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De novo Chromosomal Aberrations in the Fetus; Genetic Counseling and Clinical Outcome

The aim of this study was to examine the incidence and clinical outcome of de novo chromosomal aberrations retrospectively and provide useful data for genetic counseling in the prenatal cytogenetic diagnosis. We found 17 cases of de novo chromosomal aberrations in 5,501 cases of prenatal cytogenetic analysis and reviewed the karyotype, further study, medical records, fetal ultrasound findings and clinical outcomes. Out of the 17 de novo chromosomal aberrations, 5 had balanced reciprocal translocations and 12 had unbalanced translocations characterized as deletion, addition, or marker. In the case of the five balanced reciprocal translocations, 3 cases without abnormal ultrasound findings were carried to term after comprehensive genetic counseling. Neonates were phenotypically normal and clinical examinations were normal. Two cases with abnormal ultrasound findings were terminated therapeutically. Twelve cases of unbalanced translocations were terminated except one case with a mosaic marker chromosome. High resolution fetal ultrasound and detailed cytogenetic and molecular study will be adjunctive tools for predicting the karyotype/phenotype correlations of fetuses with de novo chromosomal aberrations, although they have limitation to find all phenotypic effects.

Key Words : *Chromosome Aberrations; Prenatal Diagnosis; Ultrasonography, Prenatal; Genetic Counseling*

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INTRODUCTION

Most structural abnormalities detected in prenatal diagnosis are generally familial inheritances (1, 2). The risk of phenotypic abnormality is very low when balanced chromosome rearrangement is inherited from a phenotypic normal carrier parent (2, 3). However, unbalanced rearrangements are likely to be associated with abnormal phenotypes because of deletion, duplication, or both (4). The incidence of de novo balanced reciprocal translocation is 1/2,000 and de novo balanced Robertsonian translocation is 1/10,000. Also, it has been reported that the risk of phenotypic abnormality is 6-7% for de novo reciprocal translocation and 3.7% for de novo Robertsonian translocation (5-7). Even a de novo balanced translocation on prenatal test could result in phenotypic abnormalities, possibly due to microdeletion adjacent to the breakpoint, undetected small deletions, gene disruption, or positional effects (8). Therefore, the interpretation and counseling on de novo chromosome rearrangements in prenatal diagnosis, compared with familial inheritance, is more difficult (3, 7). Accurate diagnosis and follow-up studies are important for genetic counseling on de novo chromosome rearrangements. Here, we report our experiences of 17 cases of de novo chromosome rearrangements detected in the prenatal diagnosis.

MATERIALS AND METHODS

Prenatal cytogenetic analyses were performed in 5,501 pregnancies at Samsung Cheil Hospital from 1995 to 1999. Indications for cytogenetic analysis included advanced maternal age, elevated maternal serum AFP levels, abnormal ultrasound findings, parental chromosome abnormalities, previous history of abnormal chromosome, family history of genetic disease, and other reasons. Specimens for cytogenetic analysis were obtained by amniocentesis, chorionic villi sampling, and cordocentesis. Preparation and analysis of chromosomes for karyotyping were performed using the usual GTG-banding method (9). The parents' chromosomes were analyzed in order to determine whether the abnormality found in the fetus was de novo or inherited. If the fetus was found to have de novo chromosome rearrangements, special techniques such as high-resolution banding, RBG banding, C-banding, NOR-banding, and FISH or CGH were applied for identification and characterization of abnormal chromosomes (9). We reviewed the obstetrical records with fetal ultrasound results

and clinical outcomes in 17 cases.

RESULTS

Seventeen de novo chromosome rearrangements were identified from 5,501 prenatal cytogenetic diagnoses. There were chromosome rearrangements with balanced reciprocal translocation in 5 cases and unbalanced chromosome rearrangements with deletion, addition, and marker chromosome in 12 cases (Table 1). Indications for chromosome analysis in 17 cases with de novo chromosome rearrangements were abnormal findings at fetal screening sonography in 9 cases, advanced maternal age in 4, and maternal serum screening positive in 4 (Table 1).

