DIAGNOSIS AND TREATMENT OF DISK ASSOCIATED WOBBLER SYNDROME IN DOGS

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Diagnosis and treatment of Disk associated wobbler syndrome in dogs

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LIST OF ABBREVIATIONS

BLHR	Body length to body height ratio
CBLR	Canal height to body length ratio
CBR	Canal height to body height ratio
CCHR	Caudal canal to cranial canal height ratio
CSA	Cross-sectional area
CSA-SC	Cross sectional area of the spinal cord
CSA-VC	Cross sectional area of the vertebral canal
CSF	Cerebrospinal fluid
CSM	Cervical spondylotic myelopathy
CT	Computed Tomography
CT-m	Postmyelographic computed tomography
CTM	Cranial tibial muscle
DAWS	Disk associated wobbler syndrome
ECRM	Extensor carpi radialis muscle
ISI	Intraspinal signal intensity
IVD	Intervertebral Disk
LOA	Limit of Agreement
MRI	Magnetic Resonance Imaging
NSAIDS	Non steroidal anti-inflammatory drugs
ROC-curve	Receiver-operator characteristic curve
SVS	Standard ventral slot technique
TE	Echo time
TMMEP	Transcranial magnetic motor evoked potential
TMS	Transcranial magnetic stimulation
TR	Repetition time
VBH	Vertebral body height
VBL	Vertebral body length
VCHcr	Cranial vertebral canal height
VCHm	Mid vertebral canal height
VCHcd	Caudal vertebral canal height

SECTION I

GENERAL INTRODUCTION

DIAGNOSIS, TREATMENT AND PROGNOSIS OF DISK ASSOCIATED WOBBLER SYNDROME

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Summary

Disk associated wobbler syndrome (DAWS) is the most prevalent and most typical cause of cervical spondylomyelopathy in dogs. It is typically seen in the middle-aged to older Doberman Pinscher. Progressive caudal cervical spinal cord compression is typically caused by protrusion of the annulus fibrosus of one or more intervertebral disks into the vertebral canal, sometimes in combination with ligamentum flavum hypertrophy and vertebral abnormalities. Clinical signs vary from neck pain to tetraplegia. The diagnosis is generally made using myelography. However, advanced imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) are increasingly used in veterinary medicine. There is a lot of controversy concerning the treatment of this disease. Many surgical techniques have been developed, but little is known about the conservative treatment. Objective data about the prognosis of this disease are scarce.

Introduction

Wobbler syndrome or cervical spondylomyelopathy is a covering term that includes several disorders of the caudal cervical vertebrae, ligamentous structures, and intervertebral disks of large breed dogs resulting in progressive spinal cord compression.[1,2] A large variety of lesions with different proposed etiologies have been attributed to this syndrome and many synonyms are found in the literature, such as spondylolisthesis [3], cervical spinal subluxation and spondylolisthesis [4], cervical vertebral instability [5,6], cervical spinal stenosis [7], cervical spondylopathy [8], spondylomyelopathy [9] and cervical malformation/malarticulation syndrome.[10] All these different clinical entities result in the same clinical signs of ataxia, paresis (predominantly affecting the pelvic limbs) and cervical pain. The term "wobbler" only refers to the characteristic "wobbling" hind limb ataxia and not as such to a specific disease entity.[1] Over years a few separate syndromes have been recognized to further characterize this complex collection of disorders.[11] The most typical and predominant cause of cervical spondylomyelopathy in dogs is the disk associated wobbler syndrome (DAWS) or disk associated cervical spondylomyelopathy.[1,12] This is seen in middle-aged large breed dogs, in particular the adult Doberman Pinscher.[1,13-16] In DAWS, cervical spinal cord compression results from the protrusion of the intervertebral disk between the sixth and seventh cervical vertebrae (C6-C7) and/or between the fifth and sixth cervical vertebrae (C5-C6), and from generally mild vertebral malformations, frequently in combination with dorsal compression resulting from hypertrophy of the ligamentum flavum.[1] Approximately 13 to 20% of dogs present with both C5-C6 and C6-C7 lesions at the time of initial diagnosis.[1,2] Many aspects of this disorder are not well understood. Although several factors have been proposed [17-21], the exact etiology, pathogenesis or underlying risk factors for DAWS are not known.[2] A contributing role of preexisting relative vertebral canal stenosis has been suggested.[17,20,21] However, more studies are necessary to confirm or reject this hypothesis. More controversies and uncertainties are associated with the diagnosis and treatment of this disorder. This chapter reviews the diagnosis, treatment and prognosis of DAWS.

Diagnosis

Clinical presentation

Animals affected with DAWS are usually 4 to 8 years of age, and Doberman Pinschers are overrepresented.[1,13-16] The most common presentation is a gait disturbance.[2] The owners commonly report a gradual onset, although the symptoms can sometimes occur or exacerbate more acutely.[1,2] A slowly progressing pelvic limb ataxia and/or paresis is usually noted. A broad-based stance can be seen in the pelvic limbs.[2,22] In dogs with apparently normal thoracic limbs, it is sometimes difficult to distinguish DAWS from a thoracolumbar lesion.[11] Progression to thoracic limb involvement with a short stilted gait can also occur.[1,2] Affected dogs often show a characteristic 'disconnected' gait, in the sense that the thoracic and pelvic limbs seem to advance at different rates. Neck pain may be seen but is usually not overtly present: a history of neck pain is seen in approximately 40% of the cases.[22] Tetraplegia is uncommon.[2]

Currently, little is known about the correlation of the type of clinical signs with the severity of clinical signs. For example, it is not yet investigated or demonstrated that a dog with clinical signs affecting all four limbs is also more severely affected than a dog with clinical signs affecting only the pelvic limbs. Although several grading systems have been used [14,21,23-25], little is known about their correlation with electrophysiological findings, medical imaging findings and outcome.

Survey radiography

Survey radiographs may be indicative for the presence of DAWS, but they are not conclusive and do not precisely indicate the site of spinal cord compression.[2] They only allow evaluation of the bony structures. This non-invasive technique is useful to rule out potential differential diagnoses such as vertebral fractures, (sub)luxations, vertebral neoplasia and diskospondylitis.[2] General anesthesia is necessary to obtain correct positioning of the dog. In dogs with DAWS, changes can be seen in the vertebral body, the vertebral canal and the intervertebral disk space. The altered shape of the vertebrae can range from varying degrees of loss of the ventrocranial border, to a triangularly shaped vertebra. Spondylosis deformans may be seen ventral to the intervertebral space, with associated changes in the opacity of the

vertebral body. Narrowing of the intervertebral disk space is frequently seen and often corresponds to the site of cord compression, although there are exceptions to this (Figure 1).[1,17,26] The vertebral canal may be stenotic, with the cranial orifice being much narrower than the caudal orifice.[17,26] Changes on survey radiographs do not always correlate with myelographic evidence of spinal cord compression.[9,17,27] Some dogs with severe radiographic abnormalities will show no spinal cord compression on myelography and demonstrate no clinical signs.[17] Conversely, survey radiographs may be normal in some dogs with DAWS, in which case spinal cord compression is only identified by myelography or MRI.[26] Even when the main site of compression is obvious, secondary sites of compression cannot be identified using plain radiography.[2]

Previous studies have used absolute measurements of the vertebral canal diameter on survey radiographs to evaluate the presence of vertebral canal stenosis.[28-30] However, these absolute measurements are influenced by radiographic magnification.[31,32] This is a variable parameter which is influenced by focus-film distance, object-film distance, and patient related factors such as the body condition score.[32] This variability, owing to magnification errors, can be resolved by the use of vertebral canal and body ratios of different measurements.[31,33] Several vertebral ratios have been developed and used in humans and horses to assess vertebral canal stenosis.[31,33-35] There is currently little known about the use of such ratios in dogs with DAWS.

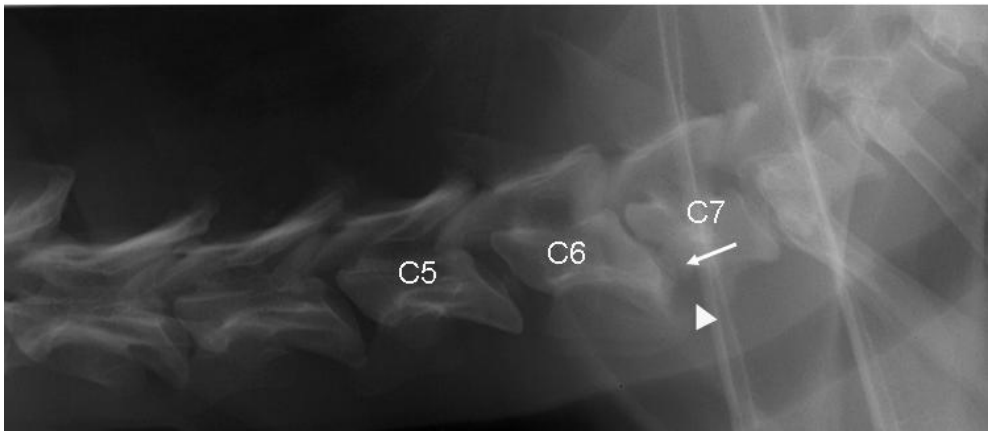

Figure 1. Survey lateral radiograph of a 4-year-old Doberman Pinscher. Severe narrowing of the intervertebral disk space between C6-C7 (arrow). New bone formation is clearly visible on the ventral aspect of C6-C7 (arrowhead). Malformation of the cranioventral border of C7.

Myelography

In myelography or contrast radiography, the spinal cord is outlined by a contrast medium injected into the subarachnoid space. Myelography has been for many years the diagnostic method of choice for identifying DAWS in the dog.[2] In lateral views, abnormalities are seen both in the ventral and dorsal aspects of the vertebral canal (Figure 2). Ventral extradural compression related to the intervertebral disk is the most common finding. The ventral contrast column may be elevated or even arrested in some dogs. Multiple sites of compression are common.[26] Dorsal compression caused by hypertrophy of the ligamentum flavum is seen in some dogs. This also frequently occurs at multiple sites. The degree of spinal cord compression caused and the clinical significance of this radiological finding are unclear, although some authors believe it is significant.[36]

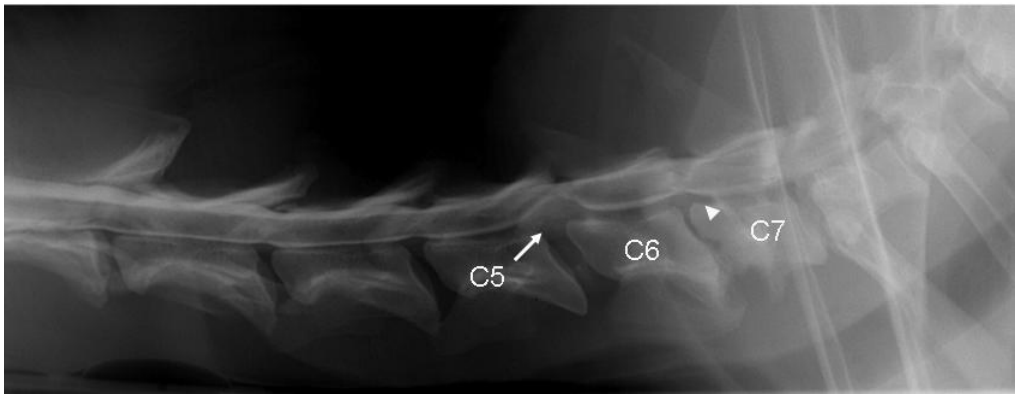

Figure 2. Lateral myelogram of the same dog as in Fig 1. Although the survey radiographs do suggest a compressive lesion between C6 and C7, severe extradural spinal cord compression is noted between C5 and C6 (arrow). A smaller compressive lesion is noted between C6 and C7 (arrowhead).

The merit of applying stress during myelography by the use of traction, flexion or extension has been discussed extensively.[1,2,11,26,27] The degree of spinal cord compression may change as the positions of adjacent vertebrae are altered. Lesions may be categorized based on whether or not compression changes in the 'stressed' positions of traction, flexion or extension. Lesions are termed static when the degree of compression remains the same,

whatever the position of the neck, whereas dynamic lesions improve or worsen, depending on the different positions of the neck.[27] Dynamic lesions can be further subdivided into traction-responsive and positional lesions. This subdivision of lesion types can give some information concerning the nature of the lesion and it helps the surgeon to decide on the best surgical procedure to perform.[2] Traction views are performed by applying tension to the head in a forward direction and to the forelimbs in a caudal direction. Compressive lesions that improve with traction are termed 'traction-responsive' (Figure 3).[1,2,11] Traction usually decreases spinal cord compression caused by the annulus fibrosus or ligamentous structures.[14] Therefore most dogs with DAWS will show traction-responsive lesions. These traction-responsive lesions can be expected to benefit from distraction-stabilization surgery.[2,11] The value of routinely performing traction-studies has been questioned by several authors.[14,37] There is currently no strict definition of a traction-responsive lesion [37], standardization of this technique is problematic [37], little is known about the optimal amount of traction required [37] or allowed, and similar surgical results have been obtained with or without the application of traction in the diagnostic protocol.[14]

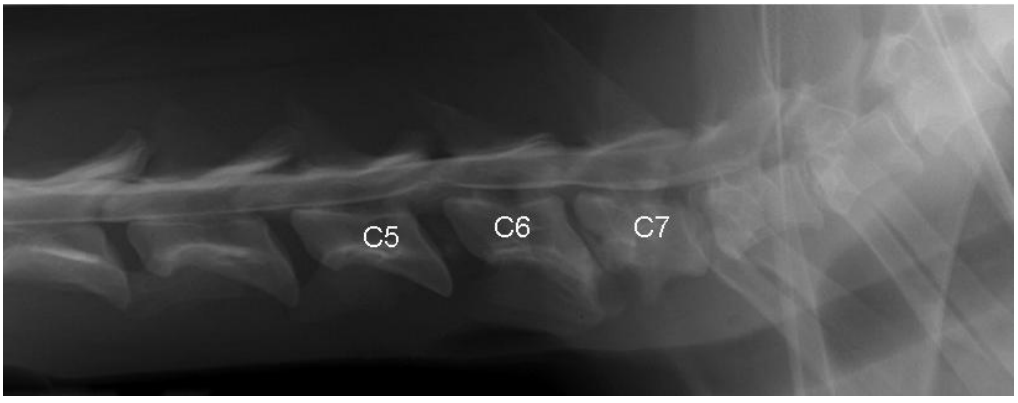

Figure 3. Myelogram of the same dog as in the previous figures while applying traction on the head. The severity of the compressive lesion reduces remarkably with traction. This is a clear example of a traction-responsive lesion.

The degree of compression can change as the neck is moved between flexed, neutral and gently extended positions.[11,26] These types of dynamic lesions are termed 'positional', as they are worsened by positions that reflect normal neck motion.[2] Extension usually exacerbates and flexion usually relieves compression in dogs with DAWS (Figure 4).[26] Flexion and extension views may be of particular interest in the evaluation of mild lesions, whose

significance is unclear when myelography is performed in a neutral position.[11] Positional studies are not without risk. The extension view can cause severe exacerbation of spinal cord compression and should be done either with extreme care or not at all.[17]

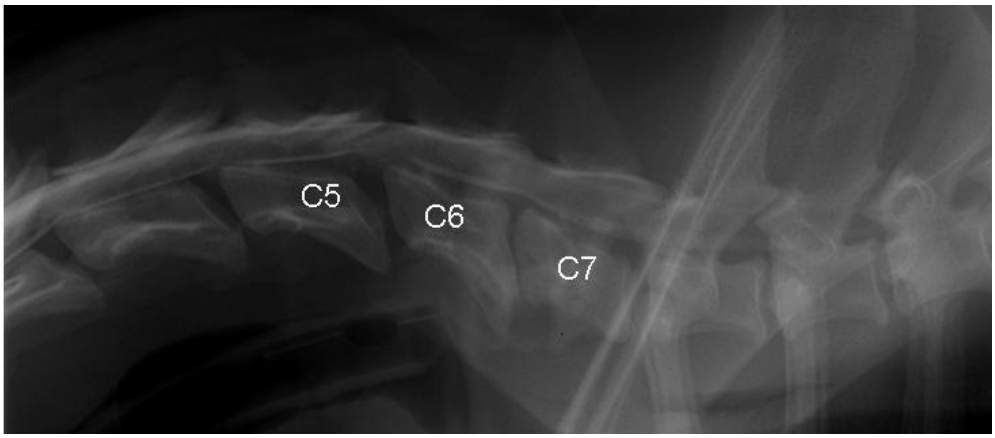

Figure 4. Myelogram of the same dog as in the previous figures while applying flexion on the caudal cervical region. The severity of the compressive lesion reduces remarkably in size with flexion. Extension was not performed due to the potential risk of exacerbation of spinal cord compression.

Although myelography is a standard procedure to confirm the diagnosis of DAWS, this rather invasive procedure is not completely without risk.[2,26] Seizures and transient neurological deterioration are the most important complications following myelography.[26] A significantly higher incidence of postmyelographic complications in Doberman Pinschers with cervical spondylomyelopathy, compared to dogs suffering from other cervical lesions, has been demonstrated.[38]

Computed Tomography and Postmyelographic Computed Tomography

Computed tomography (CT) generates successive cross-sectional images with excellent detail, particularly of the bony structures, which can be reconstructed in different planes (Figure 5A). Depending on the selected technical parameters, the reconstruction of these images, for example in a sagittal plane, can be accompanied by a loss of detail.[39] Because of difficulties in visualizing the spinal cord, conventional CT does not provide as much information as conventional myelography.[40] When CT is used in combination with a subarachnoidal injection of contrast medium (postmyelographic CT), a good delineation of

the spinal cord can also be obtained. An optimal postmyelographic CT (CTM) image is obtained when a lower dose of contrast medium is used than in a conventional myelographic study.[41] Some resorption and dilution of the contrast agent will naturally occur during a preceding conventional myelographic procedure and usually the two procedures are performed under the same anesthetic episode.[26] The normal canine cervical spinal cord has a somewhat round appearance and is surrounded by a subarachnoid space of relatively even diameter (Figure 5B). In dogs with DAWS the ventral subarachnoid space is attenuated and the spinal cord appears to be displaced from the floor of the vertebral canal (Figure 5C).[26] These abnormalities are caused by the extradural soft tissue mass of protruding annulus fibrosus. CT myelography may also provide prognostic information by detecting spinal cord atrophy in diseases that cause chronic spinal cord compression. Spinal cord atrophy is characterized by a somewhat triangularly shaped spinal cord and a relative widening of the subarachnoid space, relative to the spinal cord.[40] There is a strong connection between spinal cord atrophy in humans with cervical spondylotic myelopathy and a poor prognosis following surgery. When the transverse area of the spinal cord is less than 50% of the subarachnoid space, the prognosis is poor.[41,42] To this day, not one single similar relationship has been studied in veterinary medicine. When used in the immediate postoperative period, CTM can be used to confirm adequate removal of a compressive lesion and may demonstrate possible spinal cord re-expansion.[26]

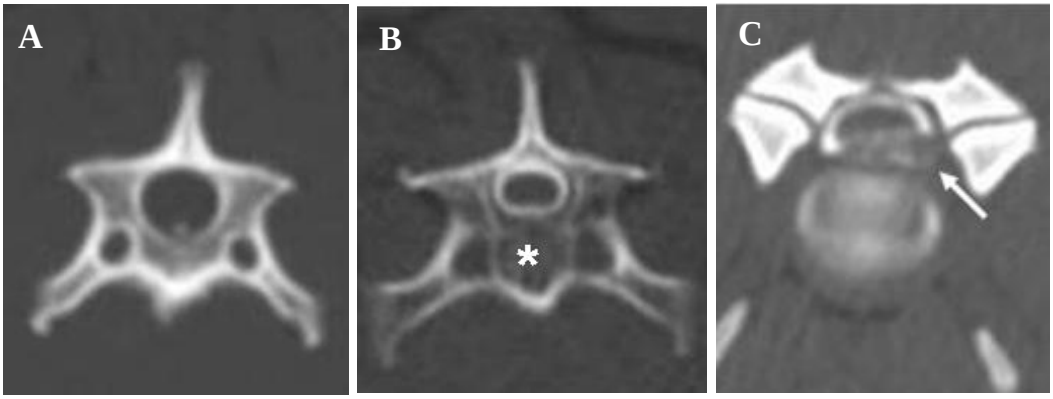

Figure 5. (A) CT image of a clinically normal dog. Spinal cord (black) is not visible. (B) CT myelography (CTM) image of the same dog. Subarachnoidal space is filled with radiolucent contrast (white). Intervertebral disk (*). Spinal cord (dark) is round and is surrounded by a subarachnoid space of even diameter. (C) CTM image of the same dog as in Figures 1-4. Protrusion intervertebral disk with spinal cord compression (arrow). The spinal cord has a flattened appearance and the subarachnoid space is clearly attenuated.

Magnetic Resonance Imaging

Although this is the technique of choice for imaging humans with degenerative diseases of the cervical spine [43], there are only a few reports on the use of Magnetic Resonance Imaging (MRI) in the diagnosis of DAWS.[21,37,44,45] MRI allows direct, non-invasive, multiplanar imaging without loss of detail and an excellent soft tissue characterization with an absence of ionizing radiation.[39,44] A distinct advantage is the ability to correctly assess the spinal cord parenchyma. Spinal cord compression, intervertebral disk degeneration, intervertebral disk protrusion and spinal cord signal changes are abnormalities that can be revealed in dogs with DAWS using MR imaging.[37,44] Spinal cord compression can be evaluated on sagittal and transverse T2-weighted images as a loss of hyperintense cerebrospinal fluid (CSF) signal around the spinal cord or as a change in shape of the spinal cord from round to oval on the transverse image (Figures 6A and 6B).[44] Intervertebral disk degeneration is characterized by a loss of hyperintensity of the disk on T2-weighted images. Abnormal spinal cord signal changes are classified either as hyperintense or as hypointense when they are compared to the normal spinal cord signal intensity adjacent to the abnormal area.[21] Hyperintense T2-weighted signal changes within the spinal cord are a common MRI feature of spinal cord diseases in humans. It is believed that they reflect a broad spectrum of spinal cord abnormalities such as edema, inflammation, vascular ischemia, gliosis and myelomalacia. The exact clinical and prognostic significance of spinal cord signal changes is not yet known (Figures 7A and 7B).[46] The possible complications that can be caused by myelography and CTM are not caused by the MR imaging, because this technique does not require the injection of a contrast medium into the subarachnoid space.[2,44] Penderis and Dennis [45] and da Costa and co-workers [37] demonstrated the application of traction during an MRI scan to differentiate between traction-responsive and traction-nonresponsive lesions. A possible disadvantage of MRI in the evaluation of the spine is the possibility of over-interpretation, which may result in false positive results.[21,39] In a recent study, 16 clinically normal Doberman Pinschers underwent MRI imaging.[21] Four of them had spinal cord compression, 12 of them had disk degeneration and, in addition, foraminal stenosis was detected in 11 of them. Mild disk protrusion or herniation was also detected in all of these clinically normal dogs. Spinal cord signal abnormalities, however, were not detected in them.[21] Since only one breed, with a well known predisposition to DAWS, was evaluated in this study, uncertainties remain considering the extrapolation of these results to other breeds. Further, little is known about the clinical relevance of these MRI abnormalities in clinically normal dogs, their influence on the clinical

interpretation of MRI studies, and methods to differentiate between clinically relevant and irrelevant abnormalities seen on MR images of the cervical vertebral column in dogs. Other disadvantages are the lack of general availability, the high cost and the long time required to complete this kind of study.[2]

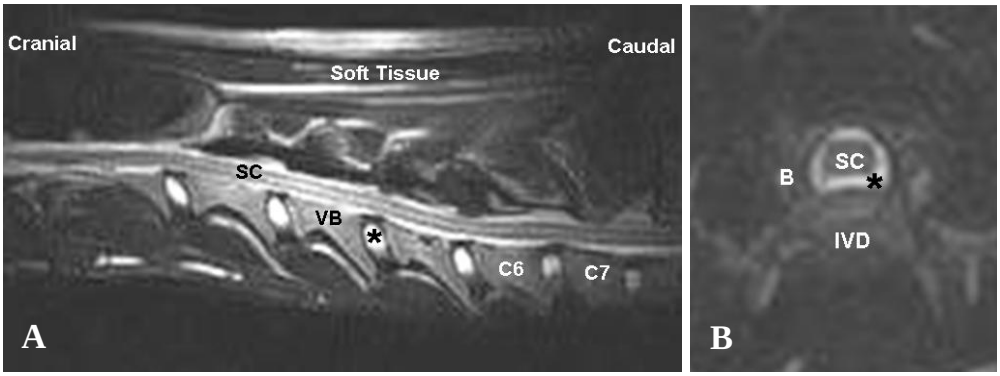

Figure 6. (A) T2-weighted sagittal MR image of a clinically normal dog. Spinal cord (SC) is surrounded by hyperintense subarachnoidal space (white). Subarachnoidal space is visible at each point. VB = Vertebral body. * = normally hydrated intervertebral disk. Between C6 and C7: partial intervertebral disk degeneration, characterized as a partial loss of hyperintensity. (B). T2-weighted transverse MR image at C5-C6 . Spinal cord (SC) has a somewhat round appearance. Spinal cord surrounded by hyperintense cerebrospinal fluid signal (*) of relatively even diameter. IVD = Intervertebral Disk. The spinal cord is surrounded by bony (B) pedicles.

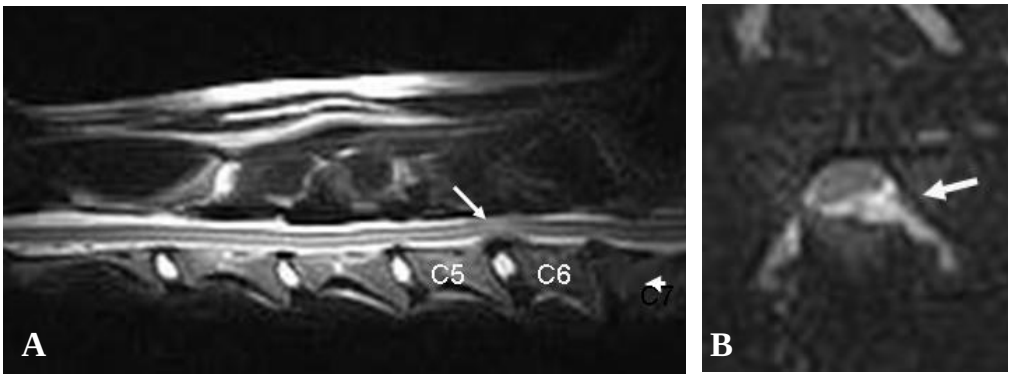

Figure 7. (A) T2-weighted sagittal MR image of same dog as Figures 1-4 and 5C. At the level of C5-C6 there is complete loss of hyperintense CSF signal around the spinal cord with subsequent spinal cord compression. A hyperintense area in the spinal cord can be noted (arrow). At the level of C6-C7 there is complete disk degeneration characterized as total loss of hyperintensity of the disk (arrowhead). (B) T2-weighted transverse MR image at the level of C5-C6. The spinal cord has an abnormal shape caused by a right-sided extradural spinal cord compression (white arrow). The hyperintense ventral subarachnoid space is attenuated at this level.

Treatment

A lot of controversy and discussion exists concerning the treatment of DAWS and the type of surgery that is most likely to give the best results in each individual case.[12]

Conservative treatment

There is little known about the natural progression of DAWS and of the results of conservative treatment. In the literature, DAWS is often defined as a progressive disease in which surgery is necessary to halt progression of symptoms.[1,2,11] The study by Denny and colleagues [8] is often cited to provide evidence that conservative therapy is ineffective in the treatment of cervical spondylomyelopathy. This paper described 35 cases of cervical spondylomyelopathy with follow-up records of 10 surgically treated and 25 untreated animals. In the group of the untreated animals only one dog could be suspected of having DAWS, based on his signalment and radiographic abnormalities, and this animal was lost during follow-up. The study dealt almost exclusively with the specific type of wobbler syndrome that typically affects immature Great Danes and Doberman pinschers. This syndrome is associated with vertebral malformation-malarticulation and has a different etiology and prognosis than DAWS.[11,12] Another, more recent study demonstrated very good results of conservative treatment with a success rate of 80%.[16] However, all dogs had to be available for at least 6 months after a diagnosis was made and animals suffering from another type of cervical spondylomyelopathy were also included. Although objective results are not available, it is possible that conservative treatment could be successful in certain cases. Conservative treatment would consist of cage confinement for several weeks in combination with anti-inflammatory drugs when needed. If the initial cage confinement is successful, the patient should gradually return to normal activity over the course of 4-6 weeks. Intermittent anti-inflammatory drug therapy may be necessary.[2,11] One study describes the successful application of physiotherapy as the sole treatment for three dogs with chronic disk associated compressive lesions of the caudal cervical spinal cord.[47]

Surgical treatment

Several surgical procedures have been described to treat DAWS. Although many authors claim their procedure has a success rate between 70% and 90%, the large number of reported techniques reflects the difficulty of treating DAWS.[23-25,48-54] All surgical procedures for the treatment of DAWS have a high potential for morbidity and postoperative complications.[1,2] There are three basic types of surgery: ventral decompression, vertebral distraction-stabilization and dorsal decompression.[2] The main factor governing the choice of surgical procedure is the appearance of the spinal cord on imaging, in particular the traction views after myelography.[1,2,11,12] Other factors include the number of sites of spinal cord compression, the degree of vertebral malformation and the presence of nerve root compression (thoracic limb lameness).[11]

Ventral Decompression

Ventral decompression by a standard ventral slot technique is, according to several authors, appropriate for single, static lesions.[2,11,22] Ventral decompressive surgery can be very challenging for dogs with DAWS because of the possibility of vertebral malformations, limited access to the caudal cervical disk spaces and intraoperative bleeding due to possible adhesions between the hypertrophied annulus and venous plexus.[2,11] It is very important to remove all of the compressive dorsal annulus and dorsal longitudinal ligament. This can be very difficult to do in chronic compressive disorders like DAWS. The two main disadvantages of this surgical technique are the inability to perform surgery on two adjacent disk spaces and the inability to treat dorsal compression due to ligamentum flavum hypertrophy.[2,11] Short-term deterioration is common, even among dogs that have good long-term results.[14] It is very difficult to interpret and compare reports on the results of ventral decompressive surgery due to the large differences in inclusion criteria and follow-up periods for the different authors. Chambers and colleagues [48] only included dogs which had a survival of at least one year after surgery in their report. In this way they ignored the dogs that were euthanized in the first year after surgery due to lack of postsurgical improvement. They reached a 100% success rate in this study. In a later study [55] they also included dogs that died postoperatively due to problems unrelated to DAWS. In this study they reached a success rate of 66%. In the study by Rusbridge and colleagues [14], cases were excluded if a minimum

follow-up period of 24 months after surgery could not be reached. For this reason, six dogs were excluded from the study and 4 of the remaining 14 dogs demonstrated a recurrence of clinical signs two years or more after surgery. This last piece of information demonstrates the most important complication in applying ventral decompression to dogs with DAWS. It is commonly believed that about 20% to 30% of the dogs undergoing single level decompression suffer a second episode of neurological signs within 2-3 years.[2,14,49] The reason for this neurological deterioration is presumed to be a recurrence at the original site or the development of a compressive lesion at an adjacent disk space, which is called adjacent segment disease or 'domino-lesion'.[2] This occurs independently of the surgical technique performed, also after distraction-stabilization techniques.[12,14]

Vertebral distraction-stabilization

The primary indications for a distraction-stabilization procedure are the presence of a traction-responsive lesion on myelography or MRI and the presence of nerve root compression.[2,11] A number of different techniques have been developed for this procedure, such as vertebral distraction and stabilization with vertebral body pins or screws and bone cement [49], a screw and washer [50], a screw and double washer [23], interbody bone cement plug [51], and cervical locking plates [24,53,54]. The two most recommended techniques are the interbody bone cement plug and vertebral body pins combined with bone cement.[2,11,22] Most of these different surgical techniques are based on the same principle.[12] A ventral slot or fenestration defect is drilled to a depth of three-quarters of the height of the intervertebral disk space. In this way the dorsal annulus is preserved and the vertebral canal is not entered into. Traction is applied to the adjacent vertebrae using vertebral distraction instruments or by manual traction on the head. The two vertebrae are then rigidly stabilized with an orthopedic implant to maintain distraction.[12] Linear traction provides immediate cord decompression by stretching the dorsal annulus, dorsal longitudinal ligament and ligamentum flavum. By stabilizing the adjacent vertebral bodies, it is assumed that the hypertrophied soft-tissue structures would then be allowed to atrophy with time.[56] The advantage of not entering the vertebral canal, as is done in direct decompressive surgical techniques, is offset partly by the risk of implant failure or other implant-associated complications such as loosening, migration or breaking of implants, vertebral end-plate fracture due to inadequate contact between the orthopedic implant and the vertebral endplate, and the increased risk of surgical infection. Implant failure can be asymptomatic in some patients.[2] As in other surgical techniques, it seems to be very difficult

to perform surgery on more than one intervertebral disk space at the same time. Adjacent segment disease occurs with the same incidence with this technique as with ventral decompressive surgery. It occurs 5 to 60 months after surgery in 20-30% of the cases and is independent of the surgical technique.[12,14,57,58] Although several theories have been developed, the exact pathogenesis and etiology of this phenomenon remain unknown.[2,12] Additional disk protrusions may result when intervertebral fusion or stabilization at one level leads to increased stress at one of the adjacent disk spaces. Degeneration and protrusion of additional disks can also result from continued natural disease progression rather than from the degeneration of a previously normal disk. The latter might indicate that DAWS is not only a multifactorial but possibly also a multifocal disease.[12] Several authors have suggested routinely fusing multiple disk spaces to reduce the incidence of adjacent segment disease.[2,11,12] In humans, the risk of new disease at an adjacent level was found to be significantly lower following a multi-level arthrodesis, than it was following a single-level arthrodesis.[59,60] Results of such an approach in veterinary medicine are currently lacking and should be explored.

Dorsal decompression

Dorsal decompression by dorsal laminectomy is normally used to relieve compression caused by dorsal lesions that do not respond to traction.[2] Such compressive lesions are usually seen in young adult large-breed and giant-breed dogs suffering from a type of cervical spondylomyelopathy, in which the compression is caused by articular and periarticular tissue proliferations, often in combination with ligamentum flavum hypertrophy.[1,2,11] Although this technique is not often used in the treatment of DAWS, several authors have reported a continuous dorsal laminectomy extending from C4 to C7 for dogs with ventral lesions at multiple intervertebral spaces. In this way, spinal cord compression is alleviated by allowing the spinal cord to ride dorsally.[36,52] The major disadvantages of dorsal decompression are the invasiveness of the surgical technique, which can be associated with significant short-term morbidity, transient deterioration in neurological status and prolonged length of hospitalization.[2] Also, the technique does not allow the removal of ventrally located disk material.[1,2,52] A possible complication is the recurrence of clinical signs. This is not caused by adjacent segment disease but rather by the formation of a laminectomy membrane at the surgical site, which is also termed constrictive fibrosis.[52] It is very difficult to interpret the

reported results of dorsal decompressive surgery for the treatment of DAWS, as it is not stated whether the compressive lesions treated were ventral or dorsal in nature.[36,52]

Prognosis

There is little objective data available on the prognosis of DAWS. Even though there is not a single specific report on the natural progression or medical treatment of dogs with DAWS, neurological and surgical handbooks do describe a generally guarded to unfavorable prognosis for patients treated medically.[2,11,22] In surgical reports, many authors claim a success rate of more than 70% or 80% immediately postoperative.[15,49,50,52] Conversely, overall long-term mortality rates vary from 19% to 43%, which suggests a less favorable prognosis.[14,15,51,52] After both ventral decompressive and vertebral distraction-stabilization techniques have been applied, a second episode of clinical signs is seen in about 20% to 30% of the cases.[2,11,12] It is very difficult to compare the results of the different surgical techniques due to the differences in case selection, in the definition of a successful outcome and in the length and descriptions of follow-up.[12] Most surgical reports deal with the 'wobbler syndrome in general' and do not focus on DAWS in particular. This could give the false impression of a favorable outcome because the surgical treatment of the specific type cervical spondylomyelopathy typically seen in young adult giant-breed dogs gives better results than the surgical treatment of DAWS.[11] Generally, patients with multiple lesions have a guarded to unfavorable prognosis.[2,11,12,22] The most plausible reason is that, when applying one of the current surgical techniques, it is very difficult to perform surgery on two adjacent disk spaces at the same time. Other potential prognostic factors are the degree of neurological dysfunction, the duration of clinical symptoms before diagnosis and the rate of spinal cord compression.[2,11,12] Patients with severe neurological dysfunction and a long period of clinical signs may have a more guarded prognosis. In some cases, surgery will only halt the progression of the disease. In these cases, irreversible spinal cord damage has probably already occurred. Several authors suggest the use of advanced medical imaging, such as CT myelography and MRI, as a prognostic tool to diagnose spinal cord atrophy.[12,40] A possible correlation between the diagnosis of suspected spinal cord atrophy and a poor outcome has not yet been investigated in veterinary medicine.

Transcranial magnetic stimulation (TMS) is a non-invasive, painless and sensitive technique to evaluate the functional integrity of the spinal cord.[61] In human medicine, TMS is used as a diagnostic and prognostic tool in patients with cervical spondylotic myelopathy.[62-66] In

veterinary medicine, it has been performed on healthy animals to standardize the method of stimulation.[67-74] To date only one study has evaluated the use of TMS in dogs with cervical spondylomyelopathy.[75] Significantly different TMS-values were demonstrated between Doberman Pinschers with and without cervical spondylomyelopathy. These promising results warrant further exploration of TMS as a diagnostic and potential prognostic tool in dogs with DAWS.

Conclusion

Disk associated wobbler syndrome is a relatively common cause of chronic spinal cord compression in adult large breed dogs. This disease can be very challenging, both for the referring veterinarian and even for the specialist. One of the key problems is the variation in definitions of and discrimination between this and other causes of cervical spondylomyelopathy. Making a diagnosis is not always straightforward, and the advantages and disadvantages of the different diagnostic procedures should be considered. DAWS is considered a surgical disease but the ideal surgical procedure still does not exist. Conversely, there is insufficient knowledge about the conservative treatment and natural progression of this disease and, in addition, there is insufficient objective data available on the potential prognostic parameters of this disease. It seems quite clear that further studies are needed to deal with the aforementioned problems.

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SECTION II

SCIENTIFIC AIMS

SCIENTIFIC AIMS

Disk associated wobbler syndrome (DAWS) is a complex disorder. Many aspects of this neurological disease are not completely understood. Currently, there is limited knowledge, controversy and discussion about potential underlying risk factors, the benefits and limitations of the different applied diagnostic techniques, results of conservative treatment, development of surgical techniques and the evaluation of objective prognostic parameters for dogs with DAWS.

Therefore, the general aim of our study was to gain more information about the diagnosis and treatment of dogs with DAWS. The specific aims of this study were:

1. To evaluate the spectrum and frequency of cervical magnetic resonance imaging (MRI) abnormalities in clinically normal Doberman Pinschers and English Foxhounds
2. To evaluate the clinical relevance and consequences for image interpretation of these MRI abnormalities
3. To evaluate methods to differentiate clinically relevant from irrelevant abnormalities seen on cervical MRI
4. To compare myelography, postmyelographic computed tomography and low-field MRI for the diagnosis of DAWS in dogs
5. To evaluate the use of linear vertebral ratios in dogs with and without clinical signs of DAWS.
6. To evaluate the results and identify potential prognostic factors after conservative treatment for dogs with DAWS
7. To evaluate the results of a classical and a new surgical technique for the treatment of DAWS in dogs.

SECTION III

MATERIALS AND METHODS

MATERIALS AND METHODS

In this thesis, 61 dogs were prospectively and 139 dogs were retrospectively studied. For all prospectively included dogs, written owner consent was obtained prior to study enrollment.

The information regarding the **retrospectively** included dogs was retrieved from the database of the Faculty of Veterinary Medicine, Ghent University, Belgium. This information included signalment, clinical history, clinical presentation, imaging studies, final diagnosis, treatment and outcome. If additional information was wanted, the owners of these dogs were contacted via a telephone interview by the author of this thesis. These dogs participated in the studies described in section IV, chapters 4.1; 5.1; 6.1 and 6.2.

The **prospectively** included dogs can be divided in three groups:

1. ***Clinically normal Doberman Pinschers (n = 20)***

   This breed was selected and included because of their known predisposition to DAWS. This group consisted of 11 males and 9 females, between 1.5 and 8 years old (median 5.0 years).

2. ***Clinically normal English Foxhounds (n = 18)***

   This breed was selected and included because of their comparable height at the shoulders and body conformation to Doberman Pinschers and the fact that there is no known breed predisposition to neurological syndromes affecting the caudal cervical vertebral column. This group consisted of 9 males and 9 females, between 1.5 and 12 years old (median 5.0 years).

3. ***Dogs with disk associated wobbler syndrome (n = 23)***

   This group included 17 Doberman Pinschers, 2 Dalmatians, 2 Whippets, 1 Weimaraner, and 1 Bernese Mountain Dog. Eleven male and 12 female dogs were included. Age ranged from 4.2 to 10.8 years old (mean 7.7 years; median 7.4 years). Neurologic signs varied from cervical hyperesthesia only (n = 2) over ataxia of the pelvic limbs without noticeable paresis (n = 6), ataxia with noticeable paresis of the pelvic limbs (n = 6), ambulatory tetraparesis (n = 6), nonambulatory tetraparesis (n = 1) and tetraplegia (n = 2).

All prospectively included dogs underwent the following investigations:

- General physical examination
- Complete neurologic examination
- Complete blood counts and biochemistry profile
- Low-field magnetic resonance imaging of the cervical region

All prospectively included Dobermann Pinschers (clinically normal and affected) underwent additionally and echocardiographic examination, standardized mucosal bleeding times, and transcranial magnetic stimulation.

All prospectively included dogs with disk associated wobbler syndrome (DAWS) underwent additionally a myelographic and postmyelographic computed tomographic examination of the cervical region. After a diagnosis of DAWS was made, the owners were free to choose between conservative or surgical treatment.

All clinically affected animals were re-evaluated after 1, 3, 6, 12, and 24 months and at additional moments if indicated. The owners of all clinically normal dogs (Dobermann Pinschers and English Foxhounds) were encouraged to have follow-up physical and neurologic examinations performed between 16 and 18 months after the initial investigations. The goal of this second neurologic examination was to determine whether any recorded abnormalities in these clinically normal dogs could be regarded as truly clinically unimportant or rather should have been regarded as indicative of an early onset of disease prior to development of clinical signs.

Neurologic examinations of all prospectively included dogs were performed by the author of this thesis.

The prospectively included clinically normal dogs participated in the studies described in section IV, chapters 1.1; 1.2; 2.1; 4.3; and 4.4. The prospectively included clinically normal Dobermann Pinschers additionally participated in the study described in section IV, chapter 2.2.

The prospectively included dogs with DAWS participated in the studies described in section IV, chapters 1.2; 2.1; 2.2; 3.1; 4.2; 4.3; 4.4; 5.2; and 6.3. Chapters 2.1; 2.2; 4.3; and 4.4 only included clinically affected Dobermann Pinschers.

SECTION IV

RESULTS

Chapter 1

LOW FIELD MAGNETIC RESONANCE IMAGING IN DOGS WITH AND WITHOUT CLINICAL SIGNS OF DISK ASSOCIATED WOBBLER SYNDROME

Chapter 1.1

LOW FIELD MAGNETIC RESONANCE IMAGING FINDINGS OF THE CAUDAL PORTION OF THE CERVICAL REGION IN CLINICALLY NORMAL DOBERMAN PINSCHERS AND ENGLISH FOXHOUNDS

LOW FIELD MAGNETIC RESONANCE IMAGING FINDINGS OF THE CAUDAL PORTION OF THE CERVICAL REGION IN CLINICALLY NORMAL DOBERMAN PINSCHERS AND ENGLISH FOXHOUNDS

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Summary

The objective of this study was to determine the spectrum and frequency of abnormalities on low field magnetic resonance imaging (MRI) examinations of clinically normal Doberman Pinschers and English Foxhounds.

Twenty clinically normal Doberman Pinschers and 17 clinically normal English Foxhounds were prospectively investigated. For each dog, MRI of the cervical vertebral column (sagittal, dorsal, and transversal T1 and T2- weighted images) was performed. The following parameters were assessed: intervertebral disk degeneration, disk-associated compression, dorsal compression, vertebral body abnormalities and intraparenchymal signal intensity changes. The association between these parameters and age, breed, gender, and localization of the assessed intervertebral disk spaces were evaluated.

Only 1 dog showed no single abnormality on the MR images. Severe MRI abnormalities were seen in 17 dogs with the occurrence or combination of complete disk degeneration (n=14) and/or spinal cord compression (n=11). Vertebral body abnormalities were observed in 8 dogs and hyperintense signal intensity changes were seen in 2 dogs. The severity of disk degeneration and disk-associated compression was significantly associated with higher age. There was a significant association of disk degeneration, disk-associated and dorsal compression with the localization of the assessed intervertebral disk space, with the caudal intervertebral disk spaces being more severely affected. The correlation coefficient between severity of disk degeneration and disk-associated spinal cord compression was 0.52.

MRI abnormalities are commonly seen in the caudal cervical vertebral column and spinal cord of clinically normal Doberman Pinchers and English Foxhounds. Such lesions are probably part of the common aging process of spinal degeneration.

Introduction

Plain radiography, myelography and computerized tomography, alone or in combination, have been utilized to diagnose neurological disorders affecting the cervical vertebral column and spinal cord.[1] Due to the invasive nature and diagnostic limitations of myelography[2,3], MRI has become a popular diagnostic tool to evaluate the spinal cord. This is an attractive diagnostic alternative because it is non-invasive, involves no radiation, is not known to be associated with any major side effects, and provides superior resolution of the anatomy of particularly soft-tissue structures in multiple anatomic planes.[4] Magnetic resonance imaging has been documented to be useful in evaluating and diagnosing a variety of disorders of the canine cervical spine.[5,6,7] The high sensitivity of MRI can cause problems in interpretation of the images, as non-significant lesions become evident.[8] A recent veterinary, and different human studies have demonstrated the existence of cervical spinal cord compressions in asymptomatic subjects.[8-15] However, little is known about the clinical relevancy, spontaneous course and prognosis of these asymptomatic cervical spinal cord compressions and whether they would justify meticulous clinical and imaging follow up or even early surgical decompression before clinical manifestation of any neurological deficit. To determine the importance of abnormalities on MR images, one must take into account the spectrum and frequency of structural abnormalities that may not cause problems. At this time, little is known about this subject in veterinary literature.

In the present study, the low field MRI features of the cervical vertebral column and spinal cord of clinically normal Doberman Pinschers and English Foxhounds were investigated. This was done with special emphasis on the caudal cervical region. It was hypothesized that structural abnormalities existed in a relevant part of the studied population and that breed, age and gender could influence the occurrence and gradation of these findings. Further, it was hypothesized that the development of certain abnormalities could be associated with the localization of the assessed intervertebral disk space. This study is part of a larger investigation to the diagnosis and treatment of disk-associated wobbler syndrome in dogs.

Materials and Methods

Animals

Thirty-seven clinically normal dogs were prospectively studied. The experiment was conducted in accordance with the guidelines of the Animal Care Committee of the University of Ghent. Written owner consent was obtained prior to study enrollment. Two groups of dogs were prospectively studied. One group consisted of 20 client-owned Doberman Pinschers. This breed was selected and included because of their known predisposition to neurological syndromes affecting the caudal cervical vertebral canal and spinal cord.[16] The other group consisted of 17 client (n = 13) and laboratory-owned (n = 4) English Foxhounds. This breed was selected and included because of their comparable conformation and activity-level to Doberman Pinschers and the fact that this breed is not predisposed to neurological syndromes affecting the caudal cervical vertebral canal and spinal cord. The dogs were defined as clinically normal on the basis of history and results of physical and neurological examinations, complete blood cell counts, and serum biochemistry analyses. All Doberman Pinschers underwent an additional echocardiographic examination and standardized mucosal bleeding times. The dogs were divided into 2 age categories: dogs younger than 5 years (10 Doberman Pinschers and 8 English Foxhounds) and dogs of 5 years or older (10 Doberman Pinschers and 9 English Foxhounds). Gender distribution was equal between groups. All owners were contacted at the end of the study to have a new physical and neurological examination performed on their dogs.

MR imaging protocol

A permanent, 0.2 T magnet [a] was used to perform MRI in all dogs. Dogs were positioned in dorsal recumbency. The forelimbs were fixed parallel to the thoracic wall. The cervical spine was positioned in a joint coil (circular transmit-receive coil) with an inner diameter 19 cm. T1 and T2, spin echo- weighted studies were performed in all dogs in a sagittal, dorsal and transverse plane. Images of this last plane were aligned perpendicular to the spinal cord. The vertebral column was imaged from the C2 to C7 in the sagittal and dorsal plane and from the C4 to C7 in the transverse plane. The field of view was 29 cm in the sagittal, 24 cm in the dorsal and 20 cm in the transverse plane. T1 weighted sagittal images were obtained with a repetition time (TR) of 700 milliseconds (ms) and an echo time (TE) of 25 ms. The T2 weighted sagittal studies were made using a TR of 2700 ms and a TE of 125 ms. Dorsal images were performed in T1 weighted sequence with TR = 600ms; TE = 25 ms and in T2

weighted sequence the settings were TR = 3900 and TE = 120 ms. Transverse T1 weighted images were performed with TR=1100 ms and TE = 25 ms, and in the T2 weighted transverse images the settings were TR = 5000 ms and TE = 120 ms. Slice thickness was 4mm in the sagittal and dorsal images and 3 mm in the transverse sequences with no interslice gap in all studies.

Interpretation of MR images

The following parameters were assessed on the MR images: disk degeneration, disk-associated spinal cord compression, dorsal spinal cord compression, spinal cord intensity changes, and vertebral body abnormalities. On sagittal and transversal images, intervertebral disk spaces C2-C3 to C6-C7 and C4-C5 to C6-C7 were evaluated, respectively. To allow comparison with existing literature, these parameters were assessed and graded in accordance with a recent veterinary study about the diagnosis and pathogenesis of cervical spondylomyelopathy.[8] All imaging studies were reviewed independently by the first (SDD) and second (IG) author, and a consensus interpretation was reached. Using the fact that disk degeneration is associated with decreased signal intensity on T2-weighted images, assessment of intervertebral disk degeneration was based on the signal intensity of each intervertebral disk on midsagittal T2-weighted images (Figure 1). A non degenerated disk (score 0) demonstrated a homogenous hyperintense signal; partial disk degeneration (score 1) was assumed when there was heterogeneous loss of hyperintense signal; complete disk degeneration (score 2) was assumed when there was complete loss of the hyperintense signal.

Figure 1. Sagittal T2-weighted MR image of a clinically normal Doberman Pinscher. Disk degeneration: no disk degeneration (disk space far left); partial disk degeneration (middle disk space); and complete disk degeneration (disk space far right). Each intervertebral disk is causing partial compression of ventral subarachnoid space (grade 1). Complete compression of dorsal subarachnoid space (grade 2) indicated by the arrow.

Disk-associated (ventral) spinal cord compression was assessed on the midsagittal and where available confirmed on the transversal (C4-C7) T2-weighted images (Figure 2). This parameter was classified as follows: score 0, no compression; score 1, partial ventral subarachnoid space compression; score 2, complete ventral subarachnoid space compression without spinal cord compression; score 3, spinal cord compression with deviation or distortion of the spinal cord. Dorsal spinal cord compression was evaluated on the same images and with the same classification as disk-associated spinal cord compression.

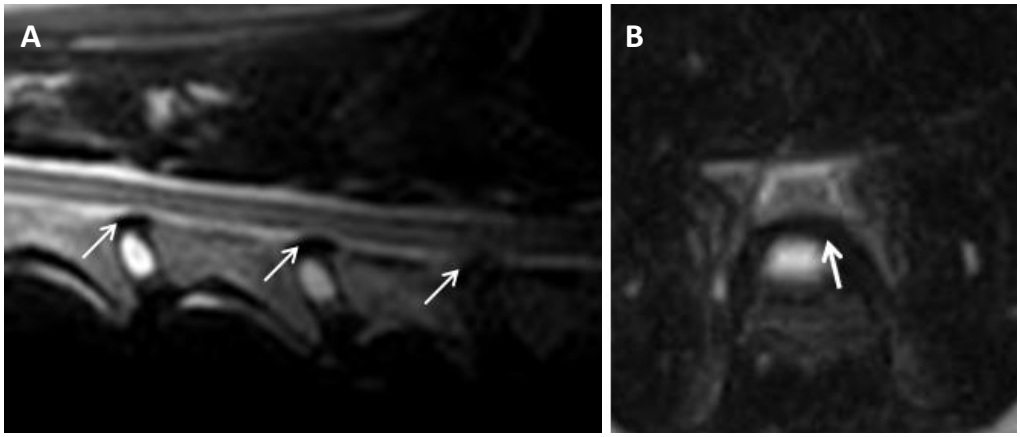

Figure 2: (A) Sagittal T2-weighted MR image of a clinically normal Doberman Pinscher: disk-associated compression: partial ventral subarachnoid space compression (grade 1 (arrow far left)); complete ventral subarachnoid space compression (grade 2 (middle arrow)); and spinal cord compression (grade 3 (arrow far right). (B) Transversal T2-weighted MRI image: Disk-associated spinal cord compression characterized by deviation and/or distortion of the spinal cord (arrow).

The degree of intervertebral disk degeneration, disk-associated and dorsal spinal cord compression were evaluated in two ways. First, the score of the most severe affected disk space in each dog was assessed. This was defined as the severity of disk degeneration or spinal cord compression in that dog. Second, the sum of the scores of all affected disk spaces in each dog was assessed . This was defined as the sum of scores for the assessed intervertebral disk spaces in that dog. Evaluation of spinal cord intensity changes were based on the relative increase in signal on T2-weighted images and/or decrease in signal on T1-weighted images when compared with the surrounding spinal cord parenchyma. Vertebral body abnormalities were evaluated on the midsagittal T1-weighted images. Vertebral body

abnormalities were defined as flattening of the cranioventral border to a triangular shape of the vertebral body (Figure 3).

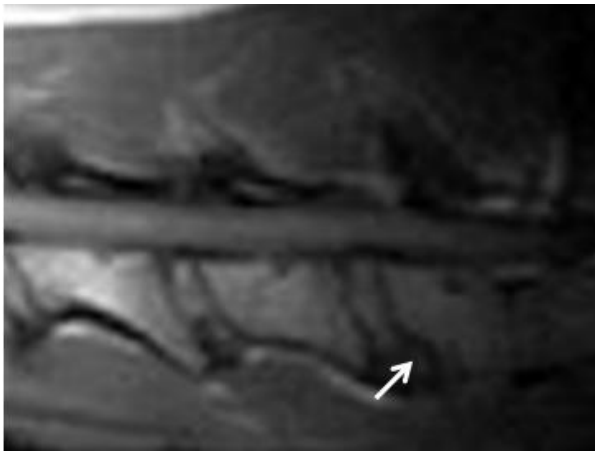

Figure 4. Sagittal T1-weighted MR image of a clinically normal Doberman Pinscher. Vertebral body abnormalities were characterized as a flattening of the cranioventral border of the vertebral body (arrow).

Data analysis

The effect of breed, age category and gender on severity and the sum of scores for the assessed intervertebral disk spaces was evaluated by the Wilcoxon rank sum test. Whether there was an association in severity of the assessed parameter with the localization of the assessed intervertebral disk space was tested in two different ways. First the Friedman test with dog as block factor was used. Second the Page test was used to test whether the severity increased with the more caudally located intervertebral disk spaces. The effect of age category on the localization of the assessed abnormality was evaluated by the Wilcoxon rank sum test. To evaluate the correlation between the different assessed parameters, Kendall correlation coefficients were determined. Significance was established at a value of $P < 0.05$.

Results

Only 1 dog showed no single abnormality on MRI examination. All other dogs demonstrated at least one abnormality for one of the different assessed parameters.

Animals

Twenty clinically normal Doberman pinschers and 17 clinically normal English Foxhounds were studied and categorized into different age categories. The group of 10 Doberman Pinschers younger than 5 years consisted of 6 males and 4 females, between 1.5 and 4.7 years old (mean 2.6 years; median 1.8 years), weighing between 30 and 46 kg (mean 33.7 kg; median 35 kg). The group of 8 English Foxhounds younger than 5 years consisted of 4 males and 4 females, between 1.5 and 4 years old (mean 2.3 years; median 1.9 years), weighing between 27 and 34 kg (mean 29.1 kg; median 27.8 kg). The group of 10 Doberman Pinschers of 5 years or older consisted of 5 males and 5 females, between 5.3 and 8 years old (mean 6.6 years; median 6.2 years), weighing between 30 and 46 kg (mean 37 kg; median 36 kg). Finally, the group of 9 English Foxhounds of at least 5 years old consisted of 5 males and 4 females, between 5 and 12 years old (mean 7.4 years; median 6 years), weighing between 28 and 38.6 kg (mean 32.5 kg; median 33 kg).

Intervertebral disk degeneration

Nine of the 37 dogs (24%) did not show any sign of intervertebral disk degeneration. Only partial intervertebral disk degeneration was seen in 14 dogs (38%). Complete intervertebral disk degeneration was seen in another 14 dogs (38%). Multiple affected disks were noticed in 10 dogs (27%). Among the 185 disks examined in all dogs, 42 showed signs of degeneration; of these, 25 were partially and 17 completely degenerated. The disks that were most frequently involved were C6-C7 (n = 29) and C5-C6 (n = 8). Other affected disks were C2-C3 (n = 3) and C4-C5 (n = 2). The severity of intervertebral disk degeneration and the sum of the scores of the assessed intervertebral disks were significantly associated with higher age category ($P = 0.005$ and $P = 0.003$, respectively), but not with breed ($P = 0.36$ and $P = 0.51$, respectively) or gender ($P = 0.98$ and $P = 1.0$, respectively). Severity of disk degeneration was significantly associated with the localization of the assessed intervertebral disk ($P < 0.0001$), with the more caudal intervertebral disk spaces being more severely degenerated ($P < 0.0001$). There was no significant association between the localization of the affected disk and age category ($P = 0.41$).

Disk-associated spinal cord compression

Three of the 37 dogs (8%) did not show any sign of disk-associated compression. Partial compression of the ventral subarachnoid space as the most severe compression was seen in 9 dogs (24%). Complete compression of the ventral subarachnoid space as the most severe compression was seen in 14 dogs (38%) and spinal cord compression with deviation or distortion of the spinal cord was seen in 11 dogs (30%). Multiple sites of any degree of compression were detected in 28 dogs (76%), with 4 dogs (11%) showing multiple sites of spinal cord compression. Among the 185 intervertebral disk spaces examined, 88 showed some degree of disk –associated compression; of these 43 showed partial compression of the subarachnoid space, 28 showed complete compression of the subarachnoid space and 17 showed spinal cord compression. The intervertebral disk spaces that were more often involved were C6-C7 (n = 26) and C4-C5 (n = 20). Other affected intervertebral disk spaces were C2-C3 (n = 15), C3-C4 (n = 14), and C5-C6 (n= 13). The severity of disk-associated compression was significantly associated with higher age category ($P = 0.048$). However, the sum of the scores for the assessed intervertebral disk spaces was not significantly associated with age category ($P = 0.13$). Severity and sum of the scores for disk-associated compressions were not significantly associated with breed ($P = 0.58$ and $P = 0.44$, respectively) or gender ($P = 0.17$ and $P = 0.46$, respectively). Severity of disk-associated compression was significantly associated with the localization of the assessed intervertebral disk space ($P = 0.0044$) with the most severe compressions at the more caudal intervertebral disk spaces ($P = 0.019$). There was no significant association between the localization of the affected intervertebral disk space and age category ($P = 0.84$).

Dorsal spinal cord compression

Sixteen of the 37 dogs (43%) did not show any sign of dorsal compression. Partial compression of the dorsal subarachnoid space as the most severe compression was seen in 11 dogs (30%). Complete compression of the dorsal subarachnoid space as the most severe compression was seen in 7 dogs (19%) and dorsal spinal cord compression with deviation or distortion of the spinal cord was seen in 3 dogs (8%). Multiple sites of any degree of dorsal compressions were seen in 9 dogs (24%). Among the 185 intervertebral disk spaces examined, 30 showed some degree of dorsal compression; of these, 19 showed partial compression of the dorsal subarachnoid space, 8 showed complete compression of the subarachnoid space and 3 showed spinal cord compression. The involved intervertebral disk spaces were C6-C7 (n = 17), C5-C6 (n = 9), and C4-C5 (n = 4). Laminar malformations or

abnormalities of the articular facets were not noticed in any dog. The MR images in the dorsal plane did not show any lateral compressions.. The severity and sum of the scores of dorsal compression were not significantly associated with age category (P = 0.66 and P = 0.71, respectively), breed (P = 0.43 and P = 0.32, respectively) or gender (P = 0.85 and P = 0.97, respectively). Severity of dorsal compression was significantly associated with the localization of the assessed intervertebral disk space (P = 0.0001) with the most severe compressions located at the more caudal intervertebral disk spaces (P = 0.0001). There was no significant association between the localization of the affected intervertebral disk space and age category (P = 1.00).

Spinal cord intensity changes

A hyperintense intramedullary signal change on T2- weighted images was seen in 2 of the 37 dogs (5%). This occurred in 2 English Foxhounds of the higher age category at C4-C5 and C5-C6, respectively. A hypointense intramedullary signal change on T1-weighted images was not noticed in any dog. There were no significant associations between spinal cord intensity changes and age category (P = 0.46), breed (P = 0.52) or gender (P = 0.12).

Vertebral body abnormalities

Vertebral body abnormalities were present in 8 of the 37 (22%) dogs. In all dogs, this was demonstrated as a flattening of the ventrocranial border of the vertebral body. These abnormalities occurred in 7 of the 20 Doberman Pinschers (35%) at the level of C7 and in 1 English Foxhound (3%) at the level of C6. The presence of vertebral body abnormalities was significantly associated with the Doberman Pinscher as breed (P = 0.043), but was not significantly associated with age category (P = 0.61) or gender (P = 0.82). In 2 Doberman Pinschers an additional abnormal position of the vertebral body with tipping or tilting of C7 was seen.

Correlation between the different assessed parameters

There existed a significant correlation between the severity of intervertebral disk degeneration and severity of disk-associated spinal cord compression (R = 0.52; P = 0.0003), the sum of the scores for disk-associated compressions (R = 0.41; P = 0.0025) and severity of dorsal compression (R = 0.31; P = 0.032). The sum of the scores for intervertebral disk degeneration was significantly correlated with the severity and sum of the scores of disk-associated compressions (R = 0.58; P <.0001 and R = 0.50; P = 0.001, respectively) and with the

severity of dorsal compression (R = 0.33; *P* = 0.0020). There existed also a significant correlation between the severity of disk-associated and dorsal spinal cord compression (R = 0.30; *P* = 0.039) and between the severity of disk-associated compression and the occurrence of vertebral body abnormalities (R = 0.32; *P* = 0.037).

Follow-up

Eighteen of the 20 Doberman Pinschers and 9 of the 17 English Foxhounds were available for physical and complete neurological examination between 16 and 18 months after the MRI examination. These examinations revealed no abnormalities. The owner of 4 other English Foxhounds was available for telephone interview 9 months after the MRI examination. According to the owner, the dogs were clinically normal. The 2 remaining Doberman Pinschers and 4 English Foxhounds died during the study period for reasons unrelated to this study. According to the owners, these 6 dogs never showed any clinical sign that could suggest a cervical myelopathy. None of these dogs was available for pathologic examination.

Discussion

In the present study, we have approached the question of the clinical relevance of cervical abnormalities identified on MR images by evaluating the range and frequency of findings in asymptomatic individuals of 2 different large breed dogs. A recent veterinary study by da Costa et al. evaluated the cervical MR images of 16 clinically normal Doberman Pinschers.[8] In that study, a surprisingly high frequency of abnormalities on MR images was seen with 12 dogs showing disk degeneration and 4 dogs demonstrating spinal cord compression. Since only 3 of these clinically normal dogs were older than 6 years and a breed was investigated with a high incidence of abnormalities in the cervical vertebral column, difficulties remain with extrapolating these data to other breeds and different age categories. For these reasons, the dogs of our study were divided into different age categories and additionally, a breed with similar body conformation as the Doberman Pinscher but no known predisposition to abnormalities of the cervical vertebral column was investigated. The results of the study reported here also indicate a surprisingly high frequency of abnormalities on MRI examinations of the studied clinically normal dogs. Although the occurrence of disk degeneration and partial compression of the ventral or dorsal subarachnoid space are not expected to complicate the clinical evaluation of MRI studies, more severe abnormalities such as spinal cord compression have the potential to cause false-positive clinical interpretations.

In 28 of the 37 dogs (76%) a degree of intervertebral disk degeneration was seen with complete disk degeneration in half of these dogs. Disk-associated spinal cord compression with deviation or distortion of the spinal cord was seen in 11 dogs (30%) with multiple sites of spinal cord compression in 4 of them. This incidence is somewhat higher in comparison with the study of da Costa.[8] This difference can probably be attributed to the larger proportion of older dogs in the study reported here. This hypothesis is fed by the fact that intervertebral disk degeneration and disk-associated spinal cord compression were significantly associated with higher age. This is in agreement with different human studies reporting age related degenerative disk disease and cervical spinal cord compression in asymptomatic patients.[9-13] Only 3 of the 37 dogs (8%) of this study showed dorsal spinal cord compression. Dorsal spinal cord compression can be caused by ligamentum flavum hypertrophy, hypertrophy of the articular facets or bony laminar changes.[17] Because none of the dogs was available for pathologic examination, we can only hypothesize about the exact nature of this finding. Since

MR images in the transversal and dorsal plane did not show any abnormalities of the articular facets or laminar malformations, the dorsal compressions were attributed to different degrees of ligamentum flavum hypertrophy. The clinical significance of this radiological finding is unclear, although some authors believe it is significant.[18] Also in agreement with different human studies, intervertebral disk degeneration and spinal cord compressions were significantly associated with the localization of the assessed intervertebral disk space with the more caudal intervertebral disk spaces (e.g. C5-C6 and C6-C7) being more severely affected.[9-13] This is of major importance because several large breed dogs are predisposed to neurological syndromes affecting the caudal cervical region.[17,19] The high frequency of these findings can cause major difficulties in the judgment of clinical significance of abnormalities on MR images. A possible explanation why the more caudal intervertebral disk spaces are more frequently affected can be situated in the difference in shape of the articular facets in the caudal cervical region between large and small dog breeds.[20] Large breed dogs have a significantly higher incidence of concave articular facets in the caudal cervical spine when compared to small breed dogs.[20] These concave shaped articular facets facilitate axial rotational motion.[20,21] Axial rotational motion is considered to be the main force leading to intervertebral disk degeneration in nonchondrodystrophic dogs, more so than axial compression, with subsequent protrusion of the outer annulus fibrosus.[22] Doberman Pinschers and male animals are considered to be predisposed to develop degenerative neurological syndromes affecting the caudal cervical region.[16,17,19] In this study, intervertebral disk degeneration and spinal cord compression were not significantly affected by breed or gender. Only the occurrence of vertebral body abnormalities was associated with the Doberman Pinscher as breed. These abnormalities were in each case characterized by a flattening of the cranioventral border of the vertebral body. Vertebral body abnormalities were seen in 7 of the 20 Doberman Pinschers (35%). This is in agreement with a study of Burbridge where a third of Doberman Pinschers had abnormally shaped caudal cervical vertebrae before 16 weeks of age.[23] The relationship between the occurrence of these vertebral abnormalities and the development of cervical myelopathy at a later moment in life is unclear. Since the occurrence of vertebral abnormalities was not associated with higher age category in these clinically normal dogs, it can be suggested that these abnormalities are not necessarily associated with the development of clinical signs at a later age. In 2 of the 37 dogs (5%) a hyperintense intramedullary signal change on T2- weighted images was seen. There exists uncertainty about the diagnostic and prognostic value of this finding. Hyperintense intramedullary signal changes are considered as a non specific finding.[24] They probably reflect a wide spectrum of

possible reversible and irreversible changes of the spinal cord parenchyma and may indicate edema, inflammation, vascular ischemia, gliosis, or myelomalacia.[25] A veterinary study suggested that this finding could be of important diagnostic value to differentiate between clinically affected and clinically normal dogs.[8] However, several human studies have described the occurrence of hyperintense signal changes in asymptomatic persons.[14,15] The results of one of these human studies suggested that this hyperintensity significantly predicted the progression from asymptomatic to clinically significant spinal cord compressions over time.[15] However, the 2 dogs with a hyperintense intramedullary signal were still clinically normal 18 months after the MRI examination.

