

A Case of Holoprosencephaly Diagnosed in the First Trimester of Pregnancy

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Abstract

Background: Holoprosencephaly is a brain malformation resulting from a primary defect in the development of the basal forebrain during early pregnancy. The absence of the "butterfly sign" is a warning sign of holoprosencephaly in the first trimester sonography.

Case: A case of holoprosencephaly and cyclopia is presented, which was diagnosed in the first trimester by the absence of the butterfly sign. Chromosomes identified by amniocentesis demonstrated a normal karyotype. Termination of pregnancy was performed in the 18th week of gestation.

Conclusion: It is impressed that holoprosencephaly can be diagnosed sonographically in the first trimester.

Keywords: Holoprosencephaly, butterfly sign, prenatal diagnosis, first trimester sonography.

Birinci Trimesterde Sonografi ile Saptanan Holoprosensefali

Amaç: Holoprosensefali erken gebelik sırasında ön beyin tabanının gelişimindeki bir defekt sonucu ortaya çıkan bir beyin malformasyonudur. Kelebek işaretinin bulunmaması ilk trimester ultrasonografide holoprosensefali için önemli bir uyarı işaretidir.

Olgu: İlk trimester ultrasonografide saptanan ve "kelebek işareti" gözlenemeyen, holoprosensefali ve siklops tanısı alan bir vaka sunulmaktadır. Amniosentez ile normal karyotip saptanmasını takiben 18. gebelik haftasında gebelik termine edilmiştir.

Sonuç: Burada Holoprosensefalinin ilk trimesterde erken ultrasonografik teşhisinin mümkün olduğu vurgulanmaktadır.

Anahtar Sözcükler: Holoprosensefali, kelebek işareti, prenatal tanı, birinci trimester sonografi.

Introduction

Holoprosencephaly is a rarely seen disorder of brain development caused by the failure of prosencephalon (the embryonic forebrain) to develop normally into the lobes of the cerebral hemispheres. While the 'alobar' form presents with the worst prognosis, the 'lobar' form represents the least complicated malformation. Ultrasonographic criteria such as presence of single ventricular cavity, absence of the third ventricle, difficulty to visualize the cavum septi

pellucidi, and the butterfly sign, fusion of the thalamus facilitate the prenatal diagnosis of the condition during the first trimester.¹ Presence of single ventricular cavity and hydrocephaly, and the absence of the butterfly sign are the most important warning signs for holoprosencephaly in the first trimester ultrasonography.² The aim of this case presentation is to demonstrate the early detection of holoprosencephaly during the first trimester scanning of patients and its evaluation within the current context of the literature on this anomaly.

Case

The patient, 20 years of age (G3 P1 A1 Y0), first cousins with her husband, and attending our clinic for routine antenatal follow-up had a history of spontaneous abortion at 8 weeks of gestation 2 years previously, and a pregnancy termination upon intrauterine exitus at 28 weeks of gestation 7 months previously. It was ascertained that there had not been exposure to teratogens, and the intrauterine parameters of TORCH group of infections were negative. Upon ultrasonography, singleton viable pregnancy of 13 weeks and 6 days was diagnosed, on the basis of a crown-rump length (CRL) of 84 mm, and nuchal thickness (NT) of 2 mm. In the plane of biparietal diameter assessment the two ventricles with chorioid plexuses and the cavum septi pellucidi were undetectable (Figure 1a). The fetal face could not be evaluated for positional reasons, and the normal fetal profile could not be observed in the intracranial sagittal plane and the ventricular system of this case with a noticeable widening of the diencephalon region (Figure 1b). Fetal karyotyping on grounds of suspicion of holoprosencephaly



Figure 1a. Cranial sonographic image at the 14th week of gestation: Holoprosencephaly and cyclops. A. Dilated ventricles and hydrocephaly. The chorioid plexuses are being pushed to the posterior fossa. The normal cerebellar structures are not visible posteriorly.



