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Case Report

Digynic triploidy in a fetus presenting with semilobar holoprosencephaly

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ABSTRACT

Objective: We present digynic triploidy in a fetus with semilobar holoprosencephaly (HPE).
Case report: A 32-year-old, gravid 1, para 0, woman underwent prenatal ultrasound examination at 12 weeks of gestation, and the ultrasound showed relative macrocephaly, a small non-cystic placenta, and a fetus with absent nasal bone and semilobar HPE. The pregnancy was terminated subsequently, and a 50-g fetus was delivered with a relatively enlarged head and premaxillary agenesis. The placenta was small and non-cystic. Postnatal cytogenetic analysis of the umbilical cord revealed a karyotype of 69, XXX. Postnatal DNA marker analysis using quantitative fluorescent polymerase chain reaction assays and the polymorphic short tandem repeat markers for chromosome 18 and 20 on the placental tissues showed a diallelic pattern with a dosage of 1:2 (paternal allele to maternal allele ratio), indicating a maternal origin of the triploidy.
Conclusion: Fetuses with digynic triploidy may present relative macrocephaly, semilobar HPE and a small placenta on prenatal ultrasound.

Introduction

Holoprosencephaly (HPE) is a developmental abnormality characterized by congenital forebrain and mid-face malformations [1]. The prevalence of HPE is estimated to be 1 per 16,000 live births [2]. Based on severity, HPE is classified into four types such as alobar HPE, semilobar HPE, lobar HPE, and middle interhemispheric variant (MIHV) [3,4]. Alobar HPE is the most severe form of which the brain is not divided at all, and the face may present extreme facial features, such as cyclopia. Semilobar HPE shows somewhat divided brain hemispheres. MIHV has a fused brain in the middle, and presents closely set eyes with a narrow nose [5]. in an epidemiologic study of HPE reported that 32.7% of cases were alobar, 18.6% were semilobar, 7.1% were lobar and 41.6% were unable to be classified. Chromosomal aberrations, Mendelian mutations, and teratogens are known causes for HPE. Chromosomal abnormalities such as trisomy 13, trisomy 18, triploidy, del (2p), dup (3p), del (7q), del (13q), del (14q), del (18p), del (21q) and are reported to be associated with HPE [1,5].

The prevalence of triploidy is approximately 1 per 100 conceptions [6]. However, most of which was terminated at first trimester due to spontaneous abortion. Zalel et al [7] reported the prevalence of triploidy at early second trimester was estimated to be 1 in every 5000 pregnancies. The cause of triploidy can be classified into two groups: diandry (paternal origin) and digyny (maternal origin). Diandry mostly takes place from fertilization with dispermy or the result of meiosis I or II nondisjunction error of

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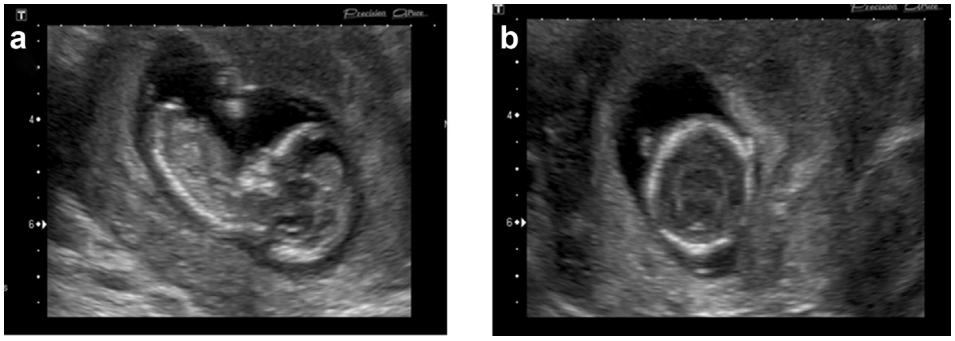

Fig. 1. Prenatal ultrasound of the fetus at 12 weeks of gestation shows (a) a relative large head and an absent nasal bone, and (b) semilobar holoprosencephaly.

spermatogenesis, while digyny mostly takes place from fertilization by a normal haploid sperm with a primary oocyte or with a diploid ovum, which was the result of meiosis II nondisjunction error of oogenesis [8,9]. In a study of 87 cases with triploidy, of which 61 cases were able to specify parental origin, Zaragoza et al [8] reported that 60 (69%) cases were diandric, of which 86% of diandry was resulted from dispermy, and 27 (31%) cases were digynic, of which 67% of digyny was resulted from failure of maternal meiosis II. Besides, Daniel et al [10] reported 19 triploidy cases, in which 58% (11/19) were diandric, and 42% (8/19) were digynic in origin.

