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# Comparison of clinical signs and outcomes between dogs with presumptive ischemic myelopathy and dogs with acute noncompressive nucleus pulposus extrusion

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## OBJECTIVE

To compare clinical signs and outcomes between dogs with presumptive ischemic myelopathy and dogs with presumptive acute noncompressive nucleus pulposus extrusion (ANNPE).

## DESIGN

Retrospective study.

## ANIMALS

51 dogs with ischemic myelopathy and 42 dogs with ANNPE examined at 1 referral hospital.

## PROCEDURES

Medical records and MRI sequences were reviewed for dogs with a presumptive antemortem diagnosis of ischemic myelopathy or ANNPE. Information regarding signalment, clinical signs at initial examination, and short-term outcome was retrospectively retrieved from patient records. Long-term outcome information was obtained by telephone communication with referring or primary-care veterinarians and owners.

## RESULTS

Compared with the hospital population, English Staffordshire Bull Terriers and Border Collies were overrepresented in the ischemic myelopathy and ANNPE groups, respectively. Dogs with ANNPE were significantly older at disease onset and were more likely to have a history of vocalization at onset of clinical signs, have spinal hyperesthesia during initial examination, have a lesion at C1-C5 spinal cord segments, and be ambulatory at hospital discharge, compared with dogs with ischemic myelopathy. Dogs with ischemic myelopathy were more likely to have a lesion at L4-S3 spinal cord segments and have long-term fecal incontinence, compared with dogs with ANNPE. However, long-term quality of life and outcome did not differ between dogs with ischemic myelopathy and dogs with ANNPE.

## CONCLUSIONS AND CLINICAL RELEVANCE

Results revealed differences in clinical signs at initial examination between dogs with ischemic myelopathy and dogs with ANNPE that may aid clinicians in differentiating the 2 conditions. (*J Am Vet Med Assoc* 2016;249:767-775)

Ischemic myelopathy and ANNPE are common neurologic emergencies in dogs that have similar clinical signs<sup>1-10</sup> such as the hyperacute onset of nonprogressive, often markedly asymmetric spinal cord dysfunction without obvious signs of pain.<sup>1,3,5,10</sup> In dogs, ischemic myelopathy is most commonly associated with embolization of fibrocartilaginous material within the spinal cord vasculature that is histologically indistinguishable from nucleus pulposus (ie, fibrocartilaginous embolism)<sup>5,6,11-13</sup> and causes sudden onset of regional ischemia resulting in necrosis of the spinal cord parenchyma.<sup>4-6,11-13</sup> In contrast,

ANNPE (previously referred to in the scientific literature as high velocity-low volume disk extrusion, type III disk extrusion, and traumatic intervertebral disk extrusion) is suspected to cause a contusive rather than a primarily ischemic injury and occurs subsequent to trauma induced by explosive extrusion of normal non-degenerate nucleus pulposus.<sup>2,8,14,15</sup> Regardless of the condition (ischemic myelopathy or ANNPE), the clinical status of affected dogs typically stabilizes or improves within 24 hours after the onset of neurologic signs without specific treatment.<sup>2-4, 10</sup> The long-term outcome for both conditions is generally favorable, although the outcome is less favorable for dogs that lose nociception in affected limbs, develop symmetric neurologic deficits, have a lesion affecting the spinal cord intumescences, or have specific MRI findings such as a lesion affecting a large area of the spinal cord.<sup>2-5</sup>

## ABBREVIATIONS

ANNPE	Acute noncompressive nucleus pulposus extrusion
CI	Confidence interval
QOL	Quality of life
SCS	Spinal cord segment

Definitive diagnosis of ischemic myelopathy or ANNPE requires histologic examination of the affected portion of the spinal cord or, for dogs with ANNPE, surgical confirmation of extruded nucleus pulposus.<sup>4-6,8</sup> Because it is rare to definitively diagnose either condition prior to the death of the patient, both conditions are presumptively diagnosed on the basis of the presence of characteristic clinical findings in conjunction with established MRI criteria.<sup>1-3,7-9</sup>

Although investigators of previous studies<sup>1,2,5,8,10</sup> have reported the characteristic clinical and diagnostic features of ischemic myelopathy and ANNPE separately, to our knowledge, no studies have been performed to compare the clinical signs and outcomes between ischemic myelopathy and ANNPE. Identification of any differences in the clinical findings and outcomes for these 2 conditions could be clinically relevant for attaining a presumptive antemortem diagnosis and developing both short- and long-term prognoses. Therefore, the aims of the study reported here were to compare the clinical signs and outcomes between dogs with a presumptive antemortem diagnosis of ischemic myelopathy and dogs with a presumptive antemortem diagnosis of ANNPE. We hypothesized that specific clinical variables could aid in differentiating between ischemic myelopathy and ANNPE and that, although short-term recovery may vary between the 2 conditions, they would have similar long-term outcomes.

