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# A Review on Holoprosencephaly Disease (CYCLOPIA): Risk Factors, Causes, Pathophysiology and Diagnosis with spotlight of various features reported in cases

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Abstract

Holoprosencephaly has a sever condition called Cylopia that is occur due to embryonic prosencephalon cleavage failure and contrast. Mostly cylopia form is holoprosencephaly, mid facial tissue is absent which causes the one eye on a single orbit. It is a sever deformity of median faciocerebal development. There are 1.05 cases in 100,000 birth, still births of cyclopean. Abnormal nose above eyes or absence of nose, single eyes or half divided eyes in single orbit are features of cyclopia, where as reduced size of oral aperture or absence of mouth, absence of mandible with ears below chin. It is as etiologically heterogeneous condition, which can be caused by genetic mutation, chromosomal defect and teratogenic environmental factors. Environmental factors can be diabetic embryopathy, retinoic acid, several anecdotal suggestion of teratogenic factor for HPE, which includes salicylates and viruses. Some list of syndrome are also involved to cause cyclopia Like steinfeld syndrome, dysgnathia complex,Pseudotrisomy 13 syndrome and Smith–Lemli– Opitz syndrome. On other hand inborn abnormalities also cause cyclopia but its come under chromosomal syndrome. Anatomical detection can be done by brain MRI, whereas in prenetal diagnosis, sonography is more significant. Ultrasound also used early detection can be done and knowledge of sonographic finding soectrum leads to accuracy of prenatal diagnosis of cyclopia. After birth the chromosomal study helps to diagnose cyclopia along with postmortem biopsy.

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## INTRODUCTION

Cyclopia is the extreme form of holoprosencephaly and that is caused by unsuccessful embryonic prosencephalon division and differentiation. Rather than becoming hemispheric, in major cases there is an absence of olfactory tracts and septum pellucidum, while the prosencephalon remains as an unseparated sphere. In peak cases, holoprosencephaly can convert into cyclopia, in which the lack of medal-facial tissue that may lead to one eye in a single orbit as shows in Figure 1 (Wilson *et al.*, 1989).

On the study of the fetus, before the preservation of the specimen in formalin for storage only the exter-

