**Prenatal Diagnosis of Alobar Holoprosencephaly with Cystic Hygroma**

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**SUMMARY**

**Objective:** Holoprosencephaly is a kind of brain anomaly characterized by inadequate cleavage of the prosencephalon during early embryogenesis. In addition, holoprosencephaly associated with cystic hygroma and hydrops fetalis has never been reported. In this article, we report a rare case of holoprosencephaly associated with cystic hygroma and hydrops fetalis diagnosed prenatally.

**Case Report:** A 28-year-old woman, gravida 2, para 0, artificial abortion 1, was referred to our antenatal clinic at 16 weeks of gestation due to fetal cystic hygroma detected by prenatal routine ultrasonography at a local hospital. In our clinic, single ventricle with fused thalami and cystic mass at the fetal neck as well as hydrops fetalis were noted by level II ultrasound. Under the impression of holoprosencephaly with cystic hygroma and hydrops fetalis, termination of pregnancy with misoprostol was undertaken. The histopathology of fetal autopsy confirmed our diagnosis and disclosed additional intracranial abnormalities.

**Conclusion:** Fetus with holoprosencephaly might have other associated structural abnormalities. Cystic hygroma and hydrops fetalis are rare associations. Meticulous sonographic examination to depict the associated defects are necessary in any fetus with holoprosencephaly. [Taiwanese J Obstet Gynecol 2006;45(2):146–149]

**Key Words:** cystic hygroma, holoprosencephaly, prenatal diagnosis

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**Introduction**

Holoprosencephaly encompasses a complex of fetal forebrain and midface malformation. It arises from incomplete cleavage of the primitive prosencephalon or forebrain. Prenatal diagnosis of holoprosencephaly has been described by many investigators since the first document presented by Kurtz et al in 1980 [1]. Although it is usually sporadic, it may occur as part of monogenic disorders, or following teratogen exposure, such as alcohol, phenytoin, and retinoic acid, as well as in association with chromosome abnormalities [2–4]. Typical ultrasound findings of alobar holoprosencephaly are absence of the falx and other midline structures with anterior complete fusion of the lateral ventricles [2–4]. Premaxillary agenesis with cleft lip with or without cleft palate are also abnormalities that can be identified by prenatal ultrasonography [2–4]. The most common sites of associated extracranial anomalies are the heart, urinary tract, and limbs. Polyhydramnios may also occur. Nevertheless, prenatal diagnosis of fetal alobar holoprosencephaly associated with cystic hygroma and hydrops fetalis has never been reported in the medical literature. In this article, we report a rare variant case of alobar holoprosencephaly with cystic hygroma and hydrops fetalis.

**Case Report**

A 28-year-old woman, gravida 2, para 0, artificial abortion 1, was referred to our hospital at 16 weeks of gestation due to fetal cystic hygroma seen sonographically by local medical practitioners. Before this pregnancy, this woman, from mainland China, had...
suffered from cervical stenosis and endometriosis, which were treated by cervix dilation and laparoscopy in Taiwan. Prenatal level II ultrasonography at our ultrasound unit revealed a fetus complicated with single ventricle (without cortical mantle), complete absence of the falx, fused thalami (Figure 1) and bilateral cystic masses around the fetal neck (Figure 2), as well as hydrops fetalis. These findings strongly suggested a case of alobar holoprosencephaly associated with cystic hygroma and hydrops fetalis. However, neither teratogen exposure nor family history could be traced for this patient.

After genetic consultation, with poor prognosis of fetal holoprosencephaly, cystic hygroma, and hydrops fetalis, termination of pregnancy was chosen by the couple. Misoprostol, 200 mg, q4h was administered vaginally, and an immature fetus of ambiguous gender was delivered uneventfully. The postmortem histopathology confirmed our prenatal findings. There were also additional features of midline cleft palate, absence of nose (arthinia) and olfactory bulb, absence of optic nerves, and narrowed anterior fossae (Figures 3 and 4). Fetal karyotyping failed due to inadequate live fetal tissue. Six months later, the woman became pregnant again and subsequently gave birth to a healthy female baby.
Discussion

