Occipital condylar dysplasia in a Jacob lamb (*Ovis aries*)

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Abstract

Jacob sheep (*Ovis aries*) are a pedigree breed known for their “polycerate” (multihorned) phenotype. We describe a four-horned Jacob lamb that exhibited progressive congenital hindlimb ataxia and paresis, and was euthanased four weeks post-partum. Necropsy and CT-scan revealed deformity and asymmetry of the occipital condyles, causing narrowing of the foramen magnum and spinal cord compression. Histopathology demonstrated Wallerian degeneration of the cervical spinal cord at the level of the foramen magnum. These findings are consistent with occipital condylar dysplasia. This condition has been infrequently reported in the literature as a suspected heritable disease of polycerate Jacob sheep in the USA, and is assumed to arise during selection for the polycerate trait. This is the first reported case in European-bred Jacob sheep. Occipital condylar dysplasia should be considered as a differential diagnosis in polycerate Jacob lambs showing ataxia. It is important to raise awareness of this disease due to its suspected heritability and link to the popular polycerate trait.

Keywords: Ataxia, Congenital, Jacob sheep, Occipital condylar dysplasia, Polycerate.

Introduction

Jacob sheep are a popular pedigree/ornamental breed used for meat production and as a source of high-quality wool. There are approximately 8,000 Jacob sheep registered with the European-based Jacob Sheep Society (mainly in the UK and Ireland) with approximately 3,000 new lambs registered annually (Richardson, 2016). In the USA, there were over 10,000 Jacob sheep registered with the Jacob Sheep Breeder’s Association in 2006 (Jacob Sheep Breeders Association, 2009).

An important heritable condition in this breed is Gm2 gangliosidosis (Tay-Sachs disease) and a diagnostic test has recently been developed to facilitate its elimination from affected flocks (Lewis *et al.*, 2014). Another potentially heritable condition of this breed, known as “occipital condylar dysplasia” has been reported in a total of four Jacob sheep in the scientific literature, and (to the authors’ knowledge) only in the USA (Johnson *et al.*, 1994; Ellis and Brown, 2014). However, there is anecdotal awareness of this condition among the American Jacob sheep-breeding community (Ellis and Brown, 2014). It is assumed to be a genetic defect (possibly resulting from selective breeding for the polycerate phenotype) as it appears to occur exclusively in four-horned sheep (Ellis and Brown, 2014). This is the first reported case of the condition in Europe. It is important to raise awareness among veterinarians and breeders of the possible existence of another potentially-heritable condition in this increasingly popular breed, in order that it be monitored and controlled if necessary.

Case details

**History, clinical findings, treatment**

The animal in question was a pedigree, four-horned male Jacob lamb with a history of progressive congenital ataxia. It was a twin lamb born to a primiparous two-year-old ewe, and its female twin and both parents were clinically normal. There was no flock history of ataxia or other neurological signs, and the lamb’s dam and grand-dam were home-bred. Its mother’s dam produced 11 healthy lambs (seven females of which are still present in this flock, and have never produced lambs with signs of occipital condylar dysplasia).

The sire was used for breeding for the past four years within this flock, and had sired 21 clinically-normal registered lambs at the time of this lamb’s birth. Before breeding, the lamb’s mother was treated with an intravaginal progesterone-soaked sponge to induce oestrus. The sire was the only ram who had access to her at the time of oestrus, and both were housed together in a well-secured shed. All ewes were routinely supplemented with copper, selenium, cobalt, potassium iodide and vitamins A, D3, E, B1 and B12, and both parents were tested and found to be negative for the causative mutation of Gm2 gangliosidosis.

The lamb in question displayed mild, bilateral, symmetrical hindlimb ataxia and paresis at birth, which worsened with age until falling and difficulty rising from recumbency were frequently observed. Low head carriage was also noted. The animal remained bright, alert and able to feed. The referring practitioner (a first-opinion mixed-practice veterinarian) performed a...
limited on-farm neurological examination, and no cranial nerve/postural reaction deficits were noted. Therefore the lesion was presumptively localised to the spinal cord.

