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Sex differences in cervical spinal cord and spinal canal development in Thoroughbred horses

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ABSTRACT. Cervical vertebral stenotic myelopathy (CVSM), a common cause of cervical spinal cord compression, is a neurological disease characterized by general proprioceptive ataxia and weakness of hindlimbs that tends to develop in young adult Thoroughbred horses. Although male horses seem to be at increased risk for CVSM, the mechanism for the occurrence of sex differences in the prevalence of CVSM is still poorly understood. Hence, we hypothesized that sex differences in the development of cervical spinal cord and spinal canal would affect the development of CVSM. This study aimed to evaluate sex differences in the development of cervical spinal cord and spinal canal in Thoroughbred horses. A total of 29 Thoroughbred horses underwent computed tomographic myelography. Thereafter, the volumes of cervical spinal cord and spinal canal were calculated. Accordingly, male horses had significantly lager cervical spinal cord volume and cervical spinal cord-to-spinal canal volume ratio than those of female horses ($P<0.05$). Sex differences in the cervical spinal cord-to-spinal canal volume ratio gradually decreased until around 1,400 days of age. Younger male horses have narrower interspace between the cervical spinal cord and spinal canal than younger female horses, suggesting that an imbalanced cervical spinal cord and spinal canal growth is one of the causes of CVSM.

KEYWORDS: cervical spinal cord, computed tomographic myelography, spinal canal, Thoroughbred

Cervical vertebral stenotic myelopathy (CVSM), which is a common cause of cervical spinal cord compression, is a neurological disease characterized by general proprioceptive ataxia and weakness of hindlimbs [3, 15, 17]. Evidence has suggested that Thoroughbred horses are at higher risk for CVSM than other breeds [15], with young adult horses tending to be at particular risk for CVSM. Another important point is that the prevalence of CVSM exhibits sex difference. Notably, studies have shown that male horses seem to be at increased risk for CVSM [4, 11]. However, the mechanism for the existence of sex differences in the prevalence of CVSM still remains poorly understood. We hypothesized that sex differences in the development of cervical spinal cord and spinal canal can affect the development of CVSM. During fetal life, the spinal cord runs throughout the entire length of the embryo, and peripheral nerves pass through the intervertebral foramina at the same level as the spinal cord origins. However, the vertebral column grows faster than the spinal cord [7], leaving the caudal end of the spinal cord terminating at a gradually higher level in the vertebral column [6, 18]. Horses have a larger cervical spinal cord than other species [1]. However, no study has yet investigated the growth of the cervical spinal cord and spinal canal in horses. Moreover, previous studies evaluating the size of cervical spinal cord and/or spinal canal had used magnetic resonance imaging (MRI) [9] or radiography [14, 19, 20]. Given that MRI evaluation is only possible on post-mortem specimens, post-mortem changes cannot be excluded. Furthermore, radiographs should be corrected for the measured value during evaluation considering that radiographs are magnified to be larger than the real size. Thus, these reports inaccurately reflect the reality of the cervical spinal cord in living horses.

Computed tomographic (CT) myelography in horses has emerged as one of the imaging diagnostic modalities for CVSM in recent years [8, 13, 21, 23]. CT myelograms can be used as an absolute value, while three-dimensional images can be used to calculate the volume of spinal cord and spinal canal. The present study aimed to evaluate sex differences in the development of the cervical spinal cord and spinal canal in Thoroughbred horses.

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MATERIALS AND METHODS

Cases

This observational descriptive study included 29 Thoroughbred horses (age range: 25–1,298 days on CT examination; mean, 410.6 days) that underwent CT myelography from June 2013 to October 2019 at the Obihiro University of Agriculture and Veterinary Medicine. All these Thoroughbred horses exhibited some clinical signs such as abnormal gaits. The study population comprised 20 male horses (age range: 42–717 days on CT examination; mean, 371.7 days) and 9 female horses (age range: 25–1,298 days on CT examination; mean, 496.9 days). The study protocol was approved by the Animal Experiment and Welfare Committee of Obihiro University of Agriculture and Veterinary Medicine (No.27-127).

