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Morphological Aspect of Congenital Anophthalmia in the Calf from the Viewpoint of Comparative Teratology

by

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Özet: Araştırmada, yeni doğmuş bir erkek danada tesbit edilen bilateral anophthalmus congenitus (Doğmalık göz yokluğu) olayı, 1976 yılı Dünyada Sağlık, Türkiye'de Körler Haftası münasebetile, morfolojik yönden incelenmiştir. Bu doğmalık körlük olayında ortaya çıkan anatomik bozukluklar ayrıntılarıyle tanıtılmış ve komparatif teratoloji açısından değerlendirilmiştir. Olayda, özellikle N. opticus ve retina şekillenmemiş, her iki orbita adipos ve fibroz bir bağdoku ile dolu bulunmuştur. Literatürde bu malformasyonun sığırda ender olmadığı verilerine dayanılarak, insandaki anophthalmus congenitus olayının nedenleri ve oluşum makanizmasının anlaşılabilmesi için, sığırın iyi bir deneme hayvanı olabileceği önerilmektedir.

Summary: A true case of bilateral anophthalmus congenitus found in a newborn male calf was investigated morphologically on the occasion of World Health Week 1976 which was made the occasion in Turkey of *Blindness Week*.

The main anatomical defects causing this blindness are described and discussed from the viewpoint of comparative teratology. The optic nerve and retina were absent, both orbits were filled with a fatty and fibrous connective tissue.

As a result of this study, and because the literature indicates that this malformation is not uncommon in cattle it is proposed that the cow would be a good experimental animal for the invesrigation of congenital anophthalmia in order to gain an understanding of the principal causes and mechanism governing the development of congenital anophthalmia in human beings.

Introduction

Congenital malformations are structural abnormalities present at birth which can be expected to interfere partly or totally with the normal functions of an individual. Although much research work has

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been done on this subject, there are many such malformations, both in human beings and in animals, whose cause is still obscure. Therefore congenital anomalies are still a challenge to medicine today. Many recent studies indicate that spontaously occuring congenital defects in animals can give life-saving clues to new environmental teratogens which are of importance to man, such as methyl-mercury which is responsible for Minamata disease. Conditions Well-known in man which can be studied in domestic animals include the Klinefelter, Ehlers-Danlos and Chediak Higashi syndromes, chimarism, congenital hearth disease (CHD), arthrogyriposis, cyclopia, intersexuality and torticollis. It is believed that a systematic and comparative approach to the problem of congenital malformations would provide a more effective strategy for their future prevention both in man and in domestic animals.

Teratology is a very important subject in Veterinary Medicine today from the standpoint of economy, and for research into the actiology of cases of human malformation.

Mulvihill (1972) and Deniz (1975) have reported that domestic animals provide good models for investigation of the causes of human congenital birth defects because of similarities in environmental factors.

The aim of the study reported in this paper was to investigate an interesting case of bilateral congenital anophthalmia in a newborn calf: this study was carried out on the occasion of World Health Week 1976, which was made the occasion in Turkey of *Blindness Week*.

Agenesis bulbi oculi and microphthalmia have been reported in the literature both in man and in animals Wiedeking 1968, (Warkany 1971, Takano-Nishimura 1971). Complete absence of the eye is very rare; many cases of microphthalmia have however been erroneously reported as anophthalmia, since clinical distinction is difficult without microscopic examination. In a true case of anophthalmia both the bulbus oculi and the optic nerve are totally absent.

Anophthalmia may occur unilaterally or bilaterally. It is reported that the main causes of anophthalmia are either a unilateral or bilateral nondevelopment of the eye-ball or a failure in normal development of the optic nerve caused by abonormal amniotic fluid (Wiesner). The hereditary morphogenesis of anophthalmia is still obscure in animals, though simple recessive inheritance has ben reported in the cow; in man anophthalmia normally shows autosomal recessive inheritance, though sometimes, in cases where prenatal consanguinity

has either been established or can be assumed it can appear to show autosomal dominant inheritance.

Warkany and Kerse have also reported a trisomy D1 13–15 causing congenital anophthalmia and microphthalmia in man. The general incidence of anophthalmia in man has been reported as 0.1 %. Takano and Nishimura (1957) report on an experiment in which in rats treated with Alloxan, microphthalmia occured in a diabetic group, and anophthalmia in a control group of Alloxan-treated non-diabetic rats.

