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CASE REPORT

Congenital bilateral clinical anophthalmia and brachygnathia superior in a fighting bull calf

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Abstract

This study describes a case of a 20-day-old male fighting bull with bilateral clinical anophthalmia and brachygnathia superior whose dam was 12.5 years old and was mistakenly dewormed with ivermectin intramuscularly in the first third of gestation in a livestock farm. A macroscopic examination of the carcass was performed, with a special focus on the ocular components. Eyeball remains were found in both orbits and a histopathological examination was performed on them. Antibodies by serological study against bovine herpes virus-1, respiratory syncytial virus and bovine viral diarrhea virus for both the cow and the calf were not detected. The calf had small orbits and inside them a white and brown mass of soft consistency. Microscopically, abundant muscular and adipose tissue was observed, alongside nervous structures and vestiges of ocular structures with stratified epithelium and abundant connective tissue with glands. No evidence that this congenital bilateral anophthalmia had infectious or hereditary origin was found. By contrast, the malformation could be related to the treatment with ivermectin during the first month of gestation.

KEYWORDS

anophthalmia, brachygnathia, fighting bull calf, ivermectin

1 | INTRODUCTION

Congenital ocular disorders are unusual in cattle. However, some ocular defects such as anophthalmia have been previously reported in different dairy cattle species (Holstein)[1,2] and fattening cattle (Japanese brown cattle), where this alteration has been studied in greater depth.[3] Anophthalmia is a birth defect in which animals are born without eyes and the orbits appear devoid of eye tissue. Anophthalmia can be classified as clinical (the eye is not detected but is there) and true anophthalmia (total absence of the eye).[4] Sometimes it is difficult to differentiate between clinical anophthalmia and microphthalmos, being necessary to have image exams to show the length of the deformed bulb. Clinical anophtalmia can cause animals with total absence of ocular tissue, vestigial remains and even small eyes that coincide with cases of extreme microphthalmos. In fact, some animals with suspected anophthalmia may be diagnosed with microphthalmia due to vestigial remnants of ocular tissue.[5] Likewise, the orbits can be underdeveloped, and the eyelids can have a reduced size.[1,2] In some cases of congenital anophthalmia, cystic or solid eyeball remains may appear in the orbits. Eyeball debris may include sclera, choroid, and

retina debris. The retina may be dysplastic and sometimes attached to a hypoplastic optic nerve. Alongside the eyeball remains, extraocular muscles, lacrimal glands, nerves, and adipose tissue can be found.[3] In cattle, congenital anophthalmia/microphthalmia unilaterally and bilaterally has been described. In this breeds, it is related to other abnormalities in the brain and in skeleton parts such as the cranium and caudal and sacral vertebrae, including animals without tails or with twisted tails. Wedge vertebrae, hemivertebrae, or sagittal clefts can be seen at the level of the lumbar, sacral, and coccygeal vertebrae, which alongside the meandering axial line of abnormal vertebrae may suggest a failure in the formation of the notochord.[3,6] Also, Holstein cows with head deformations such as brachygnathia superior and cleft lips and muzzle have been previously found.[1]

Various causes for these congenital malformations have been hypothesized, including hypovitaminosis A, fetal viral infections (bovine viral diarrhea virus, Aino, Akabane, and Chuzan viruses) and genetic factors, such as a monogenic autosomal recessive inheritance.[1,3,7,8] However, chromosomal aberrations have not been detected and most authors indicate that this congenital disorder may be originated during the embryonic development of the animal. Thus, it may be possible that the critical period of exposure to the teratogenic agent coincided with optic organogenesis, and notochordal and pharyngeal arches formation in early embryogenesis.[1,3,9] Therefore, other noninfectious teratogenic agents such as environmental factors must be considered as a cause for these malformations. The purpose of this study was to describe the pathological findings of congenital bilateral clinical anophthalmia with brachygnathia superior in fighting bull that has not been described according to the knowledge of the authors. In addition to assessing and clarifying the possible relation of treatment with ivermectin in the first month of gestation as a possible teratogenic agent responsible for the malformations observed in the animal.