Anesthesia

Horses underwent general anesthesia during CT myelography. An indwelling intravascular catheter was placed into the jugular vein. All horses were premedicated intravenously with 5 µg/kg medetomidine hydrochloride (Domitor, Nippon Zenyaku Kogyo, Tokyo, Japan) and anesthetized using intravenous administrations of 0.03 µg/kg midazolam (Dormicum, Maruishi Pharmaceutical, Osaka, Japan) and 4 mg/kg thiamylal (Isozol, Nichi-Iko Pharmaceutical, Toyama, Japan). Guaifenesin (25 mg/kg, Guaifenesin, Shinyo Pure Chemicals, Osaka, Japan) was rapidly infused until the horse became ataxic following which intratracheal intubation was performed. Anesthesia was subsequently maintained using a triple drip mixture of guaifenesin (200 mg/kg/hr), xylazine (1 mg/kg/hr, Celactar, Bayer, Tokyo, Japan), and ketamine (2 mg/kg/hr, Ketalar, Daiichi-Sankyo, Tokyo, Japan).

CT myelography

The horses were placed in the lateral recumbent position, after which a 21-gage spinal needle was inserted into the subarachnoid space via the atlanto-occipital junction. Cerebrospinal fluid was allowed to drain out of the subarachnoid space for 2 min, after which the same volume of contrast agent (140 mgI/mL, iohexol, Teva Pharmaceutical Industries, Tokyo, Japan) as the drained cerebrospinal fluid was injected into the subarachnoid space. The concentration of the contrast agent was defined according to Gough *et al*. [8]. The horses' heads were lifted for 5 min, following which the horses underwent CT myelography. The horses were placed in the dorsal recumbent position with their neck in a neutrally extended position on a large equine patient table for CT.

CT myelograms were obtained using two CT units that were newly installed during the study period. A 4-row multidetector CT (Asteion Super4, Canon Medical Systems Corp., Ohtawara, Japan) with a gantry opening of 72 cm, tube voltage of 135 kV, tube current of 150 mA, and slice thickness of 2.0 mm was used from 2013 to 2014. A 16-row multidetector CT (Aquilion LB, Canon Medical Systems Corp.) with a gantry opening of 90 cm, tube voltage of 135 kV, tube current of 300 mA, and slice thickness of 0.5 mm was used from 2015 to 2019.

Calculating the volumes of the cervical spinal cord and spinal canal

The cervical spinal cord and spinal canal volumes were calculated using the image-processing software OsiriX-N (Newton Graphics, Sapporo, Japan). The measurement range spanned from the cranial top of the C3 to the caudal end of the C6. This might be because there are variations in the forms of C2. Hence, C2 spinal canal volumes measurements might exhibit wide fluctuation. Additionally, some horses were not scanned till the caudal end of C7 via CT. Since a large number of samples in required for a robust statistical analysis, we determined the cervical spinal cord and spinal canal volumes from the cranial top of the C3 to the caudal end of the C6. The areas of the cervical spinal cord and spinal canal were measured in the two-dimensional transverse plane. Moreover, the three-dimensional images were reconstructed using the volume rendering technique. Thereafter, the three-dimensional images were used to calculate the volume of cervical spinal cord and spinal canal (Fig. 1).

Investigative analysis

This study conducted two investigative analyses. The first involved determining the relationship between cervical spinal cord volume, as well as spinal canal volume, and age in days. The second involved determining the relationship between the cervical spinal cord-to-spinal canal volume ratio and age in days. The cervical spinal cord-to-spinal canal volume ratios were calculated by dividing the cervical spinal cord volume by the spinal canal volume. Data were analyzed for differences according to sex.

