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Case Report

Prenatal diagnosis and array comparative genomic hybridization characterization of trisomy 21 in a fetus associated with right congenital diaphragmatic hernia and a review of the literature of chromosomal abnormalities associated with congenital diaphragmatic hernia

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ABSTRACT

Objective: Rapid genome-wide aneuploidy diagnosis using uncultured amniocytes and array comparative genomic hybridization (aCGH) is useful in pregnancy with abnormal ultrasound findings. The purpose of this report is to report a case of right congenital diaphragmatic hernia (CDH) associated with trisomy 21 diagnosed prenatally by aCGH and to review the literature of chromosomal abnormalities associated with CDH.

Case report: A 29-year-old woman was referred for genetic counseling at 25 weeks of gestation because of fetal CDH. The pregnancy was uneventful until 25 weeks of gestation when level II ultrasound detected isolated right CDH. Ultrasound showed that the liver and gallbladder were located in the right hemithorax, and there was levocardia. Fetal magnetic resonance imaging confirmed the diagnosis of right CDH with the gallbladder and part of the liver appearing in the right hemithorax and the heart shifting to the left hemithorax. Amniocentesis was immediately performed. About 10 mL of amniotic fluid was sent for aCGH analysis by use of the DNA extracted from uncultured amniocytes, and 20 mL of amniotic fluid was sent for conventional cytogenetic analysis. aCGH analysis revealed the result of arr 21p11.2q22.3 (9,962,872–48,129,895) × 3, consistent with the diagnosis of trisomy 21. Conventional cytogenetics revealed a karyotype of 47,XY,+21. Postnatally, polymorphic DNA marker analysis using DNAs extracted from the placenta and parental bloods showed a heterozygous extra chromosome 21 of maternal origin consistent with the result of maternal meiosis I nondisjunction.

Conclusion: Prenatal diagnosis of right CDH should raise a suspicion of chromosomal abnormalities especially trisomy 21 and the association of Morgagni hernia.

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Introduction

Rapid genome-wide aneuploidy diagnosis using uncultured amniocytes and array comparative genomic hybridization (aCGH) is useful in pregnancies with abnormal ultrasound findings. We have previously reported such an application in pregnancies with major fetal structural abnormalities such as cases of isolated ventriculomegaly [1], cystic hygroma and ventriculomegaly [2], fetal nuchal edema and mild ascites [3], and a ventricular septal defect and bilateral ventriculomegaly [4]. Here, we present an additional case of right congenital diaphragmatic hernia (CDH) associated with trisomy 21.

Case report

A 29-year-old, gravida 2, para 1, woman was referred for genetic counseling at 25 weeks of gestation because of fetal CDH. Her husband was age 29 years. The couple had a 3-year-old healthy daughter, and there was no family history of congenital malformations. The pregnancy was uneventful until 25 weeks of gestation when level II ultrasound detected isolated right CDH (Fig. 1). Ultrasound showed that the liver and gallbladder were located in the right hemithorax, and there was levocardia. Fetal magnetic resonance imaging confirmed the diagnosis of right CDH with the gallbladder and part of the liver appearing in the right hemithorax and the heart shifting to the left hemithorax (Fig. 2). Amniocentesis was immediately performed. About 10 mL of amniotic fluid was sent for aCGH analysis by use of the DNA extracted from uncultured amniocytes, and 20 mL of amniotic fluid was sent for conventional cytogenetic analysis. aCGH analysis revealed the result of arr 21p11.2q22.3 (9,962,872–48,129,895) × 3 consistent with the diagnosis of trisomy 21 (Fig. 3). Conventional cytogenetics revealed a karyotype of 47,XY,+21. Postnatally, polymorphic DNA marker analysis using DNAs extracted from the placenta and parental bloods showed a heterozygous extra chromosome 21 of maternal origin consistent with the result of maternal meiosis I nondisjunction (Fig. 4).

