e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2022; 14(5);18-24

Case Report

Alobar Holoprosencephaly: A Rare Case Report

Samira Kumar Behera[1], Lipika Behera[2], Swetambari Acharya[3], Dipika Mishra[4], Chaitali Pattnaik[5], Shushruta Mohanty[2]

[1]Associate Professor, Department of Pathology, M.K.C.G Medical College, Berhampur, Odisha, India

[2]Assistant Professor, Department of Pathology, M.K.C.G Medical College, Berhampur, Odisha India

[3,4,5]Postgraduate, Department of Pathology, M.K.C.G Medical College, Berhampur, Odisha, India

Received: 28-02-2022 / Revised: 15-03-2022 / Accepted: 20-04-2022
Corresponding author: Dr. Shushruta Mohanty
Conflict of interest: Nil

Abstract

Holoprosencephaly (HPE) is a rare congenital anomaly that occurs due to failure of prosencephalon to develop into two cerebral hemispheres. It results in brain malformation associated with multiple midline facial defects that occurs usually in 4th to 8th week of gestation. Most affected fetuses do not survive; severely affected children typically do not survive beyond early infancy, while a significant proportion of more mildly affected children survive past 12 months. We here in discuss a case of alobar holoprosencephaly in a fetus with midline facial defects that was detected clinically on USG scan. We received a dead fetus of about 21 weeks gestational age for autopsy. On external examination it had deformed facial structure like single eyeball(cyclopia) placed beneath tubular nose (Proboscis). A detail perinatal autopsy was conducted according to protocol which revealed alobar forebrain and dialated ventricles. Other visceras were normal externally and microscopically.

Keywords: Alobar, Holoprosencephaly, Cyclopia, Proboscis.

Introduction

Holoprosencephaly (HPE) is the most frequent malformation of prosencephalon. It results from incomplete division of proencephalon during 4th to 8th week of gestation. Its incidence is estimated to be 1 in 16000 live births and 1 in 250 spontaneous abortions [1]. HPE is classified into three types alobar, semilobar, and lobar. Review of literature have described another subtype, middle interhemispheric variant (MIH). The clinical features of HPE are varied and depends on the severity. However, alobar HPE is considered most serious form of the disorder and MIH is considered as milder subtype of HPE [2,3]. In HPE the embryonic forebrain fails to develop into bilateral cerebral hemispheres that leads to facial defects and brain malformations [2]. We discuss in this case report, autopsy findings done on 21 weeks fetus detected to have alobar Holoprosencephaly along with a brief discussion on pathogenesis, clinical features, management and prognosis.

Case Report:

A fetus diagnosed with Holoprosencephaly (HPE) was born to a mother with gestational age of 21 weeks at our hospital (O&G) dept. The mother was 21 yrs old who attended her routine ANC Checkups at her village. She had no history of smoking, alcohol consumption or any antenatal complications (diabetes mellitus and infections) nor use of any teratogenic medications (aspirin, lithium, retenoic acid or anticonvulsants). Her family history was unsignificant in terms of neurological disorders in the parents or siblings. Routine haematological investigations were within normal limits and serological tests for TORCH infections was negative. Ultrasound examination at 5^{th} month (anomaly scan) was indicative of fetal anomaly and was diagnosed with HPE using a 3D US. The mother was explained about the prognosis of the baby and was planned for termination of pregnancy. The abnormal fetus was sent for histopathological examination and establishment of congenital anomalies.

Anthropometry: Specimen of female fetus weighed 170 gms. CHL=21cms, HC=14 cm, CC=12 cm. Physical examination: Shows facial deformity single eye (cyclopia) placed beneath the protuberant nose (Proboscis)[Fig 1]. The skull was opened along the suture lines and the flaps were separated as the petals of a flower, basing on Barr & Benek's technique. The internal examination of the brain revealed a triangular globular structure which was identified as forebrain and a single optic nerve with dilated ventricles. [Fig.2&3] Histological section of the structure confirmed it to be eyeball and brain. Autopsy was done according to Virchow's technique and a modified 'Y' shaped incision opened the thoracic cavity and the abdomen [Fig.4] All the internal viscera were normal in development. Sections were given from all organs for histopathological analysis.

Histopathologically all the organs were within normal limits with no significant findings. The placenta and the umbilical cord findings were normal in gross and microscopic examination. The final autopsy diagnosis was given as holoprosencephaly. Karyotyping was suggested to find the chromosomal mutations but unfortunately, we could not do this due to lack of the facility at our set up.

