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<b>TITLE OF CASE</b> <i>Do not include "a case report"</i>
Multiple Congenital Ocular Abnormalities Including Microphthalmia, Microphakia and Aphakia, in a Simmental-cross Bull
<b>SUMMARY</b> <i>Up to 150 words summarising the case presentation and outcome (this will be freely available online)</i>
A twenty month old Simmental-cross bull presented to the Scottish Centre for Production Animal Health and Food Safety (SCPAHFS), University of Glasgow School of Veterinary Medicine in April 2015 with multiple congenital ocular abnormalities including bilateral microphthalmia. We present this case as an interesting presentation of idiopathic multiple congenital ocular abnormalities in the absence of congenital abnormalities affecting other body systems. This case highlights an unusual ocular presentation and illustrates the importance of a thorough clinical examination. The prognosis for cases of multiple congenital ocular abnormalities including microphthalmia is poor as no treatment is available and welfare is often compromised. It is therefore important that cases are accurately diagnosed so appropriate management decisions can be made regarding the individual and any herd investigations that are required can be instigated.
<b>BACKGROUND</b> <i>Why you think this case is important – why did you write it up?</i>
A number of congenital ocular abnormalities have been described in cattle (1–3) and the reported incidence varies from 1 in 2800 births (4) to 1 in 50,000 births (1). Microphthalmia has been described both in conjunction with other congenital ocular abnormalities (5) and also associated with congenital abnormalities affecting other body systems in cattle (6,7). We present this case of microphthalmia with concurrent aphakia, microphakia and retinal dysplasia in a Simmental-cross bull. We believe this case is an important illustration of a congenital abnormality that may be seen in practice both in the presence of or in the absence of other congenital abnormalities. As in this case, it may not be immediately apparent

that microphthalmia is present if the globes are obscured by conjunctiva, or if the palpebral fissure is similarly reduced in size; concurrent congenital ocular abnormalities may not be obvious without further examination.

## **CASE PRESENTATION** *Presenting features, clinical and environmental history*

A twenty month old Simmental-cross bull presented to the Scottish Centre for Production Animal Health and Food Safety (SCPAHFS), University of Glasgow School of Veterinary Medicine for investigation into bilateral ocular abnormalities. The farmer reported there had been gradual expansion of the bulbar conjunctivae causing the globes to become obscured and the vision to be impaired; mild abnormalities were first noticed when the bull was approximately six months old and had become more evident as the bull aged.

The animal was a homebred beef suckler bull calf out of a bought-in Simmental cross cow. The dam had successfully reared calves previously and no congenital abnormalities had been noted in any of the dam's progeny. The sire was presumed to be a Simmental stock bull that had been on the farm for the past eight years and had consistently produced healthy offspring; however, there was a possibility that the cow could have been mis-mated by a bull calf kept on the farm from the previous year. The cow was housed for the duration of pregnancy and had been fed a home produced ration of bruised barley, sugar beet pulp, soya coarse mix and *ad libitum* big bale silage. The calf was born towards the end of the 2014 calving period (June – August) and had been housed since birth due to the fact it was born to an older cow (14 years old) and was reported by the farmer to be slow to suckle. Aside from its visual deficits, the animal had otherwise been well and, although small for its age, was not ill-thriven; this is attributed to assistance from the farmer who had been feeding the animal separately after weaning (at 9 months old) to prevent bullying from others in the group. In order to facilitate individual feeding, this bull remained housed until it's admission to the SCPAHFS.

The herd had Bovine Viral Diarrhoea (BVD) negative status in accordance with the Scottish government BVD eradication scheme (8) and a vaccination programme had been in place on the farm since approximately 2003. There was no nose to nose contact with any neighbouring cattle and overall general health status of the herd was reported to be good.

### **Clinical Examination**

On admission the animal was bright and alert. General clinical examination was unremarkable; heart rate, respiratory rate and rectal temperature were all within normal limits. Appetite and thirst were normal. Behaviour consistent with bilateral visual deficits was displayed when the bull was initially moved into unfamiliar surroundings; however, once habituated to the environment, visual deficits became less evident.