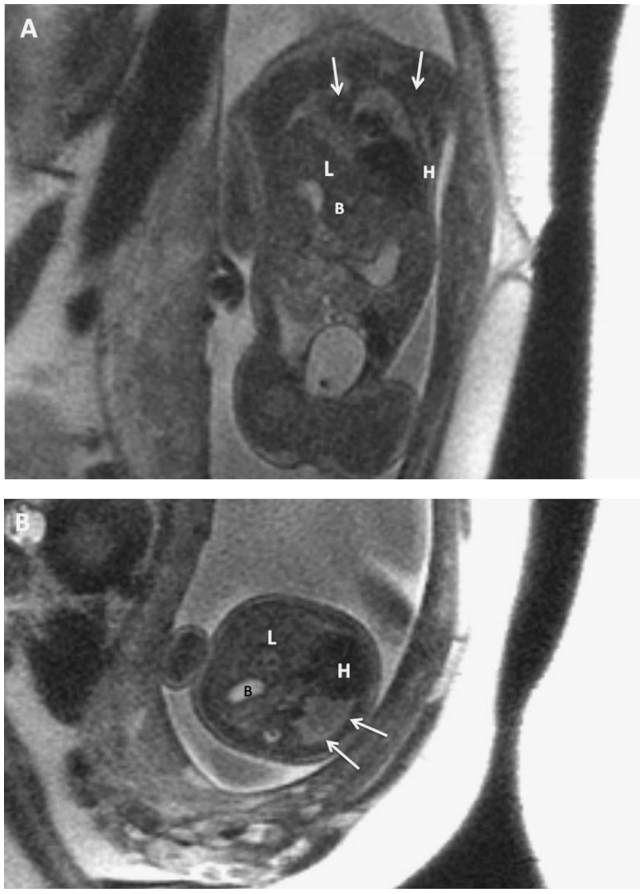

Fig. 2. Fetal magnetic resonance imaging scans in (A) coronal view and (B) axial view show right CDH. The arrows indicate the compressed lungs. B = gallbladder; CDH = congenital diaphragmatic hernia; H = heart; L = liver.

Discussion

The peculiar aspect of the present case is the association of right CDH with trisomy 21. Right CDH is uncommon and occurs in only 10% of cases with CDH, whereas left CDH occurs in 85% of cases, and bilateral CDH occurs in < 5% of cases [5]. Prenatal diagnosis of CDH should raise a suspicion of chromosomal abnormalities. About 10% of cases with CDH have chromosomal aberrations such as mosaic tetrasomy 12p or Pallister–Killian syndrome (PKS), trisomy 18, trisomy 21, trisomy 13, del(4)(p16.3) or Wolf–Hirschhorn syndrome, +der(22)t(11;22) (q23;q11) and partial trisomy 11q and partial trisomy 22, 15q26.2 deletion, 1q41-q42 deletion, and 8p23.1 deletion [6–8]. The most common chromosomal abnormalities associated with CDH are PKS, +der(22)t(11;22)(q23;q11) and partial trisomy 11q and partial trisomy 22, and trisomy 18. About 30% of the cases with PKS, 5–10% of the cases with +der(22)t(11;22)(q23;q11) and partial trisomy 11q and partial trisomy 22, and 1–2% of the cases with trisomy 18 have CDH [8,9]. The occurrence of trisomy 21 in CDH is very rare and, in trisomy 21, Morgagni hernias are more common than Bochdalek hernias (posterolateral hernias) [8]. Morgagni hernia is anterior retrosternal or parasternal hernia that can cause herniation of the liver or intestines into the chest cavity and comprises < 5% of all CDH. However, the incidence of Morgagni hernias associated with Down syndrome has been reported to be 20% [10–12].

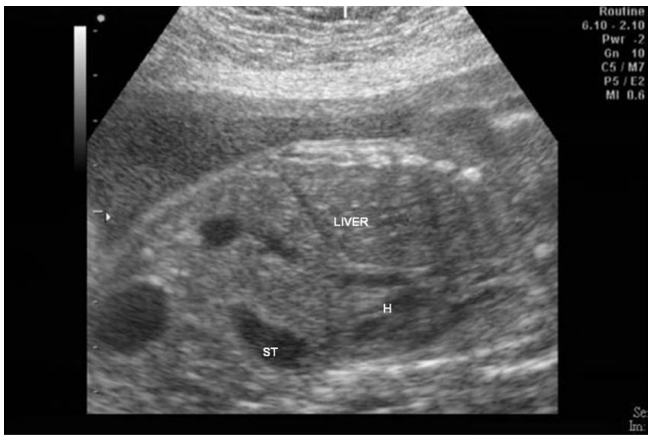

Fig. 1. Prenatal ultrasound at 25 weeks of gestation shows right congenital diaphragmatic hernia (CDH) and levocardia. H = heart; ST = stomach.

aCGH is useful for detection of microdeletion syndrome involving deletions of candidate genes associated with CDH such as *NR2F2* and *ARRDC4* at 15q26.2 [13–16], *HLX* and *DISP1* at 1q41–q42 [17–19], *SOX7* and *GATA4* at 8p23.1 [20–22], and *FGFRL1* at 4p16.3