Beaudoin and Roberts (1966), testing thyrotropin as an antithyroid medication in rats, found 24.6 % cases of anophthalmia with hydrocephalia (Nishimura 1968). Barber (1957), using Trypanblue, was able to distinguish mice heterozygous for anophthalmia from homozygous normals. In an embryological investigation he found that anophthalmic mice show an inhibition of the growth of the optic vesicle on the tenth day of gestation.

Gilbert and Gilman (1954) describe the morphogenesis of Trypanblue-induced eye defects in the rat and tested the effects of azo dyes. Some authors have reported that the administration of excessive Vitamin A (Hypervitaminos A) can cause anophthalmia in mice, rats, and rabbits. On the other hand Wiesner (1960) has reported that Hypovitaminosis A can play a role in anophthalmia in pigs. Methlyl salicylate, pantothenic acid deficiency and hypoglycemia-inducing compounds can also induce the development of anophthalmia (Warkany).

Anophthalmia is relatively more frequent as a bilateral condition. Anophthalmia and microphthalmia can occur in the same individual. In the cow anophthalmia has been reported as associated with congenital tailness (Koch, Fischer, Schumann 1957). In the horse and chicken anophthalmia is considered a lethal factor named B_7 in the horse and E_{13} in the chicken (Wiesner 1960).

Findings

The case reported in this paper is a native male calf which was born blind, and showed bilateral anophthalmia (Fig 1 and 2). The animal showed no other abnormalities. External examination revealed that both eyes were smaller than normal. The animal was unable to maintain its equilibrium. The animal was prepared for anatomical investigation, and a detailed examination was made of both orbital regions under a stereomicroscope.

a- *Left eye* (Fig 3 and 4). The superior and tertiary palpebrae were absent. The lower eyelid (palpebra inferior) was present, but not normally developed: its size was 2X1 cm, it was plicated, had few cilia and was directed within the orbital cavity. The form of the orbita was rather quadrate (Fig 4). Incisurae were found at both sides of the lacrimal process; on the external surface of the lacrimal bone a small foramen was seen through which a nerve fibre and a branch of facial artery passed into the orbita. The orbita was mostly filled with a fatty fibrous tissue mass, which was the remnant of the bulbus ocuii. Within this mass, there were two rudimentary eye muscles (M.obliquus superior et inferior) and small lacrimal gland. In the centre of the mass a rudimentary eyeball some 5–7 mm in diamater was differentiated, with a dark-pigmented tunica media and a fibrous tunica externa. The lens crystallina and the retina were absent. At the apex of the orbita there was a very small optic foramen filled with dura mater; there was no optic nerve.

b- *Right eye* (Fig. 5 and 6). The upper eyelid (palpebra superior) had only a few cilia at its medial end. The inferior atretic palpebra formed a plica on the lateral angle of the eye, directed ventrolaterally to form a rima. The margin of the inferior palpebra had normal cilia. The orbita was again filled with fatty fibrous connective tissue, the eye-muscles and rudimentary eyeball presented the same malformed appearance as in the left eye. Again there was no optic nerve, no retina, and no lens crystallina.

c- *Cranial cavity:* Investigation of the cranial cavity revelaed that the brain and the meninges were normally developed, but the volume of the total encephalon was relatively smaller than normal. The optic chiasma and optic nerves were not developed. In contrast to the optic structures, the olfactory bulbus was larger than normal. Though searched for under the stereomicroscope, the ophthalmic and oculomotor nerves could not be identified.

Discussion

In prenatal development, the activity of the albumen of the cell is at its highest level at the beginning of organogenesis. As a result, at this period the brain, eyes, ears, palates and lips are very susceptible to craniofacial malformations; the eye is particularly subjected to malformation (Warkany, Rieck). According to Böhler (in Wiesner), the main morphological results of anophthalmia and microphthalmia are as follows:

1. The retina, optic nerve and lens crystallina may fail to develop,

2. The mesodermal parts of the bulbus may fail to form, or may be malformed.

3. The ectodermal parts of the bulbus oculi which originate from the ectoderm may develop abnormally.

The sensory part of the eye forms, together with the optic nerve, an optic unit which develop from a protrution of the forebrain (prosencephalon). The lens crystallina comes from the ectoblast, the middle and external tunica of the bulbus and the meninges are mesenchymatous. In the case of anophthalmia, the optic capsule fails to form, and there is then no optic nerve and retina.

In man, the eye is extremly sensitive to teratogenetic factors: exogenic factors, such as x-rays cause both anophthalmia and microphthalmia.