Figure 1: Gross pic showing fetus presented with Single eye (cyclopia) placed beneath tubular nose (proboscis)

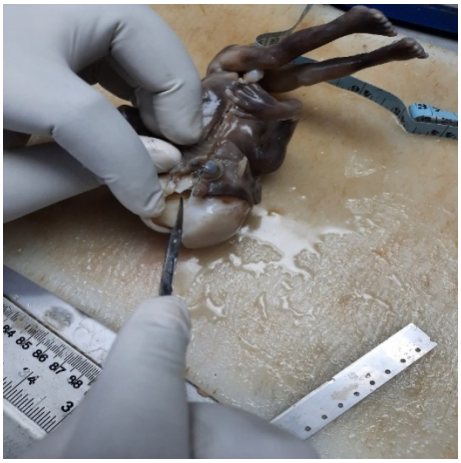

Figure 2: Gross pic showing sectioning of brain

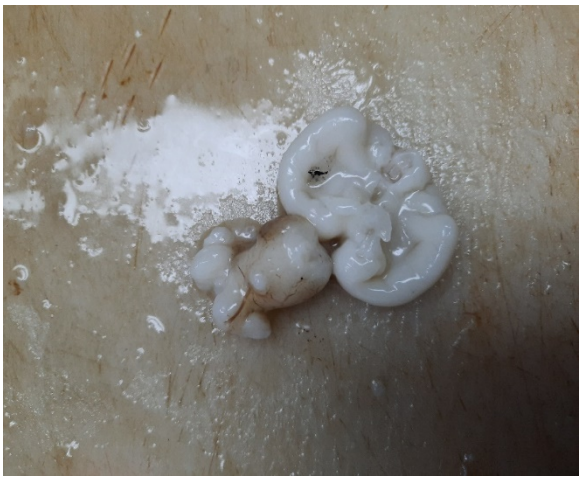

Figure 3: Showing Gross pic of the brain

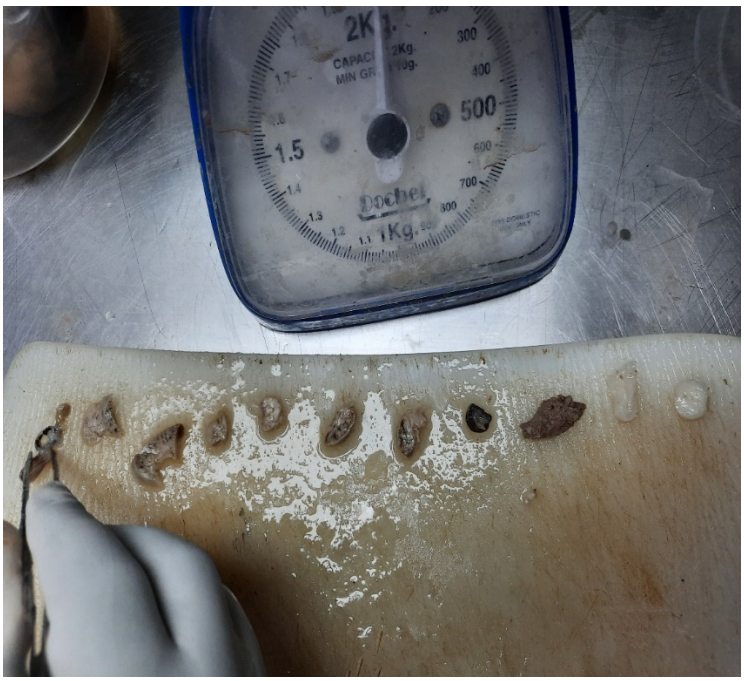

Figure 4: Sections from different organs

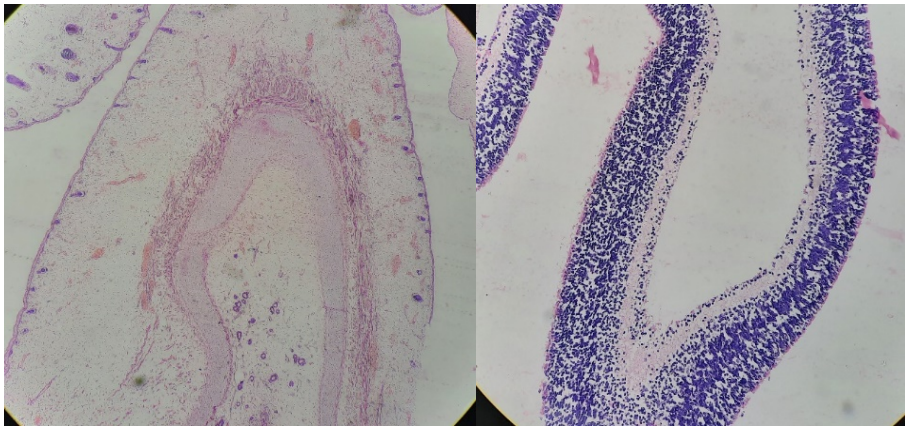

