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Differences in Epidural Pathology between Cervical and Thoracolumbar Intervertebral Disk Extrusions in Dogs

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Background: Although the basic pathophysiology is the same in both cervical and thoracolumbar intervertebral disk (IVD) extrusions, there are considerable clinical differences that have only been partially explained.

Hypothesis/Objectives: The epidural inflammatory response differs between cervical and thoracolumbar IVD extrusions.

Animals: Fifty-five dogs with cervical and 80 dogs with thoracolumbar IVD extrusions.

Methods: Clinical data and histopathologic variables were investigated. Associations between severity of epidural inflammation and clinical and pathologic variables, impact of chondrodystrophic phenotype, and localization (cervical versus thoracolumbar) were evaluated statistically.

Results: Dogs with cervical IVD extrusion were significantly older ($P < 0.001$), had less severe and longer duration of neurologic signs (both $P < 0.001$), were more painful ($P = 0.038$), and had a better outcome ($P = 0.005$) than dogs with a thoracolumbar IVD extrusion. On histopathology, cervical epidural material had less severe calcification ($P = 0.002$) and inflammation ($P < 0.001$). No significant differences regarding chondrodystrophic phenotype were found.

Conclusion and Clinical Importance: There was significantly less intensive inflammatory response in the cervical epidural space. This observation correlated positively with less nucleus pulposus calcification in cervical extrusions indicating biochemical, metabolic, and biomechanical differences between the 2 locations, which remain to be characterized in future studies.

Key words: calcification; cervical pain; epidural inflammation; IVD extrusion.

Intervertebral disk (IVD) disease is 1 of the most frequent causes of neurologic signs in dogs, and more frequently involves the thoracolumbar than the cervical spinal cord.[1,2] Cervical involvement is reported in 12.9–25.3% of dogs with IVD herniation.[3–5]

After primary damage of the spinal cord due to contusion and compression, a cascade of secondary events including hemorrhage, changes in intracellular ion concentrations, excitotoxicity, free radical production, and inflammation is triggered.[2,6] These primary and secondary changes may affect different structures within the vertebral canal after IVD extrusion, including the epidural space.[7,8] Although the basic pathophysiology is the same, clinical presentation and outcome differ considerably between thoracolumbar and cervical disk extrusions.[1,9]

Abbreviations:

AF	anulus fibrosus
CD	chondrodystrophic
IVD	intervertebral disk
NCD	nonchondrodystrophic
NP	nucleus pulposus
NSAID	nonsteroidal anti-inflammatory drug
SCI	spinal cord injury

These differences have been investigated in a variety of anatomic and histologic studies. There are substantial anatomic differences between the cervical and thoracolumbar vertebral columns, including the IVD. The vertebral canal in the cervical vertebra has a larger diameter than in the thoracolumbar vertebra, leaving more epidural space around the spinal cord.[10,11] In dogs, the thoracic IVD is narrower than the cervical IVD,[12] and the cervical IVD is nearly circular in shape when viewed craniocaudally, whereas the thoracic disks are more oval and the lumbar disks bean-shaped.[12] Additionally, there are micromorphometric differences between chondrodystrophic (CD) and nonchondrodystrophic (NCD) dogs with respect to the shapes of the nucleus pulposus (NP) and anulus fibrosus (AF), and to cell densities in specific regions within the IVD.[13]

Recently, we studied the epidural inflammatory response during thoracolumbar IVD extrusion by histologic and immunohistochemical techniques.[7] Most dogs exhibited an epidural inflammatory response, ranging from acute invasion of neutrophils to chronic lesions with a mononuclear inflammatory pattern associated with connective tissue formation and vascular proliferation. There was little involvement of lymphocytes, which in a subsequent study evaluating expression of inflammatory mediators correlated with dominance of

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The study was performed at the University of Bern, Vetsuisse Faculty, Switzerland.

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chemokine ligand 2 and matrix metalloproteinases-2 and -9 and suppression of pro-inflammatory cytokines.[8]

Importantly, with respect to the objectives of this study, we found that epidural inflammation had a significant impact on the clinical expression of IVD disease. Specifically, the extent of thoracolumbar epidural inflammation was inversely correlated with ability to regain ambulation.

This finding raises the question of whether, in addition to the anatomic features mentioned here above, regional differences may exist in the epidural inflammatory response that could help explain the well-known clinical differences between cervical and thoracolumbar IVD diseases.