Several significant correlations were noticed between the different assessed parameters. The highest of these existed between intervertebral disk degeneration and disk-associated spinal cord compression. This finding is not unexpected and is in agreement with human findings.[12] It indicates that a degenerated disk will demonstrate a higher tendency to cause spinal cord compression when compared to a non degenerated disk.

It is important to emphasize that only 2 breeds were investigated in this study. These 2 breeds are not representative for the whole canine population and it is possible that different small breed dogs will demonstrate another spectrum, frequency and distribution of abnormalities.[26] The selected breeds only represented animals with a similar body conformation with and without known predispositions to neurological syndromes affecting the caudal cervical region.

Conclusions

The results of this study indicate that a wide variety of abnormalities seen on cervical MRI may be clinically non-significant in Doberman Pinschers and English Foxhounds and that these abnormalities are seen commonly in the caudal cervical region of these breeds. This study further suggests that such lesions are part of the normal, or at least common, aging process of spinal degeneration. Therefore, caution should be taken with attributing clinical signs to structural changes seen on MRI. This is of particular importance in the clinically important caudal cervical region of large breed dogs. Randomized, blinded studies are necessary to determine the prevalence of false-positive interpretations of MRI studies of the cervical spine in clinically unaffected dogs and to investigate the use and development of diagnostic tools to differentiate between clinical relevant and clinical irrelevant spinal cord compressions seen on MRI. Such studies are currently ongoing.

Footnote: [a] Magnet: Airis Mate, Hitachi, Japan.

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Chapter 1.2

INTRA-AND INTEROBSERVER AGREEMENT OF LOW-FIELD MAGNETIC RESONANCE IMAGING IN DOGS WITH AND WITHOUT CLINICAL SIGNS OF DISK ASSOCIATED WOBBLER SYNDROME: A RANDOMIZED, BLINDED STUDY

INTRA –AND INTEROBSERVER AGREEMENT OF LOW-FIELD MAGNETIC RESONANCE IMAGING IN DOGS WITH AND WITHOUT CLINICAL SIGNS OF DISK ASSOCIATED WOBBLER SYNDROME: A RANDOMIZED, BLINDED STUDY

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Summary

The objectives of this study were to determine inter –and intraobserver agreement of cervical low-field magnetic resonance imaging (MRI) studies of dogs with and without clinical signs of disk associated wobbler syndrome (DAWS) and to evaluate the occurrence of false positive and false negative clinical assessments.

Forty-four dogs were prospectively investigated. These consisted of dogs of different breeds with DAWS (n = 21), clinically normal age-matched Doberman Pinschers (n =12), and clinically normal age-matched English Foxhounds (n = 11). For each dog, MRI of the cervical vertebral column was performed. The MRI studies were presented in a randomized sequence to four board-certified radiologists, blinded to clinical status and signalment. First the observers assessed the following criteria: disk degeneration, disk associated- and dorsal compression, intraspinal signal intensity (ISI), vertebral body abnormalities, and new bone formation. Second, they classified each MRI study as suspected to originate from a clinically affected or unaffected dog. κ and weighted κ statistics were used to evaluate inter –and intraobserver agreement.

There was good interobserver agreement in rating disk degeneration and vertebral body abnormalities. Moderate interobserver agreement was noted in rating disk associated compression, dorsal compression, ISI changes, new bone formation, and suspected clinical status. There was very good intraobserver agreement in rating disk degeneration, disk associated compression, ISI changes, vertebral body abnormalities, and suspected clinical status. There was good intraobserver agreement in rating dorsal compression and new bone formation. Two of the 21 patients were erroneously categorized as clinically normal and 4 of the 23 clinically normal dogs were erroneously categorized as clinically affected.

Some variability exists between different observers and MRI of the cervical spine can lead to false positive and false negative clinical assessments.

Introduction

Wobbler syndrome refers to a collection of disorders of the caudal cervical vertebrae and intervertebral disks of large breed dogs resulting in progressive spinal cord compression.[1] A large variety of lesions with different proposed etiologies have been attributed to the wobbler syndrome and many synonyms are found in the literature.[2-9] All these different clinical entities result in the same clinical signs, varying from cervical hyperesthesia to tetraplegia. The most common presentation is a gait disturbance. A broad-based hind limb ataxia and/or paresis of the pelvic limbs is usually noted, sometimes in combination with a short stilted gait of the thoracic limbs.[1,10] The term wobbler only refers to the characteristic 'wobbling' hind limb ataxia.[1] Over years a few separate entities have been recognized based on typical signalment and pathological changes.[11] The most typical and predominant of these syndromes is the disk associated wobbler syndrome (DAWS).[1] This is particularly seen in middle-aged to older large breed dogs. The Doberman Pinscher is overrepresented. In DAWS, caudal cervical spinal cord compression results from the protrusion of one or more intervertebral disks, and from generally mild vertebral malformations, frequently in combination with dorsal compression resulting from hypertrophy of the ligamentum flavum.[1] Until recently, plain radiography, myelography and computerized tomography, alone or in combination have been utilized to confirm a diagnosis of DAWS.[10] The last decade, the use of magnetic resonance imaging (MRI) is increasing.[12,13] This is an diagnostic alternative because it is a safe and non-invasive procedure, involves no radiation, obtains images in multiple anatomic planes without the need for reconstruction, and provides superior resolution of soft-tissue structures.[14] Excellent sensitivity (a low prevalence of false-negative findings) has been reported for MRI in the identification of neural compression by mechanical lesions in the vertebral canal.[12,13] However, the important issue of specificity (the prevalence of false-positive findings) needs clarification. Recent veterinary studies have demonstrated the occurrence of cervical spinal cord compression in clinically normal Doberman Pinschers and English Foxhounds.[15,16] This finding was associated with higher age and the more caudally located intervertebral disk spaces. It was suggested that these asymptomatic compressions were probably part of the common aging process of spinal degeneration.[16] In the present study, the low-field MRI studies of dogs that had both a radiological diagnosis of DAWS and well defined clinical signs associated with the abnormality were mixed with the MRI studies of age-matched clinically normal Doberman Pinschers and English Foxhounds. These images were randomly interpreted by four independent board-certified radiologists. The purpose of this study was to

evaluate the inter- and intraobserver agreement for different criteria assessed on low-field MRI and to quantify the frequency of false positive and false negative clinical assessments in a selected population of dogs.

Materials and Methods

Animals

Forty-four dogs were prospectively studied. The experiment was conducted in accordance with the guidelines of the Animal Care Committee of the University of Ghent. Written owner consent was obtained prior to study enrollment. Three groups of dogs were studied. The first group consisted of 21 dogs of different breeds with clinical signs and imaging findings compatible with a diagnosis of DAWS. Sixteen of these dogs were Doberman Pinschers. Other breeds included in this group were the Dalmatian (n = 2), Whippet (n = 2) and the Weimaraner (n = 1). The clinical signs varied from only cervical hyperesthesia (n = 3) to ambulatory paraparesis/ataxia with or without cervical hyperesthesia (n = 5), ambulatory tetraparesis/ataxia with or without cervical hyperesthesia (n = 10), and non-ambulatory tetraparesis with or without cervical hyperesthesia (n = 3). This group consisted of 10 males and 11 females, between 4.6 and 10.75 years old (mean 7.8 years; median 7.4 years).The second group consisted of 12 age-matched, client-owned, clinically normal Doberman Pinschers. This breed was selected and included because of their known predisposition to DAWS.[1] This group included 6 males and 6 females, between 4.6 and 8 years old (mean 6.3 years; median 6 years).The third group consisted of 11 age-matched client (n = 9) and laboratory-owned (n = 2) clinically normal English Foxhounds. This breed was selected and included because of their comparable body conformation and activity-level to Doberman Pinschers and the fact that this breed is not predisposed to neurological syndromes affecting the caudal cervical vertebral canal and spinal cord. This group included 5 males and 6 females, between 4.4 and 12 years old (mean 6.9 years; median 6 years). In all dogs a physical and complete neurological examination, complete blood cell counts, and serum biochemistry analyses were performed. All included Doberman Pinschers underwent an additional echocardiographic examination and standardized mucosal bleeding times. All clinically normal English Foxhounds and 11 of the 12 clinically normal Doberman Pinschers underwent a new physical and complete neurological examination between 16 and 18 months after the initial MRI examination. The goal of this second neurological examination was to determine if recorded MRI abnormalities in clinically normal dogs should be regarded as truly asymptomatic or rather presymptomatic. All neurological examinations were performed by the same person.

MR imaging protocol

A permanent, 0.2 Tesla (T) magnet [a] was used to perform MRI in all dogs. All MRI examinations were performed at the first authors' institution. All MRI examinations were performed under general anesthesia. Anesthesia was induced with propofol and maintained by isoflurane in oxygen. Dogs were positioned in dorsal recumbency with head and neck extended. The forelimbs were fixed parallel to the thoracic wall. The cervical spine was positioned in a joint coil (circular transmit-receive coil) with an inner diameter 19 cm. T1 weighted spin echo and T2 weighted fast spin echo studies were performed in all dogs in a sagittal, dorsal and transverse plane. The images of this last plane were aligned perpendicular to the cervical spine. The spine was imaged from the second (C2) to the seventh cervical vertebra (C7) in the sagittal and dorsal plane and from the fourth (C4) to C7 in the transverse plane. In all spines, the field of view was 29 cm in the sagittal images, 24 cm in the dorsal plane and 20 cm in the transverse plane. Slice thickness was 4mm in the sagittal and dorsal images and was 3 mm in the transverse sequences with no interslice gap in all studies.

Observers

The 44 original low-field MRI studies and 11 copies of scans were presented in a randomized sequence, to 4 independent board-certified radiologists from 4 different institutions . The observers had no knowledge of the identity or clinical status of the subject or patient. The radiologists assessed and graded the cases according to defined criteria. For this purpose, they were provided with written instructions and example figures. The MRI findings were reported by answering a predetermined questionnaire.

Interpretation of MR images

The MRI studies were interpreted in two ways. First, the observers had to assess and grade several criteria. These criteria were assessed and graded in accordance with existing veterinary literature.[15,16] Second, the four observers were asked to classify each MRI study as suspected to originate from a clinically affected (DAWS) or a clinically normal dog. The following criteria were assessed on the MR images: disk degeneration, disk-associated spinal cord compression, dorsal spinal cord compression, spinal cord intensity (ISI) changes, vertebral body abnormalities, and new bone formation (spondylosis deformans). On sagittal and transversal images, intervertebral disk spaces C2-C3 to C6-C7 and C4-C5 to C6-C7 were evaluated, respectively. Using the fact that disk degeneration is associated with decreased signal intensity on T2-weighted images [12], assessment of intervertebral disk degeneration was

subjectively evaluated on the basis of the signal intensity of each intervertebral disk on midsagittal T2-weighted images. A non degenerated disk (score 0) was assumed to demonstrate a homogenous hyperintense signal; partial disk degeneration (score 1) was assumed when there was heterogeneous loss of the hyperintense signal; complete disk degeneration (score 2) was assumed when there was a complete loss of the hyperintense signal. Disk-associated (ventral) spinal cord compression was assessed on the midsagittal and where available confirmed on the transversal (C4-C7) T2-weighted images. This criterium was classified as follows: score 0, no compression; score 1, partial ventral subarachnoid space compression; score 2, complete ventral subarachnoid space compression without spinal cord compression; score 3, spinal cord compression with deviation or distortion of the spinal cord. Dorsal spinal cord compression was evaluated on the same images and with the same classification as disk-associated (ventral) spinal cord compression. Evaluation of ISI changes were based on the relative increase in signal on T2-weighted images and/or decrease in signal on T1-weighted images when compared with the surrounding spinal cord parenchyma. Vertebral body abnormalities were evaluated on the midsagittal T1-weighted images. Vertebral body abnormalities were defined as flattening of the cranioventral border to a triangular shape of the vertebral body. New bone formation was subjectively assessed as being present or absent. A consensus opinion for suspected clinical status was obtained when at least 3 of the 4 observers agreed that the severity of the MRI features would probably cause clinical signs.

Data analysis

κ and weighted κ statistics[17] were used to summarize the inter- and intraobserver agreement in rating the MR images. Weighted κ values were used in case of ordinal data with more than two possible scores (disk degeneration, disk associated- and dorsal compression). Interobserver agreement was based on 44 original measurements of each observer. Intraobserver agreement was based on 11 different, replicate measurements for each reader. The strength of agreement was interpreted on the basis of the κ values suggested by Altman[18], as adapted from the method of Landis and Koch[17]: κ-values of 0.81 – 1.00 indicated very good agreement; 0.61 – 0.80, good agreement; 0.41 – 0.60, moderate agreement; 0.21 – 0.40, fair agreement; and 0.20 or lower, poor agreement. Sensitivity and specificity were calculated globally and for each observer seperately. The three clinical groups were compared for all MRI parameters using the sum of the assessments of the different intervertebral disk spaces over all observers. The three clinical groups were first compared globally by the Kruskall-

Wallis test, next pair wise by the Wilcoxon rank sum test. For a pair wise comparison, significance is claimed when $P<0.0133$ (Bonferroni correction). The effect of the MRI criteria on the clinical status (0- 1) was evaluated by logistic regression, using odds ratios summary statistics. We compared both clinically affected with all clinically normal dogs (clinically normal Doberman Pinschers + clinically normal English Foxhounds) and clinically affected dogs with clinically normal Doberman Pinschers. Significance is claimed when $P<0.025$ (Bonferroni correction). If no Bonferroni correction was used, significance is claimed when $P<0.05$ (global comparisons).

Results

For interobserver analysis, the 44 original MR examination cases were rated by all 4 readers. Each observer read 11 different cases twice for assessment of intraobserver agreement. If a part of the image could not be interpreted, the respective intervertebral disk spaces were not included in the statistical analysis. The main artifact encountered in this study was the truncation artifact (Figure 1). None of the clinically normal dogs developed clinical signs of cervical hyperesthesia or myelopathy during the study period.

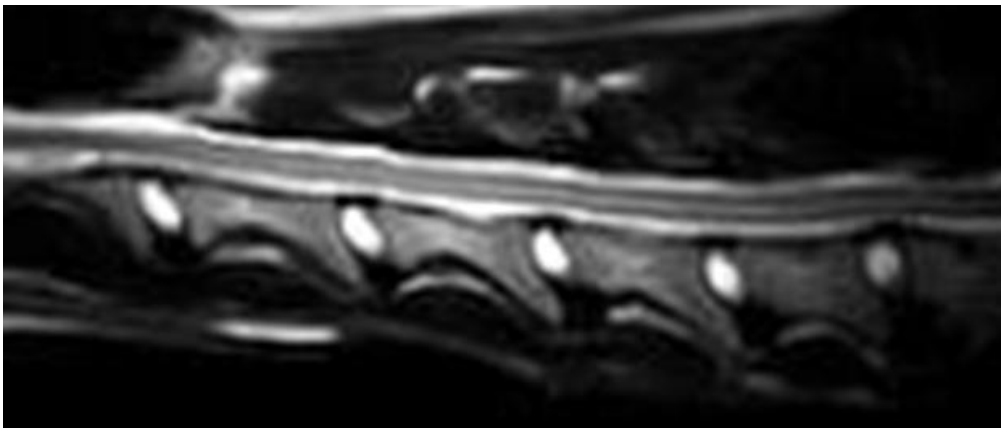

Figure 1. Sagittal T2-weighted image of a clinically normal Doberman Pinscher. A truncation artefact can be appreciated. This appears commonly as a bright line located centrally along the length of the spinal cord and can be mistaken for several pathologic conditions including a dilated central canal or a syrinx.

Interobserver agreement

κ or weighted κ values for both overall interobserver agreement and interobserver agreement between each observer are shown in Table 1. Overall, there was good agreement in rating disk degeneration (κ = 0.67) and vertebral body abnormalities (κ = 0.77). There was moderate agreement in rating disk associated compression (κ = 0.56), dorsal compression (κ = 0.51), ISI changes (κ = 0.41), and new bone formation (κ = 0.54). For ordinal findings (disk degeneration, ventral- and dorsal compression), there was typically a difference of only one grade between the observers. In 29 of the 44 cases all the observers agreed on the suspected clinical status of each individual animal. In 12 cases 3 observers, and in 3 cases only 2 observers agreed on the suspected clinical status of the dog. This resulted in a moderate overall interobserver agreement (κ = 0.54) for suspected clinical status.

Table 1. Interobserver agreement measured by using κ and weighted κ statistics and based on 44 MR examination cases

Assessed Parameter	Observers 1 and 2	Observers 1 and 3	Observers 1 and 4	Observers 2 and 3	Observers 2 and 4	Observers 3 and 4	Overall
Disk degeneration*	0.77	0.54	0.74	0.65	0.76	0.56	0.67
Disk associated compression*	0.70	0.47	0.62	0.48	0.67	0.44	0.56
Dorsal compression*	0.66	0.41	0.60	0.47	0.57	0.34	0.51
Intraspinal signal intensity	0.52	0.32	0.42	0.42	0.50	0.25	0.41
Vertebral body abnormality	0.95	0.58	0.81	0.64	0.87	0.76	0.77
New bone formation	0.71	0.40	0.38	0.50	0.58	0.66	0.54
Suspected clinical status	0.71	0.40	0.39	0.50	0.58	0.66	0.54

*For the ordinal parameters, weighted κ-coefficients were calculated

Intraobserver agreement

κ or weighted κ values for both overall intraobserver agreement and intraobserver agreement for each observer separately are shown in Table 2. Overall, there was very good agreement in rating disk degeneration (κ = 0.87), disk associated compression (κ = 0.81), ISI changes (κ = 0.82), vertebral body abnormalities (κ = 0.89), and suspected clinical status (κ = 0.91). There was good agreement in rating dorsal compression (κ = 0.77) and new bone formation (κ = 0.73).

Table 2. Intraobserver agreement measured by using κ and weighted κ statistics and based on 11 repeated readings

Assessed Parameter	Observer 1	Observer 2	Observer 3	Observer 4	Overall
Disk degeneration*	1.00	0.83	0.62	1.00	0.87
Disk associated compression*	0.98	0.78	0.49	0.92	0.81
Dorsal compression*	1.00	0.65	0.45	0.89	0.77
Intraspinal signal intensity	1.00	0.56	0.79	0.82	0.82
Vertebral body abnormality	1.00	0.81	0.90	0.88	0.89
New bone formation	1.00	0.65	0.74	0.68	0.73
Suspected clinical status	1.00	0.61	1.00	1.00	0.91

*For the ordinal parameters, weighted κ-coefficients were calculated

Clinical assessment

The percentage of correct and erroneous clinical assessments in the different groups together with the associated sensitivity and specificity for both all observers and each observer separately are shown in Table 3. If for each dog, a consensus opinion for suspected clinical status was obtained when at least 3 of the 4 observers agreed that the severity of MRI features would probably cause clinical signs related to cervical pain or myelopathy, 2 of the 21 (9.5%) patients were erroneously categorized as clinically normal (Figure 2). This occurred in 2 clinically affected Doberman Pinschers. One of these dogs demonstrated hind limb ataxia

without paresis and the other dog was tetraplegic since one day. Four of the 23 clinically normal dogs (17.4%) were erroneously categorized as clinically affected (Figure 3). This occurred in 2 clinically normal Doberman Pinschers and 2 clinically normal English Foxhounds. In 3 of the 44 dogs (6.8%) no consensus interpretation was reached (1 clinically normal Doberman Pinscher and 2 clinically normal English Foxhounds). In these 3 dogs, 2 observers suspected the dogs to be clinically affected, while the 2 other observer suspected the dogs to be clinically normal. The sensitivity of suspected clinical status on low-field MRI for the different observers ranged from 0.76 to 0.90, with an overall sensitivity of 0.85. The specificity of suspected clinical status on low-field MRI for the different observers ranged from 0.65 to 0.83, with an overall specificity of 0.71.

Table 3. Number and percentage of erroneous and correct clinical interpretations in the different groups together with the associated sensitivity and specificity based on 44 MRI examination cases

Assessed dogs	Observer 1	Observer 2	Observer 3	Observer 4	Overall
21 Patients					
Rated as affected	19 (90)	18 (86)	16 (76)	18 (86)	19 (90)
Rated as unaffected	2 (10)	3 (14)	5 (24)	3 (14)	2 (10)
12 Clinically normal DP					
Rated as affected	3 (25)	4 (33)	2 (17)	2 (17)	2* (17)
Rated as unaffected	9 (75)	8 (67)	10 (83)	10 (83)	9* (75)
11 Clinically normal FH					
Rated as affected	5 (45)	3 (27)	6 (55)	2 (18)	2* (18)
Rated as unaffected	6 (55)	8 (73)	5 (45)	9 (82)	7* (64)
Sensitivity	0.90	0.86	0.76	0.86	0.85
Specificity	0.65	0.70	0.65	0.83	0.71

DP = Doberman Pinscher, FH = Foxhound, ( ) = %, *No ¾ consensus interpretation was reached in 1 clinically normal Doberman Pinscher and 1 clinically normal Foxhound

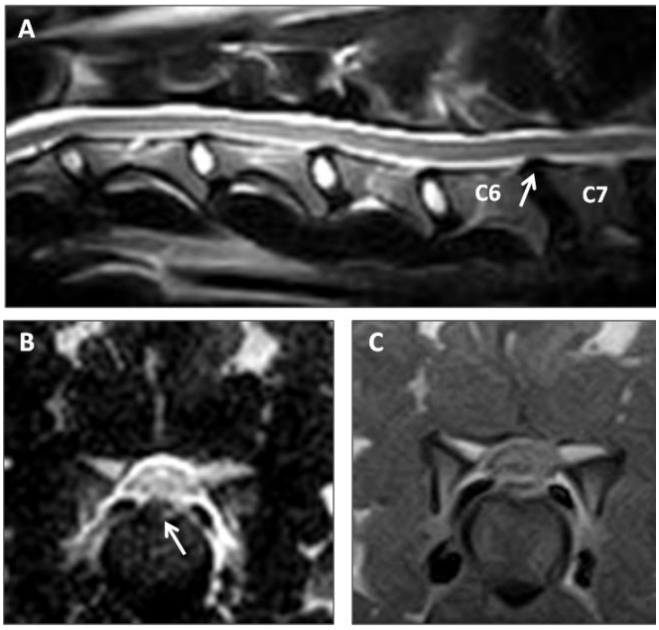

Figure 2. (A) Sagittal T2-weigthed MR image of a clinically affected Doberman Pinscher assessed by all 4 observers as clinically normal. Complete disk degeneration with mild disk-associated spinal cord compression (arrow). (B) Transversal T2-weighted and (C) transversal T1-weighted image at the level of C6-C7 show mild disk-associated spinal cord compression.

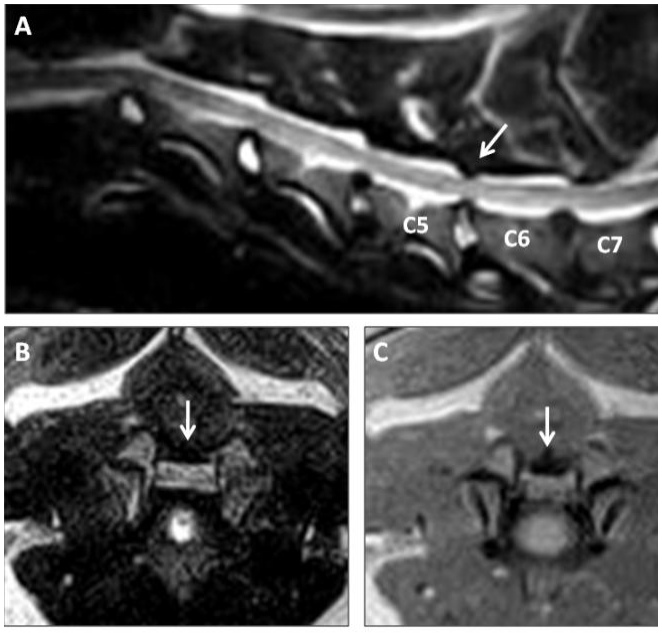

Figure 3. (A) Sagittal T2-weighted MR image of a clinically normal Foxhound assessed by all 4 observers as clinically affected. Disk-associated spinal cord compression between C5-C6 and C6-C7 and dorsal spinal cord compression between C5-C6 (arrow). (B) Transversal T2-weighted and (C) transversal T1-weighted image at the level of C5-C6 show ventral and dorsal (arrow) cord compression.

Difference between the assessed criteria

For all the assessed parameters, with the exception of new bone formation between clinically affected dogs and clinically normal English Foxhounds, there was a significant difference between all 3 clinical groups and between the clinically affected dogs and the 2 groups of clinically normal dogs separately (Table 4). For none of the assessed parameters, there was a significant difference between clinically normal English Foxhounds and clinically normal Doberman Pinschers. The odds ratios demonstrate that the presence of an abnormality, eventually associated with a higher grade (e.g. disk degeneration, disk associated and dorsal compression) significantly increased the odds of being clinically affected (Table 4).

The highest odds ratios were noted for the presence of ISI changes and vertebral body abnormalities (Table 4).

Table 4. *P*-values for global difference and between clinical groups separately together with the odds ratios between clinically affected and clinically unaffected dogs

Assessed Parameter	All groups	*Groups 1 and 2	*Groups 1 and 3	*Groups 2 and 3	OR clinically affected vs. unaffected (*P*-value)	
Disk degeneration	0.0014	0.0021	0.0050	0.42	1.25	(0.0025)
Disk associated compression	0.00025	0.00026	0.0027	0.064	1.20	(0.0007)
Dorsal compression	0.00040	0.00060	0.0024	0.69	1.28	(0.0010)
Intraspinal signal intensity	0.00005	0.00012	0.00093	0.54	2.88	(0.0007)
Vertebral body abnormality	0.0014	0.013	0.0011	0.29	2.10	(0.0015)
New bone formation	0.0061	0.0029	0.050	0.25	1.64	(0.0098)

Group 1 = Clinically affected dogs, Group 2 = Clinically normal Doberman Pinschers, Group 3 = Clinically normal Foxhounds, OR = Odds Ratio,* For pair wise comparisons, significance claimed when $P<0.0133$ (Bonferroni correction).

Discussion

In this study, we have determined the inter –and intraobserver agreement of low-field MRI assessments of a selected population of dogs with and without clinical signs of DAWS. Further, we have identified the frequency of false positive and false negative clinical MRI interpretations in this studied population. To our knowledge, no analogous studies have been done in veterinary medicine.

We found that typically, intraobserver agreement was very good and interobserver reliability was moderate except for vertebral body abnormalities and disk degeneration. For these two parameters the interobserver agreement was considered good. Thus although each reader was very consistent in interpreting the different MRI studies, some variability existed between the different readers despite standardized definitions and reader expertise. These findings are in agreement with comparable studies[13,19-22] where intraobserver agreement is generally consistently higher when compared with interobserver agreement. Since the 4 observers were from 4 different institutions, this moderate interobserver agreement can reflect a different approach to the interpretation of MRI studies. For the ordinal criteria (disk degeneration, disk associated –and dorsal compression), when there was a disagreement in interpretation, it generally involved a slight variation in the rating of the severity of a finding rather than a difference of opinion as to whether or not the finding was present. The lowest intraobserver agreement was noted for the presence of new bone formation. This can be explained by the limited ability of MRI to enable detection of signal from dense cortical bone.[23] It is suggested that bony spurs large enough to be filled with bone marrow, can be easier detected.[23] The lowest interobserver agreement was noted for ISI changes. A possible reason for this could be the fact that all MR studies were performed with a low-field MR device (0.2 T). In human medicine, there is some discussion and controversy about the relative advantages of high-field over low-field MR units. Several randomized, blinded studies have demonstrated that the use of high-field MR units results in images with higher signal-to-noise ratios, contrast-to-noise ratios and better subjective global quality of the images.[24-27] These advantages would be of particular importance in the assessment of the smallest intramedullary lesions[27], such as ISI changes. Another disadvantage of low-field MR imaging are the prolonged scanning times to complete a study. For this reason, we only performed transversal images from the caudal cervical region (C4-C7) and not from the entire cervical vertebral column. However, low-field MR imaging is associated with lower costs related to purchase and maintenance and the

advantage of access to the patient during the examination[27]. Further, the mentioned randomized, blinded studies did not demonstrate a significant difference in diagnostic accuracy between low-field and high-field MR units[24,26,27] and it is known that high-field systems are more sensitive to certain artifacts, such as motion artifacts, chemical shift artifacts and susceptibility artifacts[26,28,29]. Another possible contributing factor to the low interobserver agreement for ISI changes could be the occurrence of a truncation artifact in some of the included MR studies (Figure 1). Most commonly, truncation artifact appears as a dark or bright line located centrally along the length of the spinal cord[29]. This artifact can be mistaken for several pathologic conditions including a dilated central canal or a syrinx[29]. It occurs adjacent to areas of abrupt signal intensity change, such as between the spinal cord and CSF. Truncation artifact can be eliminated by using at least 192 phase-encoding steps, decreasing the field of view, or switching the phase- and frequency encoding directions[30].

Since previous work has revealed a high incidence of MRI abnormalities of the cervical spine in clinically normal dogs[15,16], it was not surprising that a substantial part of the clinically normal dogs was erroneously classified as clinically affected (Figure 3). This resulted in an overall specificity of 0.71 and suggests that caution should be taken with attributing clinical signs to structural abnormalities seen on MR images. This is especially important in large breed dogs, because several of these breeds are prone to the development of degenerative neurological syndromes affecting the caudal cervical region. More surprising was the fact that, depending on the observer, even up to 5 of the 21 clinically affected dogs were erroneously categorized as clinically normal (Figure 2). This resulted in an overall sensitivity of 0.85, which is lower than expected in advance. These findings suggest that abnormalities seen on MRI not always correlate with clinical signs and that minimally degenerative changes can be sufficient to cause clinical signs in predisposed dogs, while other dogs apparently can tolerate more pronounced degenerative changes without the development of clinical signs. This is in agreement with a recent veterinary study about the morphologic and morphometric MRI features of Doberman Pinschers with and without clinical signs of cervical spondylomyelopathy.[15] This study demonstrated more pronounced MRI abnormalities in some clinically normal Doberman Pinscher when compared with some affected dogs.[15]In humans, relative vertebral canal stenosis is the single most important static factor to predispose people to the development of clinically relevant cervical spondylomyelopathy.[31] In absolute stenosis, the vertebral canal diameter is sufficiently narrow to cause direct neural compression.[32] Relative stenosis implies a diameter that is less than ‘normal’ but does not

cause neural compression in itself. It carries a risk of becoming clinically significant on the development of space-occupying conditions of the vertebral canal[32], such as age related intervertebral disk degeneration and protrusion.[33] A similar relationship has been suggested to occur also in dogs.[15,33,34]

There was a significant difference for all assessed criteria between the clinically affected dogs and both groups of clinically normal dogs. The most significant difference together with the highest odd ratios was noted for the occurrence of ISI changes. This is in agreement with the study of da Costa[15] and suggests that the presence of ISI changes can be considered as a reliable and strong indicator of clinically relevant spinal cord compression seen on MRI.

A limitation of this study is the fact that MRI was the only diagnostic modality used to compare imaging studies of clinically affected and unaffected dogs. It is known that radiographic abnormalities in clinically normal subjects can also be seen with plain radiography, myelography, computed tomography, and computed tomography-myelography.[35] Since most current methods of evaluating the cervical spine (i.e., myelography and computed tomography-myelography) are invasive[10,36], comparative study of asymptomatic animals is more difficult. It should also be emphasized that MR accurately images the anatomy of the cervical spinal cord and that abnormal findings in clinically normal animals probably represent what we term clinical false results and not true anatomical false results.

Conclusions

The results of this study showed a very good intraobserver agreement for most assessed criteria but a higher variation in the assessment of the same studies between different observers. Further, we have demonstrated that low-field MRI studies of the cervical vertebral column and spinal cord can lead to a substantial number of false positive and to a lesser degree to false negative clinical assessments. Further work is needed and is ongoing to differentiate between clinically relevant and irrelevant spinal cord compressions seen on MRI and to provide further information on the existence and recognition of potential anatomical risk factors, such as relative canal stenosis.

Footnote: [a] Magnet: Airis Mate, Hitachi, Japan.

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Chapter 2

DIFFERENTIATION BETWEEN CLINICALLY RELEVANT AND IRRELEVANT SPINAL CORD COMPRESSIONS

Chapter 2.1

MORPHOMETRIC DIMENSIONS OF THE CAUDAL CERVICAL REGION IN DOBERMAN PINSCHERS WITH CLINICAL SIGNS OF DISK ASSOCIATED WOBBLER SYNDROME, CLINICALLY NORMAL DOBERMAN PINSCHERS AND CLINICALLY NORMAL ENGLISH FOXHOUNDS

MORPHOMETRIC DIMENSIONS OF THE CAUDAL CERVICAL VERTEBRAL COLUMN IN DOBERMAN PINSCHERS WITH CLINICAL SIGNS OF DISK ASSOCIATED WOBBLER SYNDROME, CLINICALLY NORMAL DOBERMAN PINSCHERS AND CLINICALLY NORMAL ENGLISH FOXHOUNDS

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Summary

Spinal cord compressions occur in clinically normal dogs. Little is known about morphometric dimensions of the cervical vertebral column in dogs with and without clinically relevant spinal cord compressions.

It was hypothesized that stenosis of the vertebral canal occurs more often in Doberman Pinschers with disk associated wobbler syndrome (DAWS) and a certain degree of spinal cord compression or canal compromise should be reached before clinical signs will occur.

Client-owned clinically normal Doberman Pinschers (n=20), Foxhounds (n=17), and Doberman Pinschers with clinical signs of DAWS (n=17) were prospectively studied. All dogs underwent magnetic resonance imaging of the cervical vertebral column**.** To evaluate vertebral canal stenosis, the canal occupying ratios of the spinal cord and epidural fat/ cerebrospinal fluid (CSF)-column were calculated from C5 to C7. To evaluate degree of spinal cord compression and amount of canal compromise, the compression ratio, remaining spinal cord and epidural fat/CSF-column area, and vertebral canal and dorsoventral vertebral canal compromise ratios were calculated at the site of most severe compression.

For each canal occupying ratio, there was a significant higher value, at the level of C7, for clinically affected Doberman Pinschers compared with clinically normal Foxhounds. The remaining spinal cord area was significantly smaller in dogs with clinically relevant spinal cord compression.

Stenosis of the caudal cervical vertebral canal occurs more often in Doberman Pinschers with DAWS. The remaining spinal cord area can be used to differentiate clinically relevant and irrelevant spinal cord compression.

Introduction

Disk associated wobbler syndrome (DAWS) is the most common and typical form of canine cervical spondylomyelopathy.[1] In this disorder, caudal cervical spinal cord compression is typically caused by protrusion of one or more intervertebral disks, sometimes in combination with dorsal compression resulting from hypertrophy of the ligamentum flavum and generally mild vertebral body malformations.[1] This syndrome occurs in several adult to older large breed dogs. The adult Doberman Pinscher is overrepresented.[1,2] This disorder can be diagnosed by a variety of imaging modalities, such myelography, computed tomography-myelography, and magnetic resonance imaging (MRI).[2] In human medicine, MRI is considered as the imaging modality of choice to diagnose most spinal cord disorders.[3] This diagnostic tool is also increasingly used in veterinary medicine. The most important advantages of MRI are the safe and non-invasive nature, the absence of radiation, the possibility to obtain images in multiple anatomic planes, and the superior resolution of soft-tissue structures.[4] A potential disadvantage of MRI in the evaluation of the vertebral column is the possibility of over-interpretation.[4] Several veterinary and human studies have demonstrated the occurrence of cervical MRI abnormalities in clinically normal subjects.[5-8] A recent randomized, blinded trial compared the low-field MRI studies of dogs with clinical signs of DAWS with those of clinically normal Doberman Pinschers and English Foxhounds.[9] The results of this study demonstrated that low-field MRI of the cervical vertebral column can lead to false positive and false negative clinical assessments. Several clinically normal dogs demonstrated spinal cord compression, while some dogs with signs of DAWS demonstrated only mild MRI abnormalities.[9] Currently, it is unknown why some dogs can tolerate cervical spinal cord compression while other dogs develop distinct clinical signs with only subtle MRI abnormalities. Further, there is little information available about the degree of spinal cord compression or amount of vertebral canal compromise necessary to result in clinical signs of cervical hyperesthesia or cervical myelopathy. In the present study, we hypothesized that the relative size of the vertebral canal and the relative amounts of vertebral canal compromise and spinal cord compression were different between dogs with and without clinically relevant spinal cord compression. For this purpose, several vertebral column dimensions were evaluated in the caudal cervical region of Doberman Pinschers with clinical signs of DAWS, clinically normal Doberman Pinschers and clinically normal English Foxhounds. To avoid individual variations, ratios of measurements were used instead of absolute measurements.

The primary goals of this study were to investigate if the relative size of the vertebral canal in Doberman Pinschers with clinical signs of DAWS was smaller than the relative size of the vertebral canal calculated in non-affected Doberman Pinschers and English Foxhound dogs and to evaluate if the amount of spinal cord compression and vertebral canal compromise in dogs with clinically relevant spinal cord compression were superior compared to the amount of spinal cord compression and vertebral canal compromise in clinically normal dogs.

Materials and Methods

Animals

Fifty-four dogs were prospectively investigated. The experiment was conducted in accordance with the guidelines of the Animal Care Committee of the University of Ghent. Written owner consent was obtained prior to study enrollment. The dogs were divided in three groups. The first group consisted of 17 client-owned Doberman Pinschers with clinical signs of DAWS. This group consisted of 6 males and 11 females, between 4.4 and 10 years old (median 7.0 years). These dogs demonstrated clinical signs varying from only cervical hyperesthesia (n = 3) to ambulatory paraparesis/ataxia with or without cervical hyperesthesia (n = 5), ambulatory tetraparesis/ataxia with or without cervical hyperesthesia (n = 7), and non-ambulatory tetraparesis with or without cervical hyperesthesia (n = 2). The second group consisted of 20 client-owned clinically normal Doberman Pinschers. This breed was selected and included because of their known predisposition to DAWS.[1,2] This group consisted of 11 males and 9 females, between 1.5 and 8 years old (median 5.0 years). The third group consisted of 17 client (n = 13) and laboratory-owned (n = 4) English Foxhounds. According to the authors, this breed was selected and included because of their comparable body conformation and activity-level to Doberman Pinschers and the fact that there is no known breed predisposition to neurological syndromes affecting the caudal cervical vertebral column. This group consisted of 9 males and 8 females, between 1.5 and 12 years old (median 5.0 years).
In all dogs, a physical and complete neurological examination, complete blood cell counts, and serum biochemistry analyses were performed. All Doberman Pinschers underwent an additional echocardiographic examination and standardized mucosal bleeding times. All owners of the clinically normal dogs were contacted at the end of the study and encouraged to have another neurologic examination performed on their dogs. The goal of this second examination was to determine if recorded MRI abnormalities could be regarded as truly asymptomatic or presymptomatic. All neurologic examinations were performed by the first author (SDD).

Magnetic Resonance Imaging and Measurements

A permanent, 0.2 Tesla magnet [a] was used to perform MRI in all dogs. Dogs were positioned in dorsal recumbency with head and neck extended. The forelimbs were fixed parallel to the thoracic wall. The cervical vertebral column was positioned in a joint coil (circular transmit-receive coil) with an inner diameter 19 cm. T1 weighted spin echo and T2 weighted fast spin

echo studies were performed in all dogs in a sagittal, dorsal and transverse plane. The images of this last plane were aligned perpendicular to the cervical spinal cord. The vertebral column was imaged from C2 to C7 in the sagittal and dorsal plane and from C4 to C7 in the transverse plane. The field of view was 29 cm in the sagittal, 24 cm in the dorsal, and 20 cm in the transverse plane. Slice thickness was 4 mm in the sagittal and dorsal images and 3 mm in the transverse sequences with no interslice gap in all studies.

All MRI studies were evaluated by the first author. Measurements were made directly at the workstation with the available imaging software [b]. The accuracy of the measurement tool was calibrated to 0.001 mm or 0.001 mm^2 for linear and circular measurements, respectively.

To evaluate relative vertebral canal stenosis, the following measurements were made from the fifth (C5) to the seventh cervical vertebra (Figure 1): the cross-sectional area (CSA) of the vertebral canal (CSA-VC) was measured on selected T1-weighted transversal images at the cranial, middle and caudal level of each assessed vertebra. The contour of the vertebral canal was defined as the separation between the hypointense signal from the cortical bone and the hyperintense signal from the epidural fat. If necessary, the canal circumference was extrapolated at the intervertebral foramen by projecting the curvature along the lateral borders of the laminas to the vertebral body/intervertebral disk. At the correspondent T2-weighted transversal images, the CSA of the spinal cord (CSA-SC) and epidural fat/CSF-column (CSA-CSF) were measured. Although an effort was made to measure only the CSF-column, it was not always possible to distinguish the hyperintense signal of epidural fat from the hyperintense CSF signal. For this reason the terminology epidural fat/CSF column will be used in the remainder of the text. From these measurements, the following ratios were calculated at each assessed level:

- Canal occupying ratio of the spinal cord: calculated as CSA-SC divided by CSA-VC.
- Canal occupying ratio of the epidural fat/CSF-column: calculated as CSA-CSF divided by CSA-VC.

These two ratios represent the portion of the vertebral canal that is occupied by the spinal cord or epidural fat/CSF-column and give an indication about the remaining free space available in the vertebral canal.[10]

Since it was the purpose to investigate if the amount of relative vertebral canal stenosis was different between the different groups of dogs, we compared the canal occupying ratios of clinically affected Doberman Pinschers, clinically normal Doberman Pinschers, and clinically normal English Foxhounds.

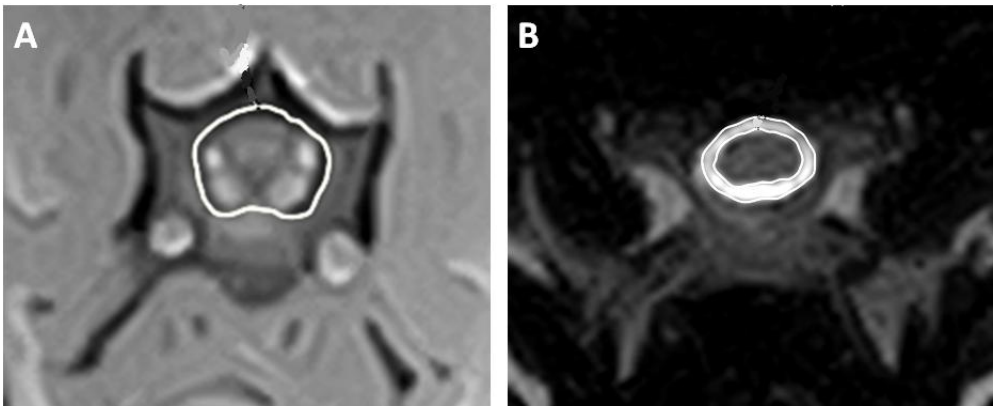

Figure 1. (A) Transversal T1-weighted image of a clinically normal Doberman Pinscher representing measurement of the cross sectional area of the vertebral canal. (B) Transversal T2-weighted image at the corresponding level representing measurement of the cross sectional area of the epidural fat/CSF-column and spinal cord.

To evaluate the degree of spinal cord compression, the site of most pronounced compression was identified at T2-weighted sagittal and transversal images. This was based on the degree of compression of the CSF-column or spinal cord. Spinal cord compression was defined as deviation or distortion of the spinal cord. If no spinal cord or CSF-column encroachment could be identified, the C6-C7 intervertebral disk space was selected. This site was chosen because most cervical spinal cord compressions in clinically normal Doberman Pinschers and English Foxhounds occur at this site.[8] The following values were calculated:

- Compression ratio (Figure 2): calculated as the smallest dorsoventral diameter of the spinal cord divided by the broadest transverse diameter at the same level.[11] A lower value represents increased dorsoventral flattening of the spinal cord.
- Remaining spinal cord area: calculated as the CSA-SC of the compressed area divided by the CSA-SC at the adjacent, non-compressed segment.
- Remaining epidural fat/CSF-column area: defined as the CSA-CSF of the compressed area divided by the CSA-CSF of the adjacent, non-compressed segment.

For the two latter ratios, the adjacent, non-compressed CSA-SC and CSA-CSF were defined as the mean value of the CSA-SC and CSA-CSF cranial and caudal to the compressed segment. Both the cranial and caudal segments were included to adjust for the cervical enlargement of the spinal cord.

To evaluate the degree of vertebral canal compromise, the following values were calculated on transversal T1-weigthed images at the site of maximum compression (Figure 3):

- Vertebral canal compromise ratio: calculated as the protruded disk area, eventually increased with the hypertrophied ligamentum flavum area, divided by the total CSA-VC at the corresponding level.[12]
- Dorsoventral vertebral canal compromise ratio: calculated as the maximum dorsoventral diameter of the protruded intervertebral disk, eventually increased with the maximum dorsoventral diameter of the hypertrophied ligamentum flavum, divided by the total dorsoventral diameter of the vertebral canal at the corresponding level.[12]

The ventral border of the vertebral canal, at the level of the intervertebral disk, was indicated by a horizontal line drawn ventral from the caudal articular facets (Figure 3).

Since it was the purpose to investigate if the degree of compression or vertebral canal compromise was different between dogs with clinically relevant and irrelevant spinal cord compression, we compared the calculated ratios from the site of most pronounced compression of dogs with clinically relevant (Doberman Pinschers with DAWS), clinically irrelevant (clinically normal Doberman Pinschers and English Foxhounds), and clinically normal dogs without spinal cord compression.

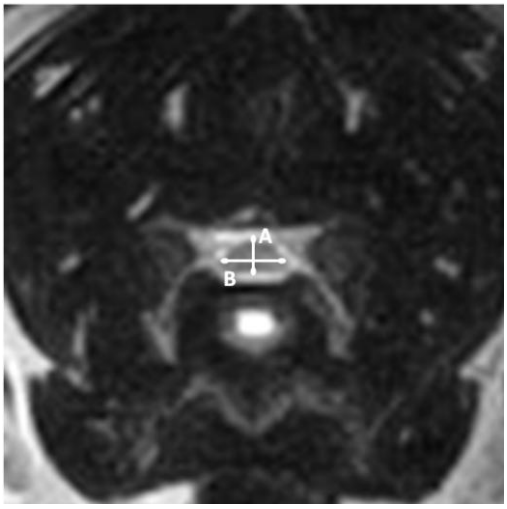

Figure 2. Transversal T2-weighted image of a clinically normal Doberman Pinscher. Compression ratio is defined as the smallest dorsoventral spinal cord diameter (A) divided by the broadest transverse diameter (B) at the same level.

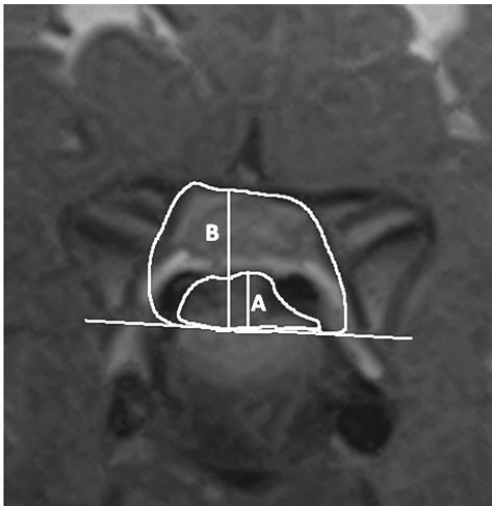

Figure 3. Transversal T1-weigthed image of a clinically affected dog. Vertebral canal compromise ratio: protruded disk area divided by cross sectional area vertebral canal. Dorsoventral vertebral canal compromise ratio: dorsoventral diameter protruded intervertebral disk (A) divided by dorsoventral diameter vertebral canal (B).

Finally, the intervertebral disk widths were measured from C2-C3 to C6-C7 on the midsagittal T2-weighted images (Figure 4). Only non-degenerated intervertebral disks were included for this purpose. Assessment of intervertebral disk degeneration was based on the signal intensity of each intervertebral disk on midsagittal T2-weighted images. A non degenerated disk was assumed to demonstrate a homogenous hyperintense signal.

Since it was the purpose to investigate if intervertebral disk width was different between the different groups of dogs[7], we compared the measurements of clinically affected Doberman Pinschers, clinically normal Doberman Pinschers and clinically normal English Foxhounds.

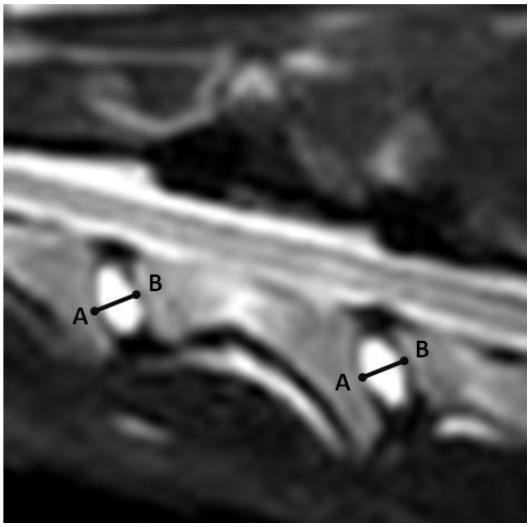

Figure 4. Intervertebral disk width (A-B) measured on midsagittal T2-weigthed images

Intraobserver agreement was tested by repeating the measurements on 20 different MRI studies by the first author. Interobserver agreement was tested by performing the same measurements on the same 20 MRI studies by the second author (IG) . For this purpose, these measurements were performed independently in a randomized sequence and both observers were blinded to signalment and clinical status of the subjects. Only the first measurements from the first author were further used to calculate the ratio values for the different groups of dogs

Statistical Analysis

The effect of group of dog, type of compression (clinically relevant, clinically irrelevant, and no spinal cord compression), assessed vertebrae, gender and age on the different measurements was evaluated by the mixed model with dog as random effect. The global significance level was set at 5%; the significance level for multiple comparisons was adjusted by Bonferroni's method. Data were summarized by their means according to dog group.

Receiver-operator characteristic (ROC) curves were created for remaining spinal cord area between dogs with and without clinical signs of DAWS (Doberman Pinschers and English Foxhounds) and between Doberman Pinschers with and without clinical signs of DAWS (Figure 5). Each value on the ROC curve represents a tradeoff between sensitivity and specificity. Visual inspection of a ROC curve guides in the detection of a value with a high sensitivity and high specificity to discriminate between clinically normal and clinically affected dogs. This value corresponds with the most upper left point on the curve.

To evaluate intra and interobserver reliability, the mean difference, the standard deviation of the difference and the lower –and upper limits of agreement (LOA) were calculated for the respective ratios.

Results

All 17 Doberman Pinschers with clinical signs of DAWS demonstrated spinal cord compression. Additionally, 6 of the 20 clinically normal Doberman Pinschers and 6 of the 17 clinically normal English Foxhounds also demonstrated spinal cord compression on MRI of the cervical vertebral column. Eighteen of 20 clinically normal Doberman Pinschers and 9 of 17 English Foxhounds underwent a new neurologic examination between 16 and 18 months after the MRI examination. These examinations revealed no abnormalities. The owner of 4 other English Foxhounds was available for a telephone interview 9 months after the MRI examination. According to that owner, the dogs were clinically normal. The remaining 2 Doberman Pinschers and 4 English Foxhounds died during the study period for reasons unrelated to this study.

Dimensions related to Vertebral Canal Stenosis

The mean value of each assessed vertebral canal occupying ratio decreased from Doberman Pinschers with clinical signs, over a lower value for clinically normal Doberman Pinschers to the lowest value for clinically normal English Foxhounds (Table 1). This resulted in a significant influence of group of dog for the canal occupying ratio of the spinal cord at the cranial and caudal vertebral body levels and for the canal occupying ratio of the epidural fat/CSF-column at the cranial vertebral body level (Table 2). When looked at the different vertebrae and different groups of dogs seperately, for each assessed canal occupying ratio a significant difference was seen between clinically affected Doberman Pinschers and clinically normal English Foxhounds at the level of C7 (Table 1). For the canal occupying ratio of the epidural fat/CSF-column at the middle aspect of the vertebral body, there was also a significant difference between Doberman Pinschers with and without clinical signs of DAWS (Table 1). There was for each assessed ratio, a significant influence of the respective assessed vertebra (Table 2). The canal occupying ratio of the epidural fat/CSF-column at the caudal vertebral level was significantly larger in female animals compared to male animals. The canal occupying ratio of the spinal cord at the middle vertebral level and the canal occupying ratios of the epidural fat/CSF-column at the cranial and middle vertebral levels were significantly lower in older animals (Table 2). Each increase of age by one month resulted in a decrease of canal occupying ratio value of the spinal cord at the middle vertebral level, and of the epidural fat/CSF-column at the cranial and middle vertebral levels by 0.00025, 0.00048, and 0.00043, respectively.

Table 1. Mean and *P*-values of vertebral canal occupying ratios in Doberman Pinschers with clinical signs of DAWS, clinically normal Doberman Pinschers and English Foxhounds

		Occupying ratio spinal cord				Occupying ratio CSF-column			
Vertebral body level	Group of dogs	Mean	C5	C6	C7	Mean	C5	C6	C7
Cranial	DAWS	0.27	0.26	0.29	0.27	0.52	0.52	0.53	0.51
	DP	0.25	0.25	0.27	0.24	0.49	0.52	0.50	0.46
	FH	0.23	0.23	0.26	0.22	0.47	0.48	0.50	0.44
	P-value DAWS and DP	0.17	0.78	0.16	0.079	0.13	0.78	0.12	0.019
	P-value DAWS and FH	0.0057*	0.064	0.08	0.0008*	0.012*	0.12	0.14	0.0029*
	P-value DP and FH	0.10	0.091	0.67	0.064	0.23	0.046	0.94	0.43
Middle	DAWS	0.24	0.26	0.25	0.22	0.47	0.50	0.47	0.44
	DP	0.23	0.25	0.25	0.20	0.45	0.49	0.47	0.39
	FH	0.22	0.24	0.25	0.17	0.44	0.48	0.46	0.36
	P-value DAWS and DP	0.40	0.74	0.77	0.036	0.17	0.73	0.71	0.0098*
	P-value DAWS and FH	0.020	0.094	0.92	<.0001*	0.11	0.37	0.49	0.0005*
	P-value DP and FH	0.091	0.14	0.67	0.020	0.78	0.54	0.25	0.25
Caudal	DAWS	0.23	0.25	0.23	0.20	0.44	0.48	0.45	0.40
	DP	0.21	0.23	0.22	0.18	0.41	0.44	0.43	0.35
	FH	0.20	0.23	0.22	0.15	0.41	0.46	0.42	0.33
	P-value DAWS and DP	0.12	0.065	0.51	0.16	0.035	0.058	0.28	0.046
	P-value DAWS and FH	0.012*	0.073	0.30	0.0005*	0.034	0.41	0.26	0.0035*
	P-value DP and FH	0.25	0.98	0.66	0.018	0.95	0.25	0.94	0.25

DAWS = Doberman Pinschers with DAWS; DP = clinically normal Doberman Pinschers; FH = clinically normal English Foxhounds; Significance when $P < 0.016$ (indicated by *)

Table 2. *P*-values for influence of age, gender, vertebra, type of compression and group of dogs on the assessed ratios

Assessed ratio		Age	Gender	Vertebra	Type of compression	Group of dogs
Occupying ratio spinal cord	Cranial	0.064	0.91	< 0.0001*	-	0.020*
	Middle	0.048*	0.92	< 0.0001*	-	0.054
	Caudal	0.22	0.10	< 0.0001*	-	0.042*
Occupying ratio epidural fat/CSF-column		0.047*	0.12	0.0006*	-	0.040*
	Cranial					
	Middle	0.034*	0.052	< 0.0001*	-	0.24
	Caudal	0.17	0.0006*	< 0.0001*	-	0.06
Compression ratio		0.22	0.16	-	< 0.0001*	-
Remaining spinal cord area		0.77	0.74	-	< 0.0001*	-
Remaining epidural fat/CSF-area		0.81	0.54	-	0.0004*	-
Vertebral canal compromise ratio		0.024*	0.70	-	< 0.0001*	-
Dorsoventral vertebral canal compromise ratio		0.024*	0.97	-	< 0.0001*	-
Intervertebral disk width		0.029*	0.056	< 0.0001*	-	0.55

Significance when $P < 0.05$ (indicated by *)

Dimensions related to Spinal Cord Compression

For each ratio there was a significant influence of type of compression (Table 2). When looked for dogs with clinically relevant, clinically irrelevant and no spinal cord compression seperately, there was for each calculated ratio a significant difference between dogs with clinically relevant spinal cord compression and dogs without spinal cord compression. Further, the compression ratio was significantly different between dogs with clinically irrelevant and dogs without spinal cord compression (Table 3). The remaining spinal cord area was significantly different between dogs with clinically relevant and irrelevant spinal cord compression (Table 3). The ROC curve for remaining spinal cord area between dogs with and without clinical signs of DAWS (Figure 5A) demonstrated that a remaining spinal cord area of 0.806 corresponded with a sensitivity of approximately 0.9 and a specificity of approximately 0.7 to discriminate between dogs with and without clinical signs. The area under the curve was 0.887 (P <0.0001). The ROC curve for remaining spinal cord area between Doberman Pinschers with and without clinical signs of DAWS (Figure 5B) demonstrated that a remaining spinal cord area of 0.828 corresponded with a sensitivity of approximately 0.9 and a specificity of approximately 0.75 to discriminate between Doberman Pinschers with and without clinical signs. The area under the curve was 0.868 (P = 0.0001). For none of the assessed ratios, there was a significant influence of age or gender (Table 2).

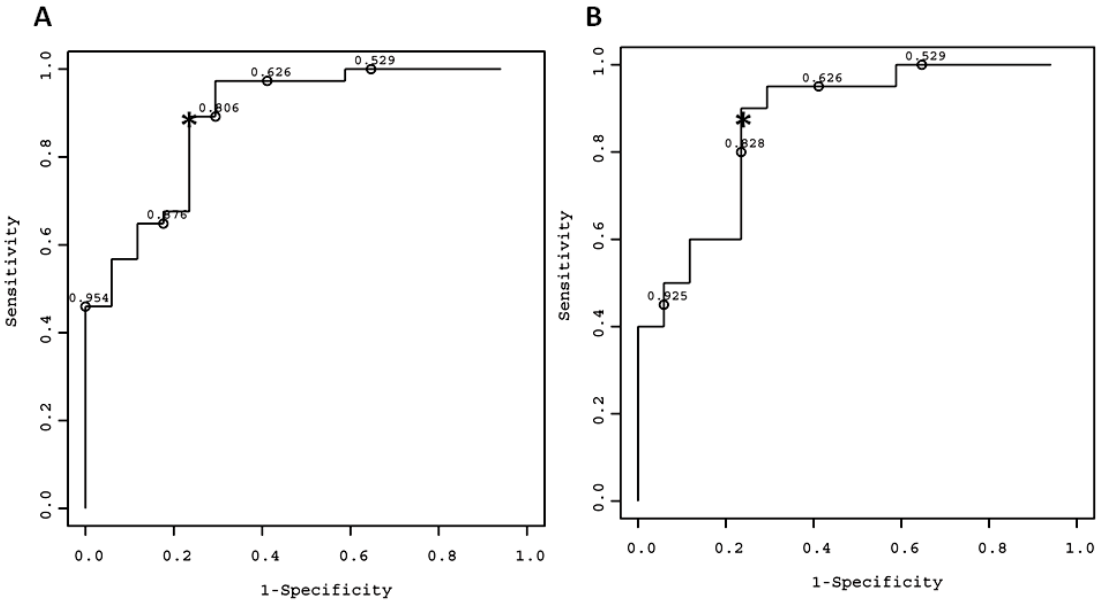

Figure 5. ROC curves for remaining spinal cord area. (A) Between Doberman Pinschers with clinical signs of DAWS and clinically normal dogs. (B) Between Doberman Pinschers with and without clinical signs of DAWS. The points on the ROC curves combining the highest sensitivity with specificity (upper most left point) are marked on the figures by an asterisk (*).

Table 3. Mean and P-values for compression ratio, remaining spinal cord –and CSF column area, and vertebral canal and dorsoventral vertebral canal compromise ratio between dogs with clinically relevant, clinically irrelevant and without spinal cord compression

Type of spinal cord compression	Compression ratio	Remaining spinal cord area	Remaining epidural fat/CSF-column area	Vertebral canal compromise ratio	Dorsoventral vertebral canal compromise ratio
Clinically relevant	0.35	0.64	0.72	0.24	0.35
Clinically irrelevant	0.42	0.84	0.85	0.19	0.30
None	0.60	0.95	0.94	0.09	0.15
P-value between clinically relevant and Irrelevant	0.10	0.0006*	0.027	0.076	0.22
P-value between clinically relevant and None	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*
P-value between clinically Irrelevant and none	<0.0001*	0.034	0.089	0.0002*	0.0002*

Significance when $P < 0.016$ (indicated by *)

Dimensions related to Vertebral Canal Compromise

For both the vertebral canal compromise and dorsoventral vertebral canal compromise ratios, there was a significant influence of type of compression (Table 2). When looked for dogs with clinically relevant, clinically irrelevant and no spinal cord compression seperately, there was for each ratio a significant difference between dogs without spinal cord compression and both groups of dogs with spinal cord compression seperately. For none of the ratios, there was a significant difference between dogs with clinically relevant and irrelevant spinal cord compression (Table 3). Both ratios were significantly influenced by higher age (Table 2). Each increase of age by one month resulted in an increase of vertebral canal compromise and dorsoventral vertebral canal compromise ratio by 0.0013, and 0.00086, respectively.

Intervertebral Disk Width

The intervertebral disk width was not significantly different between Doberman Pinschers with clinical signs of DAWS (mean: 0.56 mm), clinically normal Doberman Pinschers (mean: 0.58 mm) or clinically normal English Foxhounds (mean: 0.55 mm). The intervertebral disk width was significantly influenced by the assessed vertebra and positively associated with increasing age (Table 2). Each increase of age by one month resulted in an increase of disk width by 0.00057 mm.

Reliability of Measurements

The mean difference between both observers and within one observer, the standard deviation of the difference and the lower –and upper limits of agreement for the respective ratios are presented in Table 4.

For intraobserver reliability, the highest variability was clearly noted for both vertebral canal compromise ratios with lower and upper LOA's exceeding 10% of the mean values of the respective ratios (lower LOA vertebral canal compromise ratio, 18.4% of mean value; upper LOA dorsoventral canal compromise, 16% of mean value). The LOA's of the other assessed parameters were lower than 10% of the mean value of the respective ratios. The LOA's for interobserver agreement were considerably wider compared to intraobserver agreement. For interobserver variability, the LOA for remaining spinal cord area, epidural fat/CSF-column area, and both vertebral canal compromise ratios could be considered problematic. These LOA's approached 20% of the mean values of the respective ratios.

Table 4. Mean value and mean difference within one observer and between both observers, the standard deviation (SD) of the difference and the lower –and upper limits of agreement (LOA) for the respective ratios

Assessed Variable		Mean Value	Mean Difference	SD difference	Lower LOA	Upper LOA
Intraobserver (M1 –M2)						
Occupying ratio spinal cord	Cranial	0.292	-0.00110	0.0142	-0.0290	0.0273
	Middle	0.260	-0.00258	0.0102	-0.0231	0.0179
	Caudal	0.250	0.00129	0.00966	-0.0206	0.0180
Occupying ratio epidural fat/CSF-column	Cranial	0.542	0.00445	0.0216	-0.0387	0.0476
	Middle	0.490	0.00191	0.0112	-0.0205	0.0243
	Caudal	0.480	0.00626	0.0136	-0.0209	0.0334
Compression ratio		0.407	0.000143	0.0143	-0.0285	0.0287
Remaining spinal cord area		0.726	-0.00126	0.0306	-0.0625	0.0600
Remaining epidural fat/CSF-column area		0.818	0.00770	0.0249	-0.0420	0.0574
Vertebral canal compromise ratio		0.236	-0.00304	0.0202	-0.0435	0.0374
Dorsoventral vertebral canal compromise ratio		0.342	0.00878	0.0232	-0.0376	0.055
Intervertebral disk space		0.538	-0.0000267	0.0138	-0.0276	0.0276
Interobserver (Obs 1 – Obs 2)						
Occupying ratio spinal cord	Cranial	0.293	-0.00454	0.0254	-0.0454	0.0463
	Middle	0.261	-0.00501	0.0224	-0.0408	0.0398
	Caudal	0.250	-0.00331	0.0175	-0.0382	0.0316
Occupying ratio epidural fat/CSF-column	Cranial	0.550	-0.0119	0.0363	-0.0843	0.0607
	Middle	0.495	0.00979	0.0244	-0.0586	0.0390
	Caudal	0.480	-0.0128	0.0280	-0.0687	0.0431
Compression ratio		0.410	-0.00645	0.0223	-0.0511	0.0382
Remaining spinal cord area		0.735	-0.0195	0.0615	-0.143	0.104
Remaining epidural fat/CSF-column area		0.814	0.0168	0.0819	-0.147	0.181
Vertebral canal compromise ratio		0.234	0.00100	0.0211	-0.0412	0.0432
Dorsoventral vertebral canal compromise ratio		0.343	0.00840	0.0446	-0.0808	0.0976
Intervertebral disk space (mm)		0.534	0.00354	0.0241	-0.0446	0.0517

M1 = Measurement 1; M2 = Measurement 2; Obs 1 = Observer 1; Obs 2 = Observer 2

Discussion

In this study, we have evaluated the use of morphometric MRI dimensions of the caudal cervical vertebral column in Doberman Pinschers with clinical signs of DAWS, clinically normal Doberman Pinschers and clinically normal English Foxhounds. More specifically, we investigated if these ratios could be used to indicate relative stenosis of the caudal cervical vertebral canal in Doberman Pinschers with clinical signs of DAWS. Further, we evaluated if the degree of spinal cord compression and the amount of vertebral canal compromise were significantly larger in dogs with clinically relevant spinal cord compression. The selection of the assessed morphometric dimensions was based on already existing and established ratios in human neuroradiology.[10-12]

Little is known about the underlying cause or predisposing risk factors of DAWS. A multifactorial etiology with different contributing factors is considered most likely.[1,2] Several authors have suggested relative vertebral canal stenosis as an important static risk factor for the development of this disease.[7,13] Relative stenosis of the vertebral canal is characterized by a decrease in available space between the neural tissue and the vertebral canal. This does not cause spinal cord compression in itself but carries an increased risk of becoming clinically significant on the development of space-occupying, degenerative, conditions of the vertebral canal such as age-related vertebral disk protrusion.[14] In human medicine, a morphometric ratio between the cross sectional area of the spinal cord and the vertebral canal has been developed to quantify vertebral canal stenosis. This vertebral canal occupying ratio was significantly higher in people with cervical spondylotic myelopathy than in a normal control population.[10] The results of our study are similar. Although the mean values of all assessed vertebral canal occupying ratios were highest in Doberman Pinschers with clinical signs of DAWS, lower in clinically normal Doberman Pinschers and lowest in clinically normal English Foxhounds, this could not be completely confirmed statistically. Significant differences were only consistently seen between Doberman Pinschers with clinical signs of DAWS and clinically normal English Foxhounds at the level of C7.

