DOI: 10.1002/vms3.244

CASE REPORT

WILEY

Lobar holoprosencephaly with craniofacial defects in a Friesian calf: A case report

Mosiany L. Kisipan[1] | Samuel N. Nyaga[1] | Jesse N. Thuo[1] | Phillip O. Nyakego[1] | Caleb O. Orenge[1] | Rodi O. Ojoo[2]

[1]Department of Veterinary Anatomy and Physiology, Egerton University, Egerton, Kenya

[2]Department of Veterinary Anatomy and Physiology, University of Nairobi, Nairobi, Kenya

Correspondence
Mosiany L. Kisipan, Department of Veterinary Anatomy and Physiology, Egerton University, Egerton, Kenya.
Email: kisipanm@gmail.com

Funding Information
The authors declare that they did not receive any funding to conduct this study.

Abstract

Background: Holoprosencephaly is a forebrain deformity that results from varying degrees of separation failure of cerebral hemispheres. The condition is classified based on the degree of non-separation of the hemispheres which, in turn, determines its severity. Holoprosencephaly is usually accompanied by craniofacial defects whose severity tends to reflect the extent of brain deformities. In humans, holoprosencephaly is one of the commonest congenital brain anomalies but in animals, reported cases are scarce. The condition has multifactorial aetiology that involves interactions between several genetic and environmental factors.

Case presentation: A 4-day-old female Friesian calf with a deformed face was reported to the Faculty of veterinary medicine and surgery, Egerton University. The calf and the dam were sired by the same bull. On clinical and radiographic examination, the calf had a short snout that curved dorsally with bilateral cleft lip, right-sided cleft jaw and a largely absent primary palate. Anatomopathological examination revealed brain deformities which included ventral fusion of frontal lobes of cerebral hemispheres, large merged lateral ventricles without septum pellucidum and fornix, hypoplastic corpus callosum, high degree of non-separation between diencephalic structures, poorly developed hippocampal formation and hypoplastic olfactory lobe, optic chiasma, and nerve.

Conclusion: The case was confirmed as lobar holoprosencephaly based on characteristic anatomopathological findings. The aetiology of the defects in the present case could not be determined though they are thought to be either a result of recessive inheritance or exposure to teratogenic steroid alkaloids through materials fed to the dam during early pregnancy.

KEYWORDS
Congenital malformation, craniofacial defects, forebrain, holoprosencephaly, orofacial defects

1 | INTRODUCTION

Holoprosencephaly (HPE) is a spectrum of congenital brain malformations that results from varying degrees of failure in cleavage of forebrain into distinct left and right cerebral hemispheres (Dubourg et al., 2007; Hayhurst & McConnell, 2003; Koch et al., 2005; Solomon et al., 2012; Winter, Kennedy, & Woodward, 2015). It is one of the commonest congenital forebrain defects in humans but

reports in animals, as is the case in other congenital malformations, are generally scarce partly due to factors that hamper reporting especially in the developing world (Kisipan, Orenge, Gacheru, & Ngure, 2016). However, the defects in reported HPE in animal cases and models generally resemble those in humans (Gongal & Waskiewicz, 2008; Hayhurst & McConnell, 2003; Koch et al., 2005). HPE is usually accompanied by craniofacial defects (CFD) whose severity often correlate positively with the extent of prosencephalic deformity (Demyer, Zeman, & Palmer, 1964). Cranial anomalies range from microcephaly to macrocephaly while in the face, a variety of defects, occurring singly or commonly in combinations will be seen and include cyclopia or hypotelorism, proboscis-like nose and clefts in the lip, jaw and palate (Cho, Zeman, & Miller, 1985; Demyer et al., 1964; Dubourg et al., 2007; Mercier et al., 2011; Nourani, Karimi, & Vardanjani, 2014; Reid, Ziermann, & Gondr e-Lewis, 2015; Winter et al., 2015).

The aetiology of this condition is heterogeneous, involving an interaction between multiple environmental and genetic predisposing factors (Barr & Cohen, 2002; Dubourg et al., 2007; Hayhurst & McConnell, 2003; Hong & Krauss, 2017; Johnson & Rasmussen, 2010; Koch et al., 2005; Mouden et al., 2016; Roessler & Muenke, 1998, 2010; Solomon et al., 2010; Stashinko et al., 2004). Environmental factors generally include maternal conditions such as insulin-dependent diabetes mellitus (Dubourg et al., 2007; Johnson & Rasmussen, 2010) and exposures to potential teratogens during gestation such as alcohol, smoking, retinoic acid and infections (Hong & Krauss, 2017; Johnson & Rasmussen, 2010; Stashinko et al., 2004). Several genetic factors associated with HPE have so far been identified and these include chromosomal defects such as trisomy and a number of gene mutations (Barr & Cohen, 2002; Mouden et al., 2016; Roessler & Muenke, 1998, 2010; Solomon et al., 2010).

HPE occurs as a wide spectrum of malformations categorized on the basis of the extent of non-separation between the cerebral hemispheres which, in turn, reflects the severity of the condition (Demyer et al., 1964; Dubourg et al., 2007; Marcorelles & Laquerriere, 2010; Paulussen et al., 2010; Simon et al., 2002; Solomon et al., 2012; Winter et al., 2015). On a decreasing degree of severity, HPE is classified as alobar, semi-lobar or lobar with milder variants which include the middle interhemispheric (MIH) variant, septopreoptic variant and septo-optic dysplasia (SOD) (Hahn & Barnes, 2010; Hahn, Barnes, Clegg, & Stashinko, 2010; Simon et al., 2002; Webb & Dattani, 2010; Winter et al., 2015). Since HPE forms a continuous spectrum of defects, it is often difficult to clearly distinguish different forms of the condition.

