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Shapes of cervical articular process joints and association with histological evidence of osteochondrosis in Warmblood foals: A post-mortem study

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Abstract

Background: Osteochondrosis dissecans (OCD) of articular process joints (APJs) is involved in cervical vertebral compressive myelopathy (CVM). Biomechanical forces, important in development of OCD, depend on joint conformation. Oval and flat APJ surfaces are considered normal.

Objectives: To identify and grade gross shape variation of cervical and cranial thoracic APJ surfaces and determine association with histological evidence of osteochondrosis.

Study design: Case series.

Methods: Eight hundred and four cervical and cranial thoracic APJ surfaces of 30 foals were evaluated for shape(s) and grades, and were correlated with osteochondrosis.

Results: Three top view shapes (oval, pointed, elongated) and seven lateral view shapes (flat, convex, concave, stepped, bevelled, folded edge, raised edge) were regularly encountered. The oval top view shape was most common. Flat and bevelled were the most common lateral view shapes. General shape grade of caudal articular surfaces was significantly higher than of cranial surfaces. The combinations of an oval top view shape and the lateral view shapes folded edge, concave, or flat with additional raised edge and/or folded edge (flat +), were more likely to have OC than oval with convex, bevelled or flat lateral view shapes (normal vs. oval and folded, odds ratio [OR] 2.49 [95% confidence intervals (CIs) 1.13–5.67]; normal vs. oval and flat +, OR 2.77 [95% CI 1.15–6.85]; oval and convex vs. oval and folded, OR 3.20 [95% CI 1.35–8.20]; oval and convex vs. oval and flat +, OR 3.56 [95% CI 1.43–9.54]; oval and bevelled vs. oval and concave, OR 2.02 [95% CI 1.14–3.60]; oval and bevelled vs. oval and folded, OR 3.50 [95% CI 1.91–6.60]; oval and bevelled vs. oval and flat +, OR 3.90 [95% CI 2.00–7.70]).

Main limitations: Most foals (21/30) were less than 1 month old. Lack of observer reliability scores for shape and shape grade.

Conclusion: APJs shape might contribute to CVM by increased likelihood to have OC.

KEYWORDS
articular surface, cervical vertebral myelopathy, horse, shape

1 | INTRODUCTION

Cervical vertebral myelopathy (CVM) is the most common non-infectious, non-macro traumatic cause for neurological signs in horses. In this syndrome, neurological signs result from compression of the spinal cord and/or spinal nerves.[1–6] The cause of CVM is multifactorial and osteochondrosis dissecans (OCD), developmental malformation, repeated micro-trauma, sex and breed are factors thought to play a role in its development.[1,3–5,7,8]

Osteochondrosis tends to be more severe in CVM affected horses than in horses without CVM.[8] OCD of the APJs can cause compression of the spinal cord and nerves due to joint capsule hypertrophy[4] and instability and malalignment of adjacent vertebrae.[9] OCD can also lead to secondary osteoarthrosis with resultant compression.[2,9] OC is common in several domestic species.[10,11] The development of subclinical OC latens results from vascular failure leading to ischaemic chondronecrosis of the epiphyseal growth cartilage.[10,11] The cause of vascular failure is at this moment unknown. Although it is well known that there are predilection sites for OC, the previously suggested anatomy-related microtrauma as cause for vascular failure could not be confirmed and therefore does not explain the occurrence of these predilection sites.[10,12] Currently, anatomical differences in the amount of blood vessels and cartilage thickness are thought to explain the presence of these predilection sites.[13] Progression into clinically relevant, grossly and radiographically detectable OCD is thought to result from biomechanical overload.[10,11,14] Overload can result from external factors such as housing conditions,[14,15] but also from internal factors. For example, in pigs, certain joint and leg shapes are thought to cause biomechanical overload,[16,17] and selective breeding against these shapes has decreased the prevalence of OCD.[18] Also in equines, an association between conformation and the amount of biomechanical forces has been described,[19,20] although the effect of joint shapes on the occurrence of OC(D) has not been investigated in more detail. Because the pathogenesis of OC in horses is similar to that in pigs,[21] it is likely that also in horses different joint shapes have different effects on progression of subclinical OC to clinically relevant OCD and possibly also on the initiation of subclinical OC.

This study had three aims. First, to determine by gross evaluation if there is variation in shape of cervical and cranial thoracic APJ surfaces in foals, and if so, to categorise and to grade these shapes. For this, foals were used instead of adult horses to establish a base of shape variations within a population that is most likely not affected by secondary shape changes due to degenerative processes such as osteoarthrosis.[2,3,5] Second, to determine if there is a relationship between shape and shape grade and factors that are indicated as important in the development of CVM (e.g., location within the vertebral column and sex). Third, to investigate if there is an association between the shape of the articular surface and the histological evidence of OC in this articular surface or the opposite articular surface within the same APJ. It is hypothesised that there is variation in shape of the articular process joints, that certain shapes have a higher likelihood to develop OC and that these shapes are more common in the caudal part of the cervical vertebral column.

2 | MATERIALS AND METHODS

2.1 | Horses

The APJs of 30 Warmblood foals were grossly examined. These foals were previously used to analyse the correlation of histological evidence of OC of the articular surface of APJ with age, sex and distribution along the cervical and cranial thoracic spine.[22] The foals were privately owned by 24 different owners and either died or were euthanised for reasons unrelated to this study (Table S1). None of the foals were diagnosed with OC antemortem. Twenty-nine foals did not show neurological signs. One foal had neurological signs caused by hydrocephalus. Foals were submitted for post-mortem examination to the Division of Pathology of the Faculty of Veterinary Medicine of Utrecht University between July 2012 and July 2018 to investigate the cause of death or for explanation of clinical signs. The foals were of various breeds (28 Royal Dutch Sports Horses, one Zangersheide horse, one Westfalian horse), sex (19 males, 11 females) and age (from 9 months gestation up to 365 days). In two of the foals, bacterial sepsis with vasculitis respectively and osteomyelitis were seen in the APJs. Therefore, these foals were used for evaluation of the APJ shapes but were excluded from evaluation of OC as these changes can lead to osteochondrosis-like lesions (Figure S1).[23,24]

2.2 | Data collection

The APJs were detached from the vertebrae by sawing through the pedicles and opened. To identify possible differences within the regions implicated in CVM, the vertebral column was divided in three subregions: cranial cervical (articular surface of the caudal APJs of the second cervical vertebra up to the articular surface of the cranial APJs of the fifth cervical vertebra [C2caudal–C5cranial]), caudal cervical (C5caudal–T1cranial) and the first thoracic APJ (T1caudal–T2cranial).