## Materials and Methods

### Animals

The study was approved by the Royal Veterinary College Ethics and Welfare Committee. Dogs examined at the University of London Royal Veterinary College between November 2009 and December 2013 because of acute onset of signs of spinal cord dysfunction that became nonprogressive 24 hours after onset were considered for study inclusion. Dogs were included in the study if a board-certified veterinary neurologist (SDD) and a board-certified veterinary radiologist (RD) agreed on a presumptive diagnosis of ischemic myelopathy or ANNPE following independent review of available MRI sequences. Each investigator was unaware of (blinded to) the diagnosis on record for each dog when reviewing the MRI images. A presumptive diagnosis of ischemic myelopathy or ANNPE was made on the basis of MRI criteria as described.<sup>1,2,7</sup> Briefly, criteria for ANNPE included a focal intramedullary hyperintensity overlying an intervertebral disk space on T2-weighted images, reduction in nucleus pulposus volume, mild narrowing of an intervertebral disk space, and the presence of extraneous material or a change in signal intensity relative to that for normal epidural fat within the extradural space.<sup>2</sup> Criteria for ischemic myelopathy included a focal intramedullary hyperintense lesion on T2-weighted images and the absence of the other criteria used to diagnose ANNPE. All MRI sequences

were obtained with a 1.5-T unit.<sup>a</sup> Dogs were anesthetized for the MRI evaluation. The anesthesia protocol used for each dog varied and was selected on the basis of the individual clinical requirements for each patient. T2-weighted and T1-weighted sequences were obtained in the sagittal and transverse planes for each dog. Postgadolinium<sup>b</sup> T1-weighted, gradient echo, half Fourier acquisition single-shot turbo spin, and other MRI sequences were performed for some dogs at the request of the attending clinician. Dogs with concurrent spinal column disease (eg, vertebral fractures or Hansen type I disk disease) or that underwent spinal decompression surgery were excluded from the study as were dogs for which the medical record was incomplete or the MRI sequences were incomplete or of inadequate quality for review. All dogs included in this study were included in a previous study<sup>16</sup> that was conducted to evaluate inter- and intraobserver agreement in the differentiation of dogs with ischemic myelopathy from dogs with ANNPE by evaluation of MRI sequences.

### Medical records review

Information extracted from the medical record of each dog enrolled in the study included age, sex, breed, body weight, duration of clinical signs prior to examination, initiator of clinical signs (trauma, exercise, suspected exercise [dog was outside unobserved in an open space], or unknown), whether the patient vocalized at onset of clinical signs (yes or no), progression history of clinical signs from onset to referral or examination, medications administered before referral or examination, and physical and neurologic examination findings. During the initial examination and at the 4-week recheck examination, the severity of neurologic deficits (functional score) was assessed on a 5-point scale as described.<sup>1,2</sup> Briefly, for dogs with lesions from C1-T2, 0 = tetraplegia with absent nociception, 1 = tetraplegia with intact nociception, 2 = nonambulatory hemi- or tetraparesis with or without monoplegia, 3 = ambulatory hemi- or tetraparesis, and 4 = neurologically normal. For dogs with lesions from T3-S3, 0 = paraplegia with absent nociception, 1 = paraplegia with intact nociception, 2 = nonambulatory mono- or paraparesis with or without monoplegia, 3 = ambulatory mono- or paraparesis, and 4 = neurologically normal.

### Outcome and follow-up data collection

Information regarding short-term outcome was obtained from the medical record of each dog and included duration of hospitalization, time from onset of clinical signs (time from onset) to first improvement in clinical condition, time from onset to voluntary urination, time from onset to independent ambulation (if achieved), whether the patient was ambulatory at discharge from the hospital (yes or no), and the functional score assigned at a recheck examination 4 weeks after presumptive diagnosis. A minimum follow-up period of 3 months was required for determi-

nation of long-term outcome.<sup>17</sup> Initially, the referring or primary-care veterinarian of each study dog was contacted by telephone for an interview. For dogs that were deceased, the date and cause of death were recorded as was the last documented neurologic status. For dogs that were alive at the time of data collection, the owners were then contacted in accordance with local ethics and welfare committee guidelines to obtain follow-up information. Each owner was mailed a letter that outlined the study along with a standardized questionnaire prior to being contacted for a telephone interview. The questionnaire was verbally administered during the telephone interview, and owners were asked to grade their dog's current neurologic function (normal, strongly ambulatory with mild deficits, moderate to severe difficulty walking, or nonambulatory), urinary and fecal continence (fully continent, reduced continence, completely incontinent), and QOL (scored on a linear scale from 1 to 10 as described,<sup>18,19</sup> where 1 = QOL "could not be worse" and 10 = QOL "could not be better"). The long-term outcome was defined as successful if a dog was clinically normal or had mild residual neurologic deficits but was able to maintain normal activities and had complete fecal and urinary continence.<sup>2</sup> Long-term outcome was defined as unsuccessful if a dog was euthanized because of a lack of clinical improvement for at least 2 weeks or had marked neurologic deficits with or without complete urinary or fecal continence at the time of the telephone interview.<sup>2</sup> The same investigator (JF), who was blinded to the presumptive diagnosis of each dog, conducted all interviews. The questionnaire was approved by the local ethics and welfare committee.