The principal clinical differential diagnoses included copper deficiency and spinal abscess or trauma. Less likely differentials (given the genetic status of the lamb’s parents and knowledge of endemic infectious diseases) were GM2 gangliosidosis, infectious diseases causing congenital skeletal/cerebral malformations (e.g. Schmallenberg virus, Border disease), and other infectious conditions such as enterotoxaemia, toxoplasmosis, or otitis media.

The lamb was treated with copper methionate 20 mg/ml (0.5 ml, Ballinskelligs Vet. Products Ltd), amoxicillin-clavulanic acid 140/35 mg/ml (8.75 mg/kg, Noroclav Injection, Norbrook Laboratories Limited) and dexamethasone 2 mg/ml (1 mg/kg, Colvasone, Norbrook Laboratories Limited) for four consecutive days. Despite treatment, at four weeks of age, the lamb became recumbent and euthanasia was elected on humane grounds.

The lamb was submitted for post-mortem examination to the University College Dublin Veterinary Hospital.

**Gross post-mortem examination**

A routine, complete necropsy examination was carried out. The lamb was in good body condition, with no appreciable external conformational abnormalities. Upon dissection of the skull and spinal column, both occipital condyles were found to be markedly distorted, asymmetrical, and deviated to the right (Fig. 1).

The corresponding articular facets of the atlas were irregular in appearance, with the left facet located slightly caudal to the right. The cartilage of the articular surfaces was multifocally roughened and irregular in thickness.

The brain appeared normal in size and morphology, with no appreciable abnormalities common to teratogenic viral infections, and no macroscopic evidence of inflammation. The cervical spinal cord was narrow and bilaterally compressed in cross-section at the foramen magnum. No other gross abnormalities were present in the remaining vertebral column or spinal cord, or other tissues examined grossly at necropsy.

**CT-scan**

For better visualisation and accurate measurement of the condylar pathology, a CT-scan of the skull of the lamb was carried out subsequent to dissection using a 4 slice multi-detector (Somatom Sensation 4, Software version A40, Siemens, Germany; Fig. 2).

![Fig. 2. CT-scan of skull (ventral aspect). Both condyles are asymmetrical, irregular, and deviated to the right.](image)

The left condyle was found to measure 16.16 mm rostral to caudal x 11.4 mm wide x 13.7 mm high and extended caudoventromedially to form an angle of 41° with the nasal septum, 42° with the vertical ramus of the left mandible and 58° with the hard palate. The right condyle (measuring 11.86 mm rostral to caudal x 7.9 mm wide x 9.2 mm high) had a more flattened articular surface and extended caudoventrolaterally to form an angle of 42° with the nasal septum, 50° with the vertical ramus of the right mandible and 45° with the hard palate. At the rostral aspect of the occipital condyles, the foramen magnum measured 16.5 mm wide.

![Fig. 1. Dorsal view of skull, crown removed. Vertical line indicates normal orientation of midline. Here, there is marked lateral deviation of the foramen magnum and occipital condyles.](image)
Histopathologic examination
For histopathological evaluation, following routine fixation in 10% neutral buffered formalin, brain, spinal cord and occipital condyles (decalcified) were embedded in paraffin wax and sectioned at 5μm. Sections were stained with Gill®-2 Haematoxylin and Eosin (HE) and Luxol fast blue (Bancroft and Gamble, 2002). On histopathologic examination of the central nervous system, the principal lesions were observed in the cervical spinal cord at the point of compression (the foramen magnum). Here, the central canal appeared compressed and rectangular in cross-section. The ventral medial fissure was deviated laterally by approximately 5° from the vertical in cross-section (Fig. 3).

