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Pathology in Practice

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History

The head and cranial portion of the neck of a 1-week-old sexually intact male polycerate (multihorned; 4-horned in this case) Jacob sheep (*Ovis aries*), the product of a 4-horned ram and a 4-horned ewe breeding, was presented for postmortem examination. The lamb had been born weak and unable to stand. Gradually, the animal lost its ability to eat and died shortly after. This lamb was 1 in a set of triplets. Within the triplet group, 1 lamb was born dead (horn number not specified) and 1 male 4-horned lamb was clinically normal. Breeding of this sire to 5 additional 4-horned ewes in the flock produced 8 lambs (4 clinically normal and 4 clinically affected). Of the 4 clinically affected lambs, 2 were unable to stand at birth. One of these initially recumbent lambs was hand reared, became ambulatory, and survived with persistent hind limb ataxia **(Supplementary Video S1)**. Of the 2 clinically affected lambs able to stand at birth, 1 became recumbent by 1 week of age and was euthanized and the other survived with persistent slight hind limb ataxia, described by the owner as a wobble.

Gross Findings

The head was disarticulated at the atlanto-occipital junction, revealing severe changes in the caudal aspect of the skull. The occipital condyles were moderately irregular and asymmetric, with the left condyle base extending farther ventral than the right condyle **(Figure 1)**. There was medial deviation of the condyles and attenuation of the ventral intercondylar space, resulting in marked foramen magnum narrowing and severe spinal cord compression. The first and second cervical vertebrae were grossly normal.

Formulate differential diagnoses, then continue reading.

R. Trey Callahan, DVM[1]; Abigail R. Armwood, DVM[1]*; Elizabeth W. Uhl, DVM, PhD[1]; Cathy A. Brown, VMD, PhD[2]

[1]Department of Pathology, College of Veterinary Medicine, University of Georgia, Athens, GA
[2]Athens Veterinary Diagnostic Laboratory, Athens, GA

*Corresponding author: Dr. Armwood (abigail.armwood@gmail.com)

https://doi.org/10.2460/javma.20.11.0608

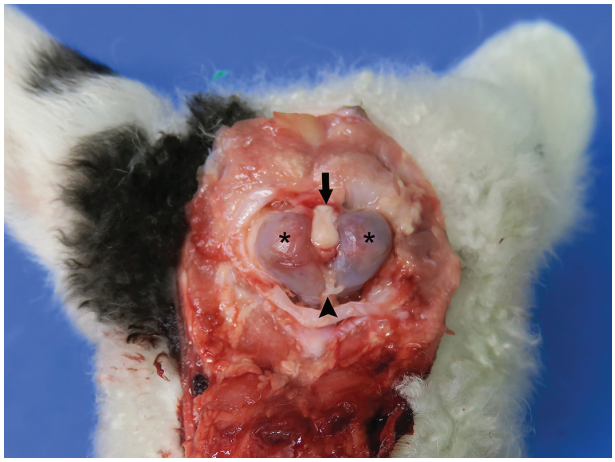

Figure 1—Postmortem image of the caudal aspect of the head of a 1-week-old male 4-horned Jacob lamb (*Ovis aries*) that had been born weak and unable to stand and gradually stopped eating and then died shortly after. The foramen magnum is markedly attenuated due to loss of the normal intercondylar space (arrowhead) and dysplasia of the occipital condyles (asterisks), which are deviated medially, resulting in severe narrowing of the foramen magnum and marked compression of the spinal cord (arrow).

Histopathologic Findings

The cervical spinal cord was moderately compressed at the foramen magnum, with white matter rarefaction. The rarefied areas were consistent with Wallerian degeneration, characterized by variably dilated myelin sheaths, spheroids **(Figure 2)**, and digestion chambers.

Morphologic Diagnosis and Case Summary

Morphologic diagnosis: severe occipital condylar dysplasia resulting in cervical spinal cord compression and axonal degeneration.

Case summary: congenital occipital condylar dysplasia in a 4-horned Jacob sheep.