Figure 5: (a) (b) LP 100X sections from nose and eye

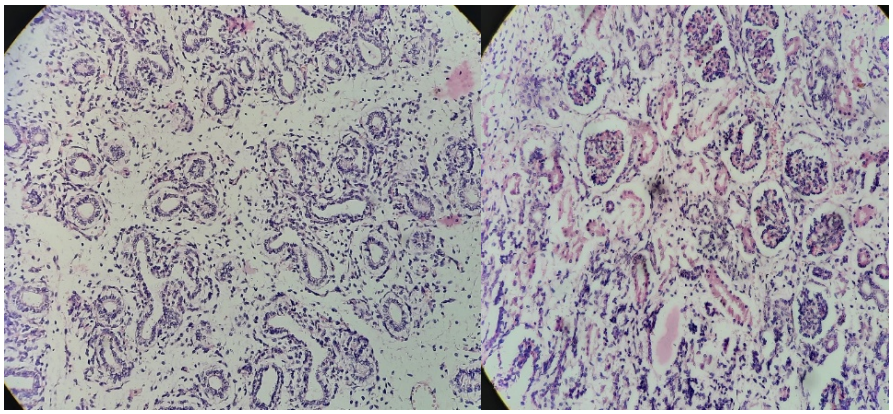

Figure 5: (c)(d) LP 100 X Histosection from lung shows unrespired lung, Kidney is within normal limit.

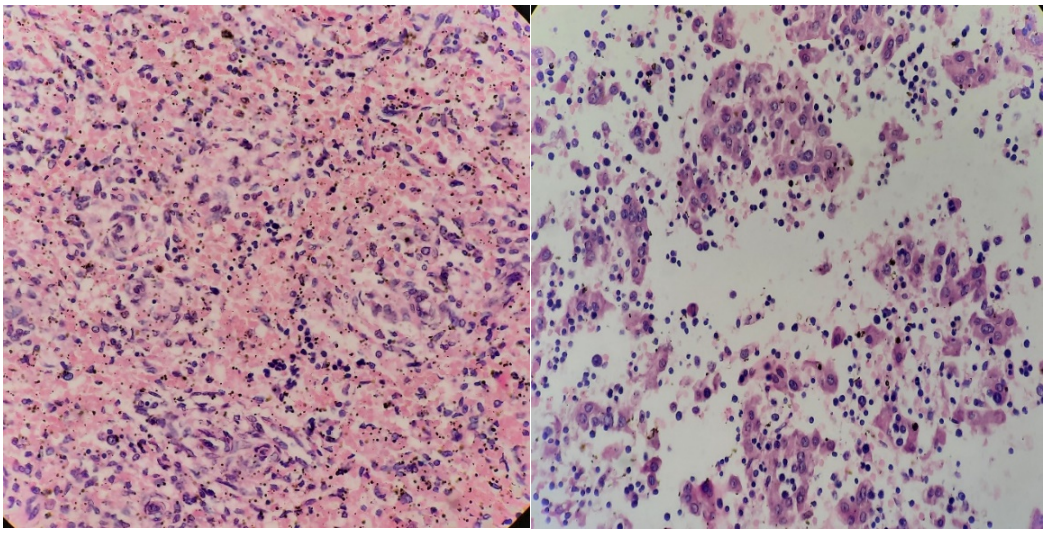

Figure 5: (e)(f) LP 100X sections from spleen shows congestion and Extramedullary haematopoeisis (EMH)
Liver shows normal hepatocytes with EMH

