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Clinical features of muscle stiffness in 37 dogs with concurrent naturally occurring hypercortisolism

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Abstract

Background: Severe muscle stiffness (SMS) in dogs with hypercortisolism (HC) is uncommon.

Objectives: To evaluate signalment, presentation, treatments, and long-term outcomes of dogs with concurrent HC and SMS.

Animals: Thirty-seven dogs.

Methods: Medical records of dogs with HC and concurrent SMS were recruited from 10 institutions. Clinical information, test results, therapeutic responses, and survival times were reviewed.

Results: All 37 dogs with HC and SMS had pituitary-dependent hypercortisolism (PDH); 36/37 weighed <20 kg. Signs and test results were typical of PDH aside from SMS, initially diagnosed in all 4 limbs in 9, pelvic limbs of 22, and thoracic limbs of 6 dogs. Hypercortisolism and SMS were diagnosed together in 3 dogs; HC

Abbreviations: ACTHst, ACTH stimulation test; ADH, adrenal dependent hypercortisolism; CBC, complete blood count; CT, computed tomography; eACTH, endogenous ACTH; EMG, electromyography; HC, hypercortisolism; LDDST, low-dose dexamethasone suppression test; MRI, magnetic resonance imaging; NCS, nerve conduction studies; PDH, pituitary dependent hypercortisolism; POMC, proopiomelanocortin; PU/PD, polyuria and polydipsia; SMS, severe muscle stiffness; UCCR, urine corticoid: creatinine ratio.

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1-36 months before SMS in 23; SMS 1-12 months before HC in 11. Mitotane or trilostane, given to control HC in 36/37 dogs, improved or resolved HC signs in 28; SMS did not resolve, remaining static or worsening in 31/36 dogs, mildly improving in 5/19 dogs given additional therapies. Progression of SMS included additional limbs in 10 dogs and the masticatory muscles of 2. The median survival time from diagnosis of SMS was 965 days (range, 8-1188).

Conclusions and Clinical Importance: Concurrent SMS and HC is uncommon, possibly affecting only dogs with PDH. Development of SMS might occur before or after diagnosis of HC. Apart from SMS, the clinical picture and survival time of these dogs seem indistinguishable from those of dogs with HC in general. However, while muscle weakness usually resolves with HC treatment SMS does not.

KEYWORDS

diver bomber sound, median survival time, myotonia, pituitary dependent hypercortisolism, rigidity, treatment

1 | INTRODUCTION

Naturally occurring and iatrogenic hypercortisolism (HC) are common disorders in dogs, causing clinical signs that include polyuria and polydipsia (PU/PD), polyphagia, thin skin, excess panting, bilaterally symmetrical truncal hair loss, and muscle weakness. Muscle weakness, secondary to chronic glucocorticoid excess, likely contributes to the “pot belly” appearance and exercise intolerance noted frequently in dogs with HC.¹ Severe muscle stiffness (SMS) is rare in dogs with HC and when present has been characterized by persistent bilateral muscle contraction of the thoracic legs, pelvic legs, or all 4 legs. The dogs reported to have concurrent HC and SMS have had typical clinical signs of HC but rather than muscle weakness they have nonpainful SMS resulting in a bilateral extremely stiff and stilted gait. Even when lying down, affected dogs exhibit severe persistent extensor rigidity. The combination of SMS in dogs with HC, clinically, has been referred to as “Cushing's myotonia.”¹⁻¹⁰

Reported electromyography (EMG) results from dogs with HC and SMS include “myotonic,” bizarre, high-frequency discharges.^{11,12} Muscle histopathology in dogs with typical HC and weakness includes Type II muscle fiber atrophy¹ while those with concurrent HC and SMS have fiber size variation, focal necrosis, fiber splitting, subsarcolemmal aggregates, and fatty infiltration.¹⁰ Evidence of demyelination in some of these dogs on nerve conduction studies (NCS) is consistent with a chronic neuropathy.¹²

To the authors knowledge, fewer than 20 dogs with HC and SMS have been described.²⁻⁷ In addition to treating HC, some of those dogs were administered medications (L-carnitine, phenytoin, methocarbamol, or diazepam) to reduce or eliminate the SMS but no treatment resolved the SMS.^{6,7} The pathogenesis, treatment, short- and long-term prognosis of dogs with HC and SMS are unclear.^{6,7} The aim of the present study was to evaluate a larger number of dogs with concurrent HC and SMS to allow analysis of signalment, presentation, treatment, and outcome.

