Incidence of Abnormalities of the Second and Third Cervical Vertebral Junction in Dogs with Atlantoaxial Instability: A Multicentre Study

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Abstract

Objective To evaluate the occurrence and frequency of abnormalities at the second and third cervical vertebral junction (C2/3) in dogs with and without atlantoaxial instability (AAI).

Study Design Retrospective multi-institutional case-controlled case series.

Animals One hundred and seventeen dogs with AAI and 117 dogs without AAI.

Methods Radiographs, together with computer tomographic images or magnetic resonance images or both, of the cranial cervical spine of dogs were reviewed for the presence or absence of intervertebral disc-related anomalies, osseous fusion of the vertebrae, spondylosis, or any other anomaly of the C2/3.

Results The incidence of anomalies affecting the C2/3 in dogs with AAI was 38.46% (n = 45) and in the control group it was 11.97% (n = 14). The majority of the observed anomalies involved the intervertebral disc. In conjunction with AAI, intervertebral disc-related anomalies were noted in 33.34%, spondylosis in 2.56%, osseous fusion in 1.71% and a hypoplasia of the spinous process in 0.85% of the cases. Summarized under the term intervertebral disc-related anomalies, a morphological alteration of the intervertebral disc was noted in 10 cases with AAI, characterized by a spherical outer shape and a minimally reduced size and a dorsal positioning in the intervertebral space.

Conclusion There is a significantly higher incidence of anomalies affecting the C2/3 in association with AAI. In conjunction with AAI, intervertebral disc-related anomalies are the most frequent pathological finding affecting the C2/3.
Introduction

Atlantoaxial instability (AAI), a cranio cervical junction abnormality, belongs to a group of conditions localized between the occiput and the axis.1 Atlantoaxial instability is a state of anatomical malarticulation between the first and second cervical vertebrae that can result in atlantoaxial subluxation and compression of the spinal cord. Atlantoaxial instability typically affects young Toy breed dogs; however, the condition is also reported in large breed dogs.2–4

A diagnosis of AAI is based on neurological examination in conjunction with imaging of the cervical spine. Radiographic findings suggestive of AAI include malformation, hypoplasia, aplasia, fracture or dorsal deviation of the dens axis, increased space between the dorsal arch of the atlas and the dorsal spinous process of the axis, dorsal deviation of the vertebral body of the axis and abnormal positioning of the dens in the fovea dentis of the atlas.2,5

Atlantoaxial instability can be considered both a congenital and acquired condition and can often be diagnosed following minor trauma in an otherwise previously asymptomatic patient.2,5–8 Several veterinary studies have revealed different congenital and developmental features of the cranio cervical junction in patients linked to AAI. Aplasia, hypoplasia, dysplasia, fracture-separation and dorsal angulation of the dens as well as absence, degeneration or failure of the transverse ligament are described to cause AAI.8–11 In addition, there are other less well-described abnormalities of the cervical spine thought to be associated with AAI that have been clinically observed, such as incomplete ossification of the atlas and block vertebrae.7,12 Furthermore, the association between AAI and second and third cervical vertebral junction (C2/3) disorders such as block vertebrae and cervical spondylosis has been reported in the human literature.13–15

To the author’s knowledge, there are not any published data in the veterinary literature that evaluate the occurrence and frequency of the C2/3 disorders in patients with AAI. The purpose of this study was to describe and evaluate the occurrence and frequency of abnormalities of the C2/3 in small and large breed dogs with or without AAI and to investigate the existence of any association between the found abnormalities and AAI. Without differentiating, whether alterations are primary or secondary to AAI, we hypothesized that pathological findings affecting the intervertebral disc at the level of C2/3 are more common in dogs with AAI, reflecting the occurrence of biomechanical changes associated with the disease.

Materials and Methods

Study Design

The study was a retrospective multi-institutional case-controlled case series. Diagnostic imaging from cases presented between January 2006 and August 2016 at eight different institutions was examined, described and statistically analysed.