## Statistical analysis

The data distribution for each continuous variable was assessed for normality by use of Shapiro-Wilk tests. Descriptive statistics were generated. The mean  $\pm$  SD was reported for continuous variables (body weight and age) that were normally distributed and the median (range) was reported for continuous variables that were not normally distributed and ordinal variables. The frequency and percentage was reported for all categorical variables. Continuous variables were compared between dogs with ischemic myelopathy and dogs with ANNPE by use of independent-samples *t* tests for normally distributed data and Mann-Whitney *U* tests for nonnormally distributed data. For continuous variables that differed significantly between dogs with ischemic myelopathy and dogs with ANNPE, a receiver operating characteristic curve was created to evaluate the ability of that variable to discriminate between the 2 conditions.

Categorical variables were compared between dogs with ischemic myelopathy and dogs with ANNPE by use of  $\chi^2$  tests. For each binary variable that had a significant  $\chi^2$  test result, the OR and associated 95% CI were calculated to quantify the strength of the association. The respective associations between

clinical and outcome variables and presumptive diagnosis were further assessed by multivariable logistic regression. Separate multivariable models were created for clinical and outcome variables. Variables with values of  $P < 0.20$  on univariate analysis were eligible for inclusion as fixed effects in those models. The dependent variable for the multivariable model for evaluation of clinical variables was the presence of ANNPE, whereas the dependent variable for the multivariable model for evaluation of outcome variables was the presence of ischemic myelopathy. The multivariable models were built in a stepwise manner with forward selection. Only variables with values of  $P < 0.05$  were retained in the final models.

To assess potential breed predispositions to ischemic myelopathy and ANNPE, the hospital period prevalence (November 2009 to December 2013) of each condition within each breed represented in the study population was calculated (ie, number of dogs of a specific breed with ischemic myelopathy or ANNPE/number of dogs of that breed examined at the Royal Veterinary College Small Animal Referral Hospital) and compared with the hospital period prevalence of ischemic myelopathy and ANNPE in 2 popular large-breed nonchondrodystrophic dog breeds (Boxer and German Shepherd Dog) without a known predisposition for either condition by the use of  $\chi^2$  tests. All tests were 2 sided, and values of  $P < 0.05$  were considered significant unless otherwise indicated. All analyses were performed with a commercially available software program.<sup>c</sup>

## Results

### Dogs

The MRI studies for 127 dogs were reviewed by the board-certified neurologist and radiologist, and they achieved a consensus diagnosis of ischemic myelopathy or ANNPE for 93 dogs. Thus, 93 dogs (51 with a presumptive diagnosis of ischemic myelopathy and 42 with a presumptive diagnosis of ANNPE) were evaluated in this study.

The 51 dogs with presumptive ischemic myelopathy included 21 neutered males, 11 sexually intact males, 14 neutered females, and 5 sexually intact females with a mean  $\pm$  SD age of  $5.9 \pm 2.8$  years and body weight of  $23.3 \pm 12.7$  kg ( $51.3 \pm 27.9$  lb). Breeds represented included English Staffordshire Bull Terrier ( $n = 11$  [21.6%]), mixed (7 [13.7%]), Labrador Retriever (5 [9.8%]), Shih Tzu (3 [5.9%]), Bichon Frise (2 [3.9%]), Border Collie (2 [3.9%]), Golden Retriever (2 [3.9%]), Schnauzer (2 [3.9%]), Whippet (2 [3.9%]), and Belgian Sheepdog, Border Terrier, Bullmastiff, Dalmatian, Doberman Pinscher, English Bulldog, English Bull Terrier, English Springer Spaniel, Great Dane, Irish Wolfhound, Jack Russell Terrier, Lhasa Apso, Rottweiler, Siberian Husky, and Yorkshire Terrier (1 [2.0%] each). The hospital period prevalence of ischemic myelopathy in English Staffordshire Bull Terriers (11/775 [1.4%]) and Whippets (2/134 [1.5%])

was significantly greater than that for Boxers (0% [0/551];  $P = 0.005$ ) and German Shepherd Dogs (0% [0/733];  $P = 0.001$ ).

The 42 dogs with presumptive ANNPE included 19 neutered males, 5 sexually intact males, 14 neutered females, and 4 sexually intact females with a mean  $\pm$  SD age of  $7.0 \pm 2.2$  years and body weight of  $22.4 \pm 8.6$  kg ( $49.3 \pm 18.9$  lb). Breeds represented included mixed ( $n = 9$  [21.4%]), Labrador Retriever (8 [19.0%]), Border Collie (5 [11.9%]), English Staffordshire Bull Terrier (4 [9.5%]), Whippet (4 [9.5%]), Lurcher (3 [7.1%]), Boxer (2 [4.8%]), Jack Russell Terrier (2 [4.8%]), and Dalmatian, English Cocker Spaniel, English Springer Spaniel, Greyhound, and Schnauzer (1 [2.4%] each). The hospital period prevalence of ANNPE in Whippets (4/134 [3%]) was significantly greater than that in Boxers (2/551 [0.4%];  $P = 0.004$ ) and German Shepherd Dogs (0/733 [0%];  $P = 0.001$ ). The hospital period prevalence of ANNPE in Border Collies (5/411 [1.2%]) was significantly greater than that in German Shepherd Dogs ( $P = 0.003$ ).