2 | MATERIALS AND METHODS

In the interest of providing a geographically broad perspective, at least 1 veterinary colleague from Asia, North America, South America, The United Kingdom, and Europe was invited to submit to 1 author (Stefania Golinelli) case information on dogs with concurrent HC and SMS. In total, 14 colleagues from 10 institutions submitted data on dogs from their personal and institutions' records.

2.1 | Dogs

For inclusion, dogs must have had at least 3 of the following clinical signs of HC: PU/PD, polyphagia, hair loss, thin skin and excessive panting. Dogs must have had obvious abnormal muscle stiffness of the thoracic limbs, pelvic limbs, or all 4 limbs; no evidence of muscle weakness; and no evidence of any other cause for SMS (ie, tetanus).

For inclusion, each dog with naturally occurring HC must have had at least 1 abnormal endocrine screening test result (low-dose dexamethasone suppression test [LDDSt]; ACTH stimulation test [ACTHst], urine corticoid: creatinine ratio [UCCR]). Each dog with iatrogenic HC must have had a history of glucocorticoid administration and abnormally suppressed ACTHst and endogenous ACTH [eACTH] results.^{1,13} Discrimination of pituitary-dependent hypercortisolism (PDH) from adrenal-dependent hypercortisolism (ADH) was determined using results of abdominal ultrasonography, LDDSt, and eACTH concentrations. Dogs with ADH must have had adrenocortical adenoma or carcinoma on adrenal histology.¹ Dogs were excluded if they had signs or laboratory abnormalities inconsistent with HC (ie, vomiting, diarrhea, poor appetite, anemia, increased serum BUN or creatinine concentration).

Data submitted for each dog were to include signalment (age, breed, sex, neuter status, body weight), history, clinical findings, complete blood counts (CBC), routine serum biochemistries, urinalyses, and endocrine test results at time of HC diagnosis, plus the time

sequence of diagnosing HC and SMS. Abnormalities detected via diagnostic imaging were to be included. Presence of concurrent disorders must have been described. If performed, results of electrodiagnostic tests (EMG and NCS), muscle, and nerve biopsies were to be submitted. Therapies employed for either HC or SMS and response to treatments were abstracted. "Progression" of SMS was defined as an inability to walk after being ambulatory at diagnosis or when stiffness was observed in additional limbs or masticatory muscles not involved when SMS was initially diagnosed. When available, cause of death was included.

2.2 | Data analysis

Collected data were managed with an electronic spreadsheet (Microsoft Excel) and analyzed using a commercial statistical data analysis software program (Prism7.0a, GraphPad Software, Inc, San Diego, California). The Shapiro-Wilk test was used to assess the normality of continuous data. General and clinical characteristics of dogs with HC and concurrent SMS were summarized using mean and SD, median and range, or absolute and percentage frequencies, as appropriate. A Kaplan-Meier curve was performed to assess survival from the time that SMS was diagnosed. Data were censored if the animal was still alive or lost to follow-up at the end of the study period and survival times were reported as medians (range).

3 | RESULTS

3.1 | Dogs

Thirty-seven dogs with HC and concurrent SMS met the inclusion criteria; 6 from the Federal University of Rio Grande do Sul (Brazil), 5 from the University of Bologna (Italy), 5 from the University of Parma (Italy), 5 from the University of California (USA), 4 from the University of Buenos Aires (Argentina), 3 from the Naya Especialidades de Sao Paulo (Brazil), 3 from the Texas A&M University (USA), 3 from the University of Pennsylvania (USA), 2 from the University of Glasgow (UK), and 1 from the Chungnam National University (Korea). The earliest date of concurrent HC and SMS diagnosis in a dog was 1984 and the most recent was 2021, with 14 males (9 intact and 5 neutered) and 23 females (5 intact and 18 neutered) in total. Breeds included 13 mixed-breed dogs, 10 Poodles, 4 Dachshunds, 2 Maltese, and 1 each Pembroke Welsh Corgi, Italian Greyhound, Jack Russel Terrier, Lhasa Apso, Italian Hound, Pinscher, Yorkshire Terrier, and Whippet. The median body weight was 7.7 kg (3.2-21) and the mean age at the time of HC and SMS diagnosis was 10.8 years (± 2.6) and 11.5 years (± 2.6), respectively.

