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A Case Report Of Alobar Holoprosencephaly: The Role Of Ultrasonographic Imaging

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Abstract: *Holoprosencephaly is a rare congenital brain malformation caused by the incomplete separation of the embryonic forebrain (prosencephalon), leading to a spectrum of cerebral and facial anomalies. The condition is classified into four types: alobar, semi-lobar, lobar, and middle interhemispheric fusion, with alobar HPE being the most severe, characterized by a lack of midline structures and a single ventricle. While the exact incidence is unclear, holoprosencephaly is associated with high mortality rates, particularly in its severe forms. Early prenatal diagnosis is crucial for guiding obstetric management, with sonography being a key diagnostic tool. A 41-year-old G3P2A0 woman was referred to our fetomaternal clinic at 32 weeks of gestation with a suspected fetal anomaly. Ultrasound examination revealed findings consistent with alobar holoprosencephaly, including fused thalami, a single ventricle, absence of the cavum septum pellucidum, and facial anomalies such as cyclopia and proboscis. Despite a normal obstetric history and the absence of risk factors such as teratogenic exposure, the severity of the condition led to the decision to terminate the pregnancy. The patient delivered a male infant with an APGAR score of 3/4, weighing 1600 grams, who exhibited all the sonographic findings. The infant did not survive post-delivery. Alobar holoprosencephaly represents the most severe form of holoprosencephaly, associated with a poor prognosis and high perinatal mortality. Prenatal ultrasonography is essential for early diagnosis, allowing for informed decision-making regarding pregnancy management. Early termination may be considered to prevent maternal trauma, given the condition's uniformly fatal outcome.*
Keywords: *Alobar Holoprosencephaly; Antenatal Detection; Developing Countries; Diagnosis; Ultrasonography.*

INTRODUCTION

Holoprosencephaly refers to a spectrum of cerebral and facial malformations that result from the absence or incomplete separation of the embryonic forebrain, known as the prosencephalon.[1,2] The prosencephalon is responsible for forming the cerebral hemispheres, thalamus, and basal ganglia.[3,4] This developmental abnormality can occur between the 3rd and 4th weeks of pregnancy and affects both the brain and facial structures of the fetus.[1,5] Holoprosencephaly is classified into four types: alobar, semi-lobar, lobar, and Middle Interhemispheric Fusion (MIH). These classifications are based on the extent of hemispheric division and the presence or absence of interhemispheric fissures, which also influence the prognosis of the condition. [2,3]Alobar holoprosencephaly is the most severe form, characterized by the absence of midline structures and lack of hemispheric division.[6] The true incidence of holoprosencephaly remains unclear, possibly due to the high mortality rate in early embryonic life associated with this condition.[1] Generally, it is considered a very rare condition globally. In one study, holoprosencephaly was reported to occur in 0.49 to 1.2 cases per 10,000-20,000 full-term births.[3] Other literature suggests that it affects approximately 1 in 250 conceptuses; however, due to the significant number of fetal deaths, its prevalence in live births is lower, ranging from 1 in 8,000 to 1 in 16,000.[2] Despite its rarity, holoprosencephaly is the most common structural malformation of the forebrain.[7,8] Therefore, early antenatal diagnosis of this malformation is critical for guiding appropriate obstetric management.[4,5] In this regard, sonography may serve as an excellent non-invasive modality for the prenatal diagnosis of holoprosencephaly.[9,10] This case report presents a fetus diagnosed with alobar holoprosencephaly via fetomaternal ultrasound, which ultimately led to pregnancy termination at 32 weeks of gestation.

CASE PRESENTATION

A 41-year-old woman was referred to the fetomaternal clinic of our hospital with an initial diagnosis of G3P2A0 at 31-32 weeks of gestation and suspected fetal hydrocephalus. The patient reported noticing an abnormality in her baby's head one day before, while visiting an obstetrician. Despite this, she continued to

