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Case Report

Congenital occipitoatlantoaxial malformation in a Brazilian sport horse foal

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Abstract
A 12-hour-old Brazilian Sport Horse foal, presenting signs of dysmaturity, was referred to the Veterinary Teaching Hospital from the Universidade Federal de Minas Gerais, Belo Horizonte, Brazil, being hospitalized for nine days before euthanasia. Clinically, neurological signs such as difficulty in maintaining head posture, tetraparesis, and asymmetric ataxia were observed, raising suspicion of cervical vertebrae abnormalities. Radiographic analysis revealed occipitalization of the atlas with asymmetric fusion of the atlas to the occipital bone and dorsal luxation of the axis; all these findings were confirmed at necropsy. Additionally, histopathology revealed axonal degeneration at spinal cord and pons as a result of nervous tissue compression at the atlantooccipital fusion area. Congenital occipitoatlantoaxial malformation (OAAM) was the definitive diagnosis in this case, and, to the best of our knowledge, it is described for the first time on a Brazilian Sport Horse.
Keywords: cervical vertebrae; congenital malformations; equine; neurological signs; occipitalization.

Introduction

In veterinary and human medicine, congenital malformations are defined as functional and/or structural disorders during intrauterine development. The etiology associated with these anomalies are genetic, environmental, toxic, infectious, or even of unknown causes (1, 2, 3, 4, 5, 6). In domestic animals, congenital cervical vertebrae malformations are uncommon (3), with reported cases in dogs (5, 7, 8, 9), cats (10), cattle (2, 11, 12), and most frequently in horses (1, 3, 13, 14, 15, 16, 17, 18).

Among horses, occipitoatlantoaxial malformation (OAAM) is the only described type that affects the development of the occipital bone, atlas, axis, and the joints between these structures (13). This condition may lead to instability and misalignment of the cervical spine, causing neurological symptoms and potentially fatal complications. The pathogenesis is still poorly understood, but heredity predisposition has been implicated in its development. Arabian horses have the highest prevalence of OAAM due to an autosomal recessive gene with no sex predilection (19). However, isolated cases have been described in Quarter Horse, Warmblood, and Andalusian breeds (13, 14, 18, 20).

The aim of this report is to describe a congenital OAAM in a Brazilian Sport Horse foal, and to characterize the clinical and pathological aspects of this condition.

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Case description

A 12-hours-old Brazilian Sport Horse male foal was referred to the Veterinary Teaching Hospital at the Universidade Federal de Minas Gerais (VH-UFMG), Minas Gerais State, Brazil, presenting absence of sucking reflex and stupor. According to the information provided by the owner, the recipient mare is multiparous, had undergone appropriate management and handling, and the gestational period lasted for 340 days. The foal was the result of Intracytoplasmic Sperm Injection (ICSI), with no history of congenital diseases in the parents. The birth was assisted and reported as uneventful. After birth, staff members reported that the foal attempted to stand and remain in a standing position but displayed muscular weakness and struggled in these unsuccessful attempts. Initially, the newborn showed interest in suckling, so it was decided to administer colostrum through a feeding bottle.

During the physical examination, the foal was found in lateral recumbency with tachycardia (140 bpm), tachypnea (90 rmpm), hypothermia (36.4°C), dry and congested mucous membranes, and a capillary refill time of four seconds. The reference values used for clinical evaluation were according to Paradis (21). Signs of dysmaturity were observed, such as bulging forehead, floppy ears, thin hair with mole-like coat (Figure 1A), and laxity of flexor tendons, added by the presence of an abnormal palpable prominence in the region of the spinous process of the axis (C2) (Figure 1B).