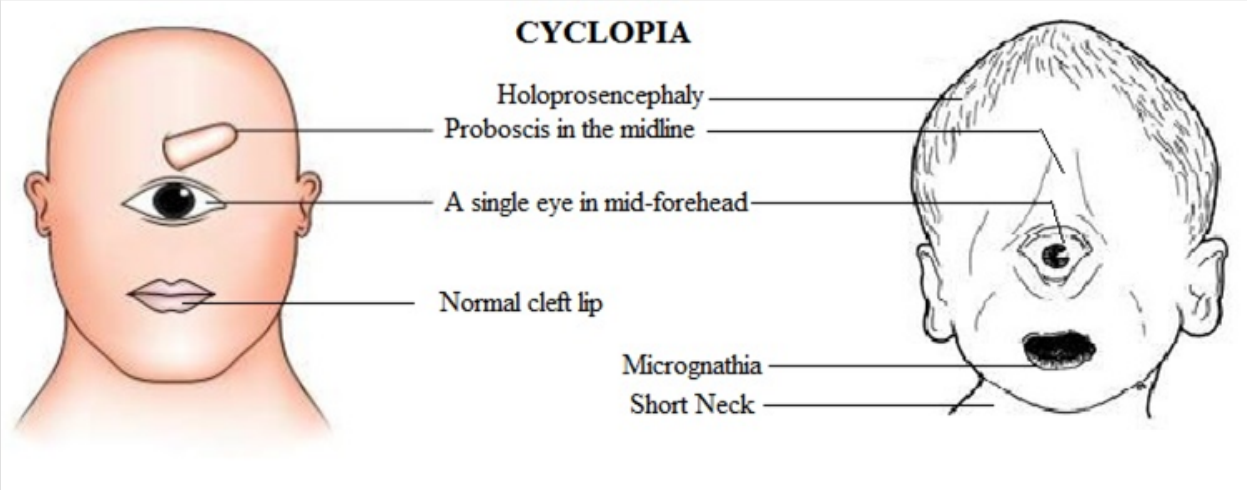


**Figure 1: Shows features of cyclopia patient.**

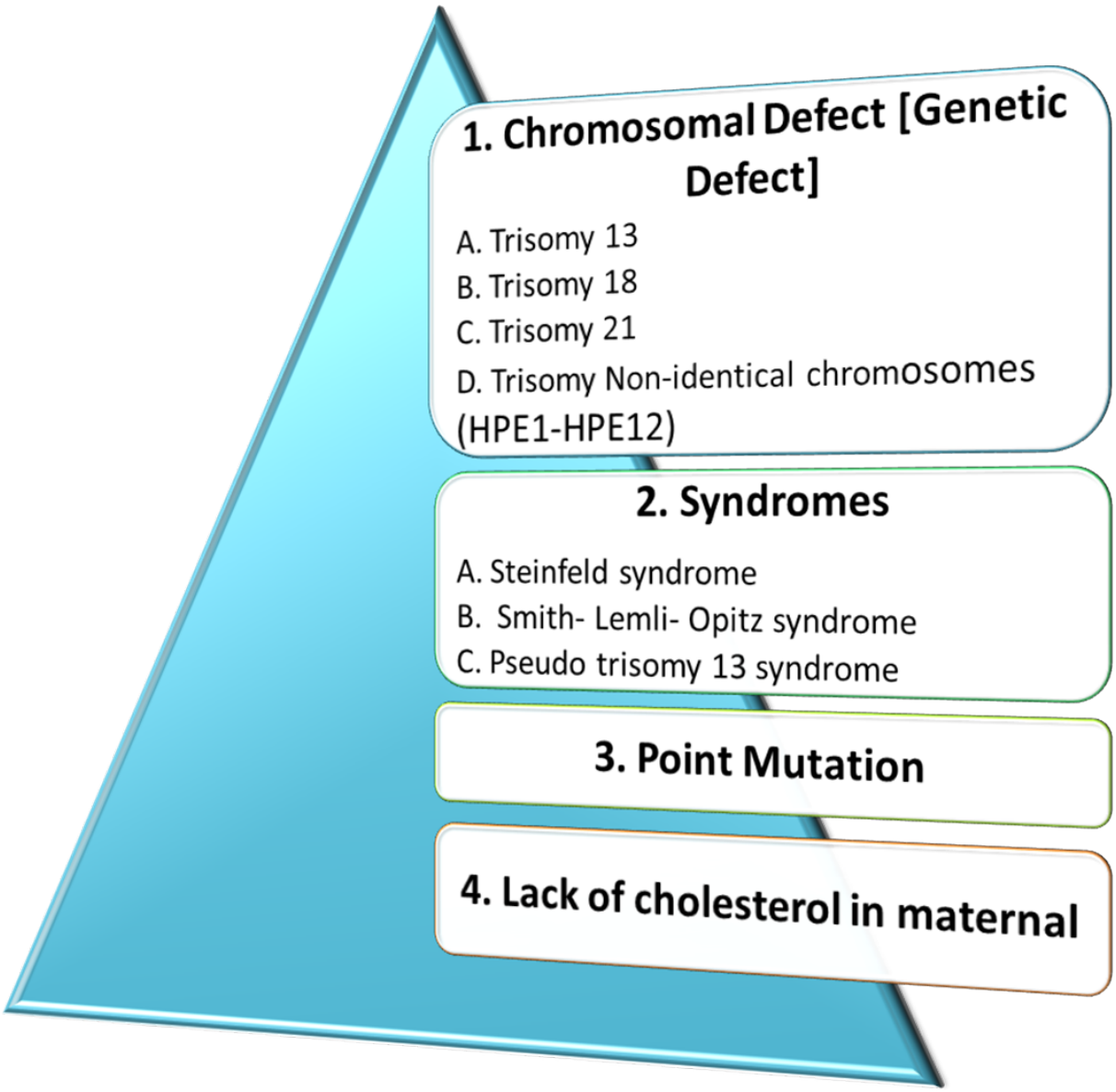


**Figure 2: List of Key features in Causes of of Cyclopia Disease.**

nal features were registered. Now we can visualize internal structures without destroying the specimen by the non-invasive nature of MRI, and can issue the data to explain the defects of morphogenesis (Situ *et al.*, 2002).

Holoprosencephaly (HPE) generally observed in 5–6% of cases with Smith-Lemli-Opitz syndrome (SLOS) (Weaver *et al.*, 2010a) and displays the most intenseform of this syndrome. The exact process of HPE formation in SLOS is not proven yet.

Cyclopia is a severe median faciocerebral growth malformation. Cyclopia is a rare fetal deformity identified by an individual palpebral fissure along with a proboscis deal with severe brain deformations. Including stillbirths, roughly1.05 in 100,000 births are determining as cyclopean. Cyclopia with HPE is a rare congenital anomaly of the forebrain system. HPE happens from incomplete division of the telencephalic vesicles. A true cyclopia is an infrequent anomaly in which the organogenetic growth of the two separate eyes is suppressed (Cannistr *et al.*, 2001).

**Historical aspects**

Latest study of teratology and mythology on cyclopia aside Cohen and by Stahl, Tourameconcede with earlier observers that real infants with those defects existed in the origin of the fantastic beings and mythological creatures (Stahl and Tourame, 2010). An educated guess suggested the population of 66,000,000 though there is no process to get the definite population number at the year 800 BC in all over the world and another guess suggested a crude birth rate of 80 per 1,000 for this period. If so, in the world population around the time Odyssey was being created, approx. 53 cases of cyclopia were born by year (Mcevedy and Jones, 1978).

Holoprosencephaly takes place in 1/16,000 live births and 1/250 at the time of embryogenesis. Approx. 1.05 in 100,000 births are recognized as newborn with cyclopia, including stillbirths (Kallen *et al.*, 1992). One diagnostic characteristic of the facial defects in holoprosencephaly is the abnormal shape in the median plane. It includes one orbit with a removed ethmoid complex, a proboscis above the eye, a single cyclopic eye, severe hypotelorism, a midline cleft lip, midfacial hypoplasia, a single upper incisor and the absence of nasal bones (Other feature shows in Table 1) (Kjaer *et al.*, 1991).

**Pathophysiology**

On observation, the Apgar score was not estimated because of severe anomalies but newborn was noticed to have a trunk with peripheral cyanosis and a pink face. Head circumference was 38 cm, respiratory rate 42/min and heart rate was 152 beats/min, a dysmorphic face,with a median single eye, micrognathia, absence of nose,a proboscis above the eye (shows in Figure 1) and many unusual abdominal abnormalities that consists a very large omphalocele including whole spleen and liver, undefined defected external genitalia and urinary bladder extrophy. The infant died after 5 hours. (Salama *et al.*, 2015).

