Taiwanese Journal of Obstetrics & Gynecology 56 (2017) 681–685

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Case Report

Monozygotic twins discordant for trisomy 21: Discussion of etiological events involved

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ARTICLE INFO

Article history:
Accepted 10 March 2017

Keywords:
Monozygotic twin
Trisomy 21
Discordant anomaly

ABSTRACT

Objective: To elucidate the etiologies of discordant trisomy 21 in monozygotic twin pregnancy.
Case report: A monochorionic diamniotic twin pregnancy with hydrops and cleft lip (twin 1) found in one fetus presented at gestational age of 17 weeks. Amniotic fluid karyotyping showed nonmosaic trisomy 21 in twin 1 (47, XY, +21 [20]) and a normal karyotype in twin 2 (46, XY [20]). Short tandem repeat (STR) polymorphism markers revealed that the two fetuses were monozygotic, and the two chromosomes 21 were maternal isodisomy in the trisomy fetus. The chromosomal constitution of placentas in the territory of trisomy 21 cotwin was 47, XY, +21 [20] and was a mosaic 47, XY+21 [12]/46, XY [8] in the normal karyotyped twin.
Conclusion: Our case of monozygotic twin with discordant trisomy 21 might start with a prezygotic maternal meiosis II non-disjunction error-caused trisomy 21 zygote, and after twinning, one remained trisomy 21, and the other twin underwent trisomy rescue and became a mosaic trisomy 21 in morula or early blastocyst stage before the formation of pre-embryo, which subsequently resulted in mosaic trisomy 21 of the placental tissue and normal chromosomal constitution of the fetus.
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Introduction

Monozygotic twins, developing from a single zygote, are almost identical in clinical phenotype and concordant in karyotypes. Monozygotic twins with discordant trisomy 21 are rare and account for about one in 385,000 cases [1]. The etiology was attributed to either originally coming from a trisomy 21 zygote due to meiosis non-disjunction then after twinning with postzygotic trisomy rescue in one fetus [2] or originating from a diploid zygote followed by post zygotic non-disjunction in one fetus after twinning [3–5]. In this case, we came across a set of monochorionic twins, where one co-twin presented with hydropic changes and cleft lip; a series of prenatal tests thus started, including amniotic fluid chromosome examination and STR analysis on amniotic fluid back-up culture and parental blood; postpartumly, chromosome check-up on fetal skin and placenta was performed. Based on the results, we sought to explore the etiological events possibly involved behind the monochorionic twin set with trisomy 21 discordancy.

Case report

A monochorionic diamniotic pregnancy occurred in a 35-year-old multigravida, nulliparous woman who conceived spontaneously. There was no known family history about trisomy. She was transferred from a local hospital due to presentation of hydrops in one twin at gestational age of 17 weeks. Sonographic examination disclosed a set of monochorionic, diamniotic twins with one fetus showing hydrops and cleft lip and another fetus as normal. Then dual amniocentesis for the two fetuses was done after sonographic exam. 20 days later, the amniotic fluid karyotyping results showed (47, XY, +21 [20]) in the hydropic fetus and (46, XY [20]) in the normal fetus. Though the single chorionicity had been confirmed

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http://dx.doi.org/10.1016/j.tjog.2017.08.019
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by sonography, the rare finding of monochorionic twin with non-identical karyotyping prompted an investigation of zygosity by STR polymorphism marker analysis using the DNA from back-up amniotic fluid culture and both parents' blood as well. After genetic counseling, the parents opted for selective termination of the aneuploid fetus three days later. Unfortunately, on the morning scheduled for feticide, the trisomy fetus was found deceased in utero, while the normal co-twin suffered bradycardia. The parents had no choice but to terminate the whole pregnancy, in spite of the zygosity result still pending. Post-delivery examination confirmed a hydropic fetus with cleft lip and the other without apparent abnormalities. The placenta was monochorionic with intertwin vascular anastomoses (Fig. 1). Fetal skin and placentas from the two twins' individual territories (Fig. 1) were sent for karyotyping.