2 | CASE REPORT

A Spanish autochthonous bovine breed 20-day-old male fighting bull was referred to the Teaching Veterinary Hospital for necropsy. The study did not require approval by the Institutional Review Board since the animals were euthanized in the place of origin following the regulations of veterinary clinical practice in accordance with national regulations (Code of Ethics for the Veterinary Profession). The data on the breeding and management of the parents were collected at the farm, as well as the specific conditions during gestation. The dam was a 12-year and 6-month-old fighting cow with an approximate weight of 350 kg that had previously had 10 more normal descendants. The sire was a 6-year-old bull that had had 86 more descendants, all of them normal. The farm, which was established in 1994, had no malformation records for any of the approximately 5000 animals that had been born since then. A serological study for the detection of antibodies against bovine herpesvirus, respiratory syncytial virus and bovine viral diarrhea virus was carried out in the cow and in the calf and it was negative. Furthermore, there were no antecedents or cases of any viral diseases such as Aino, Akabane, or Chuzan, either on the farm or in the geographical region at the time of the study. The only observation noted during pregnancy, was that the cow underwent antiparasitic treatment based on ivermectin. The dam cow was mistakenly treated at 30 ± 5 days of gestation with a dose of 70 mg (0.20 mg/kg) by intramuscular injection. Due to the management conditions of these animals, it is very difficult to know if they are pregnant and the exact days of gestation, since they are bred on wide-ranging ranches and bulls are comingled with females for several months without receiving any reproductive control.

Clinical examination of the calf revealed a narrow palpebral fissure (Figure 1A,C) and no ocular structure was found in the orbits by biomicroscopy. In addition, brachygnathia superior was observed (Figure 1B) and analyzed by helical computed tomography (CT) scan of the skull (dual slice CT scanner, General Electric HiSpeed, General Electric Healthcare). Reformatted images in sagittal, dorsal planes, maximum intensity projection, and volume rendering were obtained. The images were reviewed using a picture archiving and computer system (PACS) workstation with soft tissue (WW = 400, WL = 40) and bone (WW = 2000, WL = 550) window display settings.

Before euthanasia, the animal was sedated with xylazine and immediately necropsied, and a thorough macroscopic examination of the carcass was performed, with a special focus on the ocular components. Reduced palpebral fissures and small orbits were observed (Figure 1C). The orbits presented a white and brown mass of smooth consistency, with areas of irregular morphology (Figure 1D). In addition, prognathism was observed with an underdeveloped maxilla, which also appeared slightly rotated. Thus, the calf suffered ulcers in the rostral parts of the muzzle, caused by the mandible incisors (Figure 1B). Samples of the remains of the eyeball components were placed in 10% neutral buffered formalin for histological evaluation. Formalin-fixed tissues were routinely processed, embedded in paraffin, sectioned at 5 µm, and stained with hematoxylin and eosin (H&E) and Masson's trichrome (MT). CT showed an absence of normal ocular structure (Figure 2). 3D rendered images showed prognathism in the conformation of the skull (Figure 2A). The space of