feel fetal movements. The patient denied experiencing any symptoms, including frequent and strong labor pains, watery discharge, or vaginal bleeding. There was no family history of congenital abnormalities, and she denied a history of chronic conditions such as hypertension, diabetes, or heart disease. Her obstetric history included three previous spontaneous deliveries in 2002, 2009, and 2014, all resulting in full-term live births with weights of 2800 grams or more. This was her first marriage, and there was no history of consanguinity. From 2014 to 2024, she used contraceptive pills, and she denied any history of teratogenic drug use. The patient had attended a total of 10 antenatal check-ups, including 9 with a midwife and 1 with an obstetrician. On physical examination, the patient was fully alert, with vital signs within normal limits (blood pressure: 136/77 mmHg, pulse: 89 bpm, respiratory rate: 20 breaths per minute, temperature: 36.5°C, and SpO2: 99% on room air). Her height was 158 cm, weight 65 kg, and BMI 24.19 kg/m^2. Obstetric examination revealed a convex, soft abdomen with an abdominal circumference of 90 cm and a fundal height of 30 cm. There were no uterine contractions, and the fetal heart rate was 140-144 bpm. Internal examination showed no abnormalities in the vulva or vagina, a soft, thick cervix with 1 cm dilation, positive amniotic fluid, and the fetal head at station -1. As part of a pregnancy check-up, fasting and postprandial blood glucose levels were normal. Other laboratory results were also within normal limits.

Ultrasonography revealed a live, intrauterine singleton fetus in cephalic presentation, corresponding to a gestational age of 29 weeks and 1 day (TCD corresponding to 29 weeks and 4 days). The estimated fetal weight was 1402 grams, and the fetal heart rate was positive. The biparietal diameter (BPD) measured 8.37 cm, consistent with a gestational age of 33 weeks and 5 days. The head circumference (HC) was 28.54 cm, corresponding to a gestational age of 31 weeks and 2 days. The cerebellum measured 3.55 cm, appropriate for 29 weeks and 4 days, with a visible vermis. The cisterna magna measured 5.64 mm. Other findings included fused thalami, absence of the cavum septum pellucidum and cerebral falx, and absence of the corpus callosum, with a single ventricle present. Facial assessment showed the absence of the nasal bone, difficulty in evaluating the nostrils, and the presence of a proboscis, with no cleft detected.

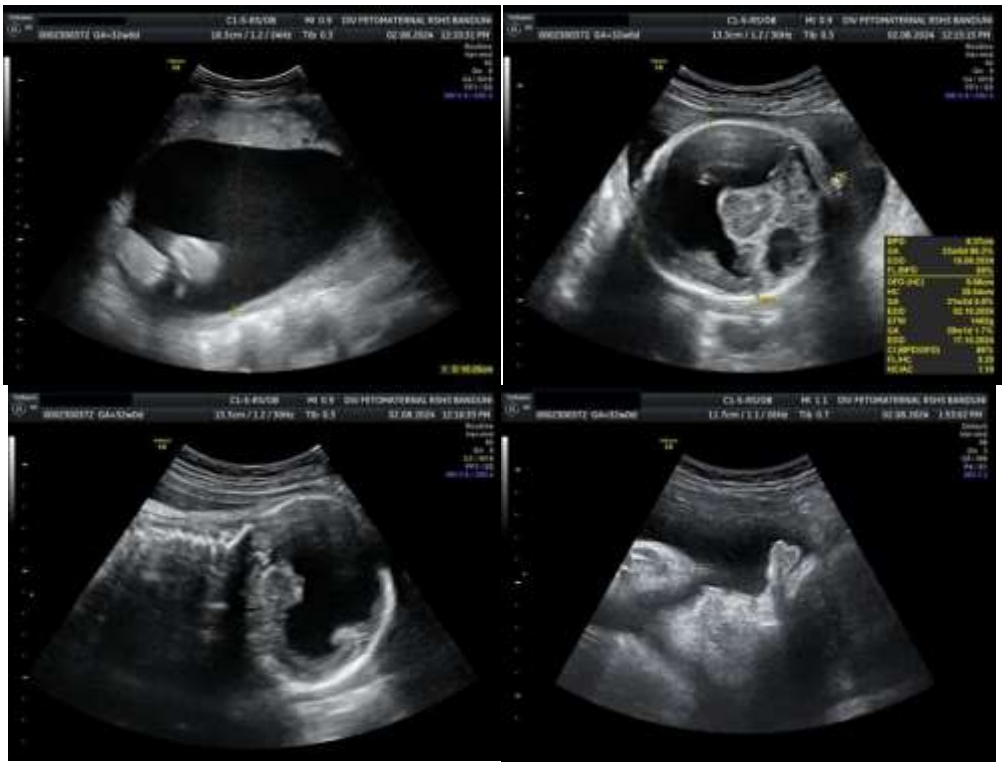

Figure 1. Ultrasonography of the baby

The placenta was located on the anterior wall of the uterus, and the amniotic fluid index (SDP) was 10.68 cm. Based on these ultrasound findings, the patient was diagnosed with G3P2A0 at 32 weeks of gestation, polyhydramnios, and alobar holoprosencephaly. It was decided to proceed with pregnancy termination using misoprostol induction. A male infant was delivered with an APGAR score of 3/4, measuring 39.5 cm in length and weighing 1600 grams. The gross specimen of the fetus showed all the findings previously observed on sonography. The analysis showed a male karyotype with Trisomy 13. No chromosomal structural abnormalities or mosaicism were found.

