Original Article

J Genet Med 2018;15(1):8-12
https://doi.org/10.5734/JGM.2018.15.1.8
ISSN 1226-1769 (Print) 2383-8442 (Online)

JGM Journal of Genetic Medicine

Role of fetal ultrasound in prenatally diagnosed *de novo* balanced translocations

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Purpose: This study aimed to investigate fetal ultrasonographic findings in cases of prenatally diagnosed *de novo* balanced translocations and the role of fetal ultrasound in prenatal genetic counseling.

Materials and Methods: We collected cases with *de novo* balanced translocations that were confirmed in chorionic villus sampling, amniocentesis, and cordocentesis between 1995 and 2016. A detailed, high-resolution ultrasonography was performed for prediction of prognosis. Chromosomes from the parents of affected fetuses were also analyzed to determine whether the balanced translocations were *de novo* or inherited.

Results: Among 32,070 cases with prenatal cytogenetic analysis, 27 cases (1/1,188 incidence) with *de novo* balanced translocations were identified. Fourteen cases (51.9%) showed abnormal findings, and the frequency of major structural anomalies was 11.1%. Excluding the major structural anomalies, all mothers who continued pregnancies delivered healthy babies.

Conclusion: Results of a detailed, high-resolution ultrasound examination are very important in genetic counseling for prenatally diagnosed *de novo* balanced translocations.

Key words: Genetic translocation, Prenatal ultrasonography, Prenatal diagnosis, Genetic counseling, Cytogenetic analysis.

Introduction

Balanced translocations are rare and occur either *de novo* or through parental inheritance. Inherited balanced translocations have been reported to be less frequently associated with major congenital anomalies than *de novo*. In a previous study, the estimated risk of a major congenital anomaly was 1.96% among those with inherited balanced chromosome rearrangements, which was similar to the estimated risk in the general population [1]. In contrast, the frequency of congenital abnormalities in *de novo* balanced chromosome rearrangements was reported as 6.1% to 6.7% and higher than inherited type [1,2]. Although there was related study published in Korea, there were only 5 cases of *de novo* balanced translocations [3]. These reference values were reported in the 1990s and early 2000s and are not representative of current developments in prenatal ultrasound diagnostic technology. Abnormal ultrasound findings are helpful in prediction of pregnancy outcomes. Especially, when chromosomal abnormalities are diagnosed prenatally, the results of ultrasound are used to predict postnatal prognosis in genetic counseling.

This study aimed to investigate fetal ultrasonographic find-

Received: May 24 2018, Revised: June 12 2018, Accepted: June 12 2018, Published: 30 June 2018

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Conflict of interest: The authors declare that they do not have any conflicts of interest.

ings and pregnancy outcomes in cases of prenatally diagnosed *de novo* balanced translocations and to provide recent results that can be useful in genetic counseling.

Materials and Methods

1. Study subjects

We retrospectively reviewed the medical records of 32,070 pregnant women who underwent prenatal cytogenetic analysis in our institute between 1995 and 2016. The indications for prenatal cytogenetic analysis included an advanced maternal age, high risk for maternal serum screening test, abnormal ultrasound findings, parental chromosomal abnormalities, and other reasons. All fetuses with *de novo* balanced translocation were subjected to nuchal translucency ultrasound or a detailed, high-resolution ultrasound examination. Nuchal translucency ultrasound examined fetal anatomy and nuchal translucency thickness between 11 weeks and 13 weeks 6 days of gestation. A detailed, high-resolution ultrasound examination was performed between 18 and 24 weeks of gestation and assessed fetal anatomy systematically. Pregnant women who continued to receive antenatal screening in our institute performed ultrasound examination again in the third trimester of pregnancy. The babies were regarded as healthy if they showed normal appearances. For this study, appropriate institutional review board approval was obtained from the Ethics Committee at Cheil General Hospital (#CGH-IRB-2017-50).

2. Prenatal cytogenetic analysis

Amniocentesis, chorionic villi sampling, and cordocentesis were performed to obtain specimens for the cytogenetic analysis. Cytogenetic analysis for fetal karyotyping were performed using the conventional GTG or GTL-banding analysis method. The chromosomes of parents of the affected fetuses were also analyzed to determine whether the balanced translocations either occurred *de novo* or were inherited. Peripheral blood of parents was used for cytogenetic analysis and the analysis was performed using same method as fetuses.

