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Successful management of discordant alobar holoprosencephaly in monochorionic diamniotic twins with normal karyotype: a case report

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Summary

Holoprosencephaly (HPE), a complex brain malformation resulting from incomplete cleavage of the prosencephalon into distinct cerebral hemispheres, is rare in newborns. Two preterm male neonates were born at 34 weeks' and five days' gestation in the monochorionic diamniotic twin pregnancy complicated with pre-eclampsia and intrahepatic cholestasis of pregnancy, and one of them was prenatally diagnosed with alobar HPE by ultrasonography with frontal bossing, hydrocephaly, hypotelorism of eyes, flat nasal bridge, macroglossia, and cheilo/palatoschisis at birth. Karyotyping by G-banding of amniocentesis specimens in normal twin and fetal umbilical blood in both fetuses showed 46, XY. This report expands discordant alobar holoprosencephaly in monochorionic diamniotic twins.

Key words: Holoprosencephaly; Monochorionic diamniotic twins.

Introduction

Holoprosencephaly (HPE) represents an absent or incomplete cleavage of the forebrain into distinct cerebral hemisphere during the fourth and eighth week of gestation [1]. It is classified into four types depending on the extent of sagittal division of cerebral cortex, thalamus, and hypothalamus: alobar (incomplete formation of hemispheres and small forebrain vesicle), semilobar (single ventricle with rudimentary lobes), lobar (well-formed lobes), and a middle interhemispheric variant (MIH, a defect of separation of the posterior portions of frontal lobes and the parietal lobes). HPE typically results in severe neurocognitive impairment with accompanying midline craniofacial anomalies, such as proboscis, cyclopia, cheilo/palatoschisis, cebocephaly, agnathia or micrognathia. However, five patients with clear phenotypic signs of microform holoprosencephaly, four of which had identified mutations in HPE associated genes, all had evidence of above-average intellectual function [2]. This could aid patient and family education, counseling, and reproductive decision making.

Case Report

The authors present a case of a male infant with alobar holoprosencephaly in a monochorionic diamniotic twin pregnancy conceived naturally. To the authors' knowledge, this is the first report on alobar HPE in one twin and the co-twin well developed in monochorionic diamniotic twin pregnancy with normal karyotype. Meanwhile the pregnancy was complicated with pre-eclampsia and intrahepatic cholestasis of pregnancy.

The patient was a 21-year- old woman, gravida 1 para 0. Initial ultrasound at eight weeks' gestation showed monochorionic twin pregnancy and gestational age was determined by last menstrual period consistent with ultrasound. At 24 weeks' and six day's gestation the patient was transferred to the present hospital because of developmental abnormality of the brain in one twin. Ultrasonography in this hospital showed alobar HPE (thalamus fusion, single brain tissue), hydrocephalus, cheiloschisis, and nose abnormality in one twin (Figures 1A, 1C) and co-twin was normal (Figure 1B). Karyotyping by G-banding of amniocentesis specimen in normal twin showed 46, XY. Despite the poor prognosis of the affected fetus, the couples declined an invasive procedure for selective fetocide of the abnormal fetus and opted to continue with the pregnancy. The maternal history was unremarkable for any infections, drug abuse, prenatal trauma or any other chronic disease. No significant family or obstetric history was elicited. Follow-up ultrasound evaluations were performed every two weeks. The hydrocephalus aggravated gradually. Polyhydramnios was found for the abnormal fetus at 31 weeks' gestation. At 32 weeks' and four day's gestation the woman was admitted to hospital for severe pre-eclampsia, intrahepatic cholestasis of pregnancy, and threatened premature labor. The woman's clinical state was stable when nifedipine GITS, magnesium sulfate, ursodeoxycholic acid, and dexamethasone were given. However, the degree of hydrocephalus in the HPE twin gradually aggravated (from 2.6 cm to 10.8 cm).

Cesarean section was performed because of spontaneous preterm labor at 34 weeks' and five day's gestation. Normal twin was male, weighing 2,190 g with apgar scores of 9 at one minute and 10 at five minutes and transferred to NICU. Malformed twin was male and 2,829 g, and died immediately after birth. The 924 g placenta was delivered. Macroscopic and histological examination confirmed a