3.2 | Clinical signs and test results

Clinical signs of HC included PU/PD (35/37 dogs), dermatologic abnormalities (22/37 dogs), polyphagia (21/37 dogs), abdominal

TABLE 1 Frequency of concurrent medical diseases

Concurrent medical diseases	Number of dogs (%)
Myxomatous mitral valve degeneration	7/37 (19)
Gallbladder diseases	5/37 (14)
Hypothyroidism	4/37 (11)
Neoplasia	3/37 (8)
Dental disease	2/37 (5)
Osteoarthritis	2/37 (5)
Diabetes mellitus	2/37 (5)
Demodicosis	1/37 (3)
Otitis externa	1/37 (3)
Herniated disk	1/37 (3)
Seizures	1/37 (3)

enlargement (17/37 dogs), lethargy (7/37 dogs), and panting (4/37 dogs). Several dogs were described as weak at the time that HC was diagnosed, before they developed SMS. No dog had muscle weakness, and all were described as having abnormally "firm" muscles when SMS was diagnosed. CBCs, serum biochemistries and urinalyses from each dog were consistent with HC. Serum creatine kinase activity results were available at diagnosis in 18 dogs; 13 were above the upper reference range (median 460 IU/L, range, 53-3318). Of the 37 dogs, 19 had concurrent medical conditions (Table 1), none of which were believed to alter the diagnosis of HC or SMS although phenobarbital (given to 1 dog) is recognized to interfere with the diagnosis of HC in some dogs.

Results of LDDSt, ACTHst, and UCCR were consistent with a diagnosis of HC in 22, 16, and 5 of 37 dogs, respectively. Test results from each dog were consistent with naturally occurring PDH; no dog had ADH or iatrogenic HC. Testing to discriminate PDH from ADH included abdominal ultrasonography (34 dogs) and eACTH (6 dogs). Pituitary magnetic resonance imaging (4 dogs) and computed tomography (2 dogs) scans were obtained after PDH had been diagnosed. Pituitary masses (2-12 mm at greatest diameter) were seen in 4 dogs.

Results of EMGs from 14 dogs exhibited complex repetitive discharges and occasional myotonic discharges, fibrillation potentials, and positive sharp waves (Figure 1). The epaxial and proximal appendicular muscles were more affected than the distal appendicular muscles. Seven dogs underwent NCS. Muscle and nerve biopsies were obtained from 7 dogs. Muscle biopsies demonstrated variation in muscle fiber size, subsarcolemmal and intermyofibrillar mitochondrial aggregates, moderate fibrosis in 5 out of 7 dogs (Figure 2). Two dogs had atrophy of type II muscle fibers, 1 of these 2 also had increased muscle fatty deposition. Nerve biopsies demonstrated hypomyelination or demyelination with occasional axonal degeneration in 5 out of 7 dogs (Figure 3). Abnormalities were not detected in the histology of 2 dogs.

One dog died 8 days after being diagnosed with HC and SMS before any treatment had been given. Thirty-six dogs were treated for HC, 30 with trilostane (median dose: 1.2 mg/kg; range, 0.5-6.3 mg/kg); 8 received the drug once daily and 22 q12. Eight dogs were treated