2 | CASE REPORT

A case of a 4-day-old female Friesian calf with facial defects was reported to the Faculty of veterinary medicine and surgery, Egerton University by a small-scale mixed crop and livestock farmer. The farmer complained of a new-born calf with a 'short' face and was unable to suckle. A team of veterinarians visited the farm to attend to the case.The patient was the first calf by a Friesian heifer bred in the farm. The dam was in a good body condition with no history of malformations in its lineage. The farmer reported that he uses a hired 'communal' bull to serve his animals and the same bull sired the dam itself. There was also no history of recent disease condition nor of any medication. From birth, the calf could not suckle but was bottle fed by the owner. The calf presented with a short 'bulldog-like' snout which curved dorsally with bilateral cleft lip, right-sided cleft jaw and a generally absent primary palate (Figure 1a–c). It exhibited snoring and abdominal breathing and did not avoid objects on its path when allowed to move about in the shed. On further examinations, it was established that the calf was bilaterally blind. It had a rectal temperature of 39.2°C, pulse of 158 beats per minute and respiration rate of 48 cycles per minute.

That evening after it had been bottle fed, the calf was transported to Egerton University where it was kept overnight in an improvised cardboard pen with hay bedding. On the following morning, lateral head radiographs were taken which showed non-ossification of face around the nasal region (Figure 2). Upon consultation among the veterinarians, the calf was euthanized on animal welfare grounds using 20 ml of 20% sodium pentobarbitone administered intravenous as a bolus. This was followed by anatomopathological examination.

Anatomopathological examination confirmed a complete bilateral cleft lip, complete right-sided cleft upper jaw, a poorly formed left upper jaw with incomplete dental pad and a complete absence of rostral part the palate and muzzle (see Figure 1c). The nasal passages were narrowed and opened rostrally to the oral cavity through the palatal defect. The lower jaws were slightly longer than the upper ones and the mandibles were curved dorsally (Figure 3). The size of the eyeballs and pupils were unequal being larger in the left eye (see Table 1). The cranial cavity was asymmetrical with its floor tilting ventrally towards the left side which also appeared to be more spacious than the right side. The right cribriform fossa and plate were absent while the left one was present as a rather deeper depression (Figure 4).

The brain was easily removed from the cranium and the resistance normally associated with optic nerves was not apparent. Dorsal longitudinal fissure was less pronounced towards the rostral pole of the organ (Figure 5a) and so was the falx cerebri. The left and right frontal lobes of the cerebral hemispheres were fused rostrally and ventrally (Figure 5b) with a gyrus crossing the midline to connect the rostral ends of frontal lobes (Figure 5c). The olfactory bulbs, the optic nerves, chiasma and tracts were all rudimentary. A coronal section of the brain revealed an enlarged and merged lateral ventricular spaceswith rudimentary occipital horns and no septum pellucidum (Figure 6a,b). The fornix was absent and the hippocampus was poorly developed. The Corpus callosum, particularly its rostral portion, was poorly formed and a strip of grey mater formed a bridge over it to connect the two cerebral hemispheres. Caudally, a transversely oriented band of white matter reminiscent of the splenium

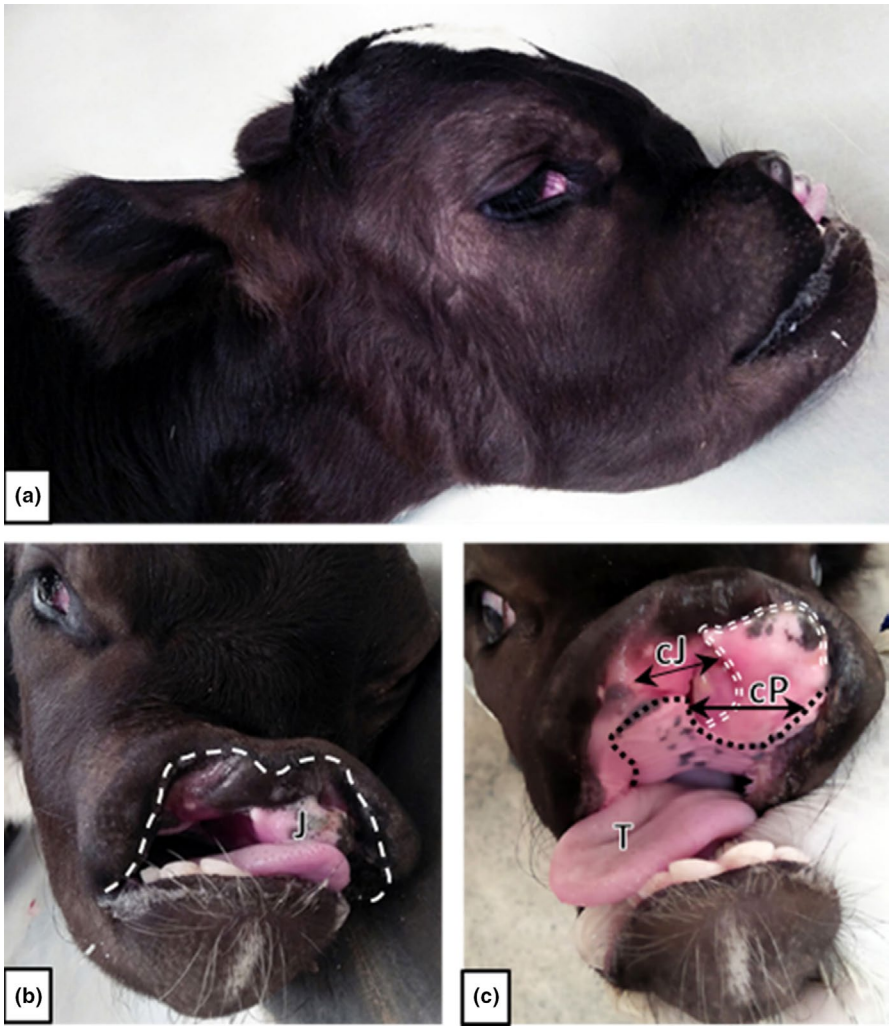

FIGURE 1 Head region photographs of the patient. (a) A short snout that curve dorsally. (b) Bilateral clefts of the upper lip with the lip margin traced with a white-dotted line and a portion of the left jaw (J). (c) Complete right-sided cleft jaw (cJ) and complete cleft palate (cP). The margin of the palate is traced with a black-dotted line while that of the jaw is traced with a white-dotted double line. Also notice the tongue (T)

of corpus callosum could be seen in the caudal end of the cavity of merged lateral ventricles.