The following lists cases reported in the literature in which anophthalmus congenitus or microphthalmus have been induced experimentally in laboratory animals:

Author and Year	Description of the case	Animal species	Teratogen (used)
Cohlan,S.Q. (1953)	Microphthalmia	Rat	Hypervitaminosis-A
Gilbert, C. and Gilman, J, (1954)	Anophthalmia	Rat	Trypanblue
Giroud, A., Martinet, M. (1956)	Microphthalmia	Rat	Hypervitaminosis-A
Barber, A.N. (1957)	Anophthalmia	Mice	Maternal Hypoxia
Giroud, A. Martinet, M. (1959)	Microphthalmia	Rabbit	Hypervitaminosis-A
Beck, F., Lloyd, J.B. (1966)	Anophthalmia Microphthalmia	Rat	Azo Dyes
Takano, K., Nishimura, H. (1967)	Anophthamia Microphthalmia	Rat Mice	Alloxan

According to the references cited, congenital anophthalmia in man has been said to have a recessive or an autosomal recessive inheritance, that the mechanism is not understood in detail. A Trisomy D_1 13–15 has also been given as a possible cause for anophthalmia in man. Toxoplasmosis and rubella can be also cited as causes for congenital anophthalmia cases in human being (Warkany). As far as

animals, anophthalmia is reported as a simple recessive character in the cow, and a lethal trait in the horse and the chicken.

In the Pig, Wiesner (1960) has reported that Hypovitaminosis-A plays a role in the development of anophthalmia, while in the mouse, the rat and the rabbit, Cohlan, Giroud and Martinet report that Hypervitaminosis-A is concerned in the development of congenital anophthalmia. Treatment with Trypanblue (Azo Dye), pantothenic acid deficiency and hypopglycaemia inducing compounds can cause blindness in mice, rats and rabbits, causing non-development of the optic capsule also anophthalmia (Gilbert-Gilmann, 1954).

It is interesting to note that in some cases anophthalmia is associated in the cow with the congenital absence of the tail. In man anophthalmia has been reported in combination with mental retardation, brain atrophy, hydrocephaly, microcephaly, CHD, ampholocel, urogenital defects, celft palate, poly-and syndactyly (Warkany).

As summarised above, the abnormal calf showed true bilateral anophthalmus congenitus. There was no retina, no optic nerve, no lens crystallina, no pupilla, no iris and no viterous body. As the blindness is caused by the nondevelopment of the optic parts of the eye this is a true case of anophthalmus congenitus. The orbita were filled with fatty fibrous tissue. In this case the exact cause could not be determinad, nor its mode of inheritance.

Anophthalmus congenitus has been reported more frequently in the cow than in other domestic animals, there is also a tendency for it to occur more frequently in males. This is also suggested by of Sjögren and Larsson's findings that a partly sex-linked recessive mode of inheritance was responsible in cases of anophthalmia with oligophrenia (Warkany).

In conclusion, I would like to propose that the cow is a good experimental animal model for investigation of human congenital anophthalmia in order to obtain an understanding of the basic principal and mechanism governing the development of this malformation, which causes total blindness.

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Fig. 1. The head of a male Calf with bilateral Congenital anophthalmia. Right view.

Fig. 2. The lelft view of the head of the Calf borne blind. After preparation of the orbital content.

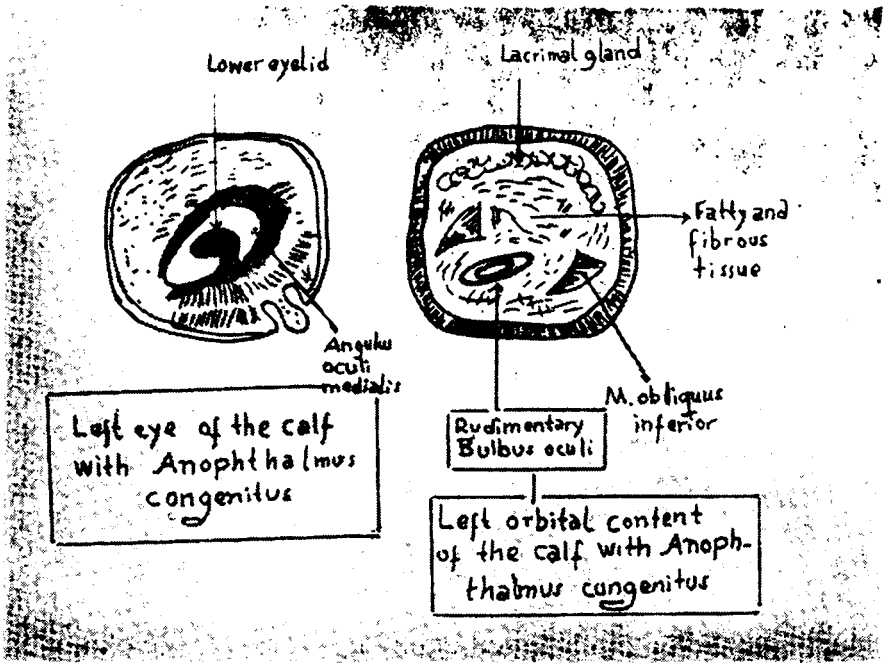

Fig. 3. and 4. Drawings showing the external and internal orbital contents of the left eye.

