</i> , <i>CHRND</i> , <i>CHRNE</i>	AChR subunits
	Kinetic changes in AChR function (fast channel syndromes)	<i>CHRNA1</i> , <i>CHRND</i> , <i>CHRNB1</i> , <i>CHRNE</i>	AChR subunits
	Defect in AChR clustering pathway	<i>LRP4</i>	LRP4
		<i>MUSK</i>	MUSK
		<i>DOK7</i> (downstream of kinase 7)	DOK7
		<i>RAPSN</i> (rapsyn)	RAPSN
	Defect in skeletal muscle voltage-gated sodium channel	<i>SCN4A</i> (sodium voltage gated channel $\alpha$ 4)	SCN4A
	Plectin deficiency	<i>PLEC</i> (plectin)	PLEC
	Pre + post synaptic	Defective glycosylation	<i>ALG2</i> (A-1,3,Mannosyltransferase)
<i>ALG14</i> (ALG14 UDP-N-Acetylglucosaminyltransferase Subunit)			ALG14
<i>DPAGT1</i> (dolichyl-phosphate N-acetylglucosaminephosphotransferase 1)			DPAGT1
<i>GFPT1</i> (glutamine-fructose-6-phosphate transaminase 1)			GFPT1
<i>GMPPB</i> (GDP-mannose pyrophosphorylase)			GMPPB

Abbreviations: ACh, acetylcholine; AChR, acetylcholine receptor; CHAT, choline acetyltransferase; CHRNE, cholinergic receptor nicotinic  $\epsilon$  subunit; COLQ, collagen-like tail subunit of asymmetric acetylcholinesterase; LRP4, low-density lipoprotein receptor-related protein 4; MUSK, muscle specific kinase.

postsynaptic AChR concentration is normal.<sup>11,66,71</sup> Neuromuscular junction autoantibody testing for the AChR is negative.<sup>11,66</sup> Administration of AChE-Is has no clinical or electrophysiologic effect,

although guanidine can result in transient electrophysiologic improvement.<sup>11,71</sup> Genetic testing for this mutation is available for this breed.<sup>11</sup>

**TABLE 4** Classification of congenital myasthenic syndromes in dogs and cats

Affected neuromuscular junction component	Mechanism of the defect of neuromuscular transmission	Protein	Gene	Species, breed
Presynaptic	Defect in ACh synthesis	ChAT (choline acetyltransferase)	<i>CHAT</i>	Dogs: Old Danish Pointing dog
Synaptic	AChE deficiency	COLQ	<i>COLQ</i>	Dogs: Labrador Retriever, Golden Retriever Cats: Sphynx, Devon Rex
Postsynaptic	AChR deficiency	AChR $\epsilon$ subunit	<i>CHRNE</i>	Dogs: Jack Russell Terrier, Heiderterrier

Abbreviations: ACh, acetylcholine; AChE, acetylcholinesterase; AChR, acetylcholine receptor; *CHAT*, choline acetyltransferase; *CHRNE*, cholinergic receptor nicotinic  $\epsilon$  subunit; COLQ, collagen-like tail subunit of asymmetric acetylcholinesterase.