Our reported mean values are somewhat lower compared with earlier reported values for Doberman Pinschers.[7] A possible reason for this difference is that the cross sectional area of the vertebral canal in our study was measured on T1-weighted and not on T2-weighted transverse images. Human studies have demonstrated different values when measurements are

performed at different pulse sequences.[15] The choice of T1-weighted images for measuring the cross sectional area of the vertebral canal in our study was based on the fact that bone is better visualized on T1-weighted images and the results of a recent veterinary study that demonstrated a high repeatability and accuracy of MRI derived vertebral canal measurements using T1-weigthed images.[16] Another possible reason for the different values between the two studies is the fact that the images of this study were obtained with a low-field (0.2T) MRI unit. On low-field transverse T2-weighted images it can sometimes be difficult to recognize the margins between the CSF-column and the surrounding epidural fat.

Several vertebral canal occupying ratios were slightly negatively influenced by increasing age. This finding is in agreement with human findings and can probably be attributed to age related spinal cord atrophy.[17]

Previous veterinary studies have already investigated the use of morphologic MRI parameters to predict the probability of the presence of clinical signs.[7,9] Increased intraspinal signal intensities on T2-weighted images of the spinal cord have been considered reliable indications of clinically significant cervical spinal cord compression.[7,9] However, there is currently little known about the use of morphometric MRI parameters in dogs with clinically relevant and irrelevant spinal cord compression. The results of this study indicate that, in agreement with human studies [5,18], a critical value of spinal cord compression should be reached before clinical signs of cervical hyperesthesia or cervical myelopathy will occur. Additionally, our data suggest that this parameter is best expressed as the remaining spinal cord area. This was the only ratio with a significant difference between dogs with clinically relevant and irrelevant spinal cord compression. The constructed ROC-curves (Figure 5) demonstrated that clinical signs will occur with a high sensitivity, of 0.9, and an acceptable specificity, of approximately 0.7, when a remaining spinal cord area of 0.8 is reached. Although the compression ratio differed significantly between dogs without compression and both groups of dogs with spinal cord compression, there was no significant difference between dogs with clinically relevant and irrelevant compressions. This suggests that as long as the cross sectional area of the spinal cord is preserved, clinical signs not necessarily occur in cases where the spinal cord is clearly deformed and compressed. Such a compensation mechanism for spinal cord compression by altering its shape while maintaining its cross sectional area occurs probably easier in a relatively wider vertebral canal.

Based on the results of this study, the amount of vertebral canal compromise by protruded annulus fibrosus, eventually combined with the amount of hypertrophied ligamentum flavum, was not considered a reliable indicator of presence of clinical signs. Since stenosis of the vertebral canal is determined by the cross sectional area of both the vertebral canal and spinal cord, it is likely that the same amount of vertebral canal compromise does not cause clinical signs in dogs with a cross sectional area of the spinal cord at the lower range of normal individual variation. The application of these two parameters in individual cases is further limited by the relatively wide LOA's for intra-and interobserver agreement. This can probably be explained by the rather irregular margins of protruded annulus fibrosis and difficulties in recognizing the ventral border of the vertebral canal at this level. Both vertebral canal compromise ratios were significantly influenced by higher age. This in agreement with a recent veterinary study evaluating the caudal cervical MRI findings of clinically normal Doberman Pinschers and English Foxhounds.[8] That study suggested that disk degeneration and protrusion in clinically normal dogs are probably part of the common aging process of spinal degeneration.

There was no significant difference between the intervertebral disk widths between the different groups of dogs. This is in contrast with a veterinary study that demonstrated significantly wider intervertebral disks in Doberman Pinschers with clinical signs of caudal cervical myelopathy compared with clinically normal Doberman Pinschers.[7] The results of our study demonstrated a significant increase in intervertebral disk width with increasing age. The reason for the conflicting results between these two studies is possibly related to differences in age of the included dogs.

We recognize some limitations of this study. First, all measurements and neurologic evaluations were performed by the same person who was not blinded to the identity and clinical status of the studied dogs. This could be a potential cause of bias. Secondly, only transverse images from the caudal cervical vertebral column were used. This makes it impossible to draw conclusions (e.g. relative canal stenosis) for the entire cervical vertebral column. Thirdly, the field strength of the MRI unit was quite low (0.2T). This could result in larger variability of measurements compared to high-field MR units and could partially explain the rather wide LOA's for interobserver agreement for some of the calculated ratios of interest. For this reason, the obtained values may not be applicable in high field MR imaging and could differ depending on software and imaging protocol. Further, it should be

emphasized that only one condition, characterized by chronic cervical spinal cord compression, was investigated. It is probably not advised to extrapolate or compare the results of this study with those of other conditions or similar conditions in different locations along the spinal cord.[19-21] Other disorders have probably different pathological mechanisms and other locations are probably characterized by other vertebral canal to spinal cord dimensions.[22]

Conclusions

In summary, the results of this study support the hypothesis that relative stenosis of the cervical vertebral canal occurs more often in Doberman Pinschers with clinical signs of DAWS. Further, it seems that a certain amount of spinal cord compression should be reached before clinical signs of cervical hyperesthesia or myelopathy will occur. The latter can be quantified by the remaining spinal cord area. However, considering the relative wide LOA for interobserver agreement, cautious should be taken with comparing measurements from different persons in individual cases.

Footnotes

[a] Magnet: Airis Mate, Hitachi, Japan.

[b] Osirix Image processing software, California, USA.

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Chapter 2.2

TRANSCRANIAL MAGNETIC STIMULATION IN DOBERMAN PINSCHERS WITH AND WITHOUT CLINICALLY RELEVANT SPINAL CORD COMPRESSION DUE TO DISK ASSOCIATED WOBBLER SYNDROME

TRANSCRANIAL MAGNETIC STIMULATION IN DOBERMAN PINSCHERS WITH AND WITHOUT CLINICALLY RELEVANT SPINAL CORD COMPRESSION DUE TO DISK ASSOCIATED WOBBLER SYNDROME

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Summary

The objective of this study was to evaluate the use of transcranial magnetic stimulation (TMS) for differentiation between clinically relevant and irrelevant cervical spinal cord compression.

Clinically normal Doberman Pinschers without (n = 11) and with (n = 6) spinal cord compression and Doberman Pinschers with disk associated wobbler syndrome (n = 16) were prospectively investigated. After sedation with acepromazine and morphine, transcranial magnetic motor evoked potentials (TMMEPs) were recorded from the extensor carpi radialis (ECRM) and cranial tibial (CTM) muscles. Onset latencies and peak-to-peak-amplitudes were measured. Subsequently, MRI was performed to evaluate the presence and severity of spinal cord compression.

There were significant differences in ECRM and CTM onset latencies between the 3 groups globally and between the clinically affected Doberman Pinschers and the 2 groups of clinically normal dogs seperately. There were no significant differences in ECRM and CTM onset latencies between the 2 groups of clinically normal dogs. There were significant differences in CTM peak-to-peak amplitudes between the 3 different groups globally and between the clinically affected Doberman Pinschers and the 2 groups of clinically normal dogs seperately. There were no significant differences in ECRM peak-to-peak amplitudes for all the different combinations and for CTM peak-to-peak amplitudes between the 2 groups of clinically normal dogs. There was a significant correlation between severity of spinal cord compression and ECRM onset latencies, CTM onset latencies, and CTM peak-to-peak amplitudes.

Transcranial magnetic stimulation can be used as a diagnostic tool to differentiate between clinically relevant and irrelevant spinal cord compression

Introduction

Disk associated wobbler syndrome (DAWS) is the most common and typical canine wobbler syndrome. Caudal cervical spinal cord compression is typically caused by protrusion of one or more intervertebral disks, sometimes in combination with dorsal compression resulting from hypertrophy of the ligamentum flavum and generally mild vertebral body malformations.[1] This wobbler syndrome occurs in several adult to older large breed dogs. The Doberman Pinscher is overrepresented.[1] The most common presentation is a gait disturbance with hind limb ataxia and/or paresis of the pelvic limbs, frequently in combination with a short stilted gait of the thoracic limbs.[1,2] This disorder can be diagnosed by a variety of imaging modalities, such as myelography, computed tomography-myelography, and magnetic resonance imaging (MRI).[2] Each of these techniques is associated with specific advantages and disadvantages.[3]During the last decade, MRI has gained popularity and several papers have described its use to characterize a variety of neurologic disorders affecting the cervical vertebral canal and spinal cord.[4-6] MRI allows direct, non-invasive, multiplanar imaging and an excellent soft tissue characterization with an absence of ionizing radiation.[7] A disadvantage of MRI in the evaluation of the spine is the possibility of clinical over-interpretation. Several human and veterinary MRI studies have demonstrated the occurrence of cervical spinal cord compressions in clinically normal subjects.[8-14] A recent randomized, blinded study compared the low-field MRI studies of dogs with DAWS with those of clinically normal Doberman Pinschers and Foxhounds.[14] The results of this study demonstrated that low-field MRI of the cervical vertebral canal and spinal cord can lead to false positive and false negative clinical assessments. Some clinically normal dogs demonstrated rather severe spinal cord compressions, while some clinically affected dogs demonstrated only mild abnormalities on MRI.

Transcranial magnetic stimulation (TMS) is a non-invasive, painless and sensitive technique for stimulating the cerebral cortex in order to evaluate the functional integrity of the fastest conducting descending motor pathways in the brain and spinal cord.[15] Magnetic motor cortex stimulation evokes synchronized descending excitatory volleys in the spinal cord pathways.[16] These excitatory volleys induce muscle twitches that are recorded as potentials in the periphery. These potentials are called transcranial magnetic motor evoked potentials (TMMEPs).[15] In human medicine, TMS is widely and routinely used to assess the integrity of the spinal cord in different disorders affecting the spinal cord, for intra-operative monitoring, and as a prognostic tool in a variety of spinal cord disorders.[17-23] In veterinary medicine, it has

been performed on healthy dogs and horses to standardize the method of stimulation or assess different anesthetic protocols to determine their impact on the recorded TMMEPs.[24-31] This technique is also used in horses with bilateral hind limb ataxia and cervical spinal cord lesions and in dogs with thoracolumbal intervertebral disk disease, cervical spinal cord disease and cervical spondylomyelopathy.[32-37]

This study investigates the clinical usefulness of TMMEPs in Doberman Pinschers with or without clinical signs of DAWS. Since TMS provides objective information about the functionality of the spinal cord, it was hypothesized that TMMEPs could be used to differentiate between clinically relevant and irrelevant spinal cord compression seen on MRI. Additionally, it was evaluated if we could confirm earlier established reference values for clinically normal Doberman Pinschers and the occurrence of a correlation between the TMMEP findings and an earlier established MRI compression scale.[37-38] This study is part of a larger investigation into the diagnosis and treatment of DAWS in dogs.

Materials and Methods

Animals

Thirty-three client-owned Doberman Pinschers were prospectively studied. The experiment was conducted in accordance with the guidelines of the Animal Care Committee of the University of Ghent. Written owner consent was obtained prior to study enrollment. Three groups of dogs were studied. The first group (Group 1) consisted of 11 clinically normal Doberman Pinschers without spinal cord compression seen on MRI. This group consisted of 6 males and 5 females, between 1.5 and 8 years old (mean 4.3 years, median 4.5 years). The second group (Group 2) consisted of 6 clinically normal Doberman Pinschers with spinal cord compression seen on MRI. This group consisted of 3 males and 3 females, between 1.6 and 7.1 years old (mean 4.0 years, median 3.9 years). The third group (Group 3) consisted of 16 Doberman Pinschers with spinal cord compression seen on MRI and who had well defined clinical signs that were associated with the MRI findings. This group consisted of 6 males and 10 females, between 4.6 and 10 years old (mean 8.6 years, median 8.7 years). These dogs demonstrated clinical signs varying from cervical hyperesthesia only (n = 2) to ambulatory paraparesis/ataxia with or without cervical hyperesthesia (n = 5), ambulatory tetraparesis/ataxia with or without cervical hyperesthesia (n = 7), and non-ambulatory tetraparesis with or without cervical hyperesthesia (n = 2). In all dogs a physical and complete neurological examination, complete blood cell counts, biochemistry analyses, echocardiographic examination, and standardized mucosal bleeding times were performed. All owners of the clinically normal Doberman Pinschers were contacted at the end of the study (16-18 months after the initial MRI and TMS evaluations) to have a new physical and complete neurological examination performed on their dogs. The goal of this second neurological examination was to determine if recorded MRI and/or TMMEP abnormalities in clinically normal dogs should be regarded as truly asymptomatic or rather presymptomatic. All neurological examinations were identical and were performed by the same person.

Transcranial magnetic stimulation

Motor cortex magnetic stimulation was performed using a commercially available magnetic stimulator [a] using a circular coil 45 mm in external diameter, which generated a peak magnetic field of approximately 4 Tesla. Maximal (i.e., 110%) stimulator output was used to ensure identifiable MMEPs. The magnetic coil was placed tangentially to the skull and in

contact with the skin, with the centre of the coil placed over the vertex.[26] To activate each hemisphere preferentially, a clockwise inducing current flow was used to stimulate the right motor cortex and an anticlockwise flow to stimulate the left motor cortex.[30] The stimulating magnet position is presented in Figure 1. Although the stimulation is painless, the mild discomfort induced by the evoked muscle contraction and the noise of stimulation can agitate some dogs. Therefore, the dogs were sedated with acepromazine (0.03 mg/kg, IV) and morphine (0.2 mg/kg, IV). Administration of this combination was analogous to previous reported literature[37] and does not influence the measured parameters of TMMEPs.[25, 26,31]

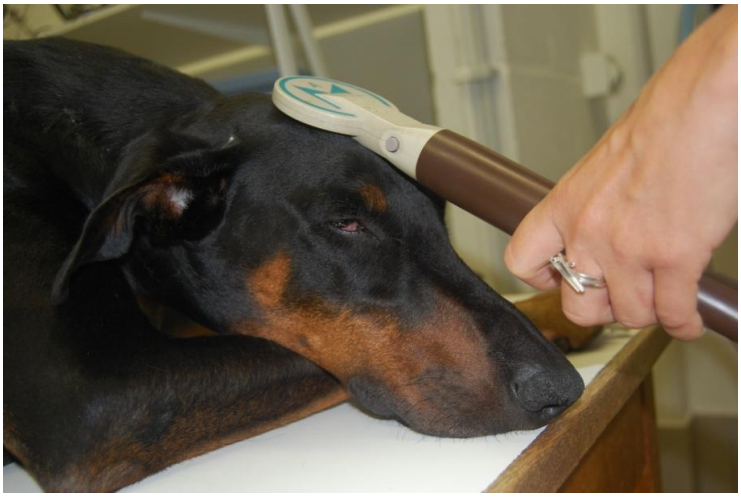

Figure 1. Position of the stimulating coil. The magnetic coil is placed tangentially to the skull and in contact with the skin, with the centre of the coil placed over the vertex.

Recording of TMMEPs

Recordings were obtained by use of an electromyography unit [b]. Magnetic motor evoked responses were recorded successively from the left thoracic, right thoracic, left pelvic and right pelvic limb from monopolar needle electrodes [c] in the muscle belly of the extensor carpi radialis muscle (ECRM) of the thoracic limb and the cranial tibial muscle (CTM) of the pelvic limb. The tip of the recording electrode was positioned in the middle of the muscle belly, just in front of the lateral humeral epicondyle for the ECRM and slightly lateral to the distal end of the tibial crest for the CTM. The reference electrode was a subdermal needle electrode [d], positioned subcutaneously over the tendons at the level of the carpal and the tarsal joint for the ECRM and the CTM, respectively. The ground electrode [d] was placed subcutaneously

over the olecranon of the thoracic limb or over the patella of the pelvic limb. The position of the different electrodes is presented in Figure 2. The low and high frequency filters were set at 20 Hz and 10 kHz, respectively. Sensitivity was set at 10 mV per division and increased in cases with low peak-to-peak amplitude (figure 5). Analysis time was 100 ms following the stimulus.

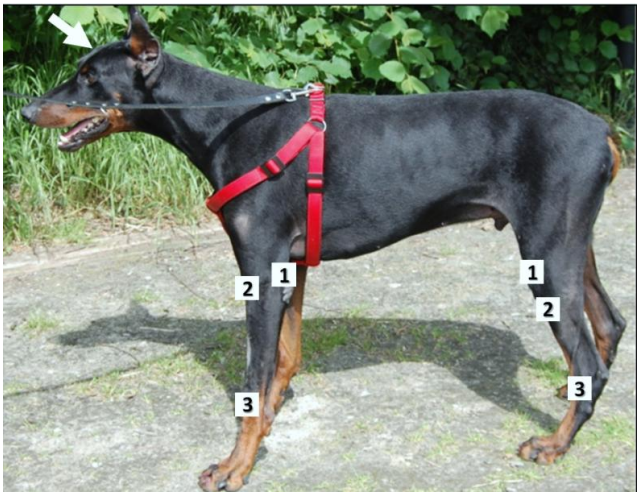

Figure 2. Position of the different electrodes for the thoracic and pelvic limbs. The point of transcranial magnetic stimulation is indicated by the white arrow. (1) Position of the ground electrodes, (2) position of the recording electrodes (3), and position of the reference electrodes.

Measurements of the TMMEP onset latency and peak-to-peak amplitude were made manually using the cursors on the oscilloscope. Onset latency (ms) was measured as the shortest time between the trigger point and the take-off of the initial phase (negative or positive); peak-to-peak amplitude (mV) was measured between the two largest peaks of opposite polarity. Individual stimulations were delivered until 2 reproducible TMMEPs were recorded. Magnetic motor evoked responses were considered absent if 4 consecutive stimulations consistently failed to elicit a reproducible TMMEP. In dogs with absent TMMEPs, onset latency was regarded as infinite and absent peak-to-peak amplitude was entered as 0 mV. The neuronal path length of each dog was measured from the vertex to the contralateral active electrode located within the ECRM or CTM using a tape measure on the surface of the skin.

MR imaging

A permanent, 0.2 T magnet [d] was used to perform MRI in all dogs. Dogs were positioned in dorsal recumbency with head and neck extended. The thoracic limbs were fixed parallel to the thoracic wall. The cervical spine was positioned in a joint coil (circular transmit-receive coil) with an inner diameter 19 cm. T1 and T2, spin echo- weighted studies were performed in all dogs in a sagittal, dorsal and transverse plane. The images of this last plane were aligned perpendicular to the cervical spine. The spine was imaged from the second cervical vertebra (C2) to the seventh cervical vertebra (C7) in the sagittal and dorsal plane and from the fourth (C4) to C7 in the transverse plane. In all spines, the field of view was 29 cm in the sagittal images, 24 cm in the dorsal plane and 20 cm in the transverse plane.

Slice thickness was 4mm in the sagittal and dorsal images and was 3 mm in the transverse sequences with no interslice gap in all studies.

Occurrence and severity of spinal cord compression was assessed at the level in the spinal cord that was most severely affected. Spinal cord compression was defined as complete subarachnoid space compression with deviation or distortion of the spinal cord. It was classified according to the degree of spinal cord deformation, displacement, and intraspinal signal intensity (ISI) changes into 4 grades[38]: grade 0, no evidence of cord compression; grade 1, mild indentation of the spinal cord with a dorsoventral cord diameter that is not less than two thirds of the expected cord diameter; grade 2, notable spinal cord indentation with a dorsoventral cord diameter that is less than two thirds of the expected cord diameter, but not associated with ISI changes within the cord; grade 3, notable spinal cord indentation associated with ISI changes. The expected spinal cord diameter was defined as the cord diameter adjacent to the site of spinal cord compression. Evaluation of ISI changes were based on the relative increase in signal on T2-weighted images and/or decrease in signal on T1-weighted images when compared with the surrounding spinal cord parenchyma.

Data analysis

The statistical analysis was based on nonparametric rank-based methods using StatXact for two reasons. First, the data could not be assumed to be normally distributed. Second, for variables such as onset latency, no value was measured for some of the subjects and therefore set to infinity. The overall comparison of the 3 clinical groups was based on the Kruskall-Wallis one-way analysis of variance. Significance was claimed when $P < 0.05$. Pairwise comparisons were based on the two-sided Wilcoxon rank sum test using Bonferroni's procedure for multiple comparisons. Significance for pairwise comparisons was claimed when

$P < 0.05/3$ (Bonferroni's correction). Kendall correlation coefficients were calculated between onset latency and neuronal path length and between the spinal compression score and onset latency and peak-to-peak amplitude. Evaluation between the left and right recorded onset latencies and peak-to-peak amplitudes was based on the signed rank test. Significance was claimed when $P < 0.05$. Receiver-operator characteristic (ROC) curves were created for both ECRM and CTM onset latencies and peak-to-peak amplitudes for clinically affected versus clinically normal Doberman Pinschers using Splus. A ROC curve helps to decide where to draw a line between a normal and an abnormal value. Each value on the ROC curve represents a tradeoff between sensitivity (ability to detect a clinically affected dog) and specificity (ability to detect a clinically normal dog). It helps to detect a value with a high sensitivity and high specificity to discriminate between clinically normal and clinically affected dogs. The area under a ROC curve quantifies the overall ability of the test (TMS) to discriminate between dogs with and without clinical signs of DAWS. A useless test (no discrimination) will have an area of 0.5 and a perfect test has an area of 1.0.

Results

The median values with associated minimum and maximum values for onset latency, peak-to-peak amplitude and neuronal path length for the 3 different groups of Doberman Pinschers are presented in table 1. Representative TMMEPs for one thoracic and one pelvic limb for the different groups of Doberman Pinschers are presented in figures 3, 4 and 5. In 11 of the 16 Doberman Pinschers with clinical signs of DAWS, TMMEPs could not be recorded in either pelvic limb. In 3 patients, TMMEPs could be recorded in only one pelvic limb and in the 2 remaining dogs TMMEPs were recorded in both pelvic limbs. The waveform of the TMMEPs recorded from the ECRM and CTM were mainly biphasic or triphasic in the clinically normal dogs (Group 1 and Group 2) and mainly polyphasic in the clinically affected dogs. The respective *P*-values for the assessed parameters between the different groups of Doberman Pinschers are presented in table 2. There was a significant difference in both ECRM and CTM onset latencies for the global comparison of the 3 clinical groups. There were also significant differences for both ECRM and CTM onset latencies between the clinically affected Doberman Pinschers and the 2 groups of clinically normal dogs seperately. There were no significant differences in ECRM or CTM onset latencies between the 2 clinically normal groups of dogs. There were no significant differences for ECRM peak-to-peak amplitudes for both the global comparison of the 3 clinical groups and between any of the 3 groups seperately. There were significant differences in CTM peak-to-peak amplitudes for the global comparison of the 3 clinical groups and between the clinically affected Doberman Pinschers and the 2 groups of clinically normal dogs seperately. There was no significant difference in CTM peak-to-peak amplitudes between the 2 clinically normal groups of dogs.

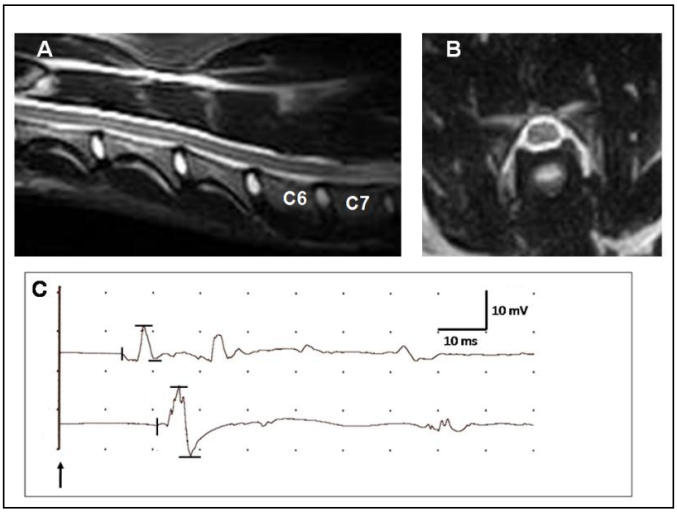

Figure 3. (A) Sagittal T2-weighted MR image of clinically normal Doberman Pinscher without spinal cord compression (Group 1). (B) Transverse T2-weighted MR image C6-C7. (C) Magnetic motor evoked potentials from the ECRM (upper trace) and CTM (lower trace). Onset latencies and peak-to-peak amplitudes within the normal values. Arrow indicates stimulus artifact. Vertical bars indicate onset latency, and horizontal bars indicate peak-to-peak amplitude.

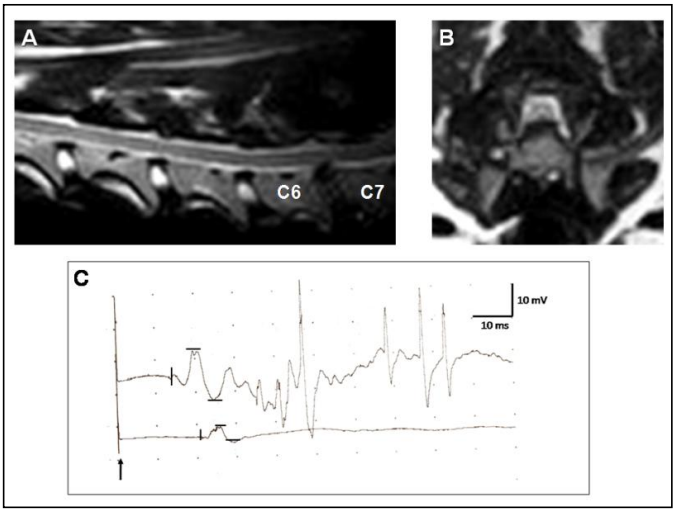

Figure 4. (A) Sagittal T2-weighted MR image of clinically normal Doberman Pinscher with spinal cord compression (Group 2). (B) Transverse T2-weighted MR image. Dorsoventral cord diameter not less than two thirds of expected cord diameter (grade 1). (C) Magnetic motor evoked potentials from the ECRM (upper trace) and CTM (lower trace). Upper wave is polyphasic. Both onset latencies within the normal values.

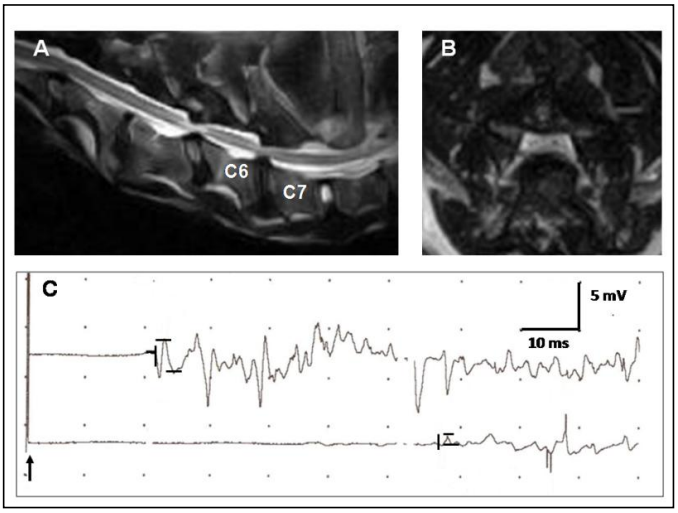

Figure 5. (A) Sagittal T2-weighted MR image of a clinically affected Doberman Pinscher (Group 3). Spinal cord compression between C5-C6 and C6-C7. Increased intraspinal signal intensity at C5-C6 (grade 3). (B) Transverse T2-weighted MR image. (C) Magnetic motor evoked potentials from the ECRM (upper trace) and CTM (lower trace). Both waves are polyphasic, both onset latencies prolonged and both peak-to-peak amplitudes decreased.

Table 1. Median onset latencies, peak-to-peak amplitudes, and neuronal path length with associated minimum and maximum values (between brackets), recorded for the Extensor carpi radials and Cranial tibial muscles for the different groups of Doberman Pinschers.

Assessed group of Doberman Pinschers	**Latency (ms)**	**Amplitude (mV)**	**Neuronal path length (cm)**
Clinically normal without spinal cord compression (Group 1)			
Extensor carpi radialis muscle	13.75 (12.25 – 16.95)	7.52 (1.86 – 19.45)	74.75 (63.0 – 82.0)
Cranial tibial muscle	21.75 (18.65 – 37.1)	5.52 (0.81 – 12.50)	125.0 (111.0 – 136.0)
Clinically normal with spinal cord compression (Group 2)			
Extensor carpi radialis muscle	13.62 (12.75 – 15.90)	6.00 (2.66 – 15.72)	71.5 (67.0 – 75.0)
Cranial tibial muscle	20.9 (19.55– 29.6)	7.50 (0.42 – 16.70)	121.5 (112.0 – 135.5)
Clinically affected (Group 3)			
Extensor carpi radialis muscle	17.72 (13.25 – 26.4)	4.06 (0.098 – 11.98)	79 (68.0 – 86.0)
Cranial tibial muscle	∞* (31.7 – 67.65)	0* (0 – 2.74)	123.0 (96.5 – 150.0)

*****In 2 of the 16 clinically affected Doberman Pinschers, TMMEPs could be elicited in both pelvic limbs and in 3 of them TMMEPs could be elicited in 1 pelvic limb. No response was recorded in the remaining 11 dogs.

Table 2. *P*-values for the different assessed parameters between the different groups of Doberman Pinschers

Assessed Parameter	Overall	Group 1 vs. 2	Group 1 vs. 3	Group 2 vs. 3
Onset latency				
Extensor carpi radialis muscle	0.00063	0.80	0.0029	0.0090
Cranial tibial muscle	< 0.0001	0.40	0.00016	0.0012
Peak-to-peak amplitude				
Extensor carpi radialis muscle	0.22	0.66	0.10	0.37
Cranial tibial muscle	0.00003	0.96	0.00027	0.0037

Significance is claimed when $P < 0.05$ for global comparison between the 3 groups overall.
Significance is claimed when $P < 0.05/3$ for pairwise comparisons (Bonferroni's correction)

On the basis of the constructed ROC curves, threshold values for both ECRM and CTM onset latencies and CTM peak-to-peak amplitudes were identified. A value of 16 ms for ECRM onset latency corresponded with a sensitivity of 0.75 and a specificity of 0.9 to discriminate between clinically normal and clinically affected dogs (Figure 6). A value of 32 ms for CTM onset latency corresponded with a sensitivity and specificity of approximately 0.9 to discriminate between clinically normal and clinically affected dogs (Figure 7). A value of 1 mV for CTM peak-to-peak amplitude corresponded with a sensitivity and specificity of approximately 0.9 to discriminate between clinically normal and clinically affected dogs (Figure 8). No threshold value with a combined high sensitivity and high specificity could be identified for ECRM peak-to-peak amplitude (Figure 9). This latter ROC curve was also associated with a rather small area under the curve compared with the ROC curves for the other assessed parameters. When compared with these threshold values, 2 dogs of Group 1 demonstrated slightly prolonged ECRM onset latencies and another dog of this group demonstrated a prolonged CTM onset latency. Three clinically affected dogs (Group 3) demonstrated normal ECRM onset latencies and another dog of this group demonstrated a normal CTM onset latency. One dog of Group 1 and 1 dog of Group 2 demonstrated and

abnormal low CTM peak-to-peak amplitude. One clinically affected dog (Group 3) demonstrated a normal CTM peak-to-peak amplitude.

In no dogs of any group were significant differences between right and left onset latencies or peak-to-peak amplitudes either for thoracic or pelvic limbs recorded. Significant correlation coefficients between the recorded onset latencies and the neuronal path lengths for all dogs was only noted for the right thoracic limb (R = 0.26, P = 0.043). A grade 0 spinal cord compression was seen in 11 clinically normal Doberman Pinschers (Group 1), grade 1 spinal cord compression was seen in 5 clinically normal (Group 2) and 5 clinically affected Doberman Pinschers (Group 3), grade 2 spinal cord compression was seen in 1 clinically normal (Group 2) and 2 clinically affected Doberman Pinschers (Group 3), grade 3 spinal cord compression was seen in 9 clinically affected Doberman Pinschers (Group 3). There was a significant correlation between grade of spinal cord compression seen on MRI and onset latency for both ECRM and CTM and peak-to-peak amplitude for CTM (ECRM onset latency: P = 0.0021, r = 0.42; CTM onset latency: P = 0.0033, r = 0.41; CTM peak-to-peak amplitude: P = 0.0033, r = -0.41, respectively). Of the 17 clinically normal Doberman Pinschers, 15 were available for physical and complete neurological examination between 16 and 18 months after the MRI and TMS examinations. These examinations revealed no abnormalities. The 2 remaining dogs were euthanized during the study period for reasons unrelated to this study. According to the owners, they never demonstrated signs suggestive of cervical hyperesthesia or a cervical myelopathy.

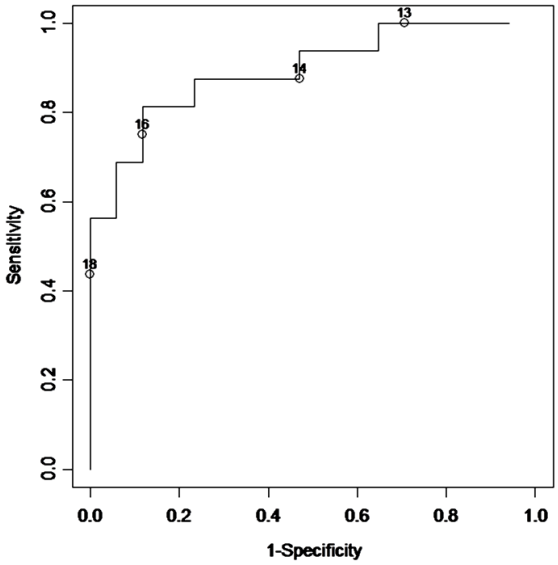

Figure 6. ROC curve for ECRM onset latency between clinically affected and clinically normal dogs. A combined high sensitivity and high specificity is obtained for a value of 16 ms.

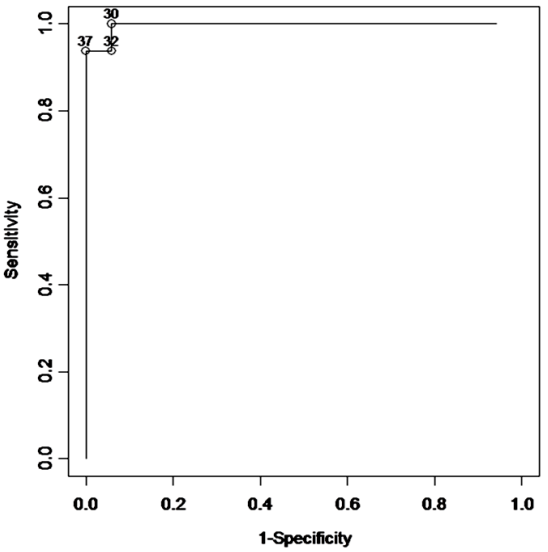

Figure 7. ROC curve for CTM onset latency between clinically affected and clinically normal dogs. A combined high sensitivity and high specificity is obtained for a value of 32 ms.

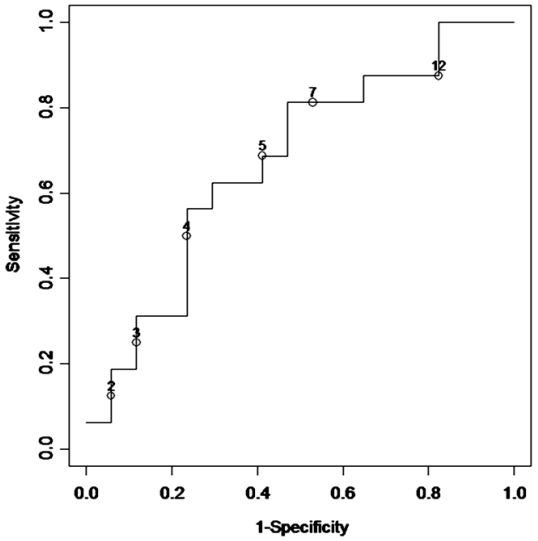

Figure 8. ROC curve for ECRM peak-to-peak amplitude between clinically affected and clinically normal dogs. No value with both high sensitivity and high specificity can be identified. Area under the curve is lower compared other constructed ROC curves.

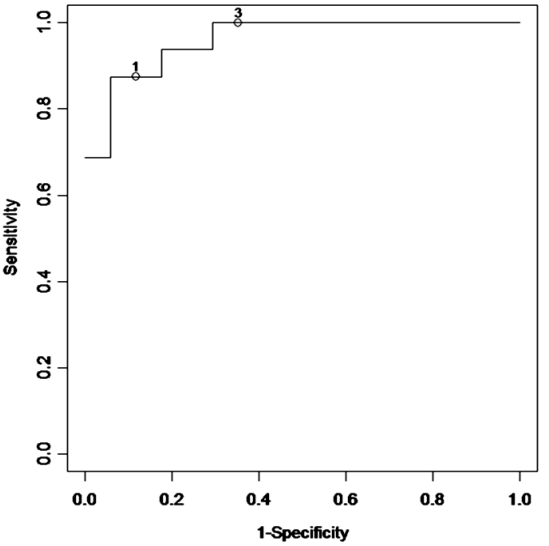

Figure 9. ROC curve for CTM peak-to-peak amplitude between clinically affected and clinically normal dogs. A value of 1 mV corresponds with a high sensitivity and high specificity.

Discussion

Previous studies have demonstrated the application of TMS as valuable diagnostic tool in dogs with cervical spondylomyelopathy and other spinal cord disorders.[32, 34, 37] However, data on TMMEP findings in dogs with clinically irrelevant spinal cord compression are scarce. The primary goal of this study was to investigate the usefulness of TMS to differentiate between clinically relevant and irrelevant cervical spinal cord compressions seen on MRI.
The median values of our clinically normal Doberman Pinschers for both ECRM and CTM onset latencies were very comparable with the mean values reported by da Costa and co-workers.[37]

Magnetic resonance images of the cervical spine show anatomic detail and degenerative changes unlike any other imaging modality, but does not reveal their clinical significance. Recent veterinary studies have shown that degenerative disease of the cervical spine may be unrelated to patient symptoms.[12-14] In a previous randomized and blinded study[14], 2 of the 6 clinically normal Doberman Pinschers of Group 2 and 2 of the clinically affected Doberman Pinschers were erroneously categorized as respectively clinically affected and clinically normal. The results of the present study demonstrate an obvious electrophysiological difference between clinically affected and clinically normal Doberman Pinschers. The TMMEPs values of clinically normal dogs with spinal cord compression seen on MRI were similar to those of the Doberman Pinschers without spinal cord compression and were significantly different from clinically affected dogs. This is in agreement with human literature.[39]

Especially, the values for the onset latencies were useful to differentiate between clinically relevant and irrelevant spinal cord compressions seen on MRI. The parameter peak-to-peak amplitude for both ECRM and CTM was less useful for this purpose.. The recorded peak-to-peak amplitudes were also associated with rather large differences between the minimum and maximum values and different values were obtained when compared to earlier reported reference values for clinically normal Doberman Pinschers.[37] Therefore, peak-to-peak amplitude can be assumed to be of limited clinical value. This is in agreement with earlier reported studies.[25,32,33,35,37] The recorded peak-to-peak amplitude is associated with a high degree of inter-trial as well as intra-individual variability and is influenced by the number of fibers recruited by the stimulus, the number of motor neurons excited by the descending

impulses, the characteristics of the target muscle, and alterations in the position of the magnetic stimulating coil over the surface of the cranium.[32] The variability appears to be spontaneous and its cause is unknown.[40]

When compared with the threshold values obtained from the ROC curves, 2 dogs of Group 1 demonstrated slightly prolonged onset latencies for ECRM and another dog from this group demonstrated a prolonged onset latency for CTM. Abnormal TMMEPs in subjects without signs of myelopathy have also been described in humans.[39, 41] None of the clinically normal Doberman Pinschers with spinal cord compression (Group 2) demonstrated abnormal increased onset latencies.

The fact that TMMEP abnormalities were more pronounced in the pelvic limbs compared to the thoracic limbs is in agreement with several veterinary and human studies evaluating the use of TMS in cervical spinal cord disease.[33,35,37,38,42] In human medicine, it is believed that TMMEP abnormalities provide direct evidence of corticospinal tract dysfunction.[15,43] Pathological studies about human cervical spondylotic myelopathy suggest that the corticospinal tracts are affected early and that the lateral corticospinal tracts are affected first in minor spinal cord compression.[44] Corticospinal and other cervical spinal cord tracts to the thoracic limbs are placed medially and fibers to the pelvic limbs are located more laterally in the somatotopic arrangement of the cervical spinal cord.[45] These facts are important to understand why TMMEPs abnormalities in progressive cervical spinal cord compression are more pronounced in the pelvic limbs. It is important to acknowledge that the actual spinal cord pathways being investigated are currently not exactly known.[46] In human medicine, it is assumed that it are mainly the corticospinal pathways (pyramidal pathways) that are stimulated by TMS.[46] Experimental studies in cats and rats, however, concluded that activation of several descending pathways, which converge on common spinal interneurons and motoneurons contribute to MMEP, meaning that MMEP evoked by TMS were not only mediated by the corticospinal tract, but also by extrapyramidal pathways.[47, 48] As neuro-anatomic knowledge advances, it becomes apparent that the pyramidal and the extrapyramidal pathways are two components of one integrated motor system in mammals and man. Its relative importance, however, differs between the different species.[49]

In only 3 of the 16 affected dogs, normal onset latencies were recorded for the thoracic limbs. This is in contrast with the study of da Costa.[37] In that study the TMMEPs of Doberman

Pinschers with and without clinical signs of cervical spondylomyelopathy were compared. Even in dogs with notable thoracic limb involvement, no significant different ECRM latencies or amplitudes were noted. The reason for this conflicting result is unclear. Other veterinary studies have demonstrated the occurrence of abnormal TMMEPs of the thoracic limbs in cervical spinal cord disorders.[33,35]

In several affected dogs, no TMMEPs could be elicited from the pelvic limbs. This finding is in agreement with previously reported human and veterinary studies.[32,33,38,42] The exact reason for this phenomenon is unknown. A possible explanation could be found in experimental animal studies where TMMEPs were recorded simultaneously from the epidural space and the peripheral nerves. In these studies, the recorded TMMEPs were abnormal or absent at the peripheral nerve level before changes were noticed in the epidural space.[50-52] The propagating impulse, although present in the spinal cord distal to the lesion, may not be strong enough to increase the postsynaptic membrane potential of the motor neuron to its threshold. Therefore, the impulse will not be present in the peripheral nerve.

There was a significant correlation noted between the MRI compression scale and the onset latencies for ECRM and CTM and the peak-to-peak amplitudes for CTM. This is a confirmation of the findings of da Costa[37] and can be explained by the fact that a grade 3 spinal cord compression was only seen in clinically affected dogs.

Although TMS is a painless, non-invasive and sensitive technique to assess the functional integrity of the spinal cord, this technique is also associated with limitations and contra-indications.[43] To perform a TMS study, the cooperation of the patient is needed. This can sometimes be difficult to accomplish in canine patients. Further, the TMMEPs abnormalities are not specific for a certain disease entity and the results should be interpreted in the context of clinical data and imaging studies. Although TMS is considered to be highly safe, patients with a history of epilepsy, electrical implants such as cardiac pacemakers, or affixed magnetic bodies such as intracranial surgery clips should be ruled out.[53, 54]

This study is limited by the rather small number of included dogs. This was especially true for the clinically normal dogs with spinal cord compression seen on MRI (Group 2). This hampered the formulation of reliable reference ranges for onset latency and peak-to-peak amplitude values for the different groups of Doberman Pinschers. For this reason, ROC

curves were constructed to identify reliable threshold values for the different assessed parameters.

Conclusions

The results of this study suggest that TMS can be considered as a useful diagnostic tool to differentiate between clinically relevant and irrelevant cervical spinal cord compression in Doberman Pinschers with and without clinical signs of DAWS. The fact that we found very comparable reference values for both ECRM and CTM onset latencies when compared to the study of da Costa[37], suggests a high repeatability of this procedure. These findings should encourage further exploration of this technique in veterinary medicine to assess different aspects of spinal cord disorders in different breeds of dogs.

Footnote: [a] Magstim Super Rapid, Acertys Healthcare

[b] Sapphire, Acertys Healthcare

[c] Monopolar needle electrode, Acertys Healthcare

[d] Subdermal needle electrode, Acertys Healthcare

[e] Magnet: Airis Mate, Hitachi, Japan

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Chapter 3

COMPARISON OF MYELOGRAPHY, POSTMYELOGRAPHIC COMPUTED TOMOGRAPHY AND LOW-FIELD MAGNETIC RESONANCE IMAGING IN DOGS WITH DISK ASSOCIATED WOBBLER SYNDROME

Chapter 3.1

INTRAOBSERVER, INTEROBSERVER AND INTERMETHOD AGREEMENT OF MYELOGRAPHY, POSTMYELOGRAPHIC COMPUTED TOMOGRAPHY AND LOW-FIELD MAGNETIC RESONANCE IMAGING IN DOGS WITH DISK ASSOCIATED WOBBLER SYNDROME

INTRAOBSERVER, INTEROBSERVER AND INTERMETHOD AGREEMENT OF MYELOGRAPHY, POSTMYELOGRAPHIC COMPUTED TOMOGRAPHY AND LOW-FIELD MAGNETIC RESONANCE IMAGING IN DOGS WITH DISK ASSOCIATED WOBBLER SYNDROME

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Summary

The objectives of this study were to determine intraobserver, interobserver, and intermethod agreement of myelography, postmyelographic computed tomography (CT-m) and low-field magnetic resonance imaging (MRI) in dogs with disk associated wobbler syndrome (DAWS)

Twenty-two dogs with DAWS were prospectively investigated. All dogs underwent myelography, CT-m and low-field MRI. After randomization, these studies were interpreted twice by four blinded observers. The following parameters were assessed by all three techniques: number, site and direction of spinal cord compression; narrowed intervertebral disk spaces; vertebral body abnormalities; spondylosis deformans; and abnormal articular facets. Intervertebral foraminal stenosis was assessed on CT-m and MRI. Intraobserver, interobserver, and intermethod agreement were calculated by κ and weighted κ statistics.

Myelography demonstrated very good to good intraobserver agreement, while CT-m and low-field MRI demonstrated only moderate intraobserver agreement for most assessed parameters. The three evaluated diagnostic techniques demonstrated moderate to fair interobserver and intermethod agreement for most assessed parameters. The site and direction of worst spinal cord compression were the most reliably assessed parameters with always very good or good intraobserver, interobserver or intermethod agreement for the different imaging modalities. Assessment of abnormal articular facets and intervertebral foraminal stenosis were the least reliably assessed parameters with poor interobserver agreement for all evaluated imaging modalities.

There is considerable variation in image interpretation between different observers and imaging modalities in dogs with DAWS. It is suggested that the evaluated diagnostic modalities should be considered as complementary to each other.

Introduction

Caudal cervical spondylomyelopathy or wobbler syndrome is a covering term to describe different causes of congenital or acquired vertebral canal stenosis in several large and giant breed dogs.[1,2] A large variety of lesions with different proposed etiologies have been attributed to this condition.[3-10] It has been recognized that the term "wobbler" only refers to the characteristic pelvic limb ataxia.[11] While progressive cervical spinal cord compression in young adult giant breed dogs is generally caused by hypertrophy of the articular facets, clinical signs of cervical hyperesthesia or myelopathy in adult to older large breed dogs are mainly caused by protrusion of one or more intervertebral disks.[1] The latter syndrome is also referred to as disk associated wobbler syndrome (DAWS) and is probably the most typical and predominant cause of caudal cervical spondylomyelopathy.[11-14] It occurs in several middle-aged to older large breed dogs. The adult Doberman Pinscher is overrepresented.[11-13,15,16] In DAWS, cervical spinal cord compression is typically caused by protrusion of the intervertebral disk between the sixth and seventh cervical vertebrae (C6-C7) and/or between the fifth and sixth cervical vertebrae (C5-C6), sometimes in combination with dorsal compression resulting from ligamentum flavum hypertrophy.[1,2,11] Other abnormalities that can be seen in dogs with DAWS are rather mild vertebral malformations consisting of varying degrees of flattening of the ventrocranial border of the vertebral body, craniodorsal tilting of the vertebral body into the vertebral canal, spondylosis deformans ventral to the intervertebral disk space, a funnel-shaped caudal vertebral canal with a narrowed cranial orifice, and intervertebral foraminal stenosis.[2,11,17,18] Although hypertrophy of the articular facets can be seen in adult Doberman Pinschers [11,18], this is not a common cause of spinal cord compression in dogs with DAWS. This disorder can be diagnosed by a variety of imaging modalities such as myelography, postmyelographic computed tomography (CT-m) and magnetic resonance imaging (MRI).[2,19] Each of these techniques is associated with specific advantages and disadvantages regarding safety, expenses and diagnostic potential.[2,19] Until the development and introduction of advanced imaging modalities, which allowed transversal imaging, myelography was considered the primary diagnostic procedure of choice.[2] The last decade, MRI is increasingly used in veterinary medicine and is replacing the more invasive imaging modalities such as myelography and CT-m.[18,20,21] Although several studies have established the use of these different diagnostic techniques to obtain a diagnosis of DAWS [17, 20-22], little is known about the relative contributions and limitations of these individual techniques for the assessment of the different anatomic structures involved in this disorder.

The purpose of this study was to compare the radiological interpretations of myelographic, CT-m and low-field MRI studies in dogs with a diagnosis and associated clinical signs of DAWS. For this purpose, 22 dogs with DAWS underwent myelography, CT-m and low-field MRI. The resulting 66 studies were randomized and twice interpreted by four blinded observers. Finally, intraobserver, interobserver, and intermethod agreement were calculated for the evaluation of number and site of present spinal cord compressions, narrowed intervertebral disk spaces, vertebral body abnormalities, spondylosis deformans, intervertebral foraminal stenosis and hypertrophied articular facets. This study was part of a larger investigation of the diagnosis and treatment of disk-associated wobbler syndrome in dogs.

Material and Methods

Animals

Twenty-two dogs were prospectively studied. The experiment was conducted in accordance with the guidelines of the Animal Care Committee of the University of Ghent. Written owner consent was obtained prior to study enrollment. Sixteen of the 22 dogs were Doberman Pinschers. Other breeds included were the Dalmatian (n = 2), Whippet (n = 2), Weimaraner (n = 1), and Bernese mountain dog (n = 1). The clinical signs varied from cervical hyperesthesia only (n = 3) to ambulatory paraparesis/ataxia with or without cervical hyperesthesia (n = 5), ambulatory tetraparesis/ataxia with or without cervical hyperesthesia (n = 11), and non-ambulatory tetraparesis with or without cervical hyperesthesia (n = 3). These 22 dogs consisted of 10 males and 12 females, between 4.6 and 10.8 years old (mean 7.8 years; median 7.4 years). In all dogs a physical and complete neurological examination, complete blood cell counts, and serum biochemistry analyses were performed. All included Doberman Pinschers underwent an additional echocardiographic examination and standardized mucosal bleeding times. All physical and neurological examinations were performed by the first author.

Imaging Protocol

All examinations were performed under general anesthesia. Anesthesia was induced with propofol to effect and maintained by isoflurane vaporized in oxygen. Ringer's lactate solution was infused IV at 10 mL/kg/hour throughout anesthesia.

In all dogs, a cervical myelogram was performed using iohexol[a] (0.2 mL/kg with a maximum dose of 10 mL) injected via cisternal puncture. In addition to standard neutral lateral views, ventrodorsal images were obtained in all but 2 dogs. For these 2 dogs, parameters that could only reliably assessed with ventrodorsal views were not included in the statistical analysis. If the diagnosis of DAWS was confirmed, CT-m was performed immediately after the myelographic procedure. For CT-m, the dogs were positioned in dorsal recumbency with the head and neck positioned at the same level as the shoulders to avoid excessive cervical extension, the thoracic limbs were fixed parallel to the chest wall. Contiguous slices were made from C4 to C7, parallel to the intervertebral disk spaces. A single row detector spiral CT [b] was used with a tube voltage of 100 kVp and 100 mAs. Slice thickness was 3 mm and a bone algorithm was used. 2D multiplanar reconstructed images were made in the sagittal plane.

After CT-m, the dogs recovered from anesthesia and were hospitalized. During hospitalization the animals were permanently monitored with special attention to the occurrence of seizures. If seizures occurred, these were treated with IV boluses of diazepam (0.5 – 1.0 mg/kg). The next day, all dogs underwent a new complete neurologic examination by the first author. Immediately after this neurological reevaluation, a permanent, 0.2 Tesla (T) magnet [c] was used to perform MRI in all dogs. Dogs were positioned the same as for CT-M. The neck was positioned in a joint coil (circular transmit-receive coil) with an inner diameter 19 cm. T1 weighted spin echo and T2 weighted fast spin echo studies were performed in all dogs in a sagittal, dorsal and transverse plane. The images of this last plane were aligned perpendicular to the spinal cord. The vertebral column was imaged from C2 to C7 in the sagittal and dorsal planes and from C4 to C7 in the transversal plane. In all spines, the field of view was 29 cm in the sagittal, 24 cm in the dorsal and 20 cm in the transversal planes. Slice thickness was 4mm in the sagittal and dorsal images and 3 mm in the transversal sequences with no interslice gap in all studies. All diagnostic procedures were performed at the first authors' institution. Dynamic studies were not routinely performed and were not presented to the different observers.

Observers

The 22 myelographic, CT-m and low-field MRI studies were twice presented to 4 observers. The observers consisted of 2 board-certified radiologists, 1 board-certified neurologist and an academic staff member with more than 10 years experience in the interpretation of myelographic, CT-m and MRI studies. The observers were blinded to signalment and clinical information of the patients. The images were presented as CD-ROMs containing each a separate randomized sequence of 22 studies of a particular diagnostic procedure (i.e. myelography, CT-m or MRI). The findings were reported by answering a predetermined paper questionnaire. After completion, the CD-ROM and respective questionnaire were returned to the first author after whom a new CD-ROM and questionnaire were retrieved. In summary, 6 CD-ROMs containing a total of 132 studies were interpreted by each observer. All images were interpreted with the same software [d] which allowed adjustment for brightness, contrast, window width, and magnification.

Interpretation of images

The following parameters were assessed on the different images: number of spinal cord compressions; site of worst spinal cord compression; directions (ventral, dorsal and/or

dorsolateral) of spinal cord compressions; direction of worst spinal cord compression (or ventral or dorsal or dorsolateral); number and sites of narrowed or collapsed intervertebral disk spaces; number and sites of abnormally shaped vertebral bodies; number and sites of abnormally positioned vertebral bodies (craniodorsal tilting); number and sites of intervertebral disk spaces with spondylosis deformans; number and sites of abnormal/hypertrophied articular facets. Additionally, the number and sites of stenotic intervertebral foraminae were assessed on the CT-m and MRI studies. In an attempt to reflect clinical practice and to avoid subjective bias, no detailed instructions or guidelines for image interpretation were provided.

Data analysis

κ and weighted κ statistics[23] were used to summarize the intraobserver, interobserver, and intermethod agreement in rating the myelographic, CT-m, and MR images. Weighted κ values were used in case of ordinal data with more than two possible scores. Intraobserver agreement was based on the double interpretations of each observer. Interobserver agreement was based on the 22 original measurements of each observer. Intermethod agreement was based on all interpretations of all observers. The strength of agreement was interpreted on the basis of the κ values suggested by Altman[24], as adapted from the method of Landis and Koch[23]: κ-values of 0.81 – 1.00 indicated very good agreement; 0.61 – 0.80, good agreement; 0.41 – 0.60, moderate agreement; 0.21 – 0.40, fair agreement; and 0.20 or lower, poor agreement. The evaluated diagnostic modalities were further pairwise compared using the chi-square test. Significance was claimed when $P < 0.05$.

Results

For intraobserver agreement, each observer interpreted twice the 22 myelographic, CT-m and MRI studies. For interobserver analysis, the original studies rated by all 4 observers were included. Calculation of intermethod agreement and comparison were based on all assessed studies of the 4 observers. In 6 of the 22 dogs, seizures occurred during the anesthetic recovery from the myelographic and CT-m procedure and in 3 dogs neurologic deterioration was noticed the day following the myelographic and CT-m procedure. This neurologic deterioration was transient in 2 of the 3 dogs and consisted in each case of more pronounced ataxia and paresis of the pelvic limbs. In none of the MRI studies, artifacts caused by the preceding myelographic study were encountered.

Intraobserver agreement

κ or weighted κ values for both overall intraobserver agreement and intraobserver agreement for each observer seperately are shown in Table 1.

For myelography, most parameters demonstrated very good or good intraobserver agreement. For the number and localization of abnormally shaped vertebral bodies and articular facets, moderate intraobserver agreements were demonstrated for myelography.

For CT-m, most parameters demonstrated moderate intraobserver agreement. The site of worst spinal cord compression, the directions of these compressions and the direction of worst spinal cord compression demonstrated very good intraobserver agreement. For the number and localization of intervertebral disk spaces with spondylosis deformans, number of intervertebral disk spaces with abnormally shaped articular facets, and localization of vertebral bodies with craniodorsal tilting a good agreement was noticed for CT-m.

For low-field MRI, most parameters demonstrated moderate intraobserver agreement. For the direction of worst spinal cord compression very good intraobserver agreement was reached. The number of spinal cord compressions and the site of worst spinal cord compression demonstrated a good intraobserver agreement. The number and localization of abnormally shaped articular facets demonstrated only a fair intraobserver agreement on MRI.

Table 1. Intraobserver agreement calculated by using κ and weighted κ statistics

Assessed Parameter		Mean	Observer 1	Observer 2	Observer 3	Observer 4
Number of compressions	mx	0.81	0.76	0.67	0.74	1.0
	CT-m	0.59	0.65	0.32	0.41	0.59
	mri	0.64	0.80	0.75	0.24	0.34
Site worst compression	mx	0.98	0.91	1.0	1.0	1.0
	CT-m	0.85	0.90	0.84	0.84	0.80
	mri	0.65	0.82	0.64	0.27	0.90
Directions compression	mx	0.74	0.46	0.74	0.73	0.89
	CT-m	0.85	0.62	1.0	0.60	0.77
	mri	0.52	0.62	0.73	0.31	0.22
Direction worst compression	mx	1.0	1.0	1.0	1.0	1.0
	CT-m	1.0	1.0	1.0	1.0	1.0
	mri	1.0	1.0	1.0	1.0	1.0
Number narrowed disk spaces	mx	0.68	0.81	0.49	0.48	0.93
	CT-m	0.49	0.52	0.55	0.40	0.48
	mri	0.53	0.68	0.32	0.42	0.51
Localization narrowed disk spaces	mx	0.79	0.83	0.77	0.57	0.88
	CT-m	0.62	0.65	0.52	0.62	0.60
	mri	0.60	0.85	0.45	0.14	0.68
Number abnormal vertebral bodies	mx	0.49	0.62	0.58	0.32	0.42
	CT-m	0.55	0.62	0.52	0.30	0.58
	mri	0.58	0.90	0.82	0.34	0.34
Localization abnormal vertebral bodies	mx	0.47	0.62	0.57	0.26	0.36
	CT-m	0.58	0.61	0.58	0.32	0.58
	mri	0.58	0.90	0.83	0.18	0.36
Number craniodorsal tilting	mx	0.72	0.66	0.78	0.73	0.45
	CT-m	0.57	0.88	0.58	0.36	0.46
	mri	0.56	0.68	0.58	0.36	0.70
Localization craniodorsal tilting	mx	0.72	0.78	0.76	0.67	0.47
	CT-m	0.61	0.88	0.57	0.41	0.48
	mri	0.59	0.69	0.60	0.41	0.68
Number disk spaces with spondylosis deformans	mx	0.85	0.87	0.82	0.82	0.92
	CT-m	0.71	0.95	0.62	0.58	0.72
	mri	0.51	0.95	0.37	0.1	0.44
Localization spondylosis deformans	mx	0.88	0.77	0.84	0.94	0.95
	CT-m	0.76	1.0	0.71	0.56	0.78
	mri	0.49	0.86	0.35	0.05	0.52
Number intervertebral foraminal stenosis	mx	-	-	-	-	-
	CT-m	0.58	0.46	0.23	0.53	1.0
	mri	0.59	1.0	0.19	0.49	1.0
Localization intervertebral foraminal stenosis	mx	-	-	-	-	-
	CT-m	0.53	0.49	0.23	0.47	1.0
	mri	0.56	1.0	0.21	0.32	1.0
Number abnormal articular facets	mx	0.55	0.83	0.22	0.48	0.52
	CT-m	0.61	0.80	-0.08	0.24	0.46
	mri	0.22	0.61	-0.04	0.005	0.21
Localization abnormal articular facets	mx	0.52	0.85	0.25	0.49	0.60
	CT-m	0.56	0.93	-0.08	0.07	0.41
	mri	0.32	0.80	0.015	0.11	0.29

Mx = Myelography, CT-m = postmyelographic computed tomography, mri = magnetic resonance imaging

Interobserver agreement

κ or weighted κ values for both overall interobserver agreement and interobserver agreement between pairs of observers are shown in Table 2.

For myelography, most parameters demonstrated fair interobserver agreement. For the site and direction of worst spinal cord compression very good interobserver agreement, and for the number and localization of intervertebral disk spaces with spondylosis deformans good interobserver agreement was reached. The evaluation of number and localization of narrowed intervertebral disk spaces demonstrated moderate interobserver agreement, and the number and localization of abnormal articular facets demonstrated only poor interobserver agreement on myelography.

For CT-m, most parameters demonstrated fair interobserver agreement. For the direction of worst spinal cord compression very good, and for the site of worst compression, number and localization of intervertebral disk spaces with spondylosis deformans good interobserver agreement was reached. For the localization of narrowed intervertebral disk spaces, and number and localization of vertebral bodies with craniodorsal tilting moderate interobserver agreement was demonstrated. The number and localization of both intervertebral foraminal stenosis and abnormal articular facets demonstrated only poor interobserver agreement on CT-m.

For low-field MRI, most parameters demonstrated fair interobserver agreement. For the direction of worst spinal cord compression very good and for the site of worst spinal cord compression good interobserver agreement was reached. Evaluation of number and localization of vertebral bodies with craniodorsal tilting demonstrated moderate interobserver agreement. For localization of narrowed intervertebral disk spaces, and number and localization of intervertebral foraminal stenosis and abnormal articular facets poor interobserver agreement was demonstrated for MRI.

Table 2. Interobserver agreement calculated by using κ and weighted κ statistics

Assessed Parameter		Mean	Observer 1 and 2	Observer 1 and 3	Observer 1 and 4	Observer 2 and 3	Observer 2 and 4	Observer 3 and 4
Number of compressions	mx	0.39	0.18	0.33	0.22	0.43	0.61	0.58
	CT-m	0.22	0.08	0.22	0.09	0.18	0.28	0.46
	mri	0.28	0.19	0.12	0.10	0.5	0.47	0.30
Site worst compression	mx	0.94	0.96	0.87	0.95	0.92	1.0	0.91
	CT-m	0.78	0.74	0.82	0.75	0.80	0.78	0.78
	mri	0.61	0.64	0.58	0.91	0.36	0.58	0.60
Directions compression	mx	0.33	0.22	0.29	0.14	0.30	0.58	0.47
	CT-m	0.22	0.015	0.059	0.047	0.26	0.41	0.50
	mri	0.22	0.076	0.10	-0.086	0.41	0.60	0.22
Direction worst compression	mx	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	CT-m	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	mri	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Number narrowed disk spaces	mx	0.46	0.50	0.27	0.63	0.49	0.49	0.40
	CT-m	0.36	0.30	0.32	0.41	0.48	0.26	0.42
	mri	0.24	0.39	0.11	0.28	0.0052	0.17	0.47
Localization narrowed disk spaces	mx	0.57	0.62	0.44	0.74	0.68	0.54	0.37
	CT-m	0.48	0.41	0.53	0.49	0.57	0.33	0.58
	mri	0.20	0.33	0.13	0.24	0.013	0.14	0.33
Number abnormal vertebral bodies	mx	0.29	0.10	0.40	0.35	0.12	0.17	0.59
	CT-m	0.22	0.15	0.19	0.11	0.20	0.55	0.083
	mri	0.25	0.32	0.27	0.32	0.29	0.18	0.13
Localization abnormal vertebral bodies	mx	0.31	0.12	0.45	0.40	0.12	0.17	0.58
	CT-m	0.25	0.19	0.23	0.11	0.25	0.62	0.095
	mri	0.28	0.33	0.36	0.35	0.34	0.20	0.079
Number craniodorsal tilting	mx	0.26	0.27	0.18	0.31	0.14	0.63	0.025
	CT-m	0.42	0.48	0.47	0.30	0.46	0.56	0.26
	mri	0.44	0.63	0.59	0.44	0.45	0.40	0.15
Localization craniodorsal tilting	mx	0.30	0.32	0.28	0.36	0.19	0.63	0.05
	CT-m	0.45	0.49	0.53	0.31	0.53	0.56	0.31
	mri	0.46	0.64	0.64	0.40	0.49	0.40	0.20
Number spondylosis deformans	mx	0.63	0.56	0.72	0.48	0.77	0.63	0.63
	CT-m	0.63	0.69	0.60	0.68	0.55	0.71	0.54
	mri	0.35	0.37	0.36	0.54	0.23	0.27	0.35
Localization spondylosis deformans	mx	0.70	0.52	0.62	0.57	0.85	0.80	0.81
	CT-m	0.68	0.70	0.68	0.75	0.66	0.71	0.58
	mri	0.35	0.37	0.37	0.59	0.22	0.22	0.34
Number intervertebral foraminal stenosis	mx	-	-	-	-	-	-	-
	CT-m	0.039	0.010	0.12	-0.041	0.064	-0.077	0.061
	mri	0.036	0.091	0.023	-0.033	0.21	-0.043	-0.035
Localization intervertebral foraminal stenosis	mx	-	-	-	-	-	-	-
	CT-m	0.062	0.11	0.16	-0.035	0.096	-0.064	0.11
	mri	0.042	0.11	0.034	-0.033	0.24	-0.047	-0.048
Number abnormal articular facets	mx	0.13	0.20	0.10	-0.044	0.052	0.22	0.24
	CT-m	0.091	0.17	0.13	0.065	0.030	0.13	0.023
	mri	0.11	0.024	0.036	0.18	0.078	0.25	0.071
Localization abnormal articular facets	mx	0.14	0.21	0.053	-0.055	0.045	0.24	0.35
	CT-m	0.11	0.24	0.10	0.10	0.040	0.11	0.089
	mri	0.14	0.057	0.11	0.33	0.13	0.18	0.021

Mx = myelography, CT-m = postmyelographic computed tomography, mri = magnetic resonance imaging

Intermethod agreement

κ or weighted κ values for overall agreement between the different imaging modalities are shown in Table 3.

