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Short clinical report

Monozygotic twins discordant for 18q21.2qter deletion detected by array CGH in amniotic fluid

M. Essaoui [a], M. Nizon [b], M.P. Beaujard [b], A. Carrier [a], J. Tantau [b], M.C. de Blois [b,c], S. Fontaine [a], C. Michot [b,c], J. Amiel [b,c], J.P. Bernard [a], T. Attié-Bitach [b,c], M. Vekemans [b,c], C. Turleau [b], Y. Ville [a,c], V. Malan [b,c,*]

[a] Service de Gynécologie-Obstétrique, Hôpital Necker-Enfants Malades, AP-HP, Paris, France
[b] Département de Génétique, Hôpital Necker-Enfants Malades, AP-HP, Paris, France
[c] Université Paris Descartes, Hôpital Necker-Enfants Malades, AP-HP, Paris, France

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ABSTRACT

Discordant chromosomal anomalies in monozygotic twins may be caused by various timing issues of erroneous mitosis and twinning events. Here, we report a prenatal diagnosis of heterokaryotypic monozygotic twins discordant for phenotype. In a 28-year-old woman, ultrasound examination performed at 26 weeks of gestation, detected intrauterine growth restriction and unilateral cleft lip and palate in twin B, whereas twin A had normal fluid, growth and anatomy. Molecular karyotyping in twin B identified a 18q21.2qter deletion, further confirmed by FISH analysis on amniocytes. Interestingly, in twin A, cytogenetic studies (FISH analysis and karyotype) on amniocytes were normal. Genotyping with microsatellite markers confirmed the monozygosity of the twins. At 32 weeks of gestation, selective termination of twin B was performed by umbilical cord coagulation and fetal blood samples were taken from the umbilical cord in both twins. FISH analyses detected mosaicism in both twins with 75% of cells being normal and 25% harboring the 18qter deletion. After genetic counseling, the parents elected to terminate the second twin at 36 weeks of gestation. In postmortem studies, FISH analyses revealed mosaicism on several tissues in both twins. Taking into account this observation, we discuss the difficulties of genetic counseling and management concerning heterokaryotypic monozygotic twins.
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1. Introduction

Traditionally, monozygotic twins have been considered genetically and phenotypically identical. However, several articles have reported phenotypic differences between monozygotic twins in either pre or postnatal settings. These differences were attributed to several causes such as intrauterine environmental factors, circulatory differences caused by placental vascular anatomy, the twinning process itself, somatic mutations, epigenetic phenomena, skewed X-inactivation in females or karyotypic differences [1]. For heterokaryotypic twins, structural chromosomal anomalies are less frequently observed than chromosomal aneuploidies [2–16]. Here, we report a prenatal case of heterokaryotypic monozygotic twins in amniotic fluid with a discordant phenotype. We discuss the mechanisms of this chromosomal anomaly and the difficulties in genetic counseling and management when confronted with heterokaryotypic monozygotic twins.

2. Clinical report

A healthy, 28-year-old woman (gravida 4, para 2), with no known family history of chromosomal or genetic disorders was received at 8 weeks of gestation for an ultrasound to date the beginning of pregnancy. Transvaginal ultrasound diagnosed a monochorionic, diamniotic twin pregnancy. At 12 weeks of gestation, nuchal translucencies measured 1 mm and 1.2 mm and crown-rump lengths were 55.9 cm and 50.4 cm in fetuses A and B respectively. Based on these measurements and maternal age, the risk for trisomy 21 was estimated at 1 in 4025 for both twins.

Ultrasound at 17 weeks of gestation showed discordant amniotic fluid volume. Doppler examinations of the umbilical arteries and ductus venosus were normal in both twins. The deepest vertical pools of amniotic fluid were 7 cm in fetus A and 3 cm in fetus B.