Therefore, the aims of this study were as follows: (1) to characterize the extruded IVD material and the inflammatory response in the epidural space histopathologically in dogs after cervical IVD extrusion by the same methods used in a previous study of thoracolumbar IVD extrusion;[7] (2) to evaluate associations between epidural inflammation and clinical signs and specific histopathologic features; (3) to evaluate associations between histologic findings and the chondrodystrophic phenotype; and finally, (4) to compare these findings to those obtained in a previous study of thoracolumbar IVD extrusion.[7]

Material and Methods

Dogs with confirmed cervical IVD extrusion presented between January 2012 and May 2016 to the Veterinary Teaching Hospital of Bern were included. Inclusion criteria were as follows: well-documented records of initial history, neurologic findings, diagnosis and course of the disease, the last neurologic examination having been completed within 12 hours before spinal surgery or euthanasia, and availability of extruded IVD material for histopathologic evaluation.

Data of dogs with thoracolumbar IVD extrusion evaluated previously[7] were used for comparison between cervical and thoracolumbar locations in the present study.

Clinical data

Breed, age, sex, duration of neurologic signs, medical pretreatment (none, corticosteroids, nonsteroidal anti-inflammatory drugs [NSAID] or both), neurologic grade, severity of pain, site of IVD extrusion, treatment (surgical or euthanasia), and outcome were obtained from medical records.

The following breeds were classified as CD: beagle, Cavalier King Charles spaniel, cocker spaniel, dachshund, English and French bulldog, Lhasa apso, Shi tzu, bichon frisé, basset hound, miniature schnauzer, Tibetan spaniel, Welsh corgi, Pekingese, and miniature poodle.[7,14] The breed distribution of dogs presented to our hospital (2010–2016) was recorded, and percentages of individual breeds were calculated.

Duration of neurologic signs was defined as the time between onset of clinical signs and surgery or euthanasia, and was grouped as follows: material collection within the first 48 hours of clinical signs (acute), within 2–7 days (subacute), or after > 7 days (chronic).[7]

The neurologic status of the dogs with cervical IVD extrusion was evaluated (maximally 12 hours before surgery or euthanasia) on a I to V scale as commonly used in veterinary literature:[7,15] grade I, spinal hyperesthesia only; grade II, ambulatory tetraparesis, ataxia, proprioceptive deficits, or some combination of these; grade III, nonambulatory tetraparesis; grade IV, tetraplegia with intact nociception; and grade V, tetraplegia with loss of nociception (most likely not applicable in cervical patients because of sudden death). In case of different grades between right and left limbs, the worst grade was used.

Pain was assessed and scored on a 0 to 2 scale:[7] 0, neither spontaneous pain (vocalization) nor pain on palpation of the vertebral column or passive movements of the neck; grade 1, no spontaneous pain, but pain on palpation of the vertebral column or passive movements of the neck; and grade 2, spontaneous pain or pain on palpation of the vertebral column or passive movement of the neck.

The actual site of the IVD extrusion was defined by magnetic resonance imaging or computed tomography and was confirmed during surgery or necropsy.

Surgical treatment

Dogs that underwent surgery received methadone (0.2 mg/kg IV) before induction of anesthesia. Dogs were intubated after induction with diazepam (0.3 mg/kg IV) and propofol (to effect IV). Anesthesia was maintained with isoflurane in 100% oxygen adjusted on the basis of anesthetic depth. Plasma-Lyte (10 mL/kg/h) was administered until the end of surgery. For analgesia, a fentanyl constant rate infusion (CRI) (2.5–10 μg/kg/h IV) was administered intraoperatively. For severe pain, a CRI of ketamine (10 μg/kg/h) was added. Before surgery, cefazolin (25 mg/kg IV) was administered and repeated every 90 minutes until the end of the surgery. During surgery, electrocardiography, noninvasive blood pressure, peripheral capillary oxygen saturation, partial pressure of carbon dioxide and temperature were monitored.

Decompression of the spinal cord was achieved by performing a standard ventral slot procedure. Postoperative analgesia was maintained with a fentanyl CRI (2.5–10 μg/kg/h IV) for the first 12 hours, than with buprenorphine (0.015 mg/kg IV or SC q8 h). Dogs received daily neurologic status evaluation with pain assessment, supportive care, and physical rehabilitation when needed (passive movement and massage 3 times per day, water treadmill twice daily).

Outcome was graded as previously reported:[7] grade 0, lack of improvement or euthanasia; grade 1, improvement of neurologic status by at least 1 grade, but unable to walk without support; grade 2, recovery to ambulation.

Histopathologic examination

In dogs that underwent surgery, epidural material (consisting of extruded IVD material, epidural fat, and hemorrhage) was collected during surgery, fixed in 10% formalin for at least 24 hours, embedded in paraffin, cut at 5-μm intervals, and stained with hematoxylin and eosin. In dogs that were euthanized, the spinal cord was removed shortly after death and fixed in 10% formalin. Cross-sectioned blocks of the spinal cord at the extrusion site were embedded in paraffin and processed for histology as described above.

All of the slides were evaluated as previously described[7] by 2 observers (cervical samples: AF and LZ; thoracolumbar samples from a previous study: AF and AO). In case of discordance, slides were re-examined and consensus was achieved.

