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A retrospective case series of clinical signs in 28 Beagles with Lafora disease

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Abstract

Background: Clinical signs and their progression in Beagles with Lafora disease are poorly described.

Objectives: To describe clinical signs in Beagles with Lafora disease.

Animals: Twenty-eight Beagles with Lafora disease confirmed by genetic testing or histopathology.

Methods: Retrospective multicenter case series. Data regarding signalment, clinical signs, diagnostic tests and treatment were retrieved from hospital data files. A questionnaire was sent to owners asking about neurological deficits, changes in cognitive functions, behavioral changes, response to treatment and survival time.

Results: Onset of clinical signs was 8.3 years (mean; range, 6.3-13.3). All dogs had myoclonic episodes as an initial clinical sign with tonic-clonic seizures in n = 11/28 (39%) and n = 12/28 (43%) later developing tonic-clonic seizures. Deficits of coordination (n = 21/25; 84%), impaired vision (n = 15/26; 58%), and impaired hearing (n = 13/26; 50%) developed later. Mental decline was observed as loss of house training (urination; n = 8/25; 32%), difficulties performing learned tasks (n = 9/25; 36%), and difficulties learning new tasks (n = 7/23; 30%). Common behavioral changes were: increased photosensitivity (n = 20/26; 77%), staring into space (n = 16/25; 64%), reduced stress resistance (n = 15/26; 58%), increased noise sensitivity (n = 14/26; 54%), and separation anxiety (n = 11/25; 44%). Twenty-one dogs were alive (median age 11.9 years; range, 9.8-18.6), and 7 dogs were dead (mean age 12.1 years; SD: 1.3; range, 10.5-12.6) at time of writing.

Conclusions and Clinical Importance: Lafora disease in Beagles causes significant behavioral changes, and mental decline as well as neurological deficits in addition to

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalography; EPM2A, epilepsy, progressive myoclonus type 2A; EPM2B, epilepsy, progressive myoclonus type 2B; MRI, magnetic resonance imaging; NHLRC1, NHL repeat containing E3 ubiquitin protein ligase 1.

myoclonic episodes and generalized tonic-clonic seizures. Nevertheless, a relatively normal life span can be expected.

KEYWORDS
behavioral changes, dog, life expectancy, mental decline

1 | INTRODUCTION

Lafora disease is a neurological storage disease caused by an autosomal recessive genetic defect resulting in myoclonus as well as focal and generalized seizures.[1,2] It was discovered in humans in 1911, but has since then been described in several other species such as dog, cat, cattle, fennec fox, and cockatiel.[3-8] Two affected genes have been identified in humans: epilepsy, progressive myoclonus type 2A and 2B (EPM2A and EPM2B) encoding the proteins laforin (carbohydrate binding phosphatase), and malin (ubiquitine ligase), respectively.[9] The absence of either protein results in poorly branched, hyperphosphorylated glycogen, which precipitates, aggregates and accumulates into Lafora bodies in neurons of all brain regions, reaching the highest densities in the substantia nigra, dentate nucleus and thalamic nuclei, which is causing neuronal malfunction.[9,10] The exact mechanism by which those deposits cause typical myoclonic epilepsy is not yet completely understood.[9]

In dogs, Lafora disease has been studied in a cohort of Miniature Wirehaired Dachshund in the United Kingdom.[11,12] Additionally, Lafora is described in several other breeds including the Basset hound, Beagle, Chihuahua, French bulldog, Pointer, Miniature poodle and Welsh corgi.[13-26] In general, Lafora disease is a rare neurological diagnosis in dogs, with Beagles being most frequently affected in Germany (personal communication Kehl A, Labogen). Similar to Miniature dachshunds a defect of a the 12-nucleotide repeat sequence that is unique to the canine NHLRC1 (EPM2B) gene has been identified in this breed.[20] Common clinical signs include spontaneous and myoclonic events triggered by noises or visual stimuli, hypnic myoclonus as well as generalized tonic-clonic seizures, which usually develop in dogs at an age of 6 to 9 years.[13,14,20,22,24,26]

In humans, progression of clinical signs results in intractable myoclonus, refractory seizures, psychosis, severe ataxia, visual impairment, dementia, and death.[9] For dogs, similar information regarding progression of clinical signs has only been reported sporadically apart from the Miniature Wirehaired Dachshund in which clinical progression of Lafora disease including dementia, blindness, aggression toward people and other dogs, deafness and loss of house training have been described.[12,22,23] Similar information regarding clinical signs and progression of those over time is not available for Beagles. Therefore, the aim of this study was to describe clinical signs and their progression of those in a larger group of Beagles with confirmed Lafora disease.

