

Case Report

Antenatal diagnosis of alobar holoprosencephaly: a case report

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ABSTRACT

Holoprosencephaly (HPE) is a structural malformation of the brain that results from the complete or incomplete noncleavage of the forebrain/ prosencephalon of the embryo into 2 hemispheres¹. We present a case of twenty-five year-old primigravida presented to the Outpatient department of Obstetrics for routine checkup and diagnosed with Alobar holoprosencephaly on 2nd level USG. Fetal MRI was performed and the findings were confirmed. Even though ultrasonography is diagnostic in the detection of fetal anomalies, MRI plays a vital role due to its multiplanar capability and excellent soft tissue resolution. The purpose of publishing this case is to sensitize the clinicians to the classical features of holoprosencephaly on various imaging modalities and to stress the importance of its detection before 20 weeks of gestation so as to allow for legal medical termination and alleviate maternal psychological trauma of bearing a deformed fetus.

Keywords: Alobar, Antenatal Ultrasound, Holoprosencephaly, Fetal brain anomaly

INTRODUCTION

Holoprosencephaly (HPE) is a structural malformation of the brain that results from the complete or incomplete noncleavage of the forebrain/ prosencephalon of the embryo into 2 hemispheres.¹

Incidence of HPE has been estimated at the maximum of 1-2 cases per 10,000-20,000 term births, and one case per 250 spontaneous abortions.^{2,3}

The prosencephalon forms the cerebral hemispheres, the thalami, and the basal ganglia. Hence abnormalities in the development of the prosencephalon result in variable fusion anomalies of these structures. This disorder is either incompatible with life or infants suffer from varying grade of mental retardation. The alobar variety is the most severe form⁴ of holoprosencephaly and incompatible with life. Sonography is an excellent non-invasive tool for pre-natal diagnosis of

holoprosencephaly. Early diagnosis by fetal ultrasonography allows for early termination of pregnancy and avoids maternal psychological trauma of giving birth to a deformed fetus.

CASE REPORT

A twenty-five year-old primigravida presented to the Outpatient department of Obstetrics for routine checkup. There was no history of consanguinity of marriage. She was a nonsmoker, non-diabetic, without teratogenic potential disease, or exposure to radiation or toxic substances abuse in the first and second trimesters of pregnancy. Moreover, there was no personal/family history of congenital malformations. The patient did not undergo screening for chromosomal abnormalities in the first trimester or any other tests to assess fetal DNA. Her general physical examination was within normal limits. On clinical examination, the gestational age corresponded to 18-20 weeks. The laboratory examination with

complete blood counts was within normal limits. Screenings for HIV, syphilis, toxoplasmosis, cytomegalovirus, hepatitis B, hepatitis C, and group B streptococcus infection were negative. Tests for blood group and rhesus D status revealed O group and Rh positivity. Ultrasonography revealed single live intrauterine anomalous fetus with an average gestational age corresponding to 19 weeks 4 days. The supratentorial brain was replaced by CSF with a thin rim of agyric brain (Figure 1) parenchyma (4.5mm) and a large horseshoe shaped monoventricle (Figure 2) noted in basifrontal region.



Figure 1: Agyric brain.



Figure 2: Monoventricle.

The monoventricle is seen communicating with large CSF intensity dorsal cyst (4.6*3.6*2.7cm) with fused thalami in between (Figure 3). The third ventricle, corpus callosum, falx cerebri and septum pellucidum were not visualized. The posterior fossa structures were normal. The umbilical cord and rest of the fetal organs were normal. Polyhydramnios was not present. Fetal MRI performed on 1.5 TMRI machine confirmed the sonographic findings.

There was no evidence of polyhydramnios or any other associated anomaly on MRI. The pregnancy was

terminated, delivering an abortus male fetus of 300g and the gross specimen of the fetus (Figure 4) showed all the findings observed on imaging.



Figure 3: Dorsal cyst.



Figure 4: Gross fetus.

Thus, this is a classic case of alobar holoprosencephaly with facial dysmorphism (Figure 5).



Figure 5: Facial dysmorphism.