Of 18 foals, the shape of the articular surface of the APJs C3–T2cranial (26 articular surfaces each) and of 12 foals the articular surface of the APJs of C2caudal–T2cranial (28 articular surfaces each) were assessed macroscopically, making a total of 804 articular surfaces. Assessment was done by one board certified veterinary pathologist (WB). The articular surfaces of the APJs were analysed for the shape of the top view (visual perspective from directly above the articular surface) and of the lateral view (visual perspective from the side of the articular surface) resulting in a minimum of two shapes for each articular surface (Figure 1). Unfortunately, no literature was found stating the normal shape of the articular surface of the APJ of foals. However, according to the literature, the normal APJ surface of horses of 1 year and older is oval in top view, and flat in lateral view, with thin, linear, smooth joint margins, irrespective of the localisation of the joint within the cervical vertebral column.[25,26] Thus, the combination of an oval top view shape with a flat lateral view shape was assumed normal. Lateral view shapes deviating from the normal flat shape were categorised. The degree of deviation from the normal shape (shape grade) was also recorded (minimal, mild, moderate,

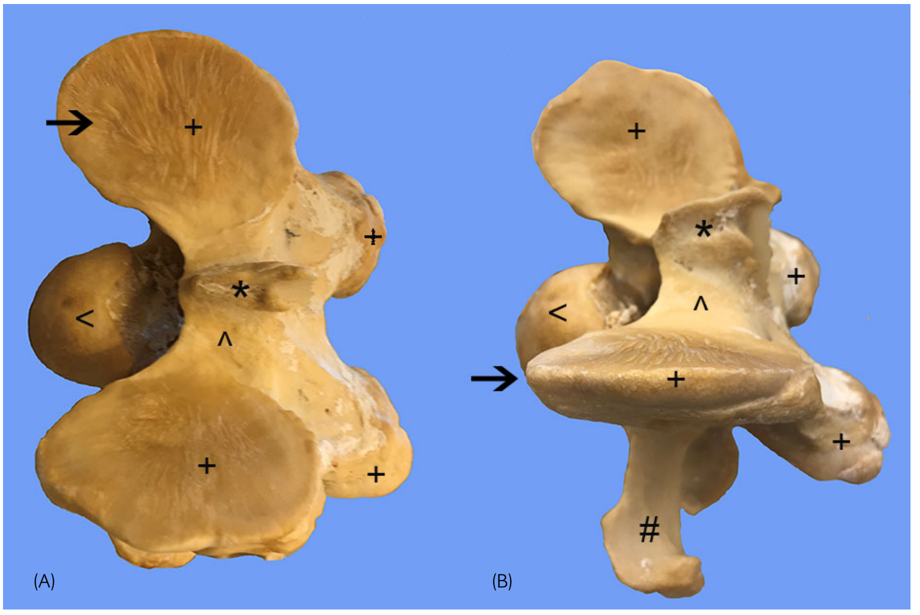

FIGURE 1 Macerated sixth cervical vertebra of a horse. (A) Top view (view perpendicular to the plane of the articular surface of the articular process joint). (B) Lateral view (view in the plane of the articular surface). + surface of the articular process, * spinous process, # transverse process, ^ dorsal lamina, < cranial extremity of the vertebral body.

severe). Because grading was performed during necropsy and could therefore not be repeated, an intra-observer reliability score could not be determined. To optimise reliable grading, it was decided to make a 2-tier grading by combining minimal and mild grades, and moderate and severe grades. A minimal to mild grade has a slope of less than 30° and/or could cover up to 1/3 of the articular surface, while a moderate-to-severe grade has a slope of 30° or more and/or could take up more than 1/3 of the articular surface. Of 28 foals, histological data on the presence of osteochondrosis, as published previously,[22] were used to analyse the correlation of the combination of the top and lateral view shapes with OC. Histological samples were taken from areas with gross morphology that could be compatible with OC, which in these foals were (multi)focal round to longitudinal indentations of the cartilage.[22] When gross changes suggestive of osteochondrosis were not present, a histological sample was taken from the centre of the articular surface. Histologically, osteochondrosis was characterised by necrotic epiphyseal cartilage (osteochondrosis latens) often associated with delayed ossification (osteochondrosis manifesta). Cartilage canal blood vessels in affected areas had lost their endothelium with occasionally presence of swollen endothelial cells or cells with pyknotic nuclei. This is consistent with osteochondrosis as described in literature.[10,11] OCD was not seen. Foals were excluded from evaluation of OC if septic osteomyelitis or arthritis were present as this can mimic osteochondrosis.[23,24] Of the 28 foals previously evaluated,[22] 27 foals had OC lesions in one up to 24 of the articular surfaces. Of the 678 articular surfaces evaluated, 143 had OC (21.1%; 95% confidence interval [CI] 18.19%–24.32%).

2.3 | Data analyses

The distribution of the different shapes was first investigated by use of a binominal logistic regression model. In this model, the distribution of normal (oval and flat) versus abnormal shaped articular surfaces was analysed with foal as random effect and sex, region within the vertebral column, and position (cranial or caudal) and side (left or right) of the articular surface as fixed effects. Model selection was done by stepwise backward elimination by use of the Akaike information criterion (AIC). The odds ratio (OR) with 95% log profile likelihood CIs were used as effect size estimates.

Next, the distribution of the different shapes between sex, age, regions, side (left–right) and position (cranial–caudal) of the articular surface was investigated in more detail by the use of a multinominal model. In this model, normal shaped articular surfaces and articular surfaces with an oval top view shape and the five most frequently encountered lateral view shapes (convex, concave, bevelled, folded edge and raised edge) were included. Shapes with the lowest prevalence (pointed and elongated top view shapes and the stepped lateral view shape; $N = 78$) were excluded from calculations. Calculation was done with a multinomial Bayesian Multilevel Model using Stan (BMRS) with logit link and with foal as random effect and age (0–24 days or 25–365 days), sex, region, side and position of the articular surface as independent variables. As reference, the normal shape combination (an oval top view shape and a flat lateral shape view) was used. The correctness of the model was investigated by an intercept-only model and visualisation of the chains and posterior distribution by use of trace plots, Z-base plots and density overlay plots. The best model was selected by Pareto smoothed importance sampling. Results were presented as OR and significance was determined by use of the 95% credibility interval (CrI).