Univariate results for comparisons of signalment and clinical variables between dogs with ischemic myelopathy and dogs with ANNPE were summarized (**Table 1**). Although the results of the overall  $\chi^2$  analysis suggested that breed distribution did not differ significantly ( $P = 0.223$ ) between dogs with ischemic myelopathy and dogs with ANNPE, results of post hoc  $\chi^2$  tests indicated that the ischemic myelopathy group contained significantly more English Staffordshire Bull Terriers than Border Collies ( $P = 0.047$ ) or sighthounds (Greyhounds and Whippets;  $P = 0.047$ ), compared with the ANNPE group. Although Labrador Retriever was one of the most commonly represented breeds in both the ischemic myelopathy and ANNPE groups, it was also one of the most commonly represented breeds in the overall hospital population during the study period, and the hospital period prevalences for ischemic myelopathy (5/1,838 [0.3%]) and ANNPE (8/1,838 [0.4%]) in Labrador Retrievers did not differ significantly from those for the 2 control breeds (Boxer and German Shepherd Dog).

The sex distribution ( $P = 0.583$ ) and mean body weight ( $P = 0.706$ ) did not differ significantly between dogs with ischemic myelopathy and dogs with ANNPE. The mean age for dogs with ANNPE was significantly ( $P = 0.033$ ) greater than that for dogs with ischemic myelopathy. However, the area under the receiver operating characteristic curve was only 0.652, which suggested that the discriminatory ability of age to distinguish dogs with ischemic myelopathy from those with ANNPE was poor.

## Clinical signs

Dogs that vocalized at the onset of clinical signs were approximately 2.5 times (OR, 2.52; 95% CI, 1.09 to 5.83;  $P = 0.029$ ) as likely to have ANNPE, compared with dogs that did not vocalize at the onset of clinical signs. Similarly, dogs with spinal hyperesthesia during the initial neurologic examination were ap-

proximately 3.0 times (OR, 2.96; 95% CI, 1.22 to 7.17;  $P = 0.015$ ) as likely to have ANNPE, compared with dogs that did not have spinal hyperesthesia during the initial neurologic examination. Of 19 dogs that vocalized at the onset of clinical signs and had spinal hyperesthesia during the initial neurologic examination, 15 had a presumptive diagnosis of ANNPE; thus, dogs that vocalized at the onset of clinical signs and had spinal hyperesthesia during the initial neurologic examination were approximately 6.5 times (OR, 6.53; 95% CI, 1.97 to 21.68;  $P = 0.001$ ) as likely to have ANNPE, compared with dogs that did not vocalize at the onset of clinical signs and did not have spinal hyperesthesia during the initial neurologic examination. Clinical variables eligible for inclusion in the multivariable model included age, vocalization at onset of clinical signs, location of spinal cord lesion, and presence of spinal hyperesthesia during the initial neurologic examination. The final multivariable logistic regression model included only vocalization at onset of clinical signs.

## Short- and long-term outcomes

Five of the 93 (5.4%) study dogs were euthanized at the time of presumptive diagnosis because of a poor prognosis, and 2 (2.2%) dogs were euthanized after 6 and 12 days of hospitalization because their clinical condition had failed to improve. Those 7 dogs (5 with ischemic myelopathy and 2 with ANNPE) were not included in any of the subsequent outcome analyses. Duration of hospitalization ( $P = 0.900$ ), time from onset to first improvement ( $P = 0.538$ ), and time from onset to independent urination ( $P = 0.217$ ) did not differ significantly between dogs with ischemic myelopathy and dogs with ANNPE (**Table 2**). Dogs with ANNPE were approximately 2.9 times (OR, 2.88; 95% CI, 1.17 to 7.10;  $P = 0.020$ ) as likely to be ambulatory at hospital discharge, compared with dogs with ischemic myelopathy. A recheck examination was performed 4 weeks after presumptive diagnosis for 31 dogs (14 with ischemic myelopathy and 17 with ANNPE). During those examinations, 1 dog with ANNPE had a functional score of 0 (had paraplegia with absent nociception), 2 dogs with ischemic myelopathy and 1 dog with ANNPE had a functional score of 2 (were nonambulatory with intact nociception), 11 dogs with ischemic myelopathy and 13 dogs with ANNPE had a functional score of 3 (were ambulatory with minor neurologic deficits), and 1 dog with ischemic myelopathy and 2 dogs with ANNPE had a functional score of 4 (neurologically normal). The functional score assigned during the recheck examination did not differ significantly ( $P = 0.669$ ) between dogs with ischemic myelopathy and dogs with ANNPE.

