Congenital Anophthalmia with Caudal Vertebral Anomalies in Japanese Brown Cattle

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(Received 25 January 1995/Accepted 14 April 1995)

ABSTRACT. Anophthalmia and caudal vertebral anomalies such as taillessness or wry tail were morphologically examined in ten Japanese Brown calves obtained in Kumamoto Prefecture. The anomalous calves lacked eyeball bilaterally or unilaterally but had small-sized eyelids and narrow palpebral fissures. A small cystic, solid or spot-like remnant of eyeball (REB) was buried in the mixture of vestigial extraocular muscles, lacrimal gland and adipose tissue of the orbit. The REB was composed of irregularly arranged elements of ocular wall such as sclera, choroid and retina. The retina was often dysplastic and connected to the hypoplastic optic nerve. These morphological changes might represent the defective processes after the formation of the optic vesicle or cup. Therefore, this eye defect may be defined as degenerative anophthalmia. The defects of the vertebral body such as wedge vertebra, hemivertebra, and sagittal cleft vertebra seen in the lumbar, sacral, and coccygial regions and the meandering of the axial line of abnormal vertebrae may suggest the failure of notochord formation in the early fetal period. From the embryological point of view, it seemed possible that the calves were exposed to teratogen at the critical time of optic organogenesis and notochordal formation. The cause of anomalies could not be determined in this study.—KEY WORDS: anophthalmia, caudal vertebral anomaly, congenital abnormality, Japanese Brown cattle.

J. Vet. Med. Sci. 57(4): 693–696, 1995

Anophthalmia is defined as a total absence of ocular tissues [23], and in cattle may be often associated with anomalies of other organs, especially caudal vertebral defects such as taillessness [11, 12, 17, 21]. Its incidence has been estimated to be low with some variations by breeds [12]. We have already reported several cases of anophthalmia from a morphological point of view [14, 15], and have later recognized sporadic occurrences of anophthalmia with caudal vertebral anomalies in Japanese Brown cattle. In this paper, therefore, we morphologically examined these cases in detail to discuss the pathogenesis from a embryological point of view.

MATERIALS AND METHODS

Ten anophthalmic Japanese Brown calves with tail abnormalities were gained from the herds in Kumamoto Prefecture and used as materials (Table 1). Information on their genetic background and raising condition of the dams during pregnancy were obtained from herd owners. After euthanasia under xylazine sedation, materials underwent gross and histological examinations in detail. Especially, the ocular components were examined in the 500 μm-thick step serial sections of the structure in the orbit, and the skeletal abnormalities in the cranium and caudal vertebral column by maceration and/or soft X ray. Postcolostrum sera were also examined to detect antibodies to viruses (Aino, Akabane, BVD-MD, Chuzan).

RESULTS

Ten anomalous calves lacked eyeball bilaterally or unilaterally but had small-sized eyelids and narrow palpebral fissures. The abnormality was associated with

Table 1. Clinical signs in abnormal calves

No.	Date of birth		Age (days)	Sex[a)]	Body weight (kg)	Age of dam (years)	Side of no eyeball	State of tail	Others[b)]
1	April	1987	9	F	25	—[c)]	Bilateral	Wry	DH
2	April	87	39	F	72	10	Bilateral	Wry	DH, DMAV
3	May	87	18	F	43	6	Bilateral	Tailless	DH, DMAV
4	April	88	7	M	33	15	Bilateral	Wry	
5	September	89	88	F	54	14	Bilateral	Tailless	DMAV
6	July	90	3	F	28	12	Bilateral	Wry	DH
7	September	91	21	F	25	9	Bilateral	Wry	DH
8	July	92	13	M	28	8	Left	Wry	
9	April	93	19	F	43	9	Right	Tailless	DMAV
10	June	93	45	F	55	13	Bilateral	Wry	Cleft lip

a) F: Female, M: Male.
b) DH: Doming of the head, DMAV: Dorsal malposition of the anus and vulva.
c) —: Not examined.