The shape grade was analysed with a binominal (minimal and mild vs. moderate and severe) logistic regression model with foal as random effect and age (as a continuous variable), sex, region, and side and position of the articular surface as fixed effects. Model selection was done by stepwise backward elimination by use of the AIC.

The association of OC incidence was analysed with a binomial logistic regression model. Two models were run: the first model with outcome OC in the observed articular surface and a second model with OC of the opposite articular surface within the same joint as outcome. Both models had foal as random effect and lateral view shape, grade, number of abnormal shapes (0, 1, ≥2) and normal against abnormal shape combination as fixed effects. The first model with OC of the observed articular surface as outcome had additionally these variables of the opposite articular surface as fixed effects. Due to low incidence of OC, the shapes with the lowest prevalence (pointed and elongated top view shapes and stepped and raised edge lateral view shapes; $N = 121$) were excluded from calculations. Also, because of the low prevalence of three abnormal shapes per articular surface, two and three abnormal shapes per articular surface were combined into two or more abnormal shapes. Model selection was done by stepwise backward elimination by use of the AIC. To determine the different ORs between the different shapes (multinominal), the model was re-run using each shape once as reference shape.

All calculations were performed with R (The R Foundation for Statistical Computing Platform) version 3.6.1 and analysed using R studio version 1.2.1335 (RStudio: Integrated Development for R. RStudio, Inc., http://www.rstudio.com/). For BMRS analysis, the bmrs package and for logistic regression the lme4 package were used.[27,28]

3 | RESULTS

3.1 | Top and lateral view shapes

Ten different shapes were regularly encountered in 756 articular surfaces (Table 1; Figures 2–4). Forty-eight articular surfaces had a more unique shape, and those shapes were not further examined. Of the 10 common shapes, three were different top view (view perpendicular to the plane of the articular surface) shapes (oval, pointed and elongated; Figure 2) and seven were different lateral view (in the plane of the articular surface) shapes (flat, convex, concave, stepped, bevelled, folded and raised edge; Figures 3 and 4).

An oval top view shape (Figure 2A,B) has an egg-shaped circumference (ratio short to long axis approximately 1:2). In the pointed top view shape (Figure 2C,D), the two opposite poles have a different width, resulting in a triangular shape. In the elongated top view shape (Figure 2E,F), the articular surface resembles a stretched oval (ratio short to long axis 1: >2).

The convex lateral view shape has a domed instead of a flat surface, while the concave lateral view shape has a depressed surface (Figure 3A–D). A stepped articular surface has a cartilage-covered surface with two or more regions with a different height resembling stairs (Figure 3E,F). The bevelled lateral view shape has a cartilage-covered, oblique-sloped edge (Figure 4A,B). The folded and the raised edge lateral view shapes have focal cartilage-covered bony projections perpendicular to the joint surface, originating from the margins and pointing downwards to the bony part of the articular surface or upwards towards the corresponding articular surface of the APJ respectively (Figure 4C–F).

3.2 | Distribution of top view shapes

The most common top view shape was oval (86 [95% CI 82.3%–89.5%; $N = 343$] −98% [95% CI 95.6%–98.7%; $N = 413$]), irrespective of the region, side, position and sex (Table 1).

TABLE 1 Distribution of absolute numbers and percentages of shapes of the articular surface of cervical and cranial thoracic articular process joint of a group of Warmblood foals ($N = 30$) aged 0 days to 1 year.[a]

	Entire examined vertebral column	Cranial cervical	Caudal cervical	Cranial thoracic	Male	Female	Left	Right	Cranial	Caudal
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Top view shape										
Oval	699 (93)	290 (95)	319 (92)	90 (88)	447 (94)	252 (90)	346 (92)	353 (93)	403 (98)	296 (86)
Pointed	24 (3)	7 (2)	9 (2)	8 (8)	12 (3)	12 (4)	14 (4)	10 (3)	8 (2)	16 (5)
Elongated	33 (4)	10 (3)	19 (6)	4 (4)	16 (3)	17 (6)	18 (4)	15 (4)	2 (<1)	31 (9)
Lateral view shape										
Flat	269 (26)	90 (21)	127 (26)	52 (37)	186 (28)	83 (22)	136 (26)	133 (26)	133 (21)	136 (32)
Convex	64 (6)	38 (9)	21 (4)	5 (3)	50 (8)	14 (4)	35 (7)	29 (5)	15 (2)	49 (10)
Concave	186 (18)	90 (21)	64 (13)	32 (23)	107 (16)	79 (20)	96 (18)	90 (17)	179 (29)	7 (2)
Bevelled	283 (27)	116 (27)	149 (31)	18 (13)	144 (22)	139 (36)	136 (26)	147 (28)	135 (22)	148 (35)
Stepped	15 (1)	6 (1)	9 (2)	0 (0)	15 (2)	0 (0)	7 (1)	8 (2)	0 (0)	15 (4)
Folded edge	191 (18)	62 (15)	97 (20)	32 (23)	140 (21)	51 (13)	97 (18)	94 (18)	124 (20)	67 (16)
Raised edge	43 (4)	23 (6)	17 (4)	3 (1)	22 (3)	21 (5)	23 (4)	20 (4)	38 (6)	5 (1)
Other[b]	48	14	16	18	35	13	24	24	19	29

[a]The regularly occurring top view and lateral view shapes have each a total sum of 100% per column.
[b]More unique top view and lateral view shapes (6% of total evaluated articular surfaces), are not further included in calculations.