Information regarding long-term outcome was available for 80 (43 dogs with ischemic myelopathy and 37 dogs with ANNPE) of the 93 (86%) study dogs; it was not available for the 7 dogs that were euthanized within 12 days after presumptive diagnosis

**Table 1**—Comparison of signalment and initial clinical variables between 51 dogs with presumptive ischemic myelopathy and 42 dogs with presumptive ANNPE.

Variable	Dogs with ischemic myelopathy	Dogs with ANNPE	P value
Sex			
Male	32 (62.7)	24 (57.1)	0.583
Female	19 (37.3)	18 (42.9)	
Age	5.9 ± 2.8	7.0 ± 2.2	0.033
Body weight	23.3 ± 12.7	22.4 ± 8.6	0.706
Duration of clinical signs before examination (d)	0 (0–6)	0 (0–3)	0.894
Initiator of clinical signs			
Exercise	31 (60.8)	27 (64.3)	0.391
Trauma	2 (3.9)	5 (11.9)	
Suspected exercise (dog outside unobserved)	9 (17.6)	5 (11.9)	
Unknown	9 (17.6)	5 (11.9)	
Vocalization at onset of clinical signs			
Yes	20 (39.2)	26 (61.9)	0.029
No	31 (60.8)	16 (38.1)	
Progression of clinical signs			
Stable	40 (78.4)	29 (69.0)	0.579
Improved	9 (17.6)	11 (26.2)	
Deteriorated	2 (3.9)	2 (4.8)	
Medication received before referral examination			
None	29 (56.9)	24 (57.1)	0.740
NSAID	18 (35.3)	14 (33.3)	
Corticosteroid	4 (7.8)	4 (9.5)	
SCS where lesion was located			
C1-C5	0 (0.0)	7 (16.7)	0.005
C6-T2	7 (13.7)	8 (19.0)	
T3-L3	21 (41.2)	11 (26.2)	
L4-S3	6 (11.8)	0 (0.0)	
T3-L3 with suspected spinal shock	17 (33.3)	16 (38.1)	
Symmetry of neurologic deficits			
Symmetric	8 (15.7)	4 (9.5)	0.609
Left lateralized	25 (49.0)	24 (57.1)	
Right lateralized	18 (35.3)	14 (33.3)	
Spinal hyperesthesia			
Yes	12 (23.5)	20 (47.6)	0.015
No	39 (76.5)	22 (52.4)	
Neurologic functional score*			
0	4 (7.8)	3 (7.1)	0.590
1	7 (13.7)	7 (16.7)	
2	25 (49.0)	15 (35.7)	
3	15 (29.4)	17 (40.5)	

Values represent number (%) of dogs, mean ± SD, or median (range) unless otherwise specified. The presumptive diagnosis for each dog was made on the basis of consensus between a board-certified veterinary neurologist and radiologist following independent review of available MRI sequences.

\*Scored on a 5-point scale; for dogs with lesions from C1-T2, 0 = tetraplegia with absent nociception, 1 = tetraplegia with intact nociception, 2 = nonambulatory hemi- or tetraparesis with or without monoplegia, 3 = ambulatory hemi- or tetraparesis, and 4 = neurologically normal. For dogs with lesions from T3-S3, 0 = paraplegia with absent nociception, 1 = paraplegia with intact nociception, 2 = nonambulatory mono- or paraparesis with or without monoplegia, 3 = ambulatory mono- or paraparesis, and 4 = neurologically normal. None of the dogs had a functional score of 4 at initial examination. Values of  $P < 0.05$  were considered significant.

and an additional 6 dogs that were lost to follow-up. Long-term follow-up information was obtained from the referring veterinarian ( $n = 27$  dogs) or owner (53 dogs) at a median of 730 days (range, 71 to 1,676 days) after presumptive diagnosis. The proportion of dogs with a successful long-term outcome did not differ significantly ( $P = 0.167$ ) between dogs with ischemic myelopathy and dogs with ANNPE (Table 2), and this result was consistent even when the 7 dogs that were euthanized within 12 days after presump-

tive diagnosis were included in the analysis. Of the 80 dogs for which long-term follow-up information was obtained, the outcome was considered successful for 59 (73.8%) and unsuccessful for 21 (26.2%). Thirty-five of the 59 dogs with a successful outcome had recovered normal neurologic function, whereas the remaining 24 dogs had minor neurologic deficits but had complete urinary and fecal continence. Of the 21 dogs that had an unsuccessful outcome, 1 was euthanized 257 days after presumptive diagnosis be-