3 | DISCUSSION

Prosencephalon, the most rostral primary brain vesicle from which the forebrain develops, undergoes cleavage during early embryogenesis to form the right and left cerebral hemispheres (Sadler, 2012). HPE results when there is failure or incomplete separation of the cerebral hemispheres and the extent of non-separation of the hemispheres forms the basis for HPE classification (Demyer et al., 1964; Marcorelles & Laquerriere, 2010; Winter et al., 2015). HPE forms can broadly be categorized into two as either classical HPE forms or HPE variants. Classical HPE forms include alobar, semi-lobar and lobar HPE while HPE variants include MIH, septopreoptic variant and SOD (Hahn & Barnes, 2010; Hahn et al., 2010; Simon et al., 2002; Webb & Dattani, 2010; Winter et al., 2015). The extent of non-separation between the cerebral hemispheres in HPE generally determines the severity of the condition (Demyer et al., 1964; Marcorelles & Laquerriere, 2010; Winter et al., 2015). In animals, some cases where marked brain malformation without profound clinical signs have been reported (Keating et al., 2016). Since screening of animals for anomalies, be it prenatal or postnatal, is not a routine, many mild cases of HPE and other congenital anomalies without obvious clinical signs will go unreported. Alobar HPE, the most severe form, results from complete failure of prosencephalon cleavage and is characterized by a single midline forebrain without an interhemispheric fissure, a single ventricle, absence of olfactory bulbs and tracts among others features. In semi-lobar HPE, there is an incomplete interhemispheric fissure mainly restricted to caudal part so that rudimentary cerebral hemispheres are apparent but with extensive non-cleavage of the frontal lobes, thalami and hypothalamus, absent or hypoplastic olfactory lobes and tracts and a partly formed corpus callosum. Lobar HPE presents a near completely formed interhemispheric fissure with non-cleavage of hemispheres confined to a ventral portion of the rostral part of frontal lobes. Other features include a partly or completely separated thalami, normal or partly formed corpus callosum but partition between lateral ventricles is absent (Dubourg et al., 2007; Gonçalves et al., 2014; Hayhurst & McConnell, 2003; Koch et al., 2005; Mercier et al., 2011; Nourani et al., 2014; Nyberg, Mack, Bronstein, Hirsch1987, & Pagon, 1987; Paulussen et al., 2010; Solomon et al., 2012; Winter et al., 2015). A middle interhemispheric variant (MIH) has also been described and is characterized by separation failure of midline structures, involving

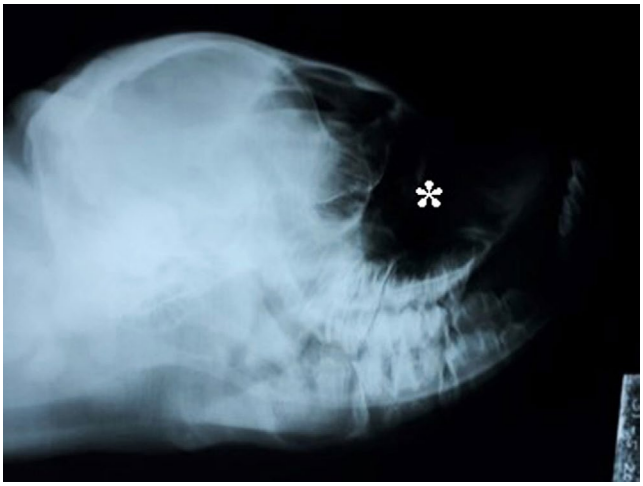

FIGURE 2 A lateral head radiograph showing diffuse radioluscence in the rostral portion of the snout (asterisk). Dorsal curvature of mandible can also be appreciated

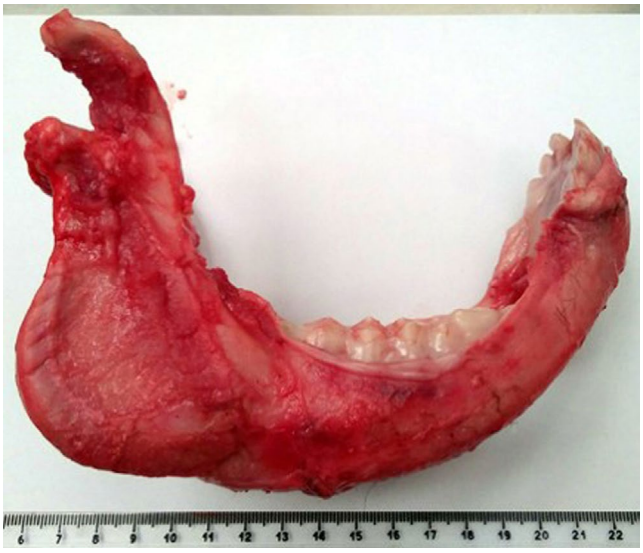

FIGURE 3 A photograph of a mandible from the affected calf. Notice its dorsal curvature

TABLE 1 Comparative parameters of the left and right eyeballs. All values are in centimetres

Aspect	Parameter	Left eyeball	Right eyeball
Whole eyeball	Diameter	2.9	2.6
Pupil	Gap between medial and lateral angles	1.9	1.7
	Gap between dorsal and ventral borders at widest part	1.4	1.3

mainly the caudal frontal lobe and parietal lobe (Dubourg et al., 2007; Simon et al., 2002; Winter et al., 2015).

It can be difficult to distinguish between different forms of HPE as characteristic defects often overlap. The features suggested to distinguish lobar from semi-lobar HPE include presence of third ventricle, rudimentary frontal horns of lateral ventricles, splenium and caudal body of corpus callosum (Volpe, Campobasso, De Robertis, & Rembouskos, 2009; Winter et al., 2015). In the present case, fusion between the left and right cerebral hemispheres is confined to the rostral and ventral parts of frontal lobe. Even though there was complete merger of lateral ventricles with no apparent frontal horns, extensive fusion of thalami with a poorly developed third ventricle, the case was still categorized as lobar HPE. In the authors' judgement, less than 50% of the frontal lobes were fused, thereby ruling out semi-lobar HPE following a suggested arbitrary criterion that classifies a condition as semi-lobar HPE if more than 50% of frontal lobes are fused (Kousa, du Plessis, Vezina, & Youssef Kousa, 2018; Winter et al., 2015). Continuity of the rostral ventral gyrus between the frontal lobes has also been earlier reported in lobar HPE (Winter et al., 2015). Cortical continuity across the hemisphere reported in this case is also a feature shared with MIH. However, MIH is characterized by fusion confined to caudal parts of frontal lobes and parietal lobe (Bulakbasi, Cancuri, & Kocao, 2016; Kousa et al., 2018; Winter et al., 2015).