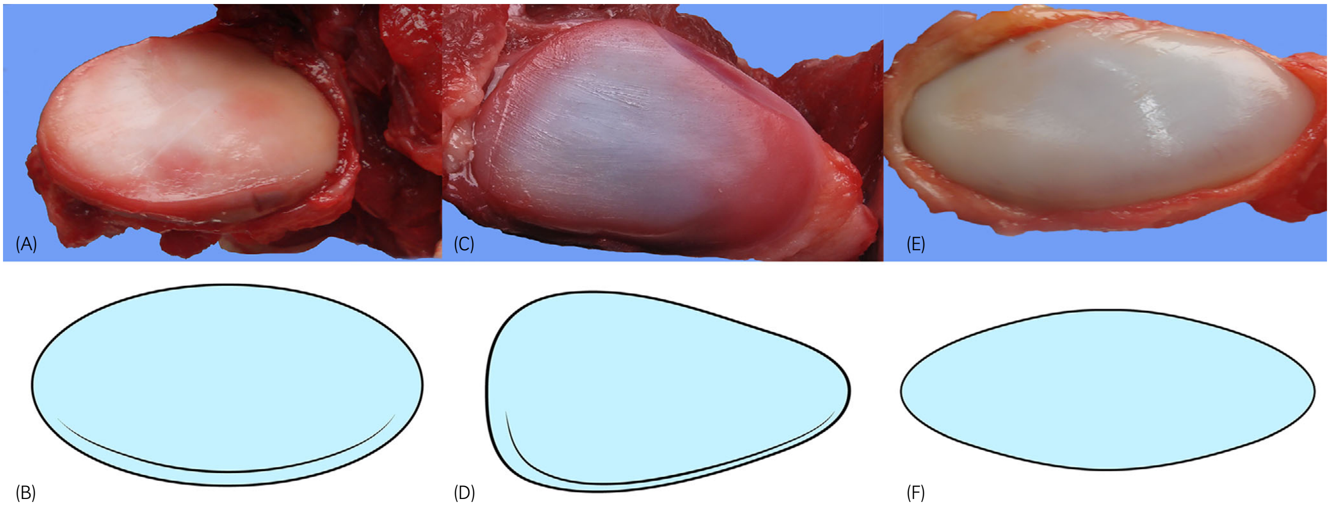

FIGURE 2 Different top view shapes found in the examined group of Warmblood foals. Both representative photos and schematic drawings for clarification are shown. A (photo) and B (drawing): oval top view shape. The circumference of the articular surface of the articular process joint is egg-shaped (ratio of the short axis to the long axis is 1:2). C (photo) and D (drawing): pointed top view shape. The width of the circumference varies at the two opposite poles, giving the articular surface a triangular shape. E (photo) and F (drawing): elongated top view shape. The circumference of the articular surface resembles a stretched oval with narrow opposite poles; the ratio of the short axis to the long axis is 1:>2.

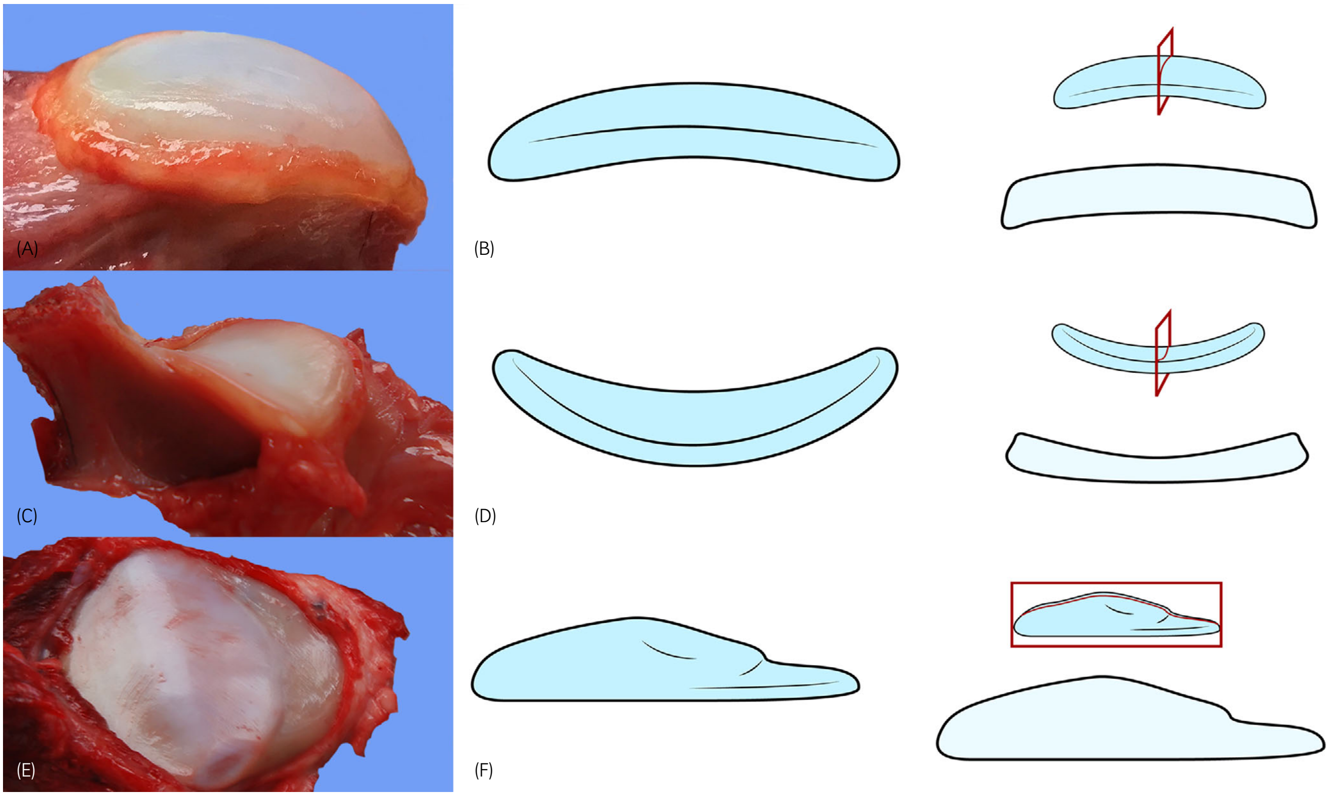

FIGURE 3 Different lateral view shapes found in the examined group of Warmblood foals. Both representative photos and schematic drawings for clarification are shown. The drawings show the lateral view shape and the shape view on cut surface (red rectangle). A (photos) and B (drawing): Convex lateral view shape. The convex shape has a domed instead of a flat surface. C (photo) and D (drawing): Concave lateral view shape. The concave shape has a depressed surface instead of a flat surface. E (photo) and F (drawing): Stepped lateral view shape. The articular surface of the articular process joint has cartilage covered differences in height, resembling a stair. At circa 5 o'clock, a cut artefact is visible in the photo.