Blood samples were collected and the cell blood count (CBC) revealed mild anemia (8.04 million/mm³; reference range (22): 8.8-10.2 million/mm³) and leukocytosis (22.950/mm³; reference range (22): 7.830 – 10.550/mm³) with neutrophilia (18.819/mm³; reference range (22): 3.470 – 5.090/mm³). In the serum biochemistry, hypoglycemia (42 mg/dL; reference range (22): 62 to 134 mg/dL) and hypoproteinemia (4.27 g/dL; reference range (22): 6.0 – 8.0 g/dL) were observed. For evaluating passive immunity transfer, a semi-quantitative immunochromatographic test was conducted to detect serum levels of Immunoglobulin G (IgG; IgG Check®, Dechra Pharmaceuticals, Cheshire, England) in the foal's serum, resulting in a partial failure, falling between the range of 400 to 800 mg/dL (Reference values: IgG < 400 mg/dL = total failure; IgG between 400 – 800 mg/dL = partial failure; IgG > 800 mg/dL = normal passive transfer). At this point, the septic score was classified as eight, with a foal considered non-septic when below 11, as proposed by Brewer et al. (23).

Emergency care for the animal started with central venous access by the right jugular vein, followed by fluid therapy with Ringer's Lactate intravenously (IV) with a bolus of 20 mL/kg. Due to potential risk of infection, given the partial failure of passive immune transfer, antibiotic therapy was performed with ceftiofur (Minoxel, Lapisa Salud Animal©, Michoacán, Mexico), 2.2 mg/kg, IV, twice a day (BID), combined with amikacin (Pareum; Ourofino Saúde Animal Ltda, São Paulo, Brazil), 25 mg/kg, IV, once a day (SID), and the non-steroidal anti-inflammatory flunixin meglumine (Flumax, J.A Saúde Animal, São Paulo, Brazil), 1.1 mg/kg, IV, SID and oxygen therapy (8L/min). A successful

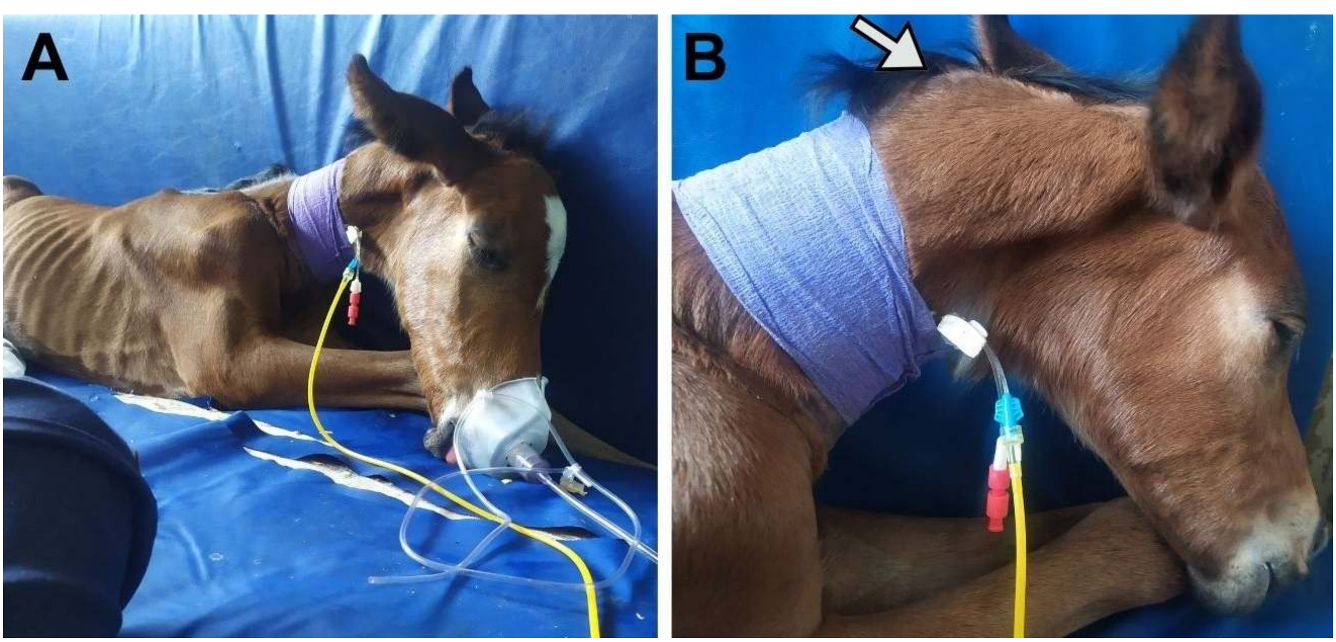

Figure 1. Clinical evaluation of a foal presenting congenital occipitoatlantoaxial malformation (OAAM). **A)** Foal admitted to VH-UFMG displaying signs of dysmaturity, such as a bulging forehead, floppy ears, and mole-like coat. **B)** Right lateral view of the head-neck region, highlighting the abnormal presence of a protrusion in the location of the spinous process of the axis (white arrow).