DISCUSSION

Holoprosencephaly is a spectrum of cerebrotal anomalies resulting from the complete or partial failure of the diverticulation and cleavage of the primitive forebrain occurring between the 18th and the 28th day of gestation, indicating that it is a disorder of gastrulation.^{4,7}

HPE is estimated to occur in 1 of 16,000 live births.⁶ During the 4th gestational week, the neural tube forms the three primary brain vesicles, namely, prosencephalon, mesencephalon, and rhombencephalon. By the 5th week of intrauterine life, the prosencephalon further divides into the telencephalon and diencephalon. The telencephalon forms the two cerebral hemispheres whereas the diencephalon forms the thalami, the hypothalamus, and the basal ganglia. The prechordal mesoderm takes part in the formation of the midline facial structures. The degree of facial dysmorphism is proportional to the severity of the intracranial abnormalities and should direct the sonologist to search for the CNS anomalies. This has led to the popular statement “face predicts the brain” by DeMeyer.⁸

Cyclopia or synophthalmia, severe ocular hypotelorism with divided orbits, and a proboscis-like nasal structure are mostly associated with alobar HPE.^{7,9}

Mild hypotelorism with flat face is the least severe facial dysmorphism. Sonography can detect up to 58% of the facial abnormalities.¹⁰

There are three main forms of holoprosencephaly proposed by DeMyer and Zeman⁷ in 1963 namely, alobar, semilobar, and lobar varieties, depending on the degree of separation of the hemispheres and the presence or absence of the interhemispheric fissure.^{7,9}

According to the National Institute of Neurological Disorders and Stroke (NINDS), the majority of cases diagnosed with HPE are of the severe type, and this condition could lead to neonatal mortality and stillbirth.¹¹

The alobar holoprosencephaly is the most severe form and shows undifferentiated holosphere of the cerebral parenchyma with a central monoventricle and fused thalami.⁵ The falx, interhemispheric fissure, corpus callosum, optic tracts, olfactory bulbs, and the septum pellucidum are absent.⁴

Absence of septum pellucidum may be associated with optic dysplasia, holoprosencephaly, corpus callosal agenesis, schizencephaly, Chiari-II malformation, hydranencephaly, porencephaly, and cephaloceles. In a study of 2007 patients, Barkovich and Norman have described the above abnormalities along with absent septum pellucidum.¹²

In our patient also, septum pellucidum was absent. A dorsal cyst may be observed in the posterior cranial fossa

in very severe forms of holoprosencephaly⁴ and some of these cases may also be associated with Dandy Walker malformation, agyria, polymicrogyria, and heterotopias.¹³

Extra cranial anomalies like limb anomalies, polydactyly, lung hypoplasia, cardiac anomalies, renal dysplasia, omphalocele, hydrops fetalis, esophageal atresia, bladder exstrophy, and gastrointestinal or abdominal anomalies may also be observed. Our case did not show any such extracranial association.^{4,10}

Optimal sonographic view for evaluating the fetal face is the coronal view with the orbits, maxilla, and anterior mandible in one plane. Three-dimensional ultrasonography (3D US) acts as a supplement to 2D ultrasonography in the evaluation of fetal craniofacial abnormalities¹⁵. The facial anomalies may not be clearly visible if the fetus is in occipitoanterior position.¹⁴

Alobar holoprosencephaly can be differentiated from hydrocephalus by the presence of midline echogenic falx, absent septum pellucidum, separated thalami, and distinct lateral ventricles in the latter¹. Hydranencephaly may also demonstrate absence or deviated falx but the thalami are not fused in this condition¹. In both hydranencephaly and Dandy Walker malformation, the falx cerebri, interhemispheric fissure, corpus callosum, and 3rd ventricle are present.⁵

The semi lobar holoprosencephaly is of intermediate severity with early midline differentiation and sagittal separation.¹⁴ It shows a rudimentary falx, partial interhemispheric fissure, absent septum pellucidum, partial separation of thalami, and large H-shaped Monoventricle. The basal ganglia show variable fusion. The facial anomalies are mild, namely, cleft lip, cleft palate, and hypertelorism.

The mildest variety of holoprosencephalies is the lobar holoprosencephaly characterized by near total cleavage of cerebral hemispheres, presence of falx, interhemispheric fissure, and absent septum pellucidum.¹⁶ The frontal horns appear squared off or box like due to the absence of septum pellucidum. The thalami and the basal ganglia are separated. It may be associated with minimal facial dysmorphism like hypertelorism.

In 1993, a new variant of HPE called “middle interhemispheric” (MIH) variant or syntelencephaly was described by Barkovich and Quint.¹⁷ In this condition, the interhemispheric fissure is formed in the frontal and occipital regions and absent in the parietal region with fusion of the hemispheres. The alobar form of holoprosencephaly is incompatible with life. Children with semilobar, lobar, and middle hemispheric variants have variable survival. Those who survive present with seizures as one of the commonest manifestations.¹⁸

The abnormalities in the molecules of cytoskeleton, signaling molecules, and molecules modulating

glycosylation in the control of neuronal migration.¹⁸ However, genetic analysis and karyotyping were not performed in our study. The role of fetal MRI is in the confirmation of the sonographic findings and detection of any other additional anomaly. Postnatal MRI with diffusion fiber tractography may detect rare association of brain stem and long tract abnormalities in holoprosencephaly.¹⁶ The lobar and middle hemispheric variants are not associated with significant abnormalities of the white matter tracts whereas the alobar and semilobar forms are associated with abnormalities of the medial lemniscus and the corticospinal tracts.¹⁶ However, in our case, no other additional anomaly was detected on fetal MRI. Postnatal 3D CT may also be used for detailed evaluation of the craniofacial abnormalities in holoprosencephaly.¹⁹