Between myelography and CT-m, most parameters demonstrated moderate intermethod agreement. For the site and direction of worst compression very good, and for the number and localization of intervertebral disk spaces with spondylosis deformans, good intermethod agreement was demonstrated. For the number and localization of abnormal articular facets, there was poor agreement between myelography and CT-m.

Between myelography and low-field MRI, most parameters demonstrated moderate or fair intermethod agreement. For the direction of worst spinal cord compression very good and for the site of worst spinal cord compression good intermethod agreement was seen. For the number and localization of abnormal articular facets, there was poor intermethod agreement between myelography and low-field MRI.

Between CT-m and MRI, most parameters demonstrated fair intermethod agreement. For the direction of worst spinal cord compression very good and for the site of worst spinal cord compression good intermethod agreement was reached. The number of spinal cord compressions, the localization of abnormal vertebral bodies, and the number and localization of intervertebral disk spaces with spondylosis deformans demonstrated moderate agreement between CT-m and low-field MRI.

Table 3. Intermethod agreement calculated by using κ and weighted κ statistics

Assessed Parameter	Myelography and CT-m	Myelography and MRI	CT-m and MRI
Number of compressions	0.57	0.44	0.47
Site of worst compression	0.83	0.74	0.69
Directions compression	0.42	0.21	0.38
Direction worst compression	1.0	1.0	1.0
Number narrowed disk spaces	0.43	0.43	0.36
Localization narrowed disk spaces	0.56	0.44	0.38
Number abnormal vertebral bodies	0.44	0.32	0.39
Localization abnormal vertebral bodies	0.46	0.33	0.41
Number craniodorsal tilting	0.44	0.25	0.34
Localization craniodorsal tilting	0.50	0.26	0.37
Number disk spaces with spondylosis deformans	0.68	0.51	0.50
Localization spondylosis deformans	0.75	0.49	0.52
Number intervertebral foraminal stenosis	-	-	0.39
Localization intervertebral foraminal stenosis	-	-	0.35
Number abnormal articular facets	0.12	0.16	0.25
Localization abnormal articular facets	0.026	0.15	0.31

CT-m = postmyelographic computed tomography, MRI = magnetic resonance imaging

Difference between the different imaging modalities

On MRI, significantly more spinal cord compressions and craniodorsally tilted vertebral bodies were diagnosed compared to myelography and CT-m, and by myelography compared to CT-m. Narrowed intervertebral disk spaces and abnormally shaped vertebral bodies were significantly more diagnosed by MRI compared to CT-m and myelography, and by CT-m compared to myelography. Spondylosis deformans was significantly more often diagnosed by CT-M compared to myelography and MRI, and by myelography compared to MRI. Intervertebral foraminal stenosis was significantly often more diagnosed by MRI compared to CT-m. Abnormal articular facets were significantly more often diagnosed by CT-m compared to MRI and myelography, and by MRI compared to myelography. All significant differences above were characterized by a *P*-value <0.0001.

Discussion

In this study, we have determined the interobserver, intraobserver and intermethod agreement of myelographic, CT-m and low-field MRI studies of a selected population of dogs with clinical signs of DAWS. Although previous veterinary reports have compared myelography with CT-m [22] or myelography with MRI [21] in Doberman Pinschers with caudal cervical spondylomyelopathy, no previous studies have compared these three diagnostic modalities in the same population of dogs.
In general, myelography demonstrated very good to good mean intraobserver agreement, while CT-m and low-field MRI demonstrated only moderate mean intraobserver agreement for most assessed parameters. The three evaluated diagnostic techniques demonstrated moderate to fair interobserver and intermethod agreement for most assessed parameters. These moderate to fair intraobserver [25], interobserver [26] and intermethod [27] agreements for CT-m and MRI are in resemblance with several human studies suggesting a disturbing variability in image interpretation by using either of the frequently used imaging techniques for assessment of cervical spondylomyelopathy.

In this study, the site and direction of worst spinal cord compression were the most reliable assessed parameters with always very good or good mean intraobserver, interobserver or intermethod agreement for the different imaging modalities. Assessment of abnormal articular facets and intervertebral foraminal stenosis were the least reliable assessed parameters with poor mean interobserver agreements for all evaluated imaging modalities.

Although the assessment of the myelographic studies resulted in relatively better intra and interobserver agreement values for several of the assessed parameters compared to CT-m and MRI, this imaging modality is associated with considerable complications and limitations.[2,19] This rather invasive procedure is not completely without risk.[2,28] As demonstrated in this study, seizures and transient neurological deterioration are the most important complications following myelography.[17,28,29] A higher risk of postmyelographic complications has been demonstrated in Doberman Pinschers with caudal cervical spondylomyelopathy compared to dogs suffering from other cervical spinal cord lesions.[29] Other reported risk factors for the development of postmyelographic complications are total volume of iohexol administered, higher bodyweight (> 20 kg), cerebellomedullary injection site compared to lumbar injection site, multiple cerebellomedullary injections, sex and breed.[29,30] Six of the 22 dogs in this study

experienced seizures during anesthetic recovery and 3 dogs were neurologically worse the day after the myelographic and CT-m examinations. This is in agreement with a recent veterinary study where 5 of 18 Doberman Pinschers with cervical spondylomyelopathy developed postmyelographic seizures.[21] Although myelography allows screening of the entire cervical vertebral column for compressive lesions, the results of this study suggest that the lack of transversal imaging limits the diagnostic potential of this technique. Lack of transversal imaging resulted in the inability to evaluate intervertebral foraminal stenosis and complicated reliable assessment of articular facet abnormalities on myelography. The latter is illustrated by the poor interobserver and intermethod agreement values of this parameter by myelography.

Based on the best intraobserver agreement, this study suggests that CT-m is the most reliable imaging technique to evaluate articular facet abnormalities. This is in agreement with human studies where CT is considered the gold standard in predicting articular facet abnormalities.[27,31] This can probably be explained by the superior visualization of bony detail by CT-m compared to MRI.[31,32] Although an optimal CT-m image is obtained with a lower dose of intrathecal contrast medium than in a conventional myelographic study [33], the same complications can occur as with myelography.[2] Because CT-m is initially limited to the transversal plane, it is not as efficient as myelography and MRI in screening the entire cervical vertebral column and is therefore generally used as a supplementary examination at specific levels of interest.[34] This was also true in our study, where myelography served to localize the lesion for subsequent CT-m examination.

In resemblance with human medicine [35], it is believed that intervertebral foraminal stenosis can be a contributing factor or even a primary cause of clinical signs in dogs with cervical spondylomyelopathy.[18] In this study, the interobserver agreement for intervertebral foraminal stenosis was very poor for both CT-m and low-field MRI. It has been postulated that intervertebral foraminal stenosis is best assessed on oblique radiographs [33], intravenous enhanced contrast CT [22,33] or gradient echo MRI sequences with magnetization transfer.[18,36,37] However, none of these studies were performed. It is possible that higher agreement values would have been reached if these studies could have been provided to the observers. In agreement with human studies, intervertebral foraminal stenosis was significantly more often diagnosed by MRI compared to CT-m.[27,32,38,39] This is probably caused by the presence of a susceptibility artifact[37], which is manifested as signal loss at the outer edges of bone due to the abrupt difference in magnetic susceptibility at bone-soft tissue interfaces. As a result the

bone appears larger than it really is and thus artifactually narrows adjacent soft tissue. This artifact can be misread as foraminal stenosis.[38] Addition of magnetization transfer to the image acquisition decreases the signal arising from soft tissue and thus increases the contrast between structures and reduces the artifacts.[36,37]

Low-field MRI also provided substantial lower intraobserver, interobserver, and intermethod agreement for the assessment of intervertebral disk spaces with spondylosis deformans compared to CT-m and myelography. This high variability of spondylosis deformans is in agreement with a recent veterinary [40] and several human studies [27,41] and is presumably related to the variable presence and composition of bone marrow in osteophytes.[41] Osteophyte signal can vary from a markedly decreased intensity when the bone is dense, to an intensity homogenous with either the disk or the adjacent vertebral body when fatty marrow is more abundant.[41]

Low-field MRI demonstrated also a poor interobserver agreement for the localization of narrowed intervertebral disk spaces, while myelography and CT-m demonstrated moderate interobserver agreement. Additionally, narrowed intervertebral disk spaces were significantly more often diagnosed by MRI compared to CT-m and myelography. Although the exact reason for this remains unclear, it can probably be explained by difficulties in discriminating the hypointense signals from a completely degenerated disk and the adjacent vertebral cortices on sagittal MR images. This can potentially result in increased variability and overinterpretation of intervertebral disk space narrowing on MRI.

Overinterpretation is a recognized problem that complicates the interpretation of cervical MR images in dogs.[18,40,42,43] Several reports have described the presence of degenerative MRI abnormalities in clinically normal dogs.[18,43] With this in mind, it is not surprising that spinal cord compressions were significantly more often diagnosed on MRI compared to CT-m and myelography. Despite this risk of overinterpretation, MRI offers several advantages over CT-m and myelography. In contrast to myelography and CT-m, MRI allows direct, non-invasive, multiplanar imaging without the need for reconstruction and an excellent soft tissue characterization with an absence of ionizing radiation.[20,44] Since MRI is independent of intrathecal contrast administration, it is not only safer than myelography and CT-m, but there is also no image degradation due to CSF-block distal or proximal to a severe compressive lesion.[41,45] It is worthwhile mentioning that limitations concerning sagittal and coronal reconstructions are less important with the use of the newer generation multislice CT units. A

distinct advantage of MRI is the ability to correctly assess the spinal cord parenchyma.[44] Although degenerative disease, especially DAWS, was suspected as the cause of myelopathy in this study, a large number of disease entities must be included in the differential diagnosis of middle aged to older large breed dogs with cervical hyperesthesia or myelopathy. With the use of MRI, myelopathy secondary to intrinsic spinal cord disease can be easily distinguished from myelopathy secondary to compressive disease.[32] Although not evaluated in this study, MRI also allows the assessment of intraparenchymal signal changes.[44] Although these changes are considered nonspecific for a certain disease entity[46,47], their presence has been suggested to be a reliable indicator of clinically relevant cervical spinal cord compression.[18,40]

The authors recognize several limitations of this study. All the included dogs had a clinical diagnosis of cervical hyperesthesia or myelopathy secondary to DAWS. As a result, it is likely that the imaging findings were influenced by the presence of specific pathological changes in the majority of patients. Therefore, the authors suggest that the result of this study should ideally be confirmed in studies where other cervical pathologies are also included. All MR images were obtained with a low-field (0.2 T) MR unit. It is possible that the use of a magnet with higher strength could have resulted in higher agreement and lower variability. Additional variation in image interpretation could be caused by the fact that the different observers did not assess the imaging studies at the same workstation. To reflect clinical practice, the observers did not receive detailed guidelines for interpretation. Although several human MRI studies have suggested that operational guidelines do not necessarily improve intraobserver or interobserver agreement in patients with cervical myelopathy [48,49], this is not yet investigated in veterinary medicine. Although efforts were made to perform each study with the cervical vertebral column in a neutral position, intermethod variability due to differences in neck position cannot be excluded.

Conclusions

In summary, the results of this suggest that there is considerable variation in image interpretation between different observers and imaging modalities in dogs with DAWS. The observed discrepancies in interpretation question the reliability of comparisons between different observers and different techniques. Analysis of the results of this study, indicate that it seems inappropriate to consider one of the evaluated diagnostic modalities as the imaging modality of choice for dogs with DAWS and that they should rather be considered as complementary to each other. Although not addressed in this study, plain CT or survey radiographs could perhaps complement MR in demonstrating bony detail and intervertebral foramina, thereby significantly decreasing the need for intrathecal contrast administration.

Footnote: [a] Omnipaque 240 mg I/ml, GE Healthcare, Diegem, Belgium

[b] Prospeed, GE Medical Systems, Milwaukee, WI

[c] Magnet: Airis Mate, Hitachi, Japan

[d] Merge Efilm, Merge eMed, Milwaukee, WI

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Chapter 4

LINEAR VERTEBRAL CANAL AND BODY RATIOS IN DISK ASSOCIATED WOBBLER SYNDROME

Chapter 4.1

RADIOGRAPHIC VERTEBRAL CANAL AND BODY RATIOS IN DOBERMAN PINSCHERS WITH AND WITHOUT CLINICAL SIGNS OF DISK ASSOCIATED WOBBLER SYNDROME

RADIOGRAPHIC VERTEBRAL CANAL AND BODY RATIOS IN DOBERMAN PINSCHERS WITH AND WITHOUT CLINICAL SIGNS OF DISK ASSOCIATED WOBBLER SYNDROME

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Summary

The objective of this study was to determine radiographic vertebral ratio values, representing vertebral canal stenosis, in Doberman Pinschers with and without clinical signs of disk associated wobbler syndrome (DAWS).

Doberman Pinschers with (n = 81) and without (n = 39) clinical signs of DAWS were retrospectively investigated. All dogs underwent lateral survey radiographs of the cervical vertebral column. Five measurements were made from C3 to C7: mid-vertebral canal height (VCHm), vertebral body height (VBH), cranial vertebral canal height (VCHcr), caudal vertebral canal height (VCHcd), and vertebral body length (VBL). Subsequently, three ratios were calculated: Canal height to body height ratio (CBR), defined as VCHm/VBH; Canal height to body length ratio (CBLR), defined as VCHm/VBL; Caudal canal height to cranial canal height ratio (CCHR), defined as VCHcd/VCHcr. The CBR and CBLR represent vertebral canal stenosis, CCHR describes vertebral canal shape.

Mean CBR and CBLR values for Doberman Pinschers with DAWS were significantly smaller when compared with these values for Doberman Pinschers without DAWS. For CBR, this was also true for all assessed vertebrae seperately. The CCHR value for C7 was significantly larger in Doberman Pinschers with DAWS. ROC statistics failed to identify a point with combined high sensitivity and specificity to differentiate between Doberman Pinschers with and without DAWS.

Doberman Pinschers with DAWS have significantly more often vertebral canal stenosis combined with a funnel-shaped vertebral canal at C7 than Doberman Pinschers without DAWS. Despite these significant differences, no reliable threshold values were identified to differentiate between both groups of dogs.

Introduction

Caudal cervical spondylomyelopathy or wobbler syndrome refers to a collection of disorders affecting the vertebrae, intervertebral disks and ligamentous structures of the cervical vertebral column resulting in spinal cord compression.[1,2] A large variety of lesions with different proposed etiologies have been attributed to this syndrome.[3-10] Several different syndromes have been recognized, based on signalment, medical imaging findings and treatment.[11,12] One of these syndromes is Disk associated wobbler syndrome (DAWS).[1,11] This is a relatively common cause of cervical spinal cord disease in adult to older large breed dogs. In DAWS, clinical signs of cervical myelopathy with or without cervical hyperesthesia are caused by protrusion of one or more intervertebral disks, sometimes in combination with ligamentum flavum hypertrophy and rather mild vertebral body abnormalities.[1] The intervertebral disk spaces between the sixth (C6) and seventh (C7) and/or between the fifth (C5) and sixth cervical vertebrae are most commonly affected.[13-16] This specific wobbler syndrome typically occurs in middle-aged large breed dogs, in particular the Doberman Pinscher.[13-16] No statistically significant sex predilection has been demonstrated, although several studies suggest a predilection for male animals.[7,9, 16-18]

Although several factors have been proposed [19-23], little is known about the etiology or predisposing factors for the development of this disorder.[2] The relative size of the vertebral canal to the spinal cord and the shape of the vertebral canal have been suggested as potential risk factors in several studies.[19,22,23] A relative vertebral canal stenosis with or without a funnel-shaped caudal vertebral canal leading to a narrowed cranial orifice, are proposed predisposing factors for the development of clinical signs of DAWS.[19,22,23] Cervical spondylotic myelopathy is considered as the human counterpart of DAWS [24] and relative stenosis of the vertebral canal is considered an important static risk factor for the development of this disease.[25-27] Quantification of vertebral canal stenosis has been evaluated in several human studies by radiography, computed tomography (CT) and magnetic resonance imaging (MRI).[27-30]Although CT and MRI are also increasingly used in veterinary medicine, widespread use is currently hampered by the rather high expenses and availability limited to referral and veterinary teaching hospitals. Although previous canine studies have used absolute measurements on survey radiographs to evaluate the presence of vertebral canal stenosis[31-33], it has become evident, especially from human studies,[34,35] that absolute vertebral canal measurements obtained from survey radiographs are influenced by radiographic magnification. Since radiographic magnification is a variable parameter which is influenced

by focus-film distance, object-film distance, and patient related factors, absolute measurements obtained from survey radiographs are difficult to use in clinical practice.[35] This variability, owing to magnification errors, can be resolved by the use of ratios of different measurements. In human medicine, a ratio between the midsagittal height of the vertebral canal and the vertebral body height has been developed to assess vertebral canal diameter.[34] This relative measure technique for assessing vertebral canal diameter is independent of radiographic magnification and has improved the sensitivity of diagnosing cervical spinal stenosis from cervical radiographs in people.[34] Vertebral canal height to body height ratios have also been used in horses to distinguish between horses with and without cervical stenotic myelopathy and between affected and unaffected intervertebral disk spaces.[36,37] The purpose of this study was to determine the values of selected radiographic ratios of the cervical vertebral canal and vertebral body in Doberman Pinschers with and without clinical signs of DAWS. Additionally, it was evaluated if the respective assessed vertebrae, age and gender influenced these dimensions.

Material and Methods

Inclusion criteria

A computer search of medical records from dogs admitted to the small animal department, Faculty of Veterinary Medicine, Ghent University between 1998 and 2009 was performed by using the following criteria: Doberman Pinscher and radiology. From this list all files of Doberman Pinschers with available conventional or digital lateral cervical radiographs were selected. To be included in this study, the radiograph had to be of good quality with the spine parallel to the table (wings of the atlas and the lateral borders of the vertebral endplates superimposed upon each other) [38], the radiographs had to be of adult dogs with closed vertebral physes, and the exposure and contrast of the radiographs had to allow good distinction of the bone structures. An obviously abnormal positioning of a vertebra, such as craniodorsal tilting, was considered as an exclusion criterium. To be included in the group of Doberman Pinschers with clinical signs of DAWS, this diagnosis had to be confirmed by myelography, CT-myelography or MRI.

Measurements

To improve visualization of the dorsal margin of the vertebral body, this was represented by a line connecting the most craniodorsal and most caudodorsal point of the vertebral body. Measurements were made directly on the neutral lateral radiographs with a graphite film marker using vernier calipers or directly at the workstation with the available imaging software [a]. The digital images could be magnified as needed, but all measurements for a given vertebra were made at the same magnification. For both the conventional and digital radiographs, the accuracy of the measurement tool was limited to 0.01 mm. The points of measurement are presented in Figure 1. The following five measurements were made from the third (C3) to the seventh cervical vertebra:

- The mid-vertebral canal height (VCHm) was defined as the distance measured from the middle of the dorsal surface of the vertebral body to the closest point of the spinolaminar line (junction between its laminae and spinous process).[34]
- Vertebral body height (VBH) was defined as the distance between the midpoint of the dorsal surface of the vertebral body to the ventral surface of the vertebral body measured parallel to the cranial vertebral endplate.

- The cranial vertebral canal height (VCHcr) was defined as the distance between the most ventrocranial point of the lamina and the craniodorsal border of the same vertebral body. The VCHcr was measured perpendicular to the dorsal surface of the vertebral body.
- The caudal vertebral canal height (VCHcd) was defined as the distance between the most dorsocaudal point of the vertebral body to the ventrocaudal point of the lamina of the same vertebra. The VCHcd was measured perpendicular to the dorsal surface of the vertebral body.
- The vertebral body length (VBL) was defined as the distance between the most dorsocranial and the most dorsocaudal point of the same vertebral body.

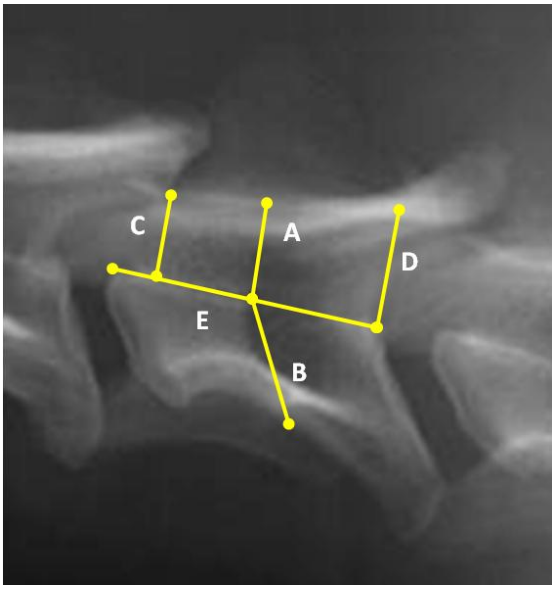

Figure 1. Radiograph of a clinically affected Doberman Pinscher. Points of measurement: VCHm (A), VBH (B), VCHcr (C), VCHcd (D), and VBL (E).

From these measurements, the following three radiographic ratios were calculated from C3 to C7:

- Canal height to body height ratio (CBR) defined as VCHm divided by VBH (Figure 2). This ratio indicates relative vertebral canal stenosis in human and equine studies.[34,36]
- Canal height to body length ratio (CBLR) defined as VCHm divided by VBL (Figure 3). This ratio represents a second ratio that is influenced directly by vertebral canal height.[36,39]
- Caudal canal to cranial canal height ratio (CCHR) defined as VCHcd divided by VCHcr (Figure 4). This ratio indicates the shape of the vertebral canal in a lateral view. Ratios > 1 represent a funnel-shaped vertebral canal narrowed cranially in a lateral view.[22]

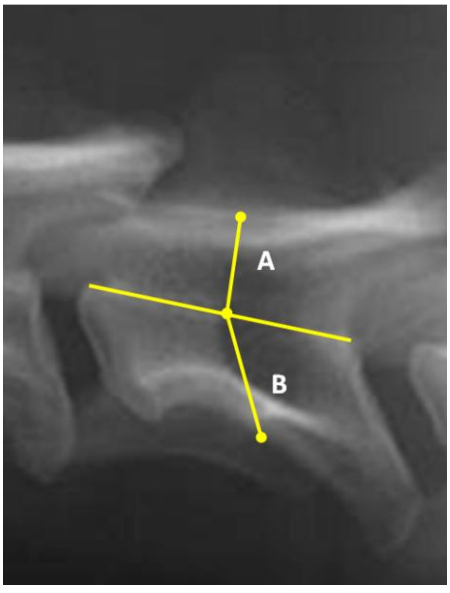

Figure 2. Canal height to body height ratio (CBR) was defined as VCHm (A) divided VBH (B).

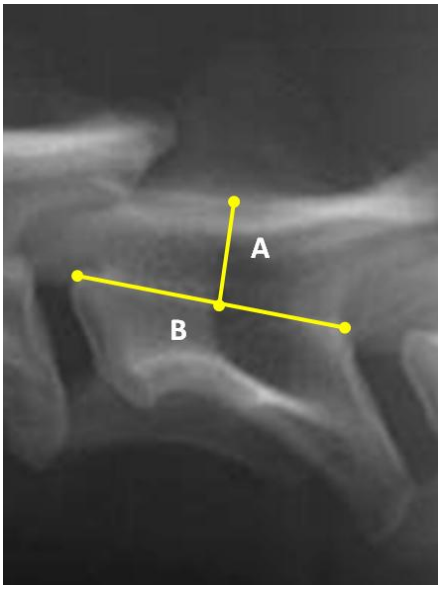

Figure 3. Canal height to body length (CBLR) was defined as VCHm (A) divided by VBL (B).

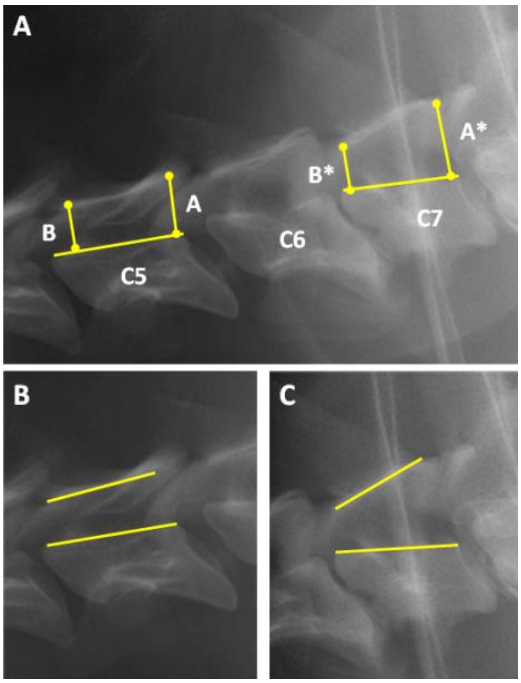

Figure 4. (A) Caudal canal to cranial canal height ratio (CCHR) was defined as VCHcd (A and A*) divided by VCHcr (B and B*). B) A value A/B around 1 represents a rather rectangular vertebral canal in a lateral view. (C) A value A*/B* < 1 represents a more funnel-shaped vertebral canal narrowed cranially in a lateral view.

All measurements were performed by the first author. He was blinded to identity, age and gender of the dogs, but not for clinical status. Reliability of measurements and ratios was tested by performing the same measurements on 65 different radiographs by the second author. This second observer was blinded to the identity, age, gender, and clinical status of each dog. Only the measurements from the first author were further used to calculate the ratio values for the different groups of dogs.

Data analysis

The effect of clinical status, assessed vertebrae (C3-C7), gender and age on the different ratios was evaluated by the mixed model with dog as random effect, using the mixed procedure of SAS (SAS Version 9.2). All ratios were normally distributed according to the Shapiro-Wilk test. F-Tests were used to test for the effects of the different factors. The global significance

level was set at 5%; the significance level for multiple comparisons was adjusted by Bonferroni's method.

Box and Whisker plots were created to demonstrate the median values, the upper and lower quartiles and the minimum and maximum values of the three assessed ratios. This was done seperately in both groups of Doberman Pinschers for the global values, different gender, and different assessed vertebrae (Figures 5, 6 and 7). Receiver-operator characteristic (ROC) curves were created for CBR, CBLR and CCHR for C5 and C7 for Doberman Pinschers with DAWS versus Doberman Pinschers without DAWS (Figures 8 and 9). A ROC curve helps to decide where to draw a line between a normal and an abnormal value. Each value on the ROC curve represents a tradeoff between sensitivity (probability that a dog with DAWS is diagnosed as such) and specificity (probability that a dog without DAWS is diagnosed as such). Visual inspection of a ROC curve guides in the detection of a value with a high sensitivity and high specificity to discriminate between clinically normal and clinically affected dogs. This value corresponds with the most upper left point on the curve. The area under a ROC curve quantifies the overall ability of the test (CBR, CBLR, and CCHR) to discriminate between dogs with and without clinical signs of DAWS. A useless test (no discrimination) will have an area of 0.5 and a perfect test has an area of 1.0.

To evaluate interobserver agreement, Bland-Altman plots for CBR, CBLR, and CCHR between the two observers were created (Figure 10). A Bland-Altman plot compares two measurement sets. It plots the difference between the two measurements on the Y axis, and the average of the two measurements on the X axis. If one method is sometimes higher, and sometimes the other method is higher, the mean differences will be close to zero. If it is not close to zero, this indicates that the two measurement methods are producing different results. Using these plots, the mean difference between the two observers, its standard deviation and the lower and upper limit of agreement (mean ± standard deviation) are given.

Results

Animals

81 Doberman Pinschers with a diagnosis of DAWS and 39 Doberman Pinschers with a final diagnosis not related to cervical vertebrae or cervical cord pathology were included. The group of Doberman Pinschers with DAWS consisted of 50 males and 31 females (male to female ratio; 1.6), between 3 and 11 years old (mean 6.8 years; median 6.6 years) with clinical signs varying from only cervical hyperesthesia (n = 15) to ambulatory paraparesis/ataxia with or without cervical hyperesthesia (n = 25), ambulatory tetraparesis/ataxia with or without cervical hyperesthesia (n = 32), and non-ambulatory tetraparesis with or without cervical hyperesthesia (n = 9). The radiographs of these 81 dogs were represented by 59 conventional and 22 digital radiographic studies.

The group of Doberman Pinschers without DAWS consisted of 27 males and 12 females (male to female ratio; 2.25), between 1.2 and 11 years old (mean 4.1 years; median 3 years). Radiographic examination of the cervical vertebral column of these dogs was performed for different reasons; part of their diagnostic work-up (n = 16), additional cervical radiographs at owners' request (n = 5), post mortem with the intention to be included in this study (n = 4), clinically normal Doberman pinschers included in a research project about the diagnosis and treatment of DAWS (n = 14). Since the latter 14 dogs were included in a prospective research, their inclusion was in accordance with the guidelines of the Animal Care Committee of the University of Ghent and written owner consent was obtained prior to study enrollment. As part of this research project, these 14 dogs received a complete neurological examination and low-field MRI of the cervical vertebral column. Of the 25 remaining dogs without clinical signs of DAWS, 16 received a complete neurological examination and 9 of them underwent myelography of the entire vertebral column. The inclusion of the remaining 9 dogs was based on the lack of historical data suggestive of cervical hyperesthesia or myelopathy. The radiographs of these 39 dogs were represented by 20 conventional and 19 digital radiographic studies.

Canal height to body height ratio

The CBR values of Doberman Pinschers with and without clinical signs of DAWS for the different assessed cervical vertebrae and different gender are presented in Table 1 and Figure 5. The mean CBR values for Doberman Pinschers with DAWS were significantly smaller when compared with the mean CBR values for Doberman Pinschers without DAWS. This was not only true for the global comparison, but also for the five assessed cervical vertebrae seperately (Figure 5). There was a significant influence of the respective assessed cervical vertebra ($P < .0001$ in both groups of dogs) with, in both groups of dogs, the highest CBR value for C3 and the lowest value for C6. In both groups of dogs, the CBR values for male dogs were significantly smaller when compared with the values for female dogs (Figure 5). There was no significant association between the age of the dogs and the CBR value in either of the groups of dogs ($P = 0.85$ and 0.40 in Doberman Pinschers with and without clinical signs, respectively). Visual inspection of the ROC curve for CBR at C5 between Doberman Pinschers with and without clinical signs of DAWS (Figure 8) demonstrated that a CBR value of 0.82 corresponded with a sensitivity of approximately 0.5 and a specificity of approximately 0.75. Visual inspection of the ROC curve for C7 (Figure 9) demonstrated that a CBR value of 0.72 corresponded with a sensitivity of approximately 0.85 and a specificity of 0.55.

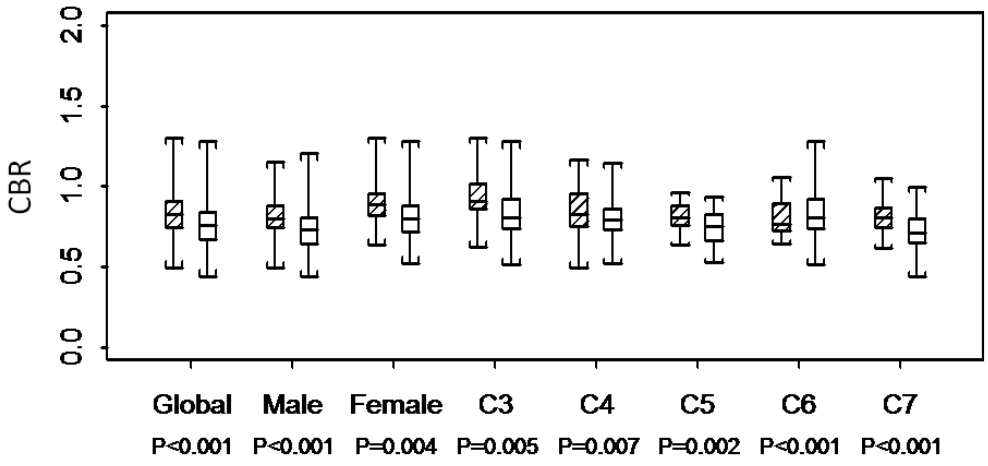

Figure 5. Box and Whisker Plots and associated *P*-values of the canal height to body height ratio (CBR) values in both Doberman Pinschers with (not striped) and without (striped) clinical signs of DAWS, globally and for different gender, and different assessed vertebrae seperately.

Canal height to body length ratio

The CBLR values for Doberman Pinschers with and without clinical signs of DAWS for the different assessed cervical vertebrae and different gender are presented in Table 1 and Figure 6. The mean global CBLR value for Doberman Pinschers with DAWS was significantly smaller when compared with the mean global value for Doberman Pinschers without DAWS (Figure 6). This was not the case for all the assessed vertebrae seperately. When the assessed vertebrae were assessed seperately, the CBLR values for C5, C6, and C7 were significantly smaller in Doberman Pinschers with DAWS (Figure 6). There was a significant influence of the assessed cervical vertebra with ($P < .0001$ in both groups of dogs), in both groups of dogs, a progressive increase in CBLR value from C3 to C7. There was no significant association between the age (($P = 0.98$ and 0.58 for dogs with and without clinical signs, respectively) and gender (Figure 6) of the dogs and the CBLR value in either of the groups of dogs. Visual inspection of the ROC curve at C5 between Doberman Pinschers with and without clinical signs of DAWS (Figure 8) demonstrated that a CBLR value of 0.39 corresponded with a sensitivity of 0.6 and a specificity of 0.65. Visual inspection of the ROC curve for C7 (Figure 9) demonstrated that a CBLR value of 0.54 corresponded with a sensitivity of 0.6 and a specificity of approximately 0.55.

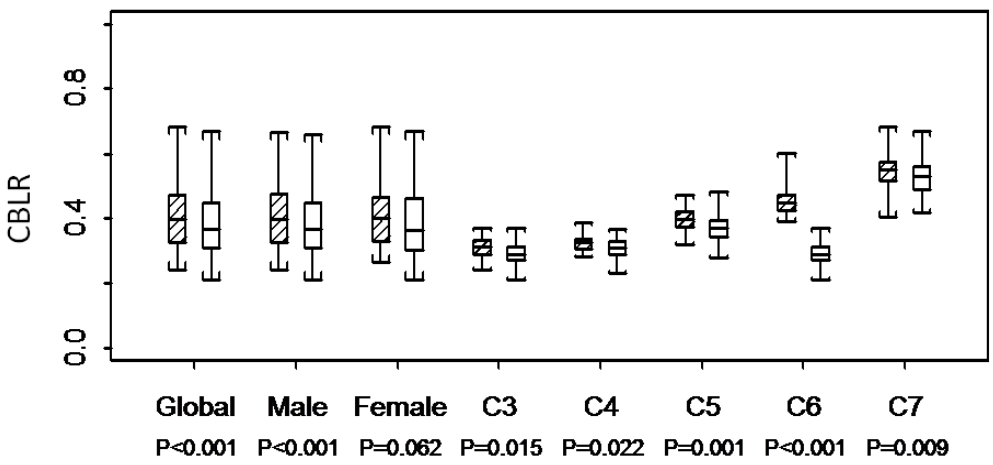

Figure 6. Box and Whisker Plots and associated *P*-values of the canal height to body length ratio (CBLR) values in both Doberman Pinschers with (not striped) and without (striped) clinical signs of DAWS globally and for different gender, and different assessed vertebrae seperately.

Caudal canal to cranial canal height ratio

The CCHR values for Doberman Pinschers with and without clinical signs of DAWS for the different assessed cervical vertebrae and different gender are presented in Table 1 and Figure 7. Although there was no global significant difference for CCHR between Doberman Pinschers with and without clinical signs of DAWS, the CCHR value for C7 seperately was significantly larger in Doberman Pinschers with DAWS (Figure 7). This indicates a more pronounced funnel-shaped vertebral canal in Doberman Pinschers with DAWS at the level of C7. In the group of Doberman Pinschers with DAWS, there was a significant influence of the assessed cervical vertebra ($P < .0001$). In this group, the value for CCHR increased progressively from C3 to C7. There was no significant association between the gender of the dogs and the CCHR value in either of the groups of dogs (Figure 7). There was a significant influence of age on CCHR in the group of Doberman Pinschers without DAWS ($P = 0.0042$). In this group, each increase of age by one month resulted in an increase of CCHR value by 0.0018. Visual inspection of the ROC curve for CCHR for C5 between Doberman Pinschers with and without clinical signs of DAWS (Figure 8) demonstrated a poor ability to discriminate between Doberman Pinschers with and without clinical signs of DAWS. Visual inspection of the ROC curve for C7 (Figure 9) revealed that a CCHR value of 1.48 corresponded with a sensitivity of 0.8 and a specificity of approximately 0.55.

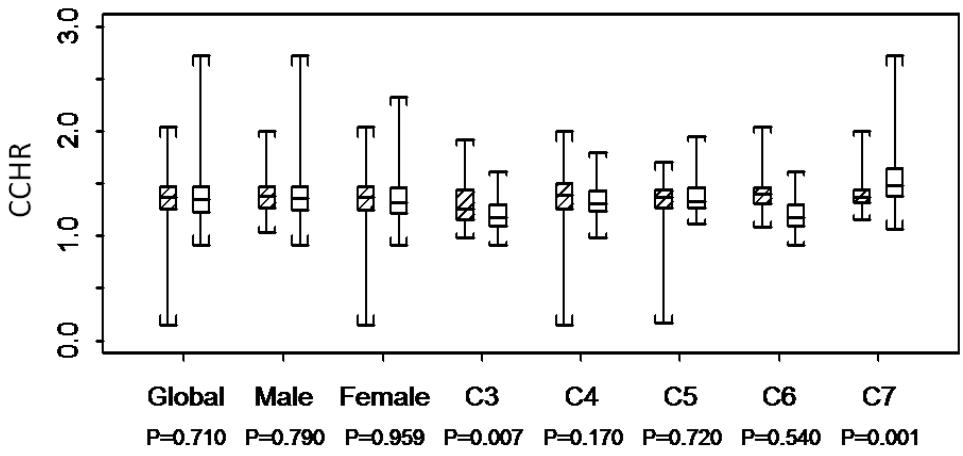

Figure 7. Box and Whisker Plots and associated *P*-values of the caudal canal to cranial canal height ratio (CCHR) values in both Doberman Pinschers with (not striped) and without (striped) clinical signs of DAWS globally and for different gender, and different assessed vertebrae seperately.

Table 1. Mean canal height to body height ratio, mean canal height to body length, and mean caudal canal to cranial canal height ratio values for Doberman Pinschers with and without clinical signs of DAWS, both globally, for different gender and for the different assessed cervical vertebrae seperately

Assessed parameter	**Global**	**Male**	**Female**	**C3**	**C4**	**C5**	**C6**	**C7**
Canal height to body height ratio								
DAWS affected	0.76*	0.73*	0.80*	0.84*	0.79*	0.74*	0.70*	0.72*
Not DAWS affected	0.84*	0.82*	0.89*	0.92*	0.86*	0.82*	0.80*	0.81*
Canal height to body length ratio								
DAWS affected	0.38*	0.38	0.39	0.29	0.31	0.38*	0.42*	0.53*
Not DAWS affected	0.41*	0.41	0.41	0.31	0.33	0.40*	0.46*	0.55*
Caudal canal to cranial canal height ratio								
DAWS affected	1.36	1.38	1.34	1.20	1.33	1.36	1.38	1.53*
Not DAWS affected	1.37	1.38	1.35	1.31	1.39	1.35	1.40	1.41*

Effect of clinical status and gender, both globally and for the different vertebrae seperately, was evaluated by the mixed model with dog as random effect. Significance for global comparisons was claimed when $P < 0.05$, significance for pairwise comparisons was claimed when $P < 0.01$. Significant differences are marked in the table (*)

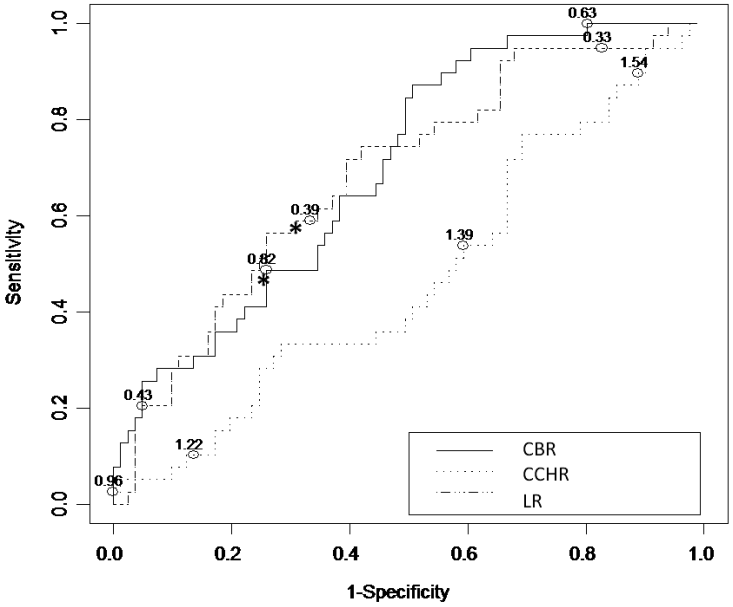

Figure 8. ROC curves for CBR, CBLR and CCHR at the level of the fifth cervical vertebra between Doberman Pinschers with and without clinical signs of DAWS. The points on the ROC curves combining the highest sensitivity with specificity for a certain ratio are marked by an asterisk (*). This was not done for CCHR.

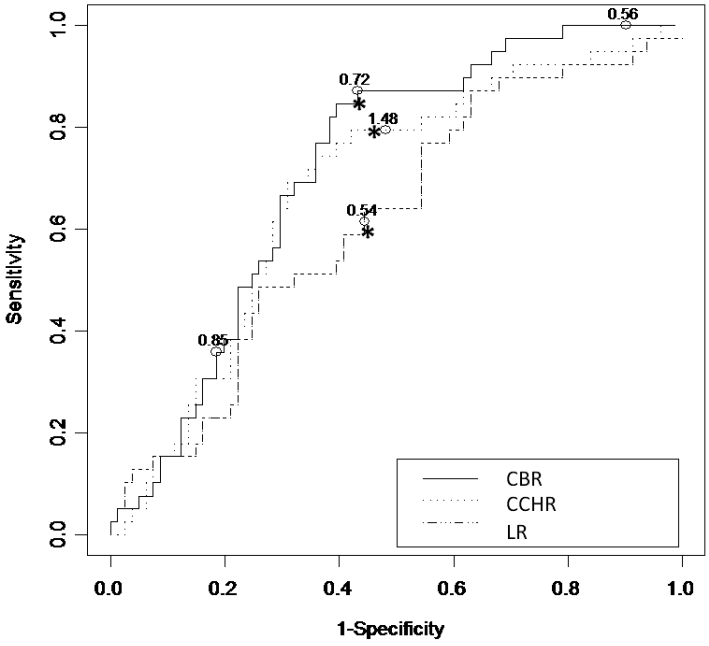

Figure 9. ROC curves for CBR, CBLR, and CCHR at the level of the seventh cervical vertebra between Doberman Pinschers with and without clinical signs of DAWSDAWS. The points on the ROC curves combining the highest sensitivity with specificity for a certain ratio are marked on the figure by an asterisk (*).

Interobserver agreement

The constructed Bland-Altman-plots between the 2 observers for the three assessed radiographic ratios are presented in Figure 10. For CBR, the mean difference between both observers was 0.0034, the vast majority of individual values of difference were close to zero, and the limits of agreement were +/- 0.068 (9 and 8% of the mean CBR value of DAWS-affected and control dogs, respectively). For CBLR, the mean difference between both observers was 0.0022, the vast majority of individual values of difference were close to zero, and the limits of agreement were +/-0.039 (10 and 9% of the mean CBLR value of DAWS-affected and control dogs, respectively). For CCHR, the mean difference between both observers was 0.0077, the vast majority of individual values of difference were close to zero, and the limits of agreement were +/- 0.14 (10% of the mean CCHR value of DAWS-affected and control dogs).

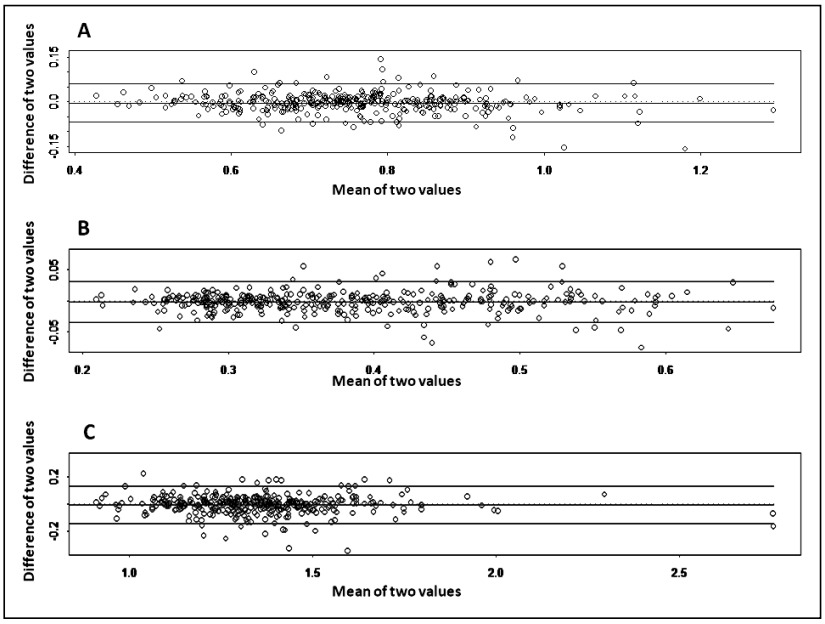

Figure 10. Bland-Altman plot for (A) CBR, (B) CBLR, and (C) CCHR. The X-axis shows the mean of the 2 values, whereas the Y-axis shows the difference between the 2 values. The horizontal lines on the figure correspond with the mean difference of the 2 values (middle horizontal line) and the 95% limits of agreement (upper and lower horizontal line).

Discussion

This study determined the values of 3 different radiographic vertebral body and canal ratios in Doberman Pinschers with and without clinical signs of DAWS. Ratios were used to exclude the effect of magnification and individual variation within the same breed of dog. Because the two measurements for each ratio are in the same anatomic plane and are similarly affected by magnification, the assessment of ratios is independent of magnification.[34,36] All 3 evaluated vertebral ratios showed significant differences between both groups of dogs. The results of this study are in agreement with earlier published studies suggesting a higher incidence of vertebral canal stenosis and the presence of a funnel-shaped caudal vertebral canal in Doberman Pinschers with clinical signs of DAWS.[19,22,,23] However, the constructed ROC curves were unable to demonstrate reliable threshold values with a combined high sensitivity and high specificity to discriminate between Doberman Pinschers with and without clinical signs of DAWS.

Significantly smaller CBR's from C3 through C7 in DAWS-affected dogs compared with control dogs supports the hypothesis that generalized relative stenosis of the entire cervical vertebral canal occurs more often in Doberman Pinschers with DAWS. This is in agreement with findings in human and equine studies.[33,36,37,40,41] In relative stenosis, the diameter of the vertebral canal is less than that expected for an individual animal, but does not cause neural compression in itself.[42]This implies decreased available space between the spinal cord and the vertebral canal and carries an increased risk of becoming clinically significant on the development of space-occupying conditions of the vertebral canal[29], such as age related intervertebral disk degeneration and protrusion. On the other hand, larger CBR and CBLR values in clinically unaffected dogs suggest that these dogs have a relatively wider vertebral canal. This can contribute to the fact that some dogs can tolerate rather severe degenerative abnormalities of the vertebral canal, such as disk-associated cervical spinal cord compression, without developing clinical signs suggestive of cervical myelopathy.[23,43,44] It is likely, that relative stenosis of the vertebral canal not only depends on the size of the vertebral canal, but also on the size of the spinal cord in the same individual.[30] However, only the vertebral canal can be visualized by survey radiographs. The CBR ratio was significantly larger in female than in male animals. This in agreement with results of human studies. [40,41] Another assessed vertebral ratio, the CBLR, also demonstrated to be significantly smaller in DAWS affected Doberman Pinschers. Since this ratio is also directly dependent on the vertebral canal

diameter, this result further supports the hypothesis of increased incidence of vertebral canal stenosis in Doberman Pinschers with clinical signs of DAWS.

A funnel-shaped vertebral canal at the level of C6 and C7 is supposed to be a risk factor for spinal cord compression at the narrowed cranial orifice of the respective vertebra.[8,19,45] This funnel-shape is represented by the CCHR.[22] A larger CCHR results in a more pronounced funnel-shaped vertebral canal (Figure 4). An osteological study comparing the CCHR between different breeds demonstrated a higher CCHR in the Doberman Pinscher breed.[22] Our study additionally demonstrated a significantly higher value for CCHR at the level of C7 in DAWS affected Doberman Pinschers when compared to Doberman Pinschers without clinical signs of DAWS. In agreement with a radiographic study in 1991[19], the CCHR value increased from the cranial to the caudal cervical vertebrae in both groups of dogs. These findings support the hypothesis that a funnel-shaped vertebral canal at the level of C7 is a potential contributing factor for Doberman Pinschers to develop DAWS-associated spinal cord compression at this site. The predilection of the C6-C7 intervertebral disk space is possibly further determined by the fact that age related intervertebral disk degeneration and protrusion in clinically normal Doberman Pinschers occur more frequently at the more caudally intervertebral disk spaces.[23,43]

The points of measurement in this study are somewhat different when compared with comparable canine and equine studies.[36,37,39,46] Vertebral body and vertebral canal height were measured from the midpoint of the dorsal surface of the vertebral body and not at the cranial part[36,37,39,46] of the vertebral body and canal. This was done because measurements of the cranial part of the vertebral canal and vertebral body can be influenced by pathological changes like narrowing of the cranial orifice, spondylosis deformans, and dorsoventral flattening of the cranioventral border of the vertebral body. Such abnormalities are commonly seen in Doberman Pinschers with DAWS and can also occur in clinically normal Doberman Pinschers.[21,43] To allow the use of distinct landmarks resulting in consistent measurements, VBL was measured at the dorsal surface and not at the center[36,39,46] of the vertebral body.

We assessed interobserver agreement using Bland-Altman plots (Figure 10). How far apart measurements can be without causing difficulties will be a question of judgment - a clinical question, not a statistical one. This decision will vary for different clinical applications. . It was concluded that all three assessed ratios demonstrated a good interobserver agreement.

The mean differences were always close to zero, the vast majority of individual values of difference were situated around zero (low variability), and the limits of agreement did not exceed 10% of the mean values. Although the ranges in limits of agreement for the different ratios suggest that the assessed measurements can be considered reliable, it can be discussed if they should also be considered clinically acceptable for the purposes of this study. The differences in mean ratio values between both groups of dogs was only 9% for CBR and 7 % for CBLR, compared to the mean values of non DAWS affected dogs. The fact that the limits of agreement approached or even exceeded these differences, question the clinical utility of these ratios in individual dogs. The biggest variability was noted for the CCHR. This can probably be explained by the superposition of the caudal articular facets on survey radiographs which can complicate correct identification of the anatomical landmarks.

Although vertebral body and canal ratios may have potential use as a screening tool for dogs that are at risk for developing clinical signs associated with DAWS, there are several reasons to believe that this is currently inappropriate. Except from the aforementioned limitation considering accurate interobserver agreement, the Box and Whisker plots (Figures 5, 6 and 7) demonstrated considerable overlap of vertebral ratio values between clinically affected and control dogs. Further, the constructed ROC curves (Figures 8 and 9) did not demonstrate ratio values with both high sensitivity and high specificity. For these reasons, screening Doberman Pinschers for relative vertebral canal stenosis by our assessed vertebral ratios is not recommended and may result in labeling many dogs stenotic that will never develop clinical signs. The different vertebral ratio values were significantly influenced by the respective assessed vertebra. Therefore, it is only possible to compare values between different dogs for the same assessed vertebra. Although the use of vertebral ratios allows the comparison of vertebral body and canal dimensions of dogs of different size and conformation[46], only Doberman Pinschers were included in this study. It is suggested that vertebral body and canal ratios are breed specific and that cervical vertebral ratios derived from data collected for one breed should not be extrapolated to other breeds.[39] Further studies are indicated to confirm this hypothesis. In this study, conventional and digital radiographs of Doberman Pinschers with and without clinical signs of DAWS were studied. Currently, little is known in veterinary literature about the agreement and accuracy of both imaging modalities to perform linear vertebral body and canal measurements. However, several studies in human endodontics have demonstrated comparable agreement and accuracy for both imaging modalities to perform linear root-canal measurements.[47-49]

We recognize several limitations of this study. First, the first author was not blinded to clinical status of the dogs. This could be a potential cause of observer bias. Secondly, because of the retrospective nature of this study, not all control Doberman Pinschers underwent a neurological examination and advanced medical imaging to exclude presence of disease. Thirdly, the control Doberman Pinschers were not consequently submitted to neurological evaluation at set times to exclude the development of clinical signs at a later moment in life. Because of the latter, there is currently no information available about the predictive value of these ratios. Therefore, the authors hope that the results of this study, will give rise to well designed, prospective studies with neurological reassesments, eventually combined with follow-up medical imaging, at predetermined time points.

Conclusions

In conclusion, the results of this study suggest that Doberman Pinschers with clinical signs of DAWS have significantly more often generalized vertebral canal stenosis combined with a funnel shaped vertebral canal at the level of C7 than Doberman Pinschers without clinical signs of DAWS. Although these ratios can provide additional information to contributing risk factors and pathogenesis of DAWS in Doberman Pinschers, the authors believe caution should be taken in the clinical application of these ratios in individual dogs. Although the differences were strongly significant, the Box and Whisker plots demonstrated considerable overlap in values, the Bland-Altman plots demonstrated limits of agreement that approached or exceeded the differences between both groups of dogs, and we were unable to identify reliable threshold values to distinguish clinically affected from control dogs. More studies are indicated to compare ratio values obtained for Doberman Pinschers with those of other breeds, to evaluate the positive predictive value of these vertebral ratios, and to assess the correlation of these radiographic ratios with values, representing vertebral canal stenosis, measured on transverse CT or MR images.

Footnote: [a] Osirix Image processing software, California, USA.

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Chapter 4.2

AGREEMENT AND REPEATABILITY OF LINEAR VERTEBRAL BODY AND CANAL MEASUREMENTS USING COMPUTED TOMOGRAPHY AND LOW FIELD MAGNETIC RESONANCE IMAGING

AGREEMENT AND REPEATABILITY OF LINEAR VERTEBRAL BODY AND CANAL MEASUREMENTS USING COMPUTED TOMOGRAPHY AND LOW FIELD MAGNETIC RESONANCE IMAGING

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Summary

The objective of this study was to evaluate agreement and repeatability of vertebral column measurements using computed tomography (CT) and magnetic resonance imaging (MRI).

Eighteen dogs with disk associated wobbler syndrome and 3 dog cadavers were retrospectively included. All dogs underwent computed tomography (CT) and low field magnetic resonance imaging (MRI) of the cervical vertebral column.

Five measurements of the 5th cervical vertebra were performed: vertebral body length (VBL), vertebral canal height (VCH), vertebral body height (VBH), vertebral canal width (VCW), and vertebral body width (VBW). Measurements were performed independently twice by 2 observers. Bland-Altman plots were created to evaluate agreement. Cadaveric vertebrae with soft tissue removed had the same variables and actual dimensions measured.

The largest discrepancy between CT and MRI measurement was for VBL (mean difference ± SD = 1.262 mm ± 1.245; $P < .001$), with the difference for all the other variables being acceptable. The 1st measurement was significantly higher than the 2nd only for VBL using CT (mean difference = 0.476 mm ± 1.120; $P = .009$), with all other variables having acceptable differences. Mean difference for all measurements between 2 observers was small, except for VBL using CT (mean difference = 0.762 mm ± 1.042; $P < .001$). Only the difference for VBL between CT and cadaver specimens was statistically significant.

Our results suggest high repeatability and good agreement for most vertebral measurements of interest. VBL measurement using CT was considered problematic. Provided limitations are understood, linear measurements of vertebral dimensions from CT and MRI images can be used clinically.

Introduction

Disorders of the vertebral column and spinal cord can be diagnosed by conventional radiography, myelography, computed tomography (CT) or magnetic resonance imaging (MRI) or a combination of techniques.[1] CT and MRI are increasingly used for the diagnosis of neurologic disorders and have largely replaced the use of more invasive techniques like myelography. These advanced medical imaging modalities have increased sensitivity, provide accurate anatomic detail, and generate cross sectional images that can be reconstructed in different planes. It is generally accepted that CT gives excellent bone detail whereas MRI is superior to evaluate soft tissue structures including bone marrow.[2-4]

CT and MRI images have been used for morphometric linear and angular measurements of the vertebral column and spinal cord in different anatomic planes.[5-9] Study results provide information about the pathogenesis, diagnosis, clinical decision-making, presurgical planning, and prognosis of different disorders affecting the vertebral column and spinal cord; however, little is known about the intra –and interobserver agreement of measurements using different imaging modalities or agreement between CT and MRI derived measurements.

Our purpose was to evaluate intraobserver and interobserver agreement, and agreement between measurements made on CT and MRI images of the 5th cervical vertebra (C5) and vertebral canal region.

Materials and Methods

MR and CT images of 18 dogs with disc associated wobbler syndrome (DAWS) were analyzed retrospectively. These dogs were originally enrolled in a study related to diagnosis and treatment of DAWS. Owner consent was obtained before study entry. Complete blood count (CBC) and serum biochemical profile were obtained for all dogs. Echocardiographic examination and standard mucosal bleeding times were performed in most dogs. To compare measurements derived from images with actual dimensions, cadavers of 3 dogs euthanatized for unrelated reasons had the same imaging protocol and then dimensions of the variables of interest were measured using vernier calipers.

CT Examination

Anesthetized dogs (n=18) and dog cadavers (3) were positioned in dorsal recumbency with the head and neck extended and thoracic limbs fixed parallel to the chest wall. Contiguous slices were made from the mid 4th cervical vertebra (C4) to the mid 7th vertebra (C7), parallel to the intervertebral disk spaces. A single row detector spiral CT (Prospeed, GE Medical Systems, Milwaukee, WI) was used with a tube voltage of 100 kVp and 100 mAs. Slice thickness was 3 mm and a bone algorithm was used. 2D multiplanar reconstructed images were made in the sagittal plane.

MRI Examination

MRI examination was performed 1 day after CT examination with the dogs positioned identically. T1 and T2 weighted sequences were performed in the sagittal, dorsal, and transverse planes. Transverse images were aligned perpendicular to the cervical spine. Images were acquired from the 2nd (C2) to the 7th (C7) cervical vertebra in the sagittal and dorsal plane and from C4 to C7 in the transverse plane by a permanent, 0.2T, MRI magnet (Airis Mate, Hitachi, Japan). The cervical spine was positioned in a joint coil with an inner diameter of 19 cm. T1 and T2 weighted images (WI) were obtained using a spin echo technique. Repetition time (TR) and time to echo (TE) of the sagittal T1 WI were TR = 700 ms and TE = 25 ms. In the sagittal T2 weighted study, TR was 2700 ms and TE = 125 ms. Transverse T1 WI were performed with TR = 1100 ms and TE = 25 ms, and in the T2 weighted transverse images the settings were TR = 5000 ms and TE = 120 ms. Settings used for dorsal images were for T1 weighted: TR = 600 ms; TE = 25 ms and for T2 weighted: TR = 3900 ms; TE =

120 ms. Slice thickness ranged from 2.5 - 4 mm in the sagittal and dorsal images and was 3 mm in the transverse sequences with no interslice gap.

Measurements (Figure 1)

All measurements were made at C5. This region was selected because it was routinely included in the scanning field and has minimal risk of pathologic findings that could interfere with the measurements (ie, vertebral body abnormalities, excessive new bone formation); such pathologic findings were considered an exclusion criteria. The DICOM (Digital Imaging and Communications in Medicine) studies were retrieved and analyzed on eFilm Workstation PACS software (Merge efilm, Merge eMed, Milwaukee, WI) with accuracy limited to 1 mm. In each dog, 5 measurements were made: vertebral body length (VBL), vertebral canal height (VCH), vertebral body height (VBH), vertebral canal width (VCW), and vertebral body width (VBW). VBL, VCH, and VBH were assessed at mid-sagittal T1 WI and at the mid-sagittal reconstructed CT images. VCW and VBW were assessed on transverse T1 W MR images and transverse CT images at the level of the caudal endplate of C5. Each observer (SDD, IG) made measurements twice and independently, with a 2 week separation between each measurement to minimize bias. Each evaluator had an interactive teaching session on methodology and was provided with written instructions. Because of possible variations in magnification, survey radiographs of the cervical spines were not included.[10]

Cadaver Measurements

After imaging the cervical spinal column of 3 canine cadavers, the soft tissue was removed to facilitate measurement of vertebral dimensions. VCW and VBW were measured at the level of the caudal endplate of C5, then the vertebral body was sectioned sagitally and VBL, VCH, and VBH were measured (Figure 1) once by investigator SDD using vernier calipers with an accuracy of 0.01 mm.

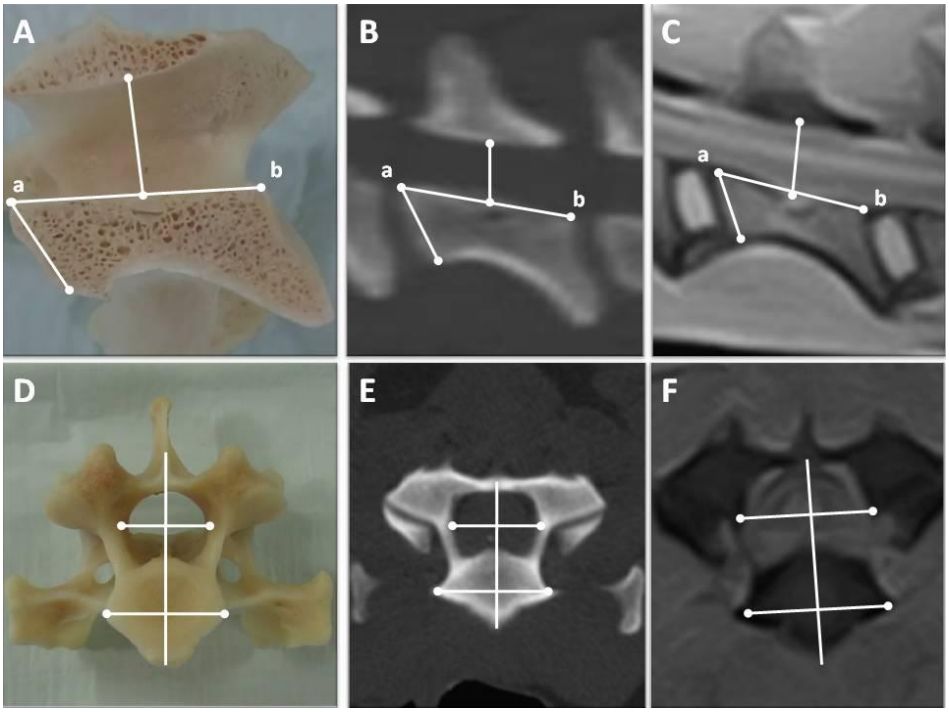

Figure 1. Points of measurement on a cadaveric specimen (A, D), CT (B, E), and MRI (C, F). A, B, C) Vertebral body length measured from (a) to (b). Vertebral canal height measured from half the distance a-b to the shortest distance to the lamina. Vertebral body height measured from (a) to the most cranioventral point of the cranial endplate. D, E, F) Vertebral canal and body width assessed at their respective broadest points.

Data Analysis

Statistical analysis for VCW, VBW, VBL, VCH, and VBH was based on the paired t-test. First, CT was compared with MRI using a paired t-test with dog-observer-measurement sequence combinations as block factor. Second, the 1st measurement of each observer was compared with the 2nd measurement of each observer (intra-observer agreement) for CT and MRI separately using a paired t-test with dog-observer combinations as block factor. Third, the 1st observer was compared with the 2nd observer (inter-observer agreement) for CT and MRI separately using a paired t-test with dog-measurement sequence combinations as block factor. Finally, CT and MRI were compared with the true value (based on cadaver measurements) by paired t-test with dog as block factor.

Evaluation of the variability next to difference was based on the Bland-Altman plot which compares 2 measurement sets with difference between measurements on the Y axis and the average of the 2 measurements on the X axis. If 1 method is higher sometimes and method 2

is higher at other times, the mean differences will be close to zero. If the mean difference is not close to zero, this indicates that the 2 measurement methods are producing different results. Using Bland-Altman plots, the mean difference between the 2 techniques, between the 2 observers and between the 2 measurements of the same observer, its standard deviation (SD), and the lower and upper limit of agreement (mean ± SD) are given (Figures 2, 3).

Results

Dogs

Of 18 dogs, 12 were Doberman Pinschers with 2 Dalmatian, 2 Whippet, 1Weimaraner, and 1 Bernese mountain dog; 7 dogs were male and 11 were female. Median age was 7.9 years (range, 4.6 years -12.8 years) and median weight was 32.2 kg (range, 11 - 44.6 kg). No abnormalities were detected on physical examination, CBC, serum biochemical profile, standard mucosal bleeding time, and echocardiographic examination. Dog cadavers were a 2-year-old female Labrador retriever, a 7-year-old male crossbreed, and an 18 month old male Bordeaux Dog.

Agreement between MRI and CT measurements

CT leads to significantly higher values than MRI for VBL (mean difference ± SD = 1.260 mm ± 1.250; P < .001) and for VBW (mean difference = 0.238 mm ± 0.701; P = .0027), whereas CT leads to significantly lower values than MRI for VCW (mean difference = -0.131 mm ± 0.530; P = .0269). CT did not differ significantly from MRI for VCH (mean difference = 0.048 mm ± 0.489; P = .374) and VBH (mean difference = -0.059 mm ± 0.585; P = .356). Bland-Altman plots indicate low variability of the difference between CT and MRI for VCH, VBH, and VCW, a somewhat higher variability for VBW, and an unacceptably high variability for VBL (Figure 2). The resulting limits of agreement (LOA) were considered clinically acceptable for all measurements except for VBL (upper LOA: 3.70 mm).

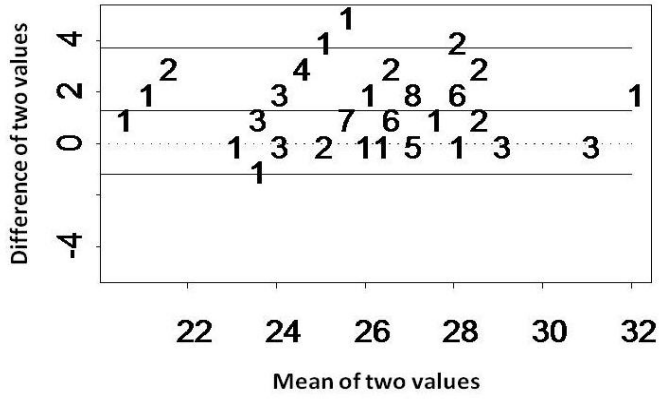

Fig 2. Bland-Altman plot for the measurement sets for vertebral body length (VBL) between CT and MRI. The X-axis shows the mean of the 2 values, whereas the Y-axis shows the difference between the 2 values. The numbers on the figure represent how many times a specific combination occurred. The horizontal lines on the figure correspond with the mean difference of the 2 values (middle horizontal line) and the 95% limits of agreement (upper and lower horizontal line). The dotted horizontal line corresponds with a zero mean difference for the measurements.