Primary facial features of cyclopia might contain a proboscis above the eye and absent nose and a median single eye or a partially divided eye in a single orbit (Related features observe in Table 1). Other facial features may include otocephaly, astomia or microstomia and absent philtrum. (McGahan *et al.*, 1990).

**Causes**

Cyclopia can result from chromosomal defects, which is basically caused by environmental teratogenic factors or genetic mutations. Generally, there is a very less data regarding to the causes of cyclopia,because cyclopia is thought to be the most extreme form of HPE so far (Dubourg *et al.*, 2007).

The commonest chromosomal disorder involved with HPE is the trisomy 13. The trisomies 18 and 21 were also recorded along with triploidy. The structure of anomalies explained in the article on 11 non-identical chromosomes enabled the recognition of 12 loci for HPE (Figure 2, Point no. 1) (Roessler and Muenke, 1998). All these loci are known as HPE1 to HPE12 and are found in the regions 5pter, 7q36 (SHH),18p11.3 (TGIF), 6q26-qter, 2p21 (SIX3),2q371–q37.3, 13q32 (ZIC2), prox 14q, 9q22.3 (PTCH1), 1q42-qter (DISP1), 20p13,and 21q33.3 (Dubourg *et al.*, 2007).

There are point mutations observed in the syndromes which cause HPE (Figure 2, Point no. 3). A mindful review of them shows that only 4, firstly the Steinfeld syndrome, secondly the dysgnathia complex, third the Pseudotrisomy 13 syndrome and at last the Smith–Lemli– Opitz syndrome had cyclopia(Figure 2, Point no. 2) (Weaver *et al.*, 2010b). In addition, only these four syndromes including cranial sclerosis along with osteopathiastriata introduced with alobar form of HPE. Rubinstein–Taybi syndrome and Martin syndrome not revealed in the OMIM database,since they were not involved with HPE (Martínez-Frías *et al.*, 1998).

They reported here a 24-week old gestation fetus having alobar HPE, Smith-Lemli-Opitz syndrome and cyclopia. This was the first case of cyclopia documented in SLOS and the severest case of HPE,

**Table 1: Shows all case reports highlight including patient detail, clinical characteristics of cyclopia patient, previous history of maternal and at last end result of case report.**

| Author | Case Report | Clinical Features | Maternal History | End Result |
|---|---|---|---|---|
| (Kumar *et al.*, 2015). | · 24 years old mother.<br>· 2nd gravida<br>· ultra-sonogram done at 21 weeks 0 days.<br>· pregnancy was termi-nated<br>· It was (22 weeks) boy | · Semi lobar and prosen-cephalon fails to develop into two hemispheres.<br>· Single eye observe in face.<br>· Diaphragmatic hernia &excess of amniotic fluid in the amniotic sac.<br>· Boy weighing about 600 gm & length of 27 cm.<br>· Absence of nose.<br>· Low set ears. | · Married at the age of 21 years<br>· 1st conception ended as a 6 month spontaneous abortion.<br>· Conceived after 1 year without any drugs.<br>· No fever/drugs/radiation/ vaginal bledding in the past.<br>· | Pregnancy was bring to close. A boy was stillborn, extremely preterm (22 weeks). |
| (Nalam *et al.*, 2018). | · 23-year-old woman<br>· At 30th week of pregnancy had some problem. | · Ultrasound at 30 weeks showed microcephaly.<br>· Baby weighing 1.02 kg<br>· Multiple congenital anomalies.<br>· Single central eye, low set ear.<br>· Omphalocele, Single umbilical artery. | · History of second degree consanguinity<br>· No history of any infectious disease.<br>· Non Smoker and Alco-holic.<br>· Not taken any terato-genic drugs. | Delivered a stillborn male baby. |
| (Goswami, 2015) | A boy child was born, after 32 weeks of gestation.<br>· Location: Dibrugarh, India.<br>· Pregnancy was compli-cated. | · Child length was 39cm, weight 1.8kg.<br>· Head circumference 20 cm.<br>· Diamond shaped orbit containing single eyeball& neck was short.<br>· Bilateral not present in thumb.<br>· Liver, gall bladder and were on left side where as spleen, heartwas on right side. | · Mother was alcoholic.<br>· No history of consan-guinity, exposure to any other teratogenic dru-gor any family history of dysmorphism. | After five minutes the child dies due to severe asphyxia. |
| (Yadav *et al.*, 2018). | · 35 year oldwoman.<br>· 34 weeks of gestation admitted in the labour room of NMCTH. | · Delivered a boy vaginally weighing 2.5 kg.<br>· the newborn was with pink face<br>· Heart rate was 134 beats per min.<br>· Head in circle shape with 38 cm, a median single eye and absence of nose.<br>· micrognathia. | · had normal vaginal delivery in all pregnan-cies..<br>· No history of diabetes.<br>· consanguineous mar-riage which may be the causing factor for this irregularity. | The baby died after 15min-utes of birth. |
| (Raman and Jagadesh, 2014). | · A 20-year-old second gravida.<br>· Come for routine obstetric ultrasonogra-phy. | · Fetal skull bones were poorly rigid.<br>· Dysmorphic with blend orbits and single median eye in the forehead.<br>· Poor osteogenesis of the skull bones and normal spine.<br>· Alobar holoprosencephaly with facial dysmorphism.' | · She has one first nor-mal girl.<br>· No history of consan-guinity of marriage. | The preg-nancy was ter-minated |

