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Case Report

1p deletion syndrome: A prenatal diagnosis characterized by an abnormal 1st trimester combined screening test, yet a normal NIPT result

Chung-Yuan Yang, Chuan-Chi Kao, Shuenn-Dyn Chang, Shih-Yin Huang*

Department of Obstetrics and Gynecology, Keelung Chang Gung Memorial Hospital, Keelung, Taiwan

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ABSTRACT

Objective: To present a case with prenatal diagnosis and cytogenetic characterization of 1p36 deletion syndrome whose first trimester combined testing is abnormal but a normal NIPT result.
Case report: A 33-year-old had an abnormal 1st trimester fetal aneuploidy screening result, but no trisomies 13, 18, 21 were detected by the noninvasive prenatal testing. Amniocentesis was performed after ultrasound showed fetal ventriculomegaly and echogenic bowel. The final conventional cytogenetics revealed a karyotype of 46, XX, del(1)(p36).
Conclusion: Every prenatal genetic screening test and diagnostic procedure has its benefit and risk. NIPT offers better sensitivity and specificity for trisomies 13, 18, and 21. Even so, for primary population screening, NIPT provides lower detection rate than sequential screening if considering detection of all chromosomal abnormalities. Diagnostic testing should be offered rather than cell-free DNA screening to pregnant women if a fetal structural anomaly is identified on ultrasound examination.

Introduction

In recent years, the discovery in the maternal circulation of cell-free fetal DNA (cffDNA) derived from placenta has led to a revolution in prenatal aneuploidy screening, which was called “noninvasive prenatal screening” or “noninvasive prenatal testing” (NIPT). NIPT is commonly used as a secondary prenatal aneuploidy screening, and offered to the high risk population or the population with screen-positive as a result of a previous screening test [1]. The candidates for prenatal aneuploidy screening test by cffDNA include maternal age ≥35 years at delivery, abnormal ultrasound findings indicating increased risk (e.g., increased nuchal translucency), an abnormal serum screening test (e.g., first trimester combined testing), a positive family history of aneuploidy (e.g., previous aneuploid pregnancy), or a parent who carries a relevant Robertsonian translocation (e.g., balanced translocation with risk for trisomy 13 or 21) [2,3]. In one large prenatal screening study, cffDNA testing for trisomy 21 had higher sensitivity, higher positive predictive value, and a lower false positive rate than standard screening with the measurement of nuchal translucency and biochemical analytes [4]. However, NIPT still had its limitation to detect other chromosome anomalies. Here, we report a case with abnormal first trimester combined testing, but normal NIPT result, and the final cytogenetic characterization of 1p36 deletion syndrome associated with ventriculomegaly and echogenic bowel demonstrated by prenatal ultrasonography.

Case presentation

A 33-year-old, gravida 1, para 0, woman was referred for genetic counseling at 15 weeks of gestation because of an abnormal result of the first trimester Down screen. The risk calculation for trisomy 21 was 1/39, with B-hCG level 2.834 MoM, PAPP-A level 0.445 MoM, and fetal nuchal translucency thickness was 2.2 mm. Then she received the noninvasive prenatal testing, and no trisomies 13, 18, 21 were detected. However, ultrasound showed fetal ventriculomegaly and echogenic bowel at our clinic at 17 weeks of gestation (Figs. 1 and 2); therefore, amniocentesis was immediately performed. Conventional cytogenetics revealed a karyotype of 46, XX, del(1)(p36) (Fig. 3). After discussion with the parents about the phenotype of fetus with 1p deletion syndrome, such as severe

* Corresponding author. Department of Obstetrics and Gynecology, Keelung Chang Gung Memorial Hospital, No. 222, Maijin Rd., Anle Dist., Keelung, 204, Taiwan.
E-mail address: singsingsing5@gmail.com (S.-Y. Huang).