Table 1. Indications for chromosome analysis and types of chromosomal rearrangement in 17 pregnancies with de novo chromosome rearrangements

Indication	Balanced	Unbalanced	Total
Anomaly at fetal screening sonography	1	8	9
Advanced maternal age	3	1	4
Maternal serum screening positive	1	3	4
Total	5	12	17

Ultrasound findings were not remarkable in 4 fetuses with unbalanced aberrations (case 1-4) (Table 2). Clinical abortions were performed at the request of both parents' for case 1 with deletion in the long arm of chromosome 18 and case 2 with Down syndrome caused by translocated chromosome 21. Of the two cases with a mosaic marker chromosome, case 3 showed negative results on both C-banding and NOR-banding. Although the fetus was known to have normal findings in high resolution fetal sonographic examination, the pregnancy ended in clinical abortion at the parents' request with-

Table 2. Summary of 17 fetuses with de novo chromosomal rearrangements on prenatal analysis

Cases	Karyotype	Indication	Ultrasound findings	Further studies	Outcome
Unbalanced					
1	46,XX,del(18)(q21)	AMA	Normal		TOP
2	46,XY,inv(9),der(14;21)(q10;q10),+21	MSS +	Normal	FISH; D21S65x3*	TOP
3	47,XY,+mar/46,XY	MSS +	Normal	C-banding (-), NOR-banding (-)	TOP
4	47,XY,+mar/46,XY	MSS +	Normal	C-banding (-), NOR-banding (+), CGH; Normal	Normal birth
5	46,XX,add(4)(q35)	Ab-US	Hydrops fetalis	FISH; wcp4+	TOP
6	46,XX,add(13)(q32)	Ab-US	IUGR, Oligohydramnios		TOP
7	46,XY,del(4)(p15.2)	Ab-US	IUGR, Diaphragmatic hernia	FISH; D4S96-	TOP
8	46,XX,del(4)(p15)	Ab-US	IUGR, Coarctation of aorta, Cystic hygroma	FISH; D4S96-	TOP
9	46,XX,del(5)(p15.2)	Ab-US	Dolichocephaly, Oligohydramnios	FISH; D5S23-	TOP
10	46,XY,del(13)(q?21)	Ab-US	Duodenal atresia, Polyhydramnios		TOP
11	46,XY,del(20)(p13)	Ab-US	Hydronephrosis	CGH; dim(20p13)†	TOP
12	45,XX,dic(15;18)(p11.2;p11.1)	Ab-US	Increased nuchal translucency (5 mm at 13 wks)	FISH; D15Z1+, D18Z1+, D18S552- CGH; dim(18p11.1)	TOP
Balanced					
13	46,XX,t(2;21)(q11.1;q22.3)	AMA	Normal	HR, RBG FISH; D21S65x2	Normal birth
14	46,XY,t(10;19)(p11.2;p12)	MSS +	Normal	FISH; wcp19+; wcp19+	Normal to 3 yrs
15	46,XY,t(3;7)(q25;p15)	AMA	Normal	HR, RBG	Normal to 5 yrs
16	46,XX,t(2;4)(q23;q28)	Ab-US	Heart anomaly	RBG	TOP
17	46,XX,t(8;20)(q24.2;q12)	AMA	Lemon-shaped skull, Ventriculomegaly, Thickened myocardium, Micrognathia	HR	TOP

AMA; advanced maternal age, TOP; termination of pregnancy, MSS +; maternal serum screening positive, Ab-US; abnormal ultrasound findings, HR; high resolution GTG-banding, RBG; reverse bands by BrdU using Giemsa, *; Three copies of locus 21q22, †; Loss of region from 20p13 to 20pter.