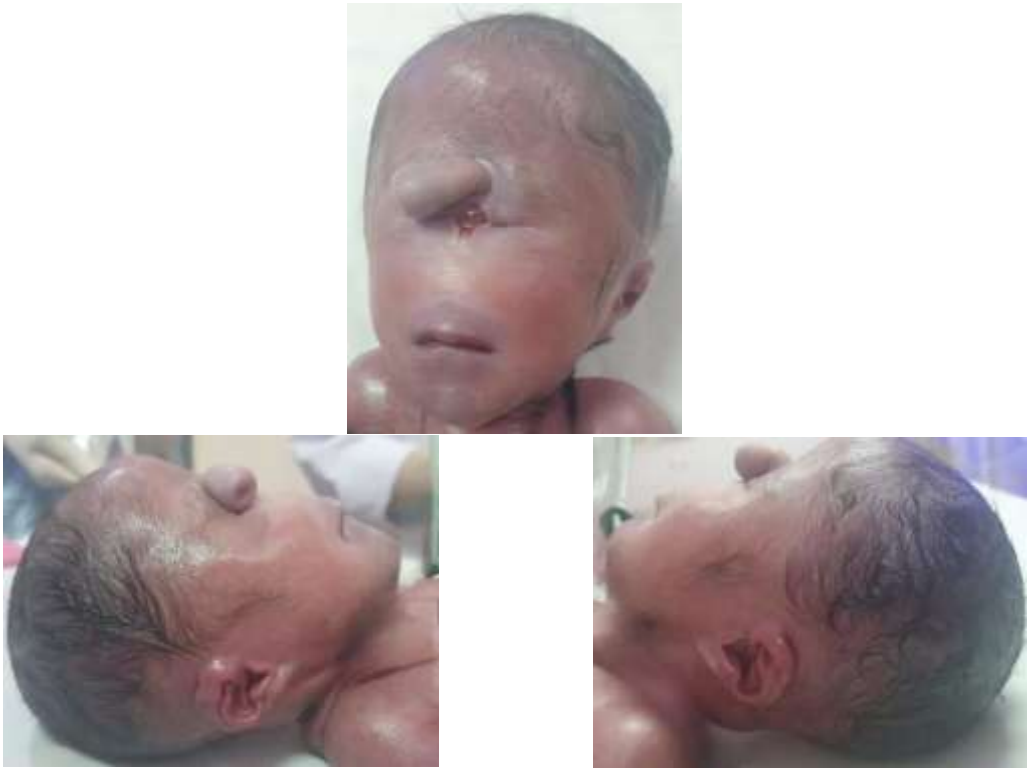

Figure 1. The fetus was born with presence of proboscis

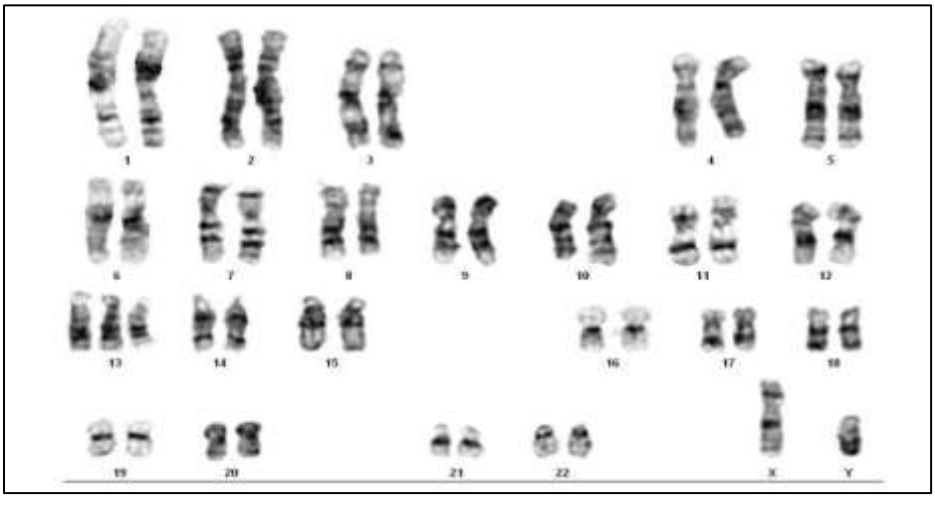

Figure 3. Chromosome Analysis Results

DISCUSSION

Our case report describes a neonate with alobar holoprosencephaly, born to a G3P2A0 mother, who was diagnosed antenatally through fetomaternal ultrasound examination. During embryogenesis, the primary neurulation process is crucial for the formation of the neural tube, which subsequently develops into three major brain structures: the forebrain, midbrain, and hindbrain. Holoprosencephaly occurs due to the incomplete division of the forebrain into the right and left hemispheres between the 18th and 28th days of gestation.[11–13] Holoprosencephaly is classified based on the extent of sagittal cleavage of the cerebral cortex, thalamus, and hypothalamus. Alobar holoprosencephaly, the most severe form, is characterized by the absence of midline structures and hemispheric division, typically associated with a single common ventricle and fused thalami, as observed in our case. Semilobar holoprosencephaly, another form, results from the incomplete separation of the forebrain, leading to partial division of the cerebral hemispheres. Lobar holoprosencephaly involves normal cortical division with two distinct thalami, but anomalies may be present in the corpus callosum, septum pellucidum, or olfactory structures. The fourth subtype, Middle Interhemispheric Variant (MIH), is characterized by incomplete separation of the frontal and posterior parietal lobes, while the frontal and occipital poles are well separated. The facial anomalies associated with holoprosencephaly can vary from subtle to severe, with the most extreme malformations often occurring in cases of alobar holoprosencephaly. In our case, the neonate exhibited cyclopia, the most severe facial malformation, marked by a single or fused eye and absence of nasal structures. A proboscis, a median primitive non-canalized nasal structure projecting from the forehead, was also noted.[1–4]

The etiology of holoprosencephaly is multifactorial, involving both genetic and non-genetic risk factors, including exposure to teratogens.[2,5,14] Maternal diabetes is the only teratogen definitively associated with a significantly increased risk of holoprosencephaly, with an incidence up to 200-fold higher in affected mothers compared to controls.[1] Some studies estimate that 1-2% of infants born to mothers with diabetes mellitus may develop holoprosencephaly.[2,3] Possible mechanisms underlying the teratogenic effects of maternal hyperglycemia include increased oxidative stress, hypoxia, apoptosis, and epigenetic changes.