Statistical analysis

Excel add-in software (Multivariate, BellCurve for Excel, Tokyo, Japan) was used for data processing. The sex differences in the cervical spinal cord volume, spinal canal volume, and cervical spinal cord-to-spinal canal volume ratios were analyzed. Scatter graphs were produced for male and female horses, wherein the y-axis indicated the measured values and the x-axis showed the ages of the horses. These plots were used to calculate the approximate curves and logarithm regression equation. The prediction values of the cervical spinal cord volume, spinal canal volume, or cervical spinal cord-to-spinal canal volume ratios were calculated by substituting the horse's age in the x-axis with the logarithm regression equation. Finally, the prediction values for the male and female horses were compared using unpaired Student's *t*-test. A *P*-value of <0.05 was considered significant.

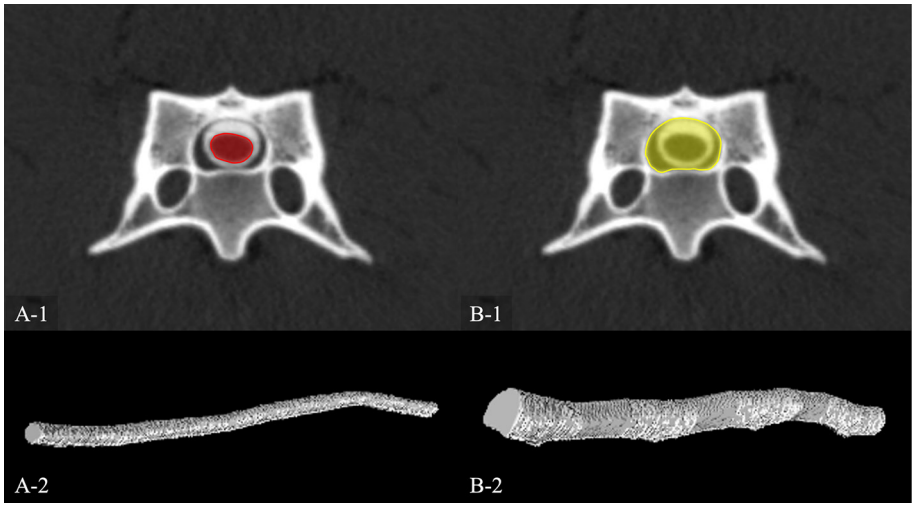

Fig. 1. Areas of the cervical spinal cord (**A-1**) and spinal canal (**B-1**) were measured in the two-dimensional transverse plane. The measurement range spanned from the cranial top of the C3 to the caudal end of the C6. The three-dimensional images were reconstructed using the volume rendering technique. Thereafter, the three-dimensional images were used to calculate the volume of the cervical spinal cord (**A-2**) and spinal canal (**B-2**).

RESULTS

Relationship between cervical spinal cord volume and age in days

The cervical spinal cord volume from the C3 to C6 was calculated. Male horses had a significantly larger cervical spinal cord volume than female horses ($P<0.05$). The cervical spinal cord volume dramatically increased until around 200 days of age, after which slow growth was observed (Fig. 2).

Relationship between spinal canal volume and age in days

The spinal canal volume from the C3 to C6 was calculated, which showed no significant difference between male and female horses ($P=0.19$). The spinal canal volume dramatically increased until around 200 days of age, after which slow growth was observed (Fig. 3).

Relationship between cervical spinal cord-to-spinal canal volume ratio and age in days

Male horses had a significantly higher cervical spinal cord-to-spinal canal volume ratio than female horses ($P<0.05$). Sex differences in the cervical spinal cord-to-spinal canal volume ratio gradually decreased until around 1,400 days of age (Fig. 4).

DUSCUSSION

Considering the lack of relevant studies in the current literature, we believe that the present study is the first to clarify the development of the cervical spinal cord and spinal canal in Thoroughbred horses.