Histopathologic characteristic of the extruded IVD material including cell types of NP, mineralization, hemorrhage, and necrosis were evaluated and graded by hematoxylin and eosin sections as described in Table 1.[7] Additionally, the epidural inflammatory reaction associated with the IVD material was evaluated including the nature of inflammatory cells (ie, polymorphonuclear

leukocytes, lymphocytes, macrophages, giant cells) and the stage of the inflammatory reaction (ie, acute, subacute, chronic, mixed) as described in Table 2.[7]

Statistical analysis

Associations within the group of dogs with cervical IVD extrusion

In dogs with cervical IVD extrusion, associations between clinical variables (ie, duration of clinical signs, neurologic grade, pain, pretreatment, outcome) or histologic variables (ie, grades of hemorrhage, calcification) and severity of epidural inflammation were evaluated by the Kruskal–Wallis 1-way ANOVA on ranks test with Bonferroni correction for multiple comparisons. The association between severity of inflammation and age was evaluated by the Kruskal–Wallis 1-way ANOVA on ranks test, and between severity of inflammation and occurrence of necrosis by the Mann–Whitney U 2-sample test.The same variables as mentioned above were compared between CD and NCD dogs by the Mann–Whitney U 2-sample test or the 2-sample *t*-test for comparison of age.

Comparing cervical with thoracolumbar IVD extrusion

For comparison of the cervical and thoracolumbar groups, previously published data were used.[7] The 2-sample *t*-test for comparison of age, the chi-square test for the CD phenotype, and the Mann–Whitney U 2-sample test were used for the remaining variables.

The threshold value for statistical significance was set at $P < 0.05$. All statistical analyses were performed using the statistical software package NCSS 2009 (http://www.ncss.com).

Results

Animals

Fifty-five epidural tissue samples of dogs with cervical IVD extrusion were included, of which 48 (87.3%) were obtained during the surgical procedure and 7 (12.7%) samples were obtained at necropsy. For comparison of cervical and thoracolumbar IVD extrusions, data from 80 dogs with thoracolumbar IVD extrusion from a previously published study were used.[7]

Table 1. Grading of the main histopathologic evaluated features of the extruded intervertebral disk material.

Loss of notochordal cells	
0	Resident notochordal cells are the predominant population
1	Significant/notable decline in notochordal cell population
2	Notochordal cells are absent
Necrosis/Eosinophilia	
0	Absence of necrotic/eosinophilic areas
1	Presence of necrotic/eosinophilic areas
Calcification	
0	Absence of calcification
1	Less than 50% of the extruded material is mineralized, mineralizations are present in some lacunae and along the periphery of the disk material:
2	More than 50% of the extruded material is mineralized and normal tissue is hardly recognizable
Hemorrhage	
0	Absence of erythrocytes
1	Few scattered erythrocytes around the disk material
2	Hemorrhage occupies up to 50% of the extruded material
3	Hemorrhage occupies more than 50% of extruded material

Table 2. Grading of the histopathologic features of the inflammatory reaction in the epidural space after intervertebral disk extrusion.

Intensity of the inflammatory response	
0	Absence on inflammatory cells
1	Presence of scattered inflammatory cells or sporadic clusters around extruded material or attached to the dura
2	Moderate invasion of the disk material
3	Extensive inflammatory reaction
Neutrophils	
0	Absence of neutrophils
1	Presence of single scattered neutrophils
2	Invasion of tissue around the extruded IVD material with neutrophils and formation of clusters
3	Abundant presence of neutrophils within and around extruded IVD material
Macrophages	
0	Absence of macrophages
1	Few macrophages mainly located around the extruded IVD material
2	Invasion of macrophages around the extruded IVD material and the presence of clusters
3	Abundant presence and epithelioid morphology of macrophages, the presence of multinucleated giant cells
Fibrovascular proliferation	
0	Absence of fibrovascular proliferation
1	Foci of fibrotic tissue at the periphery of the extruded IVD material or in dural adhesions
2	Trapping of extruded IVD material by fibrovascular tissue
3	More than 50% of the examined material consists of fibrovascular tissue
Staging	
Acute	Predominantly neutrophils and fibrin
Subacute	Focal accumulation of mononuclear cells (lymphocytes, macrophages)
Chronic	Coexistence of chronic inflammatory reaction (lymphocytes, epithelioid macrophages, and multinucleated giant cells) and fibrovascular proliferation
Mixed	Coexistence or 2 different stages

Clinical data

The study population consisted of 49 pure-bred dogs (20 different breeds) and 6 mixed-bred dogs. Pure breeds represented by >2 dogs were French bulldogs (n = 16), dachshunds (n = 5), beagles (n = 4), Dalmatians (n = 3), and Labrador retrievers (n = 3). Twenty-eight (50.9%) dogs were CD and 27 (49.1%) were NCD dogs. French bulldogs were overrepresented accounting for 29% of affected dogs, whereas their proportion of the hospital dog population was 2.5%. The median age was 8 years (range, 3 to 14 years). The median age of CD dogs was 7 and that of NCD dogs was 8 years. Thirty-three (60%) dogs were male and 22 were female (40%).