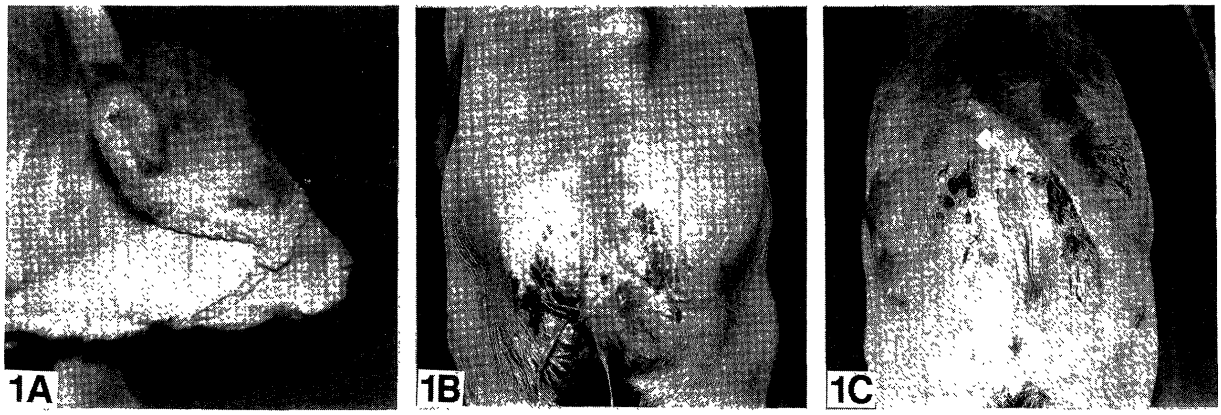

Fig. 1. Anomalies in the optic region and tail in calves.
A; No eyeball with small-sized eyelid and narrow palpebral fissure (case No. 8).
B; Taillessness with dorsal malposition of the anus and vulva (case No. 5).
C; Wry tail (case No. 2).

Table 2. Pathological changes at affected sites

No.	State of the REB[a]		Brain[b]	Cranium[c]	Caudal vertebrae[d]		
	Left	Right			Lumbar	Sacral	Coccygial
1	Solid	Solid	HOCT, MDL-PD	NO, POF, DSF	—[g]	—	—
2	Cyst	Cyst	HOCT, HCC-WL	NO, COG	—	SC(S4, S5)	WE(C1, C2), NRV[12]
3	Cyst	Cyst	HOCT, HCC-WL, DTV, HT	NO, POF, DSF, AFF	—	SC(S1), WE(S2~S4) HE(S5)	HE(C1), MA(C2~C5) Others are missing
4	ND	Spot	HOCT	NO, COG, DSF	—	WE(S4, S5)	NRV[16]
5	ND	Spot	HOCT	NO, COG	SC(2nd lumbar vertebra[e])	MA(S1~S4)[f] Missing (S5)	All are missing
6	Spot	ND	HOCT	NO, COG	SC(L5, L6)	SC(S1), WE(S2, S3)	MA(C1~C4), NRV[12]
7	Cyst	Cyst	HOCT	NO, COG			WE(C1~C3), NRV[10]
8	Cyst	Nor.	HOCT	NO, COG		WE(S4, S5)	NRV[17]
9	Nor.	Cyst	HOCT	NO, POF	SC(L6)	SC(S1) MA(S3~S5)	A deformed piece (C1) Others are missing
10	Cyst	Solid	HOCT	NO, POF, ISS			HE(C2), WE(Cl, C3) NRV[15]

a) ND: Not detected, Nor.: Normal.
b) DTV: Dilation of the third ventricle, HCC-WL: Hypoplasia of the corpus callosum with widened longitudinal fissure, HOCT: Hypoplasia of the optic chiasma and optic tract, HT: Heterotopia, MDL-PD: Mild dilation of the lateral ventricle with defective septum pellucidum.
c) AFF: Abnormal foramen at fontanellar region, COG: Constricted optic groove, DSF: Dome-shaped frontal bone, ISS: Intersphenoidal synostosis, NO: Narrow orbit, POF: Patent optic foramina.
d) HE: Hemivertebra, MA: Miscellaneous anomalies, NRV: The number of remaining vertebrae, SC: Sagittal cleft vertebra, WE: Wedge vertebra. e) There are seven segments in lumbar vertebrae. f) Fusion of the spinous processes is associated. g) —: Not examined.

taillessness or wry tail (Fig. 1, Table 1). Several calves showed the doming of the head, dorsal malpositioning of the anus and vulva, and the cleft lip. The anomalous calves were born at full term, and had normal vigor and appetite, but were slightly small in body size. According to pedigree analysis, five calves (cases No. 1 through No. 5) were sired by the bull "M", but the others had respective sires belonging to the other strains than the bull "M". The dams were advanced in age but had no genetic relation with each other. They had never delivered abnormal calves, were good in health condition and received no medical treatment during pregnancy.