Criteria for Case Selection

Radiographs, together with computer tomographic (CT) images or magnetic resonance images (MRI) or both, of the cranial cervical spine of dogs with AAI, or without AAI, were reviewed. Both small and large breed dogs were included in the study. Dogs were divided into two groups: group 1 comprised dogs with AAI and group 2 comprised dogs without AAI. To be considered a part of the affected AAI group, patients had to have clinical signs neurologically localized to the upper cervical spine and radiological findings consistent with AAI. As a matched case-control study design was used, for each case of group 1 an appropriate case was selected with regard to age, breed and gender in group 2 (control group). To be included in the control group, patients had to have imaging of the cervical spine with no radiological features of AAI and a normal AAI joint conformation. In the majority of the cases, imaging modalities were not matched. To be included in the study, diagnostic imaging had to depict the occiput–C3 or when available occiput–C4 region. Sex, breed and age at the time point of diagnostic imaging were recorded and dogs were assigned to one of two age categories for analyses: ≤ 1 and >1 year.1,5 Diagnostic imaging that did not allow proper evaluation of the region of interest was excluded. Due to the retrospective nature of the study, the various imaging modalities used and different institutes involved, positioning was not always standardized.

Image Analysis

The images were reviewed on a digital radiology imaging software (IMPAX EE, Agfa HealthCare, Belgium) by two independent observers (MS and FF). Evaluation of the C2/3 was not performed blinded as to whether AAI was present or not. Depending on the imaging modality, the following standardized imaging parameters were recorded: presence or absence of intervertebral disc-related anomalies, osseous fusion of the vertebrae, together with spondylosis, other abnormalities, or both combined affecting the C2/3. Intervertebral disc related anomalies of the C2/3 were classified depending on the presence or absence of the radiological signs of intervertebral disc disease and any other abnormality of the intervertebral disc: 1 = intervertebral disc degeneration with possible reduction of the width of the intervertebral disc, bulging of the intervertebral disc into the spinal canal, or both; 2 = Hansen type II protrusion; 3 = Hansen type I protrusion; 4 = traumatic disc extrusion; 5 = any other anomalies of the intervertebral disc. Development of spondylosis was graded into presence (1) or absence (0) of osteophyte formation within the endplate region, and presence (1) or absence (0) of osseous fusion to the adjacent vertebral bodies. Block vertebrae or osseous fusion of the C2/3 was classified depending on the presence (1) or absence (0) of partial or complete osseous fusion of the two adjacent vertebral bodies. Any other anomaly of the C2/3 was marked descriptively. If available, the initial radiology report was recorded descriptively.

Statistical Analysis

All statistical analyses were performed in NCSS 10 Statistical Software (NCSS, LLC. Kaysville, Utah, United States). For all
tests, p-values below 0.05 (¼ desired α-level) were considered as being significant. The assumption of normal distribution of interval data was tested with Shapiro–Wilk and D’Agostino’s omnibus tests.

Statistical differences between group (group 1 vs. group 2) and intervertebral disc-related anomalies, osseous fusion, spondylosis and other anomalies were tested using the chi-square test.

Results
A total of 234 dogs were enrolled in the study. Of the 117 dogs diagnosed with AAI, 60 were males and 57 were females. The mean age in group 1 at the time of imaging of the cervical spine was 3.7 years (range: 0.3–14.1 years). Thirty-six dogs were ≤1 year and 81 dogs were greater than 1 year old. Breeds included the following: Chihuahua (n = 33), Bichon (n = 6), Miniature poodle (n = 6), Dachshund (n = 6), Pomeranian (n = 6), Pug (n = 3), Cavalier King Charles spaniel (n = 3), Miniature Pinscher (n = 1), Shih-Tzu (n = 1), French bulldog (n = 1), Russian Toy terrier (n = 1), Boston terrier (n = 1), Papillon (n = 1), Pekingese (n = 1), Cocker spaniel (n = 1), Labrador Retriever (n = 1), Bernese mountain dog (n = 1), Boxer (n = 1), Doberman (n = 1), American Staffordshire terrier (n = 1) and two mixed breed dogs (n = 2).

In the control group, of 117 dogs, 62 were males and 55 were females. The mean age in group 2 at the time of imaging of the cervical spine was 4.1 years (range: 0.2–13.7 years). Thirty-five dogs were ≤1 year and 82 dogs were greater than 1 year old. Breeds included the following: Chihuahua (n = 40), Yorkshire terrier (n = 33), Bichon (n = 6), Miniature poodle (n = 6), Dachshund (n = 6), Pomeranian (n = 6), Pug (n = 3), Cavalier King Charles spaniel (n = 3) Miniature Pinscher (n = 1), Shih-Tzu (n = 1), French bulldog (n = 1), Russian Toy terrier (n = 1), Boston terrier (n = 1), Papillon (n = 1), Pekingese (n = 1), Cocker spaniel (n = 1), Labrador Retriever (n = 1), Bernese mountain dog (n = 1), Boxer (n = 1), Doberman (n = 1), American Staffordshire terrier (n = 1) and two mixed breed dogs (n = 2).