### 3.4.2 | Synaptic CMSs

#### *Acetylcholinesterase deficiency*

A synaptic CMS is identified in Labrador Retrievers,<sup>8</sup> Golden Retrievers,<sup>10</sup> Sphynxes and Devon Rexes.<sup>12,13</sup> These CMSs involve a mutation in the collagen-like tail subunit of asymmetric acetylcholinesterase (*COLQ*) gene, which anchors acetylcholinesterase (AChE) to the basal lamina of the NMJ.<sup>8,10,12,13</sup> In Labrador Retrievers, it is caused by a nonsynonymous mutation in exon 14, and is inherited in an autosomal recessive manner.<sup>8</sup> Reported onset is 2 to 3 weeks of age, electromyography (EMG) is normal, and a decremental response is observed upon RNS.<sup>8</sup> Skeletal muscle and nerve biopsy results are normal, but postsynaptic AChR concentration is marginally decreased.<sup>8</sup> Neuromuscular junction autoantibody testing for the AChR is negative.<sup>8</sup> Administration of pyridostigmine bromide results in worsening of skeletal muscle weakness and fatigability.<sup>8</sup> Genetic testing for this mutation is available for this breed.<sup>8</sup> In Golden Retrievers, it is caused by a nonconserved missense mutation in exon 13 that is inherited in an autosomal recessive manner.<sup>10</sup> Reported onset is 6 to 8 weeks of age, EMG is normal, but motor nerve conduction studies can identify a mild decrease in the amplitude of the M wave, and RNS identifies a decremental response.<sup>10</sup> Skeletal muscle and nerve biopsy results are normal, but postsynaptic AChR concentration also is marginally decreased.<sup>10</sup> Neuromuscular junction autoantibody testing for the AChR is negative.<sup>10</sup> Administration of edrophonium chloride either results in worsening of skeletal muscle weakness and fatigability or has no effect, whereas administration of albuterol results in temporary improvement of skeletal muscle weakness and fatigability.<sup>10</sup> Genetic testing for this mutation is available for this breed.<sup>10</sup> In Sphynx and Devon Rex cats, the mutation is shared, and is a missense mutation in exon 15, which is inherited in an autosomal recessive manner.<sup>12,13</sup> Reported onset is 3 to 23 weeks of age, affected cats often have decreased skeletal muscle mass and dorsal protrusion of the scapulae.<sup>12-14</sup> Electromyography can disclose positive sharp waves and complex repetitive discharges.<sup>12,13</sup> A decremental response can be observed upon RNS, but in some cats RNS is within normal limits.<sup>12,13</sup> Skeletal muscle biopsy samples frequently have dystrophic changes whereas nerve biopsy results are normal, and postsynaptic AChR concentration is normal.<sup>12-14</sup> Neuromuscular junction autoantibody testing for the AChR is negative.<sup>12,13</sup> Administration of edrophonium chloride can result in exacerbation of skeletal muscle weakness and fatigability.<sup>13</sup> Genetic testing for this mutation is available for these breeds.<sup>12,13</sup>

### 3.4.3 | Postsynaptic CMSs

#### *Primary deficiency of the acetylcholine receptor*

A postsynaptic CMS is described in Jack Russell Terriers<sup>9</sup> and in a Heiderterrier.<sup>68</sup> Both of these CMSs are associated with a mutation in the cholinergic receptor nicotinic  $\epsilon$  subunit (*CHRNE*) gene, which codes for the  $\epsilon$  subunit of the AChR.<sup>9,68</sup> In Jack Russell Terriers it is caused by a deletion mutation in exon 7, and is inherited in an autosomal recessive manner.<sup>9</sup> Reported onset is usually 6 to 8 weeks of age.<sup>9</sup> Electromyography is normal, but a decremental response is observed upon RNS.<sup>9</sup> Skeletal muscle and nerve biopsy results are normal, but postsynaptic nicotinic AChR concentration is markedly decreased.<sup>9</sup> Neuromuscular junction autoantibody testing for the AChR is negative.<sup>9</sup> Administration of AChE-Is results in electrophysiologic as well as temporary clinical improvement.<sup>9</sup> Genetic testing for this mutation is available for this breed.<sup>9</sup> In the Heiderterrier, a non-synonymous mutation in exon 31 is reported in 1 dog with skeletal muscle weakness and fatigability.<sup>68</sup> Reported onset was <1 week of age, and skeletal muscle weakness and fatigability were described to initially affect the thoracic limbs.<sup>68</sup>

## 4 | DIAGNOSIS

The combination of skeletal muscle weakness and fatigability, onset from birth or a few weeks or months of age, decremental response upon RNS, presence of affected related individuals, absence of skeletal muscle or nerve pathology, and negative NMJ autoantibody testing for the AChR is highly suggestive of a CMS.<sup>1,5,8-14,16,17</sup> Additionally, ultrastructural or in vitro electrophysiologic evidence of a junctionopathy along with having ruled out all other causes can further increase the index of suspicion of a CMS.<sup>1,16</sup> However the definitive diagnosis requires identification of a causative genetic mutation, along with clinical signs of skeletal muscle weakness and fatigability.<sup>10,16</sup> Administration of edrophonium chloride as part of a challenge test can result in transient marked improvement of skeletal muscle weakness and fatigability, but can otherwise result in exacerbation of skeletal muscle weakness and fatigability, or might have no effect depending on the CMS.<sup>1,8-11,13</sup> Hence the result of the edrophonium chloride challenge test should be interpreted in light of what is



reported for the specific CMS being investigated.<sup>1,8-11,13</sup> Although a decremental response frequently is observed upon RNS in most CMSs,<sup>8-10</sup> there is a CMS in cats in which RNS often can be normal,<sup>12,13</sup> and a CMS in dogs in which a preceding high frequency conditioning train usually is required before observation of a decremental response.<sup>11</sup> Ultrastructural and in vitro electrophysiologic testing is available at a few specialized laboratories.<sup>1</sup> Genetic testing is available for known mutations, but when negative, whole genome sequencing analysis should be considered and might permit discovery of previously unknown mutations.<sup>10,16</sup>