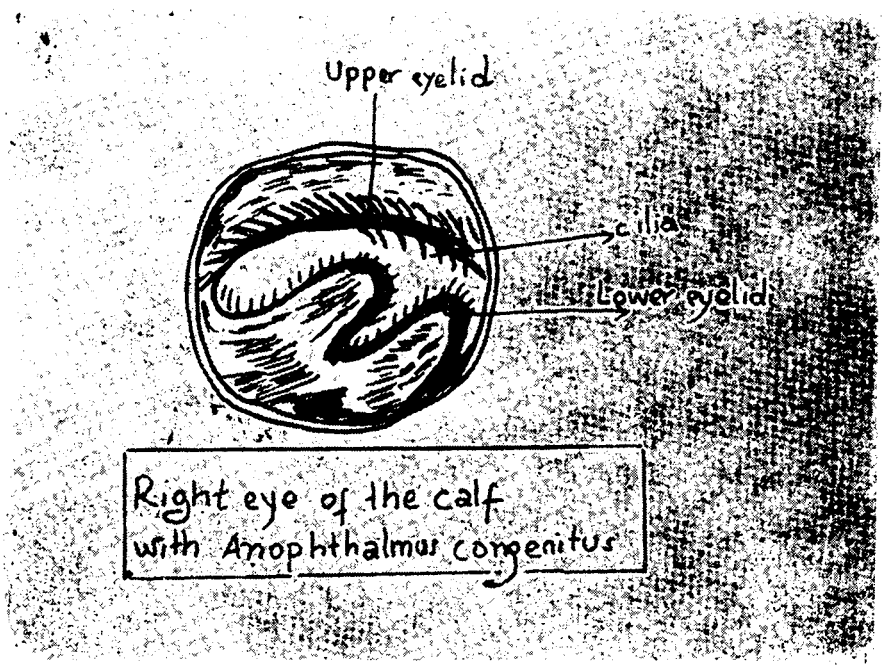

Fig. 5. Drawing of the external view of the defected right eye.

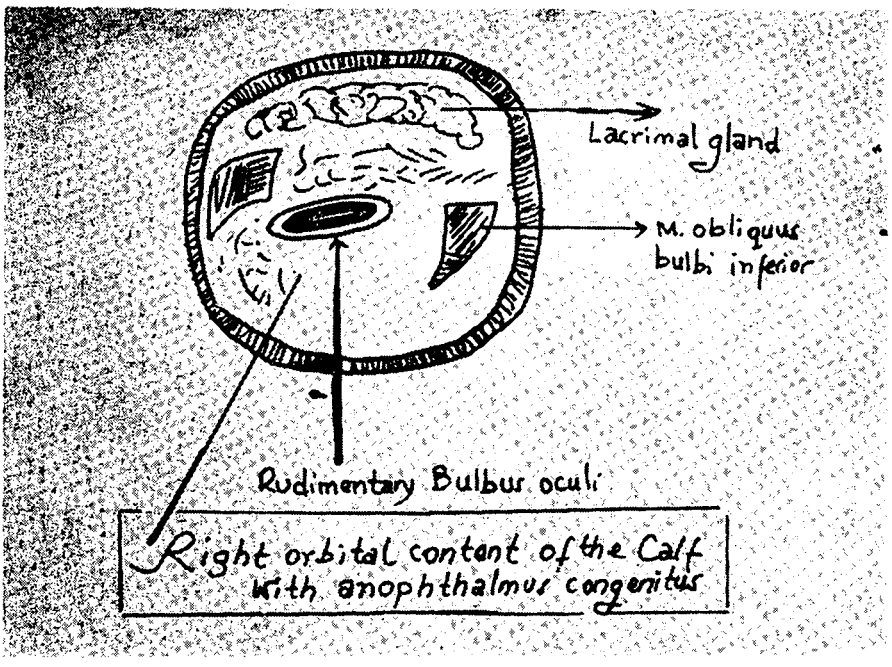

Fig. 6. The orbital content of the defected right eye is shown.