Results

Among the 32,070 available cases subjected to prenatal cy-

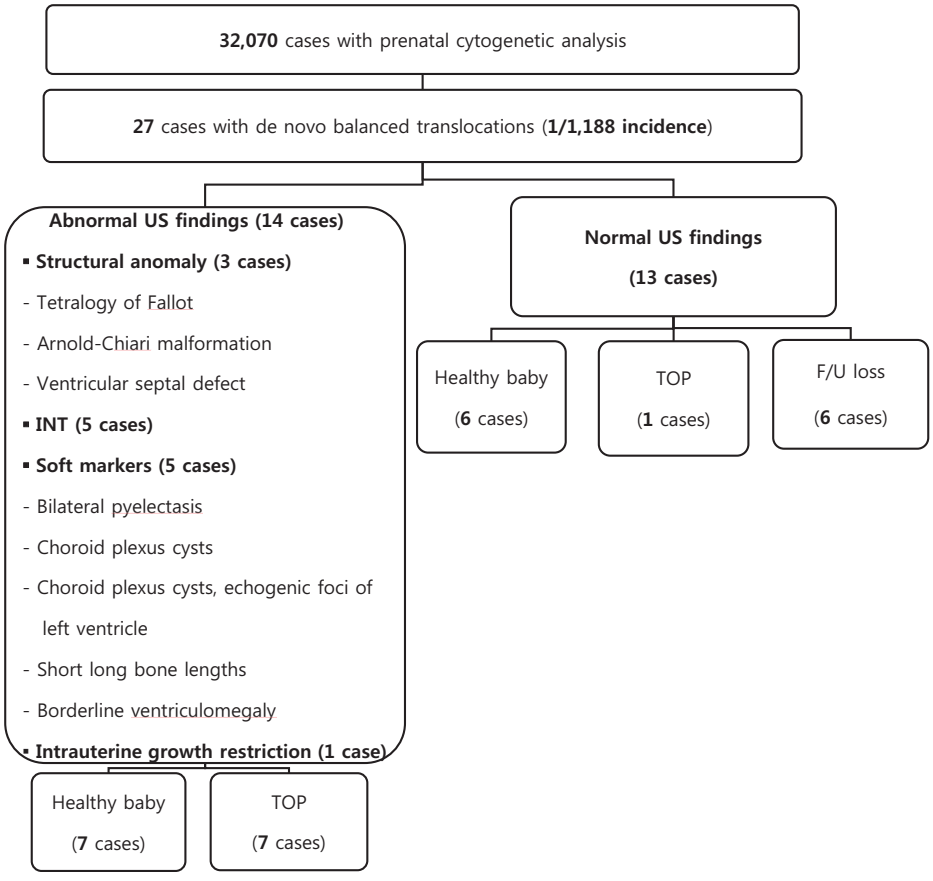

Fig. 1. Flowchart of the study. The incidence of prenatally diagnosed *de novo* balanced translocations was 1/1,188 at our institute. Abnormal ultrasound (US) findings were identified in 14 cases (51.9%). The risk of major structural anomaly in prenatally diagnosed *de novo* balanced translocations was 11.1%. INT, increased nuchal translucency; TOP, termination of pregnancy; F/U, follow up.

togenetic analysis, 27 cases with *de novo* balanced translocations were identified. The incidence of prenatally diagnosed *de novo* balanced translocations was 1/1,188 at our institute. The frequencies of *de novo* balanced reciprocal translocation and Robertsonian translocation were 1/1,603 and 1/4,581 respectively. The indications for cytogenetic analysis were advanced maternal age in 14 cases, high risk for maternal serum screening test in 7 cases, and abnormal ultrasound findings in 6 cases. Amniocentesis in 25 cases, chorionic villi sampling in 1 case, and cordocentesis in 1 case were performed. Following confirmation of the results of cytogenetic analyses, detailed, high-resolution ultrasound examinations were performed in 21 cases.