2 | MATERIAL AND METHODS

Beagles were collected retrospectively between November 2008 and January 2020 in a multicenter study including veterinary hospitals from Germany, Austria, and Switzerland. Two inclusion criteria had to be met: (a) A clinical presentation of myoclonic episodes or convulsive tonic-clonic seizures; (b) A diagnosis of Lafora disease confirmed either by the identification of a defect of a the 12-nucleotide repeat sequence of NHLRC1 gene known to cause Lafora disease in Beagles or by identification of typical PAS positive granules in liver, skin, or muscle biopsies.[9]

The following information was retrieved from hospital data files: sex, body weight, age at presentation, duration of clinical sings at presentation, type of seizures (myoclonus events versus convulsive tonic-clonic seizures), frequency of seizures, results of brain magnetic resonance imaging (MRI), results of cerebrospinal fluid analysis, initiated treatment, dietary changes, survival time, and cause of death.

In addition, a standardized questionnaire with mainly open-ended questions was sent to the owners once by mail investigating: (a) myoclonic events and generalized tonic-clonic seizures, (b) additional neurological deficits (other than myoclonic episodes or generalized tonic-clonic seizures), (c) changes in cognitive functions, (d) changes in behavior, and (e) survival time. All questions are listed in Table 1.

Additional phone call interviews with the owners were performed by the attending clinicians in cases of incomplete questionnaires or where the owner had not responded at all.

2.1 | Statistical analysis

Descriptive statistics were performed using commercial software (MedCalc 19.5.3 for Windows, MedCalc Software Ltd, Ostend, Belgium). Continuous data were tested for normal distribution using the Kolmogoroff-Smirnow test. Data were reported as mean with standard distribution or as median with range.

3 | RESULTS

Twenty-eight Beagles from 9 referral hospitals (7 in Germany, 1 in Austria and Switzerland each) were included. The median age at onset of clinical signs was 8.3 years (range, 6.3-13.3), whereas the mean age at presentation to the referral hospital was 9.8 years (SD: 1.9; range, 6.9-14.3). The median body weight was 16.4 kg (range, 11.0-27.4). The female to male ratio was 1.8.

The median duration of clinical signs, either myoclonus alone or in combination with generalized tonic-clonic seizures, at the time of presentation to the referral hospital was 9 months (range, 0.25-36). All owners reported myoclonic episodes as the initial clinical sign,

TABLE 1 Standardized questionnaire sent to owners of Beagles with confirmed Lafora disease

Question regarding myoclonic events and generalized tonic-clonic seizures:

1 Which was the first sign of Lafora disease you observed in your dog?
   - How long did your dog experience that first sign of Lafora disease when you presented your dog to our hospital?
   - How often did your dog experiences that first sign at the beginning of the disease?
   - How often does your dog experience that first sign now?

2 Does your dog experience sudden jerky movements of body parts or of the entire body?
   - If your dog experiences jerky movements as described in the last question:
   - When did those start?
   - How often where those at the beginning?
   - How often are those now?

3 Does your dog experience seizures with falling over, loss of responsiveness, excessive limb movements, drooling, chomping jaw, uncontrolled emptying of bladder and/or bowl?
   - If your dog experiences seizures as described in the last question:
   - When did those start?
   - How often where those at the beginning?
   - How often are those now?

4 Does your dog experience seizures with only some of the following signs: excessive limb movements, drooling, chomping jaw, uncontrolled emptying of bladder and/or bowl?
   - If your dog experience seizures as described in the last question:
   - When did those start?
   - How often where those at the beginning?
   - How often are those now?