Our findings showed that male horses had a significantly higher cervical spinal cord-to-spinal canal volume ratio than female horses, suggesting that the former has narrower interspace between the cervical spinal cord and spinal canal than the latter. Thus, our results indicate that insufficient spinal canal volume can affect the development of CVSM. Ample evidence has suggested male predominance in CVSM cases, with reports showing a 2:1, 3:1, and 23:1 male to female ratios [4, 5, 12]. Some owners have a special management for male horses that is separate from female horses, which may explain the observed sex-related differences [11]. Thoroughbred horses start their training during their growth period at around 20 months. Moreover, some owners start training male horses earlier than female horses given their belief that male horses are better than female horses at racing. Bone mineral density, as measured by quantitative CT, increases rapidly with age until 2 years followed by a plateau, which is similar to the equine growth curve [22]. Insufficient bone mineral density increases the incidence of orthopedic problems [10]. The articular process generally does not affect cervical spinal cord compression [2]. However, given that the articular process is adjacent the spinal cord, severe enlargement of the articular process can cause cervical spinal cord compression [15]. The high cervical spinal cord-to-spinal canal volume ratio in younger male horses suggests an increased risk of cervical spinal cord compression caused by the enlargement of the articular process.

Sex differences in the cervical spinal cord-to-spinal canal volume ratio gradually decreased until around 1,400 days of age. The growth plates of the cervical column do not close until 4–5 years of age [9, 16]. Notably, the time at which sex difference in the cervical spinal cord-to-spinal canal volume ratio disappeared corresponded with approximately the time of the completion of the cervical column growth.

The present study has a limitation. This study conducted in all predisposing CVSM horses. Ideally, this investigation should be

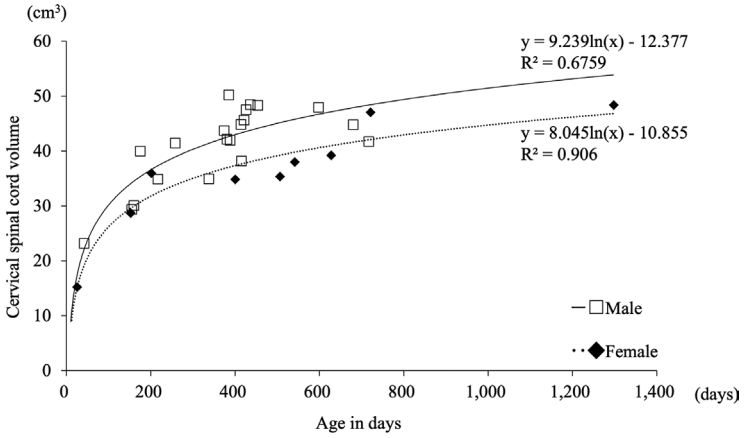

Fig. 2. Relationship between cervical spinal cord volume and age in days. Male horses had a significantly larger cervical spinal cord volume than female horses (P<0.05). The cervical spinal cord volume dramatically increased until around 200 days of age, after which slow growth was observed.

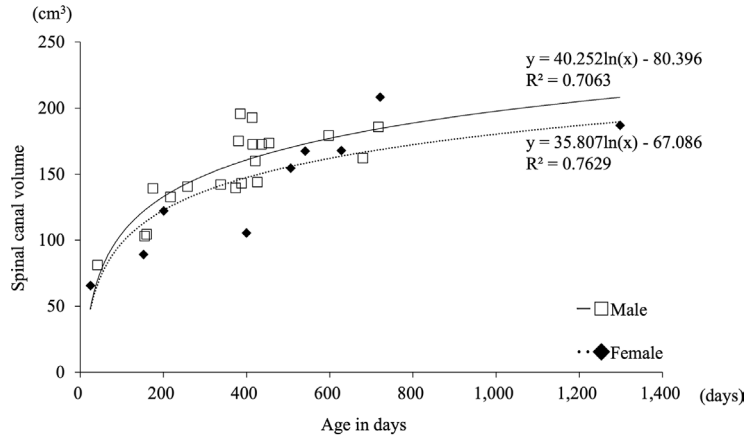

Fig. 3. Relationship between spinal canal volume and age in days. There was no significant difference in the spinal canal volume between the male and female horses (P=0.19). The spinal canal volume dramatically increased until around 200 days of age, after which slow growth was observed.