Fig. 1 summarizes the results of 27 cases with *de novo* balanced translocations. Abnormal ultrasound findings were identified in 14 cases (51.9%). The findings from these cases are summarized in Table 1. The abnormal ultrasound findings included 5 cases with increased nuchal translucency, 3 cases with major structural anomaly, 5 cases with soft markers, and 1 case with intrauterine growth restriction. The major structural anomalies included 2 cases with congenital heart diseases and 1 case with Arnorld-Chiari malformations. The risk of major structural anomaly in prenatally diagnosed *de novo* balanced translocations was 11.1% and all 3 cases such pregnancies were terminated. In 7 cases with ongoing pregnancy, all babies were delivered at term and phenotypically normal.

Thirteen cases (48.1%) showed normal ultrasound findings and pregnancy outcomes could be confirmed in 7 cases. Pregnancy was terminated in one case because of parental request; in the remaining 6 cases of ongoing pregnancy, all babies were delivered at term and were phenotypically normal (Table 2).

Discussion

Several reports have published the incidence of prenatally diagnosed *de novo* balanced translocations [1,2]. In 1991, the frequencies of approximately 1/2,000 and 1/9,000 for *de novo* balanced reciprocal translocations and Robertsonian translocations, respectively [2]. According to a study published in 2006, the incidence of *de novo* balanced reciprocal translocations was 1/1,246 and *de novo* Robertsonian translocations was 1/6,234 [1]. In our study, the incidence was higher; that may be due to not racial differences, but also advances in diagnostic techniques such as development of resolution of chromosome analysis and introduction of various additional confirmatory tests.

Balanced translocations are expected to have little effect on the phenotype due to the absence of genetic material changes, whether balanced reciprocal or Robertsonian translocations. In our study, we estimated major structural anomaly rates of

Table 1. Summary of 14 cases with abnormal ultrasound findings in prenatally diagnosed *de novo* balanced translocations

Karyotype	Ultrasound findings	Indication of karyotyping	Pregnancy outcomes
Reciprocal translocation			
46,XX,t(8;20)(q24.2;q12)	Arnold-Chiari malformations Thickened myocardium	AMA	TOP
46,XX,t(2;4)(p23;q28)	Ventricular septal defect, MR, AR	Ab-US	TOP
46,XX,t(3q;7q;12q)	INT	Ab-US	TOP
46,XY,t(3;16)(p13;q25)	INT	Ab-US	TOP
46,XY,t(2;20)(q12;p12)	INT	T21 HR on MSS	TOP
46,XX,t(8;10)(q22.1;p13)	INT	Ab-US	3,105 g healthy baby
46,X,t(X;10)(q26;q11.2)	Pyelectasis	T18 HR on MSS	TOP
46,XY,t(7q;14q)	CPC	AMA	3,440 g healthy baby
46,X,t(X;14)(p11.4;q13) [15] /46,XX [60]	CPC, LV echogenic foci	Ab-US	3,255 g healthy baby
46,XX,t(6;18)(q25.1;q23)	Short long bone lengths	AMA	3,260 g healthy baby
46,XY,t(9;13)(p21;q32)	Borderline ventriculomegaly	AMA	3,440 g healthy baby
46,XX,t(1;15;5)(p32.3;q21.1;q31.3)	IUGR	AMA	2,290 g healthy baby
Robertsonian translocation			
45,XY,der(13;14)(q10;q10)	INT	Ab-US	3,030 g healthy baby
45,XX,der(13;14)(q10;q10)	TOF	T21 HR at MSS+	TOP

AMA, advanced maternal age; TOP, termination of pregnancy; MR, mitral regurgitation; AR, aortic regurgitation; Ab-US, abnormal ultrasound; INT, increased nuchal translucency; T, trisomy; HR on MSS, high risk on maternal serum screening; CPC, choroid plexus cyst; LV, left ventricle; IUGR, intrauterine growth restriction; TOF, tetralogy of Fallot.