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*Table 1 continued*

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| (Olejek *et al.*, 2011). | · The patient, 30 weeks gestation<br>· 2nd pregnancy.<br>· initial diagnosis of hydrocephalus<br>· Before being referred to the hospital, five checks up had been done. | · Fetal pulse noted 140 beats /minute.<br>· Child weighed 1270g and was 35cm in L.<br>· The cranial observed was 27cm, and the chest circumference 24cm.<br>· High forehead with a single centrally localized eye.<br>· No nose &Complete absence of cerebral hemispheres. | · The first pregnancy had ended with a birth of a normal newborn, healthy in all prospective.<br>· Family history was unremarkable.<br>· Her husband has diabetes history. | After 2 hours Child was declared dead, due to lack of breathing. |
| (Srinivasan *et al.*, 2014). | · A 36yr-old woman.<br>· 4th pregnancy.<br>· Mother was gone under X ray examination for other diseases detection. | · A female infant with "True Cyclopia."<br>· Weighed 2910 g.<br>· Other body parts were normal.<br>· The face had a single large eye ball with a pair of eyelids and medial orbit.<br>· Absence of mouth, nose and proboscis.<br>· Ears were at a lower level.<br>· Micrognathia was observed. | · Previous all pregnancies and deliveries were healthy.<br>· Suffer from hemorrhage and infection, so a course of hexcaprone and ampicillin were given for two weeks.<br>· Treatment given before three weeks of baby's birth. | Death occurs after 20 minutes of birth, due to respiratory congestion. |
| (Rathod *et al.*, 2015). | · 32 year old F<br>· Presented in second stage of labour.<br>· Irregular check-up. | · A female fetus weighing 2200gm with multiple congenital anomalies.<br>· A single eye in mid-forehead (cyclopia).<br>· No nasal aperture in face or proboscis in the midline.<br>· micrognathia. | · Previously normal vaginal delivery.<br>· No history of any terato-genic exposure.<br>· Had uncontrolled diabetes which further-cause for this anomaly trimester. | The baby died soon after birth. |
| (Sarma, 1983). | · A 25 years Old mother.<br>· She had a second child<br>· pre-eclamspsia on the time admmsion.<br>· Blood pressure was 150 100mm Hg. | · Single orbital cavity, orbit diamond shaped.<br>· Conjunctival fornices were present.<br>· A single globe with one cornea, one iris, one pupil one lens and one retina.<br>· Had no nose and Olfactory bulbs and tracts were absent.<br>· Holoprosencephaly.<br>· Gyri and sulci were absent. | · No history of any specific infection, drug intake, radiation or bleeding during the present pregnancy.<br>· History of consanguinity present. | The boy die after 2 hours of birth. |

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*Table 1 continued*

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| (Rodrigues *et al.*, 2019). | A 30 year old female came to hospital for first antenatal check-up.<br>· She was 3rd gravida with two previous normal<br>· Third degree consanguineous marriage. | · Calvarium absent, anencephaly.<br>· A female fetus weighing 160 gm<br>· Umbilical cord measuring 3.5.<br>· Eye was noted in the midline of the face with two fused eye globes, and two separate pupils each.Nose was absent<br>· Cranial vault was absent<br>· Brain was replaced by Anencephaly.<br>· The vertebral arches were deficient. | · Immunized with 2 doses of T.T. and was taking regular iron and calcium tablets, but no folic acid supplementation.<br>· History of any alcohol consumption, hypertension, diabetes mellitus, renal disease or any other major illness. | After family counseled then termination of pregnancy. |
| (Otuaga *et al.*, 2007). | · The 37year old mother and has three healthy & normal children.<br>· The delivery done at City Nigeria in the University of Benin Teaching Hospital. | · A live girl infant with weight 1.5kg delivered by cesarean section.<br>· Multiple congenital abnormalities.<br>· Single centrally located eye, no nose and small mouth.<br>· Several facial bones were missing.<br>· Holoprosencephalic, Cardiac anomalies<br>· Presence of a holosphere in brain. | · Mother was not diabetic and gave no history associated with the complications. | Pronounced dead ten minutes following delivery. |
| (Mondal *et al.*, 2015). | · A 24 Years patient with IUD at 29 years of gestation.<br>· USG performed | · Weight of infant was 800 gms.<br>· Different measurements: Head Circumference was 20 cm, Crown Ramp length was 28 cm, Chest was 23 cm, and Femur Length was 6 cm.<br>· Histopathology confirmed eye – ball structure.<br>· Holoprosencephaly with Synophthalmia. | · No historical information of mother was found in this case. | Cause of death was multiple congenital anomalies. |
| (Babaji *et al.*, 2014) . | · A female infant born to 21-year-old female through normal vaginal delivery. | · Birth weight of infant was 2.93 kg.<br>· Fused eyes<br>· Abnormal positioned nose above the eyes.<br>· Alobar holoprosencephaly with synophthalmia forehead proboscis. | · There was neither history of consanguineous marriage nor positive family history. | Infant died after few minutes of birth. |