In a total of six affected cases, the age and gender of the control patients were not matched. These cases were only matched in terms of the breed of the patient.

In several cases, more than one imaging modality was available. In group 1, radiographs (n = 64) were the most available imaging modality, followed by MRI (n = 58) and CT (n = 47). In the control group, MRI (n = 68) was the most available imaging modality, followed by radiographs (n = 52) and CT (n = 42). The overall incidence of all alterations at the C2/3 in group 1 was 38.46% (n = 45) and in group 2 11.97% (n = 14; Table 1).

Chi-square test revealed significant differences for intervertebral disc-related anomalies (p = 0.0031) between groups 1 and 2. The incidence of intervertebral disc-related anomalies in the group with AAI was 33.34% (n = 39) and that in the group without AAI was 11.11% (n = 13). With exception of a Cocker spaniel and two mixed breed cases, all of the observed cases were small breed dogs. Intervertebral disc disease was observed in 29 cases with AAI and in 12 cases without AAI. Q1 There were not any cases with radiological evidence of […] traumatic disc extrusion in either group, when MRI was used for evaluation. A morphological alteration of the intervertebral disc in the segment C2/3 was noted in 10 cases on MRI images with AAI and in 1 case without AAI. Observed characteristics were a spherical outer shape, a minor reduction in size and dorsal positioning in the intervertebral space, in some cases simultaneously connected to signs of disc degeneration (~Fig. 1). Signs of dorsal bulging were not present in association with this morphological alteration. In some cases, a deformation of both adjacent endplates was observed. In the sagittal plane on MRI and CT and on lateral radiographs, the endplates appeared irregular, characterized by crescent-shaped endplates in the ventral aspects, resulting in a reduced intervertebral width.

Radiological assessment in two Toy breed dogs with AAI revealed evidence of osseous fusion of the adjacent vertebrae C2 and C3. One case showed a complete osseous fusion of C2/3, while the other one was partially fused.

Table 1 Row percentages table summarizing the observed incidences of the respective alterations of the C2/3 junction

<table>
<thead>
<tr>
<th>Type of observed alteration</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVD-related anomalies</td>
<td>33.34%</td>
<td>11.11%</td>
</tr>
<tr>
<td>Spondylosis</td>
<td>2.56%</td>
<td>0.85%</td>
</tr>
<tr>
<td>Osseous fusion</td>
<td>1.71%</td>
<td>0.00%</td>
</tr>
<tr>
<td>Hypoplasia spinous process</td>
<td>0.85%</td>
<td>0.00%</td>
</tr>
<tr>
<td>Total</td>
<td>38.46%</td>
<td>11.97%</td>
</tr>
</tbody>
</table>

Abbreviations: C2/3, second and third cervical vertebra; IVD, intervertebral disc.

Fig. 1 Sagittal T2-weighted magnetic resonance imaging of the cervical vertebral column from a 4-year-old female spayed Chihuahua showing atlantoaxial instability with a moderate compression of the spinal cord, syringohydromyelia in the cervical aspect and morphological alteration of the intervertebral disc second and third cervical vertebral junction.
Spondylosis deformans affecting the C2/3 was observed in one Chihuahua with AAI and in two Dachshunds and one Chihuahua without AAI. In all four cases, osteophyte proliferation on the ventral aspect of the vertebral bodies within the endplate region, without fusion, bridging or ankylosis of the adjacent vertebral body was observed. The intervertebral disc spaces were either normal or had mild degenerative changes of intervertebral disc and endplates.

One Miniature poodle with AAI had a malformation of the spinous process of C2. The entire caudal aspect of the spinous process was hypoplastic.

Discussion

Various congenital and developmental anomalies are known to be associated with AAI. First, in the current large cohort of patients, we could demonstrate that anomalies of the C2/3 were significantly more frequently observed in dogs with AAI than in those without and second that anomalies of the intervertebral disc C2/3 were the most common.