5 Do you give your dog medications for seizures? If yes, please provide the name of the medication.

6 If you give your dog medications for seizures, did it result in a change of the seizure frequency?

Questions regarding changes in behavior:

1 Did your dog become more affectionate?
2 Did your dog become more reclusive?
3 Did your dog become more attached to you?
4 Did your dog become less stress resistant?
5 Did your dog develop panic attacks?
6 Did your dog develop restless pacing?
7 Did your dog become aggressive against humans?
8 Did your dog become aggressive against other animals?
9 Does your dog play less?
10 Did your dog develop changes in the wake–sleep-cycle (ie, sleeps at different types, wakes up frequently during the night)?
11 Does your dog sleep more?
12 Did your dog become light sensitive?
13 Did your dog become noise sensitive?
14 Did your dog develop changes in appetite?
15 Did your dog start to stare into space?
16 Did your dog develop separation anxiety?

Questions regarding changes in cognitive function:

1 Did the mental capabilities of your dog decrease?
2 Did your dog lose its house training (does urinate inside)?
3 Did your dog lose its house training (does defecate in side)?
4 Did your dog develop difficulties orienting in unknown surroundings?
5 Did your dog develop difficulties performing known tasks?
6 Did your dog develop difficulties learning new tasks?

Questions regarding additional neurological deficits:

1 Did your dog develop spontaneous jerks while sleeping?
2 Did your dog develop frequent blinking?
3 Did your dog develop stiffness during walking?
4 Did your dog develop difficulties of coordination (ie, frequent stumbling)?
5 Did your dog develop difficulties going upstairs?
6 Did your dog develop an impaired hearing or appears completely deaf?
7 Did your dog develop an impaired vision or appears completely blind?

Questions regarding survival:

1 Is your dog still alive or did it die or had to be euthanized?
2 If your dog is not alive anymore, what disease did it die from or what was the reason for euthanasia?

which were accompanied by generalized tonic-clonic seizures from the beginning on in 11 dogs (39%). An additional 12 dogs (43%) developed generalized tonic-clonic seizures later in the course of the disease with a mean delay of 14.2 months (range, 2-36), thus 23 dogs (82%) developed generalized tonic-clonic seizures, whereas 5 (18%) remained free of generalized tonic-clonic seizures. Myoclonic episodes happened several times a day in 18 dogs (64%) or every few weeks in 5 dogs (17%). Owners of 5 dogs (17%) could not answer this question.

Lafora disease was confirmed by a genetic test for the NHLRC1 gene variant in 24 (86%) dogs. Twenty-three of the 24 dogs were tested homozygous, whereas 1 dog was heterozygous for the NHLRC1 gene variant. The latter was tested twice to confirm the unexpected test result. In 4 dogs, confirmation was received by a histological examination of a liver, skin, or muscle biopsy. Further diagnostic tests included brain MRI ($n = 9$) and cerebrospinal fluid (CSF) analysis ($n = 7$). Seven of the MRI scans were interpreted as normal, whereas the MRI of 2 dogs exhibited signs of forebrain atrophy recognizable due to a subjectively generalized enlarged subarachnoid space surrounding the forebrain. Cerebrospinal fluid analysis revealed normal results in 6 dogs, whereas

TABLE 2 Summary of responses to a questionnaire sent to owner of Beagles with Lafora disease regarding additional neurological deficits, changes in cognitive function and behavioral changes (n = 28)

Group of clinical signs	Clinical signs	Absolute number of dogs experiencing the clinical sign/number of responses; relative number in brackets
Additional neurological deficits	Frequent blinking	12/25 (48%)
	Impaired vision	15/26 (58%)
	Impaired hearing	13/26 (50%)
	Difficulties climbing stairs	18/25 (72%)
	Loss of coordination	21/25 (84%)
	Stiffness during walking	15/25 (60%)
	Myoclonus during sleeping	24/25 (96%)
Changes in cognitive function	Loss of housetraining (defecation)	2/25 (8%)
	Loss of house training (urination)	8/25 (32%)
	Difficulties performing learned tasks	9/25 (36%)
	Difficulties learning new tasks	7/23 (30%)
	impaired orientation in unknown surrounding	9/25 (35%)
	general mental decline	10/25 (40%)
Behavioral changes	Noise sensitivity	14/26 (54%)
	Photosensitivity	20/26 (77%)
	Sleepiness	16/26 (61%)
	Changes in wake–sleep-cycle	4/26 (15%)
	Reduced playfulness	12/26 (46%)
	Separation anxiety	11/25 (44%)
	Aggression toward humans	5/26 (19%)
	Aggression toward animals	2/26 (8%)
	Staring into space	16/25 (64%)
	Restless pacing	11/26 (42%)
	Reduced stress resistance	15/26 (58%)
	Panic attacks	7/25 (28%)
	Anxiousness	13/25 (52%)
	Reclusiveness	11/25 (44%)
	Attachment to the owner	7/25 (28%)
	Changes in appetite	4/20 (20%)

Note: Frequencies of observed clinical signs are provided as absolute and relative numbers.

