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Short Communication

Mosaic trisomy 17 at amniocentesis: Prenatal diagnosis, molecular genetic analysis, and literature review

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ABSTRACT

Objective: We present prenatal diagnosis and molecular genetic analysis of mosaic trisomy 17 and a review of the literature of mosaic trisomy 17 at amniocentesis.
Materials and Methods: A 42-year-old woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age, which revealed a karyotype of 47,XX,+17[4]/46,XX[17]. Prenatal ultrasound findings were unremarkable. She underwent repeat amniocentesis at 20 weeks of gestation. Interphase fluorescence *in situ* hybridization (FISH), array comparative genomic hybridization, and quantitative fluorescent polymerase chain reaction assays were applied to uncultured amniocytes. Conventional cytogenetic analysis was applied to cultured amniocytes and cord blood. Interphase FISH was applied to uncultured urinary cells postnatally.
Results: At repeat amniocentesis, molecular genetic analysis of uncultured amniocytes revealed no genomic imbalance in array comparative genomic hybridization, no uniparental disomy 17 in quantitative fluorescent polymerase chain reaction, and 4.7% (5/105 cells) mosaic trisomy 17 in interphase FISH analysis. Conventional cytogenetic analysis of cultured amniocytes revealed a karyotype of 46,XX (17/17 colonies). A phenotypically normal baby was delivered at 38 weeks of gestation. The cord blood had a karyotype of 46,XX. Interphase FISH analysis of uncultured urinary cells revealed 5.6% (5/90 cells) mosaic trisomy 17. The neonate manifested normal growth and psychomotor development during follow-ups.
Conclusion: Low-level mosaicism for trisomy 17 detected by amniocentesis without ultrasound abnormality can be associated with a favorable outcome. Molecular genetic analysis of uncultured amniocytes at repeat amniocentesis is useful for genetic counseling. A review of the literature shows a correlation between an adverse fetal outcome and a higher trisomy 17 mosaicism level at amniocentesis associated with ultrasound abnormality.

Introduction

We previously reported molecular genetic analysis of prenatally detected mosaic trisomy 2 [1,2], mosaic trisomy 7 [3], mosaic trisomy 12 [4], mosaic trisomy 15 [5], and mosaic trisomy 21 [6] by interphase fluorescence *in situ* hybridization (FISH), array comparative genomic hybridization (aCGH), and quantitative

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fluorescent polymerase chain reaction (QF-PCR) analyses of uncultured amniocytes. Herein, we present an additional case of mosaic trisomy 17 using the same methods. Our case demonstrates that low-level mosaicism for trisomy 17 detected by amniocentesis can be associated with a favorable outcome. Molecular genetic analysis of uncultured amniocytes at repeat amniocentesis is useful for genetic counseling.

Materials and methods

Clinical description

A 42-year-old, gravida 2, para 1, woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Amniocentesis revealed a karyotype of 47,XX,+17[4]/46,XX[17]. Among 21 colonies of cultured amniocytes, four colonies had the karyotype of 47,XX,+17, whereas the other 17 colonies had a normal karyotype of 46,XX. She was referred to the hospital for genetic counseling. The parental karyotypes were normal, and prenatal ultrasound findings were unremarkable. She underwent repeat amniocentesis at 20 weeks of gestation. Interphase FISH, aCGH, and QF-PCR assays were applied to uncultured amniocytes, and conventional cytogenetic analysis was applied to cultured amniocytes and cord blood. Interphase FISH was applied to uncultured urinary cells postnatally. A phenotypically normal 2748 g female baby was delivered at 38 weeks of gestation. She showed normal growth and psychomotor development during follow-ups at 11 months of age.

aCGH

Whole-genome aCGH on the DNA extracted from uncultured amniocytes derived from 10 mL of amniotic fluid was performed using NimbleGen ISCA Plus Cytogenetic Array (Roche NimbleGen, Madison, WI, USA). The NimbleGen ISCA Plus Cytogenetic Array has 630,000 probes and a median resolution of 15–20 kb across the entire genome.

QF-PCR

QF-PCR analysis was performed on the DNA extracted from uncultured amniocytes and parental bloods. Briefly, primers specifically flanking short tandem repeat markers on chromosome 17 region, such as D17S2180 (17q21), D17S1290 (17q23.1), and D17S1304 (17q25.1), were applied to undertake polymorphic marker analysis to exclude uniparental disomy 17 (UPD 17) and determine the parental origin of genomic imbalance if detected.