Intervertebral disc disease is one of the most commonly reported disorders resulting in neural dysfunction in dogs. Intervertebral disc disease in small breed dogs has a tendency to involve the cranial portion of cervical spine, notably the C2/3, while further caudally is more frequently involved in large breed dogs.

Different aetiological factors have been reported and discussed in regard to the development of intervertebral disc disease: multi-genetic predispositions, trauma, physiological aging, loading history and inadequate nutrition of the intervertebral disc.

A correlation between intervertebral disc disease at the C2/3 and AAI has not yet been reported.

In this study, intervertebral disc disease affecting the C2/3 was observed in 24.78% of dogs with AAI, compared with 10.26% of dogs in the control group. The incidence of observed intervertebral disc disease in the control group in this study was noticeably higher than in other veterinary literature. Signs of intervertebral disc disease represented the largest fraction of totally observed alterations concerning the C2/3. The incidence of intervertebral disc disease in the control group may have been higher than in the general population as small chondrodystrophic dogs represented a large portion of the cases enrolled in this study. The higher proportion of intervertebral disc disease observed in conjunction with AAI in this study may suggest an association between the two disease entities without being able to conclude as to which is likely the primary causative agent.

In cases with a history of trauma, the presence of both intervertebral disc disease and AAI could be expected, in the form of traumatic disc extrusion. As they are adjacent segments and depending on the type and scope of biomechanical stress, an impact on both the atlantoaxial junction and further caudally at C2/3 is possible. Since MRI for evaluation of traumatic disc extrusion has not always been available, the incidence of traumatic disc extrusion may have been underestimated.

Further morphological alterations of the disc in the vertebral segment of C2/3 were detected. These alterations were noted in 8.55% of cases with AAI and in 0.85% of cases without AAI. Although these morphological alterations are not intervertebral disc disease, individual cases also had imaging features consistent with intervertebral disc degeneration. Nearly all of these morphological alterations were observed in small and chondrodystrophic breeds of dogs. In view of this, a breed-related association has to be discussed. Evaluation of the micromorphometry and cellular characteristics of the canine cervical intervertebral disc in chondrodystrophic and non-chondrodystrophic breeds has shown that the nucleus pulposus of chondrodystrophic dogs is smaller, more spherical and more dorsally positioned in the intervertebral space compared with non-chondrodystrophic dogs. This breed-related disc composition in chondrodystrophic breeds was consequently found to result in a smaller total disc surface. Focusing on the C2/3, the intervertebral disc has been noted to be consistently dorsally flattened in comparison to the other cervical discs. It is not clear if there is a functional impairment of the intervertebral space and the adjacent segments. Because of the higher incidence of this observed alteration in the AAI group, an association between both alterations cannot be ruled out.

Osseous fusion of two or more adjacent vertebral bodies can be either congenital or acquired. Fusion of the C2/3 in association with AAI has been described previously in both the veterinary and the human literature.

In a case report from 2009, two dogs with atlantoaxial subluxation revealed congenital cervical block vertebrae of the cranial cervical spine.

Klippel–Feil syndrome, a rare congenital disorder resulting in the osseous fusion of two or more adjacent vertebrae, has been described in the human literature and can be considered the equivalent to block vertebrae in companion animals. The most commonly fused segment is the C2/3.

Acquired osseous fusion of two or more adjacent vertebrae can originate from trauma, inflammation, degeneration or surgical fusion. A long-term clinical study in human literature concluded that one-fourth of patients, who had undergone anterior cervical arthrodesis, were showing adjacent-segment disease. Irrespective of whether osseous fusion is categorized as congenital or developmental, both the human and the veterinary literature have shown that there is an increased likelihood of developing adjacent segment disease. There is evidence that biomechanical alteration resulting in increased strain occurs at segments adjacent to surgical fused vertebrae. A radiographic study evaluating the physiological range of motion of the cervical spine in healthy dogs from maximal extension to maximal flexion suggested that the greatest range of motion is in the cranial cervical spine between C2 and C5. It is supposed that a fusion of two or more adjacent vertebral segments limits the physiological range of motion within this area by immobilizing these vertebral junctions. As a consequence to the reduction in the range of motion at the affected segments, the biochemical load is shifted, resulting in increased biomechanical stress on the adjacent segments.
subsequently may lead to premature degenerative changes at adjoining segments.\textsuperscript{7,29,32} Increased intradiscal pressure and exhibition of hypermobility in the adjoining junctions were observed, possibly resulting in the development of fractures, junction instabilities and intervertebral disc disease.\textsuperscript{7,29,32}

In our study, osseous fusion of the C2/3 was observed in one dog. Merely two cases of cervical fused vertebrae located at the level of C2/3 were found in the group with AAI, while none were observed in the control group. Consistent with findings in human medicine, the incidence of fused cervical vertebrae was also very low; however, in the veterinary literature this alteration is only known to be an incidental finding.\textsuperscript{7,25} The number of cases was too low to predict an association between AAI and osseous fusion.

