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Prenatal Diagnosis of Tetralogy of Fallot Associated with Chromosome 22q11 Deletion

Microdeletion of 22q11 is responsible for DiGeorge syndrome, velocardiofacial syndrome, congenital conotruncal heart defects, and related disorders. We report our experiences on prenatal diagnosis by fluorescence in situ hybridization (FISH) for 22q11 deletion in two fetuses with tetralogy of fallot. Karyotyping and FISH of the parents revealed that one fetus inherited the disease from maternal microdeletion. These findings suggest the importance of performing FISH in pregnancies with prenatally detected tetralogy of Fallot.

Key Words : *Chromosome, Human, Pair 22; Prenatal Diagnosis; Tetralogy of Fallot; In Situ Hybridization, Fluorescence; Di George Sundrome*

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INTRODUCTION

Microdeletion within 22q11 is associated with a wide variety of birth defects. The acronym CATCH 22 (1) has been introduced to indicate the common forms of defects, namely, cardiac defect, abnormal facies, thymic hypoplasia, cleft palate, and hypocalcemia.

Velocardiofacial syndrome (2), conotruncal congenital heart disease (3), and DiGeorge syndrome (DGS) (4) lie at the end of the clinical spectrum with severe manifestations. Cardiac involvement is a prominent feature. Most of the patients were reported to have conotruncal heart defect (5).

This haploinsufficiency of 22q11 is a relatively frequent cause of birth defect (6). This condition is the second most frequent chromosomal anomaly associated with congenital heart disease. Familial cases with a high phenotypic variability among individuals have been reported, but most cases are sporadic. Fluorescence in situ hybridization (FISH) using a unique sequence DNA probe is an efficient, quick, and direct method for the detection of 22q11 microdeletions (7) and is now a widely used procedure in many laboratories (8, 9). However, only a few cases of prenatal diagnosis have been reported. We report two cases of tetralogy of Fallot in which microdeletion of chromosome 22q11 was diagnosed by FISH prenatally.

CASE REPORTS

Fetal blood sample in Case 1 and amniotic fluid in Case 2 were obtained for karyotyping and FISH. Cells harvested from cultures of phytohemagglutin-stimulated lymphocytes were spread onto slides for the production of G-banded chromosomes. FISH of metaphase chromosomes using the LSI DiGeorge/VCFS Region Dual Color Probe (Vysis) for the DGS chromosome region was carried out according to Pinkel et al. (10).

Case 1

A 29-yr-old Gravida 2 Para 1 woman underwent fetal echocardiography because her previous baby died of sepsis complicating congenital heart disease at 7 days of age. Fetal echocardiography showed tetralogy of Fallot (TOF), severe

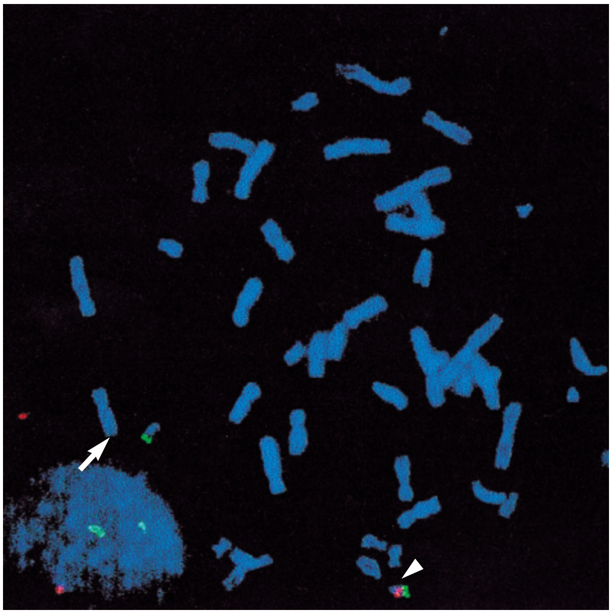

Fig. 1. Fluorescence in situ hybridization (FISH) study detecting a chromosome 22q11 deletion with LSI DiGeorge/VCFS dual color probe. The green signal shows control region with chromosome 22q13.3 and red signal is responsible for DiGeorge critical region. Arrow head shows normal chromosome 22 with green and red signals. Arrow indicated the chromosome 22 with only green signal, pointing to a deletion in chromosome.

hypoplasia of pulmonary arteries, right aortic arch with aberrant left subclavian artery arising from the descending aorta at 23 weeks of gestation. The possibility of CATCH 22 syndrome was considered because of her previous history and its strong association with TOF. A fetal blood sample was obtained for karyotyping and FISH for CATCH 22, which revealed 46,XX karyotype with a 22q11 deletion (Fig. 1). The parental karyotypings were normal. However, the mother was found to be a carrier of the deletion by FISH on lymphocytes in metaphase. She did not show unusual faces or known cardiac abnormality. The parents decided to terminate the pregnancy. The autopsy confirmed the diagnosis by fetal echocardiography, tetralogy of Fallot with normal appearing thymus.