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*Table 1 continued*

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| (Singh *et al.*, 2018). | · A male child was delivered to a 20-year-old third gravida<br>· US done showed gestational age of 9–10 weeks. Fetal heart sounds were present at that time. | · The baby weight 1000 g.<br>· Had one single midline orbit and eye (cyclopia), absent mouth (astomia).<br>· a proboscis in midline above the orbit, absent mandible (agnathia).<br>· Ears fused.<br>· On physical examination, baby had no other gross abnormalities or abdominal organomegaly.<br>· Umbilical cord had two arteries and one vein. | · Mother has a history of two spontaneous abortions in the past at 6–8 weeks of gestation.<br>· She was non-diabetic and normotensive.<br>· Had anaemia (Hb 10 g%) and was on tablet iron and folic acid.<br>· Immunized against tetanus.<br>· No past family history of holoprosecephaly. | The neonate was pronounced dead at birth. |
| (Arathi *et al.*, 2003). | · An aborted female fetus of 16 weeks gestation was observed.<br>· Second pregnancy occurs in the 26-year-old mother.<br>· Child from first pregnancy having produced a normal, healthy baby. | · Most striking anomaly was cyclopia.<br>· Absence of cleft lip was noted with micrognathia and a prominent tongue.<br>· Short forearms, but long tapering fingers.<br>· Lungs were hypo plastic, thymus absent, heart grossly malrotated, liver terminating into the atrium on the left.<br>· In the abdominal cavity a severe degree of kyphoscoliosis<br>· A single eyeball seen, covered by eyelids and a single cornea.<br>· alobar holoprosencephaly. | · There was no history suggestive of a teratogenic insult. | Pregnancy was terminated by induction. The aborted fetus was fixed in 10% formalin and dissected. |
| (Zimmer *et al.*, 1982). | · A 28 yr-old femalewas admitted at 37 wk gestation.<br>· Uterine fundal height was 50 cm.<br>· A microcephalic fetus with a BPD of 62 mm | · A cyclopic fetus was delivered by female, body weight 2400 g&brain weighed about 90 g.<br>· The cerebral hemispheres were merged without a corpus callosum.<br>· One ventricle no olfactory tracts.<br>· Boyborn with one eyeball, absence of nose and agenesis of left ear.<br>· The karyotype test was 47 XY due to trisomy D. | · Her 2nd pregnancy finished in the 5th month as a result of aborton.<br>· In her present pregnancy she was under treatment by her gynaecologist with 6 IM injections of 5000 IU amount chorionic gonadotropin each, at the time of 8th and 9th wk of gestation. | After observing, finally decided to terminate the pregnancy. |

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*Table 1 continued*

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| (Sezgin *et al.*, 2002). | · The mother's age was 38 and both parents were healthy.<br>· 3rd gravida.<br>· There were two normal sibs.<br>· Two optic nerves were observed. | · At 37 weeks a female infant born.<br>· At the birth time body weight was 1600 g, length 46 cm, and head circumference 24 cm observed with agnathia.<br>· Presence of one midline eyeand the eyelids were open.<br>· A proboscis was observed<br>· Brrain front-lobes were fused and no interhemispheric fissure. | · Mother and Father are firstly cousins in relation and the mother had taken regularly 500 g dosages of aspirin two times a day for 7 days during the first trimester in order to terminate the pregnancy. | The baby died after few minutes of birth due to salicylate amount |
| (Chukwuegbo *et al.*, 2015). | · 32 year patient delivered female new born baby.<br>· Mother already with preeclampsia.<br>· Delivery done by Caesarean. | · New born baby with deformed face<br>· A single central eye observed.<br>· Proboscis withblind-ending, no nose.<br>· Absence of corpus callosum.<br>· The heart shows a large atrial septal defect with bilateral atrial dilatation. | · No maternal history were recorded. | The baby was stillborn. |
| (Tomoda *et al.*, 1983). | · A 39-year-old gravida 2.<br>· Trisomy 13 was confirmed. | · A male fetus born with weighing 273.6 g.<br>· Anomalies were observed including: holoprosencephaly arhinencephalia, ventricular channels abnormal in the cerebellum.<br>· cyclopia with midline orbit had complete fused eyes.<br>· A tiny proboscis above the eye. | · No maternal history was recorded. | The baby fetus was aborted at 20 weeks |
| (Bustami and Amr, 1986). | · Mother's age – 38 yrs. & father's age – 55 yrs.<br>· Already have 2 children.<br>· First degree cousin consanguinity was reported by the parents. | · Birth child length was 46 cm; weight 2300 gm and head circumference 27 cm.<br>· A fused single central eye.<br>· Supraorbital proboscis and hypoplastic maxillary region were evident.<br>· Tissue culture study failed to grow for genes.<br>· Abnormal facial musculature features were seen. | · The mother delivered about three years ago a baby with spina bifida and that baby died soon after birth.<br>· At the time of delivery, polyhydramnios was evident. | The baby expired five minutes after delivery. |