There was marked dilation (ballooning) of the myelin sheaths with occasional fragmentation, affecting mainly the ventral and lateral funiculi. These dilated sheaths contained multifocal, swollen, irregular, spherical, pale, amorphous eosinophilic degenerate axons (spheroids). Low numbers of myelin sheaths contained one or more microglia with moderate amounts of eosinophilic foamy cytoplasm (Fig. 3, inset). Marked loss of myelin in these areas was seen on Luxol fast blue stain (Fig. 4). These changes are characteristic of Wallerian degeneration. Digestion chambers were observed in longitudinal sections. The spinal cord grey matter was unaffected. Similar, less marked changes were present in the dorsal funiculi. Similar degenerative axonal changes were observed throughout the cervical, thoracic and lumbar spinal cord, becoming progressively less severe towards the caudal aspect of the cord.

Fig. 3. Cross section of cervical spinal cord at the level of the foramen magnum; (4-week-old Jacob lamb with occipital condylar dysplasia.) 5° deviation of the ventral fissure from the midline and marked vacuolation of white matter in the ventral and lateral funiculi, inset; Wallerian degeneration seen as dilated myelin sheets containing spheroids (arrow) and microglia (arrow head), H&E.

Fig. 4. Cross-section of cervical spinal cord at the level of the foramen magnum; (4-week-old Jacob lamb with occipital condylar dysplasia). On Luxol fast blue stain, myelin fibres appear blue, neuropil appears pink and nerve cells appear purple. Marked loss of myelin in white matter in the ventral and lateral funiculi. Inset; dilated myelin sheaths contain no myelin or only little clumped remnants of myelin (arrowheads). Luxol Fast Blue.

No inflammatory changes or lesions indicative of lysosomal storage disease or copper deficiency were present. Histopathology of the occipital condyles revealed normal endochondral ossification. No pathological changes were found on histologic examination of the brain.

Ancillary tests
Genetic analysis, as described by Torres et al. (2010), was conducted on DNA extracted from hepatic tissue by LGC (Herts, UK). The lamb was found to have homozygous G at nucleotide position 1330 of the hexa cDNA and therefore did not show the GM2 gangliosidosis mutation. Liver copper values were within normal limits (1.2 mmol/kg; reference range: 0.06 - 2.5 mmol/kg). Routine PCR on frozen lamb liver tissue for pestivirus, Bluetongue virus and Schmallenberg virus were negative. Based on these findings, a diagnosis of occipital condylar dysplasia was made.

Discussion
The gross condylar lesions described above (asymmetry and distortion) closely resemble previous occipital condylar dysplasia cases (Johnson et al., 1994; Ellis and Brown, 2014). Johnson et al. (1994) described the disease in two lambs in Missouri. It was also reported in two lambs in Georgia, in a poster presentation by Ellis and Brown (2014). The main difference between the present case and previous reports was that one of the lambs described by Ellis and Brown (2014) developed clinical signs at four months of age (as opposed to at birth). However, the overall similarities in clinical presentation and pathologic findings suggest a common aetiology and pathogenesis. The atlanto-occipital joint forms part of the craniovertebral junction, consisting of the occiput,
atlas, axis and their supporting ligaments. It encloses the structures of the cervicomедullary junction (medulla, spinal cord and lower cranial nerves) (Smoker, 1994).

In general, craniovertebral junctional anomalies occur sporadically in most species, and defects affecting the atlanto-occipital joint in isolation are infrequent (Johnson et al., 1994). There are several well-described familial pathologies of animals affecting the craniovertebral junction, including Chiari-like malformation in Cavalier King Charles Spaniels (Loughlin, 2016), atlantoaxial instability in toy dogs (Slanina, 2016), occipitoatlantoaxial malformation in Arabian horses (Watson and Mayhew, 1986), and complex vertebral malformations in Holstein calves (Agerholm et al., 2001). Atlanto-axial instability is also a characteristic of humans with Down syndrome (Pueschel et al., 1981; Burke et al., 1985). Reported craniovertebral anomalies of sheep include vertebral canal stenosis in Suffolks (Palmer et al., 1981; Jackson and Palmer, 1983), occipitoatlantoaxial malformation in a Suffolk-cross lamb (Schmidt et al., 1993), and dens hypoplasia in a Columbia-cross lamb (Parish et al., 1984). However, occipital condylar dysplasia appears to be specific to Jacob sheep. Occipital condylar dysplasia (“coconut condyle”) has only been reported in humans as a single case report (Halanski et al., 2006).

