CASE REPORT

Fetal Holoprosencephaly

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ABSTRACT

Holoprosencephaly is a birth defect that leads to an abnormal brain development where the brain fails to divide into two hemispheres. Possible causes are environmental or genetic factors. Holoprosencephaly can include craniofacial abnormalities in most of the cases. Here we report a case of delayed diagnosis of holoprosencephaly with cyclopia, proboscis, and ethmocephaly.

Keywords: Antenatal ultrasound, Fetal malformation, Holoprosencephaly.

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BACKGROUND

Holoprosencephaly is a brain malformation with a prevalence of 1:16,000 live births and 1:250 during early embryonic development.^{1,2} It is a condition in which the prosencephalon fails to divide into left and right hemispheres between the 4th and 8th weeks of gestation. Holoprosencephaly can also be associated with craniofacial deformities alongside the brain abnormalities. The etiology of holoprosencephaly could be genetic or environmental. Examples of genetic factors are trisomies 13 and 18 or certain deletions like 18p, 7q, 2p, and 21q.³ The environmental factors that could play a role are like diabetes, infections in pregnancy, smoking, alcohol, recreational drug use, and low socioeconomic status.³ There are four types of holoprosencephaly: lobar, semilobar, lobar, and middle interhemispheric variant.² The severity of the condition is different from one case to the other.

CASE DESCRIPTION

We report a case of delayed diagnosis of holoprosencephaly in a pregnant 30-year-old female who is gravida 4 para 3 + 1. The mother is not diabetic or hypertensive and there is no history of consanguinity. She had no infections and did not smoke, drink alcohol, or use any drugs throughout her pregnancy. At 20 weeks of gestation, the diagnosis of encephalocele was made and the mother underwent two failed medical mid-trimester terminations. At 27 weeks of gestation, she was referred for advanced ultrasound. The antenatal ultrasound revealed polyhydramnios, fused thalami, absent cavum septum pellucidum, no falx cerebri, and communicating ventricles and choroid plexus (Figs 1A and B). It also revealed encephalocele and the absence of corpus callosum (Fig. 1C). On color Doppler, no vascularity was seen (Fig. 1D). On grayscale imaging, there were cyclopia and proboscis. Three-dimensional ultrasound using the surface rendering mode was used, which showed the face of the fetus. The face is dysmorphic, with cyclopia and proboscis (Fig. 2).

At 33 weeks of gestation, the mother gave birth to the neonate after the premature rupture of the membranes and undergoing the emergency cesarean section. At birth, the infant had a visible dysmorphic face of cyclopia, proboscis, and ethmocephaly. There was also encephalocele, dysmorphic ears, ambiguous genitalia, and polydactyly on only one hand (Fig. 3). The infant had died shortly after birth. The mother declined karyotyping during pregnancy or autopsy after the passing of the newborn.

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DISCUSSION

Holoprosencephaly is classified into four categories. The first one is lobar holoprosencephaly, the most severe form, which means that there is complete absence of the division of the hemispheres, so midline structures are absent. There will be absent corpus callosum, absent interhemispheric fissure, the thalami are fused, and there is only a single communicating ventricle present.⁴ This form is also associated with facial deformities like cyclopia, proboscis, ethmocephaly, and cebocephaly.⁴ The second category is semilobar holoprosencephaly, which is the incomplete division of the forebrain. This results in only partial separation of the hemispheres connected in the frontal area, with a single ventricle and partially fused thalami.⁴ The third type is lobar holoprosencephaly, which is the least severe form, is when there is normal cortical separation and two thalami are present, but the abnormalities exist in the corpus callosum, septum pellucidum, or olfactory tract or bulbs.^{4,5} The last type is the middle interhemispheric variant, which is the more recent type described in the literature. In this type, the posterior frontal and parietal lobes fail to separate but the frontal and occipital lobes are well separated.^{4,5}

The etiology of holoprosencephaly includes genetic and environmental factors. The genetic factors include trisomies 13 and 18. Approximately 40% of the cases of holoprosencephaly have a genetic factor. Out of these, about 75% of them are due to trisomy 13. There are also chromosomal deletions associated with holoprosencephaly like 18p, 7q, 2p, and 21q.⁶ Holoprosencephaly can also be familial with an autosomal dominant mode of inheritance. The most common cause of familial holoprosencephaly is the SHH gene mutation. The environmental risk factors are maternal gestational diabetes, maternal diabetes mellitus, infections

Figs 1A to D: Ultrasound findings: (A) Transthalamic view of the central nervous system showing strawberry-shaped skull, fused thalami, absent cavum septum pellucidum, and no falx cerebri; (B) Transventricular view shows communicating ventricles and choroid plexus; (C) Encephalocele and no corpus callosum; (D) Fluid-filled mass with no vascularity on color Doppler

Figs 2A and B: Ultrasound findings: (A) Surface rendering mode showing the face of the fetus, using three-dimensional ultrasound; (B) The face is dysmorphic, with cyclopia and proboscis

during pregnancy like CMV, rubella, toxoplasma, taking certain drugs during pregnancy, drinking alcohol, or smoking.⁶ Maternal diabetes increases the risk of holoprosencephaly by 200-fold.⁷

In general, the diagnosis of holoprosencephaly requires an ultrasound, fetal MRI, molecular analysis of fetal DNA, and cytogenetic analysis.^{1,5}

Figs 3A to D: Postnatal findings: (A) Severe form of holoprosencephaly; (B) Cyclopia, proboscis, and ethmocephaly; (C) Encephalocele; (D) Polydactyly on one hand

In the presented case, no risk factors were identified in the mother's history and no genetic studies were made on the infant. We considered the newborn as a case of multiple types of holoprosencephaly because of the multiple manifestations that the newborn presented with.

The first plan of management should be early diagnosis through prenatal ultrasound. This is because severe forms of holoprosencephaly are incompatible with life and should be terminated after proper counseling of the parents. In general, if the baby is born, the treatment is just supportive.^{1,5}

Diagnosing holoprosencephaly in the first trimester is important so that parents can be given options on how to handle the pregnancy. The diagnosis in the first trimester is possible through an ultrasound identifying the butterfly sign while evaluating the nuchal translucency.⁸ There are other ways to diagnose holoprosencephaly in the first trimester, such as finding the presence of a single ventricle, fused thalami, fused corpus striatum, and facial abnormalities by ultrasound.^{8,9}

In this case, the mother presented in the third trimester with a fetus with bulky encephalocele, which eliminated the choice of vaginal delivery; in addition, she had history of previous cesarean delivery. Due to her circumstances, the decision was made to deliver her by an elective cesarean section at 34 weeks.

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