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| (Yilmaz *et al.*, 1998). | · Baby boy born in a woman at the age 27.<br>· Consanguineous couple.<br>· The boy was delivered at 33 weeks through involuntarily. | · Boy was length was 40 cm, weight was 1.4kg, and observed head circumference was 30 cm.<br>· Single midline orbit with single eye of complete fused eyes.<br>· Meningomyelocel & no nose.<br>· Short length in right femur.<br>· At autopsy, there was cyclopia and a proboscis like mass above the eye.<br>· holoprosencephaly, no optic tracts or pituitary gland. | · The first two delivered children were normal.<br>· All investigations of the mother were normal.<br>· Chromosomal studies were normal karyotype (46-XY). | The child died after 5 minutes, due to severe apnea and bradycardia, |
| (Deftereou *et al.*, 2013). | 2nd gravida.<br>· Mother- 29 yrs.<br>· A non-consanguineous couple.<br>· Both mother and father were healthy. | · At birth, the new born baby weight was 1.6 kg .<br>· Microcephaly, absent nose.<br>· No external genitalia.<br>· The umbilical cord only an artery and a vein is present. | · No family history of congenital malformations.<br>· During the initial 15 days of gestation the mother was suffering from respiratory infection.<br>· The mother not taken any teratogens. | The infant died at 15 minutes postdelivery. |
| Faten Limaiem et al., 2017. | · A 36 year-old woman patient with gravida 2.<br>· Going for check up and meet her gynaecologist at 14 weeks' gestation regarding pelvic pain. | · The fetus weighed was 135 g and noted the placenta 45,4 g.<br>· Monophtalmic with almost fused eyes.<br>· Observed one lacrimal punctum in the midline.<br>· Absent of nasal structures.<br>· The brain and the rest of the body organs were Soften. | · no particular past medical history<br>· Consanguinity and hereditary diseases were denied.<br>· First pregnancy of woman was unexcited and she did not take any drugs before or during her pregnancy period. | The infant was a stillborn female baby. |
| (Situ *et al.*, 2002). | · The 21-year-old woman.<br>· The fetal heart stopped working before 7 hours of labour. | · The male fetus with crown foot length of 38.1 cm,<br>· A single eye.<br>· The tubular proboscis measured was 2.5 cm in long and 1.2 cm in wide.<br>· Alternating polydactyly was observed.<br>· The ears were low-set. | · The mother was healthy and did not suffer any internal or external illness.<br>· At the time of first stages of gestation she had not taken any medication. | The fetal heart stopped 7 h before parturition. |

to their knowledge. On the basis of molecular study, the fetus had two separate mutations a splice-site mutation and the DHCR7 geneanda deletion of the entire 3rd and 4th exons. This final deletion enclosed every 3 and 4 exons of DHCR7 (Weaver *et al.*, 2010a). The father of the fetus had an oddly low plasma, in the view of the decrease mean serum cholesterol level of heterozygote parents of the SLOS patients the total cholesterol level wasn't exceeding (Figure 2, Point no. 4). The history of pregnancy was also common for any familiar teratogen producing HPE Cunniff *et al.* (1997).

The LDL receptor in embryonic neuroepithelium associated in the transportation of placental LDL of mother, in rodents these findings were also been recorded to form HPE. Lack of cholesterol levels in maternal blood could also interrupt with fetal-cell membrane mechanisms and cell-to-cell interactions. Other functions may contain cholesterol levels in the influenced fetus and/or mother, environmental factors, other maternal or fetal genes, impaired transplacental transport of cholesterol or a pooling of these factors (Dehart *et al.*, 1997).

### Risk factors

Some particular risk factors associated with environmental along with retinoic acid, diabetic embryopathy, ethyl alcohol, and some anecdotal suggestions of teratogenic factors for HPE including salicylates and viruses (Cohen and Shiota, 2002). The maternal diabetes and maternal flu as more prevalent in HPE as compared in controls which was confirmed in South American (Orioli and Castilla, 2007). The National Birth Defects Prevention Study cases shows and discovered HPE to be associated with aspirin use, pre-existing diabetes, use of assisted reproductive technologies and lower education level (Miller *et al.*, 2010). In the same case, noted that non-genetic risk factor summary for HPE that have been inspected in case series and case reports, epidemiologic studies, and animal studies, containing therapeutic & non-therapeutic exposures, maternal illnesses, sociodemographic and nutritional factors (Johnson and Rasmussen, 2010).

### Diagnosis

MRI findings of the brain could be helpful to characterize cyclopian anatomical features. The most helpful diagnosis is done by Sonography in the fetal diagnosis of cyclopia (Filly *et al.*, 1984). There may new cyclopian syndromes still can emerge due to the demonstration of cyclopia is not fully exposed. The fetal diagnosis of cyclopia can be perform early by ultrasound and the awareness of the range of sonographic detections of cyclopia can enhance the accuracy of fetal diagnosis. The legalization of the pregnancy abortion for recorded cases in many countries all over the world should be examined (McGahan *et al.*, 1990).

Most of the nations it is still not permitted abortion due to religious, cultural and other reasons, but it is also legalized by medical law in several countries to abort the pregnancy if severe congenital anomalies found during pregnancy. In some cases, the parents were examined early that their baby has an extreme hydrocephalus, but unfortunately, they had no option to abort the pregnancy and they had to suffer the extreme psychological pain of holding a malformed fetus till term and delivering alive distorted baby who expired within just few hours after birth. These cases call for an urgent worldwide legalization of pregnancy abortion in recorded cases (Bullen *et al.*, 2001).