Fetuses with digynic triploidy can be identified in the first trimester with the usage of high resolution prenatal ultrasound and magnetic resonance imaging in recent decades, which has the appearance of a small placenta without partial mole, relative macrocephaly, facial dysmorphism, normal fetal nuchal translucency (NT) thickness and abnormalities of limbs, heart, uro-genital system [11], while diandric triploidy may represent normal fetal growth, high NT thickness, normal or partial molar placenta and multiple malformations similar to digynic triploidy [12].

Case report

A 32-year-old, gravid 1, para 0, woman had prenatal examination at our hospital. Her husband was 32 years old, and the couple didn't have a family history of congenital malformations. Ultrasound examination at 12 weeks of gestation showed a small non-cystic placenta and a fetus with a crown–rump length of 4.4 cm (about 12 weeks), absent nasal bone, a nuchal translucency thickness of 1.4 mm, relative macrocephaly (Fig. 1a) and semilobar HPE. The sonography findings of fused thalami, partially absent interhemispheric fissure, and absence of the choroid plexuses were compatible with the diagnosis of semilobar HPE (Fig. 1b). The pregnancy was terminated subsequently, and a 50-g fetus was delivered with a relatively enlarged head and premaxillary agenesis with a median facial cleft (Fig. 2a,b). The placenta was small and non-cystic. Postnatal cytogenetic analysis of the umbilical cord revealed a karyotype of 69, XXX (Fig. 3). The parental karyotypes were normal. Postnatal DNA marker analysis using quantitative fluorescent polymerase chain reaction assays and polymorphic short tandem repeat markers for chromosome 18 and 20 on the

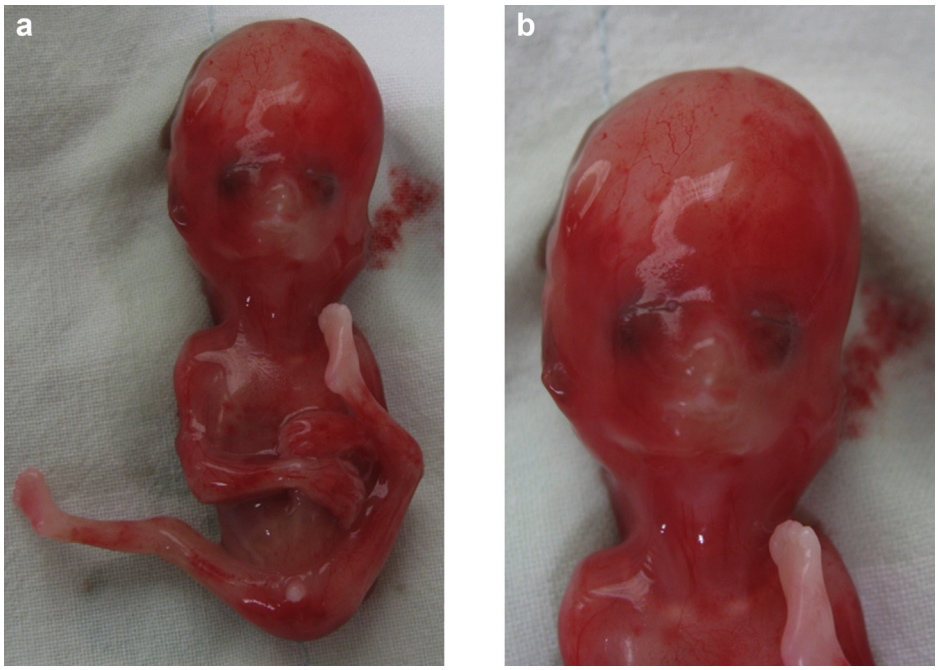

Fig. 2. The fetus at birth shows (a) relative macrocephaly, and (b) premaxillary agenesis with a median facial cleft.