* Corresponding author. Département de Génétique, Université Paris Descartes, Hôpital Necker-Enfants Malades, AP-HP, 149, rue de Sèvres, 75015 Paris, France. Tel.: +33 1 44 49 44 87; fax: +33 1 44 49 04 17.
E-mail address: valerie.malan@nck.aphp.fr (V. Malan).

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The bladder was visualized in both twins. The patient was followed-up with weekly ultrasound examination thereafter. At 21 weeks of gestation, a morphology scan was normal in twin A but technically impossible in twin B due to oligohydramnios in its sac. At 22 weeks of gestation, the pregnancy was diagnosed with stage 1 twin–twin transfusion syndrome for which photocoagulation of placental anastomoses was not required [17]. At 26 weeks of gestation, intrauterine growth restriction below the 3rd centile and unilateral cleft lip and palate were detected in twin B whereas twin A had normal amniotic fluid volume, growth and anatomy. Subsequently, amniocentesis was performed in twin B. Array CGH performed on DNA extracted from uncultured amniocytes was performed on an Agilent 60K oligonucleotide microarray customized for our laboratory (Agilent Technologies, Santa Clara, CA, USA). A terminal deletion of the long arm of a chromosome 18 with a breakpoint in the band 18q21.2 was detected (Fig. 1). The aneusomic segment was approximately 26 Mb in size with a proximal and distal breakpoints at 51 431 696 bp and 77 982 186 bp (GRCh 37, Hg19). Fluorescence *in situ* hybridization (FISH) analysis on uncultured amniocytes using a BAC (bacterial artificial chromosome) contig on the 18qter region as probe confirmed the deletion in all analyzed cells ($n = 200$). This result was confirmed in 200 cultured cells and by the karyotype in 20 metaphases (Fig. 1). Parental chromosomes were normal. As monochorionic diamniotic twins are supposed to be monozygotic, we subsequently performed amniocentesis in twin A to search for the 18qter deletion. Unexpectedly, in 200 uncultured and cultured amniocytes, no 18qter deletion was detected by FISH. Also, the karyotype performed on amniocytes from twin A detected no genomic imbalance (Fig. 1). Genotyping was then performed to confirm the monozygotic status of the twins. Polymorphic microsatellite markers, namely, D1S2651, D3S1568, D8S286, D9S166, D12S1677, D14S978, D17S1873 and D20S847 were fully informative and showed haplo-identity between both twins, indicative of a highly likely monozygosity.

At 32 weeks of gestation, after genetic counseling, pregnancy termination of twin B was request by the parents and performed by selective umbilical cord coagulation using a bipolar forceps under continuous ultrasound guidance [18]. Concomitantly, fetal blood samples were taken from both twins. An identical chromosomal mosaicism was detected in both twins with 75% of cells being normal and 25% harboring the 18qter deletion. After genetic counseling, the second twin was also terminated at 36 weeks of gestation.

At autopsy, physical examination of fetus B revealed a female fetus who displayed a unilateral cleft lip and palate, and an advanced bone age. Her weight was 1200 g (<3rd centile), her length 41 cm (<5th centile) and her head circumference 29 cm (10th centile). Internal and neuropathological examination showed no other anomaly. Physical examination of fetus A, revealed a female fetus with no internal or external organs abnormalities. Her weight was 1870 g (25–50th centile), her length 44 cm (25th centile) and her head circumference 29 cm (10th centile). FISH analyses on several tissues (at least 100 cells analyzed per tissue) showed a mosaicism with an unequal distribution of abnormal cells between the two fetuses (Table 1 and Fig. 2). The mosaic 18qter deletion in liver cells was detected by array CGH (Fig. 2).

3. Discussion

We report a prenatal case of monozygotic twins discordant in both phenotype and karyotype in amniotic fluid. In twin B, array CGH performed on amniocytes because of growth restriction and unilateral cleft lip and palate revealed a homogeneous 18q21.2qter deletion further confirmed by FISH analysis. In contrast, only normal cells were found in the amniotic fluid of twin A. However, postmortem FISH analyses in several tissues detected a low-level chromosomal mosaicism in both twins with an opposite distribution of the two clones, i.e., in twin A, there was a majority of normal cells whereas in twin B, almost all cells harbored the anomaly.