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transfusion of Hyperimmune Plasma (Hyperimmune Equine Plasma, Equoplasma, Jaquariuna, Brazil), 20 mL/kg, IV, was performed, and blood glucose levels were monitored and corrected as needed throughout the hospitalization period. After intensive care, for seven days, the patient showed clinical improvement, and the sucking reflex became present. However, the foal remained in a sternal recumbent position and was still unable to stand on its own.

Due to general clinical signs, a specific evaluation of the neurological system was recommended. The animal remained lethargic but showed increased interaction with the environment compared to its initial admission. Examination of the cranial nerve pairs, as described by Borges et al. (24, 29) and Hahn (25), revealed reduced pupillary reflexes, consistent with alterations on the optic (II) and oculomotor (III) nerves; and reduced visual threat reflex, suggesting potential involvement of the brain and cerebellum. Upon inspection and palpation of the cervical spine, prominence in the region of the spinous processes of the axis and slight left-sided scoliosis at the anatomical region of C2-C3 were noted. Also, a "click" sound could be heard when the foal raised and extended its head. When the veterinary team assisted the foal into a standing position, it displayed a wide-based stance, with difficulty supporting its head, as well as tetraparesis and asymmetric ataxia. Vertebral lesions in the cervical region were the primary differential diagnosis, although distinguishing between traumatic, congenital, or infectious origins was challenging at this stage of the examination.

A cranio-cervical radiographic study was performed, including lateral and dorsoventral projections. Abnormalities included increased radiopacity at the atlanto-occipital joint, suggestive of occipitalization of the atlas (C1), in which C1 appeared asymmetrically fused to the occipital bone. The occipital condyles were fused to the cranial region of the atlas, making them indistinguishable in the image (Figure 2A and 2B), along with the presence of misalignment of the atlas and axis with dorsal dislocation of the axis (Figure 2B). The clinical and radiographic findings were suggestive of OAAM, and due to the unfavorable prognosis, after nine days of intensive care, euthanasia was performed.

At necropsy, during the atlantooccipital joint disarticulation, resistance and lack of mobility were noted, leading to the separation of the head at the atlantoaxial joint. After dissection of the cervical muscles, it was observed that the occipital bone and atlas were completely fused, presenting a reddish surface and a spongy appearance upon sectioning. When evaluating the fused piece, dorsally, the occipital bone was partially visible, reduced in size, with the external occipital protuberance covered by the dorsal arch of the atlas. In the atlas, it was possible to identify that the dorsal cranial elements were uneven (Figure 3A). In both antimeres, the lateral alar and vertebral foramina were not observed. In the right antimere, there was a reduction in the wing of the atlas. Both transverse foramina were evident but reduced in the right antimere. Despite being present, the dorsal tubercle of the atlas was reduced and not very evident. The paracondylar