FISH

Interphase FISH analysis was performed on 105 uncultured amniocytes prenatally and 90 uncultured urinary cells postnatally using a 17q25.3-specific bacterial artificial chromosome probe RP11-196O11 encompassing 80,858,759–81,021,949 (University of California, Santa Cruz hg19) (spectrum green, fluorescein isothiocyanate) and a 17p13.3-specific bacterial artificial chromosome probe RP11-74E22 encompassing 2,586,599–2,588,382 (University of California, Santa Cruz hg19) (spectrum red, Texas Red), according to the standard FISH protocol.

Conventional cytogenetic analysis

Routine cytogenetic analysis by G-banding techniques at 550 bands of resolution was performed on cultured amniocytes at repeat amniocentesis and cord blood after birth.

Results

At repeat amniocentesis, conventional cytogenetic analysis of cultured amniocytes revealed a karyotype of 46,XX in all the 17 colonies of cultured amniocytes, and molecular genetic analysis of uncultured amniocytes revealed no genomic imbalance in aCGH. QF-PCR analysis of the DNA extracted from uncultured amniocytes and parental bloods revealed a biparental allelic pattern for chromosome 17-specific markers and thus excluded UPD 17 in the fetus. Interphase FISH analysis of uncultured amniocytes revealed 4.7% (5/105 cells) mosaic trisomy 17 compared with 2.9% (2/71 cells) in normal controls. The cord blood had a karyotype of 46,XX (40/40 cells). Interphase FISH analysis of uncultured urinary cells revealed 5.6% (5/90 cells) mosaic trisomy 17 compared with 1.6% (2/123 cells) in normal controls.

Discussion

To date, at least 29 cases (including this presentation) of mosaic trisomy 17 and/or trisomy 17 detected by amniocentesis have been reported (Table 1) [7–26]. Of these 29 cases, nine (9/29; 31.03%) [19,21–26] were associated with prominent phenotypic abnormalities, suggesting that the malformation risk should be given consideration in prenatal diagnosis of mosaic trisomy 17 by amniocentesis. In the nine cases with an apparently abnormal outcome, the percentage of trisomic cells in cultured amniocytes (1^{st} tap) varied from 23.6% to 100% (with 7 cases $\geq$ 33.3%, 5 cases $\geq$40%, and 4 cases $\geq$50%). In the 20 cases with a normal or nearly normal outcome, the percentage of trisomic cells in cultured amniocytes (1^{st} tap) varied from 4.3% to 100% (with 19 cases $\leq$ 40.9%, 17 cases $\leq$ 33%, and 14 cases $\leq$ 19.1%). These findings indicate a correlation between a higher trisomy 17 mosaicism level and an adverse fetal outcome. Of interest is that one out of 20 cases with a normal outcome was associated with 100% trisomy 17 during the first amniocentesis [11–13]. Butler et al [11] reported a case of mosaic trisomy 17 with the first amniocentesis due to elective maternal serum α-fetoprotein having trisomy 17 in 26/26 colonies and the second amniocentesis having trisomy 17 in 71.4% of 21 colonies. This particular case resulted in a normal live-born. Table 1 shows that all 20 cases with a normal outcome were associated with a normal prenatal ultrasound, whereas all nine cases with an abnormal outcome were associated with an abnormal prenatal ultrasound. Therefore, abnormal ultrasound findings in addition to a higher trisomy 17 mosaicism level are correlated with an adverse fetal outcome in cases with mosaic trisomy 17 detected by amniocentesis. The reported abnormal ultrasound findings associated with mosaic trisomy 17 at amniocentesis include intrauterine growth restriction, hypoplastic cerebellar vermis, cerebellar hypoplasia, ventriculomegaly, pleural effusion, congenital heart defects, nuchal thickening, cystic hygroma, single umbilical artery, and short long bones. Prenatal diagnosis of mosaic trisomy 17 should pay special attention to the brain, especially the cerebellum. Table 1 shows that five of nine cases with fetal abnormalities were associated with cerebellar hypoplasia and/or hypoplastic cerebellar vermis. Table 1 shows a limitation of application of cord blood sampling for the confirmation of mosaic trisomy 17 detected by amniocentesis because almost all of the cases with cord blood analysis revealed a normal karyotype. At least one case in Table 1 was associated with UPD 17 [15]. Therefore, a testing for UPD 17 should be performed in case of mosaic trisomy 17 at amniocentesis. Table 1 also shows that the male/female sex ratio for fetal mosaic trisomy 17 is 0.93 (14 males/15 females), indicating no gender bias in fetal mosaic trisomy 17.

Postnatally detected mosaic trisomy 17 has been reported in newborns with severe malformations [27,28]. Bullerdiek and