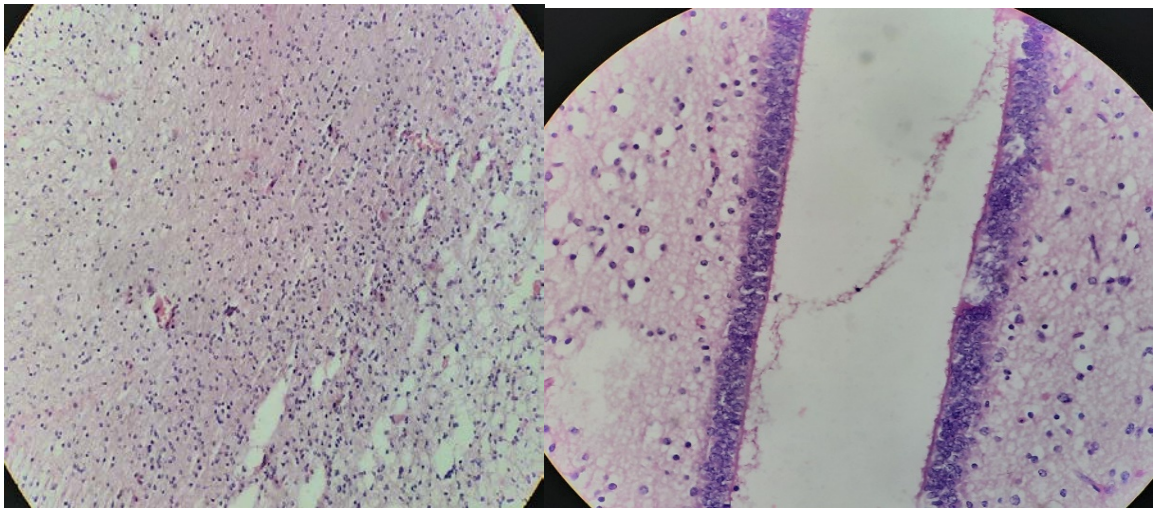

Figure 5: (g)(h) LP 100x sections from Cerebrum and cerebellum

Discussion:

The morphologic development in an embryo generally occurs in a self-organized and synchronous manner. According to the primary developmental defect, the specific organ gets affected. Midline defect results due to bilateral and symmetric structure influenced by midline events. Holoprosencephaly is the result of improper separation of forebrain into two lateral hemispheres. The normal brain development starts at the3rd to4th week of intrauterine life. If the embryo's forebrain does not divide bilaterally due to some genetic cause or as a part of a syndrome, it causes defect in the face as well as in the brain structurally and functionally. In 1984, Hartsfield *et al.* described the first known case of a child born with HPE and ectrodactyly.[4] A combination of HPE, ectrodactyly and bilateral cleft lip and cleft palate is known as Hartsfield syndrome. HPE is classified broadly into three types:

1. Alobar, which means the complete absence of division of the prosencephalon structures, resulting in completely absent interhemispheric fissure and corpus callosum, fused thalami, fused cerebral hemispheres with only one cerebral ventricle, and facial dysmorphism which include such abnormalities as cyclopia, proboscis, ethmocephaly and cebocephaly. It is the most severe form.
2. Semilobar, is regarded as moderate form of HPE that results in incomplete separation of the cerebral hemispheres: there are two cerebral hemispheres connected in the frontal area, with a singular ventricular cavity and partially fused thalami.
3. Lobar, in this case interhemispheric fissure is present, septum pellucidum is absent and frontal horns of lateral ventricles communicate freely, corpus callosum is absent hypoplastic or normal, with midline fusion of cingulate gyrus. It is the least severe form.
4. There is a fourth type described in the literature, the middle interhemispheric variant (MIH), which means a defect of separation of the posterior portions of frontal lobes and the parietal lobes, with varying lack of cleavage of the basal ganglia and thalami and absence of the body of the corpus callosum but presence of the genu and splenium of the corpus callosum. [1]

Holoprosencephaly has heterogenous etiology. There are various etiologies that have been proposed in literatures regarding etiology of HPE that includes genetic and

environmental factors. The environmental factors include maternal diabetes mellitus, maternal alcoholism, in vitro infection by TORCH infections and some drugs like retenoic acid and cholesterol synthesis inhibitors [1]. HPE can be transmitted in autosomal dominant way .Research found that HPE may have mutation in the following genes: sonic hedgehog (*SHH*), patched homolog 1 (*PTCH1*), glioma-associated oncogene family zinc finger 2 (*GLI2*), teratocarcinoma-derived growth factor 1 (*TDGF1*, also known as *CRIPTO*), TGF-β–induced factor homeobox (*TGIF*), for khead box H1 (*FOXH1*), zinc finger protein of the cerebellum 2 (*ZIC2*), SIX homeobox 3 (*SIX3*), and dispatched homolog 1 (*DISP1*). Mutation of SHH gene is the most frequent cause of familial HPE [5]

Although children with HPE are known to have normal karyotypes, in 40% of cases, numerical chromosomal abnormalities have been identified of which the most frequent is trisomy 13 [6]**.** In our case the mother was a primigravida 22 years old, non-diabetic with no history of bleeding during first trimester. There was no history of smoking, alcohol consumption, or other TORCH infections that are considered as risk factors for HPE. Genetic testing could not be performed due to lack of facility at our set up.