The etiology of holoprosencephaly is heterogeneous and unclear. There are a few theories citing the causes of mechanical, environmental, and genetic factors and infections. Factors include maternal diabetes, ethanol, cytomegalovirus infection, salicylates, antiepileptic medications, retinoic acid, aspirin, misoprostol, methotrexate, and cholesterol-lowering agents.²⁰⁻²² Association of HPE with vascular cerebral anomalies is not a rule.²⁰ Genetic causes have also been implicated. Approximately 18% to 25% of HPE cases have a recognizable monogenic syndrome and up to 45% of live births with HPE have nonrandom chromosomal abnormalities.²³ Association of cyclopia is observed with cytomegalovirus infection and maternal ingestion of salicylates even in the absence of holoprosencephaly.^{25,26} Reports of association of maternal diabetes with holoprosencephaly are also available. Fetal karyotyping is advisable in all the cases of holoprosencephaly as most of them are associated with chromosomal anomalies.²⁷ Even though karyotyping is not necessary for the diagnosis of holoprosencephaly, it will surely have a role in the identification of translocations and in the genetic counseling for future pregnancies. In a study of 33 fetuses with trisomy 13,²⁷ have detected holoprosencephaly in 13 fetuses (39%). Fifty-five percent of the fetuses with holoprosencephaly showed chromosomal abnormalities in the study.¹ However, karyotyping was not performed in our case. Advanced investigations like fetal karyotyping may not be available in all the places.

The first prenatal diagnosis of HPE was performed in 1980.²⁸ Since then, a few studies and some case reports have described the different ultrasound findings of HPE.²⁹ Fetal magnetic resonance imaging (MRI) was first described in 1990, but because of the relatively long acquisition time, its use for fetal examination was initially discouraged. With the acquisition of the ultrafast method of examination, fetal MRI has been introduced into clinical practice.³⁰ Fetal MRI is generally indicated when fetal ultrasound is suggestive of fetal abnormality or if the fetal abnormality requires further assessment.³⁰ In alobar HPE, the diagnosis can be made by ultrasonography, but a fetal MRI can be requested by a

neurosonographer for a second-level examination if deemed necessary to identify other cerebral anomalies.³¹

Diagnosis of holoprosencephaly before 20 weeks of gestation by imaging is essential in order to avoid the psychological pain of bearing the deformed fetus till term and delivering a still born baby.

CONCLUSION

Holoprosencephaly is a major malformation of the central nervous system that should be distinguished from other causes of fetal hydrocephalus. Awareness of the spectrum of sonographic findings seen with holoprosencephaly should improve the accuracy of prenatal diagnosis. Identification of concurrent facial and extra cranial malformations can help predict chromosomal anomalies and subsequent fetal outcome. Because of recent advances in development and improvement of high-resolution USG, early diagnosis of congenital anomalies such as holoprosencephaly is now possible.

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REFERENCES

1. Nyberg DA, Mack LA, Bronstein A, Hirsch J, Pagon RA. Holoprosencephaly: prenatal sonographic diagnosis. *Am J Roentgenol.* 1987 Nov 1;149(5):1051-8.
2. National Human Genome Research Institute. Learning about holoprosencephaly, 2012. Available at: <https://www.genome.gov/genetic-disorders/holoprosencephaly>.
3. Poenaru MO, Vilcea LD, Marin A. Holoprosencephaly: two case reports. *Maedica.* 2012;7(1):58-62.
4. K. C. Funk and M. J. Siegel, Sonography of congenital midline brain malformations, *Radiographics*, 1988;8(1):11-25.
5. R. A. Filly, D. H. Chinn, and P. W. Callen, "Alobar holoprosencephaly: ultrasonographic prenatal diagnosis," *Radiol*, 1984;151(2):455-9.
6. Orioli IM, Castilla EE. Epidemiology of holoprosencephaly: prevalence and risk factors. *Am J Med Genet Part C Semin Med Genet.* 2010;154C:13-21.
7. Demyer W, Zeman W. Alobar holoprosencephaly (arhinencephaly) with median cleft lip and palate: clinical, electroencephalographic and nosologic considerations. *Confin Neurol.* 1963;23(1):1-36.
8. Myer WD. Classification of cerebral malformations, *Birth Defects.* 1971;7(1):78-93.
9. O'Rahilly R, Müller F. Interpretation of some median anomalies as illustrated by cyclopia and symmelia. *Teratol.* 1989;40(5):409-21.
10. McGahan JP, Nyberg DA, Mack LA. Sonography of facial features of alobar and semilobar