The pathological changes are summarized in Table 2. The orbit contained a small cystic, solid or spot-like remnant of eyeball (REB) in all animals on the affected side except the left side in case No. 4 and No. 5 and right side in No. 6. The REB was detected in the mixture of vestigial extraocular muscles, lacrimal gland and adipose tissue and contained islets of hyaline cartilage seeming to represent the remnant of the third eyelid. The REB was histologically composed of irregularly arranged elements of ocular wall such as sclera, choroid and retina (Fig. 2). Rudimentary ciliary processes and dysplastic retina characterized by rosette formation by undifferentiated cells

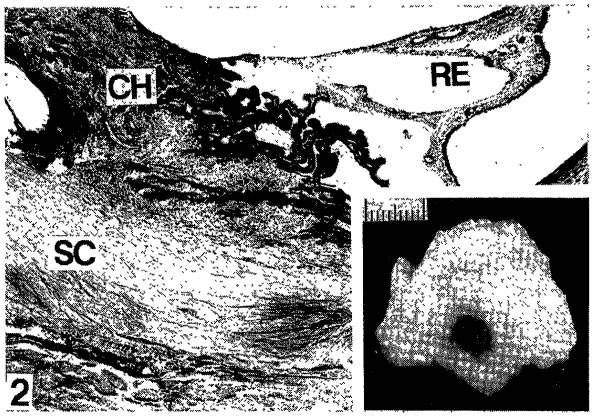

Fig. 2. Histological section of REB (case No. 8). HE stain × 15. Dysplastic retina (RE), sclera (SC) and choroid (CH) are irregularly arranged. Inset; Cut surface of small cystic REB (case No. 8). Scale; Centimeter graduated in millimeters.

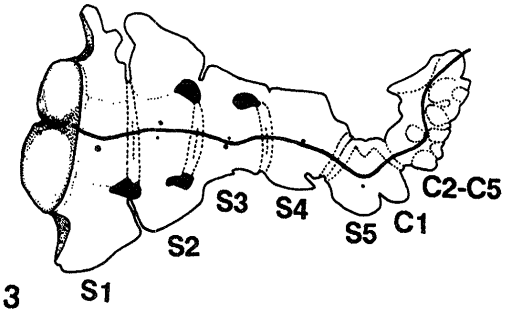

Fig. 3. Schematic presentation of vertebral abnormalities and meandering of the axial line (a thick solid line) in caudal vertebrae (case No. 3).

Table 3. Antibody titers to viruses in post-colostrum sera

No.	Aino	Akabane	BVD-MD	Chuzan
1	≧256	2	32	<2
2	2	32	<2	<2
3	64	64	8	<2
4	2	16	<2	<2
5	<2	64	2	64
6	2	64	<2	<2
7	256	128	64	<2
8	4	16	16	128
9	2	≧256	<2	<2
10	2	32	<2	<2

were often seen in the cystic and solid REB, and small masses of pigmented epithelial cells in the spot-like one. Lens-like structures were not identified in any cases. The intraorbital optic nerves connected to the retina were hypoplastic in the cystic and solid REB, and absent in the spotted one. In the intracranial region, optic nerves were hypoplastic and hollow and cylindrical in shape on the affected sides in all animals. The REB was often accompanied by the concomitant changes such as hypoplasia of the optic tract and chiasma in the brain, narrowing of the orbit and constriction of the optic groove, and/or patency of the optic foramina in the cranium. Additional abnormalities in the brain included hypoplasia of the corpus callosum with widened longitudinal fissure of the cerebrum, mild dilation of the lateral ventricle with defective septum pellucidum, dilation of the third ventricle, and heterotopia. Abnormal changes in the cranium included dome-shaped frontal bone with abnormal foramen at the fontanellar region, and premature intersphenoidal synostosis.