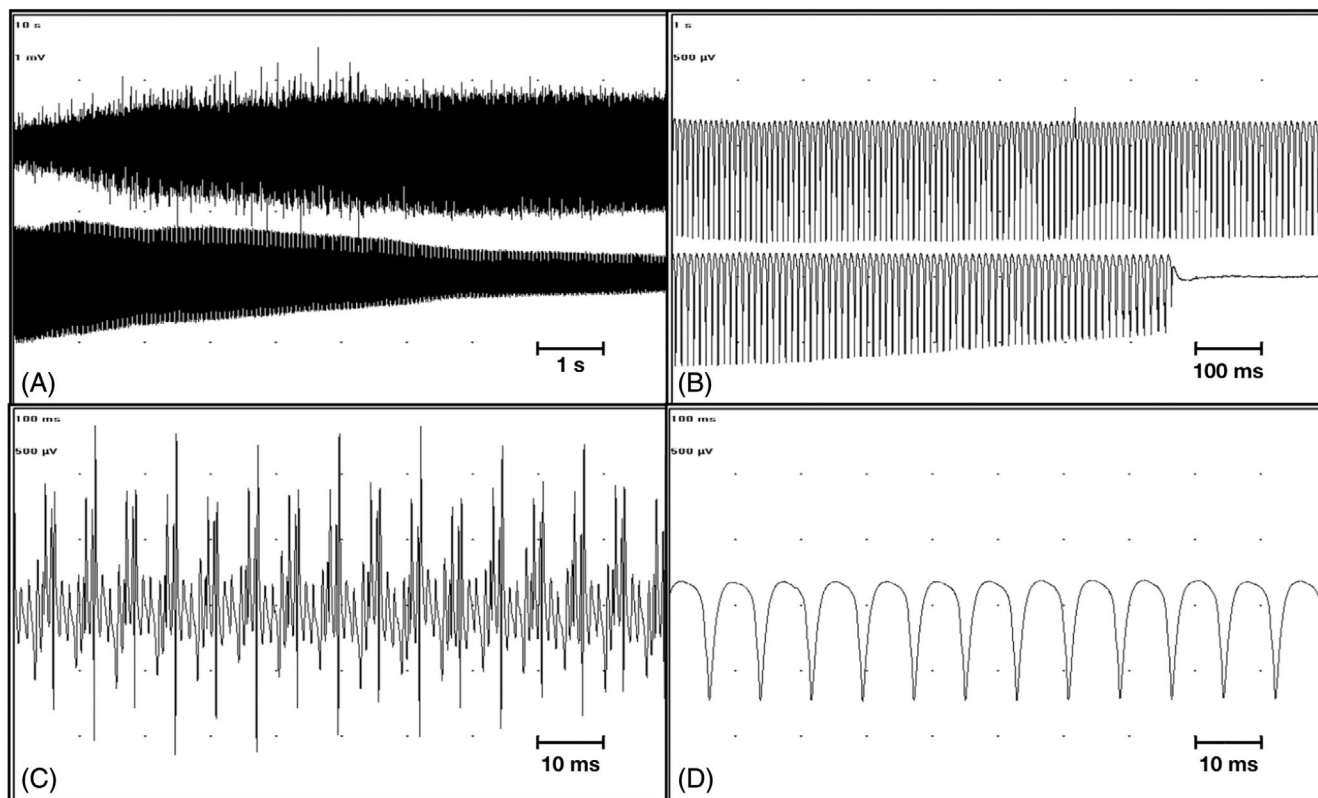


FIGURE 1 High-frequency discharges recorded at electromyography. (A) Myotonic discharges characterized by waxing and waning of amplitudes. (B) Complex repetitive discharges characterized by stable amplitudes and an abrupt end. (C) Spontaneous discharges of single muscle fibers time linked together (complex repetitive discharges). (D) Spontaneous discharges of a single muscle fiber consisting of a train of positive sharp waves



FIGURE 2 Semimembranosus muscle biopsy of 1 dog included in the study. Variation in fiber size, lobular myofibers with accumulation of mitochondria (arrows), and interstitial fibrosis (asterisks). Cryostatic section, cytochrome C oxidase staining, bar = 50 μ m

with mitotane, including 2 dogs after treatment with trilostane did not resolve HC and 1 dog that was also administered melatonin. Clinical signs of HC improved dramatically or resolved in 28/36 treated dogs. Eight dogs, each treated with trilostane, showed no resolution of HC

signs: 5 never responded despite increasing doses, 2 dogs transiently improved and then relapsed despite increasing doses; 1 dog died before completing the first month of treatment. Two dogs initially treated with trilostane without response had resolution of clinical signs after being switched to mitotane. In addition to treatment for HC, 19 of the 36 dogs were given medication for other medical conditions; 5 with ursodeoxycholic acid, 4 with levothyroxine, 3 with clopidogrel, 2 with insulin, 2 with ACE-inhibitors (ie, enalapril and benazepril), 3 with gabapentin, 1 dog each with metronidazole, amlodipine, pregabalin, phenobarbital, and firocoxib.