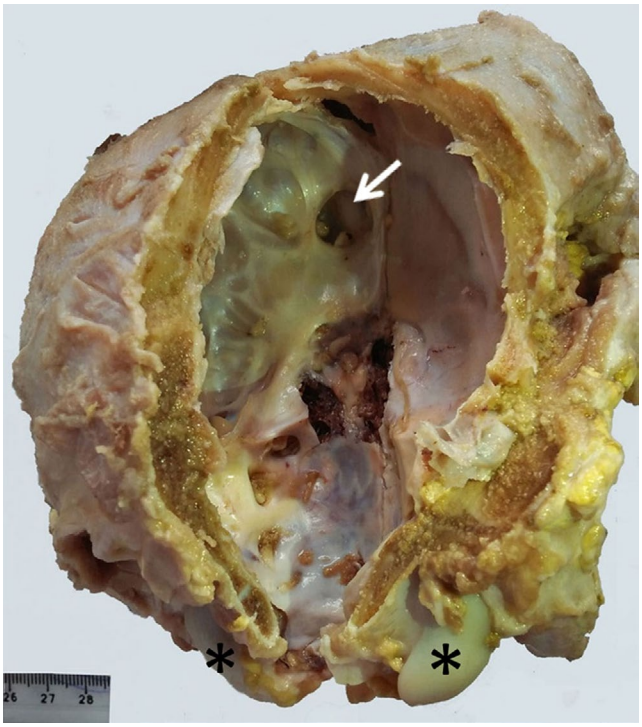

FIGURE 4 A photograph of the cranial cavity taken through an opening made on the caudo-dorsal wall of the cranium. The left cribriform fossa (white arrow) is rather deep while the right one is absent. Notice the occipital condyles (asterisks)

The other brain defects in this case were seen in the optic (optic nerves and chiasma) and olfactory structures. Poorly developed visual structures in brain (optic nerve, optic chiasma and tract) account for the bilateral blindness noticed during clinical examination of the calf and ease of removal of brain from the cranial cavity. Underdevelopment of these structures together with other midline defects such as the absence of septum pellucidum closely resemble the features seen in septo-optic dysplasia, SOD (Webb & Dattani, 2010; Winter et al., 2015).

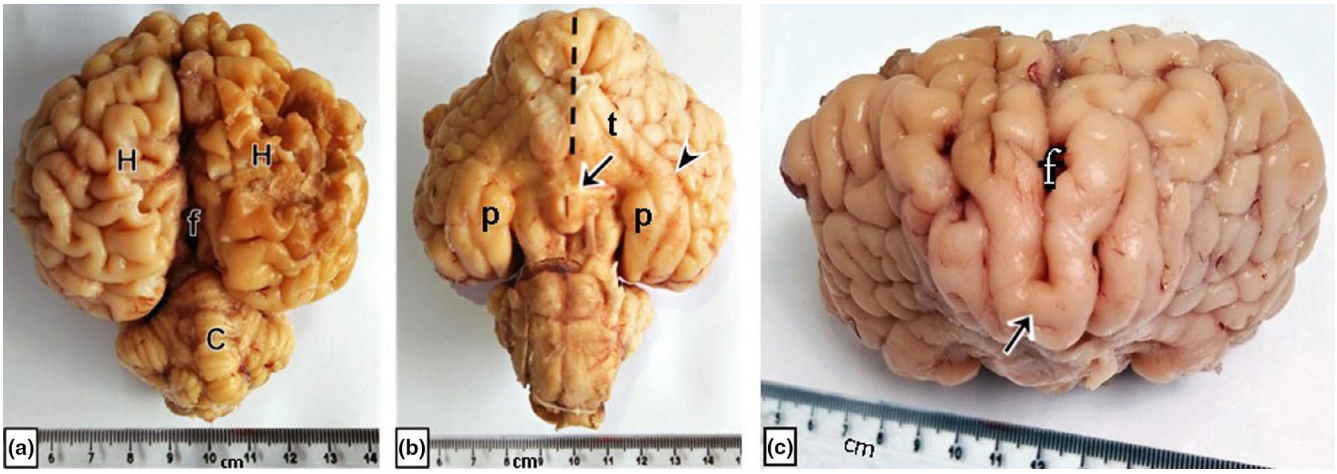

FIGURE 5 Brain photographs. (a) Dorsal view of the brain showing the cerebral hemispheres (H) intervened by an interhemispheric fissure (f). The cerebellum is also shown. (b) Ventral view of the brain showing ventral fusion of frontal lobes (along the black dotted line) and a rudimentary optic chiasma (arrow). Also shown are the pyriform lobes (p), olfactory tracts (t) and rhinal sulcus (arrowhead). (c) Rostral view of the brain showing a gyrus (arrow) crossing the midline to connect the two frontal lobes. Notice a rostral part of the interhemispheric fissure (f)