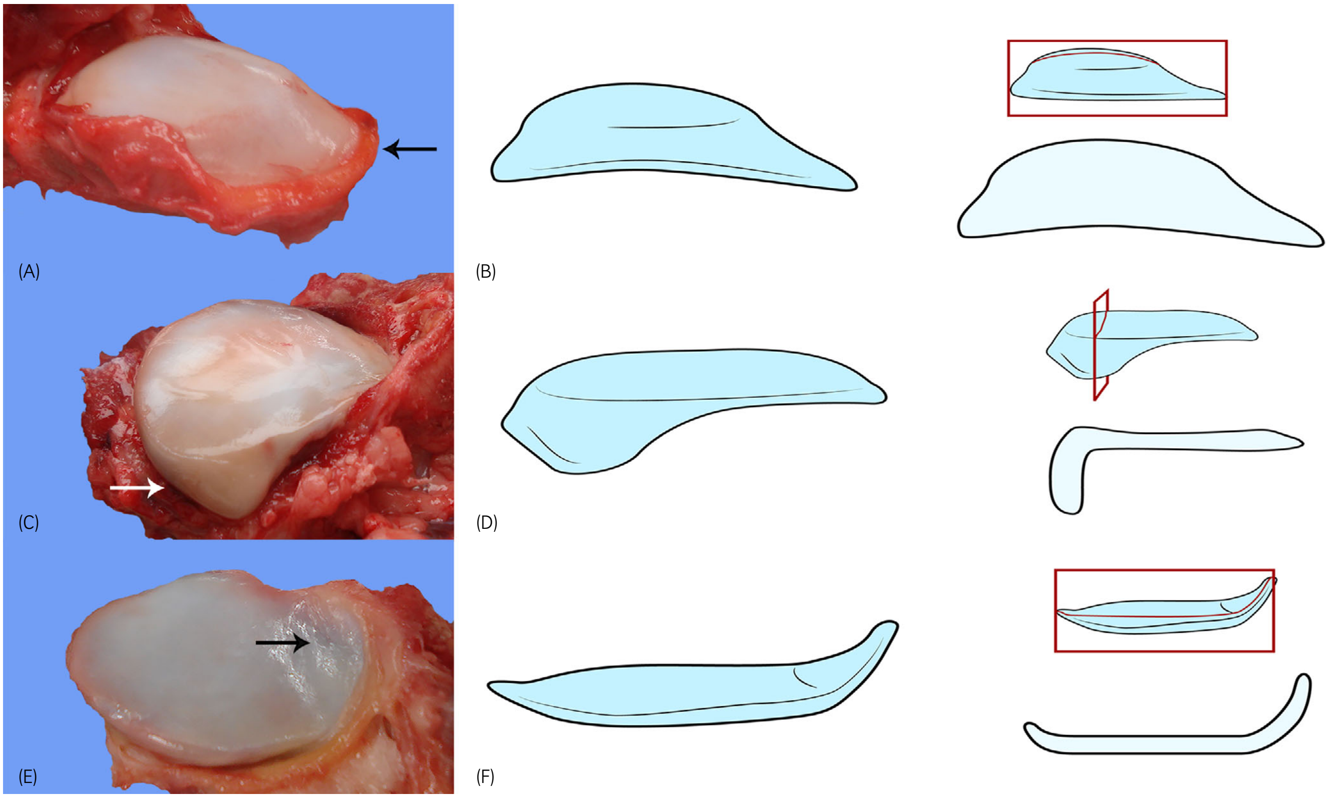

FIGURE 4 Different lateral view shapes found in the examined group of Warmblood foals. Both representative photos and schematic drawings for clarification are shown. The drawings show the lateral view shape and the shape view on cut surface (red rectangle). A (photo) and B (drawing): Bevelled lateral view shape. The edge of the articular surface is sloped and cartilage covered (arrow). C (photo) and D (drawing): Folded edge lateral view shape. The articular surface of the articular process joint (APJ) has a cartilage covered bony projection pointing downward (arrow). E (photo) and F (drawing): Raised edge lateral view shape. The articular surface of the APJ has a cartilage covered bony projection pointing upwards (arrow).

3.3 | Distribution of lateral view shapes

Bevelled (22 [95% CI 18.6%–25.0%; $N = 624$] −36% [95% CI 30.3%–39.8%; $N = 387$]) and flat (21 [95% CI 17.6%–25.3%; $N = 425$] −32% [95% CI 27.6%–36.4%; $N = 427$]) were the two most common lateral view shapes in the entire examined part of the vertebral column, the cranial and caudal neck but not the cranial thoracic region, both sexes, left, right and caudal articular surfaces but not the cranial articular surfaces. In the cranial thoracic region, the most common lateral view shapes were flat (37% [95% CI 29.2%–44.8%; $N = 142$]), concave and folded (both 23% [95% CI 16.4%–30.1%; $N = 142$]). Cranial articular surfaces were mostly concave (29% [95% CI 25.3%–32.4%; $N = 624$]) and bevelled (22% [95% CI 18.6%–25.0%; $N = 624$]) (Table 1).

3.4 | Distribution of top and lateral view shape combinations

A normal shape (oval and flat) was observed in 14.2% (95% CI 11.9%–16.8%; $N = 756$) of the articular surfaces. 60.6% (95% CI 57.1%–64.0%; $N = 756$) of the articular surfaces had one shape different from normal, 24.7% (95% CI 21.8%–27.9%; $N = 756$) two shapes (e.g., the left C7caudal articular surface of a female foal of 149 days had an oval top view shape and a flat lateral view shape with both a raised edge and a folded edge at lateral view) and 0.5% (95% CI 0.2%–1.4%; $N = 756$) of articular surfaces had three shapes (for example the left T1caudal articular surface of a female foal of 18 days had an elongated top view shape and both a bevelled and folded lateral view shape) different from normal.

The normal shape combination versus an abnormal shape combination (binomial) was not associated with sex, region, side or position of the articular surface.