Figure 1b. Intracranial sagittal plane where the ventricular system has a noticeable widening at the diencephalon region. The normal fetal profile could not be observed.

was proposed to the patient who wanted to consider termination of pregnancy after amniocentesis for cytogenetic evaluations. Despite the results of 46,XX normal karyotyping, the repetition of ultrasonography on the 18-week old fetus confirmed holoprosencephaly with cyclopia. The pregnancy was terminated with the decision of the health committee and the agreement of the patient. Further diagnoses of proboscis and hydrocephaly in addition to



Figure 2a. Postabortion (18 weeks of gestation). The case was terminated after sonographic diagnosis of proboscis and hydrocephaly in addition to cyclopia and holoprosencephaly. A. Extremities disproportionate with the body are noticeable.

cyclopia and holoprosencephaly, and observation of extremities disproportionate with the body were made on a female fetus of 190 g and

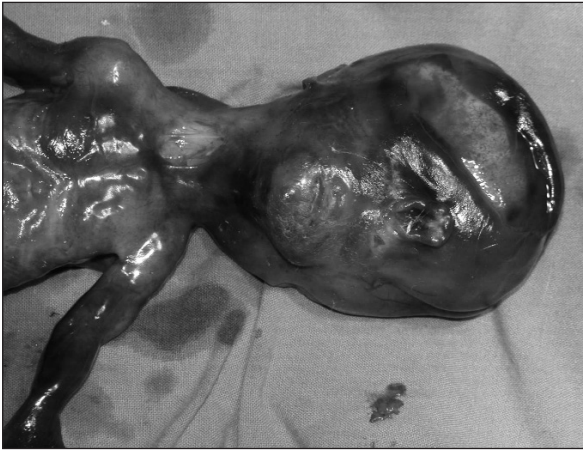


Figure 2b. Proboscis and cyclopia.

24 cm length (Figures 2a and 2b). Any anomalies in the internal organs could not be determined upon the reluctance of the patient's family to permit autopsy.

Discussion

Holoprosencephaly is a rare malformation of the brain seen in 1/16,000 live births and 1/250 pregnancies, caused by developmental abnormality of the embryonic prosencephalon.^{1,2,3} A single embryological defect results in both brain and facial malformations.^{4,5,6} Depending on the degree of the segmentation and cleavage of the prosencephalon, three classifications of the anomaly have been identified. The lobar form is the most anomalous with small brain, including lateral and third ventricles independent of each other and a monoventricular system in place of the normal ventricular formation. The two lateral ventricles appear as a single entity and the thalamus is fused. Thalamus and corpus striatum are united, corpus callosum, the fornix, optical tracts and the olfactory bulbs cannot be discriminated.^{4,5} The mid brain, the brain stem and

the cerebellum appear structurally normal. The Semilobar form is characterized by partial segmentation of the ventricles and partial fusion of the thalamus. There are rudimentary occipital lobes and a monoventricular cavity. Generally the olfactory bulbs and the corpus callosum are missing. Basal ganglia and the thalamic nuclei are in a state of fusion. The lobar type is the least anomalous form. The brain appearance is normal and the hemispheres are well cleaved but there is fusion in the rostral section. Despite enlargement, the lateral ventricles are connected. The corpus callosum may or may not exist or may be hypoplastic.

Since the skull in holoprosencephaly appears filled with fluid during sonographic examination, it is necessary to take into consideration other evidence for holoprosencephaly to discriminate hydrocephaly and hydranencephaly (Tables 1 and 2).⁷ For correct diagnosis,

Table 1. Sonographic differential diagnosis of holoprosencephaly and hydrocephaly^{1,7}

Holoprosencephaly	Hydrocephaly
Monoventricle (fused lateral ventricles)	Widened lateral ventricles (>10 mm)
Chorioid plexuses unobservable on the same plane (absence of the butterfly sign)	Waving chorioid plexuses observable on the same plane (Pending chorioids)
Fusion of the thalamic nucleus	The thalamic nucleuses are apart from each other
Cavum septum pellucidum: Undeveloped	Cavum septum pellucidum: Developed

Table 2. Sonographic differential diagnosis of holoprosencephaly and hydranencephaly^{1,7}