**Table 2**—Comparison of short- and long-term outcomes for the dogs of Table 1.

Variable	Dogs with ischemic myelopathy	Dogs with ANNPE	P value
Duration of hospitalization (d)	3 (1–18)	3 (0–58)	0.900
Time from onset to first improvement (d)	1 (0–15)	1.5 (0–10)	0.538
Time from onset to independent urination (d)	1 (0–14)	1 (0–14)	0.217
Ambulatory at discharge			
Yes	22 (47.8)	29 (72.5)	0.020
No	24 (52.2)	11 (27.5)	
Time from onset to independent ambulation (d)	1 (0–84)	2 (0–84)	0.629
Time from onset to maximum clinical improvement (mo)*	3 (1–48)	2 (0–48)	0.122
Long-term neurologic function*			
Normal	4 (14.8)	5 (19.2)	0.853
Mild deficits	20 (74.1)	19 (73.1)	
Moderate or marked deficits (patient ambulatory)	3 (11.1)	2 (7.7)	
Severe deficits (patient not ambulatory)	0 (0.0)	0 (0.0)	
Long-term urinary continence*			
Normal	19 (70.4)	21 (80.8)	0.379
Incomplete or intermittent	8 (29.6)	5 (19.2)	
Completely incontinent	0 (0.0)	0 (0.0)	
Long-term fecal continence*			
Normal	16 (59.3)	24 (92.3)	0.016
Incomplete or intermittent	9 (33.3)	1 (3.8)	
Completely incontinent	2 (7.4)	1 (3.8)	
Owner-perceived QOL score*‡	8 (5–10)	8.3 (5–10)	0.303
Long-term outcome‡			
Successful	29 (67.4)	30 (81.1)	0.167
Unsuccessful	14 (32.6)	7 (18.9)	

\*Results reported only for the 27 dogs with ischemic myelopathy and 26 dogs with ANNPE for which follow-up information was obtained via a telephone interview with the owner at least 3 months after the presumptive diagnosis was made. †Scored on a subjective scale of 1 to 10, where 1 = QOL “could not be worse” and 10 = QOL “could not be better.” ‡Long-term outcome was defined as successful if a dog was clinically normal or had mild residual neurologic deficits but was able to maintain normal activities and had complete fecal and urinary continence and unsuccessful if a dog was euthanized because of a lack of clinical improvement for at least 2 weeks or had marked neurologic deficits with or without complete urinary or fecal continence at the time of the telephone interview.

See Table 1 for remainder of key.

cause of recurrence of clinical signs, 4 had partial urinary and fecal incontinence, 6 had partial urinary incontinence only, 6 had partial fecal incontinence only, 3 had partial urinary incontinence and complete fecal incontinence, and 1 dog had severe neurologic deficits that prevented it from independently performing normal daily tasks despite the fact that it had complete urinary and fecal continence. The proportion of dogs with long-term fecal incontinence in the ischemic myelopathy group ( $n = 11$  dogs) was significantly ( $P = 0.016$ ) greater than that for the ANNPE group (2 dogs), with dogs with ischemic myelopathy being approximately 8.3 times (OR, 8.25; 95% CI, 1.61 to 42.28;  $P = 0.005$ ) as likely as dogs with ANNPE to have partial or complete fecal incontinence at long-term follow-up. Outcome variables eligible for inclusion in the multivariable model included ambulatory at hospital discharge, number of months to maximum improvement, long-term fecal continence, and outcome (successful or unsuccessful). The final

multivariable logistic regression model included only long-term fecal continence. For the 53 dogs for which long-term follow-up information was obtained from the owner, the median owner-perceived QOL score was 8 (range, 5 to 10), and all owners believed that their dogs had an acceptable QOL.

## Discussion

Results of the present study identified several differences in the clinical and short- and long-term outcomes between dogs with presumptive ischemic myelopathy and dogs with presumptive ANNPE. Compared with dogs with ischemic myelopathy, dogs with ANNPE were older at the time of presumptive diagnosis, more likely to have spinal hyperesthesia during the initial neurologic examination, and more likely to be ambulatory at hospital discharge. Although the long-term success rate did not differ significantly between dogs with ischemic myelopathy and dogs with

ANNPE, dogs with ischemic myelopathy were more likely to have long-term fecal incontinence. Those differences may have important clinical and prognostic implications.

As in previous studies,<sup>1-5,8,10</sup> most dogs with ischemic myelopathy or ANNPE evaluated in the present study had a hyperacute onset of clinical signs, which was often associated with strenuous exercise or perceived trauma. The clinical signs for the dogs of this study were frequently lateralized and generally became nonprogressive 24 hours after onset. The distributions for age at onset for dogs with ischemic myelopathy and ANNPE were likewise similar to those reported in other studies.<sup>2,8,10</sup> The fact that dogs with ANNPE tended to be older than dogs with ischemic myelopathy may be associated with differences in the pathogenesis of the 2 conditions. Age-related changes in the microstructure and biomechanics of the annulus fibrosus including alterations in collagen fiber cross-linking, decreases in water and proteoglycan content, and changes in interfiber cohesiveness have been reported in sheep,<sup>20</sup> humans,<sup>21</sup> and dogs.<sup>22</sup> Those changes might increase the likelihood for separation of annular fibers and the development of annular clefts, which provide potential pathways for extrusion of nuclear material when mechanical stress is applied to the spinal column.<sup>20</sup> Additionally, in dogs, the strength of intervertebral disks decreases with age.<sup>22</sup> Those factors collectively suggest that the risk of ANNPE may increase with age.