Within the entire examined part of the vertebral column, but also within the two separate cervical regions, and the left, right and caudal articular surfaces, the two most common shape combinations were oval and flat (flat as singular shape or flat combined with a raised and/or a folded edge lateral view shape [flat +]) (20 [95% CI 16.7%–23.3%; $N = 425$] −27% [95% CI 22.9%–31.3%; $N = 427$]) and oval and bevelled (23 [95% CI 20.1%–27.1%; $N = 531$] −30% [95% CI 25.4%–34.0%; $N = 427$]). The most common shape combinations in the cranial thoracic region were oval and flat (singular or flat + 33% [95% CI 25.9%–41.2%; $N = 142$]) and oval and concave or folded (both 22% [95% CI 15.8%–29.3%; $N = 142$]). The most common shape combinations of cranial articular surfaces were oval with a concave lateral view shape (29% [95% CI 25.1%–32.2%; $N = 624$]) and oval with a flat (singular or flat +) or a bevelled edge lateral view shape (both 21% [95% CI 17.8%–24.2%; $N = 624$]) (Table S2).

The significant ORs and 95% CrIs of the multinominal comparison for distribution can be found in Table 2. The total random effect (i.e., animal level + measurement level) due to animal level (i.e., the effect of the individual foal on the results) of this multinominal BMRS model used for assessment of the distribution of shapes was 18%.

Significant ORs were only found with the variables age, position on the vertebra (cranial/caudal) and region. Only two abnormal shape combinations were associated with age: oval and concave and oval and bevelled. The likeliness for the presence of both these shape combinations, compared with normal shaped articular surfaces, was tenfold lower in foals of 25–365 days compared with 0–24 days of age.

The distribution of the different abnormal shaped articular surfaces between the cranial versus caudal position on the vertebrae and the regions within the vertebral column is very variable (Table 2). However, the likelihood of an abnormal shape combination (oval and concave, folded or raised edge) is higher in articular surfaces cranially positioned on the vertebrae compared with caudally positioned articular surfaces, and in cervical articular surfaces compared with articular surfaces in the thoracic region (oval and convex, bevelled, or raised edge). For example, an articular surface with an oval top view and a raised edge side view is approximately a third less likely to be present caudally then cranially on the vertebrae and tenfold less likely to be present in the cranial thoracic region than the cranial cervical region compared with normal shaped articular surfaces.

TABLE 2 Significant odds ratio and 95% credibility interval of the shape combination distribution in a group of Warmblood foals ($N = 30$) age 0 day to 1 year with the assumed normal shape combination (oval top view and flat lateral view) as reference shape combination.

Variable	Odds ratio	95% credibility interval
Age (0–24 days vs. 25–365 days)		
Normal vs. oval and concave	0.1	0.1–0.3
Normal vs. oval and bevelled	0.1	0.0–0.4
Cranial vs. caudal position		
Normal vs. oval and convex	4.3	2.2–8.7
Normal vs. oval and concave	0.0	0.0–0.1
Normal vs. oval and bevelled	1.6	1.1–2.5
Normal vs. oval and folded edge	0.5	0.3–0.8
Normal vs. oval and raised edge	0.1	0.0–0.4
Region		
Cranial cervical vs. *caudal cervical*		
Normal vs. oval and convex	0.3	0.2–0.7
Cranial cervical vs. *cranial thoracic*		
Normal vs. oval and convex	0.1	0.0–0.4
Normal vs. oval and bevelled	0.2	0.1–0.4
Normal vs. oval and raised edge	0.3	0.1–0.9
Caudal cervical vs. *cranial thoracic*		
Normal vs. oval and concave	2.2	1.1–4.1
Normal vs. oval and bevelled	0.2	0.1–0.3

The most common combinations of lateral view shapes of opposing articular surfaces within the same joint were bevelled with bevelled (12.9% [95% CI 10.42%–15.75%; $N = 607$]), bevelled with a concave articular surface (8.0% [95% CI 6.16%–10.51%; $N = 607$]) and a folded edge with folded edge (7.3% [95% CI 5.44%–9.59%; $N = 607$]). 4.3% (95% CI 2.94%–6.20%; $N = 607$) of joints had two, assumed, normal shaped articular surfaces (Table S3).

3.5 | Shape grade

Of the abnormal lateral view shapes, 75% (95% CI 72.5%–78.7%; $N = 732$) had a minimal to mild and 25% (95% CI 21.4%–27.6%; $N = 732$) a moderate-to-severe grade.

The convex, concave and raised edge lateral view shapes had mostly a minimal to mild grade (37 [95% CI 24.4%–52.1%; $N = 43$] −58% [95% CI 43.3%–71.6%; $N = 43$]). Bevelled and folded shapes had generally a minimal, mild and moderate grade (23 [95% CI 18.4%–28.3%; $N = 274$] −39% [95% CI 32.3%–46.2%; $N = 187$]) (Table S4).

The total random effect (i.e., animal level + measurement level) due to animal level of the binominal logistic regression model used for examination of the distribution of shape grade was 11%.

Caudal articular surfaces had significantly higher grades than cranial articular surfaces in all three regions combined (Figure 5; Table S5) and within the separate cervical regions (Table S5).

3.6 | Incidence of OC

The total random effect (i.e., animal level + measurement level) due to animal level of the binominal logistic regression model used for examination of the correlation between shape and OC was 33%. Articular surfaces with an oval top view shape and a flat +, concave or folded lateral view shape were significantly more likely to have OC latens or manifesta than oval articular surfaces with a flat only (normal), convex or bevelled lateral view (Table 3; Figure 6).

The grade, number of abnormal shapes per articular surface, and normal compared with an abnormal shape combination were not associated with a significant likelihood to have OC. None of the variables was associated with significant likelihood to have OC in the opposite articular surface within the same joint.

4 | DISCUSSION

The shape combination which in the literature is suggested to be normal (i.e., oval and flat),[25,26] is expected to be most commonly encountered. However, this was not the case in the Warmblood foals examined. There was substantial variation in shape and there was not one combination more dominantly present, suggesting that variation