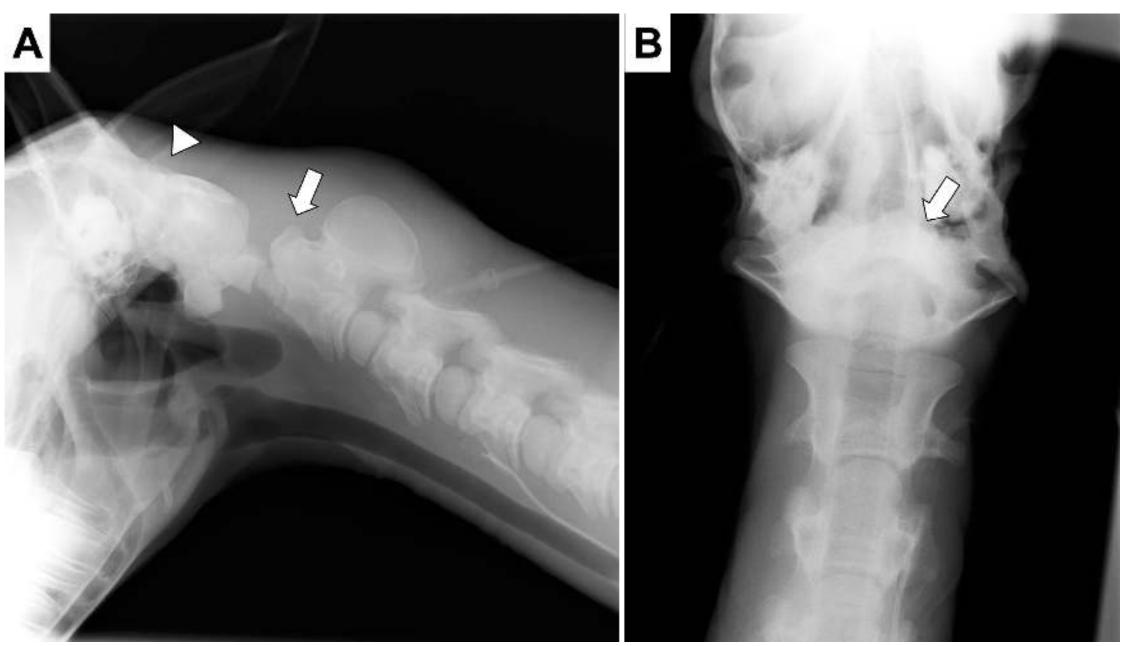

Figure 2. Radiographic findings of a foal presenting congenital occipitoatlantoaxial malformation (OAAM). **A)** Lateral radiograph of the cervical spine of a foal in a neutral position. In this case, occipitalization of C1 (arrow head) is observed, with unidentifiable occipital condyles. There is also misalignment between the atlas and axis, with dorsal dislocation of the axis (arrow). **B)** Dorsoventral radiograph of the cervical spine of foal. In this projection, occipitalization of C1 (arrow) is visible, with increased radiopacity at the atlanto-occipital joint.