- holoprosencephaly. *AJR. Am J roentgenol.* 1990 Jan;154(1):143-8.
11. National Institute of Neurological Disorders and Stroke. Holoprosencephaly information page, 2007. Available at: <http://www.ninds.nih.gov/disorders/All-Disorders/holoprosencephaly-information-page>.
 12. A. J. Barkovich and D. Norman, Absence of the septum pellucidum: a useful sign in the diagnosis of congenital brain malformations, *Am J Roentgenol*, 1989;152(2):353-60.
 13. Arathi N, Mahadevan A, Santosh V, Yasha TC, Shankar SK. Holoprosencephaly with cyclopia—Report of a pathological study. *Neurol India.* 2003 Apr 1;51(2):279.
 14. Benacerraf BR, Frigoletto Jr FD, Bieber FR. The fetal face: ultrasound examination. *Radiol.* 1984 Nov;153(2):495-7.
 15. Baba K, Okai T, Kozuma S, Taketani Y. Fetal abnormalities: evaluation with real-time-processible three-dimensional US-preliminary report. *Radiol.* 1999 May;211(2):441-6.
 16. Albayram S, Melhem ER, Mori S, Zinreich SJ, Barkovich AJ, Kinsman SL. Holoprosencephaly in children: diffusion tensor MR imaging of white matter tracts of the brainstem-initial experience. *Radiol.* 2002 Jun;223(3):645-51.
 17. Barkovich AJ, Quint DJ. Middle interhemispheric fusion: an unusual variant of holoprosencephaly. *AJNR Am J Neuroradiol.* 1993;14:431-40.
 18. Verrotti A, Spalice A, Ursitti F, Papetti L, Mariani R, Castronovo A, et al. New trends in neuronal migration disorders. *European journal of paediatric neurology.* 2010 Jan 1;14(1):1-2.
 19. Altman NR, Altman DH, Wolfe SA, Morrison G. Three-dimensional CT reformation in children. *Am J Roentgenol.* 1986 Jun 1;146(6):1261-7.
 20. Hergelegiu D, Ionescu CA, Pacu I, Bohiltea R, Hergelegiu C, Vladareanu S. Antenatal diagnosis and prognostic factors of aneurysmal malformation of the vein of Galen: a case report and literature review. *Medicine.* 2017 Jul;96(30).
 21. Edison RJ, Muenke M. Central nervous system and limb anomalies in case reports of first-trimester statin exposure. *N Engl J Med* 2004;350:1579-82.
 22. Edison RJ, Muenke M. Gestational exposure to lovastatin followed by cardiac malformation misclassified as holoprosencephaly. *New England J Medicine.* 2005 Jun 30;352(26):2759.
 23. Nanni L, Schelper R, Muenke M. Molecular genetics of holoprosencephaly. *Front Biosci* 2000;5:334-42.
 24. Byrne PJ, Silver MM, Gilbert JM, Cadera W, Tanswell AK, Cyclopia and congenital cytomegalovirus infection, *The American Journal of Medical Genetics*, 1987;28(1):61-5.
 25. R. Benawra, Mangurten HH, Duffell DR, Cyclopia and other anomalies following maternal ingestion of salicylates, *J Pediatr*, 1980;96(6):1069-71.
 26. Barr Jr M, Hanson JW, Currey K, Sharp S, Toriello H, Schmickel RD, et al. Holoprosencephaly in infants of diabetic mothers. *J pediatr.* 1983 Apr 1;102(4):565-8.
 27. Lehman CD, Nyberg DA, Winter TC, Kapur RP, Resta RG, Luthy DA. Trisomy 13 syndrome: prenatal US findings in a review of 33 cases, *Radiol*, 1995;194(1):217-22.
 28. Kurtz AB, Wapner RJ, Rubin CS, Cole-Beuglet C, Ross RD, Goldberg BB. Ultrasound criteria for in utero diagnosis of microcephaly. *Journal of Clinical Ultrasound.* 1980 Feb;8(1):11-6.
 29. Joó GJ, Beke A, Papp C, Tóth-Pál E, Szigeti Z, Bán Z, et al. Prenatal Diagnosis, Phenotypic and Obstetric Characteristics of Holoprosencephaly. *Fetal diagnosis and therapy.* 2005;20(3):161-6.
 30. Yuh WT, Nguyen HD, Fisher DJ. MRI of fetal central nervous system abnormalities. *AJNR Am J Neuroradiol.* 1994;15:459-64.
 31. Paladini D. Additional value of fetal magnetic resonance imaging in the prenatal diagnosis of central nervous system anomalies: a systematic review of the literature and related correspondence. *A plea to assess oranges only. Ultrasound Obstet Gynecol.* 2015;45(5):625-6.

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