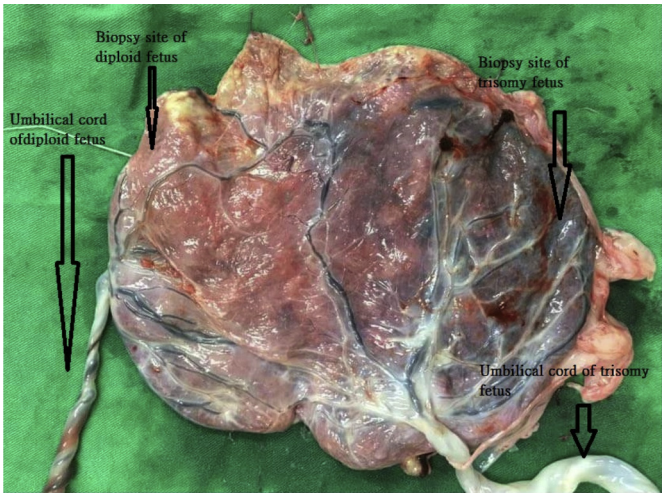

Fig. 1. Monochorionic placenta with intertwine vessel anastomoses; placental biopsies were done at each fetus' territory.

Genotyping for zygosity

All genotypes for 16 short tandem repeat (STR) markers (Amelogenin, D21S1437, D22S683, D8S1110, D10S2325, 12S1090, D17S1294, PentaD, D3S1744, D14S608, D20S470, PentaE, D4S2366, D18S536, D13S765, D6S474) were identical between the two twins, proving they were monozygotic.

Survey for extra chromosome 21

STR marker analysis of parental DNA and DNA extracted from the back-up flask of amniotic fluid culture of both fetuses was also undertaken to determine the origin of the additional chromosome 21 of the trisomy fetus. Two (D21S1435 and Penta D) of the six tested alleles (D21S1436,D21S1437, D21S1435, D21S1270, Penta D and D21S1446) were fully informative, indicating the presence of one copy of a paternally derived chromosome 21 and two identical

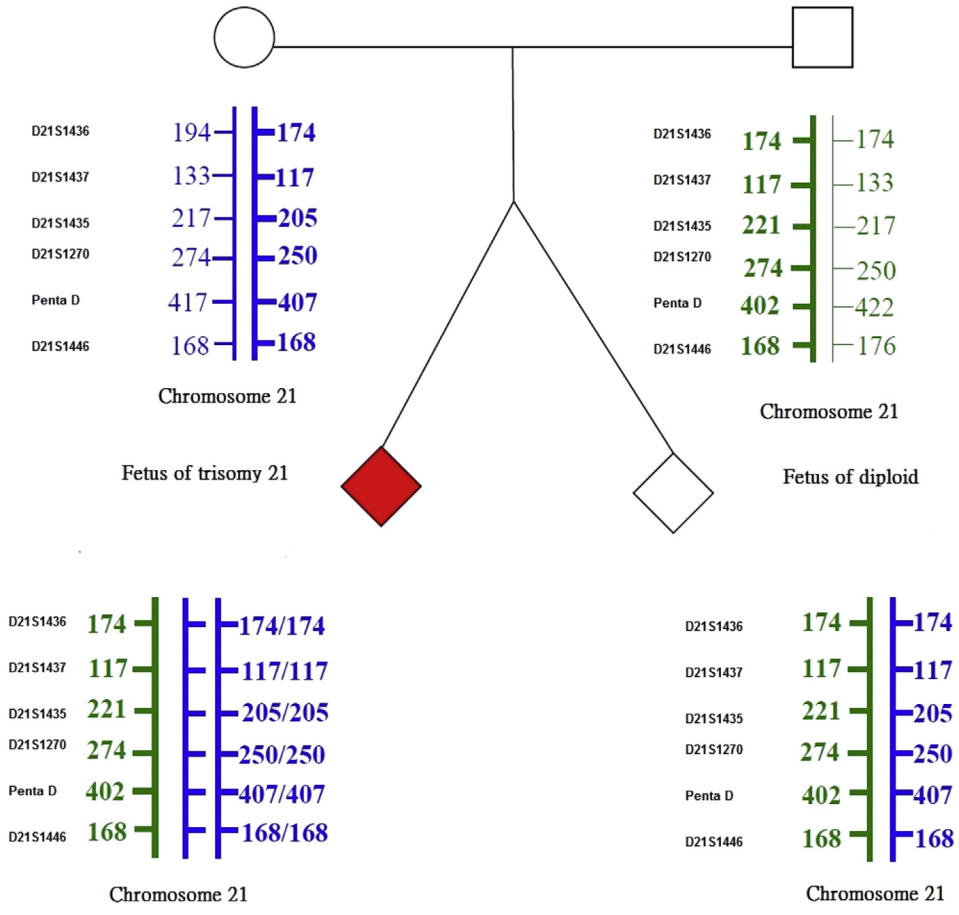

Fig. 2. Microsatellite analysis of parental DNA and DNA extracted from the amniotic fluid culture of both fetuses: The presence of one copy of a paternally derived chromosome 21 and two identical copies of a maternally derived chromosome 21 in the trisomy fetus. The additional chromosome 21 was therefore maternal in origin and there is no uniparental disomy in the normal karyotyping fetus.