Different mechanisms may be considered when genotypic dissimilarity is observed in monozygotic twins. Indeed, depending on the moment of occurrence of the chromosomal imbalance relative to the twining event, the two fetuses or only one may harbor the abnormal cells [1–19]. A mitotic nondisjunction or a structural rearrangement may occur in one embryo after the

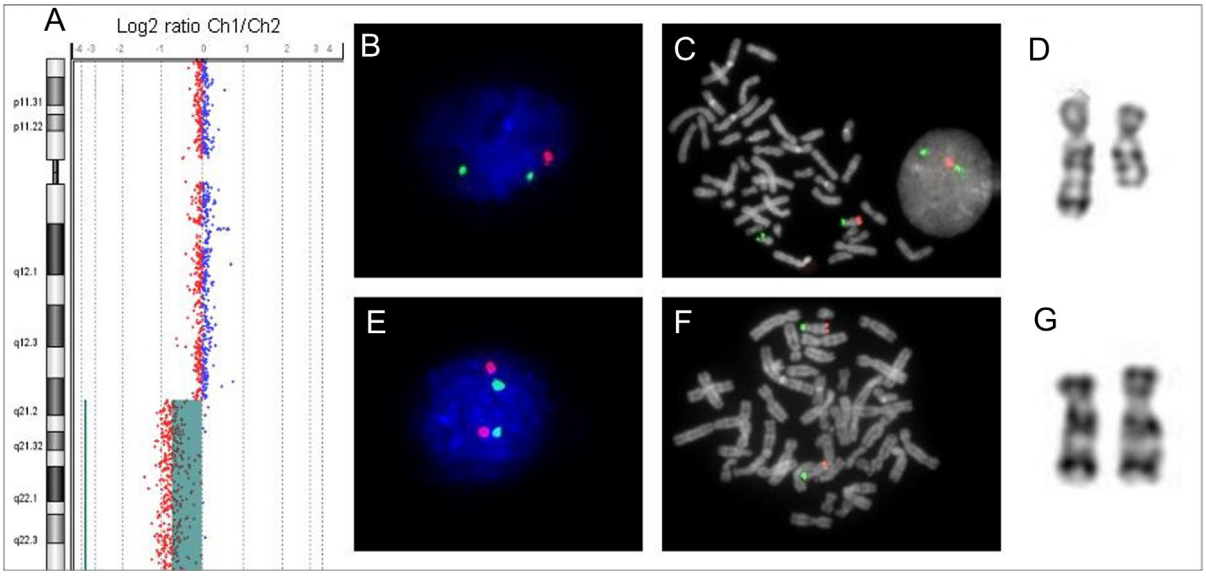

Fig. 1. Prenatal cytogenetic analyses on amniocytes from both twins. (A) Array-based comparative genomic hybridization ratio profile showing the 18q21.2qter deletion in twin B. (B–C) FISH analysis on uncultured and cultured amniocytes of twin B with a BAC contig* on the 18qter region as probe showed only one red signal in interphase nuclei (B) and metaphases (C). The green 18pter probe was used as a control probe. (D) Partial karyotype showing G-banding chromosomes 18 of the fetus B. Left: normal chromosome 18, Right: 18q21.2qter deleted chromosome. (E–F) FISH analysis on uncultured and cultured amniocytes of twin A with a BAC contig on the 18qter region as probe showed two signals in interphase nuclei (E) and metaphases (F). The green 18pter probe was used as a control probe. (G) Partial karyotype showing G-banding chromosomes 18 of the fetus A. The two chromosomes 18 are normal. *RP11-565D23, RP11-93F7, CTD-3110E17, RP11-803N2, RP11-196B3, RP11-841P22, RP11-767J19.

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