1 dog showed an albuminocytological dissociation. The heterozygous dog did neither receive a brain MRI scan nor a CSF analysis.

Treatment for myoclonic episodes was initiated using a single medication or single supplement in 17/28 dogs: levetiracetam only (n = 10), phenobarbital only (n = 2), piracetam only (n = 4), cannabidiol oil only (n = 1). Four other dogs received multi drug therapies including combinations of levetiracetam, potassium bromide, imepitoin and prednisolone. Whereas 7/28 dogs did not receive any medication for the initial myoclonic episodes. For those dogs experiencing generalized tonic-clonic seizures in addition to myoclonic events, additional anticonvulsive medication was added eventually resulting in multidrug treatments in 14/28 dogs using varying combinations of levetiracetam, phenobarbital, potassium bromide, imepitoin, piracetam, diazepam and gabapentin. Only 1 dog did not receive any medication during the entire course of the disease. The owners reported their subjective impression that treatments resulted in a temporary reduction of the frequency of myoclonic episodes in 11/28 and of generalized tonic-clonic seizures in 7/19 dogs, respectively. The response rate for dogs receiving levetiracetam (73%) or piracetam (50%) as subjectively reported by the owner seemed to be higher than using other medications. However, the application of statistically methods for analyzing the influence of any treatment on improvement of clinical signs was not possible due to the heterogeneity of applied therapies and low numbers.

The results of the questionnaires sent to the owners asking for additional signs, other than myoclonus, that had developed upon the initial presentation, for example, new neurological deficits, changes in behavior and changes in cognitive functions are presented in Table 2. The mean time span between onset of clinical signs and filling in the questionnaire by the owner was 3.9 years (range, 0.6-13.7). Not all owners did respond to all questions, therefore the number of responders is added to the table for every question. The most frequently observed additional neurological deficits were loss of coordination (80%), difficulties climbing stairs (72%) and a generalized stiff gait (60%). The most frequent changes in cognitive functions were general mental decline (40%), difficulties performing learned tasks (36%) and impaired orientation in unknown surroundings (35%), whereas photosensitivity (77%), staring into space (64%) and reduced stress resistance (58%) were the predominantly seen behavioral changes.

Seven dogs had been euthanized at a mean age of 12.1 years (SD: 1.3; range, 10.5-12.6). The mean duration of clinical signs in those dogs was 3.8 years (range, 3.0-4.6). Five of those were euthanized because of intractable generalized tonic-clonic seizures. One dog was euthanized because the owner felt that this Beagle did not have a sufficient quality of life and the remaining 1 was euthanized since it developed an otitis media/interna in addition to Lafora disease. The other 21 dogs were still alive by the end of the study with a median age of 11.9 years (range, 9.8-18.6).

4 | DISCUSSION

The onset and progression of clinical signs in 28 Beagles with confirmed Lafora disease is reported here. Affected Beagles did not only

suffer from myoclonic events and the generalized tonic-clonic seizures but also to a larger extend from obvious behavioral changes, mental decline, and additional neurological deficits. Nevertheless, those changes were seemingly acceptable to the owner since dogs died or were euthanized at an age close to the normal life expectancy of Beagles.

The onset of clinical signs at a median of 8.3 years developed relatively late considering a disease caused by an underlying genetic defect. In the literature, single case reports describe a similar age of onset of 6 to 9 years in 7 Beagles.[13,14,20,24,26] French bulldogs with Lafora disease seem to be affected at a similar age of 7 to 9 years, whereas Miniature Wirehaired Dachshunds develop clinical signs slightly earlier with an average age of 6.9 years (range, 3.5-12.0).[12,16,17] In any case, clinical signs are observed first time by the owners in adult dogs, whereas in humans with Lafora disease first symptoms are present during late childhood or adolescence (8-19 years; peak: 14-16 years).[9]