The major fact is that though HPE is a syndromic deformity with several genetic causes, both with and without a chromosomal examination and associated chromosomopathy, and postmortem autopsy can be add up to the diagnosis of cyclopia (Tonni *et al.*, 2008).

## CONCLUSIONS

Cyclopia is a rare disease which depicts the features of fetus like the absence of the facial midline bones and aproboscis presence as a nose-like structure above the single eye on the middle orbit of frontal bone of skull that mean there was a developmental defect. Diseases mostly associated were with chromosomal anomalies, majorly trisomy 13. Another cases presented with defects that are not related to HPE. The list of risk factors is involved to cause cyclopia and mainly maternal pre diabetic and maternal flu lead to develop abnormal fetus structure. The prenatal diagnosis is required to identify cyclopia and can be come to known early by ultrasound. On other hand the sonographic findings of cyclopia can upgrade the accuracy of prenatal diagnosis. In developing countries women were do not receive consistent antenatal care and do not go through prenatal diagnosis, such cases will go undetected.

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### Conflict of Interest

None.

## REFERENCES

Arathi, N., Mahadevan, A., Santosh, V., Yasha, T. C., Shankar, S. K. 2003. Holoprosencephaly with

cyclopia–report of a pathological study. *Neurology India*, 51(2):279–282.

Babaji, P., Singh, S., Sekar, S., Kumar, A., Gupta, V., Singh, A. 2014. Alobar holoprosencephaly with synopthalmia and proboscis. *Journal of Clinical Neonatology*, 3(3):176–176.

Bullen, P. J., Rankin, J. M., Robson, S. C. 2001. Investigation of the epidemiology and prenatal diagnosis of holoprosencephaly in the North of England. *American Journal of Obstetrics and Gynecology*, 184(6):1256–1262.

Bustami, F., Amr, S. 1986. Cyclopia. A case study and review. *Jordan Medical Journal*, 21:283–297.

Cannistr, C., Barbet, P., Parisi, P., Iannetti, G. 2001. Cyclopia: a radiological and anatomical craniofacial post mortem study. *Journal of Cranio-Maxillofacial Surgery*, 29(3):150–155.

Chukwuegbo, C. C., Ekanem, T., Ugbem 2015. Cyclop deformity born to an eclamptic mother: a case report and literature review. *Sch J Med Case Rep*, 3(8):667–670.

Cohen, M. M., Shiota, K. 2002. Teratogenesis of holoprosencephaly. *American Journal of Medical Genetics*, 109(1):1–15.

Cunniff, C., Kratz, L. E., Moser, A., Natowicz, M. R., Kelley, R. I. 1997. Clinical and biochemical spectrum of patients with RSH/Smith-Lemli-Opitz syndrome and abnormal cholesterol metabolism. *American Journal of Medical Genetics*, 68(3):263–269.

Deftereou, T. E., Tsoulopoulos, V., Alexiadis, G., Papadopoulos, E., Chouridou, E., Katotomichelakis, M., Lambropoulou, M. 2013. Congenital disorder of true cyclopia with polydactylia: case report and review of the literature. *Clinical and Experimental Obstetrics & Gynecology*, 40(3):460–462.

Dehart, D. B., Lanoue, L., Tint, G. S., Sulik, K. K. 1997. Pathogenesis of malformations in a rodent model for Smith-Lemli-Opitz syndrome. *American Journal of Medical Genetics*, 68(3):328–337.

Dubourg, C., Bendavid, C., Pasquier, L., Henry, C., Odent, S., David, V. 2007. Holoprosencephaly. *Orphanet Journal of Rare Diseases*, 2(1).

Filly, R. A., Chinn, D. H., Callen, P. W. 1984. Alobar holoprosencephaly: ultrasonographic prenatal diagnosis. *Radiology*, 151(2):455–459.

Goswami, D. 2015. Agnathia Holoprosencephaly and Situs Inversus in A Neonate Born to an Alcoholic Mother. *Journal of Clinical and Diagnostic Research*, 9.

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.

Kallen, B., Castilla, E. E., Lancaster, P. A., Mutchinick, O., Knudsen, L. B., Martinez-Frias, M. L., Mastroiacovo, P., Robert, E. 1992. The cyclops and the mermaid: an epidemiological study of two types of rare malformation. *Journal of Medical Genetics*, 29(1):30–35.

Kjaer, I., Keeling, J. W., Graem, N. 1991. The midline craniofacial skeleton in holoprosencephalic fetuses. *Journal of Medical Genetics*, 28(12):846–855.

Kumar, N. D., Kumaran, A. A., Balaji, S., Anupriya, R. 2015. Congenital nasal pyriform aperture stenosis: A rare cause of respiratory distress in newborn. *Journal of Clinical Neonatology*, 4(3):203–203.

Martínez-Frías, M. L., García, A., Bermejo, E. 1998. Cyclopia and sirenomelia in a liveborn infant. *Journal of Medical Genetics*, 35(3):263–264.

Mcevedy, C., Jones, R. 1978. Atlas of world population history. Middlesex Penguin. pages 357–357.

McGahan, J. P., Nyberg, D. A., Mack, L. A. 1990. Sonography of facial features of alobar and semilobar holoprosencephaly. *American Journal of Roentgenology*, 154(1):143–148.

Miller, E. A., Rasmussen, S. A., Siega-Riz, A. M., Frías, J. L., Honein, M. A. 2010. Risk factors for non-syndromic holoprosencephaly in the National Birth Defects Prevention Study. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, 154C(1):62–72.