copies of a maternally derived chromosome 21 in the trisomy fetus. Also, there was no uniparental disomy in the normal karyotyping fetus (Fig. 2).

Karyotyping of placenta and skin biopsy

Fetal skin fibroblast culture of hydropic twin showed 47, XY, +21 and 46, XY [20] of normal appearance twin.

The placenta from each fetus's territory:

Karyotype of placenta tissue biopsy from the territory of hydropic fetus revealed 47, XY, +21 [20], but a mosaic 47, XY+21 [12]/46, XY [8] from the normal twin's territory.

The investigation of the case, including studies and procedures done in their chronological, was summed up in a flow-process diagram (Fig. 3).

Discussion

Monochorionic twin with discordant trisomy 21 is a rare event and only several cases had been reported [1,3,5–10]. The etiologies had been suspected as pre-zygotic nondisjunction with trisomy rescue [1,2] or postzygotic mitotic errors [3–5].

The cytogenetic analyses of peripheral lymphocytes in fetuses of monozygotic twin with discordant trisomy 21 had been reported as blood mosaicism [5,6]. Since all published cases of monozygotic twin with discordant trisomy 21 in which the chorionicity had been reported were monochorionic diamniotic twins [1,5–8,10], the "mosaicism" found in peripheral lymphocytes in fetuses might have been the result of mixing of blood between the twins through the vascular placental anastomoses present in the monochorionic placenta. So in cases where the lymphocyte culture shows mosaicism in both fetuses but no mosaicism in fibroblast culture, it may result from blood chimerism through the vascular anastomoses present in the monochorionic placenta, hence not true mosaicism [5,6]. If the etiology of monozygotic twin with discordant trisomy 21 is caused by a postzygotic mitotic error, often times it occurs after twinning in an original disomic conceptus (zygote); mosaicism occurs in only one of the monozygotic twins, usually the abnormal one, while the other twin is normal [1,3,10]. As shown in Fig. 4, the abnormal one would have been a mosaic 45,XY,−21/47, XY, +21, but that 45,XY,−21 was nonviable.

In our case of monozygotic twins (Fig. 5), one had non-mosaic trisomy 21 in amniotic fluid and placenta and the other had normal karyotype in amniotic fluid, but mosaic trisomy 21 in placenta. So initially, the zygote should have been trisomy 21 caused by pre-zygotic nondisjunction; after twinning, one trisomic conceptus was rescued at a very early stage caused by anaphase lag, occurring prior to the formation of pre-embryo (such as morula or early blastocyst stage), in a cell that was destined to give rise to inner cell mass and to some of the extrafetal tissue, then the fetus could be 46, XY and the placenta would exhibit mosaic trisomy 21; on the other hand, the other twin that experienced no trisomy