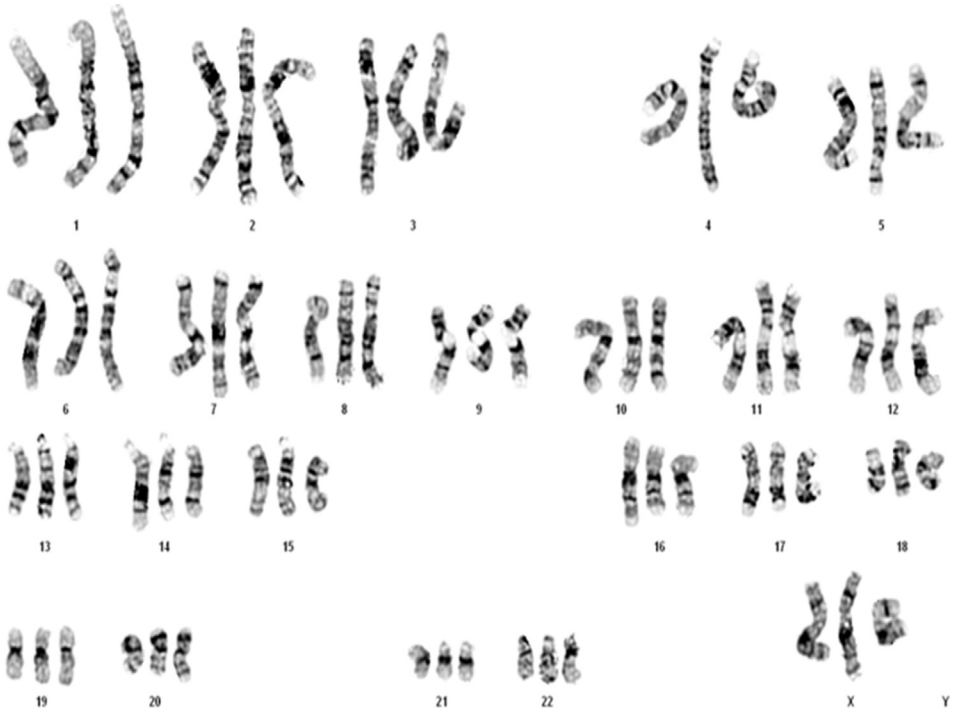

Fig. 3. A karyotype of 69, XXX.

placental tissues showed a diallelic pattern with a dosage of 1:2 (paternal allele to maternal allele ratio), indicating a maternal origin of the triploidy (Fig. 4 and Table 1).

Discussion

Our case represents a rare occurrence of triploidy detected at 12 weeks of gestation. Snijders et al [15] reported that the earlier the gestational weeks are, the higher the incidence of triploidy is. For instances, the incidences of triploidy have been reported to be 1: 50 (6th gestational week), 1: 350 (8th gestational week), 1: 1000 (10th gestational week), 1: 3500 (12th gestational week), 1: 10,000 (14th gestational week), 1: 30,000 (16th gestational week), 1: 100,000 (18th gestational week), and 1: 250,000 (20th gestational week), respectively. The difference of the incidence of triploidy in different gestational ages is because of high spontaneous abortion rates in the first trimester. Our case was additionally associated with semilobar HPE. HPE can occur in cases with triploidy. Jauniaux et al [16] reported HPE in 22.2% (4/18) of triploid cases at 10–14 gestational weeks. Philipp et al [17] reported HPE in 11.1% (2/18) of triploid cases at 10–15 gestational weeks. Daniel et al [10] reported HPE in 15.8% (3/19) of triploid cases at 8–22 gestational weeks. Mittal et al [18] reported HPE in 5% (1/20) of triploid cases at 14–25 gestational weeks. Jauniaux et al [19] reported HPE in 2.9% (2/70) of triploid cases at 13–29 gestational weeks. Toufaily et al [13] reported HPE in 3.7% (2/54) of triploid cases at 11–36 gestational weeks. On the other hand, triploidy can be detected in cases with HPE. Ong et al [5] reported triploidy in 6.2% (7/113) of cases with fetal HPE at all gestational weeks. Chen et al [1] reported triploidy in 6.8% (5/73) of cases with HPE detected after the first trimester.