Clinical finding of HPE is varied depending on the severity of the condition [4]. Few clinical features include the midfacial defects i.e absence of eyes, cebocephaly, cyclopia, Proboscis, Chielo/palatoschisis and agnathia (severe micrognathia). Among these factors cyclopia, proboscis, chielopalatoschisis are associated with severity of HPE [7]. Microcephaly or macrocephaly in some cases is indicative of hydrocephaly. Mental retardation bears a direct correlation with severity of HPE [8]. A neonate born with HPE may encounter other neurological and endocrinology associated complications. Neurological features encountered includes seizures, hypertonia, dysphagia, dysponia, extra pyramidal disorders like chorea or dystonia. Endocrinological disturbance includes hypopituatarism and DI. Brain functions might be normal and facial deformities occur at minimum in milder cases of HPE. However, in our case we had clinically only cyclopia, Proboscis and globular structure that was identified as forebrain with dilated ventricles on basis of which it was diagnosed to have severe HPE. HPE can be associated in 25 % cases with several defined multiple malformation syndromes with a normal karyotype like Smith-Lemli-Opitz, Pallister Hall or velocardiofacial syndrome [1].

Prenatal diagnostic modalities are also varied that inlcudes USG, fetal MRI, Cytogenetics and molecular analysis of fetal DNA. The facial deformities and brain abnormalities are easily detected on USG. The diagnosis could be made of alobar and semilobar holoprosencephaly only after 17 weeks, i.e when CSF production starts. The diagnosis of lobar holoprosencephaly is difficult due to diagnostic overlap with septo-optic dysplasia [9**].** Though karyotyping must be carried out in all cases of HPE to determine the genetic aetiology, it is not always feasible because of the etiologic heterogeneity and pathologic variability of HPE.

Conclusion:

Treatment of HPE is supportive and oriented towards different malformations associated with it. Prognosis is dependent on degree of fusion and malformation of brain, facial malformations and clinical complications that is present. Alobar and semilobar HPE are considered to have poorer prognosis. Children's those who are born with lobar HPE even though they survive for years they encounter lot of neurological manifestation and severe

mental retardation. The type of brain malformation varies in different types of HPE that can be established only after a thorough autopsy examination and opening of skull. Therefore, we want to stress upon the fact that autopsy examination should be done in every case of perinatal death to establish the type of congenital anomaly and thereby also gives a chance for counselling of parents for future pregnancies.

References:

1. Dubourg C, Bendavid C, Pasquier L, et al. Holoprosencephaly. J Rare Dis. 2007; 2:8.
2. National Institute of Neurological Disorders and Stroke. Holoprosencephaly information page [Internet]. 2007. Available from: http://www.ninds.nih.gov/disorders/holoprosencephaly/holoprosencephaly.htm.
3. Poenaru MO, Vilcea LD, Marin A. Holoprosencephaly: two case reports. Maedica 2012; 7(1):58-62.
4. Hartsfield JK, Bixler D, DeMeyer WE: Syndrome identification case report 119. Hypertelorism associated with holoprosencephaly and ectrodactyly**.** ClinDysmorphol 1984, **2:**27-31.
5. Gupta AO, Leblanc P, Janumpally KC et al. – A preterm infant with semilobar holoprosencephaly and hydrocephalus: a case report. Cases J. 2010; 3:35.
6. Chen H – Atlas of genetic diagnosis and counseling. Humana Press, 2006.
7. Geng X, Oliver G – Pathogenesis of holoprosencephaly. J Clin Invest. 2009; 119:1403-1413.
8. Cohen MM Jr. Holoprosencephaly: clinical, anatomic, and molecular dimensions. Birth Defects Res A Clin Mol Teratol 2006; 76(9):658-73.
9. Evans MI, Johnson MP, Yaron Y, et al. – Prenatal Diagnosis. Mc Graw-Hill Companies 2006.