

Cyclopia: A Rare Congenital Anomaly

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ABSTRACT

Cyclopia is the most extreme form of holoprosencephaly. It is characterized by the failure of the embryonic prosencephalon to properly divide the orbits of the eye into two cavities which results in babies with a single or partially divided eye in a single orbit. We report a case of a 28 years old primigravida who came for medical termination at 25 weeks of gestation and delivered a 600 grams dead female fetus with cyclopia, fetal proboscis, and neurocutaneous marker. Its incompatibility with life makes early diagnosis using ultrasonography and fetal magnetic resonance imaging essential in early management and essential counseling to parents.

Keywords: cyclopia; holoprosencephaly; proboscis

INTRODUCTION

Cyclopia is a severe manifestation of alobar holoprosencephaly. It is a developmental defect of an embryonic forebrain which is characterized by incomplete cleavage of the prosencephalon into the right and left hemisphere that occurs between the 18th and 28th days of gestation.^{1,2} Cyclopia mostly affects the embryos that are either aborted or stillborn upon delivery or die shortly after birth. Extra cranial anomalies like as polydactyly, renal dysplasia, and an omphalocele have been reported in stillbirths with cyclopia.³

Globally, holoprosencephaly affects one in sixteen thousand live newborns whereas cyclopia is seen as rarely as one in one hundred thousand newborns including stillbirth.^{3,4} There are three types of holoprosencephaly on the basis of severity. From most severe to least severe, the three types are alobar, semi lobar, and lobar. The brain is not divided and significant facial deformities are found in alobar subtype. The brain's hemispheres are partially divided and cause a moderate deformity in the semi-lobar subtype. The two hemispheres are separated from one another and have small structural flaws in lobar subtype.⁵ The most severe facial manifestation of alobar holoprosencephaly is cyclopia.⁴

CASE REPORT

A 28-years-old primigravida came for termination of pregnancy at 25 weeks of gestation based on an ultrasound scan done at 24 weeks of gestation. Ultrasound

showed a small fetal head as compared to fetal abdominal circumference and femur length. There was bilaterally dilated lateral ventricles each measuring 9mm. Fetal intracranial structures were not visualized. Nasal bone was absent.

She had taken folic acid in the first trimester along with iron and calcium in her second trimester as prescribed by her physician. There was no history of chronic medical condition, teratogenic exposure or consanguinity. Also, there was no family history of congenital anomalies or early death in family. All laboratory investigations were within normal limits.

Medical termination was done at department of gynecology of Kathmandu Medical College with mifepristone and misoprostol. She delivered a 600gm dead female fetus with multiple congenital anomalies. There was a partially divided eye in a single orbit at midline without nasal evidence of nasal structures. The proboscis was visible above the eye on the forehead (Figure 1). Micrognathia was noticeable. Head circumference of the fetus was 16.7cm and head to toe length measured 31 cm. Neurocutaneous marker resembling well-defined ecchymotic plaque in lumbosacral region extending to bilateral thighs was present (Figure 2). Other gross examination findings were normal. There were no cleft lip or palate, omphalocele, or polydactyly. There were two umbilical arteries and one umbilical vein. Due to cultural constraints, patient party denied autopsy to look for visceral malformations.

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Figure 1: Cyclopia showing partially divided eyes in single orbit, proboscis, and absent nose



Figure 2. Neurocutaneous marker on lumbosacral region

DISCUSSION

Cyclopia is a rare form of holoprosencephaly characterized by the failure of the embryonic prosencephalon to properly divide the orbits of the eye into two cavities.^{1,4} It typically presents with a median single eye or a partially divided eye in a single orbit, absent nose, and a proboscis. Cyclopia is thought to occur due to the fusion of two optic grooves as a consequence of defective development of ventral diencephalon.⁶ The proboscis is a soft, blind tube-like structure that generally appears above the central eye, or on the back. Proboscis is characteristic of a form of cyclopia called rhinencephaly or rhinocephaly.^{1,7} Extracranial malformations described in stillbirths with cyclopia include polydactyly, renal dysplasia, and an omphalocele.

During embryogenesis, the neural tube forms the three primary brain vesicles (the prosencephalon, mesencephalon, and rhombencephalon) at the 4th week and the prosencephalon further divides into the telencephalon and diencephalon by the 5th week.⁸ Holoprosencephaly results when the prosencephalon fails to develop into two hemispheres normally. Cyclopia is the most severe expression of alobar holoprosencephaly.

A 31% substantial proportion of cyclopia malformations are caused by chromosomal anomalies particularly, trisomy

13. Another 31% of the cases of cyclopia malformations are associated with defects not typically related to holoprosencephaly but more with hydrocephalus, heterotaxy defects, neural tube defects, and preaxial reduction defects which are suggestive of presence of ciliopathies or other unrecognized syndromes.^{4,9} It is more common in the female fetus which was also supported by our case.

The etiopathology of cyclopia is unclear. Most cases are sporadic. However, *Veratrum californicum*, found in corn lily or false hellebore is a risk factor which is believed to cure morning sickness. Genes that are linked to cyclopia are Sonic Hedgehog, ZIC2, TG-interacting factor, and SIX3.¹⁰ Other factors include: multiple pregnancies (especially twins), female sex, previous unexplained miscarriages, gestational diabetes, infections during pregnancy (Toxoplasma, rubella, cytomegalovirus, herpes, others), exposure to UV light, smoking, alcohol, certain medications (aspirin, lithium, anticonvulsants, hormones, retinoic acid, anticancer agents, and fertility drugs) during pregnancy, and cyclopamine which is a highly alkaloid toxin.¹¹

In our case, typical facial features of cyclopia were seen: partially divided eye in a single orbit, proboscis and absent nose. Atypical extracranial manifestation in the form of a large neurocutaneous marker on the lumbosacral, buttock, posterior and medial aspects of the thigh. It was a well-demarcated patch with black color. However, family history for congenital anomalies and consanguinity was absent. Also, mother had taken folic acid, iron and calcium as prescribed and didn't have chronic medical condition.

Patient counseling was focused on teratogenic drugs, ANC checkup and early identification via ultrasound in next pregnancy for early abortion to reduce morbidity as no cure is currently possible.

CONCLUSION

Cyclopia syndrome is an extreme facial manifestation of holoprosencephaly characterized by the failure of the embryonic prosencephalon to properly divide the orbits of the eye into two cavities. It is a rare occurrence with the paucity of information on etiopathological determinants. Antenatal diagnosis via ultrasonography plays a crucial role in early management and counseling to parents.

Data Availability: Related photograph of this case will be available on request

Informed Consent: Consent from patient's father as well as department of pediatrics KMC Teaching Hospital was taken

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