Case Report

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Prenatal diagnosis of 5p deletion syndrome: A case series report

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5p deletion syndrome, also known as Cri-du-Chat syndrome, is a chromosomal abnormality caused by a deletion in the short arm of chromosome 5. Clinical features of 5p deletion syndrome are difficult to identify prenatally by ultrasound examination, thus most cases of 5p deletion syndrome have been diagnosed postnatally. Here, we report eight cases of 5p deletion syndrome diagnosed prenatally, but were unable to find common prenatal ultrasound findings among these cases. However, we found that several cases of 5p deletion syndrome were confirmed prenatally when karyotyping was performed on the basis of abnormal findings in a prenatal ultrasound scan. Hence, it is necessary to carefully perform prenatal ultrasonography for detection of rarer chromosomal abnormalities as well as common aneuploidy.

Key words: 5p deletion syndrome, Cri-du-Chat syndrome, 5p minus syndrome, Chromosome 5.

Introduction

5p deletion syndrome, also known as Cri-du-chat syndrome, is a chromosomal abnormality caused by a deletion in the short arm of chromosome 5. It was first identified by Lejeune et al. [1] in 1963. The incidence rate is one in 15,000-50,000 live births [2]. Typical clinical manifestations are a high-pitched mewing crying sound, microcephaly, unusual facial dysmorphisms, including micrognathia, hypertelolism, and low-set ears, and mental retardation [1]. These features are difficult to identify prenatally by ultrasound examination, thus most cases of 5p deletion syndrome have been diagnosed postnatally.

Here, we report eight cases in which 5p deletion syndrome was diagnosed prenatally at our institute and investigated the findings of prenatal testing to aid in prenatal detection.

Case

We prenatally diagnosed eight cases of 5p deletion syndrome from 2007 to 2013 at Cheil General Hospital in Seoul, Korea. During this period, prenatal diagnosis using chorionic villus sampling (CVS), amniocentesis, or cordocentesis was carried out in a total of 11,328 women. Thus, in this study the incidence of 5p deletion syndrome in cases which the karyotype was confirmed prenatally was about one in 1,400. A summary of the eight cases was shown in Table 1.

1. Case 1

A 37-year-old, gravida 3, para 0 woman with a previous history of fetal hydrops was diagnosed with multiple congenital anomalies, including increased nuchal translucency (INT), hydrops of the fetus, and an abnormal heart axis at the first

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Table 1. Summary of the prenatal diagnosis of eight cases with 5p deletion syndrome

Case	MA (yr)	GA at karyotyping (wk)	Indication for karyotyping	Fetal karyotype	Result of second trimester ultrasound	Cause of 5p deletion syndrome
1	37	14.1	MCA including INT	46,XX,del(5)(p13)		*De novo*
2	31	23.5	Abnormal ultrasound findings	46,XX,del(5)(p13.3)	Small-sized cerebellum Ventriculomegaly	Not confirmed
3	23	16.5	INT Anasarca	46,XY,del(5)(p13.3)	Normal	*De novo*
4	30	18.2	Elevated MSAFP	46,XY,del(5)(p14)	Normal	Not confirmed
5	35	20.5	AMA	46,XY,del(5)(p14)	Normal	*De novo*
6	35	18.3	AMA	46,XY,del(5)(p14)[4]/46XX[24]	Normal	*De novo*
7	36	16.4	INT	46,XY,der(5)t(5;7)(p14.2;p21.2)	MCA	Paternal balanced translocation
8	34	12	Paternal balanced translocation	46,XY,der(5)t(5;10)(p15.3;q24.1)	Normal	Paternal balanced translocation

MA, maternal age; GA, gestational age; MCA, multiple congenital anomalies; INT, increased nuchal translucency; MSAFP, maternal serum alpha fetoprotein; AMA, advanced maternal age.

trimester ultrasound. Subsequently intrauterine fetal death was identified at 14 weeks of gestation. Amniocentesis was performed and the karyotype was revealed to be 46,XX,del(5)(p13). The parental karyotypes were normal.

2. Case 2

A 31-year-old, gravida 3, para 1 woman who had previously given birth to one healthy male baby was referred to our institution owing to abnormal prenatal ultrasound findings at 21 weeks of gestation. Second trimester ultrasound at 23 weeks 5 days of gestation showed abnormal findings. The results included a small-sized cerebellum (21 mm) and unilateral ventriculomegaly (10.1 mm) of the fetal brain. Amniocentesis was done on the same day and karyotyping result was 46,XX,del(5)(p13.3). In this case, the parental karyotypes were not confirmed and this woman was lost to follow up.