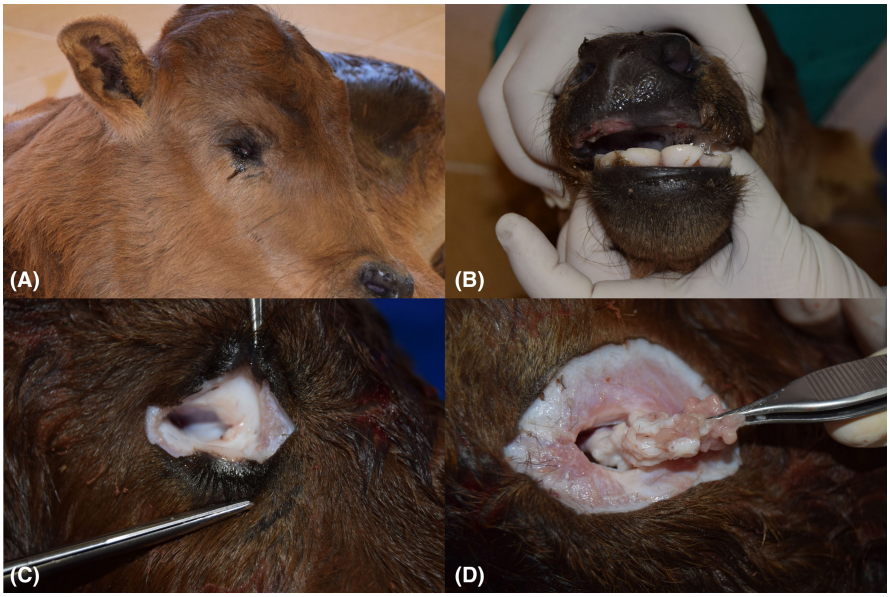

FIGURE 1 (A) Calf with anophthalmia and brachygnathia in maxilla. (B) Image showing brachygnathia with slight rotation of the muzzle and how the maxilla is recessed causing ulcers in the snout due to friction with the incisors. (C) Image showing the smaller size of the palpebral fissure. (D) Detail of remains of eyeball in the orbit.

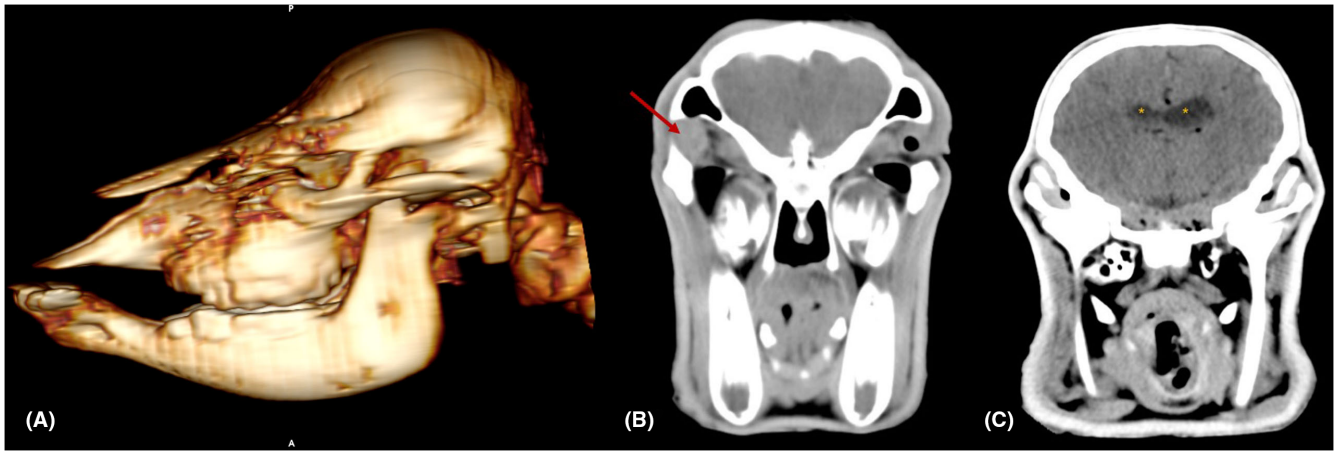

FIGURE 2 (A) CT 3D volume rendered image of the head showing the abnormal conformation of the skull bones caused by brachygnathia. (B) CT image in transverse plane and soft tissue window at the level of the orbit. A reduced orbit is seen, with absence of normal ocular structures, presenting soft tissue material consistent with vestigial ocular tissue (arrow). (C) CT image in transverse plane and soft tissue window at the level of the brain. Slight asymmetry of the lateral ventricles is observed.

the orbits was reduced in size and contained soft tissue which appeared attenuated in the image (Figure 2B). No other alterations in bone or soft tissue structures including the brain were observed, except for a slight asymmetry of the lateral ventricles (Figure 2C).