In the present study, dogs in both the ischemic myelopathy and ANNPE groups tended to be representative of large nonchondrodystrophic breeds, which was consistent with dogs with ischemic myelopathy and ANNPE evaluated in other studies.<sup>1,2,4,5,10</sup> However, results of the present study suggested certain predispositions for ischemic myelopathy and ANNPE. Compared with the general population of dogs examined at the hospital during the observation period, English Staffordshire Bull Terriers and Whippets were overrepresented in the ischemic myelopathy group and Border Collies and sighthounds (Greyhounds and Whippets) were overrepresented in the ANNPE group. Although the underlying reason for those apparent predispositions is unknown, it is noteworthy that these 4 breeds represent very active and athletic dogs.

Dogs of the present study with ANNPE were significantly more likely to vocalize at the onset of clinical signs and more frequently had spinal hyperesthesia during the initial neurologic examination, compared with dogs with ischemic myelopathy. That finding was consistent with the results of another study<sup>4</sup> and suggested that the presence of a focal area of spinal hyperesthesia might be useful for distinguishing dogs with ANNPE from dogs with ischemic myelopathy. The proposed etiology for ANNPE is an explosive extrusion of nondegenerate nucleus pulposus material into the spinal canal,<sup>2,8,9,15</sup> potentially causing pain secondary to trauma to the overlying

meninges of the spinal cord, periosteum, or dorsal longitudinal ligament, resulting in a focal area of spinal hyperesthesia.

Although most dogs of the present study had lesions localized to the T3-L3 SCSs, the proportion of dogs with lesions affecting the C1-C5 SCSs was significantly greater for the ANNPE group than for the ischemic myelopathy group, whereas the proportion of dogs with lesions affecting the L4-S3 SCSs was significantly greater for the ischemic myelopathy group than for the ANNPE group. In fact, in this study, none of the dogs with ANNPE had lesions affecting the L4-S3 SCSs, and none of the dogs with ischemic myelopathy had lesions affecting the C1-C5 SCSs. Results of other studies<sup>1,5-7</sup> involving dogs with presumptive or confirmed ischemic myelopathy also indicate that the incidence of C1-C5 lesions is low, and most suggest that lesions predominantly occur at the T3-L3 and L4-S3 SCSs. In the present study, dogs with decreased spinal reflexes in the pelvic limbs were divided into 2 groups (those with L4-S3 myelopathy and those with T3-L3 myelopathy and suspected spinal shock<sup>23</sup>) by assessment of withdrawal reflexes, myotatic reflexes, muscle tone, and the cutaneous trunci reflex. Following that categorization, the L4-S3 myelopathy group contained more dogs with ischemic myelopathy than dogs with ANNPE, a finding that was consistent with the results of other studies.<sup>1,2,5,6</sup> In the present study, all dogs with ANNPE had lesions in either the cervical or thoracolumbar portion of the vertebral column, which was consistent with the portions of the vertebral column that are predisposed to intervertebral disk herniation (Hansen type I disk disease), fractures, and luxations.<sup>8,9,24-26</sup> It has been hypothesized that variations in biomechanical forces on the vertebral column at the junctions between the fairly static thoracic portion and the more dynamic cervical and thoracolumbar portions are responsible for the predilection sites for ANNPE.<sup>2,9</sup>

Dogs with ANNPE were significantly more likely than dogs with ischemic myelopathy to be ambulatory at hospital discharge, even though the functional score at initial examination, duration of hospitalization, overall long-term outcome, and time from onset to regaining independent ambulation and urination and maximum clinical improvement did not differ significantly between the 2 groups. Ischemic myelopathy is characterized by complete loss of the blood supply to a focal area of the spinal cord, whereas ANNPE lesions are variable and contusive in nature; therefore, recovery of neurologic function may be faster for dogs with ANNPE than for dogs with ischemic myelopathy.<sup>4-6,27</sup>

In dogs, both ischemic myelopathy and ANNPE are associated with a risk of fecal incontinence.<sup>1,2,10</sup> Results of the present study suggested that dogs with ischemic myelopathy were more likely to have long-term fecal incontinence than were dogs with ANNPE. The presence of a lower motor neuron lesion at L4-S3 was not associated with an increased risk of fe-



cal incontinence in the present study. In fact, 12 of the 13 dogs with long-term fecal incontinence had a spinal cord lesion at T3-L3. This finding was consistent with the results of other studies that involved dogs<sup>2,24</sup> and human patients<sup>28</sup> in which upper motor neuron lesions were associated with a long-term reduction in fecal continence because of impaired perception of rectal distension, loss of inhibitory upper motor neuron pathways to rectal reflexes, and reduced voluntary control of the external anal sphincter. Those types of deficits may be more likely to develop with ischemic myelopathy because ischemic lesions typically affect the central and dorsal portions of the spinal cord, potentially damaging the rectal sensory tracts, whereas ANNPE lesions generally cause contusive damage to the ventral or lateral portions of the spinal cord.