3. Case 3

A 23-year-old, gravida 1, para 0 woman was diagnosed with INT (2.8 mm) and mild soft tissue edema of the fetus at 11 weeks 6 days of gestation. The result of karyotype as assessed by amniocentesis was 46,XX,del(5)(p13.3) and the parental karyotypes were normal.

4. Case 4

A 30-year-old, gravida 3, para 1 woman with one healthy baby was seen for routine antenatal care. Maternal serum alpha-fetoprotein (AFP) at 16 weeks 3 days of gestation was elevated at 7.31 MoM, and amniocentesis was done. AFP levels in the amniotic fluid were 1.04 MoM, and the karyotype was 46,XY,del(5)(p14). Second trimester ultrasound examination at 21 weeks of gestation revealed normal findings. The parental karyotypes were not examined, and this pregnant woman was lost to follow-up.

5. Case 5

A 35-year-old, gravida 3, para 0 woman was referred for genetic counseling regarding the abnormal result of an amniocentesis, which was performed due to the advanced maternal age. In our institution, amniocentesis at 20 weeks 5 days of gestation was done again, and the resulting karyotype was confirmed as 46,XY,del(5)(14). The second trimester ultrasound and parental karyotypes were normal. This woman follow-up was unavailable.

6. Case 6

A 35-year-old, gravida 1, para 0 woman was seen for routine antenatal care, and amniocentesis was done at 16 weeks 1 day of gestation owing to advanced maternal age. The karyotype was found to be 46,XX,del(5)(p14)[16]/46,XX[54], and cordocentesis was done for confirmation of mosaicism. The result of the cordocentesis was 46,XX,del(5)(p14)[4]/46,XX[24], and the parental karyotypes were normal. The result of the second trimester ultrasound was normal. After genetic counseling, the parents decided to maintain the pregnancy. A female was born at 28 weeks of gestation by cesarean section, and the cause of preterm delivery was premature prelabor rupture of membranes. Her birth weight was 1.15 kg, and her appearance was grossly normal. Neonatal follow-up was unavailable.

7. Case 7

A 35-year-old, gravida 4, para 1 woman with one healthy female baby was diagnosed with INT measuring 3.7 mm, and amniocentesis was performed at 16 weeks 4 days of gestation.

The resulting karyotype was 46,XY,del(5)(p15.1), and this result was confirmed with fluorescent *in situ* hybridization (FISH) analysis using a probe for the telemetric region of 5p (Fig. 1). The second trimester ultrasound showed the findings of multiple congenital anomalies, including intracranial and intraventricular hemorrhage, cystic hygroma, and ankle deformity of the fetus. The paternal karyotype was 46,XY,t(5;7)(p14.2;p21.2) and the maternal karyotype was normal. Following confirmation of the parental karyotype, the final fetal karyotype was determined to be 46,XY,der(5)t(5;7)(p14.2;p21.2). This pregnant woman was lost to follow-up.

8. Case 8

A 34-year-old, gravida 3, para 1 women with one baby with 5p deletion syndrome visited our hospital for antenatal care. After the first baby was diagnosed postnatally with 5p deletion syndrome, a paternal balanced translocation, 46,XY,t(5;10)(p15.3;q24.1) was confirmed. In this pregnancy, CVS was done owing to the known paternal chromosomal aberration. The result was 46,XY,add(5)(p15.3), and on the basis of the paternal karyotype, the final fetal karyotype was redescribed as 46,XY,der(5)t(5;10)(p15.3;q24.1). The prenatal ultrasound scan showed no specific findings. This pregnancy outcome was not available.

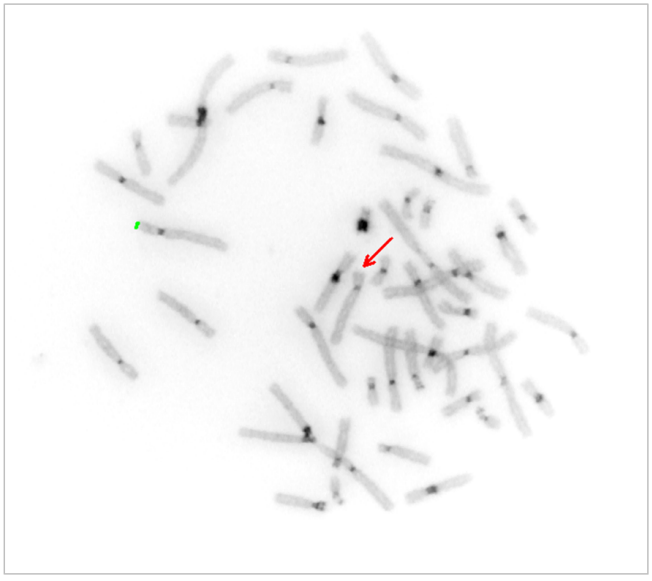

Fig. 1. Fluorescent *in situ* hybridization (FISH) analysis of case 8. The normal chromosome 5p (spectrum green signal) and deletion of the terminal region of chromosome 5p (red arrow) are shown.