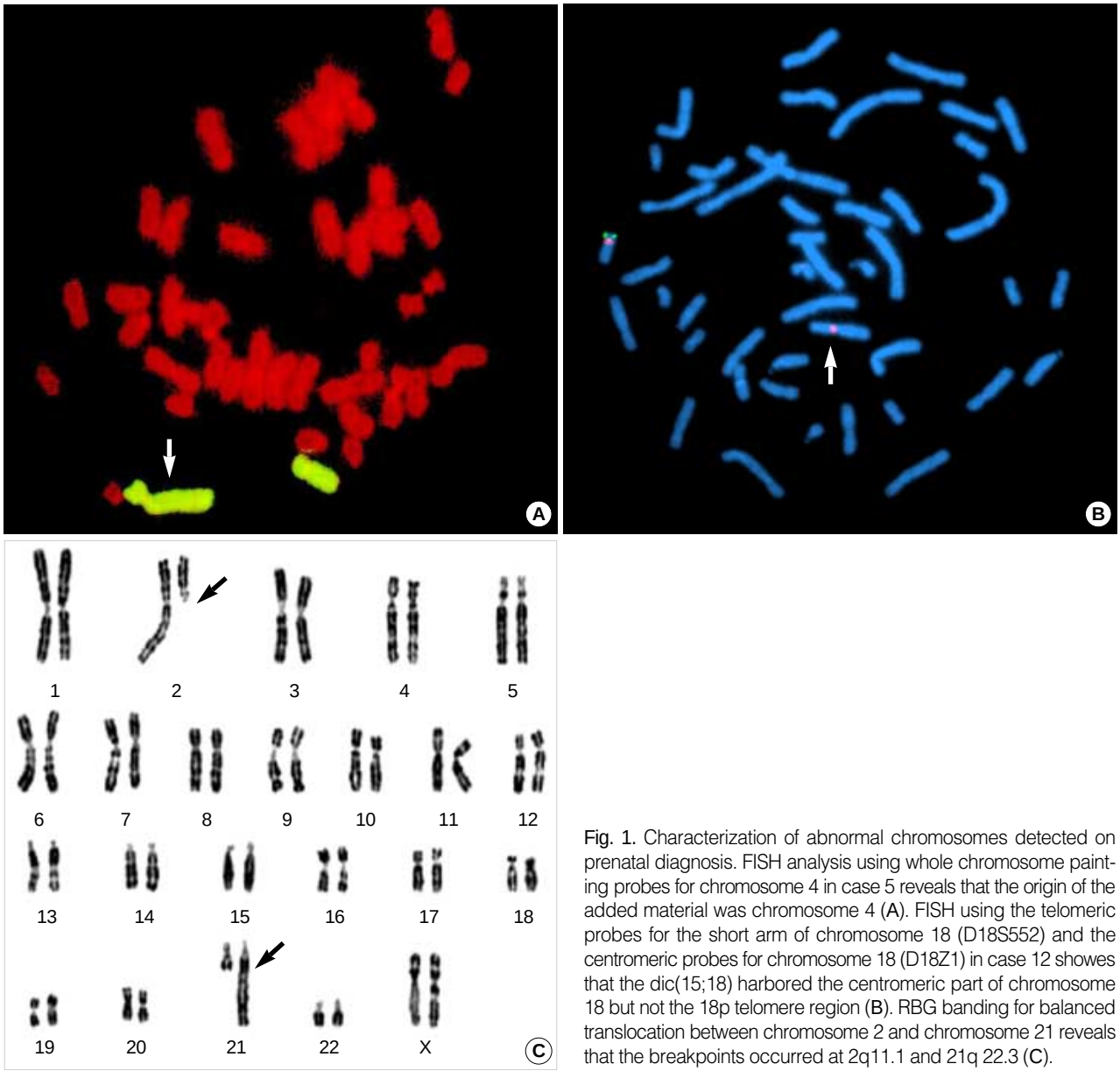

Fig. 1. Characterization of abnormal chromosomes detected on prenatal diagnosis. FISH analysis using whole chromosome painting probes for chromosome 4 in case 5 reveals that the origin of the added material was chromosome 4 (A). FISH using the telomeric probes for the short arm of chromosome 18 (D18S552) and the centromeric probes for chromosome 18 (D18Z1) in case 12 showes that the dic(15;18) harbored the centromeric part of chromosome 18 but not the 18p telomere region (B). RBG banding for balanced translocation between chromosome 2 and chromosome 21 reveals that the breakpoints occurred at 2q11.1 and 21q 22.3 (C).

out additional experiments. For another fetus with marker mosaicism, case 4, the marker chromosome was revealed to have originated from satellites by special banding techniques such as NOR-banding and C-banding and there was no gain of genomic DNA using CGH. The pregnancy was allowed to continue until the delivery at term and the baby was phenotypically normal.

Unbalanced rearrangements were detected in 8 fetuses with abnormal ultrasound findings (case 5-12). In case 5, it was revealed that the additional material of the long arm of chromosome 4 had originated from chromosome 4 by FISH with painting probes for chromosome 4 (Fig. 1A). Case 6 had severe intrauterine growth retardation (IUGR) and oligohydramniosis at 25 weeks. Cord blood karyotype was 46,XX, add(13)(q32). Autopsy showed perimembranous ventricular septal defect. In case 7, 8, and 9, deletions of the short arm of chromosome 4 or chromosome 5 were confirmed using locus-specific probes for identification of deletions of chromosome band 4p16.3 and band 5p15.2, respectively. Case 10 had polyhydramnios and duodenal atresia on ultrasound. In case 11 where it was difficult to determine the deleted arm using the routine G-banding method, it was concluded that the short arm of chromosome 20 had a partial deletion by CGH. Case 12 showed increased nuchal translucency at 13 weeks of gestation, the fetus was confirmed to have a dicentric chromosome for chromosomes 15 and 18 and partial deletion of the short arm of chromosome 18 by FISH and CGH (Fig. 1B). Autopy showed no gross anomaly.