The observed clinical signs (progressive hindlimb ataxia and paresis) were consistent with cervical spinal cord compression and subsequent Wallerian degeneration, and occur non-specifically in many of the craniovertebral junction disorders mentioned previously. Cord compression was observed grossly at the foramen magnum, and histopathological examination revealed lesions typical of compressive spinal injury (Summers et al., 1995). A number of potential clinical differential diagnoses were considered in this case. One of these was “swayback/enzootic ataxia” (copper deficiency). Clinical signs include progressive paraparesis, hyporeflexia and muscle atrophy, and it is caused by inadequate copper intake by the dam in pregnancy (Thomas, 2016). Congenital swayback can manifest grossly as bilateral, symmetrical cerebral cavitation, or be restricted to histological changes: degeneration of neurons in the red, lateral vestibular, medullary reticular, and dorsal spinocerebellar nuclei in Clarke’s column, and in the spinal motor neurons, and also Wallerian degeneration of dorsolateral and ventromedial spinal cord tracts (Cantile, 2016). Again, this diagnosis was unlikely due to the history of copper supplementation, lack of typical gross and/or histological lesions, and the liver copper analysis results. Spinal abscess or trauma were among other clinical differential diagnoses.

However, the lamb failed to respond to antibiotics and anti-inflammatory treatment, rendering this diagnosis less likely. It had been kept indoors since birth due to ataxia, thus reducing the likelihood of tick bites and subsequent abscessation, and precautions were taken to prevent omphalitis. However its tail had been docked by rubber-ring, providing a potential entry portal for pathogens. There was no history of spinal injury and no lesions consistent with injury (e.g. vertebral fracture, penetrating foreign body) or spinal abscess found at post-mortem. A further clinical differential was the lysosomal storage disease, $G_{M2}$ gangliosidosis. This has recently been described in Jacob sheep in the UK and USA (Torres et al., 2010; Porter et al., 2011; Wessels et al., 2014).

$G_{M2}$ gangliosidosis manifests as progressive ataxia in six-to-eight month-old lambs, and progresses over a period of ten days to eight weeks. Clinical signs include fore- and hind-limb abduction, ataxia and recumbency, as seen here. Histologically, neuronal cell bodies throughout the CNS are markedly distended with pale amphophilic granular material or microvacuolar change (Wessels et al., 2014). However, this was not the cause of disease in this case, as both of this lamb’s parents and the lamb itself tested negative for carrier mutations, the neurological signs occurred immediately after birth, as opposed to at several months old, and no typical histological lesions were present. Certain teratogenic viruses (e.g. Schmallenberg, Bluetongue, Border disease virus, Akabane disease virus, Wesselsbron virus etc.) can cause congenital neuronal malformations and/or abnormalities in multiple axial and appendicular bones, leading to congenital neurological signs and skeletal defects in affected neonates (Dittmer and Thompson, 2015). However, many of these viruses are exotic to Ireland (e.g. Bluetongue, Akabane disease virus, Wesselsbron virus) so were not considered likely differentials. Schmallenberg virus and Border disease virus are present in Ireland, and both diseases may cause a variety of gross cerebral defects, (e.g. hydrocephalus, hydranencephaly, porencephaly, microcephaly, cerebellar hypoplasia). In the case of Schmallenberg disease, skeletal defects (brachygnathia, arthrogryposis, kyphosis, scoliosis, torticollis, lordosis, cleft palate) are often present (Herder et al., 2012; Dittmer and Thompson, 2015). However, a single focal lesion at the level of the occipital condyles would be a highly unusual presentation of Schmallenberg virus. Additionally, this animal did not display the characteristic hairy coat or tremors of a lamb with congenital Border disease infection. It is also unlikely that these infectious diseases would only affect one animal in a flock (Dittmer and Thompson, 2015), for the lambs’ twin to be clinically normal, and for PCR on liver tissue for
Border disease virus, Schmallenberg virus and Bluetongue virus to be negative. Other infectious diseases that cause neurological signs in young lambs, such as enterotoxaemia, toxoplasmosis and otitis media, were ruled out based on the absence of typical gross and histological findings. The Jacob breed is polycerate, and to date occipital condylar dysplasia has only been reported in four-horned sheep (Johnson et al., 1994; Ellis and Brown, 2014). In addition, mild condylar asymmetry was observed in six out of eight clinically-affected polycerate Jacob skulls (Ellis and Brown, 2014). This suggests that while there appears to be an association with the polycerate gene, which is dominant over the two-horned phenotype (Kijas et al., 2016), the penetrance is variable. In the present case the sire consistently produced clinically-normal lambs for four years, and while the home-bred dam was primiparous, she and the affected lamb’s twin sibling were healthy. This suggests occipital condylar dysplasia is not a simple autosomal trait, and more research is needed to ascertain its mode of inheritance. It also raises the possibility that this case was caused by a sporadic mutation with no genetic background, given the lack of family history.