Discussion

5p deletion syndrome is a rare chromosomal aberration, and the incidence rate is one in 15,000-50,000 live births [2]. In our institute, the incidence of 5p deletion syndrome in cases in which the karyotype was confirmed prenatally was about one in 1,400.

Approximately 80% of cases of 5p deletion syndrome result from *de novo* deletions, 10-15% are due to unequal segregation of a parental balanced translocation, and rare chromosomal abnormalities cause less than 10% [2]. In this study, parental karyotypes were confirmed in six of eight cases. Four cases occurred due to *de novo* deletions, and two cases resulted from parental balanced translocation. Another study reported that cases of 5p deletion syndrome inherited from parental translocation mostly had a paternal origin [3,4]. In our study, we confirmed both cases involving parental balanced translocation were inherited from a paternal carrier.

Cases of 5p deletion syndrome show variable genotypes and phenotypes. A critical region in 5p15.2-15.3 is responsible for the typical phenotype of 5p deletion syndrome [2,5]. The deletion of 5p15.2 is known to be responsible for facial dysmorphism and intellectual disability [4,6]. Several genes have been reported to be associated with phenotype of 5p deletion syndrome. The catenin delta 2 (*CTNND2*) gene contains 26 exons at 5p15.2, and is a neuronal-specific protein that is potentially associated with cerebral neuronal development [7]. Deletion of the *CTNND2* gene has been linked with the mental retardation seen in 5p deletion syndrome [7], and Asadollahi et al. [8] reported that a small exonic deletion of the *CTNND2* gene was associated with learning problems and a low/normal intelligence quotient with or without developmental delay. Wu et al. [9] suggested that the proximal region of 5p15.3 is related to the cat-like cry and speech delay seen in 5p deletion syndrome. Additionally, the semaphorin 5A (*SEMA5A*) gene has been mapped to the critical region associated 5p deletion syndrome on chromosome 5 [10]. *SEMA5A* contains 28 exons at 5p15.31, and deletion of *SEMA5A* has been associated with autism [10]. The telomerase reverse transcriptase (*TERT*) gene has 16 exons at 5p15.33, and deletion of *TERT* has been shown to play a role in the phenotypic changes in 5p deletion syndrome [11].

The clinical characteristics of 5p deletion syndrome are difficult to find prenatally. Many studies have reported prenatal ultrasound findings of 5p deletion syndrome, but none have detected common findings among the cases [12-18]. Two cases of confirmed 5p deletion syndrome also had nonimmune fetal

hydrops [12,13], and in another case isolated bilateral ventriculomegaly was found [14]. 5p deletion syndrome has been detected prenatally in the context of Dandy-Walker syndrome and agenesis of the corpus callosum [15]. Chen et al. [16] reported that a mosaic distal 5p deletion was associated with cerebellar hypoplasia and microcephaly in a prenatal ultrasound scan. Other studies reported that abnormal findings in prenatal ultrasounds were found in cases with 5p14 deletions [17,18]; one study identified a hypoplastic nasal bone, choroid plexus cyst, cerebellar hypoplasia, and a single umbilical artery in the second trimester ultrasound [17], while another study found prenatally that the fetus had cerebellar hypoplasia, bilateral hydronephrosis, and single umbilical artery in detail scan at 24 weeks of gestation [18].

We did not find any common features between the eight cases presented in this study. However, half of the cases were diagnosed with 5p deletion syndrome when karyotyping was performed on the basis of abnormal prenatal ultrasound findings. Unlike previous mentioned articles we could review results of the first trimester ultrasound, and three of four cases (75%) showed INT; however, the second trimester ultrasound didn't reveal the same findings.

In conclusion, prenatal diagnosis of 5p deletion syndrome remains difficult. However, when abnormal ultrasound findings such as INT are detected, rarer chromosomal abnormalities, as well as common aneuploidy, should be considered. Therefore, it is necessary to carefully perform prenatal ultrasonography for the detection of chromosomal aberrations.

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