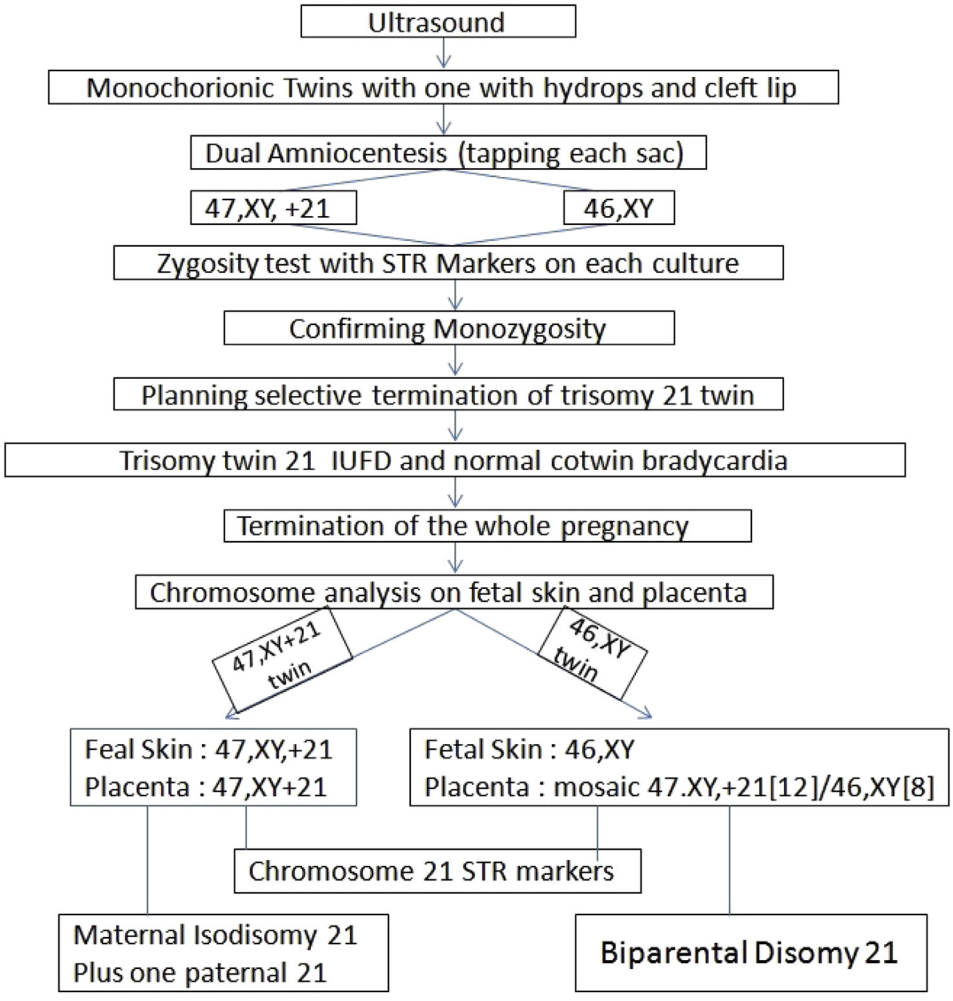

Fig. 3. The flow chart for management of the case, including procedures done and tests runs in their chronological order.

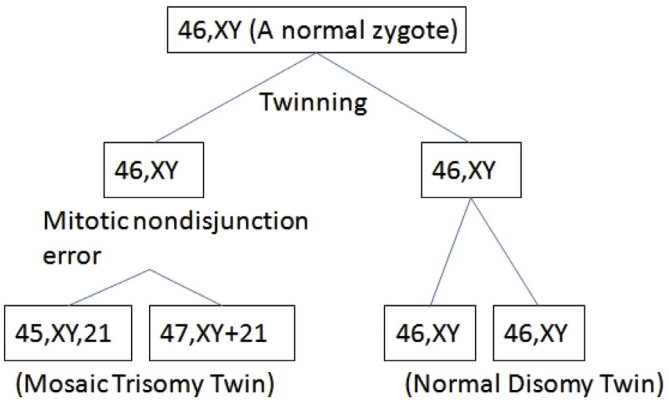

Fig. 4. Twining in an originally normal zygote; postzygotic nondisjunction error resulting in mosaicism for an abnormally karyotyped twin.

rescue would show 47, XY, +21 in both the fetus and the placenta as in our case (Fig. 5). Also, as judged from our STR report (Fig. 2), the trisomy 21 rescue did not cause in the diploid fetus uniparental isodisomy (UPD), but biparental disomy. By contrast, if the anaphase lag caused-trisomy rescue happened at a later stage, then the placenta might be completely trisomic, while the fetus showed mosaic trisomy [12]. Anaphase lagging happens when the sister chromatids fail to connect to the spindle apparatus or are too slowly drawn to its pole, thereby resulting in being excluded in the reforming nuclear membrane; this would convert trisomy in a cell to 46,N [12,13].

A fetus with aneuploidy has a high rate of spontaneous embryonic or fetal death, and expectant management in a monochorionic twin pregnancy discordant for aneuploidy may be complicated by acute transplacental exsanguination of the diploid fetus into the circulation of the demised twin, which may result in double fetal death or acute hypovolemic ischemia and end-organ damage in the healthy fetus [9]. We had therefore arranged selective termination three days after the result of karyotyping was available, but unfortunately the trisomy fetus died in the morning for scheduled surgery, when the normal co-twin also presented bradycardia. Out of concern the normal co-twin would be at high risk for severe hypoxia following acute transplacental exsanguinations caused by demise of trisomy fetus, the parents opted to terminate the pregnancy.