Fifteen (27.3%) dogs had been pretreated with corticosteroids, 23 (41.8%) with NSAIDs, 3 (5.4%) had received both, and 14 (25.5%) dogs had not received any treatment before sampling of material.

On the last neurologic examination (no more than 12 hours before surgery or euthanasia), 19 (34.5%) dogs showed neurologic signs of grade I, 22 (40%) grade II, 11 (20%) grade III, and 3 (5.5%) grade IV.

During examination, 9 (16.4%) dogs showed neither spontaneous pain (vocalization) nor pain on palpation of the vertebral column or passive movements of the neck (grade 0). Seventeen (30.9%) dogs showed pain only on palpation of the vertebral column or passive movements of the neck (grade 1), and 29 (52.7%) dogs showed spontaneous pain or excessive pain on palpation of the vertebral column or passive movements of the neck (grade 2).

Duration of clinical signs was classified as acute in 9 (16.4%) dogs, subacute in 17 (30.1%), and chronic in 29 dogs (52.7%). The time between onset of clinical signs and collection of samples (surgery or necropsy) was 1–270 days (median, 8 days).

Localization of the cervical IVD extrusion was among C2-3 in 6 dogs (10.9%), C3-4 in 15 (27.3%), C4-5 in 14 (25.4%), C5-6 in 12 (21.8%), and C6-7 in 7 (12.7%) dogs. In 1 dog, the specific localization was not recorded.

Five dogs (9.1%) were euthanized at the request of the owners without any treatment, 48 dogs (87.3%) were treated surgically, and 2 (3.6%) were euthanized after ineffective conservative treatment. Of the 48 surgically treated dogs, 43 dogs (89.6%) were ambulatory after treatment, 4 (8.3%) showed improvement of at least 1 neurologic grade (but were not able to walk without support), and 1 (2%) dog did not show any improvement.

The distribution of previous treatment, duration, neurologic grade, current treatment, pain, and outcome in dogs with cervical IVD extrusion are shown with respect to the CD phenotype in Fig. 1. Additionally, findings of a previous study in dogs with a thoracolumbar IVD[7] are shown in Figure S1 for direct comparison to the cervical group.

Histopathologic data

All samples contained epidural fat, NP, and fragments of the AF, and only 1 sample showed remnants of notochordal cells.

Hemorrhage was observed in 32 samples (58.2%). Twenty-two (40%) samples had only a few scattered erythrocytes (grade 1), 8 (14.5%) had pronounced hemorrhage, but still occupying <50% of the material (grade 2), and 2 samples (3.6%) had a grade 3 hemorrhage occupying >50% of the collected material. Twenty-three samples (41.8%) did not have hemorrhage (grade 0).

Necrotic areas were present in NP material in 35 samples (63.3%; Fig. 2B).

In 22 samples (40%), mineralized material in the NP was present in lacunae or more diffusely but involved <50% of the material (grade 1). In 19 samples (34.5%), the calcification involved >50% of the material (grade 2; Fig. 2A, D). Calcification was not present in the remaining 14 samples (25.5%; grade 0).

Inflammatory cells were found in 38 samples (69.1%). The inflammatory reaction was evaluated as grade 1 in 23 samples (41.8%) with only few inflammatory cells, as grade 2 in 7 samples (12.7%) with abundant presence of inflammatory cells, and as grade 3 in 8 samples (14.5%) with a strong invasion with inflammatory cells. The most common inflammatory cells were neutrophils (Fig. 2A) followed by macrophages (Fig. 2C). Lymphocytes were observed only rarely.

Neutrophilic invasion was rated grade 1 in 34 (61.8%), grade 2 in 9 (16.4%), and grade 3 in 1 sample (1.8%). In 11 samples (20%), no neutrophils were observed. Infiltration with macrophages was rated grade 1 in 15 samples (27.3%), grade 2 in 10 (18.2%), and grade 3 in 2 samples (3.6%). In the remaining 28 samples (50.9%), no macrophages were identified. Scattered lymphocytes (grade 1) were found in 14 samples (25.25%). Fibroblasts were found in 9 samples (16.4%); grade 1 in 4 cases, grade 2 in 3 cases, and grade 3 in 3 cases, respectively.