Twenty-three of the 37 dogs were diagnosed with SMS after the initial diagnosis of PDH had been established and treatment begun: 1 dog 1 month later, 14 dogs 2-12 months later, and 8 dogs >1 year later. Nineteen of these 23 dogs had a good response to treatment for HC, 3 failed to demonstrate a response, and 1 was euthanized before completing the first month of trilostane treatment. SMS was diagnosed before PDH in 11 dogs: in 2 dogs 2 months before diagnosis of HC, in 8 dogs 2-12 months before diagnosis of HC and in 1 dog more than 12 months before diagnosis of HC. Hypercortisolism and SMS were diagnosed at the same time in 3 dogs. When limb stiffness was initially identified, only the pelvic limbs of 22 dogs were involved, only the thoracic limbs of 6 dogs, and all 4 limbs in 9 dogs. No dog had 1 or 3 limbs involved and no dog had only unilateral involvement. Difficulty prehending, chewing, or swallowing was not reported in any

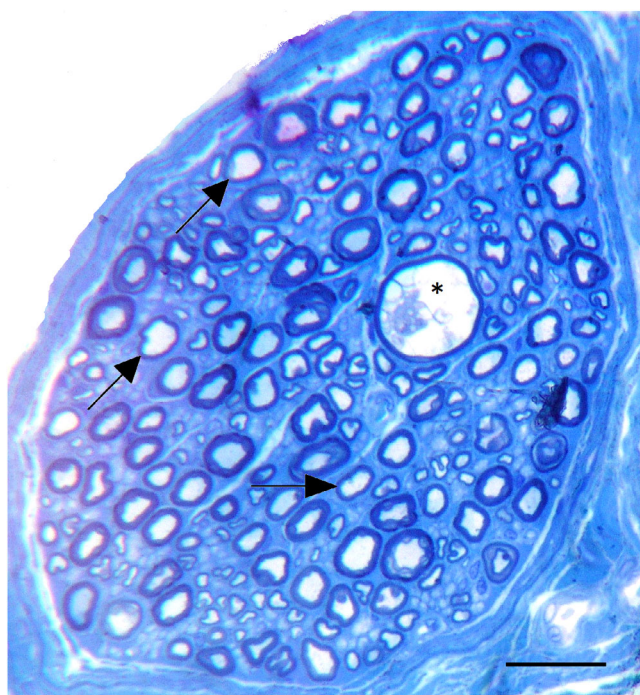


FIGURE 3 Semi-thin section of plastic embedded peroneal nerve biopsy of 1 dog included in the study. Mild loss of nerve fibers, inappropriately thin myelinated fibers (arrows), and occasional axonal degeneration (asterisk). Toluidine blue staining, 500×

TABLE 2 Frequency of severe muscle stiffness therapeutic intervention used in different dogs

Therapeutic intervention	Number of dogs (%)
Benzodiazepines	7/37 (19)
Physiotherapy	6/37 (16)
Cyclobenzaprine	3/37 (8)
Acupuncture	2/37 (5)
Mexiletine	2/37 (5)
Nonsteroidal anti-inflammatory drugs	2/37 (5)
Dantrolene	1/37 (3)
Botulin toxin	1/37 (3)
L-carnitine	1/37 (3)
Methocarbamol	1/37 (3)
Gabapentin	1/37 (3)
Cannabinoids	1/37 (3)

dog at the time that SMS was diagnosed. No dog appeared in pain to the owner or veterinarian.

Therapies directed at resolving or improving the SMS were administered to 19 dogs (Table 2). Mild improvement was noted in 5 dogs treated with diazepam, mexiletine, physiotherapy, acupuncture and cannabis. Some improvement in SMS, after administration of trilostane was stopped because of iatrogenic hypocortisolism, was observed in 1 dog also being treated with physiotherapy and diazepam. Of 5 dogs that showed mild muscle improvement, 2 were being treated with

HC-associated muscle stiffness survival

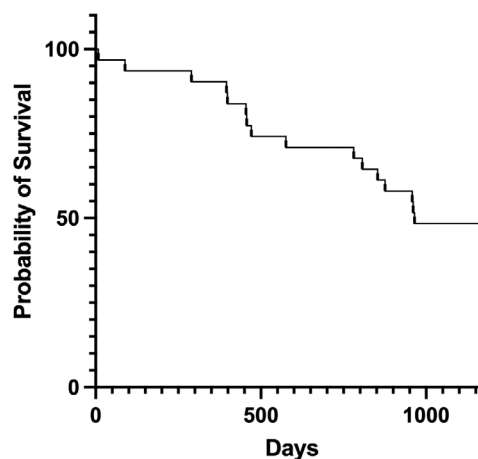


FIGURE 4 Kaplan-Meier curve to show overall survival of dogs with hypercortisolism and concurrent muscle stiffness

trilostane once daily and 3 were being treated with trilostane q12. These 5 dogs then had no further change in SMS; 20 dogs never exhibited improvement or progression in SMS after the initial diagnosis; 11 dogs exhibited SMS progression.