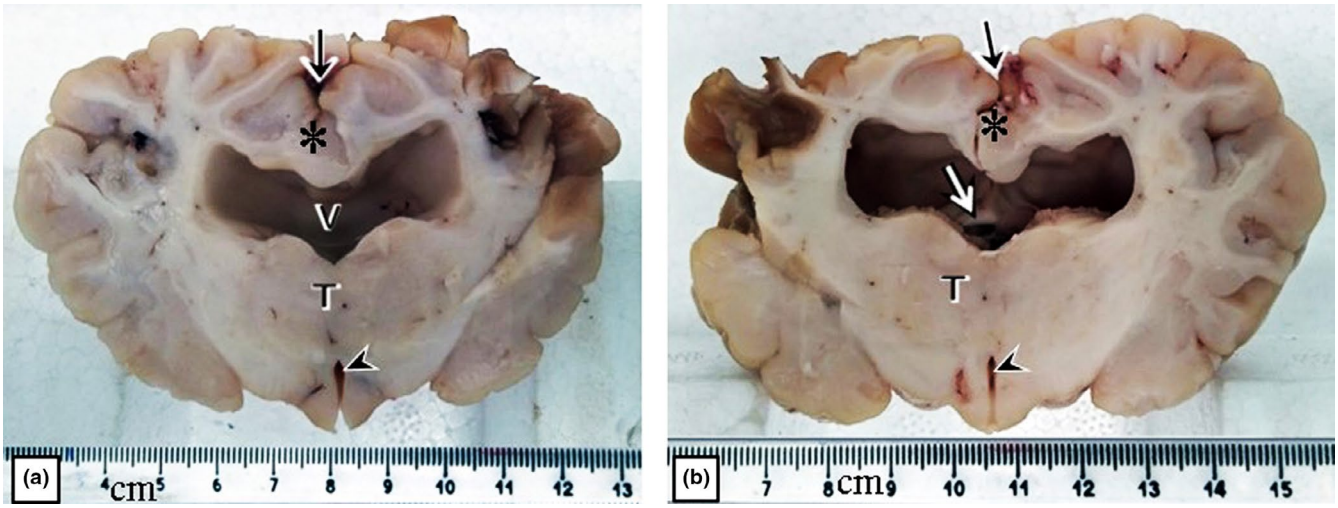

FIGURE 6 Coronal sections of the brain of HPE calf. (a) Cranial portion of the brain. (b) Caudal portion of the brain. The photographs show enlarged and merged lateral ventricles (v) with no frontal horns rostrally and rudimentary occipital horns caudally. On the caudal end of the merged ventricular space, a transversely oriented band of white matter (white arrow) can be seen. The hemispheres are connected by a bridge of grey matter (asterisks) under a less pronounced interhemispheric fissure (black arrow) while the thalami (T) are extensively fused. Notice the infundibular recess (arrowhead) of third ventricle

However, in SOD, interhemispheric fissure is fully formed (Volpe et al., 2009; Winter et al., 2015) and its previous reports generally do not indicate the presence of marked facial defects. Absence or hypoplasia of olfactory bulb and tract is a feature that had been reported in semi-lobar HPE (Dubourg et al., 2007; Koch et al., 2005). In previous report of semi-lobar HPE in a Morgan horse (Koch et al., 2005), olfactory bulbs were absent and the left and right olfactory peduncles as well as the rhinal sulci were continuous across the midline rostral to the optic chiasma. In the current case, olfactory bulb was hypoplastic but the other components of rhinencephalon were fairly well formed and the connection between the left and right components was not seen. The characteristic features that distinguish different HPE forms may still overlap underscoring the fact that HPE is a continuous spectrum of malformations.

HPE is accompanied by a spectrum of craniofacial defects (CFD) whose severity reflect the extend of brain deformity (Demyer et al., 1964; Dubourg et al., 2007; Winter et al., 2015). This is attributable to close relationship between embryonic establishment of ventral midline of CNS and facial development (Heyne et al., 2015; Marcucio, Cordero, Hu, & Helm, 2005; Sadler, 2012; Volpe et al., 2009). In some cases however, the positive correlation between extend of facial and brain defects was not apparent (Barr & Cohen, 2002; Mercier et al., 2011; Winter et al., 2015). It is reported that up to 20% of human HPE cases, including the most severe form in spectrum,the alobar

HPE, do not exhibit facial defects (Barr & Cohen, 2002; Dubourg et al., 2007; Winter et al., 2015). Some reports suggest that positive correlation between brain malformation and facial defects is a feature of HPE resulting from specific gene mutations (Mercier et al., 2011).

Orofacial clefts (OFC) are common birth defects in humans and their classification follows different systems (Gfrerer et al., 2014; Heyne et al., 2015; Khan et al., 2013; Wang et al., 2014). They constitute one of the CFD associated with HPE. OFC result from failure of closure in facial processes/prominences (Sadler, 2012; Smolec, Vnuk, Kos, Bottegaro, & Pirkic, 2010) which is precipitated by a myriad of factors including those that cause HPE (Heyne et al., 2015; Hu & Helms, 1999; Incardona, Gaffield, Kapur, & Roelink, 1998). OFC have also been reported in cattle and a classification system developed (Moritomo, Tsuda, & Miyamoto, 1999; Reinartz, Hellige, Feige, Wenning, & Distl, 2015; Smolec et al., 2010). In the present case, there was a bilateral complete cleft of the upper lip and a complete right-sided cleft of the upper jaw. On the palate, the whole rostral portion which constitutes the primary palate was missing allowing for free communication of nasal and oral cavities. The defects are most likely due to deficiency in development of nasal prominences, particularly the medial nasal prominences. This generally agrees with reported OFC in mice exposed to hedgehog signalling antagonist (Heyne et al., 2015). It appears that there was total or marked failure in development of the right medial nasal prominence, a feature that can be attributed to the wide cleft of the upper jaw with accompanying ipsilateral clefts of the lip and primary palate. On the left side, the features of the defects suggest that the upper jaw component of the medial nasal prominence developed to a large extend but the labial and palatal components did not (Sadler, 2012). Due to the absence of these upper jaw and lip components,the calf presented with a short snout that gave it a bulldog-like appearance. Deviation of the face is a common feature in cases of cattle with OFC (Lupp et al., 2012; Reinartz et al., 2015). In our case, the jaws were asymmetrical, the lower ones being longer, with dorsal deviation of the snout that mainly resulted from dorsal curvature of mandibles. The curvature of mandible has been suggested to occur due to the absence of occlusal forces between the mandibles and the missing segment of the upper jaw (Reinartz et al., 2015).