Holoprosencephaly is a complex developmental abnormality of the brain resulting from failure of cleavage of the primitive prosencephalon or forebrain [2–5]. Besides, common associated facial abnormalities include cyclopia, cebocephaly, ethmocephaly, median cleft lip, and median philtrum–premaxilla anlage. According to the medical literature [2–5], there are three major varieties of holoprosencephaly, namely alobar, semilobar, and lobar. Alobar holoprosencephaly has been further subcategorized into three different configurations: the pancake, cup, and ball variations [2–5]. In the alobar type, the interhemispheric fissure and the falx cerebri are totally absent. In addition, there is a single primitive ventricle with fused thalami on the midline, associated with the absence of third ventricle, neurohypophysis, olfactory bulbs and tracts. In the semilobar variety [2–5], the cerebral hemispheres are partially separated posteriorly. Also, there is still a single ventricular cavity. As for lobar holoprosencephaly [2–5], the derangement of the brain is subtle. The cerebral hemispheres are completely divided with variable degrees of fusion of the lateral ventricle at the level of cingulated gyrus and frontal horns. The septum pellucidum is always absent and the olfactory bulbs and tracts as well as the corpus callosum may be absent, hypoplastic or completely normal [2–5].

Holoprosencephaly is one of the most frequently occurring abnormalities in aborted embryos and fetuses, occurring in about 4 of 1,000 induced abortions [6]. The incidence of holoprosencephaly is between 0.56 and 0.63 of 10,000 live-born infants [7]. They are often associated with chromosome abnormalities, mainly trisomy 13, trisomy 18, and triploidy [8]. Early detection of holoprosencephaly, even in fetuses with normal karyotype, is very important because of its almost lethal outcome and major neurodevelopmental delay in surviving cases.

Nuchal cystic hygroma is caused by failure of communication between the jugular lymph sac and internal jugular vein, and is frequently associated with chromosomal aberrations. The incidence of nuchal cystic hygroma is 1 in 6,000 live births and 1 in 750 abortuses [9]. The common associated sonographic abnormalities are hydrops (31.3%), generalized skin edema (6.3%), and pterygium colli (6.3%). The most common chromosomal abnormality is Turner’s syndrome (45,X), followed by Down syndrome and trisomy 18 [9].

To date, alobar holoprosencephaly associated with cystic hygroma and hydrops fetalis has never been reported. To our knowledge, only one case of holoprosencephaly with cystic hygroma and chromosomal abnormality (46,XX, + (r13)) was reported by Sepulveda et al [10]; however, the case had no hydrops fetalis. It was diagnosed at the gestational age of 13 weeks and 5 days. During their study period [10], 378 women at risk of chromosomal defects received the first-trimester chorionic villus sampling (CVS), with a median gestational age of 12 weeks. Sonographic examination was performed immediately before the CVS procedure was undertaken. They stressed that evaluation of the fetal brain must include a “butterfly sign” [10]. In brief, a cross-sectional view of the fetal brain, in which two paired echogenic structures filling most of the ventricles (corresponding to the normal choroid plexus), with a characteristic appearance resembling a butterfly, should exist in normal fetuses [10]. The “butterfly sign” was not identified in three normal fetuses examined, that were diagnosed with holoprosencephaly at gestational ages ranging from 12 weeks 4 days to 13 weeks 5 days [10]. Among the three abnormal cases of alobar holoprosencephaly, nuchal translucency thickness was abnormal in one case (5.8 mm, cystic hygroma, 33%). Associated facial anomalies were found at the time of presentation in two cases (67%), and extracranial anomalies were found in two cases (67%); one with a cystic hygroma (without facial dysmorphism) and another with a small omphalocele and polydactyly.

Without chromosomal abnormalities, the recurrence risk of holoprosencephaly is estimated to be around 6%, including truly sporadic events and hereditary conditions [11]. Among the autosomal dominant cases, the penetrance is estimated to be 82% for the three major types (alobar, semilobar, lobar) and 88% when the major and minor types (atypical) are all included into consideration. Therefore, the recurrence risk for the major type is 13%, and 14% if minor types are also included [11].

We reported the first case of holoprosencephaly associated with cystic hygroma and hydrops fetalis as well as other structural abnormalities. Detailed ultrasound examination for fetuses with holoprosencephaly is strongly suggested for its common associated abnormalities. Early diagnosis and termination of pregnancy may be suggested due to its poor outcome. Although it is usually sporadic, genetic counseling and careful prenatal examination are warranted.

References