#### 4.1 | Treatment and outcome

At present, no treatment targeting the genetic etiology of CMSs in dogs or cats is available, meaning that treatment is restricted to symptomatic management of clinical signs.<sup>8-13</sup> With the recent identification of the genetic mutations responsible for some CMSs in dogs and cats, it is now clear that the causative gene plays a pivotal role as to which symptomatic treatment benefits a given CMS.<sup>8-11,13,71</sup> Efforts must therefore be made to obtain a genetic diagnosis, permitting institution of appropriate symptomatic treatment because inappropriate symptomatic treatment can result in exacerbation of clinical signs.<sup>8,10,13</sup>

In the *CHAT*-associated CMS of Old Danish Pointing dogs, administration of AChE-Is had no clinical effect.<sup>11,71</sup> Treatment for *CHAT*-associated CMSs in humans includes medications that increase the amount of ACh in the synaptic cleft, such as AChE-Is or 3,4-diaminopyridine (3,4-DAP).<sup>76,77</sup>

Administration of AChE-Is either has no effect or results in exacerbation of clinical signs in the *COLQ*-associated CMSs reported in dogs and cats.<sup>8,10,13</sup> Administration of albuterol, however, can result in a temporary improvement of clinical signs in the *COLQ*-associated CMS reported in Golden Retrievers.<sup>10</sup> Similarly, *COLQ*-associated CMSs in humans respond positively to  $\beta$ 2-adrenergic receptor agonists such as albuterol and ephedrine, which are thought to stabilize the NMJ and decrease dispersion of AChRs.<sup>76,77</sup> Acetylcholinesterase inhibitors or 3,4-DAP however are contraindicated in *COLQ*-associated CMSs in humans because they generally result in exacerbation of clinical signs.<sup>76,77</sup>

Jack Russell terriers with *CHRNE*-associated CMS generally benefit from treatment with AChE-Is, but the response can be transient because drug resistance occurs.<sup>9</sup> Similarly, *CHRNE*-associated CMSs in humans benefit from AChE-Is, but also from 3,4-DAP.<sup>76,77</sup> Additionally, drug resistance to AChE-Is also is observed in *CHRNE*-associated CMSs in humans, and addition of a  $\beta$ 2-adrenergic receptor agonist to their treatment is recommended because it counteracts the adverse effects of long-term AChE-I treatment on the NMJ.<sup>78</sup>

Given the shared pathogenesis, and similarities in the response to a given symptomatic treatment among CMSs in humans, dogs, and cats with shared causative mutations, it is logical to consider similar treatments in dogs and cats as those used in humans for a given CMS, which emphasizes the importance of correctly classifying CMSs in dogs and cats.

Most reported CMSs in dogs and cats have an unfavorable outcome and are fatal.<sup>8-13</sup> However certain Jack Russell terriers and Devon Rexes respectively affected by *CHRNE*- and *COLQ*-associated CMS can survive for years, and a suspected CMS reported in Smooth Haired Miniature Dachshunds appears to resolve spontaneously.<sup>9,14,15</sup>

## 5 | CONCLUSION

Myasthenia gravis is an autoimmune disorder that impairs neuromuscular transmission by the production of autoantibodies against the NMJ of skeletal muscle. Congenital myasthenic syndromes are a clinically heterogeneous group of genetic disorders causing aberrant neuromuscular transmission. Both conditions encompass disease groups, the recognition of which is important with regard to treatment, outcome, or both. We have provided a classification system of MG and CMSs in dogs and cats to aid recognition of the disease groups for both conditions, as well as guide treatment, refine prognosis, and provide a framework for additional studies of these conditions. This classification system has been purposefully designed to accommodate possible novel disease groups, but revisions eventually will be needed.

#### CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

#### OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

#### INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

#### HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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