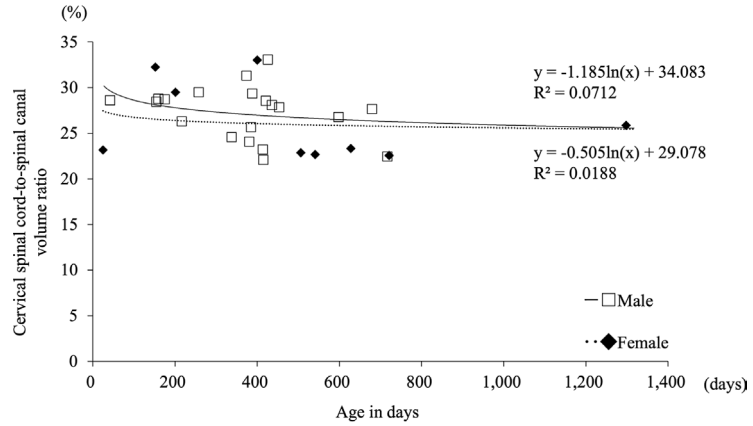

Fig. 4. Relationship between the cervical spinal cord-to-spinal canal volume ratio and age in days. Male horses had a significantly higher cervical spinal cord-to-spinal canal volume ratio than female horses (P<0.05). Sex differences in the cervical spinal cord-to-spinal canal volume ratio gradually decreased until around 1,400 days of age.

performed for non-affected horses. However, it is impossible that racehorse candidate young horses use for experiment. This study could not completely exclude the effect of predisposition toward CVSM. Hence, it remains unclear whether the sex difference observed is the cause or the result.

Younger male horses have narrower interspace between the cervical spinal cord and spinal canal than younger female horses, suggesting that an imbalanced cervical spinal cord and spinal canal growth is one of the causes of CVSM.

CONFLICT OF INTEREST. The authors declare that there were no conflicts of interest.