Spondylosis deforms through the production of periarticular osteophytes leading to osseous bridging at the endplates and ankylosis of the intervertebral disc space can lead to a fusion of adjacent vertebral bodies.\textsuperscript{24,33}

Intervertebral disc disease is considered one of the major predisposing factors in the development of spondylosis, although it is also recognized in healthy intervertebral disc and in association with aging.\textsuperscript{24,33,34} While in the veterinary literature no linkage between AAI and spondylosis of the C2/3 has been reported, cervical spondylosis in association with AAI is described in the human literature.\textsuperscript{13} The exact mechanism for this remains unclear. It is hypothesized that a cervical muscle weakness, based on the disuse of muscles due to the ankylosing nature of spondylosis, might lead to secondary AAI.\textsuperscript{13,35}

Another study in the human literature, analysing the cervical spine in patients with retro-odontoid pseudotumours and AAI, revealed a high incidence of spondylosis with ankylosing characteristics at the segments adjacent to the atlantoaxial junction.\textsuperscript{36} Spondylosis similar to previously described osseous fusion results in a reduction in mobility at the C2/3 which in turn transmits biomechanical stress to the atlantoaxial junction and therefore can be considered a risk factor for AAI.\textsuperscript{36}

Spondylosis was rare in our study. Spondylosis affecting the C2/3 was noted in three dogs with AAI and in one without AAI. Spondylosis can occur at any level of the vertebral spine, but it is predominantly observed in the thoracolumbar and lumbosacral spine.\textsuperscript{24,33,34} Although spondylosis is found across all age groups and breeds, a higher incidence in older and large breed dogs has been reported.\textsuperscript{24,34} It should be noted that large breed and older dogs represented only a small portion of the cases in this study due to a general predisposition of AAI in Toy and small breed dogs.

Hypoplasia of the spinous process of the axis is classified as occipito-atlanto-axial malformation, along with further congenital malformations of the occipital bones, atlas and axis.\textsuperscript{37} There was a single case with hypoplasia of the spinous process of the axis without any further malformations being visible. In the veterinary literature, occipito-atlanto-axial malformation is known to be a common feature in patients with AAI.\textsuperscript{38}

There are several important limitations of the study, including the retrospective nature, study population and various imaging modalities. In regard to the study population, it must be noted that the control population, although not affected with AAI, underwent clinical examination and imaging for other reasons, some of which particularly in the patients with radiographs may have included clinical signs involving the deeper parts of the cervical spine. These patients, although not showing clinical signs of AAI nor having neurological signs localized to the atlantoaxial junction, cannot be considered clinically completely normal. This means that the control group has not been randomized and that there may be, although limited, some selection bias. As various imaging modalities have been used, and these come with varying abilities at detecting the desired alterations, an adverse effect on the incidence of intervertebral disc-related anomalies, traumatic disc extrusion and spondylosis should be considered.

A further limitation of the study is that the clinical signs and longer term clinical outcomes in patients with further anomalies other than AAI and those with AAI only were not compared. This makes it impossible to draw conclusions about the clinical significance of these further anomalies from this study.

In conclusion, there was a significantly higher incidence of anomalies affecting the C2/3 in patients with both clinically and radiologically diagnosed AAI compared with those without AAI. The most common anomalies are involving the intervertebral disc. Although the clinical significance of these further anomalies cannot be derived from this study, their presence may be important when planning surgical treatment and predicting long-term patient outcome. While it may be hypothesized that the association of C2/3 anomalies with AAI may be related to biomechanical alterations that affect these two adjacent cervical vertebral motion units, the pathogenesis remains poorly understood and further prospective studies are warranted.

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Conflict of Interest
The authors declare no conflict of interest related to this study.

References