Intraobserver Agreement

For both observers, the 1st measurement was significantly higher than the 2nd measurement only for VBL using CT (mean difference = 0.476 mm ± 1.120; P = .0093). The mean difference between 1st and 2nd measurements for the other variables was always small, regardless the used technique (Table 1). The Bland-Altman plots indicate very low variability between the intraobserver difference of the 1st and 2nd measurement, except for VBL using CT for both observer (Figs 3 A, B) and a somewhat higher variability for VBW using CT for 1 of the observers. The resulting LOA were considered clinically acceptable, with the exception of the upper LOA for VBL using CT (2.67 mm).

Interobserver Agreement

There was a significant difference between all measurements for both observers, except for VBL using MRI (Table 1). Mean difference for all measurements between the 2 observers was close to zero, with the highest value for VBL using CT (mean difference = 0.762 mm ± 1.042; P < .001) (Figs 3 C, D). The Bland-Altman plots indicate low variability for VBL, VCH, and VBH using MRI and VCH, VBH, and VCW using CT and a somewhat higher variability for the other measurements. The resulting LOA were considered clinically acceptable, with the exception of the upper LOA for VBL using CT (2.80 mm) and the lower LOA for VBW using CT and MRI (-1.87 mm and -2.17 mm, respectively).

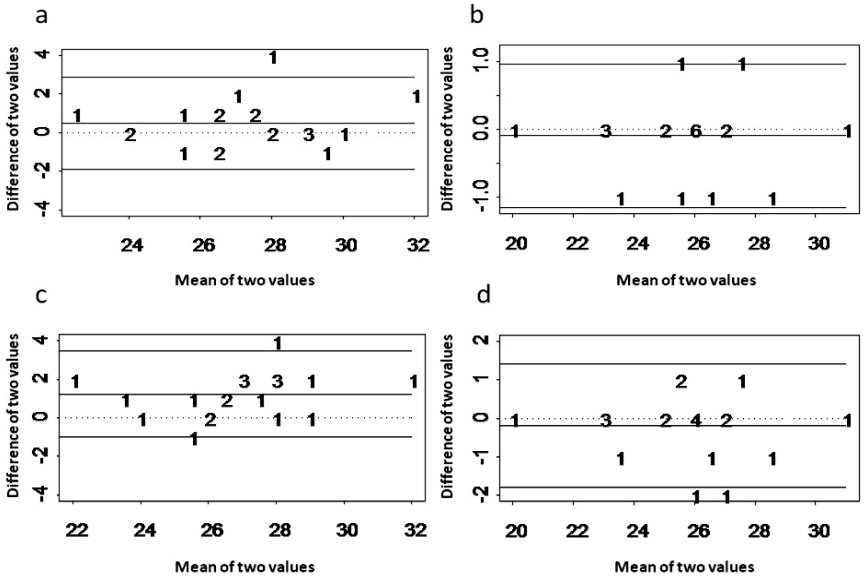

Fig 3. Bland-Altman plots for the measurement sets for vertebral body length (VBL) using CT and MRI between different observers and different times. Measurement sets for 1 observer at different times using CT and MRI (a) and (b), respectively. Measurement sets between different observers using CT and MRI (c) and (d), respectively. Overall, a higher mean difference and variability using CT (a) and (c) can be noticed when compared with MRI (b) and (d).

Cadaver Measurements

CT leads to significantly higher values than the actual dimension from the cadaveric vertebrae for VBL (mean difference = 2.220 mm ± 0.169; P = .00583). Mean differences between other measurements were lower and did not reach statistical significance.

Table 1. Mean differences, *P*-values, standard deviations and associated limits of agreement (LOA) for the different measured variables

Assessed variable	Mean difference (mm)	*P* value	SD (mm)	Lower LOA (mm)	Upper LOA (mm)
CT-MRI					
VBL	1.262	<0.001	±1.245	-1.179	3.702
VCH	0.0482	0.374	±0.489	-0.909	1.006
VBH	-0.0595	0.356	±0.585	-1.205	1.086
VCW	-0.131	0.0269	±0.530	-1.169	0.907
VBW	0.238	0.0027	±0.701	-1.135	1.611
Intraobserver (M1-M2)					
VBL CT	0.476	0.0093	±1.118	-1.715	2.667
VBL MRI	-0.143	0.0832	±0.515	-1.152	0.867
VCH CT	-0.0238	0.710	±0.408	-0.823	0.775
VCH MRI	0.0732	0.262	±0.407	-0.724	0.870
VBH CT	0.167	0.0510	±0.531	-0.874	1.207
VBH MRI	0.0952	0.323	±0.610	-1.100	1.290
VCW CT	-0.0952	0.290	±0.569	-1.211	1.021
VCW MRI	-0.0238	0.743	±0.462	-0.930	0.882
VBW CT	0.214	0.0596	±0.708	-1.174	1.603
VBW MRI	0.0714	0.538	±0.737	-1.372	1.515
Interobserver (obs1-obs2)					
VBL CT	0.762	<0.001	±1.042	-1.281	2.805
VBL MRI	-0.0476	0.570	±0.532	-1.091	0.996
VCH CT	0.167	0.0331	±0.484	-0.782	1.115
VCH MRI	0.195	0.0190	±0.505	-0.794	1.184
VBH CT	0.262	0.0099	±0.620	-0.952	1.476
VBH MRI	0.238	0.0235	±0.648	-1.031	1.508
VCW CT	0.286	0.0058	±0.628	-0.945	1.517
VCW MRI	0.0405	<0.001	±0.491	-0.557	1.367
VBW CT	-0.262	0.0468	±0.818	-1.866	1.342
VBW MRI	-0.405	0.0064	±0.901	-2.171	1.362

VBL = vertebral body length; VCH = vertebral canal height; VBH = vertebral body height; VCW = vertebral canal width; VBW = vertebral body width; M1 = first measurement; M2 = second measurement; obs1 = observer 1; obs2 = observer 2

Discussion

We are unaware of other in vivo studies in dogs comparing intra –and interobserver agreement of linear vertebral body and canal measurements using CT and MRI.

Agreement between CT and MRI Measurements

There was good agreement between most vertebral measurements using CT and MRI in dogs, similar to a report in people[10]; however, poor and clinically unacceptable agreement was observed for VBL. This was caused by a highly significant and consistently higher value for this variable using CT. Results from cadaveric vertebrae confirmed this finding and indicated a consistent and clinically important overestimation of VBL using CT compared with MRI. This important finding is in agreement with studies in people and using phantoms, [11,12] where there were larger values for measurements in the reconstructed craniocaudal or z-axis, dependent on the selected reconstruction parameters.[12] This overestimation occurred mainly in images with limited spatial resolution in the craniocaudal plane of the reconstructed CT images.[11,13] Spatial resolution of most CT scanners is less in the reconstructed sagittal plane than in the transverse (image) plane,[14] largely because of the partial volume effect.[11,13,14] The partial volume effect is explained by the fact that a CT image represents a certain slice thickness: when 2 different densities are present in a single slice, the average density is displayed in the image. This occurs where only an edge of a structure is included in the slice and results in averaging of the tissues.[15] Smaller slice thickness and overlap between slices decreases the effects of partial volume averaging.[11,13,15] This effect is illustrated in a recent study where reconstructed CT images were used for assessment of joint spaces in the canine elbow.[16] There was good agreement between reconstructed CT images and cadaveric specimens; however, slice thickness was 1.2 mm with an overlap of 0.2 mm between the slices. Disadvantages of such a detailed CT-imaging protocol are the prolonged scanning times and increased patient radiation exposure.[13]

There is uncertainty about the usefulness of MRI to assess cortical bone.[2] Our results suggest that accurate bony measurements can also be made with MRI. Further, use of devices with higher magnetic fields than the 0.2T we used would yield more anatomic detail and less variability in measurements.[17]

Intra –and Interobserver Agreement

Our data indicate that except for isolated variables, linear measurements from axial and sagittal CT and MRI images of the vertebral body and canal have high repeatability. The observed mean differences were small and largely accounted for by limitations in precision of the calibrated ruler. In agreement with others studies, intraobserver agreement was considerably higher than interobserver agreement.[18,19] This conclusion was based on lower mean differences, lower standard deviations, and lower variability evident in respective Bland-Altman plots for intraobserver agreement when compared with interobserver agreement. The relative lower intra –and interobserver agreement for VBL and lower interobserver agreement for VBH using CT when compared with MRI is likely caused by the reconstruction of these images. Sagittal reconstruction of the axial CT images can cause imprecise resolution of the bone contour leading to loss of detail and a degree of subjectivity in accurately measuring certain variables.[16] Like CT, MRI provides cross-sectional images but, unlike CT, these can be directly obtained in any plane without the need for computer assisted reconstruction and subsequent detail loss.[2] The relatively lower interobserver agreement for VBW using CT and MRI is likely caused by the irregular margins normally seen in the endplates of each vertebra. This may have affected the location of the lines traced for measurement of VBW.

Interpretation and Study Limitations

Measurements made from CT and MRI images are only useful if they have low variability, even if on average the difference is zero (no bias). On the other hand, even if measurements differ significantly from each other, but the largest part of the differences falls in an interval that is clinically acceptable, the technique is still acceptable.

It is most unlikely that measurements within and between observers, and made using different imaging modalities will agree exactly yielding identical results for all measurements, so we assessed agreement using Bland-Altman plots. The information regarding clinical significance must be interpreted with care because a significant difference does not indicate a clinically important difference or a lack of agreement between both measurement sets. Statistical significance only indicates that the mean difference is caused by a consistently higher or lower value for 1 of the 2 measurement sets. The most important and clear example in our study is the highly statistically ($P < 0.001$) greater value for VBL using CT compared with MRI. Because the mean difference, variability, and associated LOA were very high, this

difference was considered important and clinically unacceptable. How far apart measurements can be without causing difficulties will be a question of judgment - a clinical question, not a statistical one. This decision will vary for different clinical applications. We considered a mean difference >1 mm (accuracy of the measurement tool) and LOA that approached ±2 mm as clinically important. Such values can and probably will differ for different clinical objectives.

Our results are limited by the retrospective nature of the study and by the fact that the effects of different image analysis software packages were not investigated. Certain variables, like VCH and VBH are probably easier and more accurately assessed on transverse images. These measurements were not performed on the transverse images because of differences in the orientation of the transverse slices between CT and MRI images. It is possible that more precise measurement tools (1 mm in this study) would have affected the observed differences and this could be of particular interest in assessment of rather small anatomic measurements, like VCH, VBH and VBW. This in part supported by the excellent intra -and interobserver agreement for MRI measurement of VBL (Figs 3 B, D) because this measurement generally accounted for the largest distance of all assessed variables.

Conclusions

Our results suggest high repeatability and good agreement for most cervical vertebral measurements using CT and MRI. Further, we demonstrated the limitations of linear measurements in sagittal reconstructed CT images, particularly in the craniocaudal plane. Evidence from human and phantom studies suggests that this unreliability can be improved by altering the operator settings of the CT scanner[11,12,15]; however this has not been investigated in dogs. Recognizing the usefulness and limitations of CT and MRI image measurements can be of considerable importance in clinical decision-making and presurgical planning for various disorders of the vertebral column and spinal cord.

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Chapter 4.3

LINEAR VERTEBRAL CANAL AND BODY RATIOS IN DOBERMAN PINSCHERS WITH DISK ASSOCIATED WOBBLER SYNDROME, CLINICALLY NORMAL DOBERMAN PINSCHERS AND CLINICALLY NORMAL ENGLISH FOXHOUNDS

LINEAR VERTEBRAL CANAL AND BODY RATIOS IN DOBERMAN PINSCHERS WITH DISK ASSOCIATED WOBBLER SYNDROME, CLINICALLY NORMAL DOBERMAN PINSCHERS AND CLINICALLY NORMAL ENGLISH FOXHOUNDS

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Adapted from: De Decker S, Gielen I, Duchateau L, Saunders J, Polis I, Van Bree H, Van Ham L. Linear vertebral canal and body ratios in Doberman Pinschers with disk associated cervical spondylomyelopathy, clinically normal Doberman Pinschers and clinically normal English Foxhounds. American Journal of Veterinary Research. In Press

Summary

To objective of this study was to evaluate vertebral ratios, reflecting vertebral canal stenosis, vertebral canal shape and vertebral body shape in dogs of different clinical status and breed.

Client-owned clinically normal Doberman Pinschers (n=20), English Foxhounds (n=18), and Doberman Pinschers with disk associated wobbler syndrome (DAWS) (n=18) were prospectively included in this study. All dogs underwent low-field magnetic resonance imaging (MRI) of the cervical vertebral column. Five measurements were made from C3 to C7: mid-vertebral canal height (VCHm), vertebral body height (VBH), cranial vertebral canal height (VCHcr), caudal vertebral canal height (VCHcd), and vertebral body length (VBL). Subsequently, four ratios were calculated: Canal height to body height ratio (CBR), defined as VCHm/VBH; Canal height to body length ratio (CBLR), defined as VCHm/VBL; Caudal canal height to cranial canal height ratio (CCHR), defined as VCHcd/VCHcr; Body length to body height ratio (BLHR) defined as VBL/VBH. The CBR and CBLR represent vertebral canal stenosis, CCHR describes vertebral canal shape and BLHR describes vertebral body shape.

CBR, CBLR and BLHR values for Doberman Pinschers with DAWS were significantly smaller compared with both groups of clinically normal dogs. The CCHR value for C7 was significantly larger in clinically affected Doberman Pinschers compared to English Foxhounds. There were no significant differences between clinically normal Doberman Pinschers and English Foxhounds.

Doberman Pinschers with DAWS have significantly smaller midsagittal vertebral canal heights, combined with more square shaped vertebral bodies and a funnel-shaped vertebral canal at C7. Breed specificity of the assessed vertebral ratios could not be demonstrated.

Introduction

Cervical spondylomyelopathy or wobbler syndrome is a covering term to describe different causes of congenital or acquired vertebral canal stenosis in several large and giant breed dogs.[1,2] It has been suggested that the term "wobbler" only describes the characteristic pelvic limb ataxia and not as such a specific disease entity.[1] Over years a few separate syndromes have been recognized.[3] Probably the most common and typical cause of cervical spondylomyelopathy is disk associated cervical spondylomyelopathy or disk associated wobbler syndrome (DAWS).[1,4,5] In DAWS, progressive caudal cervical spinal cord compression is typically caused by protrusion of one or more intervertebral disks, sometimes in combination with dorsal compression resulting from hypertrophied ligamentum flavum and rather mild vertebral body abnormalities.[1] It occurs in several middle-aged to older large breed dogs. The adult Doberman Pinscher is overrepresented.[1,5-9]

Although the exact etiology and pathogenesis of this disorder remain unknown [1,2], preexisting relative stenosis of the vertebral canal has been suggested as a contributing risk factor for the development of clinical signs.[10-12] This hypothesis is strengthened by the results of several studies demonstrating a narrower cervical vertebral canal in Doberman Pinschers with clinical signs of cervical spondylomyelopathy compared to control dogs.[12,13] The methodology of measuring the relative size of the vertebral canal differs between reports.[10,12-16] Several human and veterinary studies have quantified vertebral canal stenosis by linear vertebral canal to body ratios.[13,15-20] Different clinical applications of such ratios have been evaluated in horses with and without stenotic cervical myelopathy [15,21] and recently in Doberman Pinschers with and without clinical signs of cervical spondylomyelopathy.[13]

Although the use of vertebral ratios offers the potential to compare vertebral body and canal dimensions of dogs of different size and conformation [16], it has been suggested that these ratios are breed specific and that values for one breed should not be extrapolated to other breeds.[20] However, little information is available to confirm or reject the latter hypothesis. The primary purposes of this study were to evaluate if these ratios were different between dogs of different clinical status and breed. Additionally, a new vertebral ratio indicating the shape of the vertebral body was evaluated. For this purpose, four different vertebral ratios were calculated in Doberman Pinschers with clinical signs of DAWS, clinically normal Doberman Pinschers and clinically normal English Foxhounds. It was hypothesized that the assessed vertebral ratios were significantly different between Doberman Pinschers with and without clinical signs, confirming a higher incidence of relative vertebral canal stenosis in

clinically affected dogs, and between clinically normal Doberman Pinschers and English Foxhounds, indicating breed specificity of these ratios.

Material and Methods

Animals

Fifty-six dogs were prospectively investigated. The experiment was conducted in accordance with the guidelines of the Animal Care Committee of the University of Ghent. Written owner consent was obtained prior to study enrollment. The dogs were divided in three groups. The first group consisted of 18 client-owned Doberman Pinschers with clinical signs of DAWS. This group consisted of 7 males and 11 females, between 4.4 and 10 years old (median 7.0 years). These dogs demonstrated clinical signs varying from only cervical hyperesthesia (n = 3) to ambulatory paraparesis/ataxia with or without cervical hyperesthesia (n = 6), ambulatory tetraparesis/ataxia with or without cervical hyperesthesia (n = 7), and non-ambulatory tetraparesis with or without cervical hyperesthesia (n = 2). The second group consisted of 20 client-owned clinically normal Doberman Pinschers. This breed was selected and included because of their known predisposition to DAWS. This group consisted of 11 males and 9 females, between 1.5 and 8 years old (median 5.0 years). The survey radiographs of 14 of these dogs were also included in a previous study about vertebral ratios.[13] The third group consisted of 18 client (n = 14) and laboratory-owned (n = 4) English Foxhounds. This breed was selected and included because of their comparable height at the shoulders and body conformation to Doberman Pinschers[a] and the fact that there is no known breed predisposition to neurological syndromes affecting the caudal cervical vertebral column. This group consisted of 9 males and 9 females, between 1.5 and 12 years old (median 5.0 years).

In all dogs, a physical and complete neurological examination, complete blood cell counts, and serum biochemistry analyses were performed. All Doberman Pinschers underwent an additional echocardiographic examination and standardized mucosal bleeding times. All owners of the clinically normal dogs were contacted at the end of the study and encouraged to have another neurologic examination performed on their dogs. The goal of this second examination was to evaluate whether the assessed vertebral ratios can be used to predict whether clinical signs will occur in a given time period. All neurologic examinations were performed by the first author.

Imaging Protocol and Measurements

A permanent, 0.2 Tesla (T) magnet[b] was used to perform MRI in all dogs. All MRI examinations were performed under general anesthesia. Anesthesia was induced with propofol and maintained by isoflurane in oxygen. Dogs were positioned in dorsal recumbency

with head and neck extended. The forelimbs were fixed parallel to the thoracic wall. The neck was positioned in a joint coil (circular transmit-receive coil) with an inner diameter 19 cm. T1 weighted spin echo and T2 weighted fast spin echo studies were performed in all dogs in a sagittal, dorsal and transversal plane. The images of this last plane were aligned perpendicular to the cervical spinal cord. The vertebral column was imaged from C2 to C7 in the sagittal and dorsal plane and from C4 to C7 in the transversal plane. In all studies, the field of view was 29 cm in the sagittal, 24 cm in the dorsal and 20 cm in the transversal planes. Slice thickness was 4mm in the sagittal and dorsal and 3 mm in the transversal images with no interslice gap in all studies.

All measurements were performed in a randomized sequence by the first author (SDD). For this purpose, he was blinded to signalment and clinical information of each dog.
Measurements were made on midsagittal T1-weighted images at the workstation with the available imaging software [c]. The images could be magnified as needed, but all measurements for a given vertebra were made at the same magnification. The accuracy of the measurement tool was limited to 0.001 mm. Reliability of linear vertebral body and canal measurements on low-field MRI was determined in a previous study by the authors.[22] The points of measurement are presented in Figure 1. The following five measurements were performed from the third (C3) to the seventh (C7) cervical vertebra:

- Mid-vertebral canal height (VCHm) was defined as the distance measured from the middle of the dorsal surface of the vertebral body to the closest point of the spinolaminar line (junction between its laminae and spinous process).[17]
- Vertebral body height (VBH) was defined as the distance between the midpoint of the dorsal surface of the vertebral body to the ventral surface of the vertebral body measured parallel to the cranial vertebral endplate.
- Cranial vertebral canal height (VCHcr) was defined as the distance between the most ventrocranial point of the lamina and the craniodorsal border of the same vertebral body. The VCHcr was measured perpendicular to the dorsal surface of the vertebral body.
- Caudal vertebral canal height (VCHcd) was defined as the distance between the most dorsocaudal point of the vertebral body to the ventrocaudal point of the lamina of the same vertebra. The VCHcd was measured perpendicular to the dorsal surface of the vertebral body.

- The vertebral body length (VBL) was defined as the distance between the most dorsocranial and most dorsocaudal point of the same vertebral body.

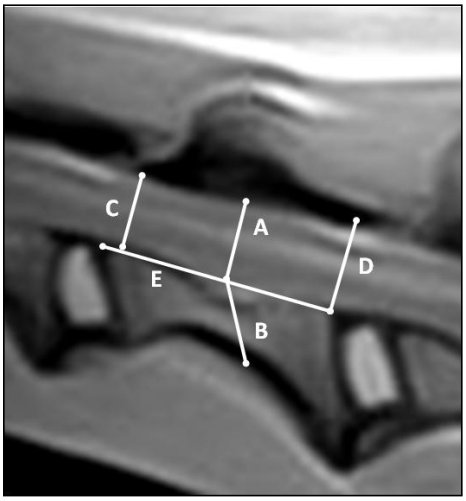

Figure 1. Mid-sagittal T1-weighted image of the cervical vertebrae of a 7-year-old clinically normal English Foxhound. The following measurements were made: VCHm (A), VBH (B), VCHcr (C), VCHcd (D), and VBL (E).

From these measurements, the following four ratios were calculated from C3 to C7:

- Canal height to body height ratio (CBR) defined as VCHm divided by VBH (Figure 2). This ratio is suggested to indicate relative vertebral canal stenosis in human and veterinary studies. [13,15,17]
- Canal height to body length ratio (CBLR) defined as VCHm divided by VBL (Figure 3). This ratio represents a second ratio that is influenced directly by vertebral canal height.[13,15,20]
- Caudal canal to cranial canal height ratio (CCHR) defined as VCHcd divided by VCHcr (Figure 4). This ratio indicates the shape of the vertebral canal in a lateral view. Ratios > 1 represent a funnel-shaped vertebral canal narrowed cranially in a lateral view.[11,13]
- Body length to body height ratio (BLHR) defined as VBL divided by VBH (Figure 5). This ratio indicates the shape of the vertebral body. A lower value represents a shorter, more square-shaped vertebral body.

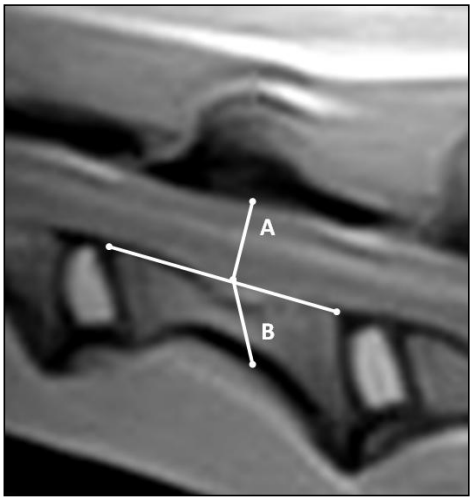

Figure 2. Same vertebra as Figure 1. Canal height to body height ratio (CBR) was defined as VCHm (A) divided by VBH (B).

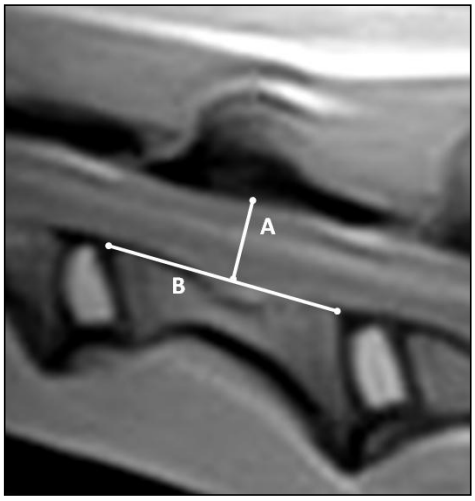

Figure 3. Same vertebra as previous figures. Canal height to body length ratio (CBLR) was defined as VCHm (A) divided by VBL (B).

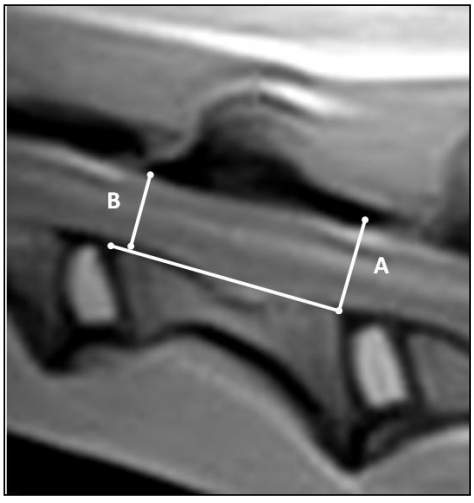

Figure 4. Same vertebra as previous figures. Caudal canal to cranial canal height ratio (CCHR) was defined as VCHcd (A) divided by VCHcr (B). A value A/B around 1, as in this case, represents a rather rectangular vertebral canal in a lateral view.

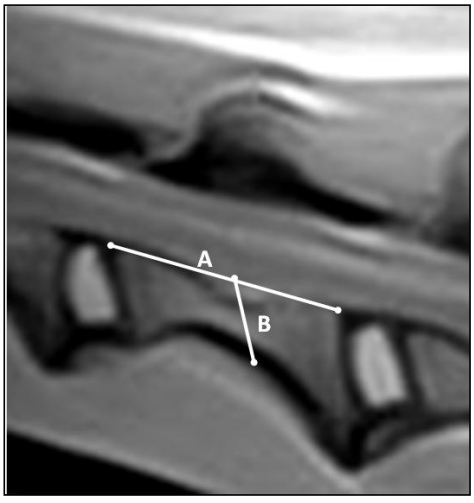

Figure 5. Same vertebra as previous figures. Body length to body height ratio (BLHR) was defined as VBL (A) divided by VBH (B).

Data analysis

The effect of group of dog (clinically affected Doberman Pinscher, clinically normal Doberman Pinscher or clinically normal English Foxhound), assessed vertebrae (C3-C7), gender and age on the different ratios was evaluated by the mixed model with dog as random effect, using the mixed procedure of SAS (SAS Version 9.2) as all ratios were normally distributed according to the Shapiro-Wilk test. F-tests were used to test for the effects of the different factors. Significance was claimed when $P < 0.05$. P –values for multiple comparisons were adjusted by Tukey multiple comparisons procedure.

Box and Whisker plots were created to demonstrate the median values, the upper and lower quartiles and the minimum and maximum values of the four assessed ratios.

Results

Canal height to body height ratio

The CBR values for the different groups, (globally and for the different assessed cervical vertebrae separately) are presented in Table 1 and Figure 6. There was a significant influence of group on the CBR value ($P < 0.001$). When looking at the different groups of dogs pairwise, the global CBR value of clinically affected Doberman Pinschers was significantly smaller compared to clinically normal Doberman Pinschers and English Foxhounds, but was not significantly different between clinically normal Doberman Pinschers and English Foxhounds (Table 1). This was not only true for the global comparison, but also for the five assessed cervical vertebrae seperately (Table 1). In each group, the CBR value was significantly influenced by the assessed cervical vertebra ($P <.001$ in each group of dog). Within each group the highest value was observed for C3 and the lowest value for C6 for clinically affected Doberman Pinschers and for C7 for clinically normal dogs. There was no significant influence of gender in Doberman Pinschers with ($P = 0.91$) and without ($P = 0.83$) clinical signs of DAWS. In the group of clinically normal English Foxhounds, the CBR value was significantly smaller in male compared to female animals ($P = 0.043$). There was a significant influence of age in both groups of Doberman Pinschers ($P = 0.017$ and 0.010 in Doberman Pinschers with and without clinical signs, respectively). Each increase of age by one month resulted in an estimated decrease of CBR value by 0.0027 and 0.0035 for Doberman Pinschers with and without clinical signs, respectively. In the group of clinically normal English Foxhounds, the CBR value was not significantly influenced by age ($P = 0.22$).

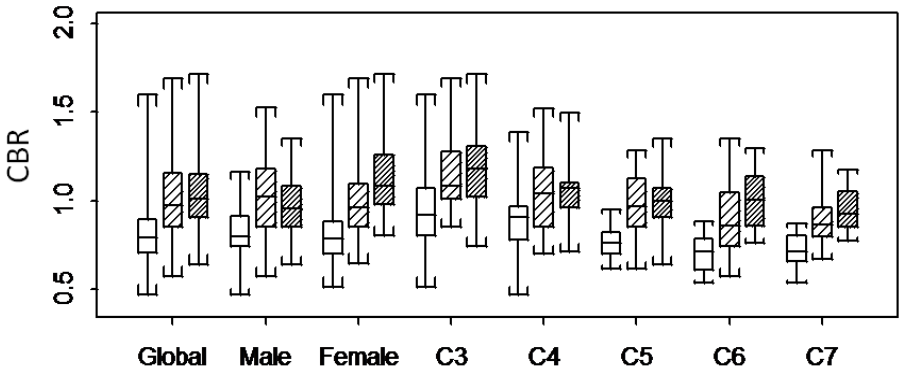

Figure 6. Box and Whisker Plots for CBR values in Doberman Pinschers with clinical signs of DAWS (not striped), clinically normal Doberman Pinschers (bright striped), and clinically normal English Foxhounds (dark striped), globally, for different gender, and different assessed vertebrae seperately. The CBR values of clinically affected Doberman Pinschers are remarkable smaller compared to both groups of clinically normal dogs. The values of both clinically normal groups are comparable.

Canal height to body length ratio

The CBLR values for the different groups (globally and for the different assessed cervical vertebrae separately)are presented in Table 1 and Figure 7. There was a significant influence of group on the CBLR value ($P < 0.001$). When looking pairwise at the different groups, the global CBLR value of clinically affected Doberman Pinschers was significantly smaller compared with clinically normal Doberman Pinschers and English Foxhounds, but was not significantly different between clinically normal Doberman Pinschers and English Foxhounds. This was not the case for all the assessed vertebrae seperately, but only for C5, C6, and C7 (Table 1). In each group, the CBLR value was significantly influenced by the assessed cervical vertebra ($P <.001$ in each group of dog).Within each group an increase in CBLR value from C3 to C7 was observed. There was no significant influence of gender in Doberman Pinschers with ($P = 0.440$) and without ($P = 0.450$) clinical signs of DAWS. In the group of clinically normal English Foxhounds, the CBLR value was significantly smaller in male compared to female animals ($P = 0.006$). There was a significant influence of age in clinically normal Doberman Pinschers ($P = 0.006$). Each increase of age by one month resulted in an estimated decrease of CBLR value by 0.0014. There was no significant influence of age in the groups of Doberman Pinschers with clinical signs of DAWS ($P =0.500$) and clinically normal English Foxhounds ($P = 0.150$).

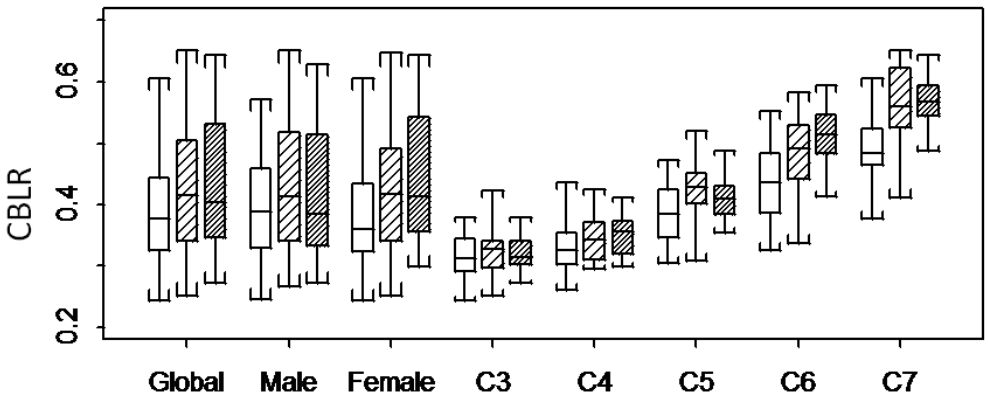

Figure 7. Box and Whisker Plots for canal height to body length ratio (CBLR) values in Doberman Pinschers with clinical signs of DAWS (not striped), clinically normal Doberman Pinschers (bright striped), and clinically normal English Foxhounds (dark striped), globally, for different gender, and different assessed vertebrae seperately. Although, the CBLR values of clinically affected Doberman Pinschers are smaller compared to both groups of clinically normal dogs, there is considerable overlap between the different groups. The values of both clinically normal groups are comparable.

Caudal canal to cranial canal height ratio

The CCHR values for the different groups (globally and for the different assessed cervical vertebrae separately) are presented in Table 1 and Figure 8. There was no significant influence of group of dogs on the CCHR value (P = 0.830). When looking pairwise at the different groups and different assessed vertebrae seperately, the CCHR value for C7 was significantly larger in Doberman Pinschers with clinical signs of DAWS compared to clinically normal English Foxhounds (Table 1). In both groups of Doberman Pinschers, there was a significant influence of the assessed cervical vertebra with in both groups the largest value noted for C7 (P = 0.001 and P < 0.001 for Doberman Pinschers with and without clinical signs of DAWS, respectively). For the group of clinically normal Foxhounds, the CCHR was not significantly influenced by the assessed vertebra (P = 0.320). There was no significant influence of gender in Doberman Pinschers with (P = 0.052) and without (P = 0.300) clinical signs of DAWS. In the group of clinically normal English Foxhounds, the CCHR value was significantly larger in male compared to female animals (P = 0.032). There was a significant influence of age in both groups of clinically normal dogs (P = 0.026 and 0.024 in clinically normal Doberman Pinschers and English Foxhounds, respectively). Each increase of age by one month resulted in an estimated decrease of CCHR value by 0.0014 for clinically normal Doberman Pinschers and an increase of CCHR value by 0.0013 for clinically normal English Foxhounds. In the group of clinically affected Doberman Pinschers, the CCHR value was not significantly influenced by age (P = 0.650).

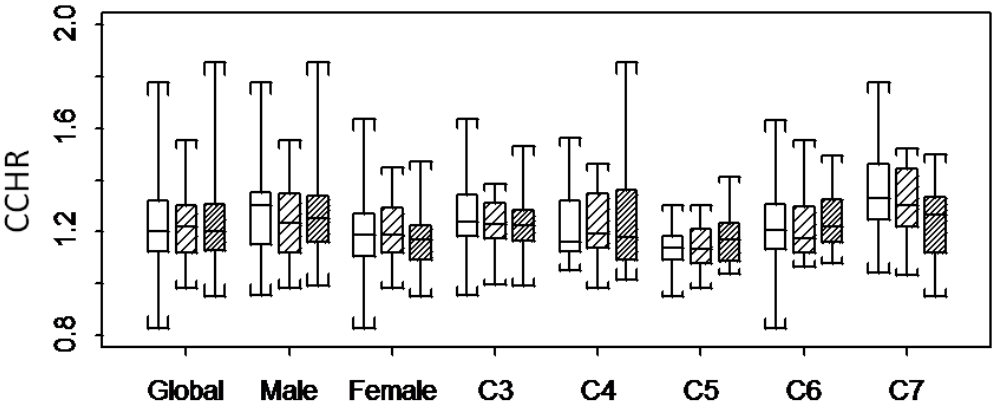

Figure 8. Box and Whisker Plots for cranial canal to caudal canal height ratio (CCHR) values in Doberman Pinschers with clinical signs of DAWS (not striped), clinically normal Doberman Pinschers (bright striped), and clinically normal English Foxhounds (dark striped), globally, for different gender, and different assessed vertebrae seperately. With the exception of the values between clinically affected Doberman Pinschers and clinically normal English Foxhounds at the level of C7, the values are comparable between the different groups

Body length to body height ratio

The BLHR values for the different groups (globally and for the different assessed cervical vertebrae separately)are presented in Table 1 and Figure 9. There was a significant influence of group of dog on the BLHR value (P = 0.002). When looked pairwise at the different groups, the BLHR value of clinically affected Doberman Pinschers was significantly smaller compared to clinically normal Doberman Pinschers and English Foxhounds, but was not significantly different between clinically normal Doberman Pinschers and English Foxhounds (Table 1). This was not the case for all the assessed vertebrae seperately. At the level of C6, there was no significant difference between clinically affected and clinically normal Doberman Pinschers, but only between clinically affected Doberman Pinschers and clinically normal English Foxhounds. There was no significant difference between any of the groups at the level of C7 (Table 1). In each group of dog, the BLHR value was significantly influenced by the assessed cervical vertebra (P <.001 in each group of dog), within each group a progressive decrease in BLHR value from C3 to C7. In neither of the groups of dogs, the BLHR value was significantly influenced by gender or age.

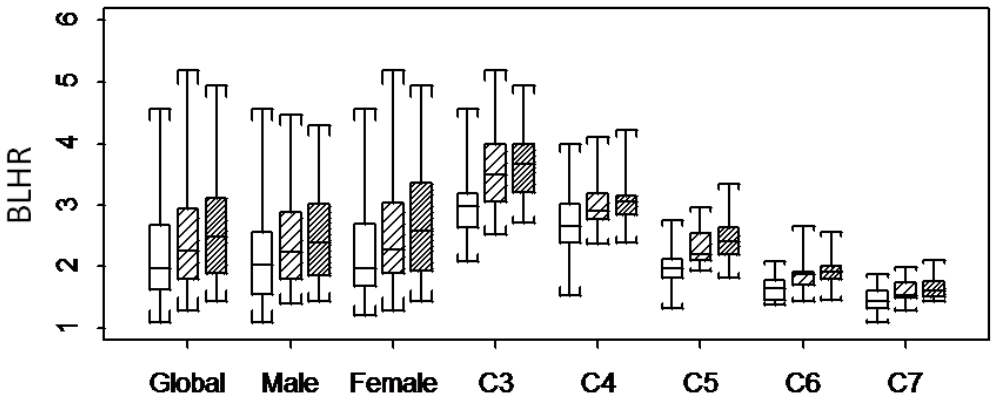

Figure 9. Box and Whisker Plots for body height to body length ratio (BLHR) values in Doberman Pinschers with clinical signs of DAWS (not striped), clinically normal Doberman Pinschers (bright striped), and clinically normal English Foxhounds (dark striped), globally, for different gender, and different assessed vertebrae seperately. The BLHR values of clinically affected Doberman Pinschers are smaller compared to both groups of clinically normal dogs. The values of both clinically normal groups are comparable

Follow-up monitoring

Eighteen of 20 clinically normal Doberman Pinschers and 9 of 17 English Foxhounds were available for physical and complete neurologic examinations between 16 and 18 months after the MRI examination of the study. These examinations revealed no abnormalities. The owner of 4 other Foxhounds was available for a telephone interview 9 months after the MRI examination of the study. According to that owner, the dogs were clinically normal. The remaining 2 Doberman Pinschers and 4 Foxhounds died during the study period for reasons unrelated to this study. According to the owners, these 6 dogs never had any clinical signs that were suggestive of a cervical myelopathy.

Table 1. Mean canal height to body height, canal height to body length, caudal canal to cranial canal, and vertebral body length to body height ratio values for the different groups of dogs, globally, and for different gender and different vertebrae seperately

Assessed parameter	Global	Male	Female	C3	C4	C5	C6	C7
Canal height to body height ratio								
DAWS affected DP	0.81[a]	0.81	0.81	0.95[a]	0.89[a]	0.76[a]	0.71[a]	0.71[a]
Clinically normal DP	1.00[b]	1.01	0.99	1.16[b]	1.05[b]	0.98[b]	0.91[b]	0.90[b]
Clinically normal FH	1.04[b]	0.97	1.11	1.16[b]	1.06[b]	1.00[b]	1.00[b]	0.96[b]
Canal height to body length ratio								
DAWS affected DP	0.39[a]	0.40	0.39	0.31[a]	0.33[a]	0.39[a]	0.43[a]	0.49[a]
Clinically normal DP	0.43[b]	0.44	0.42	0.32[a]	0.35[a]	0.42[b]	0.48[b]	0.57[b]
Clinically normal FH	0.43[b]	0.42	0.45	0.32[a]	0.35[a]	0.41[b]	0.51[b]	0.57[b]
Caudal canal to cranial canal height ratio								
DAWS affected DP	1.24[a]	1.29	1.21	1.27[a]	1.21[a]	1.14[a]	1.21[a]	1.36[a]
Clinically normal DP	1.22[a]	1.24	1.20	1.22[a]	1.22[a]	1.15[a]	1.22[a]	1.31[ab]
Clinically normal FH	1.22[a]	1.27	1.18	1.22[a]	1.24[a]	1.17[a]	1.25[a]	1.23[b]
Body length to body height ratio								
DAWS affected DP	2.17[a]	2.13	2.20	3.07[a]	2.73[a]	2.00[a]	1.64[a]	1.44[a]
Clinically normal DP	2.47[b]	2.44	2.50	3.59[b]	3.01[b]	2.30[b]	1.87[ab]	1.59[a]
Clinically normal FH	2.55[b]	2.45	2.65	3.63[b]	3.04[b]	2.43[b]	1.97[b]	1.70[a]

DAWS = Disk associated cervical myelopathy; DP = Doberman Pinscher; FH = Foxhound. Means in the same column sharing the same letter do not differ significantly from each other.

Discussion

This study determined the values of 4 different linear vertebral body and canal ratios in Doberman Pinschers with clinical signs of DAWS, clinically normal Doberman Pinschers and clinically normal English Foxhounds. It was hypothesized that these ratios represent relative vertebral canal stenosis, vertebral canal shape and vertebral body shape. Ratios were used to allow comparison of vertebral column dimensions between individual dogs of two different breeds.[16]

The results of this study were largely in agreement with a recent retrospective study, comparing radiographic vertebral canal and body ratios in Doberman Pinschers with and without clinical signs of cervical spondylomyelopathy.[13] The assessed canal height to body height (CBR), and canal height to body length (CBLR) ratio values were significantly smaller in Doberman Pinschers with clinical signs of DAWS compared to both groups of clinically normal dogs. These findings support the hypothesis of an increased incidence of relative vertebral canal stenosis in Doberman Pinschers with clinical signs of cervical spondylomyelopathy.[12,13] Although the caudal canal to cranial canal height ratio (CCHR) value at the level of C7 was largest in clinically affected Doberman Pinschers, lower in clinically normal Doberman Pinschers and lowest in clinically normal English Foxhounds, this difference was only significant between clinically affected Doberman Pinschers and clinically normal English Foxhounds. This finding indicates a more funnel-shaped caudal vertebral canal in clinically affected Doberman Pinschers and supports the hypothesis that a funnel-shaped caudal vertebral canal is a potential risk factor for developing clinically relevant spinal cord compression at the narrowed cranial orifice of the respective vertebra.[11,23-25]

A previous osteological study determined, after adjustment for different body size, the cervical vertebral canal dimensions of different dog breeds.[11] Significantly smaller vertebral canal heights were demonstrated in large dog breeds compared to small dog breeds. In the group of large breed dogs, there was also a significant difference between Great Danes and Rottweilers. In the same study, larger CCHR values were seen in large breed compared to small breed dogs, indicating a more funnel-shaped vertebral canal in large breed dogs. In the group of large breed dogs, the mean CCHR values at the caudal vertebral level (C6 and C7) were significantly larger for Doberman Pinschers compared to the other evaluated breeds.[11]

Another study [20], demonstrated significantly different radiographic cervical vertebral ratio values between Great Danes and Doberman Pinschers. For these reasons, it is suggested that vertebral ratio values are breed specific and that values for one breed should not be extrapolated to other breeds.[20] This hypothesis could not be confirmed in this study. None of the evaluated ratios demonstrated significantly different values between clinically normal Doberman Pinschers and clinically normal English Foxhounds. However, it should be emphasized that only two breeds, with a comparable body conformation, were included in this study. Inclusion of additional breeds and in particular small dog breeds could have altered our results. This is supported by another radiographic study [16] demonstrating significantly different cervical spinal cord to vertebral canal ratio values between large and small breed dogs. Therefore, the authors of this study currently do not advise extrapolating the results of this study to other breeds than the Doberman Pinscher and English Foxhound.

In this study, we have evaluated a new vertebral ratio, the vertebral body length to body height ratio (BLHR). It was assumed that this ratio gives an indication about the shape of the vertebral body. In agreement with existing literature, the vertebral bodies became progressively shorter from C3 to C7.[26] Significantly smaller BLHR values, indicating shorter and more square-shaped vertebral bodies, were demonstrated in Doberman Pinschers with clinical signs of DAWS compared to clinically normal Doberman Pinschers and English Foxhounds. Although the exact meaning of this finding is currently unknown, it seems plausible that shorter vertebral bodies may alter the biomechanical properties of the cervical vertebral column.[26] It is suspected that a decrease in length of the cervical vertebral bodies, implying a lower radius of action in intervertebral motion, results in an increased range of motion in flexion-extension.[26-28] This finding has potential consequences for some of the other evaluated vertebral ratios. The fact that vertebral body size and shape are significantly different between dogs with and without clinical signs of DAWS, questions the reliability of the assessed vertebral body and canal ratios to quantify vertebral canal stenosis. After all, the two ratios reflecting vertebral canal stenosis, CBR and CBLR, are not only affected by the mid-vertebral canal height, but respectively also directly by the height and length of the vertebral body. For this reason, the authors recommend further investigation of these vertebral ratios by correlating their values by other established ratios representing relative vertebral canal stenosis. One of these established ratios is the canal occupying ratio.[29] This ratio is measured on transversal images and quantifies the portion of the vertebral canal that is

occupied by the neural structures, thereby giving an indication about the free space available in the vertebral canal.[29]

In this study, measurements were performed on low-field MR images. A recent veterinary study [22], performed by the same authors, demonstrated very good agreement and repeatability of linear vertebral body and canal measurements by low-field MRI. In that study, low-field MRI proved to be superior to computed tomography (CT) for this purpose. This could be attributed to loss of detail and partial volume averaging during the sagittal reconstruction process associated with CT. This resulted in increased variability and a disturbing overestimation of linear measurements in the reconstructed CT-plane (z-axis). As a consequence of this, CT proved to be less appealing for the assessment of vertebral body length.[22] However, more studies are warranted to compare the reliability and agreement of conventional radiography, CT and MRI for the assessment of vertebral ratios.

None of the clinically normal dogs developed clinical signs of cervical hyperesthesia or myelopathy during the study period. However, the number of animals was rather small and they were only available for a limited follow-up period. This makes it very hard or even impossible to draw reliable conclusions about the predictive value of the assessed vertebral ratios. Although several studies have now demonstrated an increased incidence of relative vertebral canal stenosis in Doberman Pinschers with clinical signs of cervical spondylomyelopathy,[12,13] it is still not demonstrated that dogs with a relative narrow vertebral canal have an increased risk of developing clinical signs later in life. Further, it has been demonstrated that the application of vertebral ratio values in individual dogs is currently inappropriate.[13] This recommendation is supported by the results of this study. Analysis of the constructed Box and Whisker plots demonstrates considerable overlap in ratio values, although to a lesser extent for CBR, between the different groups of dogs.

Conclusions

In summary, the results of this study support the hypothesis of altered vertebral canal and vertebral body dimensions in Doberman Pinschers with clinical signs of DAWS. Breed specificity of the assessed vertebral ratios could not be demonstrated. Since in particular vertebral body dimensions were also significantly different between dogs with and without clinical signs of cervical spondylomyelopathy, further investigation regarding the correlation of the CBR and CBLR with other vertebral dimensions reflecting vertebral canal stenosis is recommended.

Footnote [c] American Kennel Club, www.akc.org

[b] Magnet: Airis Mate, Hitachi, Japan

[c] Osirix Image processing software, California, USA.

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Chapter 4.4

DO LINEAR VERTEBRAL CANAL TO BODY RATIOS PREDICT RELATIVE VERTEBRAL CANAL STENOSIS?

DO LINEAR VERTEBRAL CANAL TO BODY RATIOS PREDICT RELATIVE VERTEBRAL CANAL STENOSIS?

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Summary

The objective of this study was to evaluate if vertebral canal to body ratios predict relative vertebral canal stenosis as was suggested in previous studied.

Fifty-five dogs were prospectively investigated. These dogs consisted of Doberman Pinschers with disk associated wobbler syndrome (n = 18), clinically normal Doberman Pinschers (n = 20), and clinically normal English Foxhounds (n = 17). All dogs underwent low-field magnetic resonance imaging of the caudal cervical region. At the level of C5, two linear vertebral canal to body ratios were calculated: the canal height to body height ratio (CBR) defined as mid-vertebral canal height divided by vertebral body height and the canal height to body length ratio (CBLR) defined as mid-vertebral canal height divided by vertebral body length. Relative vertebral canal stenosis was expressed as the vertebral canal occupying ratio of the spinal cord. This was defined as the cross-sectional area of the spinal cord divided by the cross-sectional area of the vertebral canal at the same level. Pearson correlation coefficients were calculated to evaluate the correspondence of both linear vertebral canal to body ratios with the vertebral canal occupying ratio of the spinal cord.

The Pearson's correlation coefficient between CBR and the canal occupying ratio was 0.18 (P = 0.20), between the CBLR and the canal occupying ratio 0.057 (P = 0.68), and between the CBR and CBLR 0.60 (P <.0001).

Considering the very low and insignificant correlation coefficients, it is suggested that vertebral canal to body ratios do not predict relative vertebral canal stenosis.

Introduction

A narrow vertebral canal has been associated with clinically relevant cervical spondylomyelopathy in humans, dogs and horses.[1-6] It has been suggested that preexisting relative vertebral canal stenosis is a contributing risk factor for development of clinical signs later in life.[2,5,7-10] Several studies have determined absolute and relative dimensions of the cervical vertebral column in subjects with and without clinical signs of cervical myelopathy.[1-6,10-24] For this purpose, several imaging and measurement techniques have been used. Examples are measurement of absolute vertebral canal diameters by plain radiography [11-14]computed tomography [2,15], magnetic resonance imaging (MRI) [6,10,20] or cadaveric vertebrae [5,14,16,21], and the application of several ratios of spinal cord, vertebral canal and vertebral body dimensions.[1-4,6,17,19,22,24] The interpretation of absolute measurements by survey radiographs is complicated by the occurrence of radiographic magnification.[1,25] To avoid this problem, ratios of different measurements have been developed.[1,2] This relative measure technique for assessing vertebral canal diameter is independent of radiographic magnification and has the additional advantage of allowing comparison of vertebral column dimensions between subjects of different size.[1-3] The vertebral canal to body height (CBR) and vertebral canal to body length (CBLR) ratio are two such vertebral ratios that have been suggested to quantify vertebral canal stenosis in humans [1,2] , horses [3,22] or dogs.[19,24] Previous work has demonstrated significantly lower CBR and CBLR values between Doberman Pinschers with clinical signs of disk associated wobbler syndrome (DAWS) compared to clinically normal Doberman Pinschers.[24] However, the use of vertebral ratios is debatable and is associated with considerable limitations.[2,16,18,20, 24] Since, these ratios are not only dependent on the size of the vertebral canal but also on the dimensions of the vertebral body, questions arise considering their correlation with the dimensions of the vertebral canal.[16,20,26,27,30,31]

Therefore, the goal of this study was to evaluate the correlation of the CBR and CBLR values with those of an established ratio describing relative vertebral canal stenosis, the vertebral occupying ratio of the spinal cord. This ratio determines the portion of the vertebral canal that is occupied by the spinal cord, thereby giving an indication about the free space available in the vertebral canal.[4] For this purpose, we have determined the CBR, CBLR and occupying ratios of the spinal cord in 55 dogs with or without clinical signs of DAWS. Subsequently the correlation coefficients between the calculated ratios were calculated. It was hypothesized that there was a good correlation between both linear vertebral canal to body ratios and the

occupying ratio, thereby confirming the hypothesis that the assessed vertebral ratios predict relative vertebral canal stenosis.

Material and Methods

Animals

Fifty-five dogs were prospectively investigated. The experiment was conducted in accordance with the guidelines of the Animal Care Committee of the University of Ghent. Written owner consent was obtained prior to study enrollment. The included dogs were client-owned Doberman Pinschers with clinical signs of DAWS (n = 18) client-owned clinically normal Doberman Pinschers (n = 20), and 17 client (n = 13) and laboratory-owned (n = 4) English Foxhounds. The studied dogs consisted of 27 males and 28 females, between 1.5 and 12 years old (median 6.0 years). In all dogs, a physical and complete neurological examination, complete blood cell counts, and serum biochemistry analyses were performed. All Doberman Pinschers underwent an additional echocardiographic examination and standardized mucosal bleeding times. The type of clinical signs of clinically affected Doberman Pinschers ranged from cervical hyperesthesia to non-ambulatory tetraparesis and has been described previously.[27]

Imaging Protocol and Measurements

A permanent, 0.2 Tesla (T) magnet[a] was used to perform MRI in all dogs. All MRI examinations were performed under general anesthesia. Anesthesia was induced with propofol and maintained by isoflurane in oxygen. Dogs were positioned in dorsal recumbency with head and neck extended. The thoracic limbs were fixed parallel to the thoracic wall. The neck was positioned in a joint coil (circular transmit-receive coil) with an inner diameter 19 cm. T1 weighted spin echo and T2 weighted fast spin echo studies were performed in all dogs in a sagittal, dorsal and transversal plane. The images of this last plane were aligned perpendicular to the cervical spinal cord. The vertebral column was imaged from C2 to C7 in the sagittal and dorsal plane and from C4 to C7 in the transversal plane. In all studies, the field of view was 29 cm in the sagittal, 24 cm in the dorsal and 20 cm in the transversal planes. Slice thickness was 4mm in the sagittal and dorsal and 3 mm in the transversal images with no interslice gap in all studies.

All measurements were made at C5. This region was selected because it was routinely included in the scanning field, both linear vertebral ratios demonstrated significantly different values between affected and unaffected dogs in previous studies[24,27], and this level has minimal risk of pathological findings that could interfere with the measurements (i.e., craniodorsal tilting of the vertebral body and the presence of a funnel-shaped vertebral canal).

Such findings were considered an exclusion criterium. Measurements were made on the workstation with the available imaging software [b]. The images could be magnified as needed, but all measurements were made at the same magnification. The accuracy of the measurement tool was calibrated to 0.001 mm or 0.001 mm^2 for linear and circular measurements, respectively. The following three measurements were made at midsagittal T1-weighted images: mid-vertebral canal height (VCHm), vertebral body height (VBH), and vertebral body length (VBL). The points of measurement have been discussed previously [27] and are presented in Figure 1. From these measurements, the following two ratios were calculated: CBR defined as VCHm divided by VBH (Figure 2) and CBLR defined as VCHm divided by VBL (Figure 3).

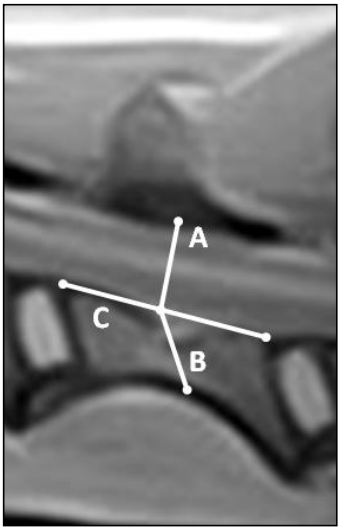

Figure 1. Mid-sagittal T1-weighetd image of the fifth cervical vertebrae in a 7-year-old clinically normal English Foxhound. The following measurements were made: VCHm (A), VBH (B), and VBL (C).

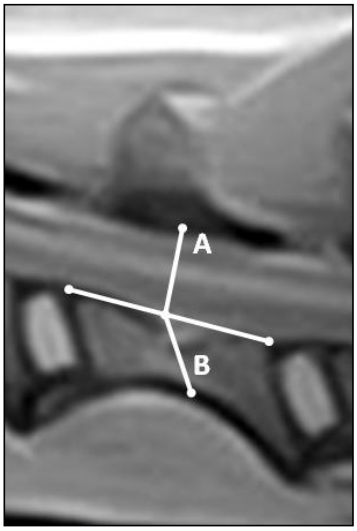

Figure 2. . Same vertebra as Figure 1. Canal height to body height ratio (CBR) was defined as VCHm (A) divided by VBH (B).

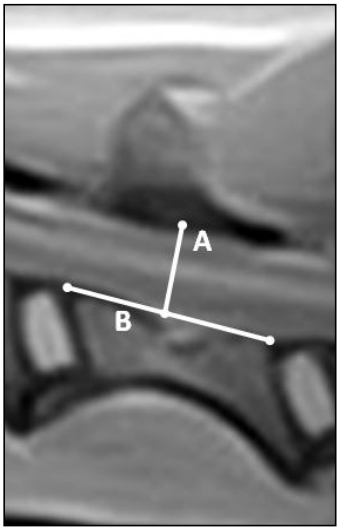

Figure 3. . Same vertebra as previous figures. Canal height to body length ratio (CBLR) was defined as VCHm (A) divided by VBL (B).

At the corresponding level, the following two measurements were performed: cross-sectional area of the vertebral canal (CSA-VC) was measured on transversal T1-weighted images, and the cross-sectional area of the spinal cord (CSA-SC) was measured on transversal T2-weighted images at the same level (Figure 4). From the latter two measurements, the vertebral occupying ratio of the spinal cord was calculated. This ratio was defined as CSA-SC divided by CSA-VC.[4]

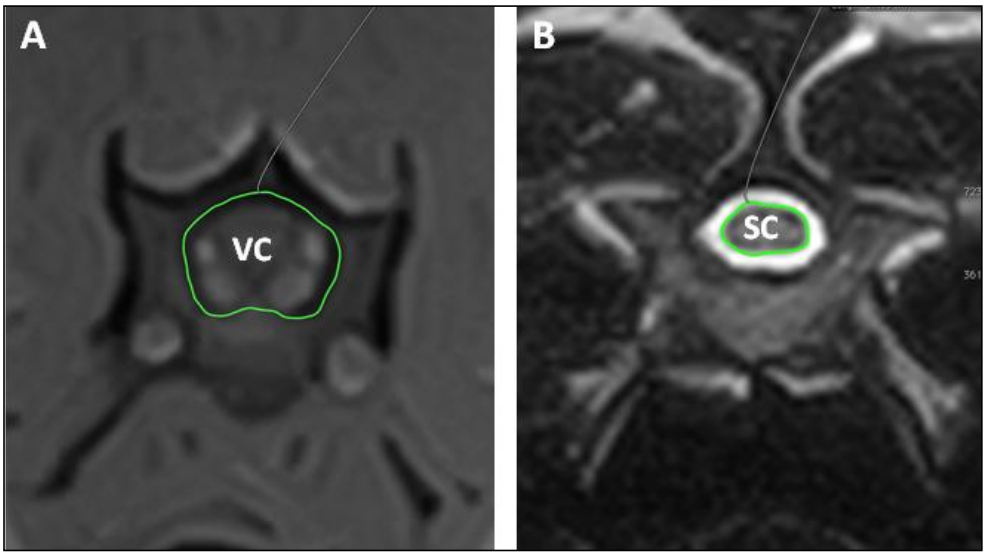

Figure 4. Transversal T1-weighted (A) and T2-weighted (B) image at the middle aspect of C5. The canal occupying ratio of the spinal cord was defined as the spinal cord cross-sectional area (SC) divided by the cross sectional-area of the vertebral canal (VC). This ratio quantifies the portion of the vertebral canal that is occupied by the spinal cord.

All measurements were performed in a randomized sequence by the first author (SDD) who was blinded to signalment and clinical status of each dog. To allow objective comparison of the sagittal and transversal ratios, the sagittal and transversal measurements were made independently of each other with at least one month interval between both measurement sessions. Reliability of both linear [28] and transversal [29] vertebral column measurements using low-field MRI was determined in previous studies by the authors.

Data analysis

To evaluate the correspondence between the different ratios, Pearson correlation coefficients (ρ) were calculated and the hypothesis of no correlation ($\rho=0$) was tested at the 5% significance level. Additionally CBR and CBLR were regressed on the canal occupying ratio of the spinal cord. In order to visualize the variation of CBR and CBLR for specific values of the canal occupying ratio of the spinal cord, two different intervals were added: 1) the 95% confidence interval for the regression line, and 2) the 95% interval for observations of CBR and CBLR for specific values of the canal occupying ratio of the spinal cord (it will contain 95% of the observations).

Results

The CBR values ranged from 0.61 to 1.3 (mean 0.91), the CBLR values ranged from 0.31 to 0.52 (mean 0.41), and the canal occupying ratio values ranged from 0.16 to 0.30 (mean 0.25). The Pearson's correlation coefficient between the CBR and the canal occupying ratio was 0.18 (P = 0.20), between the CBLR and the canal occupying ratio 0.057 (P = 0.68), and between the CBR and CBLR 0.60 (P <.0001). A perfect correlation would give a value of 1.0, no correlation zero, and a perfect inverse correlation of -1.0. The regression lines with corresponding 95% intervals (Figure 5) demonstrated a wide variation of the CBR and CBLR values for a specific value of the vertebral occupying ratio of the spinal cord.

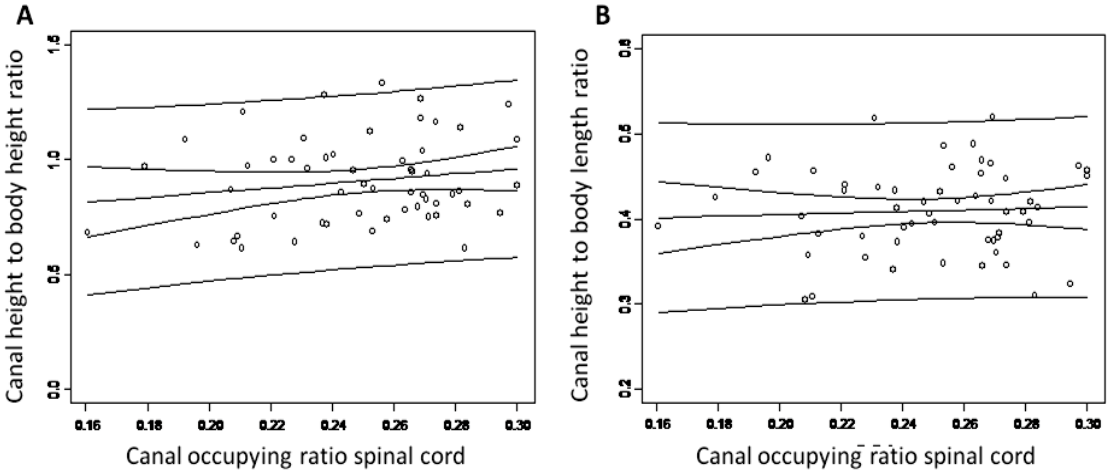

Figure 5. Regression of CBR (A) and CBLR (B) on the canal occupying ratio of the spinal cord. The middle line corresponds to the regression lines, the narrow interval corresponds to the 95% confidence interval of the regression line and the broad interval corresponds to the 95% interval for observations of CBR and CBLR for specific values of the canal occupying ratio of the spinal cord (it will contain 95% of the observations). Both figures demonstrate a wide variation in CBR and CBLR values for a specific value of the vertebral occupying ratio of the spinal cord.

Discussion

In this study we have evaluated the correlation between the canal occupying ratio of the spinal cord and two linear vertebral canal to body ratios, the canal height to body height (CBR) and the canal height to body length ratio (CBLR). In previous papers, vertebral canal to vertebral body ratios have been suggested as determinants of relative vertebral canal stenosis.[1,3,19,24] The results of this study suggest that both assessed vertebral ratios are of limited value in predicting vertebral canal stenosis. Very low correlation coefficients between the assessed linear vertebral ratios and the vertebral canal occupying ratio were demonstrated. Additionally, the calculated correlation coefficients did not reach statistical significance.

Vertebral column dimensions have been assessed previously by various methods.[1-6,10-24] The same specimen does not necessarily yield the same values when measured by different methods. However, the relationship among measurement variables should be comparable, although measurements methods are different.

In this study, relative vertebral canal stenosis was expressed as the occupying ratio of the spinal cord.[4] To better understand the rationale of this choice, understanding the concept of relative vertebral canal stenosis is necessary. In relative vertebral canal stenosis, the vertebral canal diameter is less than 'normal' but does not cause spinal cord compression in itself.[5,7] It is associated with a decreased amount of available free space between the spinal cord and the bony vertebral canal [4,7], resulting in a risk of becoming clinically relevant on the development of space-occupying conditions of the vertebral canal [7], such as age related intervertebral disk degeneration and protrusion.[2] From this point of view, it is clear that vertebral canal stenosis is dependent on two variables, the cross-sectional area of the vertebral canal and the cross-sectional area of the spinal cord. To the author's opinion, this justifies the choice of the vertebral canal occupying ratio to quantify relative vertebral canal stenosis.

There are several possibilities why linear vertebral canal to body ratios do not reliably predict vertebral canal stenosis. First, it is obvious that the dimensions of the vertebral canal are dependent on both the sagittal and transverse dimensions of the vertebral canal.[20] Both linear vertebral ratios do only take the sagittal vertebral canal height into account. Secondly, linear vertebral ratio values are not only dependent on the sagittal vertebral canal height, but also on the height or length of the vertebral body. Variability in the size of the vertebral body can affect the calculated vertebral canal to body ratio values in both a positive and negative direction, giving a false impression of a wide or narrow vertebral canal.[2,16] This issue is further highlighted by the fact that there are indications to believe that vertebral body

dimensions are different between dogs [27] and humans [2,26,30] with and without signs of cervical spondylomyelopathy. Thirdly, as specified previously, relative vertebral canal stenosis is dependent on the dimensions of the vertebral canal and the spinal cord.[4] It is obvious that a dog with a small vertebral canal diameter and a rather large spinal cord diameter will be at higher risk of developing compressive myelopathy than a dog with a small vertebral canal and also a small spinal cord diameter. The spinal cord diameter is not taken into account by the assessment of both linear vertebral canal to body ratios.

Since the results of this study indicate that linear vertebral canal to body ratios do not predict relative vertebral canal stenosis, questions arise considering the true meaning of vertebral ratios. Since both vertebral canal to body ratios are directly dependent on the midsagittal vertebral canal height, it is maybe more prudent to consider the CBR and CBLR as determinants of the mid-sagittal height of the vertebral canal.[23] This is supported by the higher and strongly significant correlation between both vertebral ratios, indicating that both vertebral ratios represent the same variable. A human study [30] comparing both the vertebral canal and vertebral body heights (i.e. anteroposterior diameter) in humans with and without clinical signs of cervical spondylomyelopathy as two separate parameters, has demonstrated that cervical myelopathy patients had not only a narrower sagittal cervical canal diameter, but also a wider vertebral body diameter than did people of the control population.[30] This obviously explains the significant different canal height to body height ratio values between both groups and suggests that not only a narrow sagittal vertebral canal but the combination of a narrow sagittal vertebral canal and a wide vertebral body are risk factors for development of cervical myelopathy.[30] However, more studies are warranted to investigate a similar relationship in dogs.

Conclusions

In summary, the results of this study indicate that the two assessed linear vertebral ratios, the CBR and CBLR, do not predict relative vertebral canal stenosis as was suggested in previous studies. Considering the fact that several studies in dogs [24,27], horses [3,22] and humans [1,26,30,31] have demonstrated significantly lower vertebral canal to body ratios in clinically affected compared to clinically normal subjects, further studies are warranted to reveal the true meaning of vertebral canal to body ratios.

Footnote [a] Magnet: Airis Mate, Hitachi, Japan

[b] Osirix Image processing software, California, USA.

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Chapter 5

CONSERVATIVE TREATMENT OF DISK ASSOCIATED WOBBLER SYNDROME

Chapter 5.1

CLINICAL EVALUATION OF 51 DOGS TREATED CONSERVATIVELY FOR DISK ASSOCIATED WOBBLER SYNDROME

CLINICAL EVALUATION OF 51 DOGS WITH DISK ASSOCIATED WOBBLER SYNDROME

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Summary

The objectives of this study were to evaluate the clinical evolution and potential risk factors of 51 dogs treated conservatively for disk associated wobbler syndrome.