Out of the five fetuses with de novo balanced rearrangements, three fetuses (cases 13, 14, and 15) showed normal ultrasound findings and were born normal (Fig. 1C). However, two fetuses had abnormal findings on sonographic examination. The karyotype of case 16 was 46,XX,t(8;20) (q24.2;q12) and the fetus showed abnormal ultrasound findings such as lemon-shaped skull, borderline asymmetric dilatation of lateral ventricles of the head, thickened myocardium, and suspicious micrognathia. The karyotype of case 17 was 46,XX,t(2;4)(q23;q28) and the fetus had a heart anomaly on sonography. In both cases the pregnancy was discontinued at the parents' request and autopsy finding was consistent with prenatal ultrasound.

DISCUSSION

Among the de novo chromosome rearrangements detected in prenatal diagnosis, most fetuses with unbalanced rearrangements showed morphologically abnormal findings (10-12). Hume et al. reported that fetal anomalies were detected by ultrasonography in 45% of cases of de novo structural rearrangement, and that there was a statistically significant increase in the incidence of fetal anomaly detection compared with familial balanced rearrangements or cytogenetic polymorphisms (13). In our study, no anomaly was observed on follow-up ultrasonography in four cases carrying the unbalanced rearrangement. Because of the parents' anxiety for abnormal phenotypes due to chromosome aberrations, three cases were terminated. One case with marker mosaicism was continued the pregnancy.

Cytogenetic analyses were referred in 8 of the 12 cases with unbalanced rearrangements due to anomalies detected on fetal screening sonography examination. Particularly, we confirmed that the deleted regions did not translocate to the other chromosomes by FISH in the cases 7 and 8 with deletions within the short arm of chromosome 4. And both had typical anomalies of Wolf-Hirschhorn syndrome such as intrauterine growth retardation, diaphragmatic hernia, and heart defects (14).

Chromosomal study was performed due to the increased nuchal translucency at 13 weeks of gestation in the case 12. We could find that there were centromere regions both in the chromosome 15 and 18. We concluded that the fetus had monosomy for the short arm of chromosome 18 using centromeric probes and subtelomeric probe.

Of five cases with balanced chromosomal abnormalities, two had fetal ultrasonographic dysmorphological characteristics. Especially, it was suspected that ultrasonographic anomalies such as ventriculomegaly and lemon sign in case 17 were most likely to be associated with a chromosomal abnormality (15).

Molecular cytogenetic techniques have been known as powerful methods for identification of complex or cryptic chromosomal rearrangements in prenatal diagnosis. There have been many reports that they would exactly identify and localize the chromosomal rearrangement (16-18). In addition, cytogenetic analysis followed by FISH studies made it possible for identification of small de novo structural anomalies and marker chromosomes unidentifiable by G-banding. Furthermore, it could give much better insights to the relation between genotype and phenotype and results using FISH provided a much better understanding for fetal anomalies (19-21).

Of the 5 de novo balanced chromosome rearrangements, we could not exclude the possibility of a submicroscopic deletion or a gene disruption at the breakpoint in two cases with ultrasonographic fetal anomaly. Resampling was undertaken for the three cases with balanced translocation and normal ultrasound findings. Additional experiments were carried out using painting probes or locus-specific probes and by special banding techniques such as high-resolution GTG banding and RBG-banding to identify the cytogenetic abnormalities more precisely.

In apparently balanced translocation cases, counseling and prediction of outcome is difficult because of the paucity of long term outcome data and diagnostic tools for the normality. Many clinicians have tried to expect the karyotype-phenotype correlation with ultrasound in abnormal chromosomal cases. In our de novo balanced translocation series, two out of five were diagnosed fetal cardiac abnormalities by ultrasound and confirmed pathologically. The others with no gross anomaly on fetal ultrasound were continued and delivered grossly healthy babies and showed normal physical and mental development until now. Although fetal ultrasound has limitation to find all anatomical anomalies and functional disabilities, detailed fetal ultrasound evaluation including echocardiography is very helpful in prediction of the prognosis of de novo balanced translocation cases. And more cases with long term follow up data are needed to establish the optimal management protocol.

In the present study, for the cases detected as having de novo chromosome abnormalities, we confirmed the rearrangements additionally using a different type of available fetus cells and performed FISH or CGH and special banding techniques such a high-resolution banding, NOR-banding, C-banding, or RBG-banding, in order to elucidate the characteristics of chromosomes more clearly. The more precise identification of these de novo chromosome abnormalities can play an important role in genetic counseling and decision-making in prenatal diagnosis.

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