[5] Other research suggests a higher incidence of holoprosencephaly in mothers over 30 years of age, which aligns with our case.[6] Additional teratogens associated with an increased risk of holoprosencephaly include ethanol, TORCH infections, retinoic acid, and drugs that disrupt cholesterol biosynthesis.[1,2,11,13] However, our patient had no history of exposure to these risk factors. Laboratory tests excluded gestational diabetes and recent toxoplasmosis or rubella infections.

Given the potential for familial recurrence of holoprosencephaly, it is recommended to take a detailed family history, particularly for relatives with intellectual retardation, microcephaly, cleft lip and/or palate, ocular abnormalities, midface flattening, or a single central incisor.[1] Our patient reported no such family history. Additionally, chromosomal abnormalities are present in approximately 30% to 50% of fetuses with holoprosencephaly, particularly when accompanied by extrafacial anomalies. Trisomy 13 accounts for approximately 75% of these cases, with other potential associations including trisomy 18 (Edwards syndrome), trisomy 17, trisomy 15, and triploidy. Therefore, prenatal karyotyping is strongly recommended.[1–3] However, due to limited resources and the test's perceived non-essential nature for confirming the diagnosis, karyotyping was not performed in this case.[15]

The primary imaging modalities for evaluating holoprosencephaly include transabdominal ultrasonography (US), transvaginal US, and magnetic resonance imaging (MRI).[3] Prenatal US, especially focused on the face and falx cerebri, can diagnose alobar and semilobar holoprosencephaly as early as the first trimester. For milder forms, fetal MRI in the third trimester offers a more sensitive diagnostic approach.[7] In the first trimester, typical US findings include midline monoventricularity and the absence of the characteristic echogenic "butterfly" sign of the choroid plexus.[15] Due to its widespread availability, the US often serves as the primary diagnostic tool for holoprosencephaly, as was the case in our patient. Additionally, the US is relatively unaffected by factors such as maternal obesity, fetal position, skeletal reverberation, and oligohydramnios.[7] The optimal sonographic view for assessing the fetal face in holoprosencephaly cases is the coronal view, which captures the orbits, maxilla, and anterior mandible in a single plane. Three-dimensional ultrasonography (3D USG) can complement 2D US by providing a more detailed evaluation of fetal

craniofacial abnormalities, as it did in our case. Visualization of facial anomalies may be challenging if the fetus is in the occipitoanterior position.[4]