The right eye was completely obscured by conjunctiva when at rest, and the globe appeared to be ventrally rotated (Figure 1); the soft tissues could be manually displaced to enable the globe to be visualised. The left eye also had protruding conjunctival tissues, but this eye was less severely affected and the globe was visible when the bull was at rest (Figure 2). Ocular examination revealed an absence of menace response in both eyes. A normal pupil could not be identified in either eye therefore pupillary light reflexes could not be assessed. Palpebral reflexes were normal in both eyes and there were no other cranial nerve deficits evident on clinical examination. The eyelids and palpebral fissure of the right eye appeared to be normal, however the palpebral fissure appeared to be reduced in size in the left eye. Unilateral epiphora was present on the right-hand side; this was attributed to tear overflow resulting from tear duct occlusion by the expansive bulbar conjunctiva on this side.

## **INVESTIGATIONS** *If relevant*

### **Ante-mortem Investigations**

Routine serum biochemistry and haematology did not reveal any significant abnormalities. This bull was serum enzyme-linked immunosorbent assay (ELISA) BVD antibody and antigen negative.

### *Ultrasonography*

The bull was sedated with xylazine at a dose rate of 0.1mg/kg (Rompun; Bayer Animal Health, Newbury, Berkshire, UK) given by deep intramuscular injection. Ultrasound examination of both globes was performed using a 7.5MHz linear transducer (Shantou Institute of Ultrasonic Instruments Co., Ltd [SIUI], Guangdong, China) as previously described (9). Significant abnormalities were identified bilaterally and no normal ultrasonographic findings were evident in either eye. Both globes were small and abnormally shaped, and the lens could not be identified in either eye.

### **DIFFERENTIAL DIAGNOSIS *If relevant***

### **TREATMENT *If relevant***

No treatment is available for microphthalmia and the decision was made to euthanase this bull due to the ultimately poor prognosis in this case.

### **OUTCOME AND FOLLOW-UP**

#### **Post-mortem Investigations**

##### *Magnetic Resonance Imaging (MRI)*

MRI imaging of the head was performed immediately post-mortem. Transverse, sagittal and dorsal T2 weighted (T2W) images of the brain and transverse T2W images of the orbits and optic nerve were obtained. MRI confirmed the clinical and ultrasonographic findings of bilateral microphthalmia and abnormal shape of both globes.

Both globes were localised within the ocular orbit and bilateral enophthalmic positioning was evident (Figure 3). Moderate, generalised atrophy of the extraocular muscles was present, involving the rectus muscles (dorsal, ventral, lateral and medial), oblique muscles (dorsal and ventral) and retractor bulbi muscle. There was also an increase in hyperintense material surrounding the eyeballs and in the retrobulbar space consistent with fat tissue. Bilaterally, the globes were irregularly shaped and markedly small (Figure 3). The internal structural anatomy of the left eye was somewhat preserved with distinction between the anterior and posterior vitreous segment; however, the volume of the material within the anterior and posterior segment was markedly reduced. On the dorsal sequences there were two ill-defined hypointense curved lines with a “seagull” shape in the left eye converging at the level of the optic disc, consistent with retinal detachment. Subjectively, bilateral hypoplasia of the optic nerve and optic chiasm appeared to be evident. Imaging of the brain did not reveal any abnormalities.

##### *Necropsy*

On post-mortem examination of the animal, both eyes were markedly smaller than normal. The right globe appeared partially ventrally rotated within the orbit and was covered by adipose tissue of the retrobulbar orbital space. On cut section, the components of the eye were disorganised in both eyes and a clear pupil was not evident in either eye. The lens of the left eye was absent (aphakia), and the lens of the right eye was very small (microphakia). In the right eye, the sclera and the choroid were markedly thickened, and the retina was disorganised and folded. The anterior segment and the vitreous cavity were completely obliterated (Figure 4). The left eye was abnormal in shape, the sclera was also markedly thickened, the retina disorganised, and the anterior and posterior chambers and vitreous cavity were markedly reduced in size. No macroscopic abnormalities were detected in the optic nerves, the brain or any other organ.