HPE is precipitated by an interaction of multiple genetic and environmental factors (Barr & Cohen, 2002; Dubourg et al., 2007; Hayhurst & McConnell, 2003; Heyne et al., 2015; Hong &Krauss, 2017; Incardona et al., 1998; Johnson & Rasmussen, 2010; Koch et al., 2005; Mouden et al., 2016; Roessler & Muenke, 1998, 2010; Solomon et al., 2010; Stashinko et al., 2004). Several genetic conditions associated with occurrence of HPE, including chromosomal anomalies and gene mutations, have been identified and these can be transmitted down the lineage (Barr & Cohen, 2002; Collins et al., 1993; Hayhurst & McConnell, 2003; Mouden et al., 2016; Paulussen et al., 2010; Roessler & Muenke, 1998, 2010; Solomon et al., 2012, 2010; Stashinko et al., 2004). From the history, though there were no records to confirm, the calf was sired by the same bull that sired the dam. Inbreeding among Kenyan dairy herds is not uncommon (Gorbach et al., 2010; Muasya, Peters, & Kahi, 2013) and it is even bound to be higher among small-scale farms where communal bulls are used for breeding. Although no genetic analyses were carried out, the current case points to a possible autosomal recessive inheritance. The condition could not be associated with any diseases, medication or other husbandry activities as none was reported in the dam during pregnancy. However, this was not based on records as the farmer did not keep any, makingit difficult to isolate the likely environmental predisposing factors. Factors in the diet are likely contributors to the genesis of the anomalies in the calf. The main source of feeds to the cows in the farm included wild fodder gathered from the roadsides, post-harvest crops remnants and also home refuse such as peelings. These are usually chopped into smaller pieces and then mixed with other feeds such as maize bran, chopped maize stalks among others to improve palatability then fed to the animals. Certain plants, including some crops such as potatoes and tomatoes, contain steroidal alkaloids known to be teratogenic (Hossain, Rawson, Aguiló-Aguayo, Brunton, & Rai, 2015; VanGelder, Vinke, & Scheffer, 1988). In fact, these steroidal alkaloids have been shown to inhibit hedgehog signalling thus causing HPE (Keeler, Baker, & Gaffield, 1990; Lipinski, Dengler, Kiehn, Peterson, & Bushman, 2007). Notably, the farm was located in a potato-growing region and the farmer himself plants the same in a portion of his land. Lack of enough land to grow adequate fodder, low income from animal products and high cost of commercial animal feeds push small-scale farmers to rely on gathered fodder whose composition and safety is uncertain. The owner of the calf, as would be the case in most small-scale farmers, was not aware that some of the crop plants could be harmful if fed to livestock. When such a condition occurs in an animal, the veterinarian has no option but to recommend euthanasia based on animal welfare considerations (Kisipan et al., 2016). The recommendation was agreeable to the owner based not only on animal welfare considerations but also on myths. Such a condition causes great economic losses and it was especially so in the current case which involved a valuable heifer belonging to a small-scale farmer who had just started developing his dairy herd.

4 | CONCLUSION

Facial defects reported by the farmer were confirmed to be OFC during clinical examination. Anatomopathological findings revealed HPE which was further classified as lobar HPE based on characteristic brain defects. Besides OFC, the other accompanying CFD included facial deviation and a defective and asymmetrical cranial cavity. The factors that could have caused the defect could not be ascertained but thought to be, most likely, a result of either recessive inheritance or exposure to teratogenic compounds from plants consumed by the dam during pregnancy. Farmer education on good animal breeding practices and feeding could help reduce the incidence of such cases.

ETHICS APPROVAL

Since the case came in as an emergency, prior ethics approval for the initial steps of the study including clinical examination through

to euthanasia was not sought but the owner's consent was obtained. Animal handling and procedures were handled professionally by qualified and duly licenced veterinarians. Later steps of the study (mainly anatomopathological examination) were approved by Egerton University ethics committee and owner's consent was obtained. In all steps, ethical policies of the journal have been adhered to.

CONSENT FOR PUBLICATION

The owner's consent to publish this work was obtained.

ACKNOWLEDGEMENTS

The authors acknowledge Messrs Dennis Ondieki and Peter Nyambati Mariita, both technologists at the department of veterinary anatomy and physiology, Egerton University, for their valuable contributions during the handling of the patient, preparation and processing of tissue specimens.

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

ORCID

Mosiany L. Kisipan https://orcid.org/0000-0003-1653-611X

REFERENCES

Barr, M., & Cohen, M. M. (2002). Autosomal recessive alobar holoprosencephaly with essentially normal faces. *American Journal of Medical Genetics*, *112*, 28–30. https://doi.org/10.1002/ajmg.10587

Bulakbasi, N., Cancuri, O., & Kocao, M. (2016). The middle interhemispheric variant of holoprosencephaly: Magnetic resonance and diffusion tensor imaging findings. *British Journal of Radiology*, *89*, 20160115. https://doi.org/10.1259/bjr.20160115

Cho, D. Y., Zeman, D. H., & Miller, J. E. (1985). Holoprosencephaly in a bovine calf. *Acta Neuropathologica*, *67*(3–4), 322–325. https://doi.org/10.1007/BF00687819

Collins, A. L., Lunt, P. W., Garrett, C., Dennis, N. R., Collins, N. R., Dennis, A. L., & Lunt, P. W. (1993). Holoprosencephaly: A family showing dominant inheritance and variable expression. *Journal of Medical Genetics*, *30*, 36–40. https://doi.org/10.1136/jmg.30.1.36

Demyer, W., Zeman, W., & Palmer, C. G. (1964). The face predicts the brain: Diagnostic significance of median facial anomalies for holoprosencephaly (Arhynencephaly). *Pediatrics*, *34*, 256–263.

Dubourg, C., Bendavid, C., Pasquier, L., Henry, C., Odent, S., & David, V. (2007). Holoprosencephaly. *Orphanet Journal of Rare Diseases*, *2*, 8. https://doi.org/10.1186/1750-1172-2-8

Gfrerer, L., Shubinets, V., Hoyos, T., Kong, Y., Nguyen, C., Pietschmann, P., … Liao, E. C. (2014). Functional analysis of SPECC1L in craniofacial development and oblique facial cleft pathogenesis. *Plastic and Reconstructive Surgery*, *134*(4), 748–759. https://doi.org/10.1097/PRS.0000000000000517

Gonçalves, R., Volk, H., Smith, P. M., Penderis, J., Garosi, L., MacKillop, E., … McConnell, J. F. (2014). Corpus callosal abnormalities in Dogs. *Journal of Veterinary Internal Medicine*, *28*(4), 1275–1279. https://doi.org/10.1111/jvim.12371

Gongal, P. A., & Waskiewicz, A. J. (2008). Zebrafish model of holoprosencephaly demonstrates a key role for TGIF in regulating retinoic acid metabolism. *Human Molecular Genetics*, *17*(4), 525–538. https://doi.org/10.1093/hmg/ddm328