Ultrasonography is instrumental in identifying and classifying the severity of abnormalities resulting from failed prosencephalic division in holoprosencephaly.[3] The diagnosis of holoprosencephaly requires the identification of both intracranial and facial structural abnormalities.[1] In most normal fetuses, midline echoes are produced by the reflection of sound waves from the acoustic interfaces in the interhemispheric fissure. However, this echo is absent in cases of alobar holoprosencephaly. Alobar holoprosencephaly is typically characterized by a single ventricular cavity forming the telencephalon, which is posteriorly enclosed by a thin, pseudocystic-appearing wall. Additional features include the absence of olfactory lobes, a rudimentary thalamus fused at the midline, and constant microcephaly.[5,8,10] These findings were consistent with those observed in our case. Sonography has been reported to detect up to 58% of facial abnormalities in holoprosencephaly.[4] The major facial anomalies associated with alobar holoprosencephaly include cyclopia or synophthalmia, severe ocular hypotelorism with fused orbits, and proboscis-like nasal structures. Cebocephaly and median cleft lip are also seen in alobar holoprosencephaly. Other milder facial anomalies may include ocular hypotelorism, iris coloboma, absence of nasal bones, a single central incisor, unilateral or bilateral cleft lip/palate, and midface hypoplasia.[12,13,16,17] In our case, the facial anomalies included cyclopia, proboscis, and the absence of nasal features.

When ultrasound findings suggest potential brain abnormalities but are inconclusive, fetal MRI is often employed as a second-line examination to confirm the diagnosis and provide a detailed evaluation of the fetal central nervous system.[3,12] Extracranial abnormalities associated with holoprosencephaly, such as limb abnormalities, polydactyly, pulmonary hypoplasia, cardiac anomalies, renal dysplasia, omphalocele, hydrops fetalis, esophageal atresia, bladder exstrophy, and gastrointestinal or abdominal abnormalities, can also be observed.[9] However, no extracranial abnormalities were identified in our case.

The main differential diagnoses to consider when establishing the diagnosis of holoprosencephaly include hydrocephalus, midline cerebral defects such as septo-optic dysplasia, hydranencephaly, and porencephalic cysts. This aligns with our case, where the patient was initially referred with suspected hydrocephalus. Holoprosencephaly can be differentiated from fetal hydrocephalus by the absence of the midline echo and the presence of thalamic fusion on ultrasonography. In contrast, infants with hydrocephalus due to aqueductal stenosis or Arnold–Chiari malformation will typically exhibit an intact falx cerebri, distinct and separate ventricles, and splayed thalami.[1,4]

Our patient was successfully delivered via vaginal delivery following the termination of pregnancy at 32 weeks of gestation. Holoprosencephaly is recognized as a highly lethal condition during the fetal period, with estimates suggesting that only 3% of conceptions with holoprosencephaly result in live births.[1] Postnatally, holoprosencephaly continues to be associated with high mortality, with an estimated overall mortality rate of 33% within the first 24 hours after birth and 58% within the first month.[2] Given the association with such a poor prognosis, early termination of pregnancy is justified in cases of alobar holoprosencephaly.[5,6] Specifically, infants with conditions such as cyclopia, ethmocephaly, and cephalocele are unlikely to survive the perinatal period and typically do not live beyond the first week of life.[16] Because of this, and due to the high risk of severe mental retardation in surviving infants with alobar holoprosencephaly, aggressive resuscitation, including mechanical ventilation, is generally contraindicated. Clinicians must conduct a follow-up meeting with the parents during the postpartum or post-termination period to review any pathological findings, discuss the potential causes and genetic implications, and assess the risk of future recurrence.[1,2,6]

CONCLUSION

Holoprosencephaly represents a spectrum of very rare congenital brain abnormalities associated with the failure of midline cleavage of the prosencephalon. Alobar holoprosencephaly, the most severe form, carries a poor prognosis. Antenatal ultrasonography serves as a valuable tool for early identification of this condition, facilitating timely decisions regarding pregnancy termination and potentially mitigating the emotional trauma experienced by the mother.

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