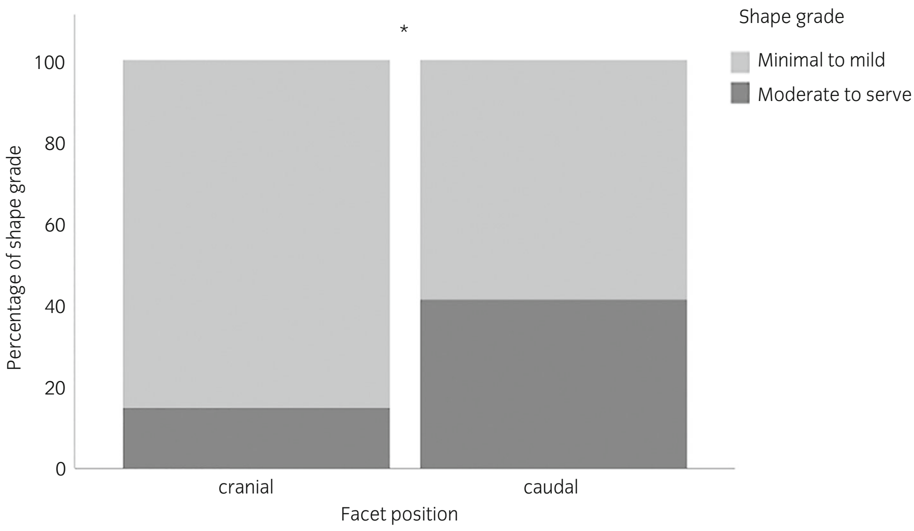

FIGURE 5 Distribution of general shape grade between cranial and caudal articular surfaces of the articular process joints (APJs). Distribution of general shape grade between cranial and caudal articular surfaces on the vertebrae of the entire examined part of the vertebral column. Caudal articular surfaces are significantly more likely to have moderate-to-severe shape grades than minimal to mild shape grades compared with cranial articular surfaces of the APJs. Minimal to mild shape grades are represented by the light grey colour. The dark grey colour represents the moderate-to-severe shape grades. * denotes that there is a significant statistical difference between these facet positions.

TABLE 3 Significant odds ratios and 95% confidence intervals of osteochondrosis of articular surfaces of the articular process joints in a group of Warmblood foals ($N = 28$) age 0 day to 1 year of the final model.[a]

Shape combination (absolute number)	Odds ratio	95% profile likelihood confidence interval
Normal (oval and flat) (107)	Reference	
Oval and folded edge (186)	2.5	1.13–5.67
Normal (oval and flat) (107)	Reference	
Oval and flat with additional lateral view shape (138)	2.8	1.15–6.85
Oval and convex (60)	Reference	
Oval and folded edge (186)	3.2	1.35–8.20
Oval and convex (60)	Reference	
Oval and flat with additional lateral view shape (138)	3.6	1.43–9.54
Oval and bevelled (256)	Reference	
Oval and concave (184)	2.0	1.14–3.60
Oval and bevelled (256)	Reference	
Oval and folded edge (186)	3.5	1.91–6.60
Oval and bevelled (256)	Reference	
Oval and flat with additional lateral view shape (138)	3.9	2.00–7.70

Note: The final model included only the shape combination of the observed articular surface.

[a]The first initial model for osteochondrosis (with binary outcome variables osteochondrosis/no osteochondrosis) of the observed articular surface, included explanatory variables osteochondrosis of the opposite articular surface, (opposite) shape combination, (opposite) shape grade, (opposite) number of abnormal shapes and (opposite) normal against abnormal shape combination. The second initial model for osteochondrosis of the opposite articular surface in the same joint, included the explanatory variables shape combination, shape grade, number of abnormal shapes and normal against abnormal shape combination.

in APJ morphology is normal for Warmblood foals. Yet, in the examined part of the vertebral column the oval and bevelled combination (24%) and the suggested normal shape combination (23%) were most prevalent and therefore both combinations should maybe be considered normal in Warmblood foals, especially as the assumed normal shape of the articular surface of APJs has only been described in horses of 1 year and older.[26] This suggestion is further supported by the fact that oval and bevelled and oval and concave shape combinations are more commonly found in younger than in older foals compared with the normal articular surface shape. Further research concerning the evolution of the shape of the articular surface of the APJ, by use of repetitive computer tomography and MRI, starting already with foetuses, would be highly informative. The assumed normal shape was taken as reference for statistic calculations, because of the slight difference in prevalence of these two most commonly encountered combinations within the entire examined vertebral column. However, sampling bias cannot be completely excluded as the foals in our study were a convenience sample. Interestingly, previous studies describing the normal shape of APJs, in which 1870 respectively 22 articular surfaces were examined, shape details were not specified for each breed.[25,26] Therefore breed-related variation as an explanation for different results cannot be ruled out. The present study suggests that the shape of the articular surface of APJs per se is not a major contributor to the development of CVM as there was no overrepresentation of any one shape combination within the different regions, sexes (factors of importance in the development of CVM), position and side of the articular surfaces.

In a recent study, bony changes of cervical and cranial thoracic APJs were described in a mixed population of horses of 1 year and older, without a distinction between top and lateral view.[26] In that study, a considerable variation in morphology was reported also. That study described, amongst others, two shapes, named ‘lipping’ and ‘flattening’, that are comparable with respectively the raised edge and folded edge lateral view shapes as described in this study. In that other study, these shapes were considered pathologic and progressive. In the present study, these shapes were already existent in newborn foals and can therefore in any case be considered congenital. An age-related prevalence of these two shapes could not be established. The folded lateral view shape (in combination with an oval top view