A recent genome-wide association study (GWAS) on the polycerate Jacob and Navajo-Churro sheep breeds has linked this trait to single nucleotide polymorphisms (SNPs) in a non-coding region of chromosome 2, upstream of the Homeobox D (HOXD) gene cluster (Kijas et al., 2016). These genes control anterior-posterior body axis and appendage development (Lemons et al., 2005). Two separate GWASs examining different polycerate sheep breeds drew similar conclusions (Greyvenstein et al., 2016; Ren et al., 2016). It is therefore tempting to speculate that OCD may be linked to alteration of HOXD gene expression by polycerate-associated SNPs. Indeed, it has been found that HOXD11 mutant mice exhibit supernumerary lumbar vertebrae, indicating that HOXD gene expression anomalies can affect vertebral column development (Davis and Capecchi, 1994). Interestingly, an association has been found between four-horned and polled phenotypes and the presence of “split-eyeId abnormalities”, which also sporadically occur in Jacob sheep (Kijas et al., 2016). This indicates that deviations from the “normal” two-horned state may be linked to abnormalities in various anatomical regions.

To the author’s knowledge, occipital condylar dysplasia has not been reported in other polycerate sheep breeds and the incidence in Jacob sheep appears low. Given the existence of pro-active breed societies who are tackling the elimination of Gm2 gangliosidosis, the paucity of occipital condylar dysplasia reports is striking and may be due to low incidence combined with misdiagnosis. Misdiagnosis may be explained by the non-specific clinical signs, similar to other neurologic conditions of lambs and to Gm2 gangliosidosis. It has been shown that the American Jacob sheep population exhibit a striking genetic divergence from other breeds, and that their inter-breed genetic diversity is low (Kijas et al., 2016). It is thought that Gm2 gangliosidosis was brought to the USA by a carrier ram from the UK (Wessels et al., 2014), and it is likely that the gene pool of American Jacob sheep is quite small, as the population arose from a relatively low number of sheep imported from Europe (Jacob Sheep Conservancy, 2016). This may explain why occipital condylar dysplasia thus far appears more prevalent in the USA than Europe.

Occipital condylar dysplasia should therefore be considered by breeders, veterinarians and pathologists as a differential diagnosis in Jacob lambs with ataxia. The molecular pathogenesis and prevalence of this condition require further investigation. This will help improve our understanding of rare-breed sheep genetics and guide future breeding decisions. Future investigations may also shed light on aspects of embryology that are relevant to both animals and humans.

Conflicts of Interest
The authors declare that there is no conflict of interest.

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