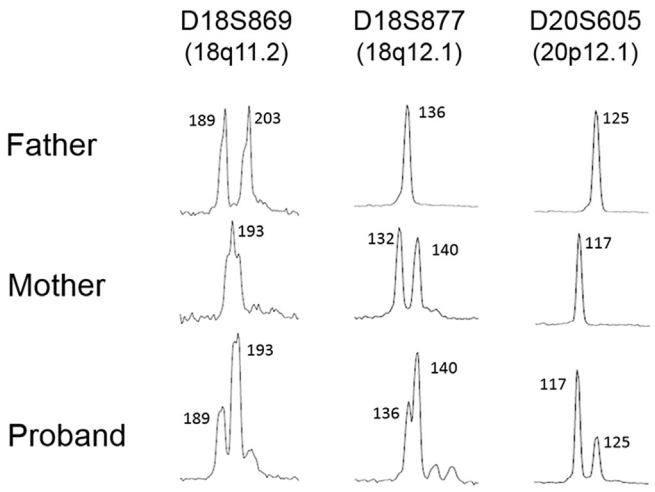

Fig. 4. Representative electrophoretogram of quantitative fluorescent polymerase chain reaction assays at short tandem repeat markers for chromosomes 18 and 20 using placental tissues and parental blood.

Triploidy in association with semilobar HPE is unusual. To our understanding, only Daniel et al [10] reported a case of mosaicism for digynic triploidy and trisomy 16 or 69, XXY (88%)/47,XY,+16 (12%) associated with semilobar HPE. Alobar type HPE is the most common form of HPE associated with HPE. Chen et al [1] reported the alobar type in 100% (5/5) of cases of triploidy with HPE. Bekdache et al [21] reported the alobar type in 53.3% (8/15), the lobar type in 6.7% (1/15) and the unclassified types in 40% (6/15) of cases of triploidy with

Table 1
Genotypic information of the fetus and the parents at STR markers specific for chromosomes 18 and 20 by quantitative fluorescent polymerase chain reaction assays using placental tissues showed a diallelic pattern with a dosage of 1:2 (paternal allele to maternal allele ratio), indicating a maternal origin of triploidy.

STRs	Location	Father	Mother	Fetus
D18S869	18q11.2	189, 203	193, 193	189, 193, 193
D18S877	18q12.1	136, 136	132, 140	136, 140, 140
D20S605	20p12.1	125, 125	117, 117	117, 117, 125

STR = short tandem repeat.

HPE. Toufaily et al [13] and Blass et al [14] each reported a single case of triploidy with alobar HPE. Our case presents semilobar HPE on the first trimester fetal ultrasound. The characteristics of semilobar HPE on fetal ultrasound include interhemispheric fissure and falx cerebri presented posteriorly, part of the corpus callosum seen in the region of the posteriorly separated hemispheres, with the anterior extent corresponding to that of the interhemispheric fissure and rare occurrence of facial dysmorphisms [20].

In the present case, we demonstrate digynic triploidy with homozygous maternal haploid alleles and relative macrocephaly, premaxillary agenesis with median facial cleft and a non-cystic small placenta on fetal ultrasound. Ultrasound is the first choice of prenatal investigation of triploid fetuses, and conventional cytogenetics and a quantitative fluorescent polymerase chain reaction based diagnostic test are necessary for the diagnosis of digynic triploidy. Currently. non-invasive prenatal testing (NIPT) has become a common screening test for chromosome abnormalities in early pregnancy. However, NIPT can identify only diandric triploidy rather than digynic triploidy due to low cell-free fetal DNA fraction [22,23]. Polymorphic marker analysis has the advantage of determination of parental origin in case of triploidy. Diandric triploidy can be associated with partial mole, which will cause maternal complications [24].

In conclusion, we have presented a rare case of digynic triploidy with semilobar HPE. Our case demonstrates the importance of fetal sonography, cytogenetic analysis, and polymorphic marker analysis in perinatal investigation of triploidy associated with HPE.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

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