Gorbach, D. M., Makgahlela, M. L., Reecy, J. M., Kemp, S. J., Baltenweck, I., Ouma, R., … Rothschild, M. F. (2010). Use of SNP genotyping to determine pedigree and breed composition of dairy cattle in Kenya. *Journal of Animal Breeding and Genetics*, *127*(5), 348–351. https://doi.org/10.1111/j.1439-0388.2010.00864.x

Hahn, J. S., & Barnes, P. D. (2010). Neuroimaging advances in holoprosencephaly: Refining the spectrum of the midline malformation. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, *154C*(1), 120–132. https://doi.org/10.1002/ajmg.c.30238

Hahn, J. S., Barnes, P. D., Clegg, N. J., & Stashinko, E. E. (2010). Septopreoptic holoprosencephaly: A mild subtype associated with midline craniofacial anomalies. *American Journal of Neuroradiology*, *31*, 1596–1601. https://doi.org/10.3174/ajnr.A2123

Hayhurst, M., & McConnell, S. K. (2003). Mouse models of holoprosencephaly. *Current Opinion in Neurology*, *16*, 135–141. https://doi.org/10.1097/01.wco.0000063761.15877.40

Heyne, G. W., Melberg, C. G., Doroodchi, P., Parins, K. F., Kietzman, H. W., Everson, J. L., … Lipinski, R. J. (2015). Definition of critical periods for hedgehog pathway antagonist-induced holoprosencephaly, cleft lip, and cleft palate. *PLoS ONE*, *10*(3), e0120517. https://doi.org/10.1371/journal.pone.0120517

Hong, M., & Krauss, R. S. (2017). Ethanol itself is a holoprosencephaly-inducing teratogen. *PLoS ONE*, *12*(4), e0176440. https://doi.org/10.1371/journal.pone.0176440

Hossain, M., Rawson, A., Aguiló-Aguayo, I., Brunton, N., & Rai, D. (2015). Recovery of steroidal alkaloids from potato peels using pressurized liquid extraction. *Molecules*, *20*(5), 8560–8573. https://doi.org/10.3390/molecules20058560

Hu, D., & Helms, J. A. (1999). The role of Sonic hedgehog in normal and abnormal craniofacial morphogenesis. *Development*, *126*, 4873–4884.

Incardona, J. P., Gaffield, W., Kapur, R. P., & Roelink, H. (1998). The teratogenic veratrum alkaloid cyclopamine inhibits sonic hedgehogsignal transduction. *Development*, *125*, 3553–3562.

Johnson, C. Y., & Rasmussen, S. A. (2010). Non-genetic risk factors for holoprosencephaly. *American Journal of Medical Genetics Part C Seminars in Medical Genetics*, *154C*(1), 73–85. https://doi.org/10.1002/ajmg.c.30242

Keating, M. K., Sturges, B. K., Sis, S., Wisner, E. R., Creighton, E. K., & Lyons, L. A. (2016). Characterization of an inherited neurologic syndrome in Toyger cats with forebrain commissural malformations, ventriculomegaly and interhemispheric cysts. *Journal of Veterinary Internal Medicine*, *30*, 617–626. https://doi.org/10.1111/jvim.13836

Keeler, R., Baker, D., & Gaffield, W. (1990). Spirosolane-containing Solanum species and induction of congenital craniofacial malformations. *Toxicon*, *28*(8), 873–884. https://doi.org/10.1016/0041-0101(90)90017-2

Khan, M., Ullah, H., Naz, S., Iqbal, T., Ullah, T., Tahir, M., & Ullah, O. (2013). A revised classification of the cleft lip and palate. *Canadian Journal of Plastic Surgery*, *21*(1), 48–50. https://doi.org/10.1177/229255031302100102

Kisipan, M. L., Orenge, C. O., Gacheru, D. N., & Ngure, R. M. (2016). A case of cranium bifidum with meningocele in Ayrshire calf. *BMC Veterinary Research*, *13*(1), 20. https://doi.org/10.1186/s12917-016-0936-9

Koch, T., Loretti, A., De Lahunta, A., Kendall, A., Russell, D., Bienzle, D., & Koch, T. G. (2005). Semilobar holoprosencephaly in a Morgan horse. *Journal of Veterinary Internal Medicine*, *19*, 367–372. https://doi.org/10.1111/j.1939-1676.2005.tb02711.x

Kousa, Y. A., du Plessis, A. J., Vezina, G., & Youssef Kousa, C. A. (2018). Prenatal diagnosis of holoprosencephaly. *American Journal of Medical Genetics*, *178*(C), 206–213. https://doi.org/10.1002/ajmg.c.31618

Lipinski, R. J., Dengler, E., Kiehn, M., Peterson, R. E., & Bushman, W. (2007). Identification and characterization of several dietary alkaloids as weak inhibitors of hedgehog signaling. *Toxicological Sciences*, *100*(2), 456–463. https://doi.org/10.1093/toxsci/kfm222

Lupp, B., Reinhardt, M., Maus, F., Hellige, M., Feige, K., & Distl, O. (2012). Right-sided cleft lip and jaw in a family of Vorderwald × Montbéliarde cattle. *The Veterinary Journal*, *192*(3), 520–522. https://doi.org/10.1016/j.tvjl.2011.06.032

Marcorelles, P., & Laquerriere, A. (2010). Neuropathology of holoprosencephaly. *American Journal of Medical Genetics Part C Seminars in Medical Genetics*, *154C*, 109–119. https://doi.org/10.1002/ajmg.c.30249

Marcucio, R. S., Cordero, D. R., Hu, D., & Helm, J. A. (2005). Molecular interactions coordinating the developmentof the forebrain and face. *Developmental Biology*, *284*, 48–61. https://doi.org/10.1016/j.ydbio.2005.04.030

Mercier, S., Dubourg, C., Garcelon, N., Campillo-Gimenez, B., Gicquel, I., Belleguic, M., … Odent, S. (2011). New findings for phenotype-genotype correlations in a large European series of holoprosencephaly cases. *Journal of Medical Genetics*, *48*(11), 752–760. https://doi.org/10.1136/jmedgenet-2011-100339