Two of 11 dogs (1 treated with trilostane, 1 treated with mitotane) with progressive SMS developed masticatory muscle involvement that caused difficulty chewing and swallowing. The dog treated with mitotane had also been managed with physiotherapy, acupuncture, and diazepam. The dog treated with trilostane had also been managed with physiotherapy, cyclobenzaprine, botulinum toxin, and diazepam. This dog was still alive at the time of writing and diazepam seemed to help with masticatory muscles relaxation. The other dog was euthanized because of SMS progression. In total, 14 dogs were euthanized, 7 because of persistent or progressive SMS, 1 because of persistent signs of HC, 6 were because of illnesses unrelated to HC, SMS, or its treatment. Three dogs died of other causes, 14 were alive at the time of writing, and 6 were lost to follow-up. Cause of death or euthanasia was not provided for 9 dogs. The median survival time from the diagnosis of SMS was 965 days (8-1188, Figure 4).

4 | DISCUSSION

Breed, sex, age, clinical signs, CBCs, routine serum biochemistries, except for creatinine kinase activities results, and urinalyses at the time of HC diagnosis in the 37 dogs with HC and SMS in this study were similar to those described for dogs with naturally occurring HC but without muscle rigidity.^{1,10-18} As a group, the dogs with HC and SMS tended to be small, only 3 dogs weighed >15 kg and just 1 dog weighed >20 kg. The percentage of dogs weighing <20 kg in this study is higher in comparison to that previously reported.¹ All 37 dogs included in this study had PDH. Dogs with ADH or iatrogenic HC

have excess glucocorticoids, and possibly other adrenal-origin steroids synthesized in a neoplastic adrenal cortex. Dogs with ADH or iatrogenic HC have low-to-undetectable concentrations of pituitary and hypothalamic hormones.¹ Dogs with PDH also have excess glucocorticoids, but the HC is secondary to excess pituitary ACTH. Concentrations of pituitary ACTH and its' prohormones above the reference range at diagnosis, remain above or increase further with adrenal-directed medical treatments.^{19,20}

Creatinine kinase activity results were above the reference range at diagnosis in the 75% of dogs in which it was measured. In both humans and dogs there are no data available about creatinine kinase concentrations above the reference range in dogs with HC. However, in humans, higher concentrations of CK are described in people with myotonic dystrophy and a mild increase was also reported in a case report of a Chow Chow with congenital myotonia.²¹⁻²³ Myotonia, delayed muscle relaxation after voluntary contraction or percussion, occurs in humans, goats, horses, mice, and dogs.²⁴⁻⁴¹ ACTH and proopiomelanocortin mutations occur in human dystrophic myotonia.⁴² In dogs, myotonic signs occur in association with various muscle diseases, as a congenital condition, and in association with HC.^{2-7,24-41} Fewer than 20 dogs with HC and concurrent myotonia or SMS are reported.²⁻⁷

In the present study, the case summaries submitted by 14 colleagues from 10 institutions located in widely separated geographic areas yielded only 37 dogs with concomitant HC and SMS, underscoring the uncommon nature of this combination of conditions. The most common clinical musculoskeletal sign in dogs with HC is nonpainful weakness, recognized by most owners as difficulty rising, abdominal distension, and reduced exercise tolerance.¹ As many as 85% of dogs with HC have been considered weak by the owner and veterinarian,¹⁴ and it is assumed that most of the remaining 15% have a sub-clinical weakness. Steroid-induced Type II muscle atrophy is common in dogs with iatrogenic and naturally occurring HC and since muscle atrophy is a likely component of muscle weakness, it is unlikely that muscle rigidity is a direct consequence of cortisol action. Several possible mechanisms to explain SMS in dogs with HC have been proposed: intracellular potassium concentrations under the reference range, abnormal calcium metabolism, higher glucocorticoid-induced protein catabolism, and alterations in the synthesis of myofibrillar proteins.³⁻⁶ However, the pathogenesis remains unclear.