Comments

The clinical history and pathological findings for the lamb of the present report were characteristic of congenital occipital condylar dysplasia (OD). Although lay sheep owners and previous publications

refer to occipital condylar dysplasia as OCD, the malformation is not necessarily limited to the condyles and the acronym OCD may be confused with the more common bone disease, osteochondritis dissecans. Occipital condylar dysplasia is described in Jacob sheep exhibiting the polycerate phenotype; however, to our knowledge, few reports[1–3] of the clinical signs and pathological findings exist. These reports[1–3] describe 5 cases of OD in polycerate Jacob sheep. Other craniocervical malformations have been described, including a congenital occipitoatlantoaxial malformation in a 9-week-old Suffolk-cross lamb,[4] vertebral canal stenosis in a 10.5-month-old Suffolk ram,[5] and a cervical deformity in a Columbia-cross lamb.[6] In an Australian study,[7] 210 of 401 (52.4%) congenital abnormalities in malformed lambs involved the skeletal system, suggesting that congenital skeletal malformations are relatively common.

Although the exact pathogenesis of OD is unknown, the malformation is only described in sheep with the polycerate phenotype, suggesting a pathogenesis related to genetic selection.[1–3] Anecdotal evidence suggests that the polycerate trait is dominant and that the 2-horned condition is recessive.

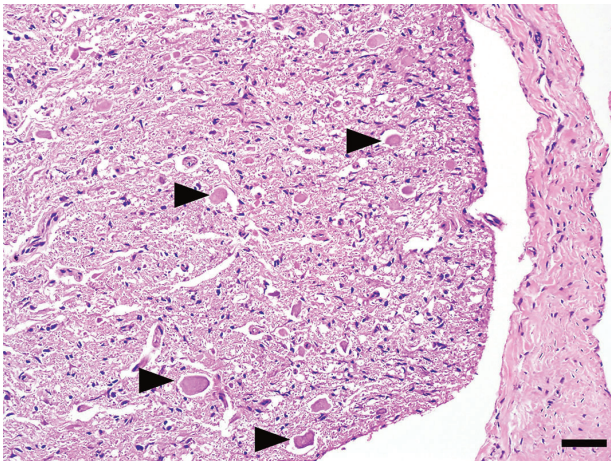

Figure 2—Photomicrograph of a section of the spinal cord at the level of the foramen magnum from the lamb described in Figure 1. Vacuolated areas of the white matter were characterized by variably dilated myelin sheaths, often containing swollen, round, eosinophilic axons consistent with spheroids (arrowheads) or rarely fragmented axons with Gitter cells. H&E stain; bar = 50 µm.

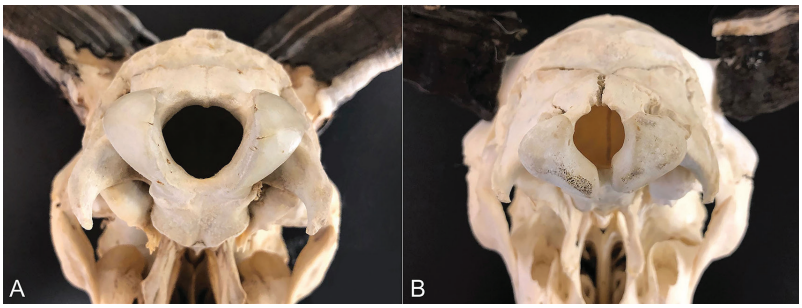

Figure 3—Photographs of the caudal aspects of the skulls of a 2-horned adult Jacob sheep with anatomically normal skull structure (A) and a 4-horned adult Jacob sheep with a narrow foramen magnum and marked condylar asymmetry, consistent with congenital occipital condylar dysplasia (B).

Although the responsible gene has not been definitively identified, a single locus on chromosome 2, separate from the gene associated with the absence of horns, appears to be responsible for the polycerate trait. Known as the *HoxD* cluster, it is likely associated with horn ontogenesis and involved in the malformation.[8] Additionally, eyelid malformations are observed in polled and polycerate Jacob sheep, suggesting normal eyelid development may be related to the 2-horn trait.[8] Interestingly, clinically unaffected polycerate Jacob sheep can have mild occipital condylar asymmetry, supporting evidence that OD is related to the polycerate phenotype gene but has variable genetic penetrance with differing degrees of phenotypic expression.[3]