Myoclonic episodes were the initial sign in all dogs, whereas 82% experienced generalized tonic-clonic seizures either as an early clinical sign or developed those later in the course of the disease. Different treatments including anticonvulsive medications as well as dietary changes were applied. It was not possible to evaluate the influence of any of those on the frequency of myoclonic or generalized seizures. However, several owners of dogs treated with levetiracetam (n = 7/10) or piracetam (n = 2/4) reported the subjective impression of a reduction of the frequency of myoclonic episodes, even though frequency was not measured. However, this effect might be only temporary, since 50% of owners reported an eventual increase of the frequency of myoclonic episodes independent from the medication used. However, no conclusion for an effective treatment can be drawn from this study. Likewise, there are conflicting results regarding potential treatments of myoclonic episodes of Beagles reported in the literature. Temporary improvement of myoclonic events was seen in 2 Beagles treated with levetiracetam, suggesting that there might be some benefit of levetiracetam, whereas another Beagle did respond solely to a proprietary diet high in antioxidants.[14,20] Another 2 Beagles did experience a marked reduction of the number and severity of myoclonic episodes under treatment with clonazepam.[26] However, so far there is no publication providing evidence that any medication can reliably reduce the frequency of myoclonic episodes in dogs with Lafora disease.

Despite ongoing myoclonic and generalized tonic-clonic seizures, affected Beagles can have a relatively normal life expectancy. Mean age of 21 dogs being still alive at the time of writing was 11.9 years. Those already euthanized reached an average age of 12 years, whereas a normal life expectancy in healthy Beagles is 12.8 years.[27] That is in contrast to humans with Lafora disease, where death usually occurs at a young adult age within 10 years from onset of signs.[9] However, the progression of clinical signs might be similar in Beagles and humans. The different age at onset of clinical signs might actually cause the difference in the live expectation between both species.

Clinicians are probably aware of the typical myoclonic and generalized tonic-clonic seizures in affected Beagles, whereas the more subtle, additional neurological deficits, changes of behavior and decline of cognitive functions might sometimes be overlooked. Those are, however, equally important to the owner, since they negatively impact the dog owner interaction. More than half of affected Beagles developed other neurological deficits including visual and hearing deficits, difficulties climbing upstairs, a generalized stiff gait and in a vast majority (84%) a lack of coordination. That observation correlates with the results of a histopathological examination performed in a Beagle with Lafora disease, where Lafora inclusion bodies were especially abundant in the cerebellar molecular layer and in Purkinje cells.[24] Similarly, cerebellar ataxia has been reported in humans as a symptom of Lafora once the disease progresses, whereas ataxia does not seem to be a hallmark of progression of Lafora in Miniature Wirehaired Dachshunds, where dementia, blindness, aggression toward people and other dogs, deafness, and loss of house training have been described.[9,12]

Half of the Beagles were affected by several behavioral changes such as sleepiness, staring into space, reduced stress resistance, anxiousness, noise sensitivity, reduced playfulness, and frequent blinking. Whereas other changes such as aggression to humans and animals, changes in sleep-wake-cycle, attachment to the owner, and panic attacks were somewhat less frequently observed. Those changes might seriously impact the general personality of the dog, the owner's common concern of their dog turning aggressive, however, seems to be at slightly lower risk. Episodes of aggression to humans or other pets were experienced by the owner in 19% and 8% only. Those numbers might comfort those owners who are concerned about their dog turning aggressive as a consequence of Lafora disease.

Obvious decline in cognitive functions such as difficulties in performing new tasks, performing known task, house training, impaired orientation in unknown surroundings were seen slightly less frequent (rarely affecting more than 40% of dogs) compared to behavioral changes. In some dogs, several of those clinical signs of mental decline coexisted, whereas others experienced only some of those signs. That implies that differences between affected dogs cannot exclusively be explained by a variation in owner perception (more attentive versus less attentive owners), but might at least partially reflect individual variations of the phenomenology of the disease. This variation in clinical signs, even with exactly the same mutation in members of 1 family, are described for humans as well, suggesting that environmental or as-yet-unknown additional genetic factors might influence the phenotypical expression of Lafora disease.[28] Likewise, such yet undefined additional factors could explain why 1 of the Beagles reported here developed typical clinical signs of Lafora disease despite being repeatedly tested heterozygous only for the defect of a the 12-nucleotide repeat sequence of NHLRC1 gene. Alternatively, another intracranial disease mimicking clinical signs of Lafora disease cannot be ruled out completely, since further diagnostic tests were not performed.