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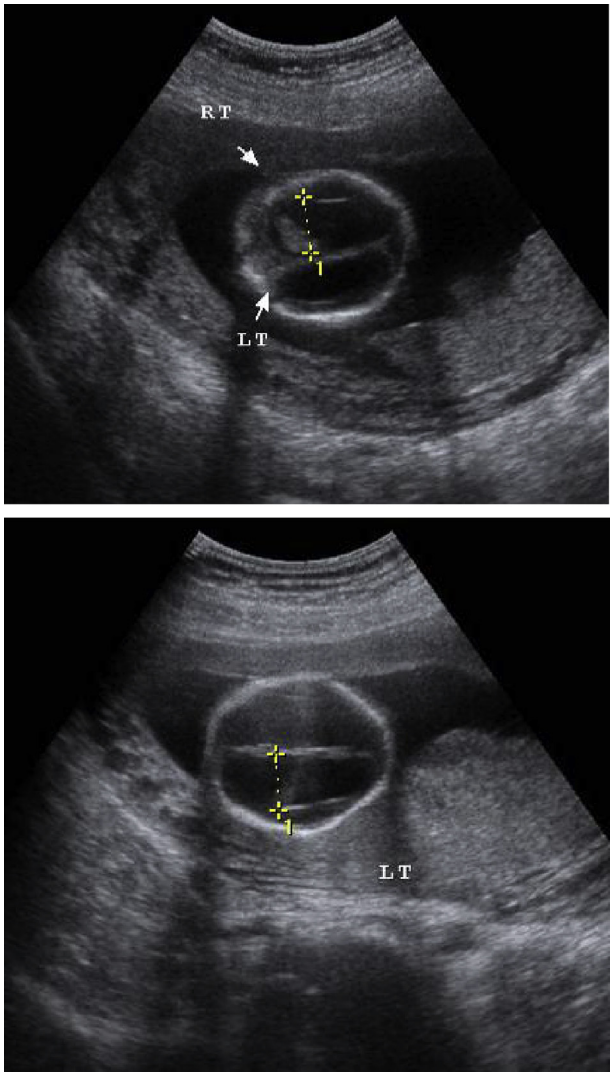

Fig. 1. Transabdominal sonogram reveals bilateral ventriculomegaly (arrows). (Right ventricle is 1.45 cm, and left ventricle is 1.37 cm, respectively).

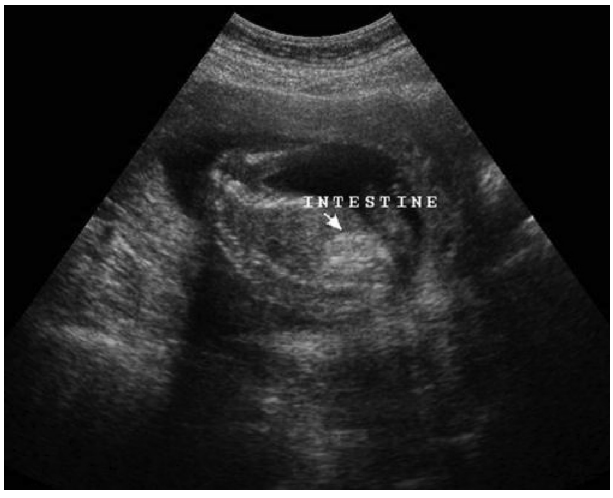

Fig. 2. Transabdominal sonogram reveals echogenic bowel of fetus (arrow).

developmental delay, cardiac malformations and craniofacial dysmorphism, they decided to terminate the pregnancy. Postnatally, fetal karyotyping extracted from cord blood was performed and confirmed the prenatal diagnosis, which confirmed the prior amniocentesis finding of lp36 deletion (see Fig. 4).

Discussion

The clinical use of noninvasive prenatal testing to screen high-risk patients for fetal aneuploidy has quickly spread across the world since its introduction at Hong Kong in August 2011 [5]. This testing can assess the presence of fetal trisomies in a pregnancy as early as 10 weeks, and the advantages of this testing are safe without any adverse side effects to the fetus. So far, many studies have pointed out that NIPT has a high sensitivity and specificity, avoid invasive diagnostic procedures, and thus reduces fetal associated risks. In addition, several large scale clinical validation studies mentioned that NIPT, with a sensitivity and specificity of >99% and a negative predictive value of almost 100%, can accurately detect fetal Down syndrome in both high and low risk pregnancy population [6–8]. Therefore, cffDNA testing was recommended as a primary screening method to examine fetal autosomal aneuploidy, because of its low rate of false positive results [4–10].