The origin of extra chromosome 21 in discordant trisomy 21 had been reported as maternal [1] or paternal origin, [8]. In our case, it was of maternal origin. In our case, judged from our chromosome 21 STR markers, two chromosomes 21 were identical from the mother, indicating maternal isodisomy of chromosome 21 (Fig. 5); Nondisjunction at meiosis II could cause uniparental isodisomy [12]. CVS result in monochorionic twin with discordant trisomy 21 had been reported as euploid in four cases [5,7,8,10] and as trisomy in one case of postpartum placenta biopsy [1]. In one case, the CVS report was diploidy but postpartum placenta cytogenetic analysis showed 46, XY, 47, XY, +21 or mosaicism in different biopsy sites [7]. In cases where dual amniocentesis was performed [1,5,7], all showed discordant trisomy 21. Thus, CVS is not encouraged in monochorionic twin with discordant anomaly, but instead dual amniocentesis should be chosen.

In conclusion, the etiology of our case of monozygotic twin with discordant trisomy 21 might result from a series events, starting with a prezygotic maternal meiosis II non-disjunction-caused trisomy 21 zygote, and after twinning, one twin continuing as trisomy 21, while the other twin undergoing trisomy rescue by anaphase lagging at an early stage before the formation of pre-embryo, thus resulting in a nonmosaic fetus and placenta mosaicism in the diploid fetal placental territory [11]. CVS for discordant anomaly in monochorionic twin is not an option since most CVS reported diploidy in MC with discordant trisomy. Owing to the risk that the fetal death of the aneuploid fetus may incur acute transplacental exsanguination of the diploid fetus into the circulation of the demised twin, prompt selective termination of the aneuploid fetus should be considered after the discordant fetal karyotyping was disclosed.

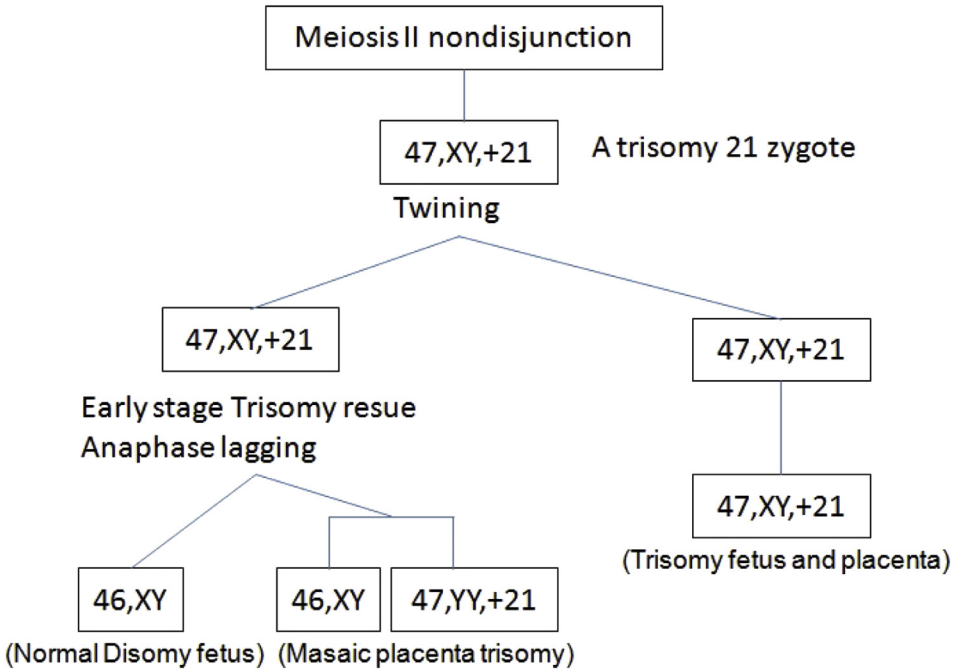

Fig. 5. Twining in originally trisomy 21 zygote, one continuing as straight trisomy 21, while the other undergoing early stage trisomy rescue by anaphase lagging, causing a normally karyotyped fetus and a mosaic trisomic placenta, like in our case.

Conflicts of interest statement

All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest.

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