### *Histology*

A number of abnormalities were identified on histological examination. Microscopically, the cornea of the right eye was undulating, exhibited moderate stromal neovascularisation and pigmentation, and was infiltrated by moderate numbers of neutrophils and fewer lymphocytes and plasma cells. There was a focal rupture of Descemet's membrane with apparent associated migration of endothelial cells into the membrane defect. The sclera was markedly thickened and composed of haphazardly arranged dense collagen. The anterior chamber was narrow and the lens of the right eye was irregular, small, degenerate and compressed by the displaced retina (Figure 5). A folded and ruptured capsule and cataractous changes with mineralisation were evident, as was a focal posterior synechia (Figure 6). At the base of the iris, the iridocorneal angle was abnormal, with only a small portion of a residual ill-defined and largely obliterated trabecular meshwork. The choroid was markedly oedematous with prominent dilation of vascular channels. Fibrosis and occasional aggregates of lymphocytes were also observed. The retina was detached from the choroid, filling the vitreous, and was markedly folded and disorganised (Figure 5). There was extensive disruption and loss of retinal pigment epithelium, extensive disarray and depletion of the inner and outer nuclear layers with absence of photoreceptors, and disorganisation and degeneration of the ganglion cell layer, with presence of numerous cells with microscopic features suggestive of glial elements. Blood-filled irregular cystic spaces were present in the disorganised retina, some of them partially lined by retinal pigment epithelium.

Prominent changes were also present in the left eye. The lens was absent, and the retina was extensively detached from the choroid and markedly dysplastic, with formation of cystic spaces, and a small focus of mineralisation. There was a small focal lymphocytic aggregate in the choroid in the posterior segment and the choroid was irregularly expanded by oedema. In a focal area between the dysplastic retina and the choroid there was a small focal deposit of trabecular bone lined by well differentiated osteoblasts, associated with a small lobule of well differentiated adipocytes, consistent with ectopic bone and adipose tissue or osseous/fatty metaplasia. There was obliteration of the irido-corneal filtration angle and formation of small cysts in the posterior pigmented iris epithelium. In the cornea, the Descemet's membrane appeared intact with a focal area of thinning/attenuation in the central portion.

No microscopic changes were found in the right and left optic nerves. Very few aggregates of glial cells were noted in the optic chiasm.

### *Possible aetiopathogenesis*

In cattle, there are reports of congenital ocular abnormalities (including microphthalmia) associated with *in utero* infection with BVD virus (10–13) and it is important to consider this as a possible aetiology, in particular in areas where BVD is endemic. BVD infection of the foetus in the early stages of gestation (at a similar time to occurrence of ocular development and before immunocompetence) can result in the birth of a calf exhibiting congenital abnormalities but antibody negative (if sampled prior to colostrum ingestion) (10,14). Consequently, it can be difficult to confirm congenital BVD infection and these animals can on occasions be mistakenly considered to not be infected with BVD virus during gestation. In this case however, the known BVD-negative status of the herd, together with the good biosecurity measures adopted by the farm and the long-standing farm BVD vaccination protocol makes congenital infection with BVD unlikely. This illustrates the importance of considering the farm history and clinical examination findings together with laboratory results and the potential pitfalls that can arise if laboratory results are evaluated alone.

Exposure of the dam to environmental toxic substances during pregnancy could not be ruled out but given the absence of other affected animals in the herd, and also because the dam was housed for the duration of gestation, it was considered to be unlikely. Excess or deficiency of vitamin A has also been related to ocular malformations in cattle (15,16), however this was also considered unlikely, as this would be expected to affect more than one animal in the herd.