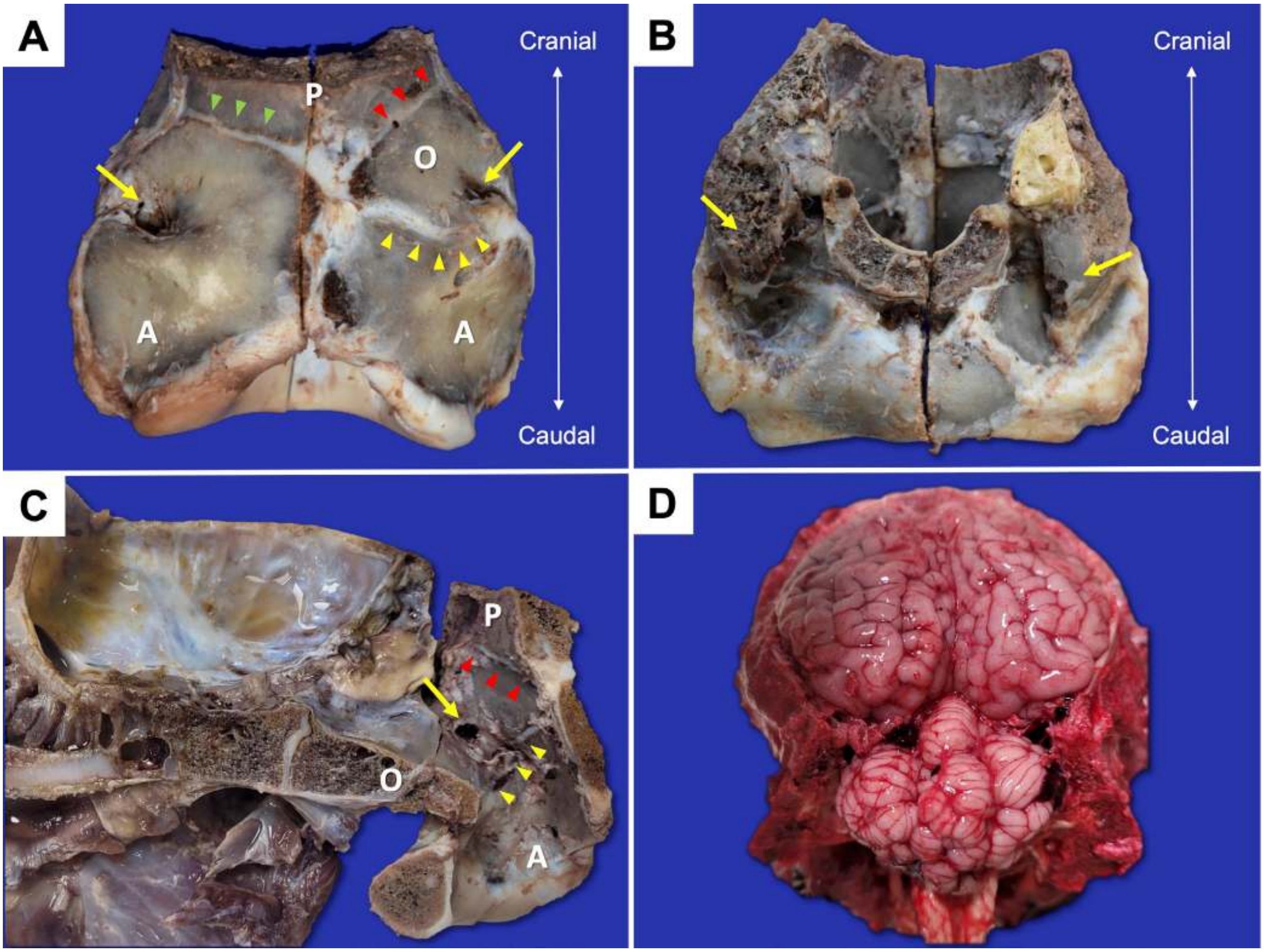

Figure 3. Gross findings of a foal presenting congenital occipitoatlantoaxial malformation (OAAM). **A)** Dorsal view: Parietal bone (P), nuchal crest, limited by the occipital bone (red arrow heads) at right and by the atlas (green arrow heads) at left. Occipital bone (O) is reduced in size and completely fusion to the atlas (yellow arrow heads). External occipital protuberance is concealed by the dorsal arch of the atlas. Atlas (A) with uneven cranial dorsal elements. In both hemispheres, alar and lateral vertebral foramina are not visible. The right hemisphere shows a reduced wing (cranial portion). Transverse foramina (yellow arrows) are evident, but they are reduced on the right hemisphere. The dorsal tubercle of the atlas appears reduced and less prominent. **B)** Ventral view: mild evidence of separation between the atlas and occipital bones. Paracondylar processes of the occipital bone (yellow arrows), occupying the fossa of the atlas. **C)** Head, lateral view: limitations between parietal bone to occipital bone (red head arrows) and atlanto-occipital fusion (yellow head arrows). The hypoglossal nerve canal (yellow arrow) is visible at the occipital bone. Notice the marked flexion of the atlanto-occipital joint. **D)** Cerebellar vermis with irregular "S"-shaped configuration.

processes of the occipital bone were occupying the fossa of the atlas, resulting in loss of mobility and marked flexion of the atlanto-occipital joint, with reduction of the occipital cerebellar fossa and moderate stenosis of the foramen magnum (Figures 3B-C). After the removal of the skull cap and exposure of the central nervous system, it was observed that the cerebellar vermis had an irregular S-shaped configuration (Figure 3D). Additionally, there was a complete fracture of the 7th right rib associated with an extensive subcutaneous hemorrhage, pulmonary edema and bronchopneumonia, and multiple gastric ulcerations near the *Margo plicatus*.