Microscopic examination of the material inside the orbit structures showed remains or ectodermal vestiges of similar ocular structures in both eyes with stratified epithelium and abundant connective tissue (Figure 3A). Likewise, remnants of dysplastic cornea appeared, with a layered flat epithelium and squamous metaplasia in some cells, and a little stroma formed by collagen fibers with different degrees of the organization (Figure 3B). Among these vestiges, remains of the third eyelid appeared, with a layered flat epithelium and a cartilaginous matrix (Figure 3C). Furthermore, in the mass found inside the orbit there was abundant fatty and muscular tissue, blood vessels and nerves (Figure 3D).

3 | DISCUSSION

In the present case report, we describe a case of bilateral clinical anophthalmia in a fighting bull calf, which appears associated with other alterations such as a smaller size of the palpebral fissure and brachygnathia superior with a certain degree of rotation in the maxilla. In our case, we have not found associated tail and vertebral alterations as have been described in cases of anophthalmia in Japanese brown cows.[3] However, we have detected

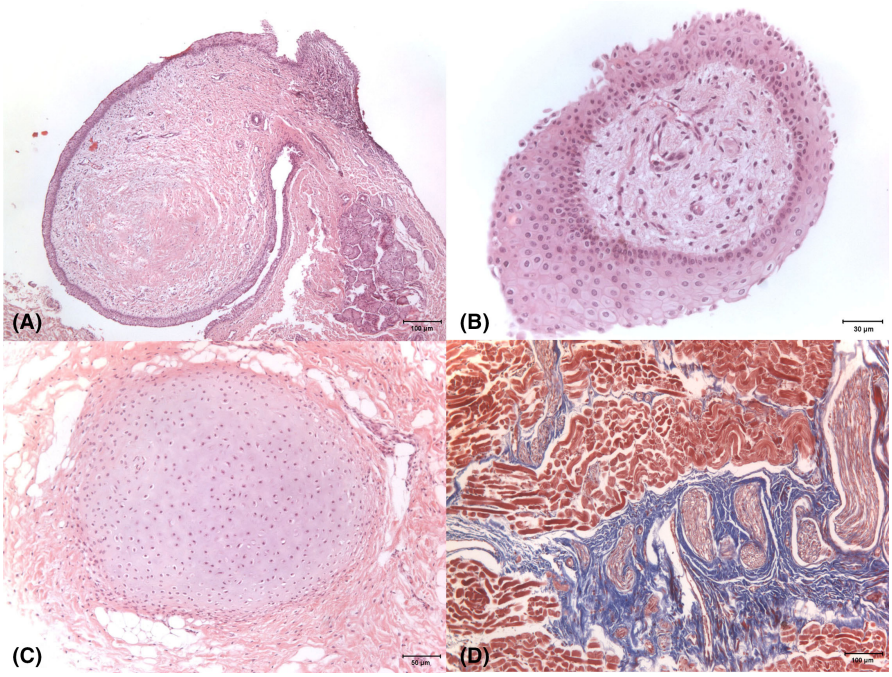

FIGURE 3 Histopathological finding in remains of eyeball. (A) Vestiges of structures of the eye with stratified epithelium and abundant connective tissue with seromucousglands (H&E). (B) Dysplastic cornea with stratified epithelium with squamous metaplasia and disorganized connective tissue (H&E). (C) Cartilaginous matrix area corresponding to remains of cartilage of the third eyelid (H&E). (D) Muscular and connective tissue areas and nervous structures present inside the orbit (MT). H&E, hematoxylin and eosin.

brachygnathia superior as has been described in German Holstein cows.[1] These facts indicate a high heterogeneity in the clinical manifestations of these congenital disorders in cattle, which could be not characteristic of hereditary genetic processes. Some authors hypothesize, bilateral anophthalmia may be hereditary and caused by an autosomal recessive gene, although it has not been demonstrated, since chromosomal aberrations have not been detected.[1] In addition, a similar anophthalmia syndrome with alterations in the lips and palate has been described in humans with a normal karyotype.[10] Although fighting bull cattle has a high level of inbreeding, it should be noted that with about 5000 animals born since establishment, this farm had no record for this alteration and this malformation has not been described previously within the fighting bull race, with 1500 farms and around 50,000 fighting bulls born every year. Thus, possible environmental causes such as infectious or teratogenic agents must be considered in the development of these malformations. In our case, we can rule out the presence of viruses that could affect embryonic development as teratogenic agents,[7,11] since the serological study showed no antibodies against the typical viruses found in cattle in these geographical regions (bovine herpesvirus 1, respiratory syncytial virus, and bovine diarrhea virus) both in the cow and in the calf. Furthermore, the farm had no record data of viral diseases, including Aino, Akabane, or Chuzan, which have been related to congenital anophthalmia[14] and no other alterations compatible with viral processes were detected at the time of the study.