Holoprosencephaly	Hydranencephaly
Falx cerebri absent	Falx cerebri might be present
Cerebral cortex might be present	Cerebral cortex undeveloped
Thalamic fusion present	Thalamic fusion absent
Hypocampal structures located peripherally	Hypocampal structures in continuity to the ambient cistern

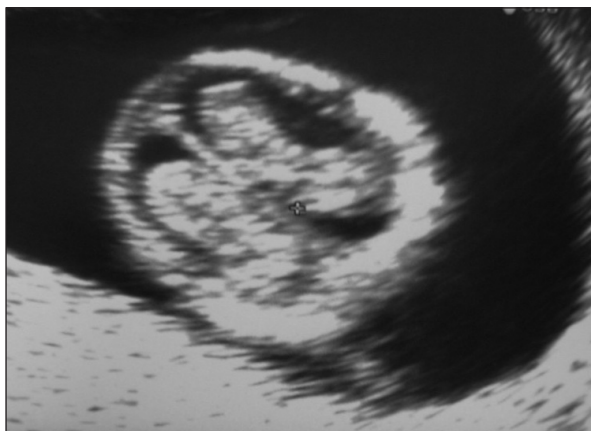


Figure 3a. Normal sonographic image of the fetal head at the first trimester. A. The fetal brain (Transverse view = Biparietal plane) showing the chorioid plexuses which is referred to as the "butterfly sign"



Figure 3b. Normal fetal profile and intracranial structures at sagittal view.

it is important that the cavum septi pellucidum should be unobservable. Even in the lobar form of this anomaly the septum pellucidum is undeveloped.^{4,5,7} The associated facial malformations include median cleft lip (premaxillary agenesis), cebocephaly, ethmocephaly and cyclopia, the severest of facial malformations, characterized by median monophthalmia, synophthalmia or anophthalmia. The nasal and the medial facial

bones are absent with, generally, a proboscis which can be doubled (Figures 2a and 2b). Apart from the facial malformations, polydactylism, exomphalos, renal dysplasia, hydrops fetalis can be seen and are mostly related to chromosomal abnormalities. In the presented case the results of chromosomal analyses carried out were normal.

The alobar and the semilobar forms are fatal, the former being associated with severe mental retardation.¹ Etiologically, the chromosomal anomalies, especially trisomy 13, autosomal dominant or recessive disorders appear sporadically in most cases.¹ Sepulveda et. al., have drawn attention to the "butterfly sign" in the diagnosis of holoprosencephaly in the first trimester of pregnancy. In the routine investigation of the fetal brain the transverse view should include both of the chorioid plexuses (Figures 3a and 3b) which is referred to as the "butterfly sign". To demonstrate the significance of the butterfly sign for the diagnosis of holoprosencephaly in high risk populations, before villous biopsy at 11-14 weeks of gestation, a total of 378 gravid women were scanned ultrasonographically, according to the proposed procedures of the Fetal Medicine Foundation, and the presence of the butterfly sign was evaluated. In three of these cases the butterfly sign was unobservable and these were diagnosed with holoprosencephaly. The absence of the butterfly sign in the first trimester was pointed out to be an important sign for holoprosencephaly and valuable for the early diagnosis of this anomaly.⁸ Tongsong et al. have reported, in the three cases diagnosed with holoprosencephaly in the first trimester, the presence of a single ventricular cavity, fusion of the thalamus, absence of cavum septi pellucidum associated, in all three fetuses, with extracranial (facial) anomalies as detected by sonography and have drawn atten-

tion to the importance of the observation of a single ventricular cavity in the first trimester for the diagnosis of holoprosencephaly.⁹

In the case presented here hydrocephaly and a single ventricular cavity were observed during the sonographic investigation in the first trimester and the butterfly sign was not detected (Figure 1). It is intended to confirm the importance of these observations as important signs for the early detection of holoprosencephaly especially during the cranial investigation and assessment of the nuchal thickness by ultrasonography in the first trimester of pregnancy.

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