The inflammatory response was characterized as acute in 9 samples (24.3%) with a predominance of neutrophils and fibrin. In 19 cases (51.4%), a focal accumulation of mononuclear cells (lymphocytes, macrophages) was present, indicative of a subacute stage, whereas in the remaining 5 samples (13.5%), the inflammation was considered chronic because of infiltration with lymphocytes, epithelioid macrophages, and multinucleated giant cells, as well as fibrovascular proliferation (Fig. 2D). In 4 samples (10.8%), at least 2 different stages coexisted. The distribution of necrosis, calcification, and inflammation in cervical samples is shown with respect to CD phenotype in Fig. 3. Additionally, the findings of a previous study of dogs with a thoracolumbar IVD extrusion[7] are shown in Figure S2 for direct comparison to the cervical group.

Statistical analysis

Associations within the group with cervical IVD extrusion

In dogs with cervical IVD extrusion, there were no statistically significant associations between intensity of epidural inflammation and clinical variables including age ($P = 0.779$), CD phenotype ($P = 0.324$), duration of clinical signs ($P = 0.216$), neurologic grade ($P = 0.142$), type of initial treatment ($P = 0.308$), pain score ($P = 0.749$), and outcome ($P = 0.192$). Lower neurologic grade was positively associated with better outcome ($P = 0.002$).

Additionally, the intensity of inflammation of the extruded IVD material was positively associated with extent of calcification ($P = 0.004$), but not with extent of hemorrhage ($P = 0.004$) or the presence of necrosis ($P = 0.532$). No association between age and extent of calcification was found ($P = 0.372$).

Comparing dogs with cervical IVD extrusion with respect to their CD phenotype, CD dogs were significantly younger than NCD dogs ($P = 0.047$) and more painful ($P = 0.002$).

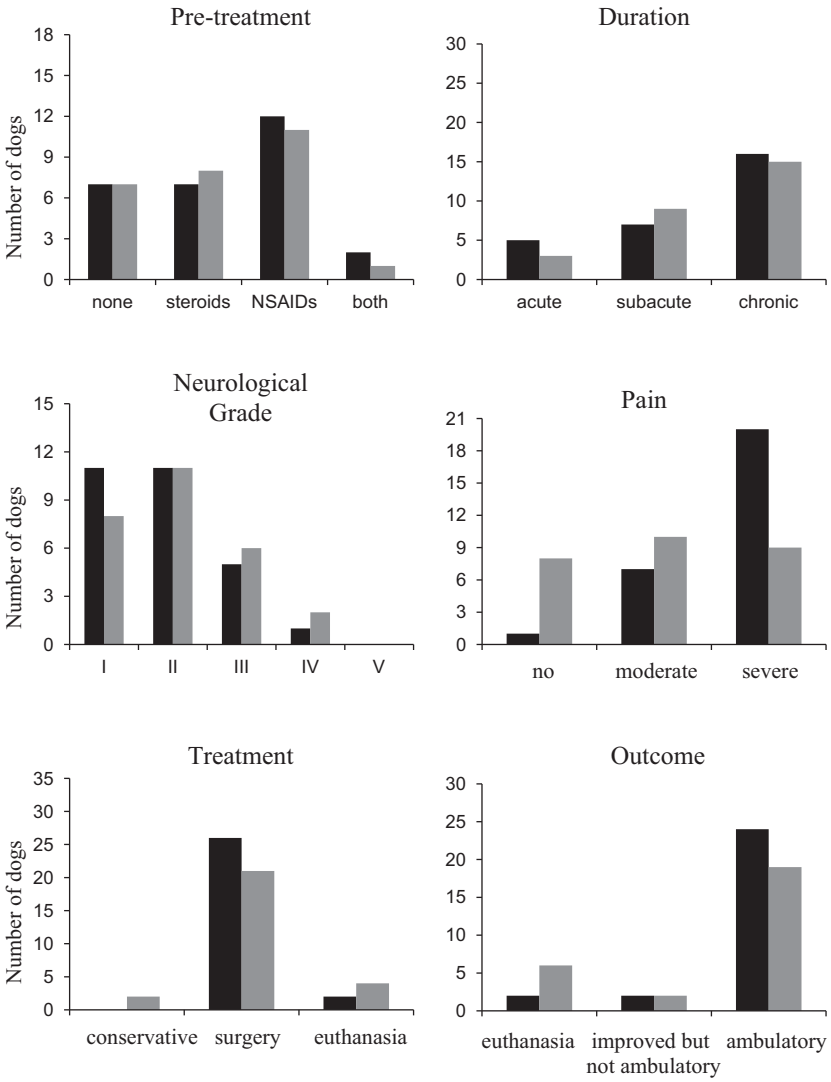

Fig 1. Distribution of clinical factors among 55 dogs with cervical intervertebral disk extrusion. Chondrodystrophic breeds are indicated by black and nonchondrodystrophic by gray columns.

Otherwise, no significant differences were observed between groups.