In light of both the farm and individual history in this case, it is considered that this is most likely to be a sporadic case of congenital multiple ocular abnormalities, possibly with an underlying genetic aetiology. Genetic mutations causing congenital multiple ocular abnormalities have previously been described in cattle (17,18) and cannot be ruled out in this case, as their presence was not assessed. A number of

genetic mutations are described in beef cattle (19) and for some of these, rapid and accessible techniques such as polymerase chain reaction (PCR) have been developed to aid diagnosis (20,21). In Japanese Black cattle, mutations of the WFDC1 gene have been identified as a cause of multiple congenital ocular abnormalities (17,18); however, in the Holstein breed, a different gene mutation (in the MITF gene) has been associated with congenital microphthalmia (7), a mutation also associated with multiple congenital abnormalities (including some ocular abnormalities) has been reported in the German Fleckvieh breed (22). Although the Fleckvieh breed is closely related to the Simmental breed, to our knowledge, gene mutations in the British Simmental breed causing congenital ocular abnormalities have not yet been determined; therefore, as the responsible gene mutation is unknown, whole genome sequencing would be required to conclusively exclude or confirm a possible underlying genetic defect in this case, possibly with an initial focus on WFDC1 and MITF genes.

Given that this was an isolated case and that both the sire and dam of this animal are no longer used (due to their age), further herd investigation has not been performed. In different circumstances, for example if a new bull had been used or if multiple cases were reported, further herd investigation should be considered as there is the potential for this condition to have an adverse effect on herd production and individual animal welfare.

## **DISCUSSION** *Include a very brief review of similar published cases*

The dimensions of the normal adult bovine eye shows breed variation but the axial depth is typically reported to be greater than 30mm irrespective of breed (23,24). The markedly reduced size of the globes as determined post-mortem in this case was substantially different to normal ocular dimensions in adult cattle and confirmed the initial clinical diagnosis of microphthalmia. The lens of the left eye was absent, and the lens of the right eye was very small which is the likely reason for being unable to image the right lens with ultrasonography. No macroscopic abnormalities were detected in the optic nerves, the brain or any other organ on post-mortem examination, which was in contrast to the MRI findings where bilateral hypoplasia of the optic nerves and optic chiasm was reported to be subjectively apparent. The discrepancy between the MRI findings and the gross post-mortem findings is difficult to explain; however, in the absence of either specimens, or MRI images, from an age and breed matched normal animal for comparative purposes, it is possible that this discrepancy has occurred as a result of the degree of the abnormality reported and the subjective nature of the assessment performed.

Microphthalmia is associated with abnormal development of the optic vesicle, or later in development through failure to establish intraocular pressure which normally contributes to growth and expansion of the globe (25). The bovine eye is well developed by the end of the second trimester of gestation and the lens is fully developed by 60 days gestation (14); insults to the dam during this period of pregnancy have the potential to adversely affect foetal ocular development *in utero*. Abnormal lens formation has been shown to result in the development of microphthalmia in sheep (26) and other ocular defects in birds (27) but to our knowledge it is not yet known if this is the case in cattle.

Although microphthalmia can often initially appear to be the only ocular abnormality present on clinical examination, it often occurs in association with other ocular abnormalities that are less immediately obvious. A number of authors have reported cases of multiple, concurrent congenital ocular defects including microphthalmia, aphakia, microphakia and retinal dysplasia (4,28,29); microphthalmia has also been reported to be present in cases of calves born with congenital abnormalities affecting multiple body systems (7). Congenital ocular abnormalities in cattle have been associated with infection *in utero*, genetic mutations and maternal hypovitaminosis A during the time of ocular development, and can also occur as a sporadic event (2,3,6,7,16,28,29). Teratogenic toxins have been reported to cause congenital ocular abnormalities in other ruminants (30), but this is rarely reported in cattle.