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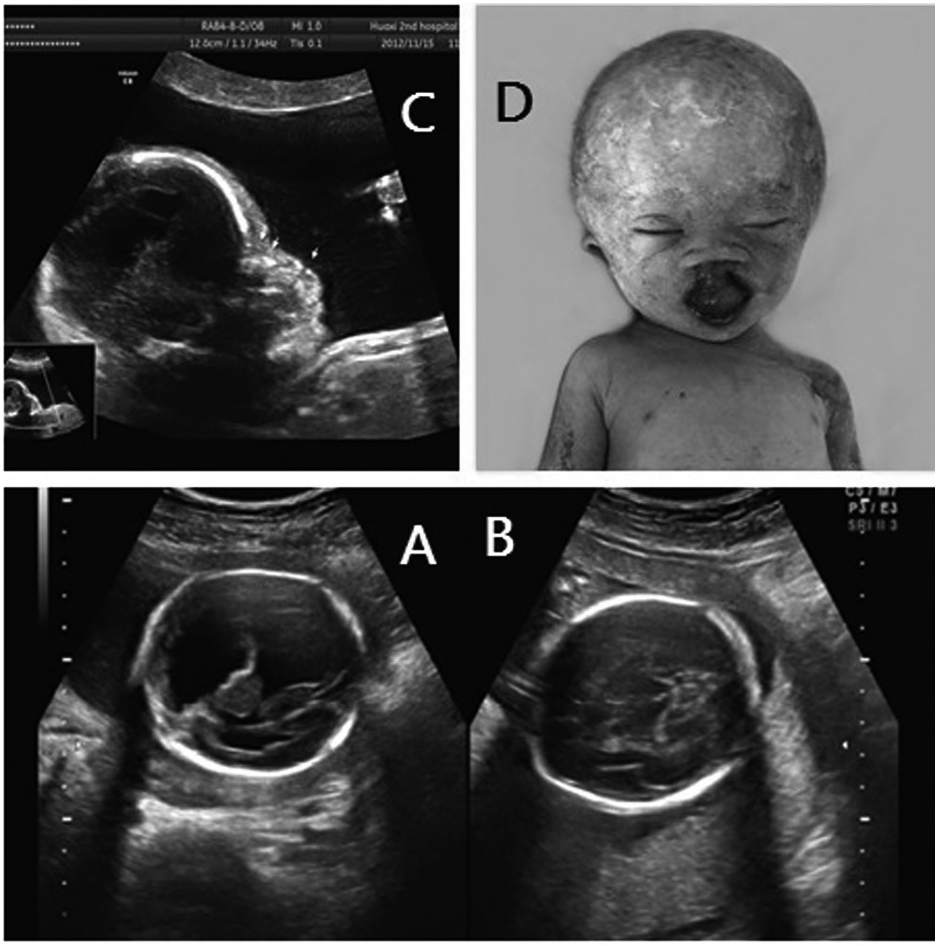

Figure 1. — Prenatal ultrasonography show alobar holoprosencephaly (thalamus fusion, single brain tissue), hydrocephalus (1A); cheiloschisis and nose abnormality (1C) in one twin, but the co-twin was normal (1B). Frontal view of the fetus showing frontal bossing, hydrocephaly, hypotelorism of eyes, flat nasal bridge, macroglossia and cheilo/palatoschisis (1D).

monochorionic diamniotic pregnancy, with velamentous insertion of umbilical cord in malformed twin and margin insertion in normal twin.

Physical examination of the malformed twin revealed frontal bossing, hydrocephaly (head circumference 41 cm), hypotelorism of eyes, flat nasal bridge, macroglossia, and cheilo/palatoschisis (Figure 1D). The anterior fontanel was 7×7 cm. Further postmortem examination of the malformed twin was not performed because the couples did not consent to it. Karyotyping by G-banding of fetal umbilical blood specimen at birth in both twins verified 46, XY. The normal twin stayed in NICU for four days and discharged. The infant is being followed up and achieves developmental milestones as is appropriate for the age. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Discussion

HPE is estimated to occur in one in 10,000 to 20,000 live births [3]. However, the incidence of HPE in twins is still unclear. The etiology of HPE is heterogeneous and has been shown to be associated with chromosome aberrations, maternal diabetes, exogenous teratogens, cytomegalovirus, ethanol, and salicylate [4-8]. Trisomy 13 and 18 are the most frequently identified chromosomal abnormalities accounting for 40% of the HPE cases. The genes known involved in the pathogenesis of HPE include HPE gene 1 (HPE 1), HPE 2 (SIX3 gene), HPE 3 (SHH gene), HPE 4 (TGIF gene), and HPE 5 (ZIC2 gene). Mutation of the SHH gene is the most common cause of syndromic and familial HPE [9].

Interestingly, alobar HPE in a male twin without chromosomal abnormality was identified in the present case. The case reports on HPE occurred in twins are few. Only seven unique cases were searched by the present authors. A case of cyclopia, HPE, and micrognathia in a female twin with normal karyotype was reported before, but whether the twin was dizygotic or monozygotic was unclear [10]. A preterm dizygotic twin baby diagnosed with HPE was also reported without chromosomal abnormality [11].

In present case, the twins were monochorionic diamniotic with normal karyotype, but only one of them had HPE. Similarly, a case of acardius with well-developed brain with lobar HPE and intracerebral retina-like pigmented tissue was reported in only one of the monochorionic diamniotic twin [12]. Only one twin suffered from HPE, but the co-twin was devoid of any major structural anomalies were also reported in the other two cases of monozygotic twins,

however, the subtype of chorion and amnion were not reported by the authors: a male infant with HPE and otocephaly [13, 14]; one twin with semilobar HPE and inv dup(15) marker chromosome and missense SHH gene mutation 1085 C 1 T (Ser 362 Leu) [14]. HPE and ectopia cordis were found in only one of diamniotic-dichorionic twin, however, whether the twin was monozygotic or dizygotic was not reported [15]. Congenital nasal pyriform aperture stenosis (CNPAS) in one neonate and lobar HPE in the other infant was reported in the monochorionic monoamnionic twin [16]. However, CNPAS is considered to be a mild representation of the HPE spectrum [17]. It is important for doctors to recognize that even with monozygotic twins only one twin may have HPE.

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