Although additional lambs from this flock were not necropsied, this 4-horned ram produced both clinically normal and affected 4-horned lambs with ambulatory abnormalities ranging from hind limb ataxia to tetraparesis. This finding further supported that OD has a complex inheritance pattern, as epigenetic factors or other genes in addition to the polycerate gene may also be involved. Although half of the 4-horned lambs from the same sire of the lamb of the present report were clinically affected, OD is more commonly a sporadic event that affects a single lamb. Jacob sheep originate from a relatively small genetic pool; however, this ram was newly acquired on the farm and was not related to this ewe by at least 4 generations. The ewes had previously produced clinically normal 4-horned lambs. This sire was subsequently culled. Other phenotypic features (eg, 4 incompletely formed or malpositioned horns) may be associated with OD (personal observation of author CAB). Identification of a genetic mutation or mutations and epigenetic factors would help prevent OD perpetuation by breeders. Collection of whole blood, liver, ear notch, or tail hair samples for DNA assessment from affected animals and their relatives may aid in identification of the responsible gene or genes.[9] Nutritional disease does not appear to be associated with OD, as 4-horned animals from a wide geographic distribution are affected and only polycerate animals are affected. The flock of the lamb of the present report was on pasture with supplemental hay and access to a sheep-specific mineral block.

Clinical signs reported in OD lambs are consistent with cervical myelopathy secondary to cervical spinal cord compression, including hind limb ataxia, ataxia in all 4 limbs, or paresis.[1–3] Not all animals with lesions consistent with OD are affected neurologically, as condylar malformations may be subtle and not result in clinical disease.[3] Moreover, the severity of the condylar abnormalities may not correlate to the neurologic disease severity. Rather, clinical disease is linked to the degree of foramen magnum narrowing and associated spinal cord compression.

Other differential diagnoses based on clinical signs alone included congenital lysosomal storage diseases (eg,

G_{M2} gangliosidosis[10]), neonatal copper deficiency, trauma, vertebral subluxation or other vertebral malformations, wobbler syndrome,[11,12] or infectious diseases, including but not limited to spinal abscesses, toxoplasmosis, otitis media, Schmallenberg virus, or pestivirus. Unlike OD, G_{M2} gangliosidosis (an autosomal recessive lysosomal storage disease) typically presents in animals > 6 months old.[10] Additional ancillary procedures, such as fluorescent antibody testing, PCR assay, culture, and radiography, can exclude other differential diagnoses. Computed tomography provides detailed imaging, facilitates measurements of the occipital condyles, and can help diagnose OD antemortem or provide additional information during postmortem examination.[2,3]

Gross changes vary extensively between affected animals **(Figure 3)**. Anatomic changes range from mild condylar asymmetry and narrowing of the foramen magnum to extensive angular condylar abnormalities and marked attenuation of the foramen magnum, as seen in this case. Though the malformation was limited to the occipital condyles in the lamb of the present report, affected polycerate sheep can have other clinically important noncondylar abnormalities, including misshapen craniocervical vertebrae, lateral deviation of areas of the skull, and asymmetry of other craniofacial bones, such as the bullae and paracondylar processes.[3] Because a genetic mutation has not yet been identified, the diagnosis of OD is based on the gross changes in correlation with the signalment, clinical signs, and gross spinal cord compression at the foramen magnum.

Histologic changes in OD are nonspecific and consistent with those seen in any compressive spinal cord injury. The physical compression of the spinal cord leads to Wallerian degeneration of the white matter.[2,3] Axonal degeneration can manifest clinically on a spectrum from ataxia to the inability to stand, as seen in the lamb of the present report. As histologic changes in OD are generally nonspecific, gross examination is essential for the definitive diagnosis.

Due to the increasing popularity of 4-horned Jacob sheep, especially within the US, it is vital to increase awareness of OD among farmers, breeders, clinical veterinarians, and diagnosticians. Congenital occipital condylar dysplasia is an important differential for neurologic disease and ataxia, especially in young Jacob sheep with the polycerate phenotype, and can be misdiagnosed if the involved veterinarians and pathologists are uninformed of the disease. By increasing awareness, breeders and veterinarians can mitigate the potentially heritable disease to avoid unnecessary perpetuation of the condition. Additional research is necessary to characterize the prevalence and pathogenesis of and potential genetic mutation or mutations associated with OD in polycerate Jacob sheep.

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Supplementary Materials

Supplementary materials are posted online at the journal website: avmajournals.avma.org