Among the general cattle population, congenital ocular abnormalities are reported to be uncommon (31); however in some breed populations, the incidence of congenital ocular abnormalities has been observed to be higher than that in the general population (5,18,32). As previously mentioned, an autosomal recessive hereditary disorder causing multiple congenital ocular defects (Multiple Ocular Defects [MOD] syndrome) is recognised in Japanese Black cattle (5) and a mutation in the WFDC1 gene has been identified as the underlying aetiology for this condition (17,18). Wiedemar and Drögemüller

(2014) described a case of multiple congenital abnormalities including microphthalmia in a Holstein calf caused by mutation of the MITF gene; however further post-mortem examination of the eyes was not reported, therefore it is unknown whether additional ocular abnormalities were also present (7). In the Hereford breed, a syndrome of congenital microphthalmia associated with hydrocephalus (Hereford encephalopathy-microphthalmia syndrome) has been known to occur for a number of years (6,33). This syndrome is thought to be hereditary; however, to our knowledge the underlying aetiology for this syndrome has not yet been definitively determined.

In the case reported, all eye components were present bilaterally, with the exception of the lens of the left eye. Aphakia and retinal dysplasia have been reported to be associated with microphthalmia in a number of species including cattle (5,17,34–36); however, the thickening of the sclera was a striking finding in this case. The presence of an abnormally thickened sclera has been reported in cases of microphthalmia in humans and it has been suggested that the abnormal collagen fibres may prevent the early development of the globe (37) although to our knowledge this has not been reported in cattle.

### **LEARNING POINTS/TAKE HOME MESSAGES 3 to 5 bullet points – this is a required field**

- Microphthalmia (possibly concurrent with other ocular abnormalities) should be considered a potential differential diagnosis in cases where the conjunctiva appears to be bulging or unnaturally abundant. Thorough clinical examination is required to determine an accurate diagnosis.
- Advanced imaging was performed in this case and can be used to confirm a diagnosis if available; however, although abnormalities of internal ocular structures may not be readily identifiable, microphthalmia is readily diagnosed with clinical examination and further imaging is rarely warranted in practice. If further imaging is required for diagnostic confirmation, ultrasonography using a linear probe such as that commonly used in UK farm animal practice can be used. This can be particularly useful in assessing globe size and the presence of a normal lens, although as in this case, the absence of a lens can be more difficult to definitively determine as a microphakic lens may be difficult to image.
- Definitive confirmation (or ruling out) of congenital infection with infectious agents such as BVD virus can be difficult and a thorough history of the farm health status and biosecurity protocols should be obtained to aid identification of potential underlying aetiologies.
- There is no treatment or cure for congenital ocular abnormalities. The condition may have a genetic aetiology and affected animals should not be bred from.
- Lesser affected animals may be able to be fattened for slaughter if fit to transport, however euthanasia on welfare grounds should be considered in more severely affected animals such as described in this case.

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**FIGURE/VIDEO CAPTIONS** *figures should NOT be embedded in this document*

**Figure 1.** Right eye: note how the globe is completely obscured by conjunctiva and ventrally rotated

**Figure 2.** Left eye: the left globe is visible but notably small compared to that seen in normal cattle

**Figure 3.** Transverse plane T2 weighted MRI image at the level of the eyeballs. Note the small eyes with enophthalmic positioning.

**Figure 4.** Macroscopic image of the cut section of the right eye. The sclera and choroid are markedly thickened, the pupil and lens are inconspicuous and there is obliteration of the anterior and posterior chamber as well as the vitreous. The retina is displaced and folded and there are several blood-filled cystic spaces.

**Figure 5.** Low power microscopic image of the right eye. There is extensive disruption of the eye globe architecture. The retina is markedly folded, hypocellular, disorganised, and displaced into the vitreous (arrows). Blood-filled cystic spaces are present in the choroid and in the retina (arrowheads). Haematoxylin & Eosin x 0.4.

**Figure 6.** Closer microscopic view of the right eye. The lens is irregular, small degenerate and fragmented (asterisk). There is a focal adhesion between the iris and the lens consistent with posterior synechia (arrows). Haematoxylin & Eosin x 1.25.

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