Medical records of dogs treated conservatively for disk associated wobbler syndrome were reviewed and owners were contacted regarding clinical evolution and survival of their animals. Relationships between age, treatment prior to diagnosis, type of neurological signs, results of medical imaging, and outcome were determined.

Fifty-one dogs underwent conservative treatment for disk associated wobbler syndrome. A successful outcome was achieved in 45% (23/51) of the patients. Median follow-up period was 18.5 months and median survival time was 47 months. Eighty-five percent of the dogs, who had to be euthanized due to disk associated wobbler syndrome, were so in the first year after diagnosis. Outcome score was influenced by type of neurological signs and additional radiographic and/or myelographic abnormalities. Outcome score was not significantly associated with age, number of protruded intervertebral disks, occurrence, type and results of treatment prior to diagnosis.

Conservative treatment of disk associated wobbler syndrome is overall associated with a guarded prognosis. It can be considered in cases without clinical signs obvious affecting the four limbs and without additional radiographic and/or myelographic abnormalities.

Introduction

The wobbler syndrome or cervical spondylomyelopathy refers to a collective of disorders of the cervical vertebrae and intervertebral disks of large breed dogs resulting in spinal cord compression. The term 'wobbler' mainly refers to the typical pelvic limb ataxia.[1] A large variety of lesions with different proposed aetiologies have been attributed to this syndrome and over years a few separate entities have been recognized.[1-3] The most typical and predominant of these entities is disk associated wobbler syndrome (DAWS). This specific wobbler syndrome is seen in middle-aged large breed dogs, in particular the Doberman Pinscher.[1,3,4] In DAWS, caudal cervical spinal cord compression results from protrusion of intervertebral disks (IVDs) and generally mild vertebral malformations, sometimes in combination with dorsal spinal cord compression resulting from hypertrophy of the ligamentum flavum.[1] Clinical signs vary from cervical hyperaesthesia to tetraplegia. A slowly progressive pelvic limb ataxia and paresis is the most common presentation.[1,4] In dogs with apparently normal thoracic limbs, it is sometimes difficult to distinguish DAWS from a thoracolumbar lesion.[3] Progression to thoracic limb involvement with a short stilted gait can occur.[1,3] Affected dogs often show a characteristic 'disconnected' gait, in the sense that the thoracic and pelvic limbs seem to advance at different rates. Neck pain may be seen but is usually not overtly present.[4] Tetraplegia is uncommon.[4]

There is a lot of controversy about the treatment of DAWS.[2] It is often defined as a progressive disease in which early surgery is necessary to halt progression of symptoms.[3] Several surgical procedures have been described for DAWS.[5-9] Reported short-term success rates after surgery are high and vary around 80%, but there exists a high rate of recurrence. This is most often due to the development of adjacent segment disease and occurs in 20-30% of initially successfully treated dogs, independent on the surgical technique.[2,10]

Although very little is known about the conservative treatment or natural progression of DAWS, conservative therapy is seldom favoured in treating this disease.[1,3,4] The aim of this retrospective study is to evaluate the clinical evolution of dogs treated conservatively for DAWS and to asses potential risk factors associated with this modality of treatment. It was hypothesized that age, occurrence, type and results of treatment prior to diagnosis, type of clinical signs, the number of protruded IVDs, and presence of additional radiographic and/or myelographic abnormalities could influence the outcome of dogs treated conservatively for DAWS.

Materials and Methods

Medical records of dogs with DAWS diagnosed at the Department of Small Animal Medicine and Clinical Biology, Ghent University, Belgium, between 2001 and 2006 were reviewed. Information was searched using a clinical software program and standardized data sheets. Terms used were disk associated wobbler syndrome, wobbler syndrome, and caudal cervical spondylomyelopathy. Information regarding medical imaging findings was obtained from the available radiographs and myelograms. If these were not available, the information in the medical records was used. Only dogs that were treated conservatively were included in the study. Information retrieved included signalment, occurrence, type and results of treatment prior to diagnosis, duration of clinical signs, physical and neurological examination findings, medical imaging findings, treatment, and follow-up data. A dog was excluded if diagnosis was not confirmed by radiography and myelography, if concurrent orthopaedic problems were identified before or after diagnosis of DAWS, if the owners elected euthanasia at the moment of diagnosis, if the dog was lost to follow-up during the study period, or if the dog died within 6 months after diagnosis for reasons unrelated to DAWS.

To determine an association between type of neurological signs and outcome, the dogs were categorized into 3 different groups. This categorization was based on the typical clinical presentations of dogs with DAWS. The details of these groups are presented in table 1.

Survey radiographs of the cervical portion of the vertebral column and a cervical myelogram were performed in all dogs. Special attention was given to the number of protruded IVDs and additional radiographic and/or myelographic abnormalities. Additional radiographic abnormalities were defined as an altered shape of the vertebral body which could range from varying degrees of loss of the ventrocranial border, to a triangular shaped vertebral body. Dogs with laminar/pedicular malformations were not included in the study. Additional myelographic abnormalities were defined as the occurrence of concomitant dorsal compression caused by ligamentum flavum hypertrophy. To allow statistical comparison, dogs with additional radiographic and/or myelographic abnormalities and more than one protruded IVD were both categorized into one group (table 1).

Conservative treatment was initiated based on the owners decision to decline surgery. Dogs were considered to have conservative treatment if no surgery was undertaken during the study period. After a diagnosis of DAWS was made, owners were advised to start with an oral declining prednisolone (Prednisolone®; Kela) therapy for 3 weeks (one week 1 mg/kg, SID;

one week 0,5 mg/kg, SID; one week 0,25 mg/kg, SID) and restricted exercise for 4 weeks. Owners were advised to use a harness instead of a collar when walking the dog.

Follow-up information was obtained by recheck examinations or by a telephone questionnaire with the owner, the veterinarian or both by the first author (SDD). Owners were asked to evaluate their dog's clinical outcome and to assess the clinical evolution over time. Survival time was defined as the time between the onset of clinical signs (as noted by the owners) and moment of death. If a dog died after a period of 6 months or more after diagnosis for reasons unrelated to DAWS, the neurological status at the moment of death was used to evaluate the dog's clinical outcome. To allow statistical comparison of the different potential prognostic parameters, the dogs were given an outcome score from 1 to 11. The relationships between these outcome scores and their corresponding clinical outcome are presented in table 2. A successful outcome was defined as an outcome score of 9 or higher. This definition of success included only dogs that did not show worsening of clinical signs after a diagnosis of DAWS was made. Their neurological symptoms were unchanged or had improved.

The effect of the type of treatment (NSAIDS, corticosteroids or both) prior to diagnosis on the result at the time of diagnosis (improvement or not) was tested by the Fisher exact test. The effect of the occurrence, type, and results of treatment prior to diagnosis on the outcome score was tested by the one-sided Wilcoxon rank sum test. The effect of type of neurological signs, number of protruded IVDs and the presence of additional abnormalities on radiography and/or myelography on the outcome score was tested by the one-sided Wilcoxon rank sum test. The effect of age as a continuous covariate on the outcome score was investigated by the proportional odds model. Significance was established at a value of $P \leq 0.05$. Kaplan Meier curves were used to visualize the estimated survival as a function of time.

Table 1. Distribution of dogs with DAWS

Variable		**Number of dogs (%)**
Type of neurological signs		
Group 1	Cervical hyperesthesia or monoparesis of 1 front limb (nerve root signature)	7/51 (13.7%)
Group 2	Ataxia and/or paresis only affecting the hind limbs with or without cervical hyperesthesia	13/51 (25.5%)
Group 3	Ataxia and/or paresis affecting the four limbs with or without cervical hyperesthesia	31/51 (60.8%)
Number of protruded IVDs		
One		31/51 (60.8%)
More than one		20/51 (39.2%)
Additional radiographic and/or myelographic abnormalities		
None		24/51 (47.1%)
Present		27/51 (52.9%)

IVD = Intervertebral Disk

Table 2. Neurological outcome score and clinical evolution for dogs treated conservatively for DAWS

Neurological Outcome Score	Clinical evolution	Number of dogs (%)	
1	Progressive deterioration with euthanasia within the first 6 months after onset of clinical signs	4/51	(7.8%)
2	Progressive deterioration with euthanasia between 6 and 12 months after onset of clinical signs	8/51	(15.7%)
3	Progressive deterioration with euthanasia between 12 and 18 months after onset of clinical signs	7/51	(13.7%)
4	Progressive deterioration with euthanasia between 18 and 24 months after onset of clinical signs	3/51	(5.9%)
5	Progressive deterioration with euthanasia after more than 24 months after onset of clinical signs	1/51	(2.0%)
6	Progressive deterioration, but still alive	1/51	(2.0%)
7	Rapid and sustained clinical improvement for minimum 24 months, followed by a rapid and progressive deterioration	2/51	(3.9%)
8	Rapid and sustained clinical improvement for minimum 36 months, followed by a rapid and progressive deterioration	2/51	(3.9%)
9*	Lack of evolution in clinical signs after diagnosis	1/51	(2.0%)
10*	Clinical improvement, but not free of clinical signs	22/51	(43.1%)
11*	Free of clinical signs	0/51	(0.0%)

* An outcome score of 9 or higher is considered as a successful outcome

Results

The medical records of 78 dogs were reviewed. Twenty-seven dogs were excluded due to the following reasons: diagnosis not confirmed by radiography and myelography (n = 6), concurrent orthopaedic problems identified before or after the time of diagnosis (n = 3), owners elected euthanasia at the moment of diagnosis (n = 10), dogs died or were euthanatized within 6 months after diagnosis for reasons unrelated to DAWS (n = 3) and 5 dogs were lost to follow-up. Fifty-one dogs were included in the study. The Doberman pinscher (n = 32) was the predominant breed, other breeds included the Bernese mountain dog (n = 6), the Rottweiler (n = 3), the Bouvier des Flandres and Labrador retriever (n = 2 of each breed), the Boxer, Bullmastiff, Leonberger, Pointer, Pomeranian, and Weimaraner (n = 1 of each breed). Among the dogs, 34 were males and 17 were females. The dogs ages ranged from 2.9 years to 12.9 years (mean, 7.4 years) and the dogs body weight ranged from 14.4 to 53.5 kg (mean, 37.4 kg).

The duration of clinical signs prior to diagnosis varied from 1 day to 2.5 years (median, 92 days). Forty of the 51 dogs received treatment prior to diagnosis by the referring veterinarian. The details about the type and associated results of this treatment are presented in table 3. Treatment with corticosteroids prior to diagnosis was significantly associated (P =0 .001) with improvement at the moment of diagnosis when compared to treatment with non steroidal inflammatory drugs (NSAID's) or a combination of both. Details regarding type of neurological signs are presented in table 1. Three of the 7 dogs in group 1 showed neck pain, 2 dogs showed lameness of 1 thoracic limb and 2 of them showed a combination of both. Six of the 13 dogs in group 2 and 21 of the 31 in group 3 also showed neck pain or a reluctance to move the head in combination with ataxia and/or paresis. None of the 51 dogs was non-ambulatory at the moment of diagnosis. Radiographs and myelograms were available for 46 dogs. In the other 5 dogs, the information regarding medical imaging could be retrieved from the medical records. All compressive lesions were disk associated. Thirty-one dogs showed 1 protruded IVD. Two, 3 and 4 protruded IVDs were seen in 17, 2 and 1 dog, respectively. The compressive lesion was situated between the sixth and seventh cervical vertebra (C6-C7) in 30 dogs, between C5-C6 in 1 dog, between C5, C6 and C7 in 15 dogs, between C4, C5 and C6 in 2 dogs, between C4, C5, C6 and C7 in 2 dogs and between C3, C4, C5, C6 and C7 in 1 dog. Additional radiographic and/or myelographic abnormalities were found in 27 of the 51 dogs. Vertebral body abnormalities were seen in 13 dogs and dorsal compression caused by ligamentum flavum hypertrophy in 12 dogs. A combination of both was seen in 2 dogs.

Additional dynamic studies (traction, flexion and extension) were not routinely performed in all cases. For 14 of the 51 dogs follow-up information was collected from one (n = 8) or more (n = 6) recheck examinations and a telephone questionnaire at the moment of study enrolment. For 33, 1 and 2 of the 51 dogs follow-up information was collected by a telephone questionnaire with the owner, veterinarian or both, respectively. Median follow-up period was 18.5 months (range 1 to 46 months). None of the dogs underwent surgery during the study period. At time of writing, 15 dogs were still alive and 36 dogs died or were euthanatized. Of these 36 dogs, 27 dogs were euthanatized due to progression of clinical signs related to DAWS. The remaining 9 dogs died for reasons unrelated to DAWS. Reason for euthanasia as a result of DAWS in each case was progression of clinical signs to non-ambulatory paraparesis/paraplegia or non-ambulatory tetraparesis/tetraplegia. Since further diagnostic investigations were not performed at the moment of euthanasia, it was presumed that the clinical progression to a non-ambulatory state was caused by DAWS. Cervical hyperaesthesia or thoracic limb lameness was never a reason for euthanasia. Fifty-two per cent (14/27) of the dogs, who had to be euthanatized as a result of DAWS, were so in the first 6 months and 33.3% (9/27) between 6 and 12 months after diagnosis. Median survival time of all the dogs was 47 months (range 1.5 to 60 months). This is presented in figure 1. In all of the dogs that died of reasons unrelated to DAWS, the neurological status had improved at the moment of death and as a consequence of this, these dogs were included in the group of clinical improvement (outcome score 10). Of the 15 dogs that were still alive at the moment of study enrolment, only 2 of them were available for a period less than 6 months after diagnosis. These 2 dogs were both available for a period of 3 months after diagnosis

Forty-five per cent of the dogs (n = 23) achieved a successful outcome. This included dogs with an unchanged (n=1) or improved (n = 22) neurological status at the moment of study enrolment. None of the dogs improved to a symptom free clinical status (outcome score of 11). There was no significant effect of age (P = 0.77), number of protruded IVDs (P = 0.31), occurrence (P = 0.065), type (P = 0.29) and results (P = 0.07) of treatment prior to diagnosis on the outcome scores of dogs treated conservatively for DAWS. Dogs with clinical signs obvious affecting the four limbs (P = 0.05) and additional abnormalities on radiography and/or myelography (P = 0.03) had significantly lower outcome scores when compared to dogs without these additional abnormalities and clinical signs not obvious affecting the four limbs. There was no clinical difference between dogs with additional radiographic or myelographic abnormalities.

Table 3. Occurrence, type and results of treatment prior to diagnosis

Treatment prior to diagnosis	**Positive effect of treatment prior to diagnosis**	**No positive effect of treatment prior to diagnosis**	**Number of dogs**
None			11/51
Corticosteroids	14/17	3/17	17/51
NSAID's	5/16	11/16	16/51
Combination of corticosteroids and NSAID's	3/7	4/7	7/51
Total treatment prior to diagnosis	22/40	18/40	40/51

NSAID's = Non steroidal inflammatory drugs

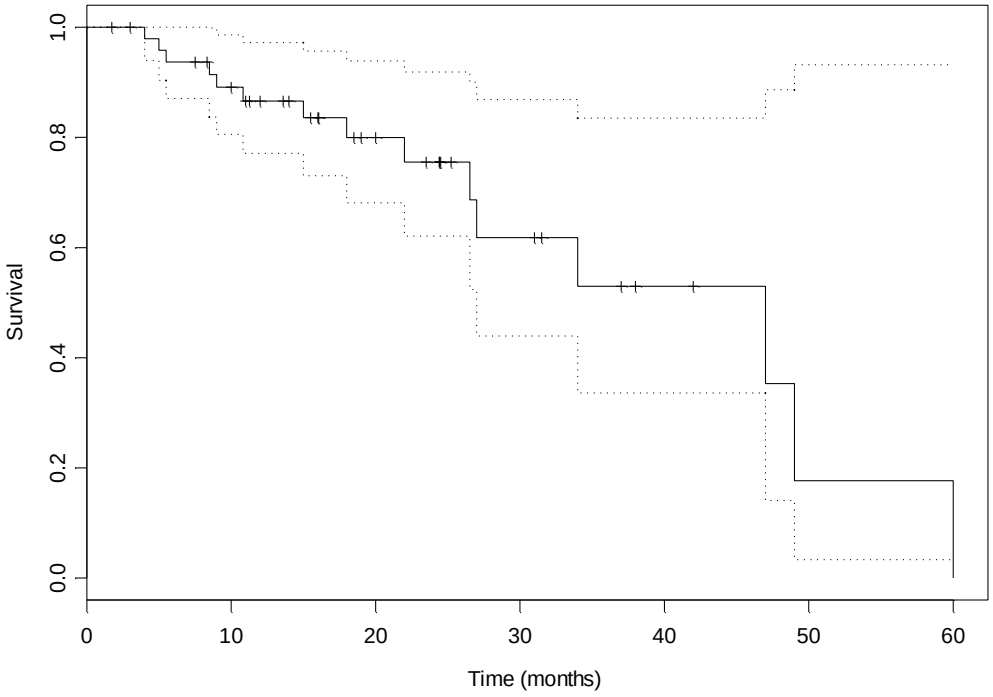

Figure 1. The estimated survival curve and its 95% confidence interval (based on the Kaplan Meier estimate) from first symptoms to death in dogs treated conservatively for DAWS.

Discussion

The signalment and clinical signs of the dogs in our study were similar to those in previously reported studies.[7-10] The mean age was approximately 7.5 years, with male dogs and the Doberman Pinscher breed being overrepresented.

There is a lot of discussion about the treatment of DAWS.[2] In the current literature, DAWS is often defined as a progressive disease in which early surgery is necessary to halt progression of symptoms.[3,4] Little is known about the conservative treatment or natural progression of this disease.

The study by Denny and others [11] is often cited to provide evidence that conservative therapy is ineffective in the treatment of the wobbler syndrome.[1] However, this study handled almost exclusively about a wobbler syndrome typically seen in immature Great Danes and Doberman Pinschers. This syndrome is associated with vertebral malformation-malarticulation and has a different aetiology and prognosis compared with DAWS.[1,2,12] A recent study by da Costa and others [13] compared the results of conservative and surgical treatment of 104 dogs with cervical spondylomyelopathy. It is unclear how many of these dogs suffered from DAWS or another type of wobbler syndrome. In that study, 54% of the conservatively treated dogs improved and 26% stayed the same and it was concluded that conservative treatment improved or stabilized the clinical condition in 80% of patients with a long term follow-up. In another study, the same authors described the clinical and magnetic resonance imaging follow-up of 9 Doberman pinschers treated medically for wobbler syndrome.[14] In 7 of these 9 dogs a diagnosis of DAWS was made. At the time of the follow-up evaluation 5 of these 9 medically treated dogs improved and 2 stayed the same. Important differences between these 2 studies[13,14] and the study reported here are that our study deals exclusively with DAWS and that there are different inclusion criteria regarding follow-up between the studies. In the first study by da Costa [13], the dogs had to be available for at least 6 months and in da Costa's second study [14] for at least 12 months after diagnosis of wobbler syndrome. This is important because in the study reported here, 85% of the conservatively treated dogs that progressed to non-ambulatory paraparesis/tetraparesis did so in the first 12 months after diagnosis. If we exclude those dogs without a minimum follow-up period of at least 6 months or 12 months after diagnosis, our success rates for conservative treatment of DAWS would be more favourable. Another possible explanation for the difference in results between this study and

the studies by da Costa [13,14] could exist in the fact that 40 of the 51 dogs in the study described here already received treatment prior to diagnosis. It is possible that the majority of dogs were referred because medical treatment at the referring veterinarian was no longer working. Although not significant, this hypothesis is partly supported by the fact that dogs with treatment prior to diagnosis had a tendency to have lower outcome scores (table 3). It is also possible that the dogs in the study described here, had clinical signs for a very long time before referral (median, 92 days). There is no detailed information available regarding duration of clinical signs and treatment prior to diagnosis in the two studies by da Costa.[13,14] The information of the study described here, suggests that in cases where a conservative treatment of DAWS fails, the dogs will experience a rather continuous progression of neurological signs despite medical therapy and that 6 and 12 months after diagnosis can be considered as critical time-points to evaluate the results of conservative treatment for DAWS. The dogs in this study had a median survival time of 47 months. This is comparable with the results of one of the studies by da Costa [13]. This median survival time can be considered as a long survival period even when compared with some surgical reports.[10] However, it should be noted that survival time in this study was defined as the time between the onset of clinical signs (as noted by the owners) and moment of death and not as the time between diagnosis and moment of death.

Cervical spondylotic myelopathy (CSM) is considered as the human counterpart of wobbler syndrome in the dog.[15] This is a multifactorial degenerative disease where cervical spinal cord compression is caused by posterior osteophyte formation, ligamentum flavum hypertrophy, sometimes in combination with disk displacement and ossification of the posterior longitudinal ligament.[16] Also in this human syndrome, there is uncertainty about the role of conservative versus surgical treatment.[16] There exist only randomized trials regarding mild to moderate forms of CSM.[17,18] One of these human studies reported no significant difference in outcome between nonoperative and surgical treatment [17], while other results suggest favourable results of surgically treated patients.[18] In CSM, indicators for a poor prognosis with nonoperative treatment are suggested to be the duration of symptoms prior to diagnosis, severity of clinical signs and severity of vertebral canal stenosis.[19-21] The number of stenotic levels does not have any influence on the outcome of humans treated conservatively for CSM [21] and the influence of age is controversial.[19,21] The results of our study suggest that the outcome of medically treated dogs with DAWS could be influenced by the type of neurological deficits and additional radiographic and/or myelographic abnormalities and not

by age, occurrence, type and results of treatment prior to diagnosis or number of protruded IVDs. This is in relative agreement with the results of conservative treatment of CSM in humans. However, it is not sure that the categorization based on type of clinical signs used in this study, truly reflects the severity of clinical signs. Additional dorsal spinal cord compression caused by ligamentum flavum hypertrophy could represent advanced vertebral canal stenosis. Vertebral body malformations could be an indication of a certain grade of instability. This can lead to further progression of the clinical signs instead of stabilization at a certain level. Further investigations, like measurement of the degree of spinal cord compression, are warranted to assess these hypotheses. Although the treatment protocol for DAWS used in this study is in accordance with reported literature [14], the prolonged use of corticosteroidal drugs is controversial.[1] Improvement in cases of chronic spinal cord compression can be attributed to diminishing vasogenic edema, which results in return of function without removing the mass.[22] Prolonged use of corticosteroids can be accompanied by several well known side effects. Further studies are necessary and are currently undertaken to find alternatives for corticosteroidal drugs to treat chronic myelopathies.[23]

We recognize a few limitations of this study. First, due to the retrospective nature of this study, final neurological examination findings were not available. However, reason for euthanasia as a result of DAWS was in each dog progression of clinical symptoms to a nonambulatory status. Additionally, dogs with concurrent orthopaedic diseases were excluded from this study as they could interfere with the outcome perception of the owners. Secondly, the results of this study could have been biased because dogs that were euthanatized at the moment of diagnosis were excluded and none of the included dogs was presented with a nonambulatory status at the moment of diagnosis. It is possible that these dogs represented a patient group with severe clinical signs and a poor prognosis. On the other hand however, the possibility exists that many dogs with mild clinical signs are never admitted to a referral hospital. Thirdly, there was no detailed and reliable information available about the exact amount of exercise restriction and dose, duration, intermittent use and side-effects of the medication protocol after a diagnosis of DAWS was made.

Conclusions

Despite the inherent limitations of this study, our findings suggest that dogs with DAWS have overall a rather guarded prognosis with conservative treatment. The clinical course of conservatively treated dogs is variable with some patients experiencing a non progressive clinical course with improvement and stabilization of clinical signs. Conservative therapy can be appropriate in some patients with DAWS. Type of clinical signs and additional radiographic and/or myelographic abnormalities can be considered as prognostic parameters in the conservative treatment of this disease. Six and 12 months after making a diagnosis of DAWS seem to be important time-points to evaluate the clinical efficacy of conservative treatment for this specific wobbler syndrome. More-thorough evaluation, including a prospective, large population randomized study with predetermined time points for evaluation are necessary to further evaluate the efficacy of different conservative treatment modalities for dogs with DAWS.

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Chapter 5.2

EVOLUTION OF CLINICAL SIGNS AND PREDICTORS OF OUTCOME AFTER CONSERVATIVE TREATMENT FOR DISK ASSOCIATED WOBBLER SYNDROME IN DOGS

EVOLUTION OF CLINICAL SIGNS AND PREDICTORS OF OUTCOME AFTER CONSERVATIVE TREATMENT FOR DISK ASSOCIATED WOBBLER SYNDROME IN DOGS

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Summary

The objectives of this study were to evaluate the evolution of clinical signs, their correlation with magnetic resonance imaging (MRI) and transcranial magnetic stimulation (TMS) and to assess potential prognostic parameters after conservative treatment for disk associated wobbler syndrome (DAWS) in dogs

Twenty-one Client-owned dogs with DAWS were prospectively investigated. After neurological grading, animals underwent low-field MRI and TMS with measurement of onset latencies and peak-to-peak amplitudes from the extensor carpi radialis and cranial tibial muscles. From MR images, the following dimensions were calculated; remaining spinal cord area, compression ratio, vertebral occupying ratio, canal height to body height ratio, canal height to body length ratio, and canal compromise ratio. Intraparenchymal intensity changes were noted and graded. Dogs were reevaluated after 1, 3, 6, 12 and 24 months

Eight of 21 dogs (38%) were successfully treated. Negative outcome was generally characterized by rapid and continuous progression of clinical signs. All dogs with a negative clinical evolution 1 month after diagnosis had also a final unsuccessful outcome. Outcome was further significantly associated with remaining spinal cord area and vertebral canal compromise ratio. Prognosis was not significantly affected by clinical presentation or TMS. There were no significant correlations between clinical presentation, MRI and TMS.

Conservative treatment of DAWS is associated with a rather guarded prognosis. Selected MRI parameters and clinical evolution 1 month after diagnosis can be considered prognostic indicators. The lack of correlation between clinical presentation, medical imaging, electrophysiological evaluation and outcome is disturbing and warrants further investigation

Introduction

Disk associated wobbler syndrome (DAWS) is a multifactorial, complex and incompletely understood neurological syndrome. It occurs in adult to older animals of several large dog breeds.[1] The adult Doberman Pinscher seems particularly vulnerable to the development of this disorder.[1-3] In DAWS, progressive caudal cervical spinal cord compression is typically caused by protrusion of one or more intervertebral disks, sometimes in combination with ligamentum flavum hypertrophy and vertebral abnormalities.[1] The clinical signs can vary from neck pain only to tetraplegia.[1-3] The most common clinical presentation is a gait disturbance.[1] The owners commonly report a gradual onset, although the signs can sometimes occur or exacerbate more acutely. A slowly progressing ataxia and/or paresis of the pelvic limbs are usually noted.[1,4] Clinical signs affecting all four limbs with a short stilted gait of the thoracic limbs can also occur.[1,2] Affected dogs often show a characteristic 'disconnected' gait, in the sense that the thoracic and pelvic limbs seem to advance at different rates.[4] This wide variety in onset and type of clinical signs has resulted in the development of several grading systems describing the severity of neurological deficits.[5-13]

There is a lot of controversy about the treatment of DAWS.[14] In general, it is considered a surgical condition and a multitude of surgical techniques have been developed.[1-4] Although favorable results have been reported, surgical treatment of DAWS is associated with considerable difficulties and complications.[1,15] On the other hand, there is little known about the results of nonoperative treatment for dogs with DAWS. Recent veterinary studies have described the short [13] and long-term [13,16,17] results after conservative treatment and it was concluded that this type of treatment can be considered in selected cases. However, there is currently little prospective data available about the evolution of clinical signs [16] and the evaluation of prognostic indicators for dogs treated conservatively for DAWS. [13,17]

The primary goal of this study was to describe the detailed evolution of clinical signs during conservative treatment for DAWS. Additionally, we assessed several prognostic indicators and evaluated the correlation between initial clinical presentation, electrophysiological evaluation of the cervical spinal cord by transcranial magnetic stimulation (TMS), and the degree of spinal cord compression and intraparenchymal signal intensity (ISI) changes assessed on low-field MRI. It was hypothesized that dogs with more severe neurological deficits would have more pronounced TMS abnormalities, spinal cord compression and ISI changes. Additionally it was hypothesized that dogs with higher age, longer duration of clinical signs, more severe neurological deficits, and more pronounced TMS abnormalities, a

narrower vertebral canal, more pronounced spinal cord compression, more pronounced vertebral canal compromise, and ISI changes would have a less favorable prognosis after conservative treatment of DAWS. To quantify these vertebral column dimensions, ratios of absolute measurements were used to allow comparison between different individual dogs and breeds.

Material and Methods

Animals and Clinical Presentation

Twenty-one dogs were prospectively studied. The experiment was conducted in accordance with the guidelines of the Animal Care Committee of the University of Ghent. Written owner consent was obtained prior to study enrollment. Detailed data considering the clinical presentation are presented in table 1. Seventeen of the 21 dogs were Doberman Pinschers. Ten male and 11 female dogs were included. Age ranged from 4.2 to 10.8 years old (mean 7.7 years; median 7.4 years). Duration of clinical signs, as noted by the owners, ranged from 1 day to 2 years (mean 4.6 months; median 1 month). In all dogs, a physical and complete neurological examination, complete blood cell counts, and serum biochemistry analyses were performed. All included Doberman Pinschers underwent an additional echocardiographic examination and standardized mucosal bleeding times. Neurologic status at the time of study enrollment was graded from 0 to 6. Grade 0 (n = 0) was defined as neurological normal. Grade 1 (n = 2) was defined as cervical hyperesthesia only without neurological deficits. Grade 2 (n = 6) was defined as ataxia of the pelvic limbs without noticeable paresis. These dogs did not demonstrate appreciable ataxia in their thoracic limbs. Two of these 6 dogs demonstrated nerve root signature of the right thoracic limb. Grade 3 (n = 6) was defined as ataxia with noticeable paresis of the pelvic limbs. These dogs did not demonstrate appreciable ataxia in their thoracic limbs. Grade 4 (n = 4) was defined as ambulatory tetraparesis. These dogs typically demonstrated a broad based ataxia with paresis of the pelvic limbs in combination with a short stilted gait of the thoracic limbs; Grade 5 (n = 1) was defined as nonambulatory tetraparesis. These dogs were able to rise and make a few steps before collapsing. Grade 6 (n = 2) was defined as tetraplegia. These dogs were unable to rise or support their weight independently. Cervical hyperesthesia was identified in 17 of 21 dogs. This was generally presented as resistance to extension of the neck. In all dogs, gait evaluation was videotaped for later review and all neurologic examinations were performed by the same person (SDD).

Transcranial magnetic stimulation

All 17 included Doberman Pinschers underwent TMS. Only this breed was included to allow comparison with existing literature. [18,19] Transcranial magnetic stimulation is a non-invasive, painless and sensitive technique for stimulating the cerebral cortex in order to evaluate the functional integrity of the fastest conducting descending motor pathways in the brain and

spinal cord.[20] Magnetic motor cortex stimulation evokes synchronized descending excitatory volleys in the spinal cord pathways.[21] These excitatory volleys induce muscle twitches that are recorded as potentials in the periphery. These potentials are called transcranial magnetic motor evoked potentials (TMMEPs).[20]

Magnetic stimulation was performed by a magnetic stimulator [a] using a circular coil 45 mm in external diameter, which generated a peak magnetic field of 4 Tesla. Maximal (i.e., 110%) stimulator output was used. The coil was placed tangentially to the skull in contact with the skin, with the centre of the coil placed over the vertex.[22] A clockwise inducing current flow was used to stimulate the right motor cortex and an anticlockwise flow to stimulate the left motor cortex.[23] Dogs were sedated with acepromazine (0.03 mg/kg, IV) and morphine (0.2 mg/kg, IV).[19]

Recordings were obtained by use of an electromyography unit.[b] Magnetic motor evoked responses were recorded from monopolar needle electrodes [c] in the muscle belly of the extensor carpi radialis muscle (ECRM) of the thoracic limbs and the cranial tibial muscle (CTM) of the pelvic limbs. The reference and ground electrodes were subdermal needle electrodes.[d] The low and high frequency filters were set at 20 Hz and 10 kHz, respectively. Sensitivity was set at 10 mV per division. Analysis time was 100 ms following the stimulus.Onset latency (ms) was measured as the shortest time between the trigger point and the take-off of the initial phase; peak-to-peak amplitude (mV) was measured between the two largest peaks of opposite polarity. Individual stimulations were delivered until 2 reproducible TMMEPs were recorded and were considered absent if 4 consecutive stimulations failed to elicit a reproducible TMMEP. In dogs with absent TMMEPs, onset latency was regarded as infinite and absent peak-to-peak amplitude was entered as 0 mV. The neuronal path length was measured using a tape measure.

MR imaging protocol and assessed parameters

A permanent, 0.2 Tesla (T) magnet [e] was used to perform MRI. Anesthesia was induced with propofol and maintained by isoflurane in oxygen. Dogs were positioned in dorsal recumbency. The neck was positioned in a joint coil (circular transmit-receive coil) with an inner diameter 19 cm. T1 weighted spin echo and T2 weighted fast spin echo studies were performed in a sagittal, dorsal and transverse plane. The images of this last plane were aligned perpendicular to the spinal cord. The vertebral column was imaged from C2 to C7 in the sagittal and dorsal plane and from C4 to C7 in the transverse plane. The field of view was 29

cm in the sagittal, 24 cm in the dorsal and 20 cm in the transverse plane. Slice thickness was 4mm in the sagittal and dorsal and 3 mm in the transverse sequences with no interslice gap.

Relative vertebral canal stenosis was expressed by the canal occupying ratio of the spinal cord.[24] This ratio was defined as the cross sectional area (CSA) of the spinal cord, measured on transversal T2-weighted images, divided by the CSA of the vertebral canal, measured on transversal T1-weighted images.[24,25] These measurements were always performed at the mid vertebral level from C5 to C7. This ratio represents the portion of the vertebral canal that is occupied by the spinal cord and gives an indication about the remaining free space available in the vertebral canal.[24]

Midsagittal vertebral canal height was expressed by the vertebral canal height to body height (CBR) and vertebral canal height to body length (CBLR) ratio.[26] Measurements were made on midsagittal T1-weighted images from C3 to C7. The CBR was defined as the mid-vertebral canal height divided by the mid-vertebral body height.[26-28] The CBLR was defined as the mid-vertebral canal height divided by vertebral body length (Figure 1).[26,28,29] The CBR and CBLR were only calculated in the included Doberman Pinschers to allow comparison with existing literature.[26,30]

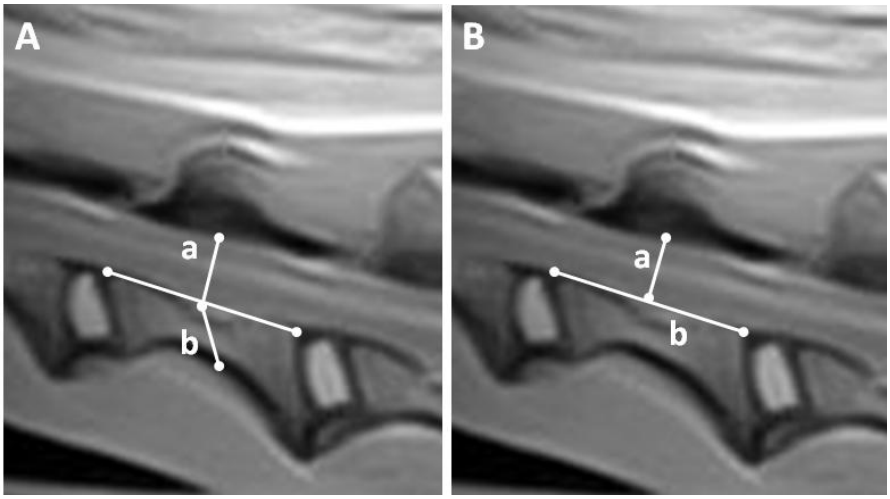

Figure 1. Sagittal T1-weighted image in a Doberman Pinschers with clinical signs of cervical hyperesthesia and pelvic limb ataxia. (A) Canal height to body height ratio is defined as midvertebral canal height (a) divided by the midvertebral body height (b). (B) Vertebral canal height to body length ratio is defined as midvertebral canal height (a) divided by midvertebral

To evaluate the degree of spinal cord compression, the compression ratio and remaining spinal cord area were calculated at the site of most pronounced compression. Measurements were made on transversal T2-weighted images. The compression ratio was defined as the dorsoventral diameter of the spinal cord divided by the transverse diameter at the same level.[31] A lower value represents increased dorsoventral flattening of the spinal cord (Figure 2). The remaining spinal cord area was defined as the CSA of the compressed spinal cord segment divided by the CSA at the adjacent, non-compressed spinal cord segment. The adjacent, non-compressed CSA of the spinal cord was defined as the mean value of the CSA cranial and caudal to the compressed segment.[25]

To evaluate the degree of vertebral canal compromise, the vertebral canal compromise ratio was calculated at the site of most pronounced compression.[32,33] Measurements were made on transversal T1-weighted images. This ratio was defined as the protruded disk area divided by the total CSA of the vertebral canal at the corresponding level.[32,33] (Figure 3)

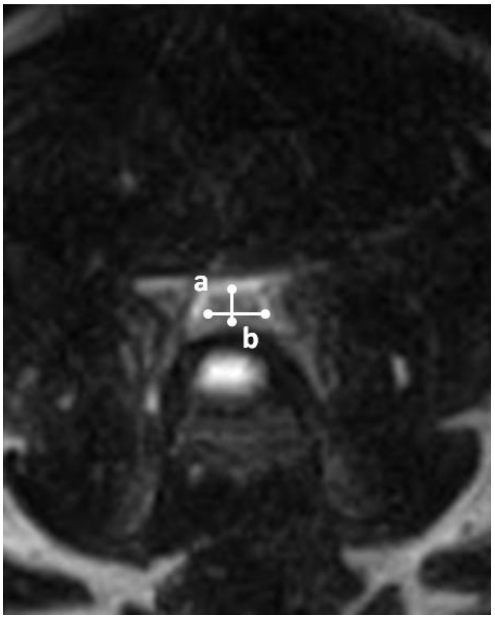

Figure 2. Transversal T2-weighted image of a 4-year-old Doberman Pinscher with cervical hyperesthesia. Compression ratio is defined as dorsoventral spinal cord diameter (a) divided by the transverse diameter (b) at the same site

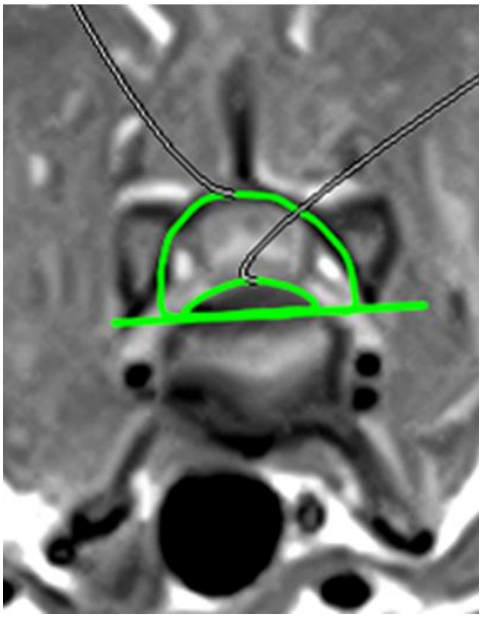

Figure 3. Transversal T1-weighted image of a 10-year-old Whippet with cervical hyperesthesia and pelvic limb ataxia. Vertebral canal compromise ratio is defined as protruded disk area divided by the total vertebral canal area.

Intraparenchymal signal intensity changes were graded from 0 to 3 on the basis of published grading scales in human neuroradiology.[34-36] Grade 0 was defined as no ISI changes on T2 or T1-weighted images. Grade 1 was defined as a light (obscure) hyperintense ISI change on T2-weighted images (Figure 4A). Grade 2 was defined as an intense (bright) hyperintense ISI change on T2-weighted images (Figure 4B). Grade 3 was defined as a hyperintense ISI change on T2-weighted images, corresponding to a hypointense ISI change on T1-weighted images.

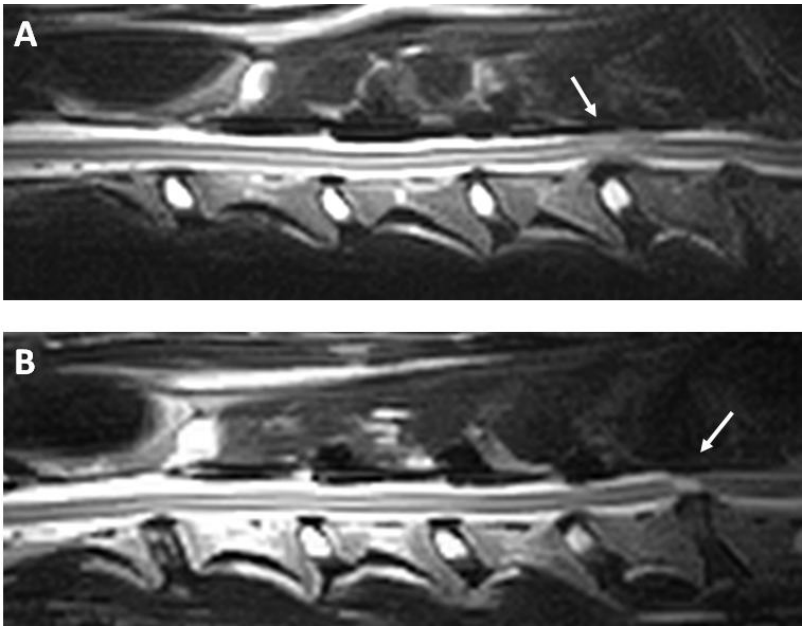

Figure 4. (A) Grade 1 intraparenchymal signal intensity change was defined as a light (obscure) hyperintense ISI change on T2-weighted images (arrow). (B) Grade 2 was defined as an intense (bright) hyperintense ISI change on T2-weighted images (arrow)

All MRI studies were evaluated by the first author. For this purpose, the measurements were performed in a randomized sequence and he was blinded to signalment and clinical status of the subjects. To minimize bias, five MRI studies of clinically normal Doberman Pinschers were included. However, these values were not included in the statistical analysis. Measurements were made directly at the workstation with the available imaging software [f].

Treatment and Follow-up

After diagnosis, all treatment options were explained to the owners and they were free to choose between conservative or surgical treatment. Conservative treatment consisted of 4 weeks restricted exercise which was followed by a gradual increase of the activity level, the use of a body harness instead of a neck collar was advised and medical treatment consisted of a tapering schedule of oral prednisolone during 3 weeks (starting dose 1 mg/kg SID, during the first week; 0.5 mg/kg SID during the second week; and 0.25 mg/kg/week during the last week). At each moment during the study, the owners could elect for a surgical intervention.[37] Dogs were reassessed 1, 3, 6, 12 and 24 months after diagnosis by direct physical and neurological examinations and at additional moments when requested by the owners or authors. During each of these evaluations the dogs were videotaped to allow objective assessment of the dog's gait at a later time. All owners were contacted at the end of the study period for a telephone-interview about the dog's clinical status. The moment of euthanasia due to nonambulatory status or switching over to surgical treatment were considered the endpoints for unsuccessful conservative treatment. All evaluations were performed by the first author. Conservative treatment was considered unsuccessful when there was deterioration in neurological status, when there was lack of improvement in more severely affected cases (grades 3 to 6) or when it was impossible to taper the dose of corticosteroids.

Neuropathology

Of two dogs, neuropathology of the cervical spinal cord was performed. The cervical spinal cord was fixed in 10% neutral buffered formalin, processed and embedded in paraffin. Tissue sections were cut at 5 µm, stained with hematoxylin and eosin (HE) and assessed by a neuropathologist (AO).

Data analysis

The effect of the different factors on success or failure was analyzed by the logistic regression model. The effect of the different factors on time to event (euthanasia or surgery) was analyzed by the Cox proportional hazards model. As response variable, the time from diagnosis was considered. Most of the covariates were continuous or binary in nature. However, the onset latency and peak-to-peak amplitude for the pelvic limbs were artificially considered as a binary variable (either absent or present). Pearson's correlation coefficients were calculated between the different parameters associated with clinical presentation (age, duration of clinical signs, and type of clinical signs), MRI (degree of spinal cord compression

and ISI changes) and TMS findings in the thoracic limbs. Kendall Tau correlation coefficients were calculated between TMS findings of the pelvic limbs, clinical presentation and MRI. Significance was claimed when $P < 0.05$.

Receiver operator characteristic (ROC) curves were created for the vertebral canal compromise ratio and the remaining spinal cord area between successfully and unsuccessfully treated cases. A ROC curve helps to identify a value with combined high sensitivity and high specificity to differentiate between successfully and unsuccessfully treated cases. This value corresponds with the most upper left point on the curve.

Results

Follow-up and evolution of clinical signs

The evolution of clinical signs for each individual dog is presented in Table 1. A successful outcome after conservative treatment for DAWS was seen in 8 of 21 dogs (38%). Follow-up period for these 8 successfully treated dogs ranged from 1 to 3.1 years (mean 1.9 years; median 2.0 years) after diagnosis. Seven dogs (33%) were euthanized, between 24 days and 10.2 months (mean 4.7 months; median 5.0 months) after diagnosis of DAWS, because of progression of clinical signs to a non ambulatory status. Five other dogs (24%) underwent surgery because of neurological deterioration. This decision was made between 2 and 3.5 months (mean 2 months; median 2.4 months) after the moment of diagnosis. One dog (4.8%) (Case 18) was, despite neurological deterioration, still alive 2.3 years after a diagnosis of DAWS was made. All dogs that were clinically worse at their first neurological reevaluation, 1 month after diagnosis, experienced a further progressive neurological deterioration to a non-ambulatory status or to a status that necessitated the owners to change over to a surgical procedure. The opposite was true for dogs that demonstrated an improved neurological status at their first neurologic reevaluation. Thus none of the dogs that demonstrated an improved clinical status 1 month after diagnosis experienced an unsuccessful outcome after conservative treatment for DAWS. An exception to this typical evolution of clinical signs was seen in one dog (Case 18). Although this dog was worse, 1 month after diagnosis, he started to improve more than 3 months after diagnosis. He experienced an acute but transient neurological deterioration after 12 months. However, he progressively worsened again after 24 months and has deteriorated to non ambulatory tetraparesis (Grade 5) at moment of writing. A rather acute relapse of clinical signs was also noted in 4 of the 8 successfully treated cases. These episodes occurred between 4 and 9 months (mean 7.8 months; median 9.0 months) after a diagnosis of DAWS was made. These episodes were in each case successfully treated with a new tapering dose of prednisolone during 3 weeks and exercise restriction during 4 weeks. Two other dogs of the successfully treated group experienced a rather waxing and waning course of their clinical signs with predominantly better periods alternating with rather short worse periods.

In general, the evolution of clinical signs followed the preconceived gradation system (Table 1). However, some dogs could present on two subsequent reevaluations with the same neurological grade while there was a clear clinical improvement or worsening present, for

both the owners and clinician. In these cases, the change in clinical signs was always presented as a change in the grade of ataxia or paresis (Table 1).

Corticosteroid treatment

The medical treatment in 20 of the 21 included dogs consisted of a tapering dose of oral prednisolone. This had no single effect in 1 dog (Case 19), only a temporary effect in 3 dogs, and could not be tapered in 6 other dogs (table 1). Impossibility to taper the corticosteroid treatment was the main reason to switch over to surgery in 4 of these 6 dogs. The 2 other dogs received a prolonged use of prednisolone over several months (Cases 1 and 12). The owners of the remaining 10 dogs reported a positive effect from the moment the prednisolone treatment was initiated and were able to taper and discontinue this medication over the advised 3 week period. Side effects possibly related to prednisolone administration were seen in 12 of the 20 dogs. These included polyuria/polydipsia (n = 12), polyphagia (n = 4), skin changes (n = 2), weight gain (n = 2), panting (n = 1), restless behavior (n = 1), muscle atrophy predominantly affecting the masticatory muscles (n = 2), and hepatopathy (n =1). The most severe side effects were seen in the two dogs with a prolonged treatment of high doses prednisolone.

Table 1. Clinical presentation and clinical evolution of 21 dogs treated conservatively for DAWS

Dog	Signalment	Duration Signs	T0	T1	T2	T3	T4	T5	Outcome	Additional Remarks
1	Doberman, M, 5.8y	9m	3	4	4	4	-	-	Euthanasia after 10m (grade 5)	Not able tapering CS
2	Doberman, Fc, 8.5y	1y	2	4	-	-	-	-	Euthanasia after 1.5m (grade 5)	Temporary effect CS
3*	Doberman, M, 6.3y	1y	3	2	1	1	1	-	Follow-up 1.5y	Wax and wane
4	Doberman, M, 5.3y	1m	4	5	-	-	-	-	Euthanasia after 1m	Temporary effect CS
5	Doberman,, Fc, 5.7y	21d	1	2	-	-	-	-	Surgery after 2m (grade 4)	Not able tapering CS
6	Doberman, Mc, 4.6y	1y	1	2	-	-	-	-	Surgery after 2m (grade 4)	Not able tapering CS
7	Doberman, Mc, 7.4y	2d	3	3, paresis $^{+}$	-	-	-	-	Surgery after 2m (grade 3, paresis $^{++}$)	Not able tapering CS
8	Doberman, Fc, 9.6y	7d	3	3, paresis $^{+}$	-	-	-	-	Surgery after 2m (grade 3, paresis $^{++}$)	Not able tapering CS
9*	Doberman, Fc, 4.4y	4m	2	0	0	0	0	-	Follow-up 1y	
10	Doberman, Mc, 8.1y	7d	2	3	4	-	-	-	Euthanasia after 5m (grade 5)	Temporary effect CS
11	Doberman, M, 7.3y	1y	4	4, paresis $^{+}$	5	-	-	-	Surgery after 4m (grade 6)	No CS
12	Doberman, Fc, 10y	2y	3	3	3	3	-	-	Euthanasia after 7m	Not able tapering CS
13*	Doberman, Fc, 7y	2m	4	3	2	2	2	2	Follow-up 2.2y	Wax and wane
14*	Doberman, Fc, 9.8y	1d	2	1	0	0	0	0	Follow-up 3.1y	Episode clinical relapse after 9m
15	Doberman, F, 8.9y	21d	3	3, paresis $^{+}$	4	6	-	-	Euthanasia after 6m	Not able tapering CS
16*	Doberman, Fc, 5.5y	2d	6	2	0	0	0	0	Follow-up 2y	Episode clinical relapse after 4.5m
17*	Doberman, F, 9y	1d	6	4	2	2	2	-	Follow-up 1y	
18	Whippet, M, 10.3y	1m	2	4	4	2	4	5	Neurological worse after 2.2y	Episode clinical relapse after 12m
19	Whippet, M, 10.8y	7d	5	-	-	-	-	-	Euthanasia after 24d (grade 6)	No improvement
20*	Dalmatian, Fc, 9.4y	4.5m	4	4	3	2	2	2	Follow-up 2y	Episode clinical relapse after 9m
21*	Weimaraner, M, 7.3y	7d	2	2, ataxia $^{-}$	0	0	0	0	Follow-up 2.8y	

M = male, Mc = male castrated, F = female, Fc = female castrated, y = year; m = month, d = day, T0 = moment of diagnosis, T1, 2, 3, 4 and 5 = 1, 3, 6, 12, and respectively 24 months after diagnosis, + or - indicates worse or improved clinical status, CS = corticosteroids, Successfully treated dogs are indicated by asterisk (*)

Prognostic parameters

Outcome was significantly associated with the vertebral canal compromise ratio, the remaining spinal cord area and the CBR at the level of C6 (Table 2). The constructed ROC-curve for the vertebral canal compromise ratio demonstrated that a value of 25.9 corresponded with a sensitivity of 0.9 and a specificity of 0.85 to discriminate between successfully and unsuccessfully treated cases (Figure 5A). The constructed ROC-curve for remaining spinal cord area demonstrated that a value of 62.6 corresponded with a sensitivity of 0.7 and a specificity of 0.85 to discriminate between successfully and unsuccessfully treated cases (Figure 5B). Outcome was not significantly associated by any of the other MRI parameters. Although, none of the dogs with an initial grade 3 ISI changes (n = 2) had a successful outcome, the severity of ISI changes was not significantly associated with outcome (Table 2). Outcome of conservative treatment for DAWS was not significantly influenced by age, duration of clinical signs prior to diagnosis, neurological grade, onset latencies or peak-to-peak amplitudes for both thoracic and pelvic limbs (Table 2). The time from diagnosis to the endpoint for unsuccessfully treated cases (euthanasia or surgery) was significantly influenced by the vertebral canal compromise ratio and the CBR at the level of C6. Time from diagnosis to the endpoint was not significantly associated by any of the other clinical, MRI or TMS parameters (Table 2).

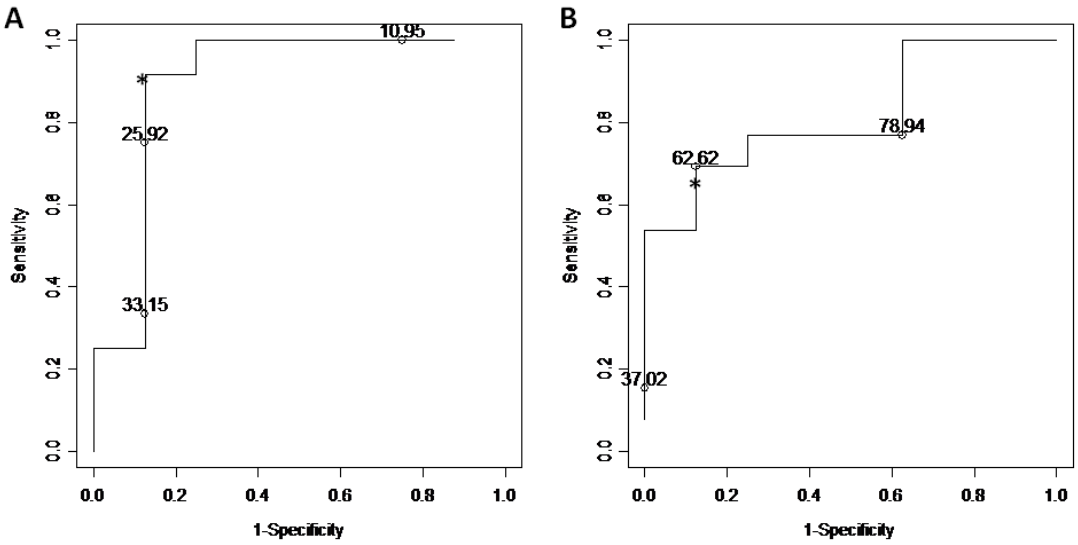

Figure 5. (A) ROC-curve for vertebral canal compromise ratio demonstrates that a value of 25.9 corresponds with a sensitivity of 0.9 and specificity of 0.85 to discriminate successfully and unsuccessfully treated cases. (B) ROC-curve for remaining spinal cord area demonstrates that a value of 62.6 corresponds with a sensitivity of 0.7 and a specificity of 0.85 to discriminate successfully and unsuccessfully treated cases.

Table 2. *P*-values between different assessed prognostic indicators and outcome and time from diagnosis to endpoint (surgery or euthanasia) for dogs treated conservatively for DAWS

Assessed Parameter		**Outcome**	**Time diagnosis to endpoint**
Age		0.55	0.78
Type of clinical signs		0.19	0.40
Duration of clinical signs		0.35	0.41
Occupying ratio spinal cord	C5	0.23	0.28
	C6	0.97	0.72
	C7	0.34	0.33
Canal height to body height ratio	C3	0.18	0.23
	C4	0.55	0.62
	C5	0.19	0.40
	C6	0.036*	0.032*
	C7	0.17	0.24
Canal height to body length ratio	C3	0.97	0.78
	C4	0.066	0.055
	C5	0.31	0.55
	C6	0.076	0.20
	C7	0.21	0.44
Compression ratio		0.32	0.26
Remaining spinal cord area		0.032*	0.072
Vertebral canal compromise ratio		0.013*	0.012*
ISI changes		0.12	0.067
Onset latency	Thoracic limbs	0.14	0.13
	Pelvic limbs	0.13	0.57
Peak-to-peak amplitude	Thoracic limbs	0.48	0.098
	Pelvic limbs	0.13	0.098

Significance was claimed when $P < 0.05$. Significant comparisons are identified by asterisk(*)

Correlation between the different assessed parameters

There was a significant correlation between the compression ratio and ISI changes (P = 0.0014) and between the onset latency and the peak-to-peak amplitude of the pelvic limbs (P <.0001). There were no significant correlations between any of the other clinical, MRI or TMS parameters (Table 3).

Table 3. Correlation coefficients and associated *P*-values (between brackets) between clinical presentation, spinal cord compression, ISI changes and Transcranial magnetic stimulation

Assessed Parameter	Age	Duration clinical signs	Compression ratio	Remaining spinal cord area	ISI changes	Onset latency thoracic limbs	Peak-to-peak amplitude thoracic limbs	Onset latency pelvic limbs	Peak-to-peak amplitude pelvic limbs
Age	1.00	-0.053 (0.82)	0.041 (0.86)	0.21 (0.35)	0.15 (0.52)	0.15 (0.55)	-0.29 (0.27)	0.24 (0.21)	-0.19 (0.33)
Duration clinical signs	-0.053 (0.82)	1.00	-0.046 (0.84)	-0.35 (0.12)	-0.026 (0.91)	-0.26 (0.31)	-0.13 (0.62)	-0.19 (0.35)	0.13 (0.51)
Neurological grade	0.18 (0.44)	-0.17 (0.45)	-0.031 (0.89)	0.35 (0.12)	0.16 (0.48)	-0.24 (0.35)	0.23 (0.38)	0.31 (0.14)	-0.21 (0.31)
Compression ratio	0.041 (0.86)	-0.046	1.00	0.43 (0.051)	-0.65 (0.0014)	-0.021 (0.94)	-0.24 (0.34)	0.027 (0.89)	0.063 (0.75)
Remaining spinal cord area	0.21 (0.35)	-0.35 (0.12)	0.43 (0.051)	1.00	-0.38 (0.088)	-0.12 (0.66)	0.14 (0.58)	-0.009 (0.96)	0.099 (0.61)
ISI changes	0.15 (0.52)	-0.026 (0.91)	-0.65 (0.0014)	-0.38 (0.088)	1.00	0.20 (0.45)	0.12 (0.66)	0.00 (1.00)	0.00 (1.00)
Onset latency thoracic limbs	0.15 (0.55)	-0.26 (0.31)	-0.021 (0.94)	-0.12 (0.66)	0.20 (0.45)	1.00	-0.20 (0.44)	-0.099 (0.61)	0.045 (0.82)
Peak-to-peak amplitude thoracic limbs	-0.29 (0.27)	-0.13 (0.62)	-0.24 (0.34)	0.14 (0.58)	0.12 (0.66)	-0.20 (0.44)	1.00	-0.19 (0.33)	0.099 (0.61)
Onset latency pelvic limbs	0.24 (0.21)	-0.19 (0.35)	0.027 (0.89)	-0.009 (0.96)	0.00 (1.00)	-0.099 (0.61)	-0.19 (0.33)	1.00	-0.85 (<.0001)

ISI = Intraparenchymal signal intensity. Significance was claimed when P < 0.05. Significant comparisons are identified by asterisk (*)

Imaging follow-up and neuropathological findings

In 1 dog (Case 18) a second MRI study was performed because of acute deterioration after 12 months clinical improvement. The initial MRI study in this dog revealed a spinal cord compression at the level of C6-C7. The second MRI demonstrated a comparable amount of disk protrusion and spinal cord compression at the original site and the development of a second spinal cord compression at C5-C6 (Figure 6).

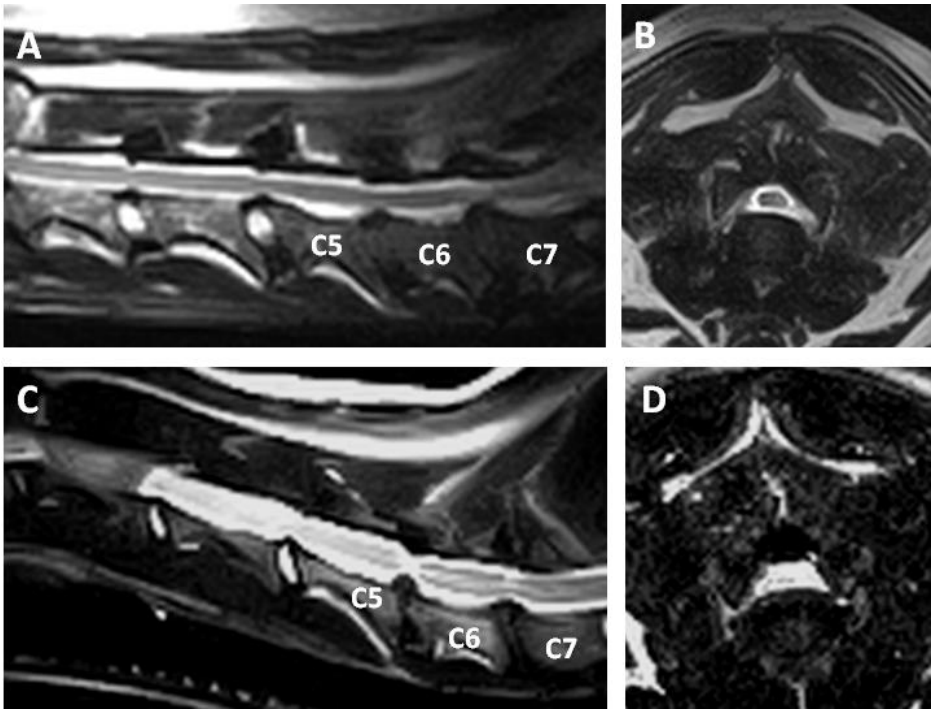

Figure 6. Sagittal and transversal T2-weighted images of a 10-year-old Whippet (Case 18) at moment of diagnosis (A and B) and at moment of acute deterioration 12 months later (C and D). The transversal images (B and D) are at the level of C5-C6. The initial MR images demonstrate spinal cord compression at the level of C6-C7 (A and B). The second MRI study reveals a stable to slightly improved compression at the level of C6-C7 and an additional spinal cord compression at the level of C5-C6 (C and D).

In two other dogs (Cases 1 and 4), a second MRI study was performed immediately after euthanasia because of progression of clinical signs to a nonambulatory status. The initial MRI studies in both cases demonstrated spinal cord compressions at the levels of C5-C6 and C6-C7. The follow up MRI studies revealed in both cases more pronounced spinal cord compressions and an increase in ISI changes. Case 1 presented initially with a grade 2 ISI change at the level of C5-C6 that progressed to an ISI change grade 3. The first MRI study in the other dog (Case 4) demonstrated a grade 1 ISI change at the level of C6-C7. The second MRI demonstrated an ISI grade 2 at the level of C6-C7 and grade 3 ISI change at the level of C5-C6 (Figure 7). The follow up MRI studies in all three dogs demonstrated spinal cord atrophy, characterized as a relative increase in hyperintense cerebrospinal fluid/epidural fat area to spinal cord area (Figure 8).

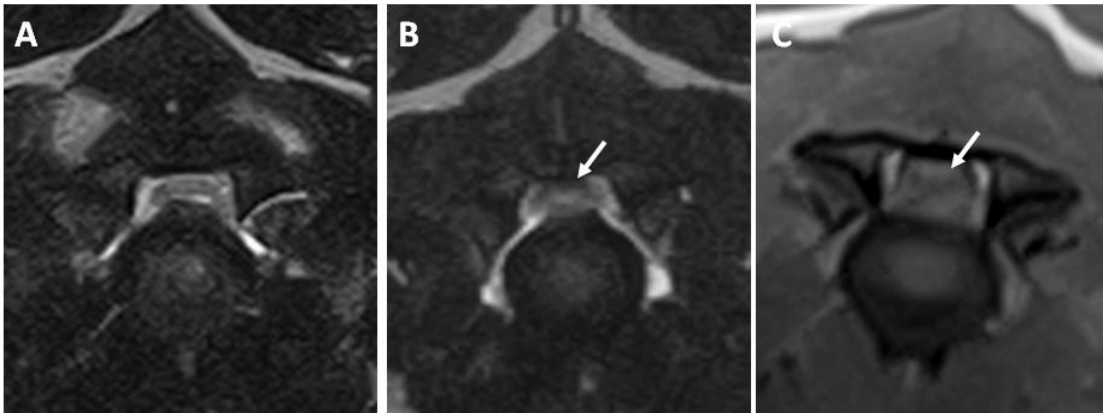

Figure 7. Transversal images at the level of C5-C6 in Case 4 at the moment of diagnosis (A) and immediately postmortem (B and C). Transversal T2-weighted image at the moment of diagnosis demonstrates no ISI changes (A). The second MRI study reveals hyperintense ISI changes on transversal T2-weighted images (B) and hypointense ISI changes on transversal T1-weighted images (C).

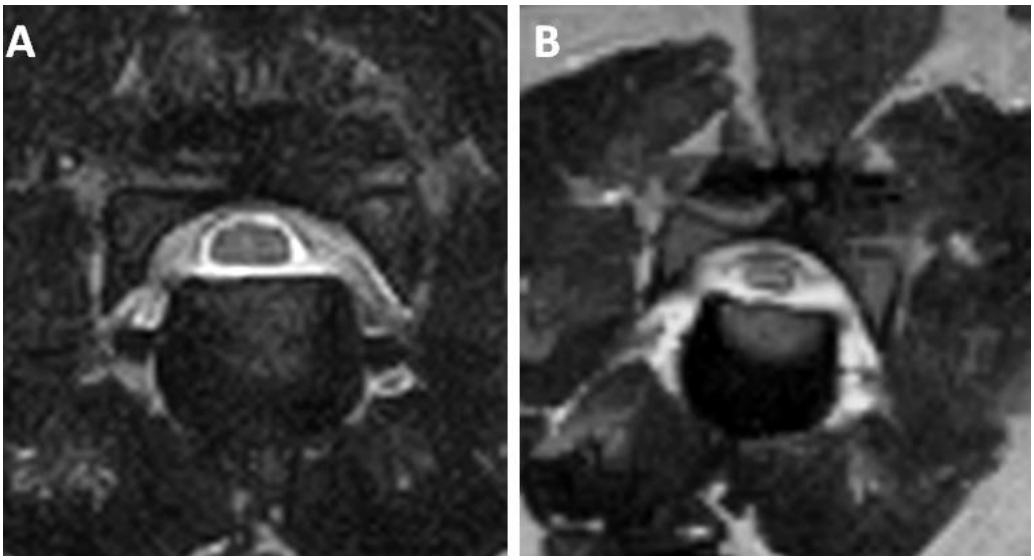

Figure 8. Transversal T2-weighted images at the cranial vertebral body level of C6 in a 10-year-old Whippet at moment of diagnosis (A) and 12 months after diagnosis (B). A relative increase in hyperintense cerebrospinal fluid/epidural fat area to spinal cord area can be note in (B). This finding suggests spinal cord atrophy.