Causes of anophthalmia and include failure in the formation of the optic primordium in the forebrain, suppression or abnormal development of the forebrain, and rupture or degeneration in the optic vesicle.[12] The pathological findings in our study, with the presence of rudimentary epithelial structures in the remains of ocular tissue, as well as the presence of a dysplastic cornea, could indicate that the origin may be a defect occurred after the formation of the optic vesicle or cup during optical organogenesis and in the first pharyngeal arch during the development of the maxilla.[3,9]

In the bovine fetus, the optical organogenesis begins at day 20 or 21 of gestation with the evagination of the optic primordium; at day 23, the formation of the optic vesicle occurs, and the optic dome is formed by day 30 of gestation.[13,14] On the other hand, maxilla originates from the second pharyngeal arch, which begins its development on the 24th day of gestation.[9] Therefore, the action of a teratogenic agent on those days of fetal development could alter the normal development of the eyes and maxilla. Animal reproduction studies have shown ivermectin to have teratogenic effects when administered in the first third of gestation, inducing a significant increase in resorption sites, post-implantation loss and external, visceral and skeletal abnormalities.[15] In a study of pregnant women who received ivermectin during pregnancy, some evidence of miscarriage, stillbirth, or birth defects were found, although the number of cases was too low to be conclusive, as only less than 100 women received the drug during the first trimester of pregnancy, when the fetus is more vulnerable to its effect.[16] In our case, exposure to ivermectin coincides with the critical period of the embryogenic development of the eyes and the maxilla (day 30 ± 5 of gestation) and a

teratogenic effect of ivermectin could be involved in the origin of this malformation. Furthermore, plasma ivermectin concentrations in the dam cow could have been higher than recommended due to handling difficulties of these types of animals at the time of injection, caused by their aggressive behavior. Additionally, an intramuscular injection was made instead of a subcutaneous injection.[17] On the other hand, the dose was based on an estimated weight of 350 ± 25 kg, since the animal could not be weighed. As a result, the calf could have had a slightly higher concentration of ivermectin in plasma than recommended.

In the present study, we found no evidence that the bilateral congenital clinical anophthalmia observed had an infectious or hereditary origin. By contrast, our results show that it could be related to ivermectin treatment in the pregnant cattle. Ivermectin is not recommended in pregnant women and the FDA has assigned it to pregnancy category C, as animal studies have revealed evidence of teratogenicity, but at doses that were also maternotoxic for pregnant women.[18] Thus, it is possible that ivermectin, if applied at the recommended dose or slightly higher and intramuscularly instead of subcutaneously in the first month of gestation in pregnant cattles, could have an adverse effect on embryogenesis and therefore teratogenicity.

AUTHOR CONTRIBUTIONS

Juan Seva: Conceptualization; data curation; formal analysis; investigation; methodology; resources; supervision; validation; writing – original draft; writing – review and editing. **José Manuel Sanes:** Conceptualization; investigation; methodology; resources; validation; writing – review and editing. **Juan Manuel Bueno:** Conceptualization; investigation; methodology; resources; validation; writing – review and editing. **Carlos De Jódar:** Data curation; methodology; resources; validation; writing – review and editing. **Marta Soler:** Conceptualization; formal analysis; investigation; methodology; resources; validation; writing – original draft; writing – review and editing. **Alejandro Bayón:** Conceptualization; data curation; formal analysis; investigation; methodology; resources; validation; writing – original draft; writing – review and editing. **Ester Párraga-Ros:** Conceptualization; formal analysis; investigation; methodology; validation; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

CONSENT

Written informed consent was obtained from the animal owner to publish this report in accordance with the journal's patient consent policy.

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