Lung, heart, liver, spleen, kidneys, brain, cerebellum, and spinal cord samples were collected, fixed in 10% buffered formalin, embedded on paraffin, and stained with hematoxylin and eosin for subsequent microscopic analysis. Histopathological evaluation revealed, at the cervical spinal cord, pons, and cerebellum (white matter), multiple areas with axonal degeneration, compatible with Wallerian degeneration, characterized by swollen axon, with eosinophilic and homogenized cytoplasm, round in transversal sections (spheroids) and areas with digestion chamber containing axonal fragments and macrophages (Figure 4A and 4B).

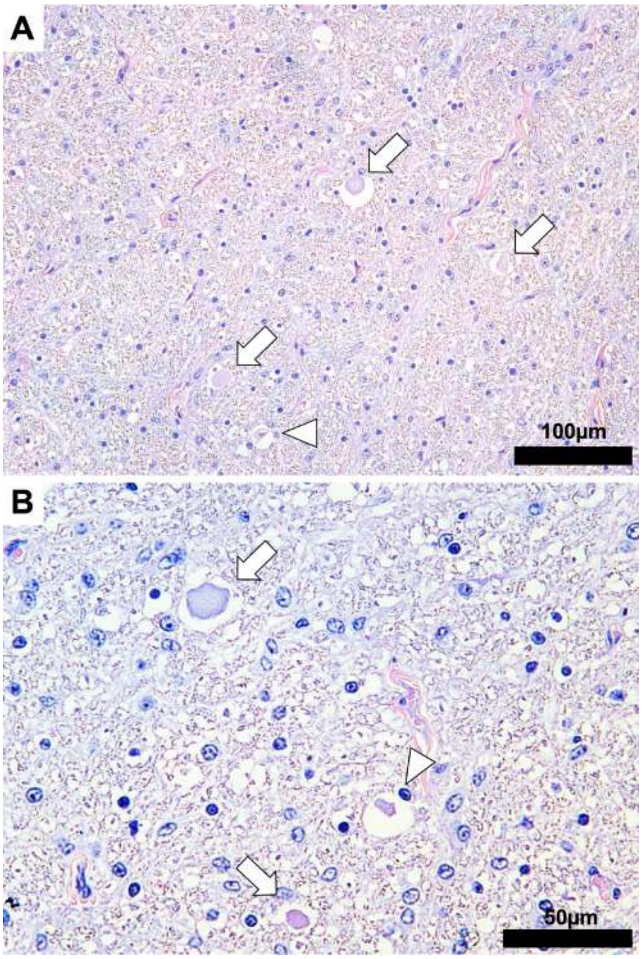

Figure 4. Histopathological findings of a foal presenting congenital occipitoatlantoaxial malformation (OAAM). Cervical spinal cord. White matter presenting axonal degeneration (arrows) and digestion chamber (arrow head). HE, Scale bar: 100µm **(A)** and 50µm **(B)**.

Also, there were marked diffuse splenic lymphoid hypoplasia with mild multifocal neutrophilic splenitis.

For this report, all procedures strictly adhered to humane animal care and all applicable laws and regulations, as well as the journal's ethical policies.

Discussion

To the best of our knowledge, this is the first report of OAAM in Brazilian Sport Horse foal, with a detailed characterization of the clinical and pathological aspects. In this case, the diagnosis was performed based on clinical neurological evaluation, radiographs, and necropsy.

Malformation of the cervical spine in horses is categorized based on anatomical variations and clinical signs (14). Four subtypes of morphological variations have been described: (i) occipitalization of the atlas and atlantization of the axis (more prevalent in the Arabian breed); (ii) congenital asymmetric occipitoatlantoaxial malformation; (iii) asymmetric atlanto-occipital fusion (3). Importantly, all these variations involve some degree of occipitoatlantoaxial fusion (17). In the present case, the foal had congenital asymmetric occipitoatlantoaxial malformation once it was observed that the occipital bone was reduced in size and completely fused to the atlas.