Comparing cervical with thoracolumbar IVD extrusion

Comparing the data obtained in dogs with cervical IVD extrusion to analogous data obtained in a previous study of dogs with thoracolumbar IVD extrusion,[7] dogs with cervical IVD extrusion were significantly older ($P < 0.001$), had significantly longer duration of clinical signs ($P < 0.001$), had less severe neurologic grade ($P < 0.001$), were more painful ($P = 0.038$), and had better outcome ($P = 0.005$) than did dogs with thoracolumbar IVD extrusion.

On histopathology, dogs with a cervical IVD extrusion had less severe calcification ($P = 0.002$) and more often had NP necrosis ($P < 0.001$) compared to dogs with thoracolumbar IVD extrusion. The inflammatory response was less severe in the cervical as compared to the thoracolumbar epidural space ($P < 0.001$).

No significant differences were found between groups with respect to CD phenotype ($P = 0.374$), initial treatment ($P = 0.125$), hemorrhage ($P = 0.077$), or staging of the inflammation ($P = 0.078$).

Discussion

Clinical signs, course, and outcome differ considerably between dogs with thoracolumbar and cervical IVD extrusions. Dogs with cervical IVD disk extrusions usually have less severe neurologic signs and therefore have better outcome with respect to ambulation. However, they appear to be more painful than do dogs with thoracolumbar IVD extrusions.[1,16,17] Several investigators have suggested that these observations may be a consequence of anatomic differences with respect to the size of the epidural space, presumably resulting in less severe mechanical damage to the cervical than to the thoracolumbar spinal cord.[10,11]

Because of the reported clinical and anatomic differences, we wanted to investigate whether there might be

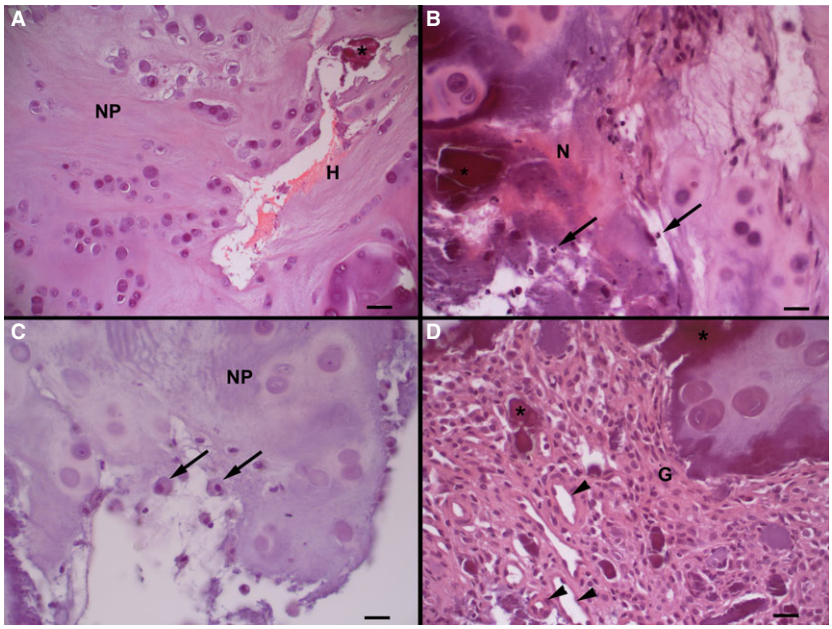

Fig 2. Histopathologic sections of cervical extruded intervertebral disk material; H/E. (A) Nucleus pulposus (NP) with a small amount of calcification (asterisk). A moderate amount of hemorrhage (H) is also present. Bar 50 μm; (×200). (B) NP with a moderate amount of calcification (asterisk) and necrosis (N). A few neutrophils (arrows) are invading the extruded material. Bar 20 μm; (×500). (C) A moderate amount of macrophages (arrow) invades the nondegenerated NP. Bar 20 μm; (×500). (D) Degenerated NP material with a moderate amount of calcification (asterisk). The chronicity of the inflammatory reaction is characterized by extensive granulation tissue (G) and neovascularization (arrow heads). Bar 20 μm; (×500).

differences in the epidural pathology between cervical and thoracolumbar IVD extrusions. We evaluated the inflammatory reaction in the cervical epidural space after IVD extrusion, and its association with clinical and various histopathologic variables. Additionally, we compared these findings statistically to results of a previous study that evaluated the same variables in the thoracolumbar area.[7]

Clinical presentation with a chronic course, pain, and limited motor impairment in our study population was typical of dogs with cervical IVD extrusion.[6,16] As expected, we found an association between the severity of neurologic signs and outcome, which is likely correlated with the grade of parenchymal damage of the spinal cord as previously shown in dogs with thoracolumbar IVD extrusions.[18]

