Congenital disorder of true cyclopia with polydactylia: case report and review of the literature

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Summary

Cyclopia is a rare type of holoprosencephaly and a congenital disorder characterized by the failure of the embryonic forebrain to properly divide the orbits of the eye into two cavities (the embryonic forebrain is normally responsible for inducing the development of the orbits). As a result a birth defect in which there is only one eye is developed. This eye is centrally placed in the area normally occupied by the root of the nose. As a rule, there is a missing nose or a non-functioning nose in the form of a proboscis (a tubular appendage) located above the central eye. In this report the macroscopic, radiographic, and immunohistochemical findings of a case of true cyclopia in a female fetus are described. Cyclopia is a lethal condition that is associated with dramatic symmetric deformities of the nose, skull, orbits, and brain.

Key words: Cyclopia; Proboscis; Polydactylia; Holoprosencephaly; Sonic Hedgehog (SHH).

Introduction

The term "cyclopia" derives from Cyclops, the one-eyed giants of Greek mythology, who had a single round eye in the center of the forehead. The word "cyclops" itself comes from the Greek terms "kyklos" (circle) + "ops" (eye) [1].

Generally, cyclopia occurs in the second week of gestation [2] and can be caused by chromosomal abnormalities [3-5] (most frequently it is trisomy 13 and trisomy 21) [6, 7] as well as gene mutations [8]. The Sonic Hedgehog (SHH) molecular pathway, holds a central role, especially SHH protein, the inhibition of which stops brain's division into two distinct hemispheres, resulting in one optic lobe and one olfactory lobe, and consequently in one eye [9, 10]. Also, certain toxins can cause cyclopia, a good example is cyclopamine or 2-deoxyjervine, a teratogenic alkaloid toxin that is found in wild plants [11].

Approximately 1.05 in 100,000 births are identified as cyclopian; including stillbirths [12]. Expecting alcoholic and drug-addicted mothers have a two-hundred fold chance of having a cyclopic fetus, most likely due to high amounts of toxins entering the body [13]. The sex distribution shows a female predominance [14].

Case Report

The authors present a rare case of true cyclopia in a female fetus that was born on July 2004 in the Department of Obstetrics and Gynecology of the University General Hospital of Alexandroupolis and received by the Laboratory of Histology-Embryology of Medical School of Democritus University of Thrace for further examinations.

The fetus was stillborn after 32 weeks of gestation and weighed 1,444 gr. There were orbital malformations- true cyclopia - single median eye in single median orbit (Figure 1) and associated brain malformations, namely alobar holoprocencephaly. There was a non-functioning nose in the form of proboscis measuring 15 mm in length and 10 mm in diameter with a single orifice above the central eye (Figure 2). The radiographic findings included fusion of the thalami with resultant absence of the third ventricle. The cerebrum was presented as a "pancake-like" mass of tissue located anteriorly in the skull. A single large ventricle was found posteriorly. There was an absence of the interhemispheric fissure, falx cerebri, and corpus callosus. The outer appearance of the rest of the body was normal, except for the existence of an extra finger in both the above limbs (polydactylia). In the placenta, many necrotic points were found, along with interspersed hemorrhagic areas and severe calcinosis, whereas the embryonic membranes presented acute inflammation.

Immunohistochemical study was carried out to define the expression of SHH in brain tissue of this case using the polyclonal antibody SHH according to the manufacturer's instructions. The immunohistochemistry was applicated with vectastain, ABC kit. As a positive control, the authors used normal brain tissue originating from an embryo at the same gestational age. The results show that the SHH staining was absent in the present case, in contrast to the normal one (Figure 3).

Discussion

The positioning of the eyes contributes significantly to facial proportions [7]. The migration of the eyes from their fetal lateral location toward the median plane determines to a great extent the "character" of the face, varying from a "wide-eyed" hyperteloric appearance to a narrow "foxy" hypoteloric appearance [7]. In cyclopia, the fronto-nasal prominence is missing, failing to descend to the maxillary