However, there are some limitations and restricts of cffDNA testing in clinical practice, including twin pregnancy and maternal obesity [3,11]. The ability to detect fetal trisomy with cffDNA is dependent upon assay precision and fetal fraction in the sample, and the fetal fraction of cffDNA in maternal plasma increases with serum PAPP-A and free β-hCG and decreases with maternal weight [12]. Moreover, the cost of the test was higher than serum immunoassays, and there are no sufficient obstetric experts or resources available to provide formal genetic counseling for all low risk women [13]. Until now, NIPT is not commonly used as a primary screening test, and worldwide organizations of obstetrics recommend offering this test only to women at high risk for having a child with Down syndrome [1–4]. It is true, for trisomy 13, 18, 21, and sex chromosomal aneuploidies, NIPT represents a highly accurate screening option. Nevertheless, the sensitivity and specificity of other uncommon aneuploidies were not good as aforementioned aneuploidies. In addition, chromosomal abnormalities such as unbalanced translocations, deletions, and duplications will not be detected by NIPT. Therefore, screening by means of cffDNA is not designed to detect all aneuploidies. When fetal anomalies are detected, invasive diagnostic testing and cytogenomic microarray analysis are more likely to detect chromosomal imbalances than NIPT and may be a better testing option [14,15].

Chromosome 1p36 deletion syndrome (OMIM 607872) has an estimated frequency of 1 in 5000 live births, and the syndrome is associated with multiple congenital anomalies and mental retardation [16]. Although 1p36 deletion is the most common subtelomeric terminal deletion syndrome, only few cases have been reported prenatally [17–24]. Chromosome 1p36 deletion syndrome may prenatally manifest elevated maternal serum α-fetoprotein levels, congenital heart defects and cerebral malformations. Prenatal diagnosis is usually indicated when there are some abnormalities of sonographic findings, such as congenital heart defects, ventriculomegaly and midface hypoplasia, which should alert clinicians to the possibility of chromosome 1p36 deletion syndrome [17]. Although ventriculomegaly alone is a common finding on prenatal ultrasound with a usually normal outcome, Campeau et al. suggested that brain abnormalities (especially ventriculomegaly) in the context of other abnormalities or IUGR, should increase the index of suspicion and need for adequate visualization of a 1p36 deletion [19]. In this present case, we still suggested an additional

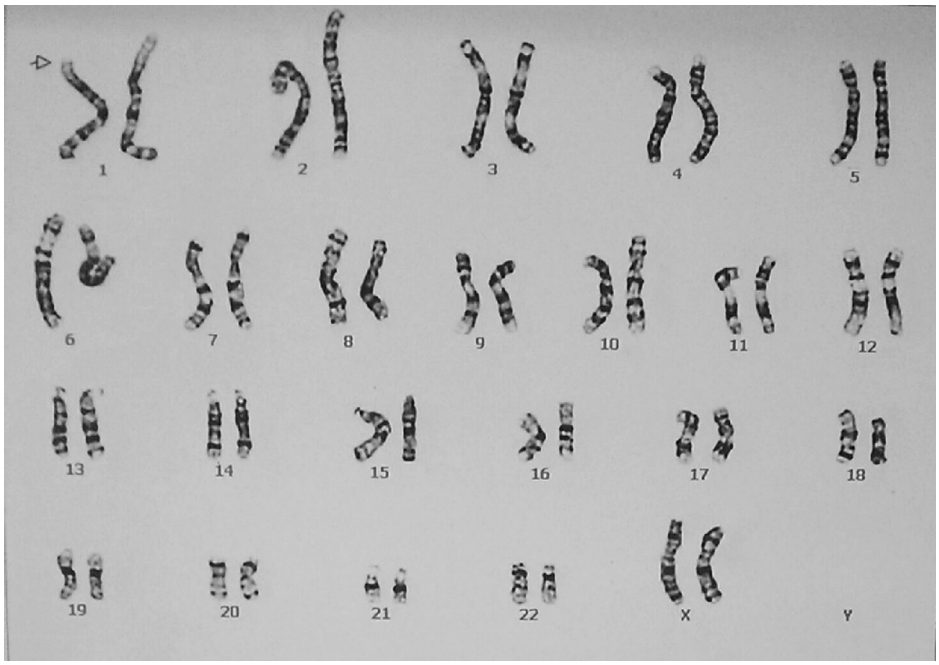

Fig. 3. Conventional cytogenetics revealed a karyotype of 46, XX, del(1)(p36).