Table 2. Summary of 13 fetuses with normal ultrasound findings in prenatally diagnosed *de novo* balanced translocations

Karyotype	Indication of karyotyping	Pregnancy outcomes
Reciprocal translocation		
46,XX,t(2;21)(q11.1;q22.3)	AMA	3,705 g healthy baby
46,XY,t(10;19)	T21 HR on MSS	3,855 g healthy baby
46,X,t(Y;11)(q1?1.2;q2?3)	T21 HR on MSS	3,655 g healthy baby
46,XX,t(2;6)(p24;q23.3)	T21 HR on MSS	3,545 g healthy baby
46XX,t(17q;22p)	AMA	TOP
46,XY,t(11;22)(q23;q11.2)	AMA	Lost to follow-up
46,XX,t(7;15)(q36.1;q15)	AMA	Lost to follow-up
Robertsonian translocation		
45,XY,der(13;13)(q10;q10)	AMA	2,905 g healthy baby
45,XY,der(13;14)(q10;q10)	AMA	3,410 g healthy baby
46,XX,t(14;15)(q24.3;q26.2)	AMA	Lost to follow-up
46,XY,t(13;21)	AMA	Lost to follow-up
45,XX,der(14;15)(q10;q10)	AMA	Lost to follow-up
45,XX,der(13;15)(q10;q10)	T21 HR on MSS	Lost to follow-up

AMA, advanced maternal age; T, trisomy; HR on MSS, high risk on maternal serum screening; TOP, termination of pregnancy.

10.5% and 12.5% for *de novo* balanced reciprocal and Robertsonian translocations, respectively. However, these frequencies may have been overestimated. Our analysis included 6 cases wherein a cytogenetic diagnosis was performed because of abnormal ultrasound findings. Therefore, we recalculated the risk, as these cases would have introduced ascertainment bias. After excluding the 6 cases, we determined major structural anomaly rates of 7.1% for *de novo* balanced reciprocal translocations, 14.2% for *de novo* Robertsonian translocations, and 9.5% for all *de novo* balanced translocations. A previous study reported frequencies of serious congenital anomaly of 6.1% for *de novo* balanced reciprocal translocations and 3.7% for Robertsonian translocations; these serious congenital anomalies included neurodevelopmental disorders, as well as major structural anomalies [2]. Peng et al. [1] reported a major structural anomaly rate of 8.3% among cases of prenatally detected *de novo* balanced translocations. These figures were higher than the usual estimated frequency of 2% to 3% for congenital anomalies at birth. This discrepancy may be attributed to the mechanisms by which gene disruption at chromosomal breakpoints cause abnormal gene function [4]. Therefore, the ultrasound examination should be carefully performed considering a high incidence of major congenital anomaly if a *de novo* balanced translocation is confirmed prenatally.

Prenatal genetic counseling for *de novo* balanced translocations should include both neurodevelopment disorders and structural anomalies. Short-term follow-up studies reported frequencies of 6.1% to 12.5% for congenital abnormalities among cases of *de novo* balanced chromosome rearrangements [1,3,5-8]. Sinnerbrink et al. [9] evaluated the long-term follow-up data of children aged 3 to 11 years who have been diagnosed with *de novo* balanced chromosomal rearrangements. The results of this study were as follows: In children with a prenatally detected *de novo* balanced chromosomal rearrangement, there was no significant differences of intelligence, educational ability, mental health, and child development compared with general population. In our study, we did not investigate a long-term follow-up of the affected babies. However, after excluding cases involving major structural anomalies, all mothers with ongoing pregnancies gave birth to healthy babies.

The development of next-generation sequencing (NGS) technologies or chromosomal microarray has allowed cases previously classified as *de novo* balanced translocations to be identified as unbalanced translocations. Among individuals with postnatally diagnosed *de novo* balanced chromosomal rearrangements and abnormal phenotypes, 40% to 100% are found to have a genomic imbalance detectable by a comparative genomic hybridization array or single-nucleotide polymorphism array [10-12]. In the future, re-analyses of *de novo* balanced translocations and ultrasound results by applying NGS technology is expected to yield more interesting results.

In summary, we concluded that the frequency of major congenital anomalies prenatally diagnosed *de novo* balanced translocations was as high as 10%, but the prognosis of the affected fetuses without major anomalies did not significantly differ from those of the general population. Therefore, our results suggest that the results of a detailed, high-resolution ultrasound examination are a very important factor in genetic counseling for prenatally diagnosed *de novo* balanced translocations.

Acknowledgements

This research was supported by a grant of the Korean Health Technology R&D Project through the Korean Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HC15C1336).

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