Observing signs of progressive muscle stiffness is subjective for both owners and veterinarians. One report suggested that SMS appeared well after observing other clinical signs of HC.⁴ In another report, HC and SMS were diagnosed at about the same time.⁶ The time of SMS diagnosis versus time of HC diagnosis in the 37 dogs of this study varied. Twenty-three of 37 dogs (62%) were diagnosed with HC 1 month to 3 years before being diagnosed with SMS, 3 (8%) were diagnosed with HC and SMS at about the same time, and 11 dogs (30%) were diagnosed as having SMS 1 month to 1 year before being diagnosed with HC. Similar to the earlier reports, the limbs involved varied. The majority of dogs (60%) were affected in the pelvic limbs first while 24% had all 4 limbs affected when diagnosed. All dogs diagnosed as having HC and SMS that underwent EGM examinations had

myotonic discharges. In these dogs no other abnormalities were identified on muscle biopsies.

Despite successful medical management of HC in 28 of 36 treated dogs, only 5 dogs exhibited "mild" SMS improvement, which was followed in each dog by persistent SMS. The SMS persisted or worsened from the time of diagnosis in 31 dogs for which 19 dogs were treated with sodium channel blockers, for example, mexiletine, and muscle relaxing drugs, for example, methocarbamol, dantrolene, cyclobenzaprine, benzodiazepines, calcium antagonists, and L-carnitine. Such drugs have been efficacious in managing humans with myotonia.⁴³⁻⁴⁵ One of 36 treated dogs included in this study received botulinum toxin, which was associated with mild muscle relaxation. Botulinum for humans with myotonia has been beneficial.^{46,47} Two of 36 dogs treated with physiotherapy exhibited mild muscle relaxation, but there have been no reports of responses to physiotherapy in people with myotonia. The use of cannabinoids and acupuncture resulted in a mild to moderate improvement in 1 dog. Acupuncture has been of some value in humans. Use of cannabinoids in people with myotonia has been associated with some positive results.^{48,49} Too few dogs were treated with any single modality to draw conclusions about efficacy.

In addition to worsening limb stiffness, 2/36 of dogs developed progressive difficulty eating and drinking because of masticatory muscle involvement. Inability to eat or drink because of masticatory muscle involvement has not been previously described. One dog did have masticatory muscle abnormalities on EMG in a previous report, but clinical manifestations were not discussed.³ Masticatory muscle involvement has been described in both human myotonic dystrophy and myotonia congenita.^{50,51} Similar to the 2 dogs in this study, masticatory muscle involvement described in humans was preceded by leg muscle involvement.

The goal of treating dogs for HC is resolution of clinical signs, achieved by lowering circulating cortisol concentrations.¹ Whether dogs are treated with mitotane or trilostane, owner opinion is recognized as key when determining if a dogs' signs have completely or partially resolved versus dogs with no response. There is no consensus on laboratory testing to aid in monitoring trilostane treatment for dogs with HC and the ACTHst is recognized as ideal for monitoring mitotane treatment.⁵²⁻⁵⁴ Owner observations were a key component in managing the 35 dogs that survived >1 year. In addition, all dogs in this study treated with mitotane were monitored with ACTHst results while dogs treated with trilostane were monitored with ACTHst results or prepill serum cortisols.

The duration of survival after diagnosis of SMS in 3 dogs with HC in previous studies were 2383, 1902, and 1182 days, respectively.^{6,7} The median survival time from initial diagnosis of SMS in the dogs included in this study was 963 days (range, 8-1188 days). The median survival time for dogs with HC when treated with trilostane or mitotane has been reported to be 549 to 998 days.⁵⁵⁻⁵⁸ Despite most dogs having persistent or worsening SMS, owners chose continued care. However, owners of 50% of the dogs in this study ultimately chose euthanasia because of persistent or worsening SMS, highlighting the impact that this condition can have on the dog's and owner's quality of life.

There are several limitations of this study. None of the dogs in this study were treated with hypophysectomy or with drugs targeting the pituitary gland or hypothalamus. Limitations were also associated with the retrospective design of this project and the inclusion of cases from multiple hospitals. Multi-institutional case management was necessary because of the rarity of SMS with HC in a canine population. However, this factor introduced differences in data collection, follow-up, and case treatment based on clinician discretion and varying institutional protocols.

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CONFLICT OF INTEREST DECLARATION

Stefania Golinelli is the recipient of a PhD scholarship from Dechra Veterinary Products Ltd at the University of Bologna. Dechra Veterinary Products Ltd did not have any input in the design of the study, the analysis and the interpretation of data or in the writing of the manuscript. Other 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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