Overall, most owners of the dogs of the present study perceived that the long-term QOL for their pets was good, even though some dogs continued to have a reduction in fecal continence. Owner-perceived QOL is an admittedly subjective measure and prone to bias. Consequently, it was not surprising that the clinical status (ie, long-term neurologic function and extent of urinary and fecal continence) varied among dogs that were assigned the same QOL score. Unfortunately, a gold standard for assessing QOL in companion animals has yet to be established.<sup>29</sup> Regardless, results of the present study indicated that the owner-perceived long-term QOL did not differ significantly between dogs with ischemic myelopathy and dogs with ANNPE. It is possible that the clinical status of the 7 dogs that were euthanized within 2 weeks after the presumptive diagnosis and excluded from the outcome analysis might have improved had they not been euthanized. However, it is unlikely that those dogs would have had a successful outcome, and when the analysis for long-term outcome was repeated with those dogs included and coded as unsuccessful outcomes, the results did not change.

The main limitation of the present study was that, because of its retrospective nature, patient assessments could not be standardized. Also, dogs were required to have only a presumptive, and not a definitive (postmortem), diagnosis of ischemic myelopathy or ANNPE for study enrollment. Inclusion of only dogs with a confirmed postmortem diagnosis of ischemic myelopathy or ANNPE would likely have biased the study population toward more severely affected patients, which in turn would have strongly affected the outcome results. The presumptive diagnosis for each dog of this study was made on the basis of consensus between a board-certified neurologist and radiologist following independent review of available MRI sequences; therefore, we have a high level of confidence that the presumptive diagnosis was correct for most dogs.

Findings of the present study indicated that dogs with ANNPE were generally older at disease onset and more likely to have spinal hyperesthesia during the

initial examination, compared with dogs with ischemic myelopathy. Although dogs with ANNPE were more likely to be ambulatory at hospital discharge (which suggested a quicker improvement in initial neurologic signs) than were dogs with ischemic myelopathy, the long-term outcome and QOL were good for dogs with either condition, provided that nociception was intact. Dogs with ischemic myelopathy were more likely to develop long-term fecal incontinence than were dogs with ANNPE. These findings can be used by clinicians as supporting data when discussing a presumptive diagnosis of ischemic myelopathy or ANNPE with owners and advising them of the potential prognosis and long-term outcomes.

## Acknowledgments

The authors declare that there were no conflicts of interest.

## Footnotes

- Intera 1.5T, Philips Healthcare, Eindhoven, The Netherlands.
- Gadovist (1.0 mmol/mL), Bayer, Newbury, Berkshire, England.
- SPSS Statistics, version 22, IBM Inc, Chicago, Ill.

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#### From this month's AJVR

### Efficacy of intravenous administration of hyaluronan, sodium chondroitin sulfate, and N-acetyl-D-glucosamine for prevention or treatment of osteoarthritis in horses

David D. Frisbie et al

#### OBJECTIVE

To evaluate the efficacy of IV administration of a product containing hyaluronan, sodium chondroitin sulfate, and N-acetyl-D-glucosamine for prevention or treatment of osteoarthritis in horses.

#### ANIMALS

32 healthy 2- to 5-year-old horses.

#### PROCEDURES

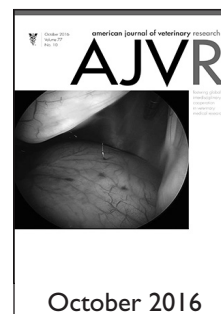
The study involved 2 portions. To evaluate prophylactic efficacy of the test product, horses received 5 mL of the product (n = 8) or saline (0.9% NaCl) solution (8; placebo) IV every fifth day, starting on day 0 (when osteoarthritis was induced in the middle carpal joint of 1 forelimb) and ending on day 70. To evaluate treatment efficacy, horses received either the product or placebo (n = 8/treatment) on days 16, 23, 30, 37, and 44 after osteoarthritis induction. Clinical, diagnostic imaging, synovial fluid, gross anatomic, and histologic evaluations and other tests were performed. Results of each study portion were compared between treatment groups.

#### RESULTS

Limb flexion and radiographic findings were significantly worse for horses that received test product in the prophylactic efficacy portion than for placebo-treated horses or product-treated horses in the treatment efficacy portion. In the prophylactic efficacy portion, significantly less articular cartilage erosion was identified in product-treated versus placebo-treated horses. In the treatment efficacy portion, joints of product-treated horses had a greater degree of bone edema identified via MRI than did placebo-treated horses but fewer microscopic articular cartilage abnormalities.

#### CONCLUSIONS AND CLINICAL RELEVANCE

Results suggested that caution should be used when administering the evaluated product IV to horses, particularly when administering it prophylactically, as it may have no benefit or may even cause harm. (*Am J Vet Res* 2016;77:1064-1070)



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