Moritomo, Y., Tsuda, T., & Miyamoto, H. (1999). Craniofacial skeletal abnormalities in anomalous calves with clefts of the face. *Journal of Veterinary Medical Science*, *61*(10), 1147–1152. https://doi.org/10.1292/jvms.61.1147

Mouden, C., Dubourg, C., Carré, W., Rose, S., Quelin, C., Akloul, L., … David, V. (2016). Complex mode of inheritance in holoprosencephaly revealed by whole exome sequencing. *Clinical Genetics*, *89*(6), 659–668. https://doi.org/10.1111/cge.12722

Muasya, T., Peters, K. J., & Kahi, A. K. (2013). Breeding structure and genetic variability of the Holstein Friesian dairy cattle population in Kenya. *Animal Genetic Resources*, *53*, 127–137. https://doi.org/10.1017/S2078633613000039

Nourani, H., Karimi, I., & Vardanjani, H. R. (2014). Synophthalmia in a Holstein cross calf. *Veterinary Research Forum*, *5*(4), 333–335.

Nyberg, D. A., Mack, L. A., Bronstein, A., & Hirsch2, J., & Pagon, R. A., (1987). Holoprosencephaly: Prenatal Sonographic Diagnosis. *American Journal of Neuroradiology*, *8*, 871–878.

Paulussen, A. D. C., Schrander-Stumpel, C. T., Tserpelis, D. C. J., Spee, M. K. M., Stegmann, A. P. A., Mancini, G. M., … Herbergs, J. (2010). The unfolding clinical spectrum of holoprosencephaly due to mutations in SHH, ZIC2, SIX3 and TGIF genes. *European Journal of Human Genetics*, *18*(10), 999–1005. https://doi.org/10.1038/ejhg.2010.70

Reid, S. N., Ziermann, J. M., & Gondr e-Lewis, M. C., (2015). Genetically induced abnormal cranial development in human trisomy 18 with holoprosencephaly: Comparisons with the normal tempo of osteogenic–neural development. *Journal of Anatomy*, *227*, 21–33. https://doi.org/10.1111/joa.12326

Reinartz, S., Hellige, M., Feige, K., Wenning, P., & Distl, O. (2015). Phenotypic classification of variability of non-syndromic congenital cleft lip and jaw in Vorderwald × Montbéliarde cattle. *Acta Veterinaria Scandinavica*, *57*, 87. https://doi.org/10.1186/s13028-015-0177-0

Roessler, E., & Muenke, M. (1998). Holoprosencephaly: A paradigm for the complex genetics of brain development. *Journal of Inherited Metabolic Disease*, *21*(5), 481–497. https://doi.org/10.1023/A:1005406719292

Roessler, E., & Muenke, M. (2010). The molecular genetics of holoprosencephaly. *American Journal of Medical Genetics Part C Seminars in Medical Genetics*, *154C*, 52–61. https://doi.org/10.1002/ajmg.c.30236

Sadler, T. W. (2012). *Langman's Medical Embryology*, 12th ed.. Philadelphia: Lippincott Williams & Wilkins.

Simon, E. M., Hevner, R. F., Pinter, J. D., Clegg, N. J., Delgado, M., Kinsman, S. L., … Barkovich, A. J. (2002). The Middle Interhemispheric Variant of Holoprosencephaly. *American Journal of Neuroradiology*, *23*, 151–155.

Smolec, O., Vnuk, D., Kos, J., Bottegaro, N. B., & Pirkic, B. (2010). Repair of cleft palate in a calf using polypropylene mesh and palatal mucosal flap: A case report. *Veterinarni Medicina*, *55*(11), 566–570.

Solomon, B. D., Bear, K. A., Wyllie, A., Keaton, A. A., Dubourg, C., David, V., … Muenke, M. (2012). Genotypic and phenotypic analysis of 396 individuals with mutations in Sonic Hedgehog. *Journal of Medical Genetics*, *49*, 473–479. https://doi.org/10.1136/jmedgenet-2012-101008

Solomon, B. D., Mercier, S., Vélez, J. I., Pineda-Alvarez, D. E., Wyllie, A., Zhou, N., … Muenke, M. (2010). Analysis of genotype-phenotype correlations in human holoprosencephaly. *American Journal of Medical Genetics Part C Seminars in Medical Genetics*, *154C*(1), 133–141. https://doi.org/10.1002/ajmg.c.30240

Stashinko, E. E., Clegg, N. J., Kammann, H. A., Sweet, V. T., Delgado, M. R., Hahn, J. S., & Levey, E. B. (2004). A retrospective survey of perinatal risk factors of 104 living children with holoprosencephaly. *American Journal of Medical Genetics*, *128A*, 114–119. https://doi.org/10.1002/ajmg.a.30070

VanGelder, W. M. J., Vinke, J. H., & Scheffer, J. J. C. (1988). Steroidal glycoalkaloids in tubers and leaves of Solanum species used in potato breeding. *Euphytica*, *39*(3), 147–158. https://doi.org/10.1007/BF00043378

Volpe, P., Campobasso, G., De Robertis, V., & Rembouskos, G. (2009). Disorders of prosencephalic development. *Prenatal Diagnosis*, *29*, 340–354. https://doi.org/10.1002/pd.2208

Wang, K. H., Heike, C. L., Clarkson, M. D., Mejino, J. L. V., Brinkley, J. F., Tse, R. W., … Cox, T. C. (2014). Evaluation and integration of disparate classification systems for clefts of the lip. *Frontiers in Physiology*, *5*, 163. https://doi.org/10.3389/fphys.2014.00163

Webb, E. A., & Dattani, M. T. (2010). Septo-optic dysplasia. *European Journal of Human Genetics*, *18*, 393–397. https://doi.org/10.1038/ejhg.2009.125

Winter, T. C., Kennedy, A. M., & Woodward, P. J. (2015). Holoprosencephaly: A survey of the entity, with embryology and fetal imaging. *Radiographics*, *35*, 275–290. https://doi.org/10.1148/rg.351140040

How to cite this article: Kisipan ML, Nyaga SN, Thuo JN, Nyakego PO, Orenge CO, Ojoo RO. Lobar holoprosencephaly with craniofacial defects in a Friesian calf: A case report. *Vet Med Sci*. 2020;6:454–461. https://doi.org/10.1002/vms3.244