Immediately after completion of the MRI studies of the two euthanized dogs, their cervical spinal cords were removed and submitted for neuropathological examination. Both spinal cords were dorsoventrally flattened at the site of compression, and the border between grey and white matter was not identifiable. In the cervical spinal cord cranial to the compression (Figure 9), Case 1 showed whitish discoloration of the cuneate fascicles. Histologically, both animals showed a marked tissue loss and collapse of grey and white matter, which was replaced by gliosis. Multifocally, this loss of tissue resulted in empty spaces that were separated by strands of glial tissue. The central canal was severely dilated and ruptured with loss of ependymal lining. These changes were associated with interstitial edema in the surrounding grey matter. Rostrally and caudally of the compressive lesion marked Wallerian degeneration and gliosis was present in the cuneate fascicle and ventral funiculi, respectively. Both dogs showed chronic axonal degeneration and loss in multiple nerve roots. Neuropathological diagnosis was a chronic segmental myelomalacia due to compression (Figure 10).

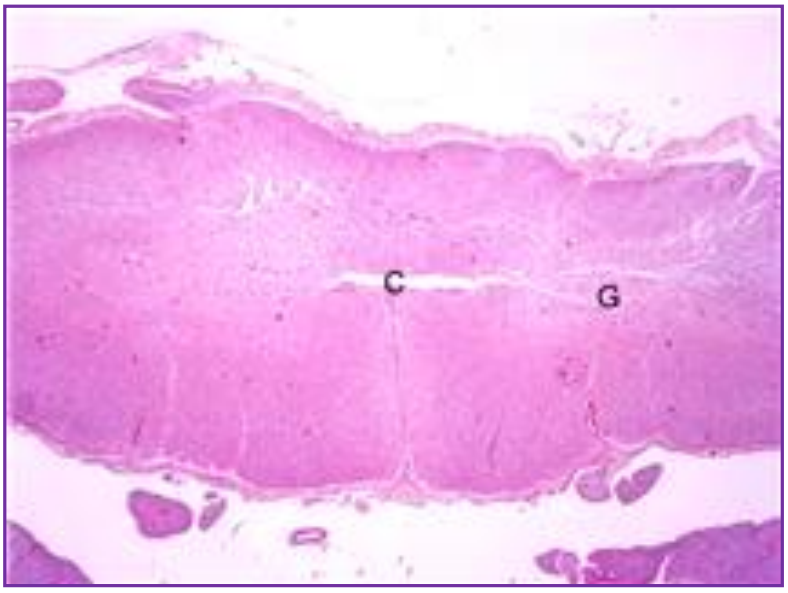

Figure 9. Marked dorsoventral compression of the spinal cord at the level of C5-C6 in Case 4. The central canal (C) is dilated and ruptured. Due to tissue necrosis and gliosis the grey matter (G) is collapsed and the boundary between grey and white matter blurred. H&E, 20x magnification.

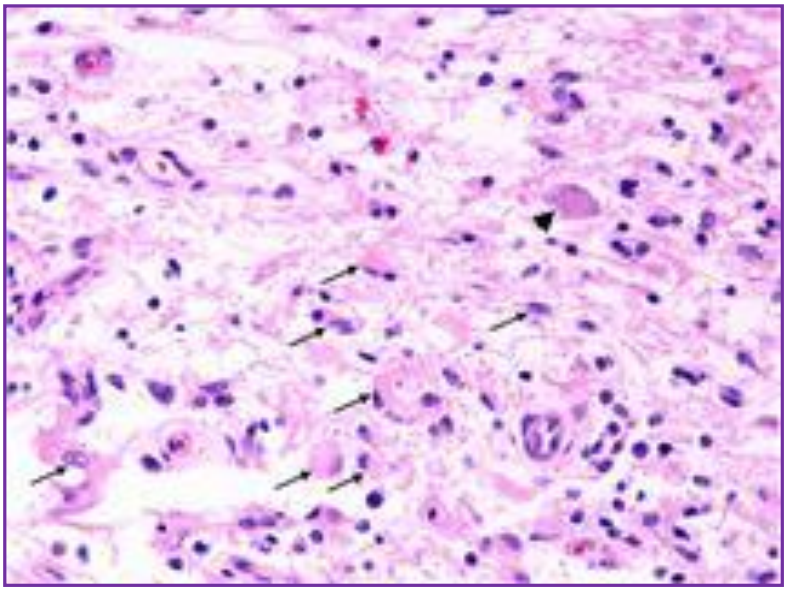

Figure 10. Same animal and same location as figure 10. Higher magnification. Loss of grey matter results in empty spaces that are separated by strands of glial processes. Necrotic grey matter has been replaced by gliosis with hypertrophic astrocytes (arrows). One intact neuron is left (arrowhead). H&E, 400x magnification.

Discussion

In this study we have assessed the evolution of clinical signs and potential prognostic factors for dogs treated conservatively for DAWS. Additionally, we have evaluated the correlation between clinical presentation, selected MRI parameters and electrophysiological evaluation of the spinal cord by TMS. To the best of the authors' knowledge, this is the first prospective study describing the results of serial neurologic evaluations to gain more information about the natural progression and results of nonoperative treatment in dogs with DAWS.

In this study, only the minority of dogs could be managed successfully by conservative treatment. This is in agreement with a recent retrospective study from the same authors.[13] Also in agreement with this earlier study [13], failure of conservative treatment was generally characterized by a progressive deterioration of clinical signs after initial diagnosis. Importantly, the neurological status one month after diagnosis appears to be a crucial moment in the evaluation of conservative treatment for DAWS. All unsuccessfully treated dogs had neurologically worsened one month after diagnosis, whereas the opposite was true for successfully treated dogs. Therefore, this first reevaluation offers the potential of rapid identification of dogs that are likely to further deteriorate to a nonambulatory status. These dogs should be identified as soon as possible, before irreversible spinal cord damage occurs, to preserve their chances for recovery after surgery. Again in agreement with the previous study [13], the majority of unsuccessfully treated dogs were euthanized within the first 6 months after the moment of diagnosis. This suggests that unsuccessfully treated cases generally develop a rather rapid and catastrophic neurologic deterioration instead of a slowly progressive course. This finding is in agreement with human findings [38-41] and highlights further the importance of early recognition of unsuccessfully treated cases. The success rates of this and the earlier reported study are considerable lower compared to the study of da Costa.[17] In that study, 80% of dogs improved or stabilized after conservative treatment for cervical spondylomyelopathy. This difference can probably be attributed to the fact that da Costa et al. included in their study only dogs, which were available for follow up for at least 6 months after diagnosis of cervical spondylomyelopathy.[17]

Several dogs experienced, after a long period of stable improvement, an acute episode of neurological deterioration. The occurrence of a second episode of clinical signs after initial recovery is a common and important complication after surgical treatment of DAWS.[1-4,15]

These episodes are generally caused by the occurrence of adjacent segment disease.[2] This is the development of a new compressive lesion at the disk space adjacent to the surgically treated site.[2] There is controversy about the exact etiology and pathogenesis of this complication.[14] While it is generally considered a true surgical complication[1-4], some authors believe that the occurrence of adjacent segment disease is part of the natural progression of DAWS.[14] If the latter is true, DAWS should not only be considered a multifactorial but also a multifocal disease.[14] The occurrence of adjacent segment disease in dogs treated conservatively for DAWS would support the theory that this phenomenon is part of the natural progression of DAWS. Unfortunately, a new MRI scan at the moment of such a clinical relapse was only performed in one of these dogs (Case 18). The first MRI study revealed a spinal cord compression at the level of C6-C7. The second MRI study revealed an additional spinal cord compression at the level of C5-C6 (Figure 6).

Besides clinical evolution one month after diagnosis, prognosis of dogs treated conservatively for DAWS was also influenced by the degree of spinal cord compression, expressed by the remaining spinal cord area, and the amount of vertebral canal compromise. This is in agreement with human findings [33,41-43] and suggests that severe spinal cord compression and vertebral canal compromise are indications for surgery in dogs with DAWS. The constructed ROC-curves (Figure 5) demonstrated threshold-values with an acceptable high sensitivity and specificity for both parameters to differentiate between successfully and unsuccessfully treated cases. However, previous work by the authors has demonstrated less than optimal interobserver agreement for the assessment of these parameters by low-field MRI.[25] Therefore, we currently not recommend the application of the calculated threshold values for clinical decision making in individual patients. Further exploration of these morphometric dimensions by other imaging modalities is suggested.

Hyperintense ISI changes are considered a reliable morphologic parameter to discriminate clinically relevant from irrelevant spinal cord compressions.[9,44] In human medicine, there is considerable controversy considering the prognostic value of ISI changes in patients with cervical spondylotic myelopathy. Some authors have found a correlation between the outcome of surgical or conservative treatment and increased signal intensity on T2-weighted images [35,45-47], but others have not.[34,40-42,48] Some consider this finding predictive for outcome only in cases with multilevel manifestation [49,50] or in combination with hypointense changes on T1-weighted images.[36,48,51-53] It has been suggested that high-intensity signal changes on T2-

weighted images are nonspecific and may indicate edema, inflammation, ischemia, gliosis, and myelomalacia which may be or may be not reversible [47,54], whereas low signal changes on T1-weighted images may represent myelomalacia, which is considered irreversible.[52,55] Two dogs in this study were diagnosed with the combination of a hyperintense ISI change on T2-weighted images corresponding to a hypointense ISI change on T1-weighted images. Although none of these dogs recovered, the number of animals can be considered too small to draw reliable conclusions. Two other dogs that progressed to a nonambulatory status underwent a postmortem MRI study. Both dogs initially presented with only hyperintense ISI changes. The second MRI, performed postmortally, demonstrated additionally to the hyperintense ISI changes on T2-weighted images also hypointense ISI changes on T1-weighted images. Neuropathological examination of these two dogs revealed segmental chronic myelomalacia and gliosis in both cases (Figures 9 and 10).

Outcome of dogs treated conservatively for DAWS was not significantly influenced by any of the other assessed MRI or any of the assessed clinical parameters. Although earlier studies have demonstrated significantly different TMS-values between Doberman Pinschers with and without clinical signs[18,19] and clinically relevant and irrelevant spinal cord compressions [19], the results of this study suggest that TMS is not a useful technique to select patients eligible for conservative treatment of DAWS.

One of the imperfections considering the literature on canine cervical spondylomyelopathy are the multitude of reported neurological grading scores for dogs with this disorder.[5-13] This limits clinician communication, multicentre trials and the comparison between different studies.[56] An objective grading system is ideally characterized by high inter-rater agreement, good correlation to imaging findings that represent tissue disruption, good correlation with electrophysiology findings, and are predictive of long-term functional outcome.[56] In this study, there was no significant correlation between the type of clinical signs, amount of spinal cord compression, electrophysiological evaluation by TMS and outcome. Several factors could have contributed to this concerning finding. First, it seems obvious that the used grading system was not ideal. This is illustrated by the fact that several dogs presented on serial neurologic examinations with distinct improvement or deterioration, while their neurological grade remained the same. This can be explained by a significant range of injury severity, such as grade of ataxia or paresis, within a single grade. Second, it is clear that neurological impairment scores have limitations. Grading scores do not inform about the

underlying mechanism of spinal cord damage and are imperfect at discerning structural versus functional lesions.[57] This is illustrated by the fact that both dogs with tetraplegia regained an ambulatory status, 2 to 3 weeks after diagnosis. Both dogs presented with very acute clinical signs and it can be hypothesized that acute concussion played a more important role than chronic compression of the spinal cord. This can explain why these dogs had a better outcome than some other dogs with less severe but more chronic neurologic signs.

Medical treatment in this study consisted of corticosteroid administration. The rationale for this was to diminish vasogenic edema, which results in return of function without removing the protruded annulus.[58] However, the prolonged used of corticosteroids is controversial and can be accompanied by several side effects.[2,58] Most of the dogs in this study demonstrated some of the more common side effects of corticosteroid treatment. Although the majorities were rather innocent such as polyuria and polydipsia, one of the dogs developed liver failure. Although it is difficult to prove a causative relationship, hepatopathy has been associated with glucocorticoid excess.[60] This necessitates the investigation and development of alternative medications to treat chronic spinal cord compressions in dogs. Preliminary results with 4-aminopyridine derivates are promising.[61]

The most important limitations of this study are the rather small number of included dogs and the fact that all imaging studies were performed with a low-field MRI device. It is possible that the inclusion of more dogs and the use of a MR unit with a higher field-strength could have altered our result. Additionally, our definition of endpoints for unsuccessfully treated cases does not allow for reliable calculation of survival time for dogs treated conservatively for DAWS. It is obvious that the time period between diagnosis and euthanasia is generally longer than the time period between diagnosis and the decision to switch over to surgical treatment. These endpoints are also different between individual owners. Some owners will switch over to surgery after only slight neurological deterioration. Other owners will always decline surgery and will consider the neurological signs acceptable as long as the animals are ambulant.

Conclusions

In summary, the results of this study suggest that the prognosis for dogs treated conservatively for DAWS should be regarded as rather guarded. Progression of clinical signs in unsuccessfully treated cases is rather fast with progression to a nonambulatory status generally in the first 6 months after diagnosis. Reevaluation 1 month after diagnosis offers the potential for early recognition of unsuccessfully treated cases, thereby giving the opportunity to change over to surgical treatment before irreversible spinal cord damage has occurred. Although the degree of spinal cord compression and vertebral canal compromise seem to be of importance for decision whether to treat surgically or conservatively, it is currently unknown why some dogs suffer a rapid and dramatic progression of clinical signs, while the clinical course is more benign in other dogs treated conservative for DAWS. The lack of correlation between clinical presentation, imaging findings, electrophysiological findings and outcome is disturbing and warrants further investigation.

Footnote: [a] Magstim Super Rapid, Acertys Healthcare

[b] Sapphire, Acertys Healthcare

[c] Monopolar needle electrode, Acertys Healthcare

[d] Subdermal needle electrode, Acertys Healthcare

[e] Magnet: Airis Mate, Hitachi, Japan

[f] Osirix Image processing software, California, United States

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Chapter 6

SURGICAL TREATMENT OF DISK ASSOCIATED WOBBLER SYNDROME IN DOGS

Chapter 6.1

SURGICAL TREATMENT OF DISK ASSOCIATED WOBBLER SYNDROME IN DOGS BY A STANDARD VENTRAL SLOT PROCEDURE: A RETROSPECTIVE STUDY OF 12 CASES

SURGICAL TREATMENT OF DISK ASSOCIATED WOBBLER SYNDROME IN DOGS BY A STANDARD VENTRAL SLOT PROCEDURE: A RETROPSECTIVE STUDY OF 12 CASES

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Summary

There is lot of controversy about the treatment of disk associated wobbler syndrome (DAWS). This retrospective study describes the clinical evolution of 12 dogs treated surgically by a standard ventral slot technique. Duration of follow-up ranged from 1 to 59 months. Nine of the 12 dogs clinically recovered. However, six of these 9 dogs developed a second episode of clinical signs. Two of these dogs could be further managed by conservative treatment. The 4 other dogs were euthanized. The results of this study are compared to literature. Special attention is given to inclusion criteria and follow-up data.

Introduction

Cervical spondylomyelopathy (CSM) or wobbler syndrome in dogs is a covering term to describe different causes of progressive caudal cervical spinal cord compression. These disorders result in a typical clinical presentation of a broad-based ataxia with rather mild paresis of the pelvic limbs, frequently in combination with a short and stilted gait of the thoracic limbs.[1] Neck pain is not always overtly present.[1,2] Based on signalment and etiology, separate syndromes have been recognized.[3,4] The most common and most typical cause of CSM is probably disk associated wobbler syndrome (DAWS).[1,4] In DAWS, ventral spinal cord compression is caused by protrusion of one or more intervertebral disks, sometimes in combination with dorsal compression caused by ligamentum flavum hypertrophy, an abnormal position of the vertebral body with craniodorsal tilting into the vertebral canal and rather mild vertebral malformations.[1] These vertebral malformations range from cranioventral flattening of the vertebral body to a triangular shaped vertebral body. The intervertebral disk space between the sixth (C6) and seventh (C7) vertebral bodies is most commonly affected.[1-3] Multiple site of spinal cord compression can occur with concurrent compression between the fifth (C5) vertebral body and C6.[1-3] Although the adult to older Doberman Pinscher is overrepresented, several large breed dogs can be affected by this disorder.[1-3] The exact causes and/or underlying pathogenesis of the different types of CSM are currently unknown.[1,2] A multifactorial etiology is considered most likely.[1] There is a lot of controversy about the treatment of DAWS.[4] It is classically considered a surgical disorder with very low success rates for conservative treatment.[2,3] However, recent veterinary studies have demonstrated success rates between 45 and 80% after conservative treatment for DAWS.[5-6] Many surgical techniques have been developed for this disorder.[7-14] The large number of described techniques reflects the difficulty of treating this disease and indicates that the ideal surgical technique does not yet exists.[4] The existing surgical techniques are typically divided in two categories: direct decompressive and distraction-stabilization techniques.[2] Although initial success rates of 80% have been described, each of these techniques is associated with comparable difficulties and complications. The most common problems are the difficulty of performing surgery on two adjacent disk spaces, implant failure and the occurrence of a second episode of clinical signs.[2,15] The latter is considered the most important postoperative complication and is generally caused by the development of a new compressive lesion at an adjacent disk space. Therefore, this complication is called adjacent segment disease.[2,4]

This retrospective study describes the results of 12 dogs treated surgically for DAWS by a standard ventral slot technique (SVS). This technique is considered a standard type of direct decompressive surgery whereby the affected intervertebral disk is removed. The results of this study are being compared with those of other similar reports. This comparison will be focused on inclusion criteria and follow-duration of the different described studies.

Material and Methods

The medical records of dogs diagnosed with DAWS at the Faculty of Veterinary Medicine, Ghent University, Department of Clinical Biology and Medicine of Small Animals between 2001 and 2005 were retrospectively analyzed. Only dogs treated surgically by a SVS could be included in the study. Information considering signalment, clinical presentation, diagnosis, treatment and follow-up were derived from the medical records. Diagnosis always was made by cisternal myelography under general anesthesia. Dynamic myelographic studies were not routinely performed. In all dogs, a SVS, as originally described by Swaim[16], was performed. The maximum sizes of the SVSs did never exceed 1/3 of the vertebral body length and 1/3 of the vertebral body width. In dogs with more than one spinal cord compression, the site of most severe compression was operated. This was subjectively evaluated on the available myelograms. Postoperative care consisted in all dogs of an oral tapering prednisolone (Prednison, 5mg®, Kela) course during 3 weeks and cage confinement during 4 weeks. Information considering follow-up of the animals was obtained by reevaluations at the Faculty of Veterinary Medicine and/or a telephone questionnaire with the owners and/or the referring veterinarians.

Results

Twelve dogs were included in the study (Table 1). Nine of 12 dogs were Doberman Pinschers. The 12 dogs consisted of 7 males and 5 females. Age ranged from 3.7 months to 10.75 years (mean 7 years; median 7.6 years). Duration of clinical signs varied from 1 day to 6 months (mean 69 days; median 74 days). Clinical signs varied from only neck pain (n = 1), to ambulatory paraparesis and ataxia with or without neck pain (n = 2), ambulatory tetraparesis and ataxia with or without neck pain (n = 8) to tetraplegia without apparent signs of neck pain (n = 1). In all Doberman Pinschers a pre-anesthetic echocardiographic examination was performed. In all dogs, a ventral extradural spinal cord compression between C6-C7 was seen. Three of the 12 dogs demonstrated an additional compression between C5-C6. Dorsal spinal cord compression was not seen in any of the dogs. In 8 of 12 dogs, additional vertebral abnormalities were seen: abnormal position with craniodorsal tilting of C7 (n = 4). abnormally shaped C7 (n = 5), and spondylosis deformans ventral to C6-C7 (n = 7). In all dogs, a SVS was performed. Excessive intraoperative bleedings necessitated preliminary ending of the surgery in one dog (dog 3). The compressive tissue was already removed at that moment. No perioperative complications were seen in any of the other dogs. Two of the dogs (dogs 9 and 12) demonstrated an initial immediate postoperative clinical improvement. After a few days however, they experienced a progressive neurological deterioration. In 1 of these dogs (dog 9), a new myelographic examination was performed 10 days after the surgical procedure. This demonstrated a collapsed intervertebral disk space with ventral extradural spinal cord compression at the operated site. No further examinations were performed in the other dog (dog 12). The owners of both dogs declined a new surgical procedure and both dogs were euthanized after 1 month because of lack of clinical improvement. The remaining 10 dogs were available for a 1-month-postoperative neurological reevaluation at the Faculty of Veterinary Medicine and a telephone questionnaire at the moment of study enrollment. The follow-up period ranged from 1 month to 5.9 years (mean 2.2 years; median 1.9 years). Nine of 12 dogs (75%) improved postoperatively and regained a neurologically normal status. One dog (dog 11) experienced a slowly progressive neurological deterioration after surgery. However, this dog was still alive at the moment of study enrollment. Six of 9 dogs (66%) with initial clinical improvement developed a second episode of clinical signs. The time period of clinical recurrence ranged from 11 months to 5.9 years (mean 2.5 years; median 2.3 years). In only one of these 6 dogs (dog 6) a new myelographic examination was performed. This new myelographic examination demonstrated a new extradural spinal cord compression at C5-C6.

This finding was consistent with the development of adjacent segment disease. The details of this case are described elsewhere.[17] Two of the 6 dogs with a recurrence of clinical signs could be further managed conservatively. This conservative treatment consisted in both dogs of cage confinement during 4 weeks and a tapering oral prednisolone (Prednison 5 mg®, Kela) treatment during 3 weeks. The 4 other dogs were euthanized. Finally, only 5 of the 12 dogs (42%) could be considered as successfully treated for DAWS. These animals were the 3 dogs with initial and definitive clinical improvement and the 2 dogs that could be managed successfully after their clinical relapse by conservative treatment.

Table 1. Twelve dogs treated surgically by a standard ventral slot technique for Disk associated wobbler syndrome

Dog	Signalment	Duration of clinical signs	Clinical Signs	Site Spinal cord compression	Follow-up Period	Clinical follow-up
1	Doberman, M, 7y 1m	2 m	Ambulatory tetraparesis	C6-C7	59 m	Initial recovery, recurrence signs 59 m
2	Doberman, F, 5y 7m	3 w	Neckpain and ambulatory tetraparesis	C6-C7	48 m	Initial recovery, recurrence signs 43 m
3	Doberman, Fc, 9y 4m	3 d	Neckpain and ambulatory tetraparesis	C6-C7	11 m	Initial recovery, recurrence signs 11 m
4	Doberman, Fc, 4y	3,5 m	Ambulatory paraparesis	C6-C7	22 m	Initial recovery, recurrence signs 22 m
5	Doberman, M, 8y 8m	2 m	Ambulatory paraparesis	C6-C7	39 m	Initial recovery, recurrence signs35 m
6	Weimaraner, M, 3y 8m	1 d	Tetraplegia	C6-C7	47 m	Initial recovery, recurrence signs 22 m
7	Doberman, M, 4y 11m	2 m	Neckpain and ambulatory tetraparesis	C5-C6 en C6-C7	47 m	Neurologically normal
8	Doberman, F, 9y 5m	1 w	Neckpain	C6-C7	13 m	Neurologically normal
9	CV, M, 7y	1 m	Neckpain and ambulatory tetraparesis	C6-C7	1 m	No improvement
10	Doberman, Fc, 7y 10m	6 m	Ambulatory tetraparesis	C6-C7	9 m	Neurologically normal
11	CV, M, 10y 9m	6 m	Ambulatory tetraparesis	C5-C6 en C6-C7	24 m	Slow, progressive deterioration
12	Doberman, M, 7y 5m	4 m	Neckpain and ambulatory tetraparesis	C5-C6 en C6-C7	1 m	No improvement

M = male, F = female, Fc = female castrated, d = days, w = weeks, m = months, y = years, C6-C7 = site of worst compression

Discussion

This study describes the results of 12 dogs treated surgically by a classical surgical technique for DAWS. The obtained success rates are considerable lower compared to previously reported studies. Possible reasons for this are the specific characteristics of the follow-up period in our study.

In the present study, the mean age at moment of diagnosis was 7 years and the Doberman Pinscher was the most included breed. This is in agreement with previously reported studies.[5-11,18]

DAWS-associated spinal cord compressions are classically categorized as dynamic or static spinal cord compressions.[3] The amount of spinal cord compression decreases or increases with different positions of the neck in dynamic studies, while it stays the same in static compressions.[2,3] To differentiate between dynamic and static lesions, dynamic myelographic studies can be performed with traction, flexion and extension.[2] In dogs with DAWS, the severity of spinal cord compression generally improves with craniocaudal traction and flexion of the cervical vertebral column.[2,15,18] The reported surgical techniques for DAWS are typically divided in distraction-stabilization and direct decompressive surgical procedures.[2,3] The rationale for performing a traction-stabilization procedure is the fact that spinal cord compression generally decreases after craniocaudal cervical traction. Many of these techniques have been developed. However, the principle of these different techniques is rather similar.[1,2,4] After a standard ventral approach; the largest part of the intervertebral disk is removed. The vertebral endplates and the dorsal portion of the annulus fibrosus is generally preserved, avoiding entering the vertebral canal. Subsequently, craniocaudal cervical traction is performed and the vertebral bodies are secured in this position by a large variety of orthopedic implants.[1,2,4] By the performed traction, the ligamentous structures (intervertebral disk, dorsal longitudinal ligament, and flaval ligament) are stretched. In this way, the degree of spinal cord compression is immediately reduced and as a consequence of the stabilization, additional atrophy of the hypertrophic ligamentous structures can occur which results in further reduction of the spinal cord compression.[1,4] A disadvantage of this type of surgery is the potential of implant failure such as iatrogenic spinal cord or vascular damage, loosening of the implant and fractures of the vertebral endplates by a suboptimal endplate implant contact.[2]

The most common applied direct decompressive surgical technique is the standard ventral slot (SVS) technique.[2,3] In a SVS, the affected intervertebral disk space and a part of the adjacent vertebral endplates are removed after a standard ventral approach of the cervical spinal cord.[14] By completion of a SVS, the vertebral canal is entered which immediately relieves the spinal cord compression (Figure 1). A disadvantage of this technique is the impossibility to relieve dorsal compressions caused by ligamentum flavum hypertrophy.[2,3] The choice between these two types of surgery is generally based on the results of traction-studies performed during myelography. In traction-responsive lesions, distraction-stabilization procedures are advised.[2] In static lesions, direct decompressive surgery is advised.[2] The importance of performing these dynamic studies is questioned by the study of Rusbridge.[18] In this study, 14 dogs were treated by a direct decompressive surgery (SVS) and 14 other dogs were treated by a distraction-stabilization procedure (pins and polymethylmethacrylate) without performing preceding dynamic studies. The results in both groups of dogs were similar. Further, there is a lot of discussion and obscurity considering the definition and objectivity of these dynamic studies.[18,19] For these reasons, dynamic studies were not routinely performed in our study and all dogs were treated by a SVS procedure.

Performing a SVS procedure in a dog with DAWS is even for an experienced neurosurgeon a technical challenge. The limited access to the caudal cervical region, potential for vertebral malformations and excessive spondylosis deformans can complicate this surgical procedure (Figure 2).[3] Since DAWS is typically a chronic condition, adhesions can occur between the protruding intervertebral disk, dorsal longitudinal ligament and the internal venous plexus. These adhesions increase the risk for intraoperative laceration of the venous plexus with subsequent hemorrhages.[3] This was the case in one of the dogs of this study (Dog 3). Additionally, these adhesions complicate the complete removal of the protruded intervertebral disk and hypertrophied dorsal longitudinal ligament.[3] However, it is very important to remove all the protruded tissue. After completion of a SVS, a partial collapse of the intervertebral disk space can occur. This can cause prolapse of the remaining tissue into the vertebral canal with subsequent spinal cord compression. This new compression can cause incomplete clinical recovery or even persistent neurological deterioration after surgery.[1] This can be an explanation for the clinical evolution in 2 of our dogs (Dogs 9 and 12). Even after complete removal of all protruded material is it not unusual for the dogs to experience a transient neurologic deterioration.[18] Such a deterioration immediate postoperative does not affect the changes of recovery after a longer follow up period.[18] The exact cause of this transient

deterioration, after decompression of chronic spinal cord compressions, is currently unknown. It is hypothesized that reperfusion injuries with release of free-oxygen-radicals play a major role in this phenomenon.[20]

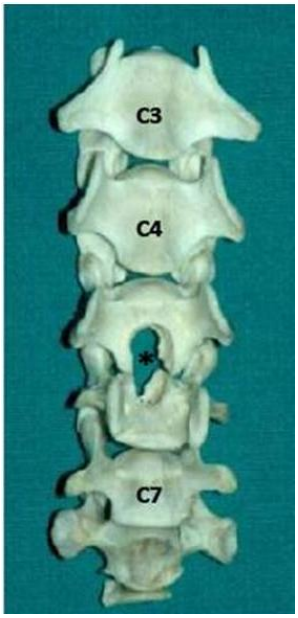

Figure 1. Ventral projection of an anatomical model with a completed SVS (*) between C5 and C6. The sizes exceed somehow the ideal sizes of a SVS

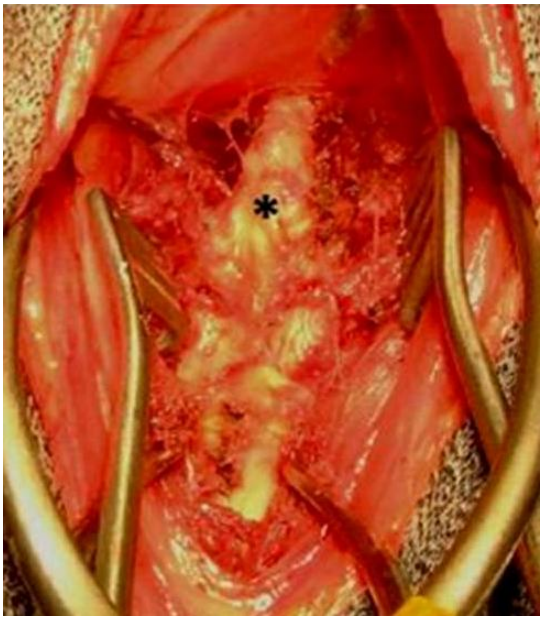

Figure 2. Intraoperative photograph during the ventral approach of a SVS between C6 and C7. Excessive new bone formation (*) complicates further completion of the surgical procedure

Classically, an initial success rate of 70-80% has been reported for the surgical treatment of DAWS by a SVS.[2-4] The most important reasons for lack of initial improvement are the occurrence of irreversible spinal cord damage preoperatively and remaining spinal cord compression postoperatively.[2] From this point of view, it is not surprisingly that 1 of the 3 dogs with multiple spinal cord compressions at time of diagnosis did not recover after surgery. The occurrence of multiple sites of spinal cord compression at the moment of diagnosis is one of the most common difficulties in the surgical treatment of DAWS. With the existing surgical procedures, direct decompressive and distraction-stabilization techniques, it is currently very difficult or even impossible to treat 2 adjacent intervertebral disk spaces at

the same time.[2,15] A new type of implant which allows combination of direct decompression and distraction-stabilization at 2 adjacent disk spaces is currently used at the authors institution.[21] The preliminary results are promising.

Classically, 20 to 30% of initially recovered dogs experiences a second episode of clinical signs.[2-4] This complication is called adjacent segment disease and it occurs independent on the applied surgical technique.[4,18] The exact cause of adjacent segment disease is currently unknown.[2] Some authors believe that these new compressive lesions occur as a result of altered biomechanical properties caused by the initial surgical procedure at the adjacent intervertebral disk space. Others believe that DAWS is not only a multifactorial but also a multifocal disease.[4,17,22,23] If the occurrence of adjacent segment disease can be attributed to a multifocal character of DAWS, it could be considered to always fuse or stabilize routinely two adjacent intervertebral disk spaces during the initial surgical procedure.[4] Results from human studies support this approach.[24,25]

The success rates of this retrospective study are remarkably lower than previously reported studies. Although 75% (9/12) of dogs initially recovered after surgery, 66% (6/9) experienced a second episode of similar clinical signs. In only 1 of these dogs adjacent segment disease was confirmed by a new myelographic examination. In the other dogs, the occurrence of adjacent segment disease could only be presumed. This resulted in a definitive success rate of 42% (5/12 dogs). However, it is very difficult to compare the results of this study with those of earlier reported studies.[4] Chambers reported in a first study [7] a success rate of 100%. However, the dogs included in this study had to be available for at least 12 months postoperatively and the mean follow-period was only 16 months. In this way, dogs that did not recover after surgery or deteriorated in the first 12 months postoperatively were all excluded from the study. In a second study [26], he reported a success rate of 66%. This time, the immediate postoperative period was included but he considered the treatment of dogs that died for reasons unrelated to DAWS (e.g. pneumonia) also as unsuccessfully. In a recent study by da Costa [5], the dogs had to be available for at least 6 months postoperatively and the animals were treated by a variety of surgical techniques without making any difference between them. Additionally, most studies pay little attention to the occurrence of multiple sites of spinal cord compression at the time of diagnosis and the development of adjacent segment disease after initial recovery from a SVS for the treatment of DAWS.[5,7,26,27] In the study by Rusbridge [18], the dogs were followed during the whole postoperative period, the

occurrence of multiple sites of spinal cord compression was noted, and the development of adjacent segment disease was described. The results of their study are similar to those of our study. The most important information about these different studies is presented in Table 2. Comparison between different studies reporting the results of a SVS technique for the treatment of DAWS is further complicated by the large variety in clinical presentation of dogs with DAWS.[4] It seems logical that older dogs with more chronic and progressive clinical signs will be less likely to experience a good postoperative recovery than young dogs with an acute and non-progressive onset of signs.[2] However, the correlation between clinical presentation and clinical outcome is not yet investigated for dogs with DAWS. Although many veterinary studies have described new surgical techniques for the treatment of DAWS, little is known about objective prognostic parameters for this disease.[15]

Table 2. Overview earlier reported studies about treatment of DAWS by a SVS technique

Study	Number of dogs	Number recovered	Inclusion criteria	Follow-up time	Information second episode clinical signs	Additional remarks
This study	12	9		Until 59 m (mean 27 m)	6/9 clinical relapse	
Chambers *et al.* (1982)	12	12	Available at least 12 m postoperatively	12 to 26 m (mean 16 m)	No information	
Read *et al.* (1983)	11	7	No information	No information	No information	4/11 remaining spinal cord compression on necropsy
Chambers *et al.* (1986)	27	18	Cause of death unrelated to DAWS also considered as unsuccessful treatment	Until 48 m	No information	5/9 cause of death unrelated to DAWS 4/9 remaining spinal cord compression on necropsy
Rusbridge *et al.* (1998)	14	13	Surviving dogs available at least 24 m postoperatively	Until 40 m	5/13 clinical relapse	
da Costa *et al.* (2008)	37	30	Available at least 6 m postoperatively	6 to 156 m (mean 32 m)	Incomplete information	8/37 other types of surgery than SVS

m = months

Conclusions

The results and associated discussion of this retrospective study demonstrate the most important limitations and difficulties considering the surgical treatment of DAWS by a SVS technique. An important complication is the occurrence of a second episode of clinical signs in a remarkable part of the initially recovered dogs. Therefore, the prognosis of dogs treated by a SVS technique for DAWS should be considered as rather guarded. Further studies are warranted to optimize the conservative and surgical treatment of this challenging disease.

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Chapter 6.2

COMPLICATIONS IN A DOG WITH DISK ASSOCIATED WOBBLER SYNDROME

COMPLICATIONS IN A DOG WITH DISK ASSOCIATED WOBBLER SYNDROME

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Summary

This case describes the occurrence of a second episode of clinical signs of disk associated wobbler syndrome almost 2 years following ventral decompressive surgery and a rather rare complication after myelographic examination in the same dog.

Introduction

Disk associated wobbler syndrome (DAWS) is the most predominant and typical wobbler syndrome in the dog, and it typically affects middle-aged large-breed dogs. The clinical presentation can vary from neck pain only to tetraplegia. The most typical clinical signs are a paraparetic wide-based, uncoordinated ataxia of the pelvic limbs, in combination with a short stilted gait of the thoracic limbs. Myelographic examination is the diagnostic method of choice.[1,2] Although the incidence of postmyelographic complications has dramatically decreased since the use of the newer generation water-soluble, non-ionic contrast media (e.g. iohexol and iopamidol), this diagnostic technique is not completely without risk and different myelographic complications have been described.[3] The most important of these are transient neurological deterioration and seizures.[4] DAWS is considered to be a progressive disease in which early surgical intervention is necessary to halt the progression of symptoms.[1,2] Many different surgical techniques have been described and many authors claim between 70 and 80% success rates immediately postoperatively.[1,2,5] Despite initial success, 20-30% of these dogs will suffer from a second episode of clinical signs. This can be caused by spinal cord compression at the same intervertebral disk space or compression at one of the adjacent intervertebral disk spaces. The latter is termed adjacent segment disease or a 'domino lesion' and may occur after both ventral decompressive and vertebral distraction-stabilization techniques.[1,2,6] The exact cause of this phenomenon is unknown but it might indicate that DAWS is not only a multifactorial but possibly also a multifocal disease.[6]

Case Description

A 4-year-old male Weimaraner dog weighing 30 kg was admitted to the Department of Small Animal Medicine and Clinical Biology with the complaint of non-ambulatory tetraparesis, which had started on the previous day. The owners had not noticed any abnormalities in the days or weeks prior to presentation. Physical examination revealed no abnormalities. Abnormalities on neurological examination were conscious proprioceptive deficits in all four limbs, increased spinal reflexes in the hind limbs and decreased spinal reflexes in the right front limb. Neck pain could not be elicited. The neurological examination was suggestive of a cervicothoracic spinal cord lesion. All complete blood count (CBC) and biochemistry panel values were within normal limits. A cardiologic examination including an echocardiogram was unremarkable. The dog was premedicated with methadone (0,1 mg/kg, IV, Mephenon®). Anesthesia was induced using propofol (100 mg, IV, Rapinovet®) and maintained with isoflurane in oxygen. Survey radiographs of the cervical spine were unremarkable. A cervical myelogram was performed using iomeprol (0.2 ml/kg with a maximum dose of 8-9 ml, 300 mgI/ml, Iomeron 300®) injected via cisternal puncture. In addition to standard lateral and ventrodorsal views, lateral views were obtained with the neck in flexion and gentle extension of the cervical region. A ventral, extradural compressive lesion was observed at the level of the intervertebral disk space between the sixth and seventh cervical vertebra (C6-C7) (Figure 1). The spinal cord compression worsened with gentle extension and improved with flexion. In addition, a slight dorsal deviation without attenuation of the ventral contrast column between C5-C6 and C4-C5 was observed. However, no narrowing of the contrast columns was present. Based on these findings, DAWS affecting C6-C7 was diagnosed. Examination of cerebrospinal fluid (CSF) revealed no abnormalities. Anesthetic recovery was uneventful and the dog was scheduled for decompressive surgery. Ventral decompressive surgery was performed 6 days following diagnosis. The preanesthetic medication included acepromazine (0.01 mg/kg, IV, Placivet®), methadone (0.1 mg/kg, IV, Mephenon®), and atropine (0.02 mg/kg, IM, Stellatropine®). Anesthesia was induced with thiopenthal (350 mg, IV, Pentothal®) and maintained with isoflurane in oxygen. Preoperative corticosteroid (30 mg/kg, IV, Soludeltacortef®) treatment was administered. A standard ventral slot was made at the level of C6-C7. Protruded annulus fibrosus and dorsal longitudinal ligament were removed. Anesthetic recovery was uneventful. Progressive postoperative neurological improvement was

observed. Six days after surgery, when the dog could walk unassisted, he was discharged from hospital. The clinical symptoms further improved over the next weeks and months. On follow-up examination 11 months later, the dog had improved greatly but still showed conscious proprioceptive deficits and ataxia in the right hind limb. According to the owners, these symptoms were not progressive in nature and had been present since the dog regained ambulatory status after surgery.

Twenty-two months following surgery, the dog was re-admitted to the Department of Small Animal Medicine and Clinical Biology with the complaint of a progressive deterioration of neurological status in the last two months. The dog showed severe but ambulatory ataxia of the hind limbs and a short stilted gait of the front limbs. Physical examination revealed no abnormalities. Neurological examination demonstrated the aforementioned ataxia and conscious proprioceptive deficits of the right hind limb. Neck pain could not be elicited. A CBC and a biochemistry panel were unremarkable. General anesthesia was performed as during the first myelogram, the only difference being that thiopenthal (400 mg, IV, Pentothal®) was used instead of propofol for the induction of anesthesia. Survey radiographs of the cervical region demonstrated a severe narrowing of the intervertebral disk space between C6 and C7, and new bone formation at the ventral aspects of C6-C7 and C5-C6 (Figure 2). A cervical myelogram was performed using the same protocol as the first time. The myelographic study revealed ventral deviation of the dorsal contrast column at C4-C5 and mild dorsal deviation of the ventral contrast column at the levels of C4-C5, C5-C6 and C6-C7. The spinal cord was clearly attenuated at the level of C4-C5 (Figure 3). These radiographic findings could be explained by ventral compression due to intervertebral disk protrusion and by dorsal compression due to hypertrophy of the ligamentum flavum. DAWS, affecting C4-C5, was diagnosed on the basis of these findings. The owners declined another surgical procedure and preferred a conservative therapy. During anesthetic recovery the dog started shivering and developed hyperthermia (39.9°C). He did not show symptoms compatible with epileptic seizure such as loss of consciousness, tonic-clonic movements or autonomic signs (involuntary salivation, urination and defecation). An adverse reaction to the myelographic contrast medium was suspected. Cooling therapy, fluid therapy (Hartmann's at a rate of 3.5 ml/kg/h), and antibiotic therapy with cefalexine (20 mg/kg, IV, q8h, Cefacidal®) were instituted, and a single dose of corticoids (10 mg/kg, IV, Soludeltacortef®) was given. The dog stopped shivering after a few hours. The hyperthermia disappeared as soon as he stopped shivering. Although the dog was conscious, he appeared exhausted and was hospitalized for observation. He further recovered during the night and was discharged from

the clinic the next day. The conservative therapy consisted of cage confinement for 4 weeks and a diminishing oral corticosteroid therapy for 3 weeks (1 week 1 mg/kg SID, 1 week 0.5 mg/kg SID and 1 week 0.25 mg/kg SID, Prednisolone®). The owners were contacted by telephone 46 months after the surgical procedure (24 months following the recurrence of clinical signs). According to the owners the clinical status of the dog had improved, although the dog still showed ambulatory ataxia, which was brought under control with intermittent oral corticosteroid (Prednisolone®) therapy as needed.

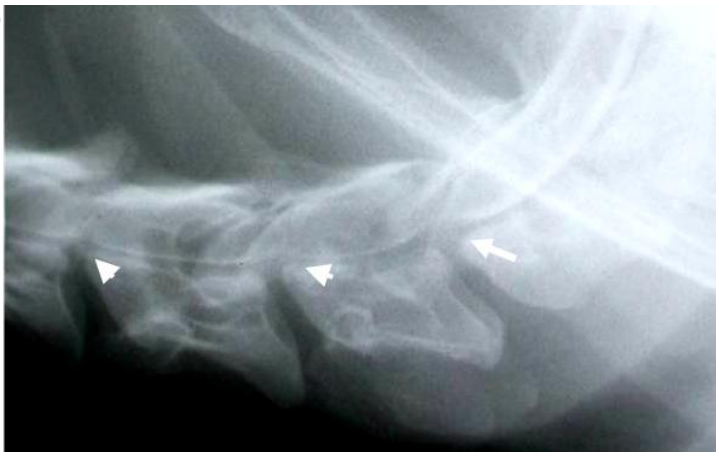

Figure 1. Lateral myelogram at initial presentation showing extradural spinal cord compression at C6-C7 (arrow) and milder lesions at C5-C6 and C4-C5 (arrowheads).

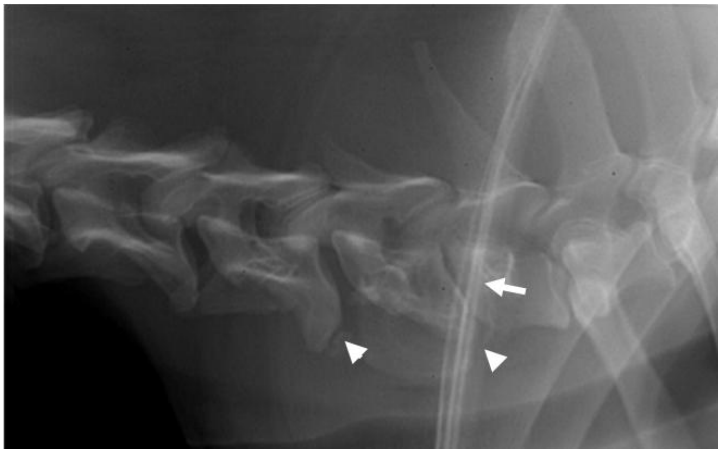

Figure 2. Survey radiograph 22 months following surgery. Severe narrowing of the intervertebral disc space between C6-C7 (arrow) and new bone formation at C6-C7 and C5-C6 (arrowheads).

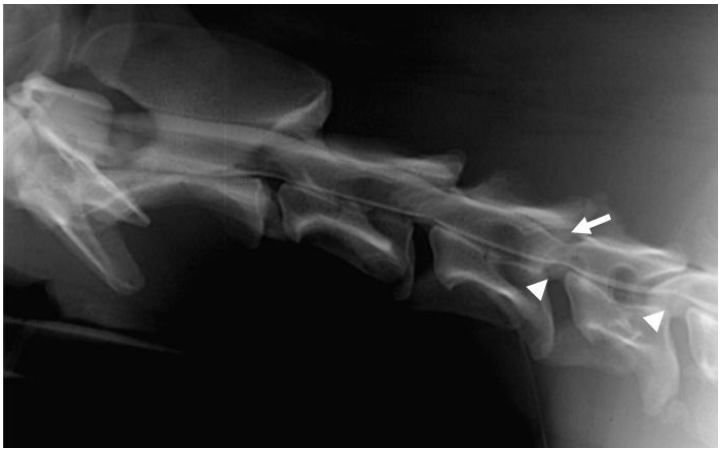

Figure 3. Neutral myelogram 22 months following surgery. Dorsal compression at C4-C5 (arrow) and milder ventral lesions at C4-C5 and C5-C6 (arrowheads) resulting in severe narrowing of the spinal cord at C4-C5.

Discussion

Disk associated wobbler syndrome (DAWS) is a relatively common cause of neurological dysfunction in middle-aged, large breed dogs. The most typical presentation is a chronic progressive gait disturbance, mainly affecting the hind limbs. An acute onset of clinical signs, as in this dog, also occurs.[1,2]

Although myelography is the diagnostic method of choice in veterinary medicine, this diagnostic technique is not entirely without risk. Exacerbation of neurological abnormalities the day after myelography and seizures during recovery are the most important and most common complications.[3,4,7] Fortunately, this neurological deterioration is typically transient and resolves spontaneously after a few days. Lewis and Hosgood demonstrated a higher risk of postmyelographic complications in dogs with DAWS compared to dogs suffering from other cervical spinal cord lesions.[4] In a retrospective study of 66 dogs undergoing cervical myelography, deterioration of neurological status was the most common complication, occurring in 21% of the dogs. Dogs with DAWS, extradural neoplasia and meningitis or myelitis had a significantly greater likelihood of neurological deterioration the day after myelography, compared to other dogs.[4] Seizures occurred in 9% of the dogs after myelography. All of these were Dobermann Pinschers afflicted with DAWS.[4] Other occasionally reported myelographic complications in human and veterinary medicine include headache, nuchal pain, nausea, vomiting, meningeal irritation, hyperthermia, neurobehavioral disturbances (altered mental state), hypotension, bradycardia during injection of contrast medium, and death.[3,4] The complication that occurred in the dog described in this case could possibly have been caused by an adverse reaction to the potentially irritant contrast medium, which is a very rare complication. The veterinary literature lacks comparable data of cases with the same unusual complication of a possible adverse reaction after myelography. The prior list of possible complications illustrates the main disadvantage of myelography: that it is a rather invasive diagnostic procedure. Advanced and less invasive medical imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), have been developed and introduced into veterinary medicine in the last decades. Little is known about their diagnostic value for dogs with DAWS.[2,7]

There is a lot of controversy about the treatment of DAWS.[6] Several surgical techniques have been developed and these can be divided into direct decompression by ventral or dorsal decompressive surgery, and indirect decompression by linear traction combined with intervertebral stabilization.[1,2] Performing direct ventral decompressive surgery by creating a ventral slot is a common way to treat dogs with DAWS. Although this is a standard neurosurgical technique, it can be a technical challenge in dogs with DAWS.[1] Intraoperative bleeding, vertebral malformations, difficult accessibility of the caudal cervical region and difficult removal of all protruding material can complicate the surgical procedure.[1,2,5] The dog in the present case improved remarkably after surgery, although he continued to demonstrate residual signs in his right pelvic limb. Incomplete removal of all protruding annulus fibrosus or dorsal longitudinal ligamentous tissue at the time of decompressive surgery is the most likely reason. After a ventral slot procedure, there is the risk of mild collapse of the intervertebral disk space. This will give the opportunity for incompletely removed tissue to prolapse into the vertebral canal and cause residual or even worse spinal cord compression.[1,2,8] This hypothesis is fed by the fact that the second myelographic examination still showed a mild dorsal deviation of the ventral contrast column at the level of the previously operated site.

Twenty-two months after the surgical procedure, the dog experienced a deterioration of the clinical signs. According to the second myelographic examination, a new compressive lesion had developed at the level of C4-C5. This complication, which is termed adjacent segment disease, is the most common and most important complication after surgery for DAWS.[6] It occurs 5 to 60 months after surgery in 20-30% of the cases and is independent of the surgical technique.[9-11] Although several theories have been developed, the exact pathogenesis and etiology of this phenomenon remain unknown. Additional disk protrusions may result when intervertebral fusion or stabilization at one level leads to increased stress at one of the adjacent disk spaces. Degeneration and protrusion of additional disks can also result from continued natural disease progression rather than from the degeneration of a previously normal disk. Another possibility is a combination of these factors.[1,2,6,9,11] In retrospect, a close examination of the preoperative myelogram in the present case suggests that there could already have been disk degeneration and a mild degree of disk protrusion at two other sites (C4-C5 and C5-C6) in the cervical vertebral column at the time of the initial diagnostic evaluation. Therefore, it seems logical that the development of the second episode of clinical signs in our dog can be attributed to the natural progression of the disease. Whether the

vertebral fusion caused by the ventral slot technique performed played a cooperative role in the development of this adjacent segment disease is unclear. The same surgical technique is also used to treat other cervical compressive lesions. Acute intervertebral disk disease with extrusion of the nucleus pulposus (Hansen type I) is commonly treated surgically (with excellent results) by ventral decompression through a ventral slot.[12] Reported complications following the ventral slot procedure for intervertebral disk disease include venous sinus hemorrhage, neurological deterioration, Horner's syndrome, respiratory complications, hypotension and bradycardia, cardiac arrhythmias and instability with subsequent subluxation of the surgical site.[12,13] Adjacent segment disease is a complication that very seldom occurs after ventral decompressive surgery for acute cervical intervertebral disk disease.[12] A recent report described the postsurgical complications, with emphasis on vertebral subluxation, in 9 dogs after a ventral slot procedure in the caudal cervical region.[13] Two of these dogs were older Dobermann Pinschers with DAWS. Only one of these 9 dogs developed adjacent segment disease. Not surprisingly, this occurred in one of the dogs with DAWS.[13] This data supports the hypothesis that the occurrence of adjacent segment disease is a complication related to the natural progression of this disease rather than to a true postoperative complication. This could be suggestive of a possible multifocal nature of DAWS. Several authors have suggested routinely fusing multiple disk spaces to reduce the incidence of domino lesions.[1,2,6] In humans, the risk of new disease at an adjacent level was found to be significantly lower following a multi-level arthrodesis, than it was following a single-level arthrodesis.[14] Results of such an approach in veterinary medicine are currently lacking and should be explored.

Conclusions

Although myelography is the method of choice for DAWS, further investigation is warranted to assess the clinical use of less invasive and more advanced medical imaging techniques like CT and MRI. Several surgical techniques have been described to treat DAWS, but none of them can avoid the possible development of a domino lesion. Further investigation is warranted to develop a surgical technique that avoids or decreases the incidence of this surgical complication.

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Chapter 6.3

SURGICAL TREATMENT OF DISK ASSOCIATED WOBBLER SYNDROME BY A DISTRACTABLE VERTEBRAL TITANIUM CAGE IN 7 DOGS

SURGICAL TREATMENT OF DISK ASSOCIATED WOBBLER SYNDROME BY A DISTRACTABLE VERTEBRAL TITANIUM CAGE IN 7 DOGS

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Summary

The objective of this study was to evaluate a distractable titanium cage for the treatment of disk associated wobbler syndrome (DAWS)

Seven dogs with DAWS were prospectively investigated. After total discectomy of C5-C6 and C6-C7, the median part of the vertebral body of C6 was removed with preservation of the lateral walls and dorsal cortex. The removed cancellous bone was collected. The implant was placed in the bony defect of C6. After placement, the titanium cage was distracted and affixed by 4 screws. Finally, the implant was filled and covered with the collected cancellous bone. Dogs had follow-up examinations 1, 3, 6, 12 and 24 months postoperatively. Six months after surgery, cervical radiographs and computed tomography (CT) were performed.

Although no intraoperative complications occurred, correct placement of the cage was technically challenging. Revision surgery was necessary in two dogs because of implant loosening and aggravation of vertebral tilting. All dogs improved after discharge from the hospital. In one dog, recurrence of clinical signs was seen postoperatively. This was caused by articular facet proliferation at an adjacent intervertebral disk space. Radiographs six months postoperatively demonstrated cage subsidence in 4 dogs. In all dogs, CT was suggestive for fusion of the bone graft with the vertebral body.

Although results are promising, technical adaptations will be necessary to make this specific surgical technique, designed for humans, suitable for routine use in dogs. Total discectomy, combined with median corpectomy, vertebral reconstruction and fusion offers potential as surgical treatment for dogs with static or traction responsive, multi-level DAWS.

Introduction

Disk associated wobbler syndrome (DAWS) is a neurological disorder in which caudal cervical spinal cord compression is caused by protrusion of one or more intervertebral disks, sometimes in combination with rather mild vertebral body abnormalities and dorsal compression resulting from hypertrophy of the ligamentum flavum.[1] The intervertebral disk spaces between the sixth (C6) and seventh (C7) cervical vertebrae and/or between the fifth (C5) and sixth cervical vertebrae are most often affected.[1,2] Up to 39 % of dogs have multiple sites of cervical spinal cord compression at the time of diagnosis.[3] This disorder is seen in middle-aged to older large breed dogs. The adult Dobermann Pinscher is overrepresented.[1,2] Although clinical signs can vary from neck pain only to tetraplegia, the most common clinical presentation is a gait disturbance. A slowly progressing hind limb ataxia and/or paresis of the pelvic limbs are usually noted, sometimes in combination with a short stilted gait of the thoracic limbs.[1,2]

The treatment of DAWS is rather controversial.[4] Although conservative treatment can be applied in selected cases [3,5], DAWS is considered a surgical condition.[1,2] Several surgical procedures have been described to treat this disorder.[6-16] Two basic types of surgery can be recognized: direct decompressive and vertebral distraction-stabilization techniques.[1,2,17] The main factor governing the choice between these two types of surgery is the appearance of the spinal cord on imaging, in particular the traction views after myelography or magnetic resonance imaging (MRI).[1,2,17-19] Other factors include the number of sites of spinal cord compression, the degree of vertebral malformation and the presence of nerve root compression.[17] Although many authors claim success rates between 70% and 90%, the large number of reported techniques [6-16] reflects the difficulty of treating DAWS. All surgical procedures for the treatment of DAWS have a high potential for morbidity and postoperative complications.[2,17] The most common problems encountered are the difficulty of treating multiple sites of compression, iatrogenic spinal cord damage, implant failure, and adjacent segment disease.[2,17,20]

The goal of this study was to evaluate the use of a distractable titanium cage (ADDplus, Ulrich GmbH & Co. KG, Ulm, Germany), with a well established use in human medicine [21], for the surgical treatment of DAWS in dogs. It was hypothesized that this implant allows the combination of distraction-stabilization and direct decompression at two adjacent intervertebral disk spaces in one surgical procedure. The technical considerations, complications, radiological and long-term clinical follow-up data associated with the use of

this new surgical technique for the treatment of DAWS are described. This study is part of a larger investigation about the diagnosis and treatment of DAWS in dogs.

Materials and Methods

Animals

Seven dogs with a diagnosis and corresponding clinical signs of DAWS were prospectively studied. The study was conducted in accordance with the guidelines of the local Animal Care Committee. Owner consent was obtained before study entry. After physical and neurological examinations were performed, complete blood count (CBC) and serum biochemical profiles were obtained for all dogs. Echocardiographic examination and standard mucosal bleeding times were performed for all included Doberman Pinschers. Since all dogs were enrolled in a study about the diagnosis and treatment of DAWS [22], this diagnosis was made by a combination of myelography, computed tomography-myelography and low field (0.2 Tesla) MRI for each dog. Although tractions studies were included in the myelographic imaging protocol, the results of these studies were not considered an inclusion or exclusion criterium for this study.

Implant (Figure 1)

The studied implant acts as a combination of distractable vertebral body replacement and anterior plating. It consists of a distractable cylinder with lateral openings and a central cavity for packing by graft material. At both ends of the cylinder, wings with 2 holes for screw fixation allow direct fixation to the adjacent vertebral bodies, preempting the need for additional ventral plating. Spikes on both ends provide anchorage of the implant in the vertebral endplates. Fixation of the implant is possible with cancellous bone screws or self-expandable monocortical screws (Osmium screws, Ulrich GmbH & Co. KG, Ulm, Germany). These latter screws are a two-component system consisting of a screw and bolt. Expansion of the screw is achieved by inserting the bolt. Placement and distraction of this implant requires specific instrumentation provided by the manufacturer.

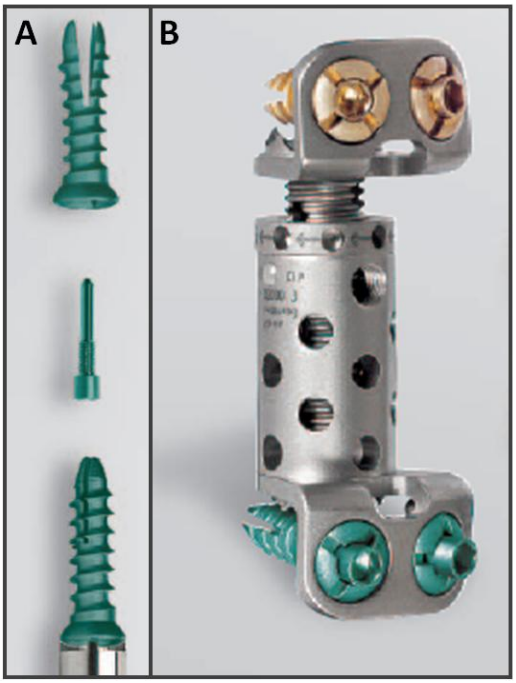

Figure 1: (A) Self-expandable titanium monocortical screw. (B) Distractable titanium vertebral cage

Preoperative Planning and Anesthesia

Before inclusion of client-owned dogs in this study, the surgical procedure was performed on a canine cadaver to evaluate feasibility of this human surgical technique in canine patients.

After owner commitment for surgery, the following vertebral body dimensions were measured by computed tomography (CT) or MRI: vertebral body length, height, and width at several levels of C6, and vertebral body height at the caudal aspect of C5 and the cranial aspect of C7. Based on these measurements, the size of the implant and screws was determined.

Following pre-anesthetic evaluation, the patients were premedicated with a combination of 0.01-0.02 mg/kg acepromazine and 0.1-0.2 mg/kg methadone IV, tailored to individual needs. Anesthesia was induced with 0.2 mg/kg diazepam IV, immediately followed by 6-8 mg/kg propofol IV to effect. Anesthesia was maintained with isoflurane in oxygen. During aseptical preparation of the surgical site, the dogs received 20 mg/kg amoxycillin-sodium/potassium-clavulanic acid (Augmentin™P500; GlaxoSmithKline s.a./n.v., Genval, Belgium) IV and 4

mg/kg carprofen IV. A physiological monitor (Cardiocap; Datex Engstrom Instrumentation, Helsinki, Finland) recorded the electrocardiogram and invasive blood pressure measurements during anesthesia. Respiratory frequency, inspiratory and expiratory gasses were measured using an anesthetic multigas monitor (Capnomac Ultima®; Datex Engstrom Instrumentation, Helsinki, Finland). A pulse-oxymeter (NPB-190; Nellcor Puritan Bennett Europe BV, 's Hertogenbosch, The Netherlands) was used to measure arterial oxygen saturation and heart rate. Eucapnia (end-tidal carbon dioxide between 35-45 mmHg) was assured by instigation of intermittent positive pressure ventilation when necessary. Intra-operative analgesia was achieved with a continuous rate infusion (CRI) of 5-10 µg/kg/hour of fentanyl. Ringer's lactate solution was infused IV at 10 mL/kg/hour throughout anesthesia.

Surgical Technique

Dogs were positioned in dorsal recumbency with the thoracic limbs pulled in a caudal direction and the neck in a neutral position. The surgical procedure was performed by a standard ventral approach to expose the vertebral body of C6, the caudal portion of C5 and the cranial portion of C7. The intervertebral disks of C5-C6 and C6-C7 were removed as complete as possible by fenestration and the use of Caspar rongeurs. The largest part of the vertebral body of C6 was removed by a pneumatic drill. The lateral walls and dorsal cortex of the vertebral body were preserved to protect the vertebral arteries and the internal vertebral venous plexus. Bleeding of the cancellous bone was controlled by bone wax. During drilling, small amounts of saline solution were added to prevent flaring up of the bone dust. The remaining bony debris was carefully collected and transferred to a sterile receptacle containing a sponge moistened with fresh blood. After the defect in C6 was created, the remaining annulus fibrosus was removed by Kerrison rongeurs. With the exception of 2 dogs, the longitudinal dorsal ligament was left in place. In these 2 dogs, the dorsal longitudinal ligament was subjectively assessed to be hypertrophied. The cartilage from the vertebral endplates was removed by a Caspar curette to promote vascular ingrowth and incorporation of the spikes of the implant in the adjacent vertebral endplates. The implant was placed in the bony defect of C6 (Figure 2A). After placement, the titanium cage was distracted by a mechanism inherent to the implant (Figure 2B). After distraction, a set screw was placed to maintain the desired amount of distraction (Figure 2C). In 4 dogs, the placement and distraction of the titanium cage was done under fluoroscopy guidance. Subsequently, the implant was fixed by 2 titanium screws in the caudal part of C5 and 2 titanium screws in the cranial part of C7 (Figure 2C). In 4 dogs, self expandable monocortical screws were used. In 3

dogs, cancellous bone screws were placed monocortically. The reasons for the latter were to decrease the expenses associated with the use of the self expandable screws, that the implant is not only affixed by screws and that the screws have only a temporary function until bony fusion occurs. Finally, the implant was filled and covered with the preserved cancellous bone (Figure 2D). Care was taken that the lateral edges of the corpectomy defect were bridged completely by the cancellous bone graft. Wound closure was routinely. Radiographs were taken immediately postoperative in all dogs (Figure 3).

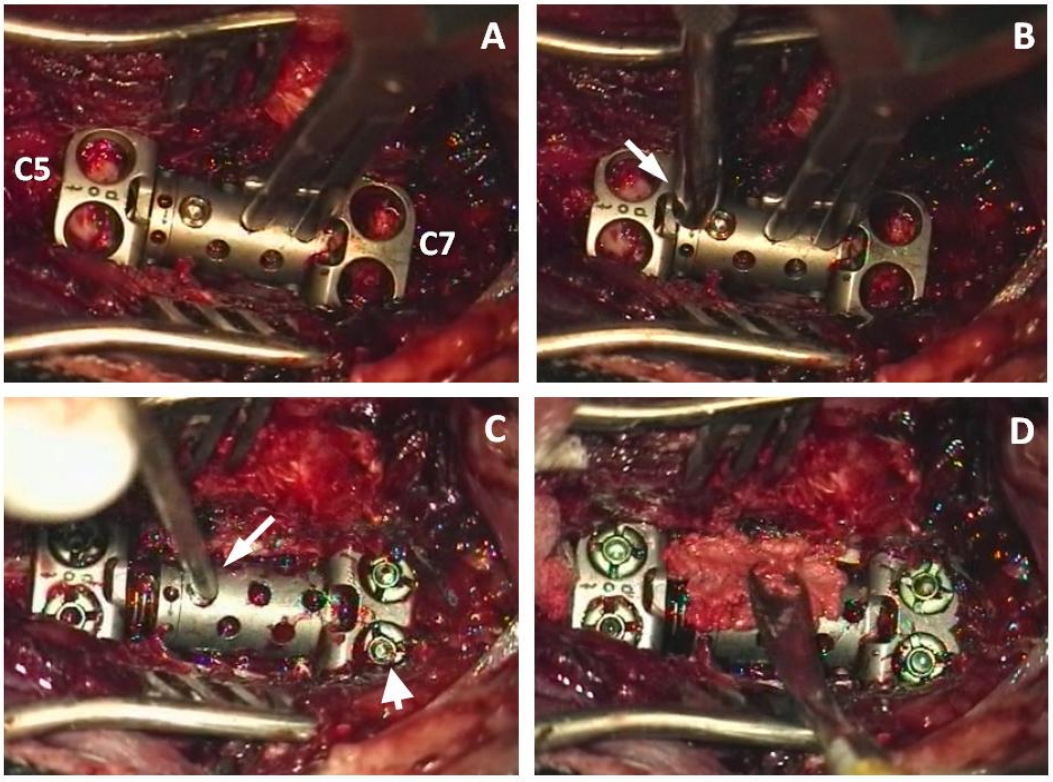

Figure 2: Intraoperative pictures of dog 1. (A) After the median corpectomy was created, the titanium cage was placed in the bony defect of C6. (B) Distraction of the implant by a mechanism inherent to the implant design (arrow)(C) Placement of set screw to maintain distraction (arrow). Fixation of the distracted cage by self-expandable monocortical screws (arrowhead). (D) Cage was filled and covered by autogenous cancellous bone graft.

Postoperative care

At the end of surgery a transdermal patch (Durogesic™, Janssen-Cilag n.v./s.a., Berchem, Belgium), delivering fentanyl at a rate of approximately 4 µg/kg/hour was placed on a shaved area of the thorax and was maintained for the next 3 days. The dogs were placed on a CRI of a combination of morphine and ketamine, delivered IV at a rate of 0.12-0.24 mg/kg/hour for both morphine and ketamine and adjusted to the individual needs of the patient. This CRI was gradually diminished over the next post-operative days. If the dogs were too agitated during hospitalization, and after analgesia was found to be sufficient, additional acepromazine was administered (1-3 mg/kg PO every 6 hours, based on individual needs). Oral carprofen (2 mg/kg) was administered twice daily during the hospital stay and was continued once daily at home during one week. The caudal cervical vertebral column was immobilized for 6 weeks by the use of a well padded cervicothoracic splint made from fiberglass casting tape. This splint was replaced every 2 weeks or sooner if problems were present. Further, the owners were advised to provide activity restriction during the first 6-8 weeks after surgery.

Follow-up

Dogs were reassessed 1, 3, 6, 12 and 24 months after surgery by direct physical and neurological examinations and at additional moments when indicated necessary by the owners or the authors. During each of these evaluations the dogs were videotaped to allow objective assessment of the dog's gait at a later time. All owners were contacted at the end of the study period for a telephone-interview about the dog's clinical status. All evaluations were performed by the first author. Six months after surgery, new cervical radiographs and a CT-scan were performed to evaluate the position and incorporation of the implant in C6. In one dog an additional MRI-scan was planned immediately after the CT-scan to evaluate the MRI compatibility of this titanium implant. These additional imaging studies were performed under general anesthesia.