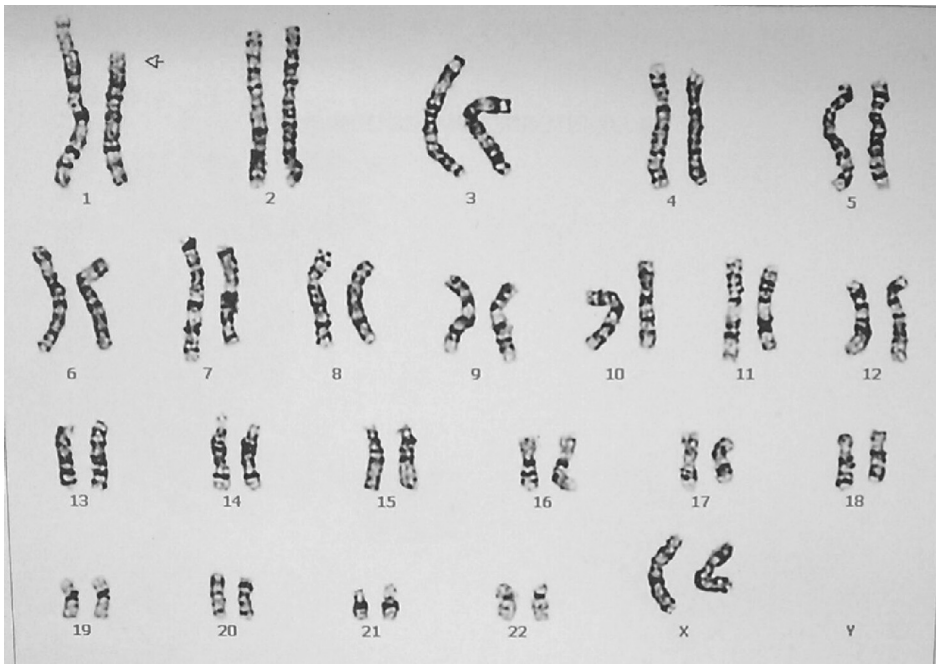

Fig. 4. Conventional cytogenetics revealed a karyotype of 46, XX, del(1)(p36).

amniocentesis due to the abnormal ultrasound finding (ventriculomegaly and echogenic bowel), even though the patient had a normal result of NIPT, and finally 1p deletion syndrome of this fetus was diagnosed.

Compared with current aneuploidy screening tests, cffDNA screening has a higher sensitivity and specificity for trisomy 21 than traditional serum based biochemical screening. However, for primary population screening, cffDNA provides lower detection rate than sequential screening if considering detection of all chromosomal abnormalities. In a recent study of 450,000 women in California, the detection rate for all chromosomal abnormalities was 81.6% in sequential screening group, and cffDNA potentially had only detected 70–75% of these abnormalities. The lowest detection rate for cffDNA occurred in women who were <25 years old, because the relative percentage of chromosomal abnormalities other than trisomy 21, 18, or 13 is greater in younger women [25–28]. The measurement of nuchal translucency can not only calculate the risk for the fetal trisomies 21, 18 and 13 but also give information about other chromosomal defects and some congenital fetal anomaly, such as neural tube defects, cardiac anomalies

or ventral wall defects [29]. Some atypical chromosomal abnormalities are associated with increased nuchal translucency (NT) thickness (≥3.5 mm), and abnormal levels of free β-hCG (<0.2 or ≥5.0 MoM) or PAPP-A <0.2 MoM, but the abnormalities would be missed by targeted NIPT [30]. Trisomies can occur with any chromosomes, but often result in miscarriage. The most common types of autosomal trisomy that survive to birth in humans are trisomy 21, 18 and 13. According to the evidence mentioned above, NIPT is a reliable tool for prenatal trisomy 21 screening and should be an informed patient choice. But that pre-test counseling regarding the limitations of NIPT is warranted. Women who undergo cffDNA aneuploidy screening should also be provided other modalities such as maternal serum alpha-fetoprotein, and ultrasound scan [26].

In conclusion, every test and diagnostic procedure has its benefits and risks. All the prenatal genetic screening tests, including NIPT and integrated (or sequential) screening (e.g., first-trimester only or second-trimester screening), are designed to decrease the risk related to invasive procedure such as amniocentesis. NIPT offers better sensitivity and specificity for trisomies 13, 18, and 21, and this technology is perhaps only a few steps away from an eventual whole genome fetal sequencing from non-invasively isolated cffDNA [31]. However, these prenatal screening tests are not yet ready to replace invasive diagnostic procedures. We suggest women who are interested in NIPT to receive detailed counseling, and the counseling will explain the benefits and limitations of the cffDNA test with adequate informed consent. Actually, the procedure-related risks of miscarriage following amniocentesis and CVS are much lower than currently quoted [32]. Diagnostic testing should be offered rather than cell-free DNA screening to pregnant women if a fetal structural anomaly is identified on ultrasound examination and invasive diagnostic testing should be offered to confirm screen-positive test results.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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