Also similar to dogs with thoracolumbar IVD extrusion,[7,19] an inflammatory reaction was present in the cervical epidural space in 70% of affected dogs. This observation conflicts with another study in which only 27% of dogs had an inflammatory response.[20] However, in that study, half of the dogs had type 2 IVD herniation.[20] This finding confirms previous observations in patients with thoracolumbar extrusions according to which inflammation only occurs after entry of NP material into the epidural space.[7,21,22]

The type of the inflammatory reaction observed after IVD extrusion has been considered either a reaction of the innate or of the adaptive immune system.[7,23] Extruded thoracolumbar disk material of dogs was characterized by upregulation of chemokine ligand-2 attracting monocytes, and of matrix metalloproteinases (MMP)-2 and MMP-9, combined with a downregulation of T-cell cytokines and pro-inflammatory genes indicating that the epidural reaction is dominated by infiltrating macrophages with tissue-remodeling functions.[8,24] Accordingly, and in agreement with previous studies describing lesions in the thoracolumbar region,[7,19] we found a predominance of neutrophils being replaced by macrophages in the epidural space after cervical IVD extrusion of increasing duration, whereas only a few lymphocytes were present indicating a response to tissue injury, chemical irritation, or both by the extruded IVD material rather than as an antigen-specific reaction.[7,25]

However, comparing the extent of the inflammatory response, dogs with cervical IVD extrusion displayed significantly less intense inflammation than those with thoracolumbar IVD extrusion. The larger cervical epidural space[10,11] may limit tissue injury and chemical irritation by the extruded NP within the vertebral canal, consequently provoking less inflammatory reaction. Although this view remains speculative, in our previous study, we had postulated that calcified disk material may be the trigger of the inflammation. Indeed, also in the cervical area, the extent of calcification of extruded material was significantly associated with the severity of epidural inflammation. Significantly less mineralization was found within the extruded material in the cervical than in the thoracolumbar epidural space, thus possibly explaining the different intensity of the inflammatory response between the 2 spinal locations.

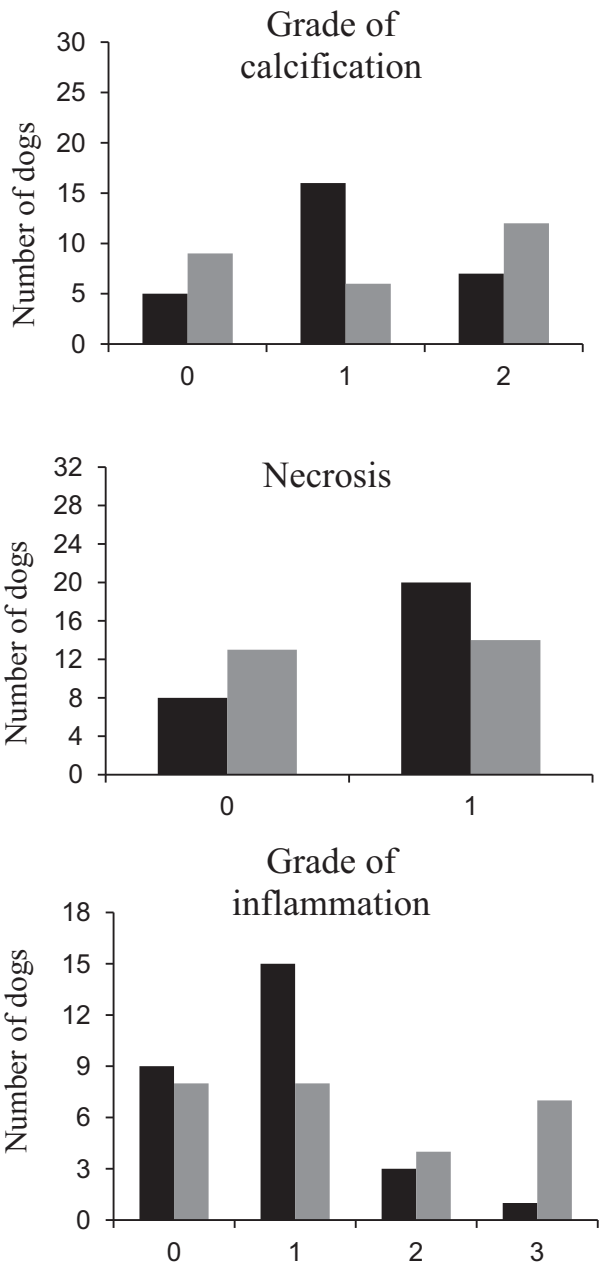

Fig 3. Distribution of calcification, necrosis, and inflammation grades in the epidural material of 55 dogs with cervical intervertebral disk extrusion. Chondrodystrophic breeds are indicated by black and nonchondrodystrophic by gray columns.