The interpretation of results of the findings presented above is complicated by the fact that several of the changes observed in affected dogs (ie, loss of house training, difficulties performing known tasks, difficulties in learning new tasks, impaired orientation in unknown surroundings) could be part of the normal aging process or cognitive dysfunction of older dogs.[29,30] However, the magnitude of

those behavioral changes being similar as in dogs with cognitive dysfunction suggests mental decline beyond the degree that can be expected in normally aging dogs. That assumption is supported by the fact that mental decline characterized by rapidly progressive dementia with apraxia is a hallmark of disease progression in humans with Lafora as well.[9] Therefore, mental and behavioral changes are most likely part of the manifestation of Lafora disease in Beagles rather than physiological changes of aging dogs. Similarly, dementia, deafness, blindness, aggression, and loss of house training occur in Miniature Wirehaired Dachshunds once Lafora disease progresses.[12]

There are similar changes in dogs with idiopathic epilepsy.[31,32] Dogs with idiopathic epilepsy are at risk of developing cognitive dysfunction, with 13.4% being affected up to 8 years of age and reaching a peak of 14.2% in dogs older than 14 years.[32] That risk does increase further in dogs with cluster seizures or a high seizure frequency. Common signs of cognitive dysfunction in those dogs are impaired recognition of owners, difficulties in orientation, staring blankly and getting lost at home, reduced trainability, nonsocial fear, aggression, attention seeking behavior which are close to the clinical signs seen in Beagles with Lafora.[31,32] Two different theories are discussed to explain mental decline in dogs with seizures. Either seizures and dementia reflect a common underlying disease or cognitive dysfunction is caused by progressive brain damage from seizure activity.[32] Both mechanisms could be true for Lafora as well. Therefore, it is difficult to determine if mental and behavioral changes in the Beagles described here are expressions of the underlying disease or secondary to seizure activity. However, the latter is less likely since behavioral changes and mental decline are seen in a much higher proportion of Beagles with Lafora than in dogs with cognitive dysfunction associated with idiopathic epilepsy in the age group 8.1 to 14 years (5.3%), which is the typical time span for manifestation of Lafora disease in Beagles.[32]

In summary, it is not possible to determine definitely if the behavioral changes and the mental decline observed in Beagles with Lafora disease are caused by the disease itself, by seizures or seizure medication, by the normal aging process, by additional age-related cognitive dysfunction or by varying combinations of those.

The major limitation of this study is the retrospective design. Data regarding clinical signs at presentation and results of diagnostics test were retrieved from hospital files, but information regarding behavioral and mental changes of affected dogs solely relied on the owner's recollection. Therefore, reliability of information retrieved from owners might be heavily influenced by subjective perception and by the time that has elapsed between observation of the pet and answering the questionnaire.

Another point of discussion might be the classification of clinical signs used here. It is solely based on the phenomenology of clinical signs. We have subdivided sudden episodes into myoclonic events and generalized tonic-clonic seizures, where in fact we do not know if myoclonic events are none-epileptic myoclonic jerks or if they are a manifestation of electrical seizure activity as well. Similar, noise and light sensitivity, classified here as behavioral changes might represent focal seizures too. Those questions would have to be addressed by obtaining electroencephalogram (EEG) recordings during those myoclonic episodes, which was not done in the study presented here. However, there are conflicting EEG findings identified in 3 Beagles. Neck and forelimb contractions induced by intermittent photic stimulation in 2 dogs were accompanied by polyspike activity on EEG in 1 case report, whereas erratic myoclonus without EEG correlates was found in another Beagle.[24,26]

However, data reported here allow educating owners about expected progression of Lafora disease in Beagles. About two thirds of affected dogs develop generalized tonic-clonic seizures in addition to myoclonic events. Different behavioral changes, additional neurological deficits as well as mental decline are common. Clinical signs are generally progressive, even though temporary improvement of the frequency of myoclonic events can be seen under treatment in some cases. However, affected dogs can have a normal life expectancy if owners are willing to accept clinical signs.

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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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