Mondal, S., Pradhan, R., Adhya, S. 2015. Case Report: Holoprosencephaly with synophthalmia: A perinatal Autopsy. *Journal of Indian Academy of Forensic Medicine - MedIND*, 37(1).

Nalam, R., Suchitra, J., Ramaiah, D. 2018. Case report of cyclopia baby - A rare lethal anomaly. *Indian Journal of Case Reports*, 4(2).

Olejek, A., Bodzek, P., Skutil, M., Zamłyński, J., Stołtny, P. 2011. Cyclopia–literature review and a case report. *Ginekologia Polska*, 82(3):221–225.

Orioli, I. M., Castilla, E. E. 2007. Clinical epidemiologic study of holoprosencephaly in South America. *American Journal of Medical Genetics Part A*, 143A(24):3088–3099.

Otuaga, P., Eweka, Oni, Ebite, S., Mondal, R., Pradhan, S., Adhya 2007. Cyclops Deformity In Benin City, Nigeria: A Case Report. 10.

Raman, R., Jagadesh, G. M. 2014. Antenatal Diagnosis of Alobar Holoprosencephaly. *Case Reports in*

*Radiology*, 2014:1–4.

Rathod, S., Samal, S. K., Begum, J. 2015. Holoprosencephaly with cyclopia: a rare case report. *International Journal of Otorhinolaryngology and Head and Neck Surgery*, 1(1):37–37.

Rodrigues, L., Arakeri, S., Dwarampudi, R. 2019. Rare association of cyclopia with craniospinal rachischisis. *Indian Journal of Pathology and Microbiology*, 62(2):283–283.

Roessler, E., Muenke, M. 1998. Holoprosencephaly: A paradigm for the complex genetics of brain development. *Journal of Inherited Metabolic Disease*.

Salama, G. S., Kaabneh, M. A., Al-Raqad, M. K., Al-Abdallah, I. M., Shakkoury, A. G., Halaseh, R. A. 2015. Cyclopia: A Rare Condition with Unusual Presentation - A Case Report. *Clinical Medicine Insights: Pediatrics*, 9:CMPed.S21107–CMPed.S21107.

Sarma, C. M. 1983. Case report; human cyclopia. *Indian Journal of Ophthalmology*, pages 35–36.

Sezgin, İ., Süngü, S., Bekar, E., Çetin, M., Ceran, H. 2002. Cyclopia-astomia-agnathia-holoprosencephaly association: a case report. *Clinical Dysmorphology*, 11(3):225–226.

Singh, K., Sharma, S., Agarwal, K., Kalra, A. 2018. Cyclopia-otocephaly-agnathia-synotia-astomia complex: A case report. *Journal of Clinical Neonatology*, 7(3):177–177.

Situ, D., Reifel, C. W., Smith, R., Lyons, G. W., Temkin, R., Harper-Little, C., Pang, S. C. 2002. Investigation of a cyclopic, human, term fetus by use of magnetic resonance imaging (MRI). *Journal of Anatomy*, 200(5):431–438.

Srinivasan, K. R., Joseph, N. A. R., Koteswary, P. 2014. True cyclopia-very rare anomaly. *Journal of Clinical and Diagnostic Research : JCDR*, 8(8):1–2.

Stahl, A., Tourame, P. 2010. De la tératologie aux monstres de la mythologie et des légendes antiques.

Tomoda, K., Shea, J. J., Shenefelt, R. E., Wilroy, R. S. 1983. Temporal Bone Findings in Trisomy 13 With Cyclopia: A Case Report in a Fetus. *Archives of Otolaryngology - Head and Neck Surgery*, 109(8):553–558.

Tonni, G., Ventura, A., Centini, G., Felice, C. D. 2008. First trimester three-dimensional transvaginal imaging of alobar holoprosencephaly associated with proboscis and hypotelorism (ethmocephaly) in a 46,XX fetus. *Congenital Anomalies*, 48(1):51–55.

Weaver, D. D., Solomon, B. D., Akin-Samson, K., Kelley, R. I., Muenke, M. 2010a. Cyclopia (synophthalmia) in Smith-Lemli-Opitz syndrome: First reported case and consideration of mechanism. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, 154C(1):142–145.

Weaver, D. D., Solomon, B. D., Akin-Samson, K., Kelley, R. I., Muenke, M. 2010b. Cyclopia (synophthalmia) in Smith-Lemli-Opitz syndrome: First reported case and consideration of mechanism. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, 154C(1):142–145.

Wilson, W. G., Shanks, D. E., Sudduth, K. W., Couper, K. A., McIlhenny, J. 1989. Holoprosencephaly and interstitial deletion of 2(p2101p2109). *American Journal of Medical Genetics*, 34(2):252–254.

Yadav, S. K., Giri, A., Sah, V. K. 2018. Cyclopia: A Rare Congenital Malformation. *Journal of Nobel Medical College*, 7(2):70–73.

Yilmaz, F., Uzunlar, A. K., Kilinç, N., Bayhan, G., Gürkan, F., Yayla, M. 1998. A case of cyclopia. *Perinatoloji Dergisi*, pages 84–85.

Zimmer, E. Z., Divon, M. Y., Halperin, M., Peretz, B. A. 1982. Cyclopia with trisomy D. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 13(4):215–219.