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REFERENCES

1. Bahar S, Bolat D, Selcuk ML. 2013. The segmental morphometric properties of the horse cervical spinal cord: a study of cadaver. *Scientific World Journal* **2013**: 734923. [Medline] [CrossRef]
2. Claridge HAH, Piercy RJ, Parry A, Weller R. 2010. The 3D anatomy of the cervical articular process joints in the horse and their topographical relationship to the spinal cord. *Equine Vet J* **42**: 726–731. [Medline] [CrossRef]
3. Craig LE, Dittmer KE, Thompson KG. 2015. Bones and joints. pp. 16–163. In: Jubb, Kennedy & Palmer's Pathology of Domestic Animals Vol. 1, 6th ed. (Maxie, M. G. ed.), Saunders Elsevier, Amsterdam.
4. Dimock WW. 1950. "Wobbles" an hereditary disease in horses. *J Hered* **41**: 319–323. [Medline] [CrossRef]
5. Falco MJ, Whitwell K, Palmer AC. 1976. An investigation into the genetics of 'wobbler disease' in thoroughbred horses in Britain. *Equine Vet J* **8**: 165–169. [Medline] [CrossRef]
6. Ghazi SM, Ranjbar R, Khaksary Mahabady M. 2016. Allometric growth rate of the spinal cord in relation to the vertebral column during prenatal life in male and female goats (*Capra hircus*). *Majallah-i Tahqiqat-i Dampizishki-i Iran* **17**: 243–246. [Medline]
7. Ghazi SR, Gholami S. 1994. Allometric growth of the spinal cord in relation to the vertebral column during prenatal and postnatal life in the sheep (Ovis aries). *J Anat* **185**: 427–431. [Medline]
8. Gough SL, Anderson JDC, Dixon JJ. 2020. Computed tomographic cervical myelography in horses: Technique and findings in 51 clinical cases. *J Vet Intern Med* **34**: 2142–2151. [Medline] [CrossRef]
9. Janes JG, Garrett KS, McQuerry KJ, Pease AP, Williams NM, Reed SM, MacLeod JN. 2014. Comparison of magnetic resonance imaging with standing cervical radiographs for evaluation of vertebral canal stenosis in equine cervical stenotic myelopathy. *Equine Vet J* **46**: 681–686. [Medline] [CrossRef]
10. Kobayashi M, Ando K, Kaneko M, Inoue Y, Asai Y, Taniyama H. 2007. Clinical usefulness of the measurement of bone mineral content by radiographic absorptiometry in the young Thoroughbred. *J Equine Sci* **18**: 99–106. [CrossRef]
11. Levine JM, Adam E, MacKay RJ, Walker MA, Frederick JD, Cohen ND. 2007. Confirmed and presumptive cervical vertebral compressive myelopathy in older horses: a retrospective study (1992–2004). *J Vet Intern Med* **21**: 812–819. [Medline]
12. Levine JM, Ngheim PP, Levine GJ, Cohen ND. 2008. Associations of sex, breed, and age with cervical vertebral compressive myelopathy in horses: 811 cases (1974–2007). *J Am Vet Med Assoc* **233**: 1453–1458. [Medline] [CrossRef]
13. Lindgren CM, Wright L, Kristoffersen M, Puchalski SM. 2021. Computed tomography and myelography of the equine cervical spine: 180 cases (2013–2018). *Equine Vet Educ* **33**: 475–483. [CrossRef]
14. Mayhew IG, Donawick WJ, Green SL, Galligan DT, Stanley EK, Osborne J. 1993. Diagnosis and prediction of cervical vertebral malformation in thoroughbred foals based on semi-quantitative radiographic indicators. *Equine Vet J* **25**: 435–440. [Medline] [CrossRef]
15. Mayhew IG. 2008. Multifactorial and idiopathic disorders. pp. 392–429. In: Large Animal Neurology, 2nd ed. (Mayhew IG ed.), Wiley-Blackwell Publishing, Hoboken.
16. Rooney JR. 1972. The musculoskeletal system. pp. 489–499. In: Equine Medicine & Surgery 2nd ed. (Catcott EJ and Smithcors JF eds.), American Veterinary Publications, Wheaton.
17. Rush BR. 2011. Cervical stenotic myelopathy. pp. 1174–1178. In: Adams and Stashak's Lameness in Horses 6th ed. (Baxter GM ed.), Blackwell Publishing, West Sussex.
18. Siniwatz F. 2010. Development of central and peripheral nervous system. pp. 121–162. In: Domestic Animal Embryology (Hyttel P, Sinowatz F and Vejlsted M eds.), Saunders Elsevier, Amsterdam.
19. Tomizawa N, Nishimura R, Sasaki N, Nakayama H, Kadosawa T, Senba H, Takeuchi A. 1994. Relationships between radiography of cervical vertebrae and histopathology of the cervical cord in wobbling 19 foals. *J Vet Med Sci* **56**: 227–233. [Medline] [CrossRef]
20. Tomizawa N, Nishimura R, Sasaki N, Hayashi Y, Senba H, Hara S, Kadosawa T, Takeuchi A. 1994. Morphological analysis of cervical vertebrae in ataxic foals. *J Vet Med Sci* **56**: 1081–1085. [Medline] [CrossRef]
21. Tucker R, Hall YS, Hughes TK, Parker RA. 2022. Osteochondral fragmentation of the cervical articular process joints; prevalence in horses undergoing CT for investigation of cervical dysfunction. *Equine Vet J* **54**: 106–113. [Medline] [CrossRef]
22. Yamada K, Sato F, Higuchi T, Nishihara K, Kayano M, Sasaki N, Nambo Y. 2015. Experimental investigation of bone mineral density in Thoroughbreds using quantitative computed tomography. *J Equine Sci* **26**: 81–87. [Medline] [CrossRef]
23. Yamada K, Sato F, Hada T, Horiuchi N, Ikeda H, Nishihara K, Sasaki N, Kobayashi Y, Nambo Y. 2016. Quantitative evaluation of cervical cord compression by computed tomographic myelography in Thoroughbred foals. *J Equine Sci* **27**: 143–148. [Medline] [CrossRef]