Results

Animals (Table 1)

Six of the seven dogs were Doberman Pinschers. There were 4 males and 3 females. Age range at time of diagnosis was 4.6 – 10.5 years (mean and median 7.3 years). Duration of clinical signs at time of diagnosis ranged from 1 day to 2 years (mean 7.8 months; median 5 months). Clinical signs at this moment ranged from neck pain only to ambulatory ataxia affecting all 4 limbs. Onset of clinical signs was insidious in 3 dogs, acute in 2 dogs and insidious with an acute deterioration in 2 dogs. Five dogs were initially treated conservatively with unsatisfactory results. Conservative treatment consisted of activity restriction and oral steroidal or non-steroidal anti-inflammatory drugs. The duration of this conservative treatment varied from 1 to 7 months (mean 2.8 months; median 2 months). The clinical signs at the time of surgery ranged from ambulatory ataxia affecting only the pelvic limbs to tetraplegia. Two dogs had one site of spinal cord compression at C6-C7. The remaining 5 dogs had 2 sites of spinal cord compression at both C5-C6 and C6-C7. Subjective evaluation of the myelographic traction studies revealed traction responsive lesions in 5 of the 7 dogs.

Table 1. Signalment and clinical presentation of 7 dogs with DAWS

Dog	Signalment	Duration and onset of signs	Clinical signs at diagnosis	Conservative treatment	Clinical signs at surgery	Site(s) of compression
1	Dalmatian, M, 10.5 yrs	24 months, acute deterioration	Neck pain and ambulatory tetraparetic	None	Ambulatory tetraparetic	C5-C6-C7
2	Doberman Pinscher, Mc, 4.5 yrs	12 months, acute deterioration	Neck pain	1 month	Neck pain and ambulatory paraparetic	C5-C6-C7
3	Doberman Pinscher, Fc, 5.5 yrs	3 weeks, insidious	Pelvic limb ataxia	3 months	Ambulatory tetraparetic	C5-C6-C7
4	Doberman Pinscher, M, 8 yrs	12 months, insidious	Neck pain and ambulatory paraparetic	7 months	Tetraplegic	C5-C6 -C7
5	Doberman Pinscher, Fc, 6 yrs	5 months, insidious	Ambulatory tetraparetic	None	Ambulatory tetraparetic	C6-C7
6	Doberman Pinscher, Fc, 9.6 yrs	1 week, acute	Neck pain and paraparetic	1 month	More pronounced paraparetic	C5-C6-C7
7	Doberman Pinscher, Mc, 7.5 yrs	1 day, acute	Neck pain and paraparetic	2 months	Ambulatory tetraparetic	C6-C7

M = male, Mc = Male castrated, Fc = female castrated, yrs = years,

Surgical Management and Postoperative Findings (Table 2)

No intraoperative complications occurred in any of the dogs. In each dog, it was technically very challenging to correctly place the titanium cage. The craniodorsal-caudoventral inclination of the cranial endplate of C7 complicated gentle and correct placement of the caudal part of the implant. More specifically, it was difficult to place the cage deep enough to provide good contact between the wings of the implant and the cranioventral surface of C7. For this reason, the cranial endplate of C7 was mechanically remodeled to facilitate cage placement in 2 dogs (dogs 2 and 4). This remodeling consisted of a focal thinning of the vertebral endplate by the pneumatic drill. Care was taken to remove as less bone as possible to preserve the mechanical strength of the vertebral endplate, avoiding collapse of the implant into the vertebral body. The collected cancellous bone was, in each case, sufficient to cover the complete body of the titanium, thus making it unnecessary to harvest additional cancellous bone graft from a distant site. The duration of the surgical procedures ranged from 3.25 to 5.5 hours (mean 4.2 hours), with the shorter surgical times for the most recent surgical procedures. The postoperative radiographs demonstrated in each dog a correct position of the cage in C6 (Figure 3). However in all cases, there was a suboptimal implant-cranial C7 endplate contact. Mechanical remodeling of the endplate in dog 2 resulted in a better implant-endplate contact. In one dog (dog 3), severe craniodorsal tilting of C7 was noticed. This was already present preoperatively, but it was subjectively assessed as less severe at that moment. This dog immediately underwent revision surgery. During this second surgery, the most craniodorsal point of the vertebral body of C7 was removed, the amount of distraction was decreased and the screws were placed more cranially in C7 to improve the position of this vertebra (Figure 4). Following this complication, cage placement and distraction was always performed under fluoroscopy guidance to evaluate the position of the implant and adjacent vertebrae during surgery and the longitudinal dorsal ligament was preserved in the subsequent cases to provide additional stabilization of the adjacent vertebral bodies. The neurological status of 4 dogs improved immediately after surgery, 2 dogs remained initially the same, and 1 dog experienced a transient neurological deterioration. Dog 5 experienced an acute neurological deterioration 4 days after surgery. Radiographs (Figure 5A) demonstrated a major implant failure with loosening of the implant. During revision surgery, the implant was replaced and held in place by pins and polymethylmethacrylate (Figure 5B). This dog further recovered uneventfully. After this complication, the self expandable monocortical screws were used in the following cases. Duration of hospitalization ranged from 4 to 11 days (mean

5.7 days; median 4 days). At moment of discharge 5 of the 7 dogs were able to ambulate independently. One of the 2 non-ambulatory dogs (dog 6) regained an independent ambulatory status within one week after discharge from the hospital. All dogs tolerated well the cervicothoracic splint. One dog (dog 2) developed bilateral axillary skin abrasions which were successfully treated with topical antiseptics.

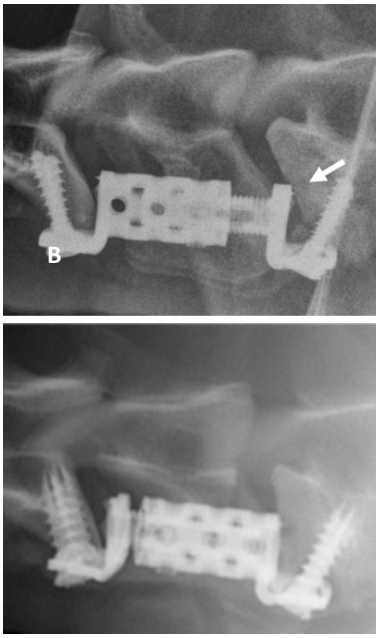

Figure 3: Postoperative radiographs. (A) Cancellous bone screws were used. Suboptimal contact between titanium cage and cranial vertebral endplate of C7 (arrow). (B) Self-expandable monocortical screws were used. Mechanical remodeling of C7 vertebral endplate resulted in better implant-endplate contact.

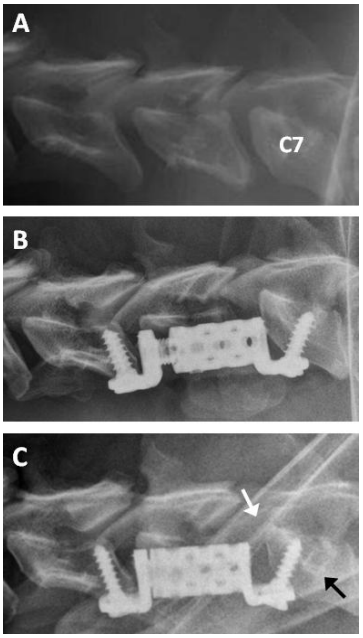

Figure 4: Radiograph after diagnosis (A), surgery (B), and revision surgery (C) of dog 3. (A) Craniodorsal tilting of C7 at the time of diagnosis. (B) Subjectively worse tilting after surgery. (C) Better position of C7: less distraction, most craniodorsal point C7 removed (white arrow), and screws placed more cranially in C7. Original position of the screws (black arrow).

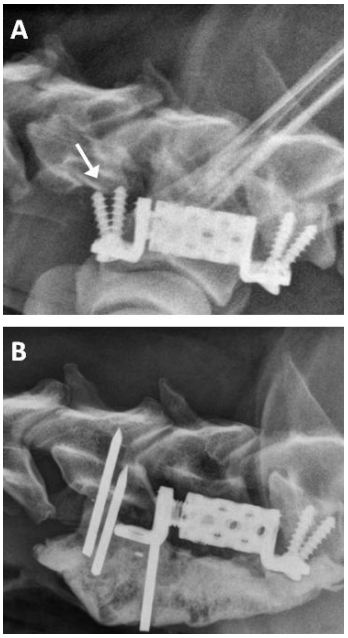

Figure 5: (A) Survey radiograph 4 days postoperative in dog 5. Implant failure (arrow). (B) Survey radiograph after revision surgery. The caudal screws are still in place. It was impossible to replace the cranial screws in C5. Therefore, the implant was held in place with 2 Steinmann pins in C5 and PMMA.

Clinical Follow-up (Table 2)

Follow-up ranged from 7 months to 2.7 years (mean 1.7 years; median 1.8 years). Based on neurological reevaluations and assessments of the gait on video, all dogs improved clinically and regained independent ambulatory status. At moment of writing 4 dogs (dogs 2, 3, 5, and 6) were still alive. Three of these dogs were neurologically normal. The remaining dog (dog 5) remained slightly ataxic in the pelvic limbs. The 3 other dogs (dogs 1, 4 and 7) died during the study period. Dog 7 experienced a rapid clinical recovery and was neurologically normal at the first follow-up examination. Four months postoperatively, he experienced a neurological deterioration and was presented with neck pain and non-ambulatory tetraparesis. Magnetic resonance imaging revealed a right sided extradural dorsolateral compression at the level of C4-C5 (Figure 6). This was presumably caused by articular facet proliferation and was not present at the previous CT and MRI examinations. On the sagittal T2-weighted images, the implant was seen as an area of signal loss which correlated reasonably well with the actual extent of the implant. A hyperintense band between the area of signal dropout and the normal vertebral body was noticed (Figure 7A). The owner preferred conservative treatment by activity restriction and oral prednisolone. Although initial improvement was seen, the dog was euthanized 11 months postoperatively because of progression to tetraplegia. The owner declined autopsy.

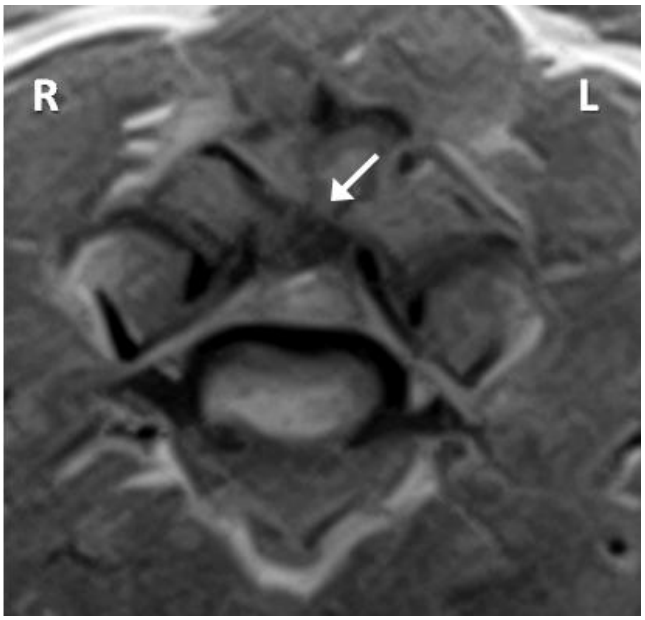

Figure 6: T1-weighted transversal image at the level of C4-C5, 4 months postoperative in dog 7. Right sided extradural dorsolateral compression can be noted (arrow). This is probably caused by articular facet hypertrophy

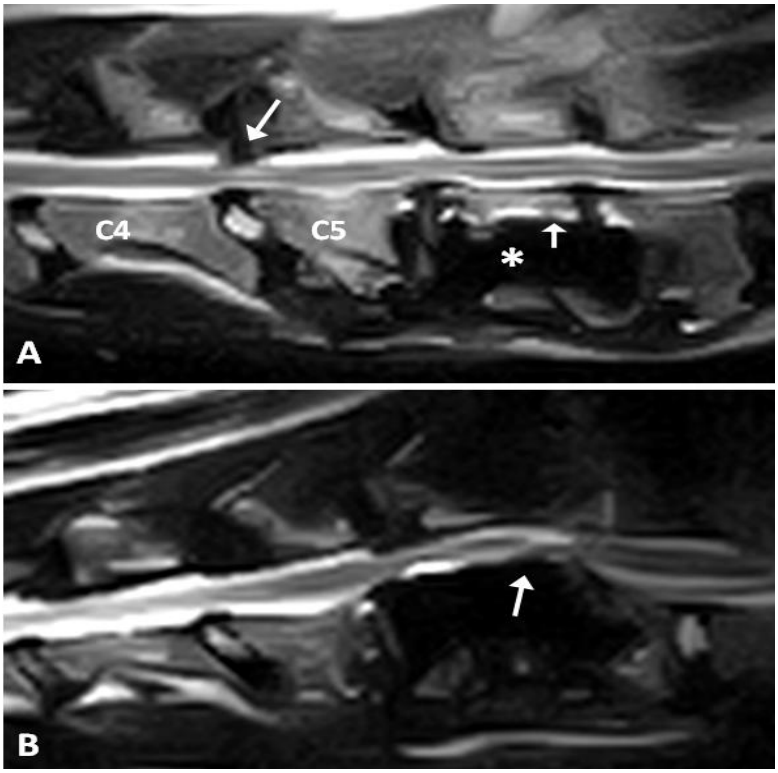

Figure 7: Postoperative T2-sagittal MR images in dogs 7 (A) and 3 (B). (A) Dorsal spinal cord compression at C4-C5 (large arrow). Implant seen as area of signal loss which correlated well with actual extent of implant (asterisk). Hyperintense band between area of signal loss and vertebral body (small arrow). (B) Unacceptable large susceptibility artefact and distortion (arrow).

The 2 remaining dogs died for reasons unrelated to cervical spinal cord pathology. Dog 4 progressed to tetraplegia before the owners elected surgery. This dog experienced a slow but positive clinical evolution postoperatively and regained ambulatory status 6 months postoperatively. At 7 months postoperatively, respiratory problems occurred. Thoracic radiographs revealed a diffuse alveolar pattern and a mass lesion at the level of the right cranial lung lobe. The owners elected euthanasia and declined autopsy. Dog 1 experienced a rapid recovery and regained a clinical free status. Nineteen months postoperatively however, the dog was presented with clinical signs of paraparesis and lumbosacral pain. Neurological examination was suggestive for a L3-S3 neuroanatomical localization. The owner declined

further diagnostics and the dog was euthanatized 22 months postoperatively because of progression of clinical signs. Autopsy revealed the presence of lumbosacral stenosis with severe cauda equina compression. Gross pathological inspection of C6 demonstrated good incorporation of the titanium implant which was covered by a dense tissue (Figure 8A). After 72 hours of fixation in formalin, the vertebral tissue was decalcified in a nitric acid (70cc), hydrochloric acid (50cc) and aqua dest. (880cc) solution during a week. The tissue that surrounded the titanium implant was carefully removed from the implant, processed, embedded in paraffin wax, sectioned at 4 µm, and stained with hemotoxylin and eosin (HE), according to standard techniques and microscopically examined to confirm a bony fusion of the bone graft with the lateral edges of the vertebral body. The tissue-samples at both lateral and ventral sides showed connective tissue and mature cancellous bone (Figure 8B). The spinal cord underneath the titanium implant showed no signs of compression.

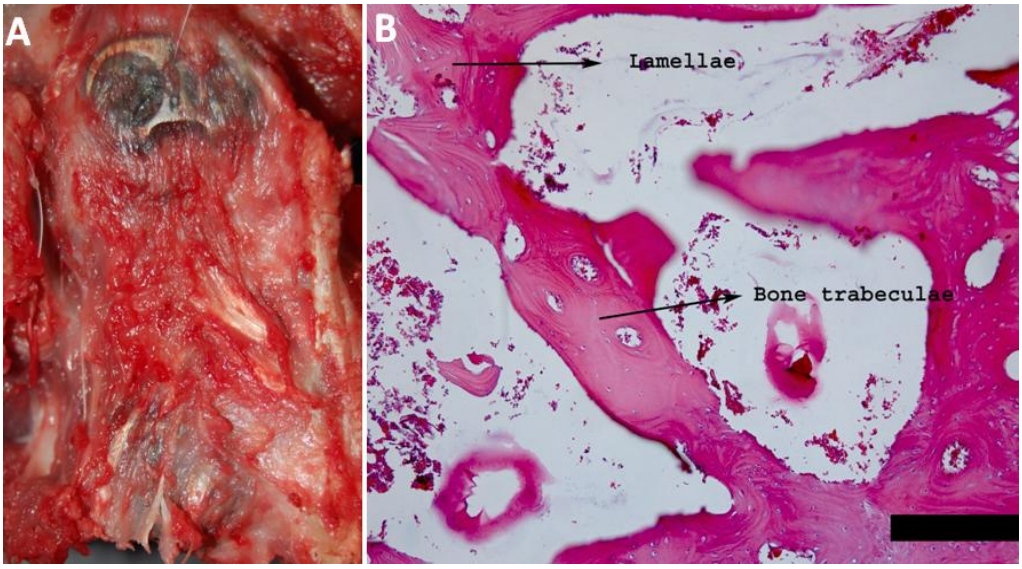

Figure 8: Pathological (A) and histopathological (B) examination of autogenous cancellous bone graft in dog 1. (A) Good incorporation of the cage into vertebral body. (B) HE staining of a trabeculum composed of cancellous bone. Magnification 10X. Bar = 100x (250 micrometer).

Imaging Follow-up (Table 2)

All dogs underwent survey radiographs and CT of the caudal cervical region 6 months postoperatively. Computed tomography was not performed in dog 5 because of the presence of stainless steel implants. Survey radiographs demonstrated correct position of the implant in all dogs, but displacement of the screws was noticed in all dogs where the cancellous bone screws were used. Subsiding of the cage into the cranial vertebral endplate of C7 was noted in 4 dogs (Figure 9). In all cases, CT revealed tissue with bone density around and within the implant. (Figure 10). In 4 of the 6 dogs a slight streaking artifact was noticed which did not interfere with interpretation of the images. An additional MRI scan was performed in dog 3 at the same time as the CT examination. The sagittal T2-weighted images demonstrated image distortion and the implant was seen as an area of signal loss which extended clearly the actual extent of the implant. As a consequence of this, the spinal cord could not be evaluated (Figure 7B).

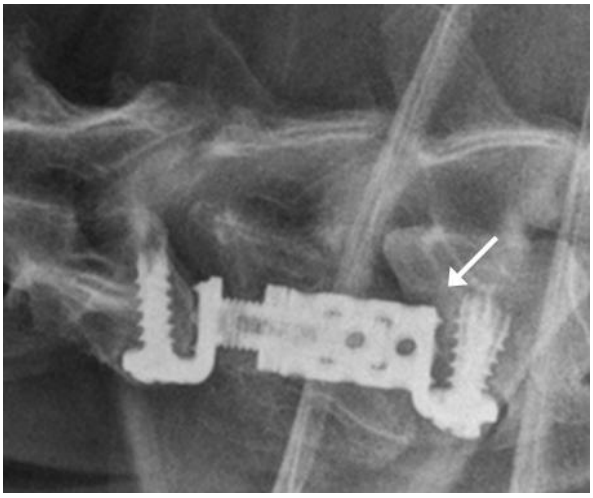

Figure 9: Lateral survey radiograph, 6 months postoperatively in dog 6. Cage subsidence into the cranial vertebral endplate of C7 is evident (arrow).

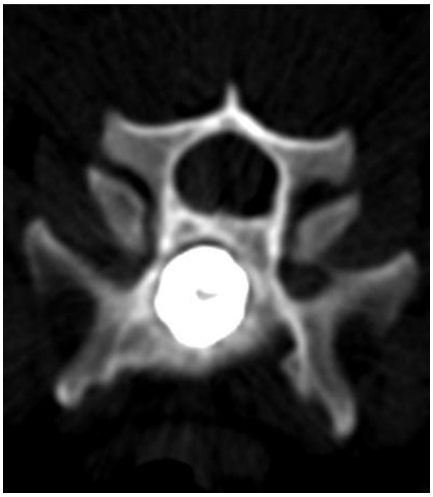

Figure 10: CT, 6 months postoperatively in dog 2.,Implant surrounded by tissue, isodense to bone.

Table 2. Perioperative complications, hospitalization time, and follow-up of 7 dogs treated surgically by a distractable vertebral titanium cage for disk associated wobbler syndrome

Dog	Perioperative complications	Hospitalization time	Follow-up time	Imaging Follow-up	Clinical Follow-up
1	None	4 days	22 months († due to DLSS)	Correct position implant / screws Bone formation around implant	Neurologically normal
2	None	4 days	32 months	Correct position implant / screws Cage subsidence, bone formation around implant	Neurologically normal
3*	Aggravation vertebral tipping	4 days	29 months	Correct position implant with displacement screws, bone formation around implant	Neurologically normal
4*	None	11 days	7 months († due to lung mass)	Correct position implants with displacement screws, cage subsidence, bone formation around implant	Ambulatory tetraparetic with proprioceptive deficits
5*	Implant loosening after 4 days	8 days	24 months	Correct position implants	Mild pelvic limb ataxia without proprioceptive deficits
6	None	5 days	18 months	Correct position implant / screws Cage subsidence, bone formation around implant	Neurologically normal
7	None	4 days	11 months († due to tetraplegia)	Correct position implant / screws Cage subsidence, bone formation around implant	Recurrence clinical signs, 4 months postoperatively

*****Cancellous bone screws used, † = Euthanasia, DLSS = Degenerative lumbosacral stenosis

Discussion

In this study, we have evaluated the use of a distractable titanium cage for the treatment of DAWS in dogs. To the best of the author's knowledge, this surgical approach consisting of a combination of discectomy, median corpectomy, vertebral reconstruction and fusion has not yet been reported in veterinary medicine. In human medicine, this and similar types of surgery are used for several neurologic disorders such as cervical spondylotic myelopathy, disk herniations at two adjacent sites, traumatic fractures, and vertebral metastases.[21,23] Specifically for the surgical treatment of DAWS in dogs, this technique has the potential advantages of treating 2 adjacent disk spaces by one surgical implant, combine direct decompression and distraction-stabilization during one surgical procedure, avoid iatrogenic spinal cord or vascular damage by the use of self-expandable monocortical screws, induce bony fusion by the use of an autogenous cancellous bone graft, and the titanium composition of the implant should facilitate follow-up by advanced medical imaging such as CT and MRI. Although no intraoperative complications occurred, correct placement of the titanium cage proved to be technically challenging. Especially the craniodorsal–caudoventral inclination of the vertebral endplate of C7 complicated correct placement of the cage. This can be explained by the fact that these implants are originally designed for use in human spinal surgery where the cervical vertebrae are characterized by a rectangular shape instead of the rather trapezoid shape in dogs.

A potential intraoperative complication in the surgical treatment of DAWS is iatrogenic spinal cord or vascular damage by bicortical implant insertion.[20] To avoid this complication, the titanium cage was affixed by self-expandable monocortical screws in 4 dogs. Although recent developments in the surgical treatment of this condition have introduced the use of locking plates which allow monocortical screw placement [13,14,16], the system described in this study offers a promising alternative for monocortical screw placement.

An autogenous cancellous bone graft was used to promote bony fusion. An autograft is a tissue taken from one part of the body and transplanted to another site in the same individual.[24] Cancellous bone grafts stimulate osteogenesis, osteoinduction, and osteoconduction and are typically used in situations where rapid bone formation and fusion are the desired outcomes.[25] The site for obtaining an autogenous cancellous bone graft during

cervical spinal surgery in dogs is typically the greater tubercle of the humerus.[2] The main disadvantage of autograft techniques is the limited amount of graft that can be harvested and donor site-related morbidity such as pain, and postoperative bleeding.[26] During this surgical technique, the removed vertebral bone material itself was used for reimplantation into the titanium cage[27], which avoids the above-mentioned complications that are possible after autograft harvesting. Six months after surgery, fusion of the graft with the lateral walls of the vertebral body and bone growth within and around the titanium cage was suggested by CT in all patients (Figure 10). This was confirmed during pathological and histopathological examination in one of our dogs (Figure 8).

In agreement with comparable human studies[27-32], cage subsidence into the adjacent caudal vertebral body was the most common complication. Subsidence is characterized as cage migration into the vertebral endplate of the adjacent vertebral body (Figure 9). Although this complication did not cause clinical signs in any of our dogs, this should not be taken too lightly. Cage subsidence may result in partial loss of distraction. Since the dorsal longitudinal ligament was left in place in most dogs, loss of distraction can cause prolapse of this ligament into the vertebral canal with subsequent spinal cord compression. Several risk factors for cage subsidence have been evaluated and identified in human studies.[27,29,30,32-35] These include limited contact area between the cage and the vertebral endplate [27,30,32,33], decreased integrity and strength of the vertebral endplate [33,35], size of the implant [32], intraoperative overdistraction [29], and postoperative neck movements.[33,34] Several of these factors could have contributed to cage subsidence in our study. The major factor is most likely the primary configuration of the cage with a relatively small contact area with the vertebral endplates of the adjacent vertebral bodies. In 2 dogs, the cranial endplate of C7 was mechanically remodeled to optimize the contact area between the cage and the endplate. This could have reduced the mechanical strength of the vertebral endplate resulting in an increased risk of cage subsidence. Although, the dogs received a cervicothoracic splint postoperatively, limited neck movement is difficult to accomplish in canine patients. This is especially true for dogs with a rather nervous character such as the Doberman Pinscher. Currently little is known about the amount of distraction that can be applied without causing overdistraction.[19] Therefore, we cannot exclude the role of overdistraction as a contributing factor for cage subsidence in our study.

All dogs improved initially postoperatively. In one dog however, recurrence of clinical signs was seen due to articular facet proliferation at an adjacent intervertebral disk space. Recurrence of clinical signs can be considered as the most common and most important

complication after surgery for DAWS.[2,4,17] This is generally caused by disk protrusion at one of the adjacent intervertebral disk spaces and is therefore called adjacent segment disease.[2,4,17] It occurs in 20-30% of the cases and is independent of the surgical technique.[2,4,17,36-38] Although several theories have been developed, the exact pathogenesis and etiology of this phenomenon remain unknown in both veterinary and human medicine.[2,4,37-40] Additional disk protrusions may result when intervertebral fusion or stabilization at one level leads to increased stress at one of the adjacent disk spaces. On the other hand, it can also result from continued natural disease progression rather than from the degeneration of a previously normal disk. A combination of these 2 mechanisms is also possible.[2,4,37,38] Although the dog in the present study did not develop classical adjacent segment disease, it can be hypothesized that adjacent articular facet proliferation was initiated or exacerbated by stabilization of the neighboring caudal intervertebral disk spaces which resulted in an increased range of motion and associated stress at the C4-C5 disk space.[41] It has been previously suggested to routinely fuse multiple disk spaces, as was performed in this study, to reduce the incidence of adjacent segment disease.[2,4] In humans, the incidence of adjacent segment disease was found to be significantly lower following a multi-level arthrodesis, compared to single-level arthrodesis.[39,42] Due to the limited number of dogs included in our study, it was impossible to evaluate such an approach for this purpose in dogs with DAWS.

After implantation of the more common stainless steel implants, postsurgical MR imaging is often complicated by the occurrence of susceptibility artifacts and image distortion.[43] Susceptibility artifacts are typically seen as signal loss extending the actual dimensions of the implant and increased signal (in the form of a bright band) between the area of signal dropout and normal appearing regions of the image (Figure 7).[43] This can result in an impossibility to evaluate the region of interest on the respective MRI studies. The considerably more expensive titanium implants are generally recognized as being more compatible with MRI.[43-45] However, conflicting results have been reported in human studies.[44,45] This is in agreement with the findings in two of our dogs where a postoperative MRI was performed. In one of them the area of signal loss extended only minimally beyond the area of the implants, while an unacceptable large artifact hampered the evaluation of the spinal cord in the other dog. The presence and extent of magnetic susceptibility artifacts are altered by the composition, density, orientation and position of the implant and field strength and selected parameters of the MRI device.[44] Greater susceptibility artifacts occur with implants with a higher paramagnetic effect such as ferromagnetic substances, greater mass implants, implants located

near the vertebral canal, the use of MR devices with a greater magnetic field strength, and the application of image sequences with a longer echo time (TE) such as T2-weighted spin-echo and gradient-echo sequences. [44]

Conclusions

Although the results of this surgical approach for the treatment of DAWS are promising, we do not believe that this specific surgical implant is suitable for routine use in dogs. Specifically, the anatomic differences between dogs and humans and the high expenses of the implants and specific instruments make the use of this specific implant less appealing. Therefore, we suggest a change in the design of the cage to facilitate cage placement and optimize implant vertebral endplate contact or an alternative for vertebral reconstruction which is adjusted for canine vertebrae to permit a similar surgical approach for veterinary purposes. Reported alternatives for vertebral reconstruction usually follow the next principle: structural support can be obtained by a variety of implants such as titanium mesh cages [46], hollow cylindrical polymethylmethacrylate struts [47], cortical allografts [48], or polymethylmethacrylate.[49] The majority of these implants can be filled with several types of grafting material to promote fusion and subsequent stabilization can be accomplished by ventral plating.[50]

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SECTION V

GENERAL DISCUSSION

General discussion

The main goals of this thesis were to gain new insights in the diagnosis and treatment of disk associated wobbler syndrome (DAWS) in dogs. The sections considering the diagnosis of this complex disease focused on the investigation of the possibilities and limitations of advanced imaging techniques such as magnetic resonance imaging (MRI). Additionally, we assessed potential applications of linear vertebral body and canal ratios in dogs with and without DAWS. The sections considering the treatment of DAWS focused on the results of conservative treatment and the development of a new surgical technique for this challenging neurological syndrome.

Diagnosis of disk associated wobbler syndrome

A diagnosis of DAWS can be made by a variety of imaging modalities such as myelography, postmyelographic computed tomography (CT-m) and MRI.[1] Until recently, myelography was considered the imaging modality of choice to diagnose DAWS. However, the last decade MRI has become more popular.[2-4] Advantages of MRI are its safe and non-invasive nature, the possibility to obtain images in multiple anatomic planes without the need for reconstruction, and the superior resolution and sensitivity for soft tissue structures.[5] However, this very high sensitivity can become disadvantageous as non-significant lesions can become apparent.[5] This is since several decades a recognized limitation of MRI in human neuroradiology.[6-10] However, this has not yet extensively been investigated in veterinary medicine. In 2006, da Costa and colleagues compared cervical MRI studies of 16 Doberman Pinschers with clinical signs of cervical spondylomyelopathy with cervical MRI studies of 16 clinically normally Doberman Pinschers.[11] They found a surprisingly high incidence of degenerative abnormalities, including spinal cord compression, in the group of clinically normal dogs. Minor limitations of this study were the fact that the clinically normal dogs all belonged to a breed predisposed to the development of DAWS and that these dogs were not followed up in time.[11] Therefore, it remains difficult to draw reliable conclusions considering the clinical relevancy of these abnormalities. To answer the question if these abnormalities should be regarded as clinically irrelevant or rather presymptomatic, we included in our studies, next to clinically normal Doberman Pinschers, also clinically normal dogs that belonged to a breed with a similar body conformation as the Doberman Pinscher not predisposed to neurological syndromes affecting the caudal cervical spine. This breed was the English Foxhound. Additionally these dogs underwent a new neurological examination at the end of the study.

The following parameters were assessed on cervical MRI studies: intervertebral disk degeneration, disk-associated spinal cord compression, dorsal compression, vertebral body abnormalities and intraparenchymal signal intensity (ISI) changes. The results of this study were comparable to the findings of da Costa et al.[11] We found a surprising high incidence of degenerative abnormalities, including spinal cord compression in 30% of the dogs. Except for the occurrence of vertebral body abnormalities, there were no significant differences between the clinically normal Doberman Pinschers and English Foxhounds. The occurrence and severity of the degenerative abnormalities were generally associated with higher age and the more caudally located intervertebral disk spaces. None of the dogs developed clinical signs suggestive of cervical hyperesthesia or myelopathy during the study period. It was concluded that the observed abnormalities are probably part of the common aging process of spinal degeneration.

Since MRI abnormalities were commonly seen in the caudal cervical vertebral column and spinal cord of clinically normal Doberman Pinschers and English Foxhounds, questions arise considering the reliability of cervical MRI interpretation in older large breed dogs. Therefore we assessed the intra and interobserver agreement of low-field MRI assessments in dogs with and without clinical signs of DAWS. This was done in a randomized and blinded study with 4 observers of 4 different institutions. In agreement with human findings[12,13], there was generally very good intraobserver agreement and moderate interobserver agreement for most assessed parameters. Thus although each reader was very consistent in interpreting the different MRI studies, some variability existed between the different readers. The lowest intraobserver agreement was noted for the presence of spondylosis deformans. This can be explained by the limited ability of MRI to enable detection of signal from dense cortical bone.[6] The lowest interobserver agreement was noted for ISI changes. This can be explained by the presence of a truncation artefact[14] in some of the included studies and the fact that a low-field instead a high-field MRI unit was used in this study.[15] Seventeen percent of the clinically normal dogs were erroneously categorized as clinically affected and ten percent of the clinically affected dogs were erroneously categorized as clinically normal. This resulted in an overall sensitivity of 0.85 and specificity of 0.71 to discriminate dogs with and without clinical signs of DAWS using low-field MRI.

These findings necessitate the investigation of diagnostic tools to aid in the discrimination of clinically relevant from irrelevant spinal cord compressions seen on MRI. For this purpose,

we investigated morphologic MRI parameters, morphometric MRI parameters and transcranial magnetic stimulation (TMS). The most reliable morphologic MRI parameter to discriminate clinically relevant from irrelevant spinal cord compressions was the occurrence of ISI changes. This finding is in agreement with the earlier mentioned study of da Costa.[11]

We calculated several morphometric MRI dimensions to express relative vertebral canal stenosis, degree of spinal cord compression and amount of vertebral canal compromise. These dimensions were based on existing dimensions in human neuroradiology.[16-18] Relative vertebral canal stenosis was expressed by the vertebral occupying ratio of the spinal cord and cerebrospinal fluid (CSF) column.[16] Degree of spinal cord compression was expressed by the compression ratio[17], remaining spinal cord area and the remaining CSF-column area. Degree of vertebral canal compromise was expressed by the vertebral canal compromise ratio and the dorsoventral vertebral canal compromise ratio.[18] Intra and interobserver agreement were calculated by κ-statistics. The results of this study demonstrated that clinically affected Doberman Pinschers have a significantly narrower vertebral canal compared to clinically normal English Foxhounds at the level of C7. This finding supports the hypothesis that relative vertebral canal stenosis is a potential risk factor for Doberman Pinschers to develop clinical signs of DAWS.[11,19] The degree of spinal cord compression, expressed by the remaining spinal cord area, was the only significant different parameter between dogs with clinically relevant and irrelevant spinal cord compressions. This finding is in agreement with human findings [20] and suggests that a certain degree of spinal cord compression should be reached to result in clinical signs of cervical hyperesthesia or myelopathy. A reliable threshold value of 0.8 was identified to differentiate clinically affected from unaffected dogs. Unfortunately the interobserver agreement for this and other calculated parameters was far from ideal. Therefore, we currently do not recommend application of these values in individual dogs.

Transcranial magnetic stimulation (TMS) is a non-invasive, painless and sensitive technique for stimulating the cerebral cortex in order to evaluate the functional integrity of the fastest conducting descending motor pathways in the brain and spinal cord.[21] In human medicine, TMS is widely used to assess the integrity of the spinal cord in different disorders for diagnostic purposes, intraoperative monitoring, and as a prognostic tool in a variety of spinal cord disorders.[22-28] In veterinary medicine, it has been performed on healthy dogs and horses to standardize the method of stimulation.[29-36] This technique is also used in horses with bilateral hind limb ataxia and cervical spinal cord lesions and in dogs with thoracolumbar intervertebral disk disease, cervical spinal cord disease and cervical spondylomyelopathy.[37-42]

The specific aim of our study was investigate the clinical usefulness of TMS to differentiate Doberman Pinschers with or without clinically relevant spinal cord compressions. For this purpose, the included Doberman Pinschers were categorized as having no spinal cord compression, clinically irrelevant spinal cord compression and clinically relevant spinal cord compression on cervical MRI. The mean TMS-values of the Doberman Pinschers in our study were comparable to the mean values from a recent veterinary study comparing TMS in Doberman Pinschers with and without clinical signs of cervical spondylomyelopathy.[42] This suggests a high repeatability of this procedure. Additionally, the Doberman Pinschers with clinically irrelevant spinal cord compression demonstrated similar values as the Doberman Pinschers without spinal cord compression and significantly different values to the clinically affected Doberman Pinschers. This indicates that TMS can be used to differentiate between clinically irrelevant and relevant cervical spinal cord compressions in Doberman Pinschers. Additionally, reliable threshold values were identified to differentiate clinically normal from clinically affected Doberman Pinschers.

Although previous veterinary studies have compared myelography with CT-m [43] or myelography with MRI [3] in Doberman Pinschers with caudal cervical spondylomyelopathy, no previous studies have compared these three diagnostic modalities in the same population of dogs. Therefore, we assessed the intraobserver, interobserver and intermethod agreement of myelography, CT-m and MRI in 22 dogs with DAWS. The following parameters were assessed by 4 observers for all three techniques: number, site and direction of spinal cord compressions; narrowed intervertebral disk spaces, vertebral body abnormalities; spondylosis deformans and abnormal articular facets. Intervertebral foraminal stenosis was assessed on CT-m and MRI. Myelography demonstrated very good to good intraobserver agreement, while CT-m and low-field MRI demonstrated only moderate intraobserver agreement for most assessed parameters. The three evaluated diagnostic techniques demonstrated moderate to fair interobserver agreement for most assessed parameters. These moderate to fair intraobserver [44], interobserver [45] and intermethod [46] agreements for CT-m and MRI are in resemblance with several human studies suggesting a disturbing variability in image interpretation by using either of the frequently used imaging techniques. Therefore, it is suggested that the evaluated diagnostic modalities should be considered as complementary to each other. Although the assessment of the myelographic studies resulted in relatively better intra and interobserver agreement values for several of the assessed parameters compared to CT-m and MRI, this imaging modality is associated with considerable complications and limitations.[1] In

agreement with other studies, seizures and transient neurological deterioration were the most important complications following myelography.[47,48,49] Six of the 22 dogs in this study experienced seizures during anesthetic recovery and 3 dogs were neurologically worse the day after the myelographic examination. This is in agreement with a recent veterinary study where 5 of 18 Doberman Pinschers with cervical spondylomyelopathy developed postmyelographic seizures.[3]

Although several factors have been proposed [11,19,50-52], little is known about the etiology or predisposing factors for the development of DAWS.[1] The relative size and shape of the vertebral column have been suggested as potential risk factors in several studies.[11,19,50] A relative vertebral canal stenosis with or without a funnel-shaped caudal vertebral canal leading to a narrowed cranial orifice, are proposed predisposing factors for the development of clinical signs of DAWS.[11,19,50] Although previous canine studies have used absolute measurements on survey radiographs to evaluate the presence of vertebral canal stenosis [53-55], it has become evident, especially from human studies, that absolute vertebral canal measurements obtained from survey radiographs are influenced by radiographic magnification.[56,57] In human and veterinary studies, ratios between different dimensions of the vertebral canal and vertebral body have been developed to assess vertebral canal diameter and vertebral canal shape.[56,58,59] This relative measure technique is independent of radiographic magnification and allows comparison between individual animals. The purposes of our studies were to determine the use of selected radiographic and MRI derived linear ratios of the cervical vertebral canal and vertebral bodies in Doberman Pinschers with clinical signs of DAWS, clinically normal Doberman Pinschers and clinically normal English Foxhounds. Midvertebral canal height was expressed by the canal height to body height ratio (CBR) and the canal height to body length ratio (CBLR). These ratios are suggested to represent relative vertebral canal stenosis.[56,58] Vertebral canal shape was expressed by the caudal canal height to cranial canal height ratio (CCHR)[19] and vertebral body shape was expressed by the body length to body height ratio (BLHR). The CBR, CBLR and BLHR values were significantly lower in the clinically affected Doberman Pinschers. The CCHR value at the level of C7 was significantly higher in Doberman Pinschers with DAWS. This suggests that Doberman Pinschers with DAWS have significantly smaller midsagittal vertebral canal heights, combined with more square shaped vertebral bodies and a funnel-shaped vertebral canal at C7. This confirms the hypothesis that altered vertebral canal size and shape are potential risk factors for Doberman Pinschers to develop clinical signs of DAWS.[11,19,50-52] In contrast to

earlier reported human [56] and equine [58] studies, no reliable threshold values could be identified for any of the assessed ratios to differentiate clinically normal and clinically affected Doberman pinschers. This limits the use of these ratios as a screening tool to identify Doberman Pinschers with an increased risk of developing DAWS. Breed specificity of these ratios could not be demonstrated, since none of the calculated ratios demonstrated significant differences between clinically normal Doberman Pinschers and clinically normal English Foxhounds. Although suggested in earlier reports [56,58], we could not identify a significant correlation between the CBR, CBLR and relative vertebral canal stenosis, expressed by the vertebral occupying ratio. The latter suggests that linear vertebral canal to body ratios do not predict relative vertebral canal stenosis. This finding is in agreement with several human studies [60-64] and raises questions considering the true meaning of linear vertebral canal ratios.

Treatment of disk associated wobbler syndrome

There is a lot of controversy about the treatment of DAWS.[65] Although very little is known about the results of conservative treatment or the natural progression of this disease, it is generally considered a surgical condition.[1,66,67] Many surgical techniques have been developed.[68-78] The multitude of the existing techniques reflects the difficulty of treating this disease and the fact that the ideal surgical technique does not yet exists.[65] The most common problems associated with the surgical treatment of DAWS are the difficulty or even impossibility to treat multiple sites of spinal cord compression, implant failure, iatrogenic damage to vascular or neural tissues, and the development of a second episode of clinical signs after initial recovery.[2] The latter is termed adjacent segment disease.[2] The aims of our studies were to gain more insights in the natural progression of DAWS, evaluate the results of conservative treatment, and investigate a new surgical technique for this challenging neurological syndrome. This new surgical technique is an established human neurosurgical technique [79] and allows the combination of direct decompression and distraction-stabilization at two adjacent disk spaces during one surgical procedure, promotes bony fusion by recycling the removed cancellous bone, avoids iatrogenic damage by the use of self-expandable monocortical screws, and allows evaluation by advanced medical imaging due to its titanium composition.

Our two studies about the conservative treatment of DAWS demonstrated similar results. Only a minority of the included dogs could be treated successfully by conservative management. Failure of conservative treatment was generally characterized by a rather rapid and dramatic progressive neurological deterioration. Most of the unsuccessfully treated cases

reached their endpoint (euthanasia or switching over to surgery) in the first 6 months after diagnosis. These results differ remarkably to those of the study of da Costa et al.[80] In that study, 80% of dogs treated conservatively for cervical spondylomyelopathy stabilized or even improved after conservative treatment. An important inclusion criterion of that study was that all dogs had to be available for at least 6 months after diagnosis.[80] This can probably explain the large difference between this study and our studies.

The degree of spinal cord compression, amount of vertebral canal compromise and additional radiographic abnormalities, such as vertebral body malformations and ligamentum flavum hypertrophy, can be considered prognostic indicators for dogs treated conservatively for DAWS. Degree of spinal cord compression and amount of vertebral canal compromise are also considered prognostic indicators in humans treated conservatively for cervical spondylotic myelopathy.[81-84] Reevaluation 1 month after diagnosis seems very crucial in the evaluation of conservative treatment of DAWS in dogs. All dogs that were neurologically worse 1 month after diagnosis experienced a further neurologic deterioration that forced the owners to switch over to surgery or elect euthanasia. The opposite was true for all dogs that demonstrated neurological improvement after 1 month. Several dogs experienced an acute deterioration of clinical signs after a long period of improvement. One of these dogs underwent a second MRI and this revealed the occurrence of adjacent segment disease. The occurrence of adjacent segment disease in dogs treated conservatively, suggests that this complication may be part of the natural progression of DAWS, indicating a possible multifocal character of this syndrome.[65]

There were no significant correlations between clinical signs, degree of spinal cord compression, electrophysiological evaluation by TMS and outcome. This is concerning and warrants further investigation.

Although the results of our new surgical technique were promising, technical limitations make this human technique [79] less appealing for routine use in dogs. Human vertebrae have a rectangular shape, while canine vertebrae have a rather trapezoid shape. This causes a craniodorsal-ventrocaudal inclination of the vertebral endplates in dogs. This inclination complicated correct positioning of the implant, originally designed for rectangular human vertebrae. In all dogs, CT follow-up was suggestive for fusion of the bone graft with the lateral edges of the vertebral bodies. In agreement with human studies, variable results were obtained considering the MRI compatibility of the titanium implant.[85]

Limitations of the study and Future perspectives

All MRI studies in this study were performed with a low-field MRI device. Although there is discussion about the relative advantages of high-field MRI over low-field MRI, it cannot be excluded that the use of an MRI device with higher magnetic strength would have resulted in less variability in image interpretation. Several morphometric MRI dimensions were evaluated in this study. Some of these dimensions, such as the remaining spinal cord area and vertebral canal compromise ratio can be considered as potential diagnostic or prognostic parameters. However, the calculation of these morphometric dimensions was associated with problematic limits of agreement for interobserver agreement. Therefore, we suggest further exploration of these morphometric dimensions with other imaging techniques such as high-field MRI and postmyelographic computed tomography. One of the disadvantages of low-field MRI are the prolonged scanning times. Therefore, transversal images were only made for the caudal cervical region. This makes it impossible to extrapolate our results, such as our findings considering relative vertebral canal stenosis, to the entire cervical vertebral canal.
Although this study has evaluated the conservative and surgical treatment of dogs with DAWS, our study design does not permit comparison of both treatment modalities. This is only possible with a randomized and blinded study design. However ethical objections can be made by such an approach, since blinding for conservative or surgical treatment would necessitate sham surgeries and randomization could result in withholding the most appropriate treatment for an individual patient.

Although this study has provided new information about the diagnosis and treatment of DAWS in dogs, several questions remain unanswered. Although several studies, suggest a contributing role of congenital relative vertebral canal stenosis, the exact pathogenesis and etiology of this condition remain unknown. The high prevalence of this syndrome in the Doberman Pinscher could be suggestive for a hereditary condition or factors associated with the typical body conformation of the Doberman Pinscher. Recent developments in canine genetics have created the opportunity for extensive genetic studies. Such studies are suggested to determine the exact etiology and pathophysiology of DAWS in dogs.

The exact role of dynamic studies in the diagnostic workup is controversial.[3] These studies are subjective in execution and interpretation, it is unclear if these studies are necessary to predict the appropriate surgical technique [86], and little is known about patient and pathology related factors that influence the response to traction. Therefore, further studies are suggested to standardize these studies and to reveal their relative contributions and limitations to the diagnosis and treatment of DAWS.

Conclusions

In conclusion, this thesis demonstrated that degenerative MRI abnormalities commonly occur in the caudal cervical vertebral column of older clinically normal Doberman Pinschers and Foxhounds. These clinically irrelevant abnormalities can cause false positive and false negative clinical MRI interpretations. Clinically relevant and irrelevant spinal cord compressions can be differentiated by morphologic MRI parameters, morphometric MRI parameters and transcranial magnetic stimulation. The interpretation of myelographic, postmyelographic and MRI studies is associated with considerably interobserver and intermethod variability. Although significantly different values for several linear vertebral ratios have been demonstrated, their clinical use seems rather limited. Several of our studies support the hypothesis that relative vertebral canal stenosis and a funnel-shaped vertebral canal are potential contributing factors in the development of clinical signs of DAWS.

The conservative treatment of DAWS is associated with a rather guarded prognosis and failure of conservative treatment is generally characterized by a rather rapid and continued progression of clinical signs. Although the results of our new surgical technique are promising, technical adaptations are necessary to make it more appealing for routine use in dogs.

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SUMMARY

Summary

Disk associated wobbler syndrome (DAWS) is a complex and incompletely understood, multifactorial neurological syndrome. There is controversy and uncertainty about several aspects of the diagnosis and treatment of this disease. In this thesis several aspects concerning the diagnosis and treatment of DAWS in dogs were evaluated.
It can be divided in the following sections.

As a general introduction **(Section 1)** a brief review is given about the current literature on the diagnosis and treatment of DAWS in dogs. Additionally, points of controversy and suggestions for further research are mentioned.

The scientific aims **(Section 2)** of this thesis were to evaluate the spectrum and frequency of cervical magnetic resonance imaging (MRI) abnormalities in clinically normal Doberman Pinschers and English Foxhounds, to evaluate their influence on clinical MRI interpretation, and to assess possibilities to differentiate these clinically irrelevant from relevant abnormalities. Furthermore, myelography, postmyelographic computed tomography (CT-m) and MRI were compared in dogs with DAWS and the use of linear vertebral ratios was investigated in dogs with and without DAWS. Additionally, we evaluated the results of conservative management and a new surgical technique for the treatment of DAWS in dogs.

The results of this thesis are presented in **Section 3**, which is divided in **6 chapters**.

Chapter 1 describes the low-field MRI findings in dogs with and without DAWS. In the **first part of chapter 1**, the incidence of degenerative MRI abnormalities in the caudal cervical region of clinically normal Doberman Pinschers and Foxhounds was assessed. Degenerative MRI abnormalities were commonly seen in the caudal cervical region of older Doberman Pinschers and Foxhounds. In the **second part of chapter 1**, the intraobserver and interobserver agreement of low-field MRI was evaluated in dogs with and without DAWS. Additionally, the sensitivity and specificity of this technique to differentiate clinically normal from clinically affected dogs was assessed. Generally very good intraobserver and moderate interobserver agreement was noted. The overall sensitivity of low-field MRI was 0.85 and the overall specificity was 0.71.

Chapter 2 describes possibilities to differentiate clinically relevant from irrelevant findings seen on cervical MRI. The **first part of chapter 2** evaluates morphometric MRI dimensions for this purpose. A relative narrower vertebral canal was demonstrated in clinically affected Doberman Pinschers and a certain degree of spinal cord compression, expressed by the remaining spinal cord area, should be reached to result in clinical signs. The **second part of chapter 2** evaluates the clinical usefulness of transcranial magnetic stimulation (TMS) for this purpose. Doberman Pinschers with clinically irrelevant spinal cord compressions demonstrated similar values as Doberman Pinschers without spinal cord compression and significantly different values compared to those with clinically relevant spinal cord compressions. Morphometric MRI dimensions and TMS can be used to differentiate clinically relevant from irrelevant spinal cord compressions.

Chapter 3 compares the use of myelography, postmyelographic computed tomography and low-field MRI for the diagnosis of DAWS in dogs. There was considerable variation in image interpretation between different observers and different imaging modalities and it is suggested that the evaluated diagnostic techniques should be considered as complementary to each other.

Chapter 4 describes the use of radiographic and MRI derived linear vertebral ratios in dogs with and without DAWS. The **first part of chapter 4** describes significantly different radiographic vertebral ratio values between clinically affected and clinically normal Doberman Pinschers. These findings suggest a smaller vertebral canal height and a more pronounced funnel-shaped vertebral canal at the level of C7 in clinically affected Doberman Pinschers. The **second part of chapter 4** compares the use of CT and MRI to perform linear vertebral body ad canal measurements. A higher accuracy and less variability with MRI is suggested. The **third part of chapter 4** describes significantly different MRI derived vertebral ratio values in Doberman Pinschers with DAWS. This confirms the findings of the first part of this chapter and additionally suggests the occurrence of more square shaped vertebral bodies in clinically affected Doberman Pinschers. Breed specificity of these ratios could not be demonstrated in this part. The **fourth part of chapter 4** evaluates the correlation of linear vertebral canal to body ratios with relative vertebral canal stenosis, expressed by the vertebral occupying ratio. No significant correlations could be demonstrated, indicating that linear vertebral ratios do not predict relative vertebral canal stenosis.

Chapter 5 describes in two studies (**chapter 5.1 and chapter 5.2**) the results of conservative treatment in dogs with DAWS. Both studies demonstrated similar results. Conservative treatment of DAWS was associated with a rather guarded prognosis. Failure of conservative treatmentwas associated with a rather rapid and dramatic progression of clinical signs to a non ambulatory status. Neurological evolution 1 month after diagnosis, degree of spinal cord compression, amount of vertebral canal compromise, and additional radiographic abnormalities, such as vertebral body malformations and ligamentum flavum hypertrophy, are considered potential prognostic indicators. No significant correlation was demonstrated between type of clinical signs, degree of spinal cord compression on MRI, electrophysiological evaluation by TMS and outcome.

Chapter 6 describes the surgical treatment of DAWS in dogs. The **first part of chapter 6** describes the results of a retrospective study about the treatment of DAWS by a standard ventral slot procedure. Although 75% of dogs experienced an initial clinical recovery, 66% of these dogs developed a second episode of clinical signs, resulting in a final success rate of 42%. The **second part of chapter 6** described the occurrence of a rather unusual postmyelographic complication and the development of adjacent segment disease in the same dog. The **third part of chapter 6** evaluates the use of a distractable vertebral titanium cage for the surgical treatment of DAWS. This new surgical technique allows combination of direct decompression and distraction-stabilization of two adjacent disk spaces during one surgical procedure, promotes bony fusion by an autogenous bone graft, avoids iatrogenic damage by the use of self expandable monocortical screws, and allows follow up by MRI due its titanium composition. Although the results were promising, technical adaptations seem necessary to make this technique appealing for routine use in dogs with DAWS.

In conclusion, the studies presented in this thesis provide new information considering the diagnosis and treatment of DAWS in dogs. Degenerative MRI abnormalities commonly occur in the caudal vertebral column of older clinically normal Doberman Pinschers and Foxhounds. These abnormalities are associated with false positive and false negative clinical MRI interpretations. Clinically relevant and irrelevant spinal cord compressions can be differentiated by morphologic MRI parameters, morphometric MRI parameters, and TMS. Relative vertebral canal stenosis occurs more often in Doberman Pinschers with clinical signs of DAWS. The interpretation of myelographic, CT-m and low-field MRI studies is associated with considerably interobserver and intermethod variability. Although significantly different

values for several linear vertebral ratios have been demonstrated, their clinical use seems rather limited. Conservative treatment of DAWS is associated with a rather guarded prognosis. Although the results of our new surgical technique are promising, technical adaptations are suggested.

SAMENVATTING

Samenvatting

Het discus geassocieerd wobbler syndroom (DAWS) is een complex en niet geheel opgehelderd, multifactoriëel neurologisch syndroom. Er bestaat discussie en onzekerheid over verschillende aspecten betreffende de diagnose en behandeling van deze aandoening. In deze thesis werden verschillende aspecten over de diagnose en behandeling van DAWS bij de hond geëvalueerd. De thesis kan worden onderverdeeld in de volgende onderdelen.

Als algemene inleiding **(Sectie 1)** wordt een bondig overzicht gegeven over de bestaande literatuur betreffende de diagnose en behandeling van DAWS bij de hond. Bijkomend worden er enkele controversiële punten en suggesties voor verder onderzoek aangehaald.

De wetenschappelijke doelstellingen **(Sectie 2)** van deze thesis bestonden uit het nagaan van het spectrum en de frequentie van degeneratieve veranderingen vastgesteld op cervicale magnetische resonantie (MR) bij klinisch gezonde Dobermann Pinschers en Foxhounds, het nagaan van de invloed van deze veranderingen op de klinische interpretatie van MR en het nagaan van mogelijkheden om klinisch relevante van klinisch relevante afwijkingen op MR te onderscheiden. Verder werden myelografie, postmyelografische computer tomografie (CT-m) en MR met elkaar vergeleken voor de diagnose van DAWS en werden de klinische toepassingen onderzocht van lineaire verhoudingen van de wervelkolom bij honden met DAWS. Bijkomend werden de resultaten van een conservatieve behandelingwijze en een nieuwe chirurgische techniek voor de behandeling van DAWS geëvalueerd.

De resultaten van deze thesis worden weergegeven in **Sectie 3**. Deze is onderverdeeld in **6 hoofdstukken.**

Hoofdstuk 1 beschrijft de MR bevindingen bij honden met en zonder klinische klachten van DAWS. In het **eerste deel van hoofdstuk 1**, werd de incidentie van degeneratieve MR afwijkingen in de caudaal cervicale regio bij klinisch gezonde Dobermann Pinschers en Foxhounds nagegaan. Degeneratieve MR afwijkingen werden frequent gezien in de caudaal cervicale regio van oudere Dobermann Pinschers en Foxhounds. In het **tweede deel van hoofdstuk 1** werd de overeenkomst binnen en tussen verschillende waarnemers nagegaan voor de interpretatie van MR studies bij honden met en zonder klinische klachten van DAWS. Bijkomend werd de sensitiviteit en specificiteit van deze techniek nagegaan om een

onderscheid te maken tussen klinisch gezonde en klinisch aangetaste honden. Er werd over het algemeen een zeer goede overeenkomst gezien binnen dezelfde waarnemer, maar slechts een matige overeenkomst tussen verschillende waarnemers. De algemene sensitiviteit en specificiteit van MR om klinisch gezonde van klinisch aangetaste honden te onderscheiden was respectievelijk 0.85 en 0.71.

Hoofdstuk 2 beschrijft mogelijkheden om een onderscheid te maken tussen klinisch relevante en irrelevante afwijkingen op MR van de cervicale regio. In het **eerste deel van hoofdstuk 2** worden hiervoor morfometrische dimensies bepaald op de MR studies. Een relatief nauwer wervelkanaal werd vastgesteld bij Dobermann Pinschers met klinische klachten van DAWS en een zekere graad van ruggenmergcompressie, uitgedrukt door de resterende ruggenmergoppervlakte, moet worden bereikt om te resulteren in klinische klachten. In het **tweede deel van hoofdstuk 2** wordt hiervoor de klinische toepassing van transcraniële magnetische stimulatie (TMS) onderzocht. Dobermann Pinschers met klinisch irrelevante ruggenmerg compressie toonden vergelijkbare TMS-waarden met klinisch gezonde honden en significant verschillende waarden vergeleken met de klinisch aangetaste Dobermann Pinschers. Morfometrische MR dimensies en TMS kunnen worden gebruikt om het onderscheid te maken tussen klinisch relevante en irrelevante ruggenmerg compressies.

Hoofdstuk 3 vergelijkt het gebruik van myelografie, postmyelografische computer tomografie (CT-m) en MR voor het stellen van een diagnose van DAWS. De resultaten toonden een duidelijke variatie in interpretatie van de beelden tussen verschillende personen en verschillende beeldvormingtechnieken. Het lijkt dat de verschillende onderzoekstechnieken als aanvullend op elkaar moeten beschouwd worden.

Hoofdstuk 4 beschrijft het gebruik van lineaire dimensies berekend door middel van radiografie en MR bij honden met en zonder klinische klachten van DAWS. Het **eerste deel van hoofdstuk 4** beschrijft significant verschillende radiografische dimensies tussen klinische gezonde Dobermann Pinschers en Dobermann Pinschers met DAWS. Deze bevindingen suggereren een kleinere hoogte van het gehele wervelkanaal en een meer uitgesproken trechtervorm van het caudaal cervicale wervelkanaal bij klinisch aangetaste honden. Het **tweede deel van hoofdstuk 4** vergelijkt het gebruik van CT en MR om lineaire metingen van het wervelkanaal en wervellichaam uit te voeren. MR lijkt gepaard te gaan met een grotere accuraatheid en minder variatie. Het **derde deel van hoofdstuk 4** beschrijft significant

verschillende lineaire dimensies bekomen met MR bij Dobermann Pinschers met DAWS. Deze bevindingen bevestigen de resultaten bekomen in het eerste deel van dit hoofdstuk en suggereren bijkomend dat de wervellichamen van klinisch aangetaste Dobermann Pinschers meer vierkantvormig zijn. De resultaten van dit deel van de studie konden geen rasafhankelijkheid van de berekende dimensies aantonen. Het **vierde deel van hoofdstuk 4** gaat de correlatie na tussen lineaire dimensies van de wervelkolom en relatieve stenose van het wervelkanaal. Er kon geen significante correlatie worden aangetoond tussen de berekende dimensies en relatieve stenose van het wervelkanaal. Deze bevindingen suggereren dat lineaire dimensies van het wervelkanaal geen relatieve stenose van het wervelkanaal weerspiegelen.

Hoofdstuk 5 beschrijft in twee studies **(hoofdstuk 5.1 en hoofdstuk 5.2)** de resultaten van conservatieve behandeling in honden met DAWS. Beide studies toonden gelijkaardige resultaten. Conservatieve behandeling van honden met DAWS was geassocieerd met een eerder gereserveerde prognose. Falen van een conservatief behandelingsbeleid was gekenmerkt door een eerder snelle en dramatische progressie van de klinische klachten tot een niet-ambulante status. Neurologische evolutie 1 maand na diagnose, graad van ruggenmergcompressie, graad van "vulling" van het wervelkanaal en bijkomende radiografische afwijkingen, zoals een afwijkend wervellichaam en ligamentum flavum hypertrofie, lijken potentiële prognostische indicatoren. Er kon geen significante correlatie worden aangetoond tussen de ergheid van de klinische klachten, de graad van ruggenmergcompressie vastgesteld op MRI, elektrofysiologisch onderzoek van het halsruggenmerg en het klinische resultaat van conservatieve behandeling.

Hoofdstuk 6 beschrijft de chirurgische behandeling van DAWS. Het **eerste deel van hoofdstuk 6** beschrijft een retrospectieve studie over de behandeling van DAWS door middel van een standaard ventral slot techniek. Hoewel 75% van de honden initieel herstelden postoperatief, kende 66% van deze succesvol geopereerde honden een tweede episode van klinische klachten. Dit bracht het definitieve succespercentage op 42%. Het **tweede deel van hoofdstuk 6** beschrijft een eerder ongewone postmyelografische complicatie en het optreden van een dominoletsel bij eenzelfde hond. Het **derde deel van hoofdstuk 6** onderzoekt het gebruik van een uitrekbare titanium kooi voor de chirurgische behandeling van DAWS. Deze nieuwe chirurgische techniek laat de combinatie toe van directe decompressie en distractie-stabilizatie ter hoogte van twee aanpalende tussenwervelschijven, moedigt beenderige fusie

aan door gebruik te maken van een autologe botgreffe, vermindert de kans op iatrogene schade van de vasculaire en neurale structuren door gebruik te maken van zelfuitzetbare monocorticale schroeven en laat, door zijn compositie van titanium, opvolging toe door middel van MRI. Hoewel veelbelovende resultaten werden verkregen, lijken technische aanpassingen noodzakelijk om een routinematig gebruik van dit implantaat mogelijk te maken.

We kunnen concluderen dat de studies gepresenteerd in deze thesis nieuwe inzichten verschaffen in de diagnose en behandeling van DAWS bij de hond. Degeneratieve afwijkingen worden regelmatig gezien ter hoogte van de caudaal cervicale regio bij oudere Dobermann Pinschers en Foxhounds. Deze afwijkingen kunnen aanleiding geven tot vals positieve en vals negatieve klinische interpretaties van MRI studies. Klinisch relevante en klinisch irrelevante ruggenmergcompressies kunnen van elkaar worden onderscheiden door morfologische MR parameters, morphometrische MR parameters en TMS. Relatieve stenose van het wervelkanaal komt vaker voor bij Dobermann Pinscher met klinische klachten van DAWS. De interpretatie van myelografische, CT-m en MR studies gaat gepaard met aanzienlijke variatie tussen verschillende personen en de verschillende onderzoekstechnieken. Hoewel significant verschillende lineaire dimensies van de cervicale wervelkolom werden bekomen in Dobermann Pinschers met DAWS, lijken deze dimensie een eerder beperkte klinische toepasbaarheid te hebben. Conservatieve behandeling van DAWS gaat gepaard met een eerder gereserveerde prognose. Hoewel veelbelovende resultaten werden bekomen met de nieuwe chirurgische techniek, lijken technische aanpassingen noodzakelijk.

CURRICULUM VITAE

Curriculum Vitae

Steven De Decker werd geboren op 19 februari 1981 te Antwerpen. Na het behalen van het diploma Wiskunde-Wetenschappen aan het Stedelijk Lyceum te Antwerpen, startte hij in 1999 aan zijn studies Diergeneeskunde. In 2005 behaalde hij zijn diploma van Dierenarts met grote onderscheiding aan de Universiteit Gent.

Onmiddellijk daarna begon hij aan een 1 jaar durend roterend internship aan de Vakgroep Geneeskunde en Klinische Biologie van de Kleine Huisdieren, Universiteit Gent. Tijdens dit jaar verdiepte hij zich in de problematiek omtrent het discus geassocieerd wobbler syndroom bij de hond. Dit resulteerde in de succesvolle aanvraag van een doctoraatsmandaat.
Dit doctoraat, onder begeleiding van Prof. Dr. Luc Van Ham, ging van start op 1 januari 2007 en vond plaats op de Vakgroep Geneeskunde en Klinische Biologie van de Kleine Huisdieren, Universiteit Gent. Naast zijn onderzoek was hij ook actief werkzaam in de kliniek neurologie en neurochirurgie.

Sinds oktober 2008 is Steven board-member van de European Society of Veterinary Neurology (ESVN). Hij vervult hier de rol van ESVN-representative.

In 2009 won hij de John Prestus Award voor beste orale presentatie op het jaarlijkse symposium van de European Society of Veterinary Neurology in Bologna, Italië. In 2010 won hij de Neurosurgery Delegates 2nd Poster Prize op het jaarlijkse symposium van de European Society of Veterinary Neurology in Cambridge, Verenigd Koninkrijk.

Op 5 juli 2010 startte hij een specialisatie opleiding in neurologie & neurochirurgie aan de Royal Veterinary College in Londen.

Steven De Decker is auteur of medeauteur van meer dan 20 wetenschappelijke presentaties op internationale congressen en meer dan 20 publicaties in nationale en internationale wetenschappelijke tijdschriften.

Curriculum Vitae

Steven De Decker was born on 19 February 1981 in Antwerp, Belgium. After graduation from high school in Sciences-Mathematics at a community school in Antwerp, he started his Veterinary studies in 1999. He graduated in 2005 with big distinction from Ghent University, Belgium.

After graduation, he completed a one-year-during small animal rotating internship at the Department of Medicine and Clinical Biology of the Small Animals, Ghent University, Belgium. During this year, he became intrigued by the problems and controversies concerning disk associated wobbler syndrome in dogs. This resulted in the successful application of a PhD scholarship to investigate this challenging syndrome. This PhD, under supervision of Prof. Dr. Luc Van Ham, started on 1 January 2007 and was performed at the Department of Medicine and Clinical Biology of the Small Animals, Ghent University, Belgium. During his research, he was also involved in the clinical activities of the service Neurology & Neurosurgery.

Steven is since October 2008, a board member of the European Society of Veterinary Neurology (ESVN), where he fulfils the role of ESVN-representative.

In 2009, he won the John Prestus Award for best oral presentation on the Annual Symposium of the European Society of Veterinary Neurology in Bologna, Italy. In 2010, he won the Neurosurgery Delegates 2nd Poster Prize on the Annual Symposium of the European Society of Veterinary Neurology in Cambridge, United Kingdom.

On 5 July 2010, he started specialisation training in Neurology & Neurosurgery at the Royal Veterinary College, University of London.

Steven De Decker is author or co-author of more than 20 scientific presentations on international conferences and more than 20 publications in national and international scientific journals.

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