Although genetic causes are a potential etiology reported more frequently in Arabian foals, diagnostic testing is not easily available (19), and was not performed in this case. Nevertheless, another aspect to be considered is the relationship between ICSI and the occurrence of congenital malformations. In humans, multiple factors can influence the outcomes of ICSI, such as the fertility condition of the parents, embryo quality, and the technique employed (26). Lacamara et al. (2017) conducted a systematic review and reported an increase of 7.1% in the risk of having a congenital malformation for individuals conceived by ICSI, compared to 4.0% for naturally conceived children. In equine medicine, establishing the correlation between congenital malformations in horses, as already demonstrated in humans, becomes much more challenging. In the present case, the foal was generated through ICSI. However, no history of congenital alterations from previous offspring of the same parents was reported. Future investigations into the equine population should be encouraged before any correlation or causality should be made.

The clinical signs associated with this condition vary from stillborn foals, tetraparesis at birth, progressive ataxia, congenital cervical scoliosis, and head tilt (3). In this case, the foal presented tetraparesis, spasticity, and asymmetric ataxia, as described in five Arabian foals with the same morphological lesion (3). A clicking sound was heard when the foal extended and raised its neck, signs that may be related to the misalignment between the atlas and axis. The cervical external prominence was attributed to dorsal dislocation of the axis and marked evidence of its spinous process (3).

Ataxia can be explained in this case by the compressive injury secondary to the congenital bony malformation, which leads to axonal degeneration, observed especially at the cerebellum, pons, and cervical spinal cord (13). Compressive changes in the nervous tissue lead to deficits in proprioception and in the animal's ability to maintain a standing position. Wallerian degeneration can occur in cases of neural compression, as in traumatic spinal cord injuries or compressions caused by tumors (28). When a nerve is compressed, its ability to transmit signals is interrupted, leading to degeneration of the nerve axons downstream of the compression site (28). In severe cases, like the present report, degeneration can be irreversible with permanent loss of neural function (20, 28). In this case, the gross findings confirmed the OAAM with atlanto-occipital fusion associated with important histopathological features in the cerebellum, pons, and spinal cord. These pathological findings justify the neurological clinical

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signs such as locomotor abnormalities, increased base for body support, and decreased visual threat reflex (29).

Radiography is a cost-effective and field-accessible examination, often sufficient to establish the diagnosis (30). In this report, the foal had a complete absence of the atlanto-occipital articular space, unidentifiable occipital condyles, and misalignment between the atlas and axis. These radiographic findings contribute to the ante-mortem diagnosis of OAAM (31). Importantly, radiographic positioning must be correct once degrees of obliquity may lead to erroneous clinical interpretations. Myelography and computed tomography can provide additional information about the severity of the lesion but are not essential for reaching a diagnosis (30, 31).

Differential diagnoses for OAAM cases include spinal cord trauma, cervical osteomyelitis, cervical spondylomyelopathy, and cervical vertebral stenosis (3, 14). Equine protozoal myelopathy and type I herpesvirus myelopathy are causes of progressive ataxia in foals but are less common in animals under 12 months of age (3). Treatment for foals with OAAM is not recommended due to the loss of the atlanto-occipital joint, cervical instability, and spinal cord compression (14). Euthanasia was chosen in this case due to the unfavorable prognosis.

The occurrence of OAAM in other breeds, such as Quarter Horse, Warmblood, and Andalusian horses, demonstrates that it is not an exclusively congenital alteration in Arabian foals (3, 13, 14, 20). Therefore, OAAM should also be considered a differential diagnosis in Brazilian Sport Horse foals with neurological signs and cervical pathology.

Conflict of Interest

The authors declare no competing interests.

Author contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by all the authors, more specifically: Silva IE, Rabelo AA, and Torres LE: clinical and radiography evaluation; Silva IE, Fantini P, Miranda ALS and Maranhão RPA: clinical and radiography interpretation, description and review of literature; Nascimento AEJ and Oliveira AR: necropsy and histopathological analysis, interpretation, description and review of literature; Ocarino NM and Serakides R: pathological evaluation and interpretation of the bone malformation; Carretta Junior M: anatomical characterization and interpretation of the bone malformation. The first draft of the manuscript was written by Silva IE and Nascimento AEJ and reviewed by Oliveira AR. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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