LETTER TO THE EDITOR

Rapid Diagnosis of Trisomy 18 Using Uncultured Amniocytes in Late Second Trimester in a Pregnancy with Fetal Congenital Heart Defects, Arthrogryposis, Omphalocele, and Mega Cisterna Magna

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A 33-year-old, gravida 3, para 2, woman was referred to the hospital for genetic counseling at 26 weeks of gestation because of fetal anomalies. Prenatal ultrasound revealed intrauterine growth restriction, an atrioventricular septal defect, omphalocele, arthrogryposis of bilateral hands, and mega cisterna magna (Fig. 1). The fetal biometry was equivalent to 24 weeks. About 33 mL amniotic fluid was aspirated, of which 10 mL was used for array comparative genomic hybridization (aCGH) analysis using uncultured amniocytes, 5 mL for quantitative fluorescent polymerase chain reaction (QF-PCR) analysis using uncultured amniocytes, and 16 mL for conventional cytogenetic analysis using cultured amniocytes. The aCGH investigation using whole-genome ISCA Plus Cytogenetic array (Roche NimbleGen, Madison, WI, USA) on uncultured amniocytes showed the result of trisomy 18 [arr cgh 18p11.32q23 (1e7,810,771,248)/C2 3] (Fig. 2). QF-PCR assays revealed a 1:2 ratio of two parental alleles in chromosome 18-specific polymorphic DNA markers. The result was consistent with a homologous duplication of chromosome 18 and the diagnosis of trisomy 18 (Fig. 3). Conventional cytogenetic analysis using cultured amniocytes revealed a karyotype of 47,XY,+18 (Fig. 4). The pregnancy was continued to 32 weeks of gestation, and a dead malformed fetus was delivered with facial dysmorphisms, omphalocele, and arthrogryposis of the hands.

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Molecular cytogenetic technologies such as interphase fluorescence in situ hybridization, multiplex ligation-dependent probe amplification, aCGH, and QF-PCR for rapid aneuploidy diagnosis (RAD) without the need for cell cultures have been well described [1–5]. In the present case, application of aCGH and QF-PCR on uncultured amniocytes has replaced cord blood sampling for RAD. Amniocentesis in late gestation is easier and less invasive than cord blood sampling. The present case shows that aCGH and QF-PCR using uncultured amniocytes are useful alternatives to cordocentesis for RAD in late gestation.

The present case manifested an atrioventricular septal defect, arthrogryposis, omphalocele, and mega cisterna magna on prenatal ultrasound. Congenital heart defects (CHD), omphalocele, arthrogryposis, and mega cisterna magna have been associated with trisomy 18 [6–9].

Snijders et al [10] observed CHD in 52% of the fetuses with trisomy 18 (n = 137). Chaoui et al [11] found chromosomal abnormalities in 22.7% (46/203) of the fetuses with CHD including trisomy 18 (n = 15), trisomy 21 (n = 13), trisomy 13 (n = 5), 45,X (n = 5), triploidy (n = 2), and other rearrangements (n = 6). Prenatal diagnosis of an atrioventricular septal defect has been associated with a high risk of aneuploidy up to 49.1–57.9% [12,13]. Delisle et al [12] reported aneuploidy in 57.9% (22/38) of the fetuses with an atrioventricular septal defect including trisomy 21 (n = 19), trisomy 18 (n = 1), trisomy 13 (n = 1), and mosaic trisomy 19q (n = 1). Huggon et al [13] reported aneuploidy in 49.1% (107/218) of the fetuses with an atrioventricular septal defect including trisomy 21 (n = 86), trisomy 18 (n = 13), trisomy 13 (n = 4), and other rearrangements (n = 4).

Mega cisterna magna has been observed in 6.7% (6/89) of the fetuses with trisomy 18 [6]. Chen [6] observed central nervous system (CNS) anomalies in 22.5% (20/89) of the fetuses with trisomy 18 including holoprosencephaly (n = 5), neural tube defects (n = 2), hydrocephalus (n = 2), Dandy–Walker malformation (n = 5), and mega cisterna magna (n = 6).

Chen [14] reported aneuploidy in 36.1% (415/1148) of the fetuses with prenatally detected omphalocele. Among the 415 fetuses with omphalocele and aneuploidy, 66.7% (277/415) had trisomy 18, 17.3% (72/415) had trisomy 13, and 6.3% (26/415) had trisomy 21. Snijders et al [10] observed omphalocele in 31% of the fetuses with trisomy 18 (n = 137). Chen [7] observed omphalocele in 13.5% of the fetuses with trisomy 18 (n = 89).

Trisomy 18 has been associated with arthrogryposis, preaxial upper limb reduction, overlapping fingers, rocker-bottom feet, and talipes. Snijders et al [10] observed abnormalities of the hands and feet in 72% of the fetuses with trisomy 18 (n = 137). Chen [8] observed arthrogryposis in 25.8% (23/89) of the fetuses with trisomy 18. In his observation, the wrist was more frequent than the ankle, and the left side was more frequent than the right side in cases with asymmetry.
Fig. 2 (A) Whole genome view and (B) chromosomal view of array comparative genomic hybridization analysis on uncultured amniocytes show a duplication of chromosome 18 (arrows), consistent with the diagnosis of trisomy 18.
In conclusion, prenatal diagnosis of CHD, arthrogryposis, omphalocele, and mega cisterna magna should raise a suspicion of aneuploidy. We suggest that aCGH and QF-PCR using uncultured amniocytes are useful for RAD in pregnancy with fetal anomalies detected in late gestation.

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References