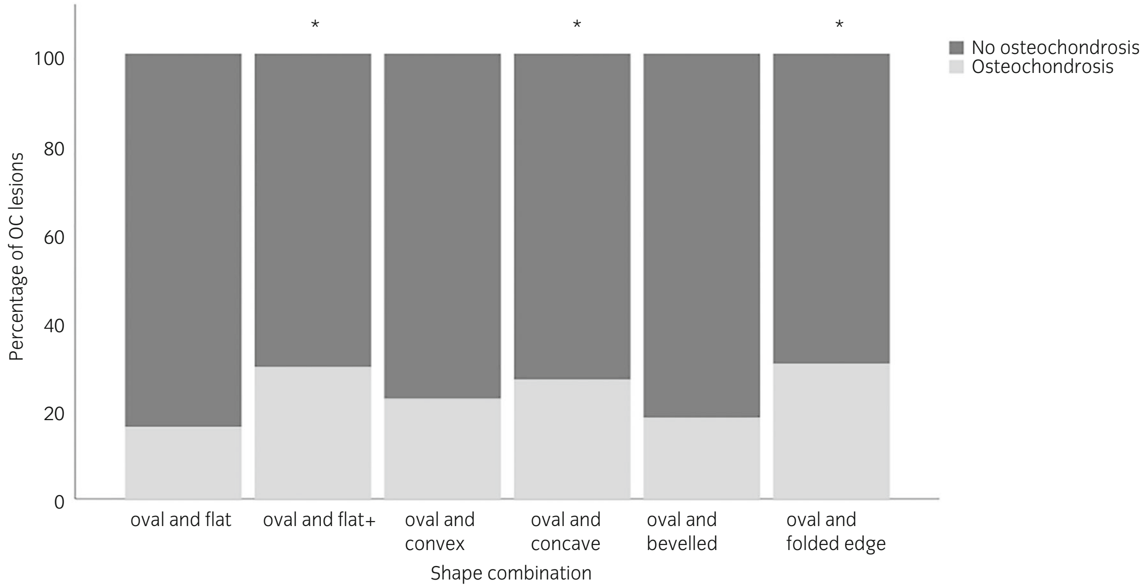

FIGURE 6 Percentage of osteochondrosis in the articular surface of articular process joints with different shape combinations. Articular surfaces with an oval top view shape and a flat lateral view shape with an additional raised edge and/or a folded edge combined (flat +), a concave or a folded edge lateral view shape are significantly more likely to have osteochondrosis than an oval top view shape with solely a flat lateral view shape, a convex or a bevelled lateral view shape. The percentage of articular surfaces not affected by osteochondrosis are depicted with the dark grey colour. The percentage of articular surfaces that do have osteochondrosis are depicted with the light grey colour. * denotes the shape combinations that have a statistically significant increased likelihood to have osteochondrosis.

shape) was positively associated with OC and therefore indeed associated with pathology in foals. Whether these two shapes are also associated with pathology in older horses, such as increased likelihood to develop osteoarthrosis, needs to be investigated.

OC's first developmental stage, OC latens, is characterised by necrosis of the epiphyseal cartilage and results from necrosis of blood vessels in the cartilage canals.[11,21] These cartilage canals are symmetrically present in contralateral joints, only present within a certain age-range, and their course is consistent within species. Therefore, OC lesions develop in young animals, tend to occur in certain predilections sites and are frequently bilaterally symmetric.[10,11,21] Local differences in amount of blood vessels and thickness of the cartilage are thought to account for the occurrence of these predilection sites.[13] In the present study, several specific shape combinations were more likely to have OC latens and OC manifesta while OCD was not observed. The cause for this difference in likelihood is not clear, however shape-associated differences in number of blood vessels and thickness of cartilage cannot be excluded. Still, it is possible that the other shape combinations are just as likely to result in OC in older foals, as half of the foals examined were less than 1 week old, and the time window for development of radiologically and grossly detectable APJ OC is suggested to last up to approximately 5 months.[29]

Variances in joint shape likely lead to changes in biomechanical stress and therefore differences in likelihood to develop OCD.[10] It is to be expected that environmental stress, such as housing conditions but also normal movement, increases the biomechanical forces on a joint and can as such potentially contribute to OCD development.[10] As half of the foals examined were less than 1 week old, the contribution of biomechanical stress caused by movement was most likely limited and therefore it cannot be excluded that certain shape combinations are associated with OCD in older foals.

Sepsis can cause a vasculitis and subsequently OC-like lesions.[23,24] Thus, all examined joints were carefully evaluated for septic changes and the articular surfaces of two foals which showed signs of sepsis after histological evaluation were excluded from further assessment. Although sepsis as cause for OC lesions in the remaining foals seems highly unlikely, several of the foals included did die or were euthanised because of infection. As no histological serial sections of the articular surfaces, nor bacterial culture of the joints were performed, OC-like lesions due to sepsis cannot be ruled out completely.

OC can lead to gross changes, including focal thickening of cartilage, soft and red cartilage, flattening of cartilage and irregular cartilage with possible invaginations.[10,30,31] All articular surfaces included, had smooth, white cartilage and the concave and convex lateral shapes compromised the entire articular surface. Also, the folded and raised edge shapes were composed of cartilage covered bone, seamlessly and firmly attached to the rest of the articular surface, and were therefore not loose cartilage flaps. Only five of the articular surfaces with histologically confirmed OC had gross changes suggestive for OC. These changes consisted of (multi) focal round to longitudinal indentations of the cartilage.[22] Therefore the different shapes described in this study are most probably conformational shape differences and not the result of OC. This is supported by the relative limited numbers of different shapes.

The suspected differences in biomechanical loading associated with different shapes could influence the likelihood to develop osteoarthrosis as seen in other joints.[32] Non-congruent shapes of opposite articular surfaces within one APJ can result in malarticulation which may directly lead to compression of nervous tissue, or secondary to compression by developing osteoarthrosis. Indeed, the development of CVM in older horses has been suggested to result from progression of subclinical malformation-mal-articulation leading to chronic microtrauma.[5] Therefore, certain shape combinations could still contribute to the development of CVM, although they do not have increased likelihood to have OC. However, to confirm the suspected role of shape in the development of osteoarthrosis leading up to CVM, more research, for example long term computer tomographic evaluation with eventually pathological evaluation, is necessary.

Both shape categorisation and scoring of the shape grade were made as objective as possible by use of ratios of the axis's, width at the poles, measurements of slope degree and ratio to the articular surface. Objectivity could not be substantiated by use of an intra- or inter-observer reliability score as scoring was only done once during necropsy by a single person (WB). The reliability and reproducibility of the shape categorisation was however improved by the use of representative pictures and schematic drawings. The reliability of grading of the shapes was increased by reducing the original 4-tier grading scale to a 2-tier grading scale.

In conclusion, articular surface shape of the cervical and cranial thoracic APJs is highly variable in Warmblood foals. Certain shape combinations are associated with a higher incidence of OC in young Warmblood foals and thus might contribute to the development of CVM.

AUTHOR CONTRIBUTIONS

Wilhelmina Bergmann contributed to study design, data collection and study execution, data analysis and interpretation and preparation of the manuscript. Wilhelmina Bergmann takes responsibility for the integrity of the data. Guy C. M. Grinwis and Andrea Gröne contributed to study design, data analysis and interpretation and preparation of the manuscript. Johannes C. M. Vernooij contributed to data collection and study execution, data analysis and interpretation and preparation of the manuscript.

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COMPETING INTERESTS

No competing interests have been declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL ANIMAL RESEARCH

Research ethics committee oversight not currently required by this journal: the study was performed on archived material collected previously during post-mortem examinations.

INFORMED CONSENT

Explicit informed consent for enrolment of client-owned horses in this study was not stated but horse owners gave general permission for post-mortem examination and retention of tissues for research.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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