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Fig. 1

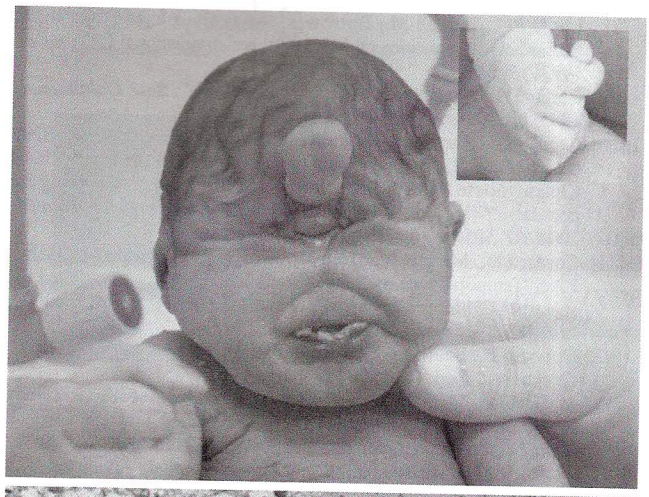

Fig. 2

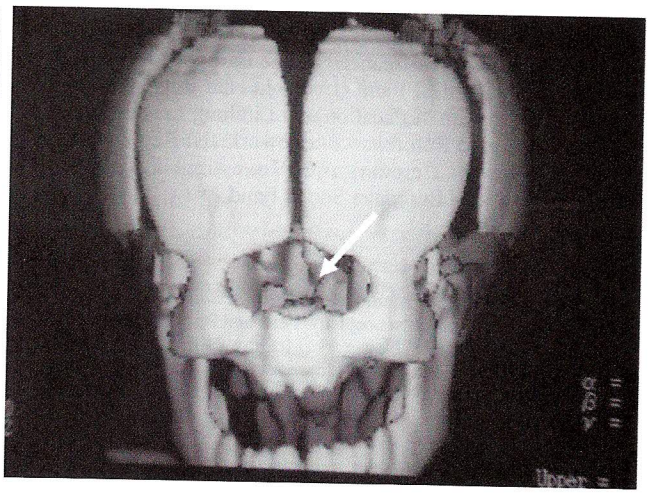

Fig. 3

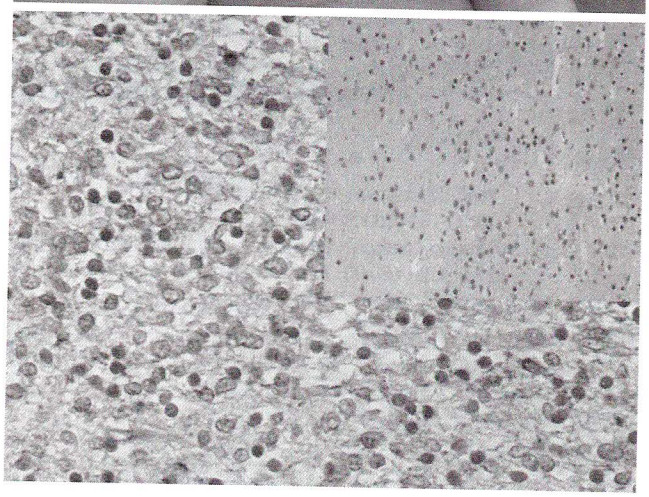

Figure 1. — Macroscopic appearance of the fetus, including a single eye under the proboscis and polydactylia (inset).

Figure 2. — CT-3DMPR (multiple planar reconstraction). Single orbit is indicated with an arrow.

Figure 3. — Tissue section. Immunostain SHH x200 (inset: negative control).

level, which accounts for the converged eyes, absent or displaced nose, and hypoplasia or aplasia of the premaxilla and incisor teeth [7]. Cyclopia is the most severe malformation of holoprosencephaly with a single median orbit that may be anophthalmic, monophthalmic, or synophthalmic [7]. There is no nose, but a variable proboscis is usually present [7]. It must be due to failure in the development of the ethmoid. A remnant of the missing ethmoid may be the proboscis above the eye [13, 15]. This failure in ethmoid bones development results in extensive consequences in facial development and malformations of the entire middle and upper face. Proboscis structure is represented by a "tube-like" cartilage with a central canal which is lined with squamous epithelium, as well as respiratory and olfactory mucosa [13, 15]. It is interesting to mention that olfactory fibers pass from the proboscis into the extradural space of the ethmoidal notch forming a collection of tissue similar to the inferior layer of the normal olfactory bulb [13]. The location of proboscis indicates the failed horizontal separation of orbital and olfactory anlagen, due to rostral shift of the olfactory placodes, consequent upon separation of the terminal notochord from the oropharyngeal membrane [7, 8]. The proboscis represents the anterosuperior part of the normal nasal cavity developed in the absence of median components. As a conclusion, cyclops face constitutes a model for the study of the development of the normal face [13]. Also complete absence of the pituitary gland has been sometimes described in the cyclopic infant [7]. Radiographic findings in other cases showed hypoplasia of frontal, ethmoidal, sphenoid, maxillary, and zygomatic bones and absence of nasal, vomerine, and lacrimal bones [9]. Cyclopia may be associated with holoprosencephaly, the most common developmental defect of the forebrain with an incidence of 1:250 during embryogenesis [1]. However, the observed cases are less frequent, due to intrauterine lethality, one case in 100,000 stillbirths. Seventy-five percent are of the cyclop fetuses born alive and die within a few minutes [9]. The cyclopia proportion in female and male fetuses is 2:1 [11]. A relation to the multiple genes have been implicated in ventral forebrain induction [1]. During normal differentiation of the cephalic midline structures, there is increased expression of *pax-2* gene and inhibition of *pax-6* gene from the notochord [7]. Inappropriate expression of these genes may result in cyclopia [7]. Mutation of the *SHH* gene has also been implicated in the formation of cyclopia [4, 6]. Other genes that play a role in the formation of these defects include genes that code the hedgehog signal transduction proteins patched (Ptc) and smoothened (Smo) [10], as well proteins of the gli family that are related with polydactyly and ZIC2 and SIX3 [4, 6].

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