The vertebral column showed vertebral abnormalities with various severity such as wedge vertebra, hemivertebra and sagittal cleft vertebra in the lumbar to coccygial region. In the caudal part of the lumbar region, mildly affected vertebrae were often encountered. In the sacral and coccygial regions, many types of anomalous vertebrae were often irregularly fused to form miscellaneous anomalies. In addition the spinous processes and vertebral arches fused in the sacral region, and lumbar vertebrae with a sagittal cleft increased in number in case No. 5. In tailless calves, caudal vertebrae were severely deformed and reduced. In these abnormalous vertebrae, the axial line of the vertebral column was meandered in relation to vertebral abnormalities such as hemivertebra on the convex side and the loss or partial fusion of an oposite half segment on the concave side, and wedge vertebra wide on the convex side and narrow on the concave side (Fig. 3). Apart from above-mentioned defects, renal fusion was seen in case No. 4. Antibodies to Aino and Akabane viruses were detected very frequently, but those to BVD-MD and Chuzan viruses much less frequently in the sera from the calves examined. Their antibody titers are shown in Table 3.

DISCUSSION

Failure of optic anlage formation from the forebrain, completely suppressed or abnormal development of the entire forebrain, and breakdown or degeneration of the optic vesicle are suspected to be involved in the etiology of anophthalmia. These changes are called primary, secondary, and degenerative anophthalmia, respectively [19]. In the present study, the bizarre histological features in the REB suggest the developmental eye defects during optic organogenesis. Especially, dysplastic retina seems to have resulted from the improper apposition of the inner and outer layers of the optic cup [23]. These changes in ocular tissues and the existence of hypoplastic optic nerve might reflect the defective processes after the formation of optic vesicle or cup. In some cases (Nos. 1, 2 and 3), the brain showed hypoplasia of the corpus callosum due to failure of neural fold closure, dilation of the third and lateral ventricles due to disturbance of the flow of cerebrospinal fluid, and heterotopia due to disorder of neuroblast migration [3]. Since these findings do not seem to relate directly to the development of optic anlage from the forebrain, the state of the eye defect in the calves was defined as degenerative anophthalmia. The developmen-

tal error of the eye might be concomitantly accompanied by the hypoplasia of the optic tract and chiasma in the brain, narrowing of the orbit, constriction of the optic groove and patency of the optic foramina in the cranium, diminution of the eyelids, and narrowing of the palpebral fissures.

Vertebral malformation may be intimately correlated with failure in notochord, somite, and/or neural tube formation [20]. Especially, the defects of the vertebral body such as wedge vertebra, hemivertebra, and sagittal cleft vertebra have been reported to be related to the failure of notochord formation in the early fetal period [1, 4, 9, 16, 18, 22]. In the present study, the morphological changes in the caudal vertebrae such as vertebral anomaly and meandering of the axial line of vertebrae may possibly be due to the persistant existence, partial loss and irregular tortuous movement of the notochord from the etiological point of view.

In the bovine fetus, primodial optic evagination appears at day 20 or 21 of gestation, and the optic vesicle is formed at day 23 and the optic cup at day 30 of development [2, 5, 6]. The notochord emerges at day 18 or 19, and extends into the future sacral and proximal tail structure at day 26 or 27 [7, 8]. It may be possible that the critical period of exposure to teratogen coincided with optic organogenesis and notochordal formation in early embryogenesis. In the present study, although antibodies to Aino and Akabane viruses were very frequently detected in the postcolostral sera, calves did not show characteristic morphological changes induced by Akabane virus infection such as nonpurulent encephalomyelitis, hydranencephaly and arthrogryposis with dysplastic muscular change [10]. The relationship between abnormal bovine birth and Aino virus infection remains unknown [13]. Therefore, it was impossible to relate the morphological changes in the examined cases to these viral infections. Although the cause of anomalies could not be estimated in this study, the advanced ages of the dams may be noteworthy in the future studies.

ACKNOWLEDGEMENTS. The authors wish to thank Dr. K. Hamana, Department of Veterinary Medicine, Faculty of Agriculture, Kagoshima University, for his useful advice. This work was supported by General Research Organization at Tokai University.

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