At variance to what has been described previously,[26] in our study, mineralization of the NP was not only present in CD but also in NCD dogs. Interestingly, even though dogs with cervical IVD extrusion were older, there was significantly less mineralization of extruded material in the cervical than in the thoracolumbar region. This finding suggests that depending on their location, IVDs are likely not only different in their clinical features[12] but also in their composition and metabolism. In humans, the NP of the cervical vertebral column contains more collagen and less polyanion compared to NP of the thoracic or lumbar vertebral column.[27] With increasing age, the collagen content of the NP increases in the thoracolumbar vertebral column but remains consistently high in cervical disks, and increases in the AF in all regions.[27] In contrast, the content of polyanion and chondroitin sulfates generally decrease with increasing age, which correlates with decreasing water content.[27] Although similar pathophysiologic changes have been described in dogs,[28] studies comparing the composition and age-related changes of IVD at different spinal cord levels are lacking.

The type of initial anti-inflammatory treatment was not associated with the extent of inflammatory response either in the cervical or in the thoracolumbar groups. However, because of longer duration of clinical signs in patients with cervical IVD extrusion, a longer duration of initial treatment is likely and may influence the inflammatory reaction.

Although our study confirms the well-known tendency for a chronic course in patients with cervical IVD disease,[16] histopathologic staging of the inflammatory reaction (acute, subacute, or chronic) did not reflect the clinical course nor was there a significant difference between the cervical and thoracolumbar groups in this respect. This finding confirms our previous conclusion that IVD extrusion is a dynamic process with a preclinical stage of disk degeneration and extrusion of variable duration.[7,14,28,29]

Most dogs with cervical IVD extrusion still were able to ambulate. Again, the larger epidural space in the cervical region likely results in less severe spinal cord compression, and consequently less parenchymal damage. However, dogs with cervical IVD extrusion were significantly more painful than those with IVD extrusion in the thoracolumbar segment, did not respond adequately to medical treatment, and ultimately required surgical removal of the extruded IVD material.

Pain is an important clinical component of cervical IVD disease[6,16] and may arise from several structures including the IVD, facet joint capsules, dorsal root ganglia, vertebral ligaments, vertebral periosteum, and meninges.[30] Noxious stimulation of the dura leads to activation of trigeminal neurons or dorsal horn neurons,[31–33] but limited information is available about the distribution of nociceptors in the meninges of dogs.[34] Mechanical stimulation of those nociceptors may elicit pain and this may be particularly true for the cervical spinal cord considering its much wider range of motion in the upper and lower parts. Chemical stimulation associated with inflammation might hypersensitize nociceptors, but no significant association was found between the severity of pain and inflammation in another study.[7] Moreover, as discussed above, there was significantly less inflammation in the cervical IVD disease group. Therefore, we believe that the more severe spinal cord parenchymal damage associated with thoracolumbar IVD extrusion could compromise nociceptive pathways such as the spinothalamic tracts or dorsal columns leading to impaired pain sensation and explaining the finding of significantly less pain in

thoracolumbar IVD extrusions. Assessment of pain is subjective, and in our study, only a simple pain score was used.

The distribution of CD and NCD dogs was nearly equal in our study population. This observation differs from the commonly cited predominance of type 1 herniation (extrusion) in CD dog breeds.[26] In accordance with our findings, in other studies, 62–92% of NCD dogs with IVD disease had IVD extrusion.[35,36] Thus, NCD dog breeds more often experience type 1 herniation than previously thought. In general, NCD with IVD extrusion were older and less painful than CD dogs.

In accordance with previous studies, dachshunds (28.5%) were overrepresented in the group with thoracolumbar IVD extrusion.[18,29,37] Although the beagle and dachshund have been reported to be most frequently affected by cervical IVD extrusion,[9,16,38] French bulldogs (29%) were in our group of dogs with cervical IVD extrusion. Dachshunds and French bulldogs are common but are not among the 20 most frequent breeds in Switzerland,[39] and they were not overrepresented in the hospital population (2.5% and 1.3%, respectively).

In conclusion, our study identified clear differences in epidural space pathology between cervical and thoracolumbar IVD extrusions. Notably, there was a significantly less severe epidural inflammatory response in the former, indicating a response of the innate immune system. This finding correlated positively with significantly less NP calcification in cervical extrusions indicating biochemical, metabolic, and biomechanical differences between the 2 locations, which remain to be characterized in future studies.

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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.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Distribution of clinical factors among 80 dogs with thoracolumbar intervertebral disc extrusion evaluated in a previous study of Fadda et al. Chondrodystrophic breeds are indicated by black and non-chondrodystrophic by gray columns.

Figure S2. Distribution of calcification, necrosis and inflammation grades in the epidural material of 80 dogs with thoracolumbar intervertebral disc extrusion evaluated in a previous study of Fadda et al. Chondrodystrophic breeds are indicated by black and non-chondrodystrophic by gray columns.