Case 2

A 37-yr-old woman was referred for fetal echocardiography because of abnormal cardiac axis deviated to the left at fetal ultrasound screening. She had a normal female baby. Amniocentesis for fetal karyotyping was performed because of the old maternal age at 15 weeks of gestation at a local clinic. The result was normal. Fetal echocardiography at 21 weeks of gestation revealed tetralogy of Fallot with severe pulmonary stenosis. The fetal thymus was visible in front of the great arterial trunk. The parents decided to terminate the pregnancy. The FISH study from amniotic fluid drawn before termination revealed the 22q11 microdeletion. Autopsy was refused. Parents had normal karyotype without 22q11 deletion.

DISCUSSION

Chromosome 22q11 deletion causes a contiguous gene syndrome that includes DiGeorge syndrome (DGS) (4), velocardiofacial syndrome (VCFS) (2), and conotruncal anomaly face syndrome (CAFS) (3). Wilson et al. acronymed the common forms of defects associated with chromosome 22q11 deletion as CATCH 22 syndrome. The most severely affected patients have serious life threatening heart defects. The least severely affected patients have only mild facial anomalies and some developmental delay without cardiac defects (11). However, most of the patients with chromosome 22q11 microdeletion who have survived infancy were mildly to moderately retarded (12).

The estimated incidence of deletion of chromosome 22q11 is 1 in 4,000 live births (13). Cardiovascular abnormalities have been reported in 83% of those with 22q11 deletion (14). This condition is the second most frequent chromosomal anomaly associated with congenital heart disease, next to Down syndrome. Congenital heart defects characteristically involve the conotruncal region, tetralogy of Fallot (TOF), interrupted aortic arch, and truncus arteriosus being the most common lesion. TOF is the most common cyanotic congenital heart disease, occurring in approximately 10% of infants with congenital heart disease. The improvements in routine ultrasound techniques are expected to increase dramatically the number of cases with prenatally detected cardiac defects (15). Prenatal diagnosis of tetralogy of Fallot aids parental counseling and enables the early inhibition of optional treatment at a pediatric cardiac center, which may further improve treatment outcomes (16).

Chromosome 22 microdeletion occurs de novo in most cases, with only 8% being inherited (13). When one of the parents carries the deletion, either symptomatic or not, the fetus has a 50% risk of inheriting the abnormality. Thus, parental screening is necessary to identify the parents who have a 50% risk of affected offspring. For familial cases, prenatal genetic diagnosis should be offered. Preimplantation genetic diagnosis with in vitro fertilization can be considered to prevent termination of further affected pregnancy since FISH in a single cell has been a feasible method (17). Even though neither parent has the deletion, it is expected that there will be a low risk of having a further child with a 22q11 deletion since gonadal mosaicism (18) cannot be ruled out (6).

In a series of 17 nonsyndromic children with congenital conotruncal heart defects, five were found to have a 22q11 deletion (19). However, it is now well established that nearly all patients with the microdeletion exhibit subtle but typical facial features (20, 21). The prevalence of the 22q11 microdeletion in newborn infants with congenital conotruncal cardiac anomalies was reported to be about 48% (22). They suggested that FISH should be performed in newborn infants with conotruncal defect and at least one additional manifestation of the CATCH 22 phenotype. The prevalence of 22q11 deletion in tetralogy of Fallot patients was reported to be 13% (23). These data from postnatal studies are not applicable to prenatal diagnosis, since dysmorphic features may not be accessible to ultrasound survey and every conotruncal heart defect detected in the fetal period is potentially related to the 22q11 microdeletion. Very few data are available concerning the prognosis for fetuses diagnosed prenatally as having a 22q11 deletion. Prenatal diagnosis of 22q11 deletion was reported in a fetus with a known affected sister and father (24), in a fetus of a patient with the deletion and velocardiofacial syndrome (13), in a fetus of a mother with congenital heart disease (25), and in a fetus with interrupted aortic arch type B (26). The discovery of a conotruncal heart defect associated with a 22q11 deletion during pregnancy might indicate a severe form of this syndrome, which is known to show a great phenotypic variability.

Whether molecular cytogenetic studies should be offered when a conotruncal heart defect is diagnosed during fetal life remains controversial. Among the pregnancies with prenatally detected heart defect, about 11.5% of the cases have the deletion (5). According to the increasing awareness among obstetricians, echocardiographists and geneticists, one can predict that there will be a dramatic increase in demand for prenatal diagnosis of 22q11 deletion. Prenatal detection allows time for genetic counseling. It is also helpful in making choices and arrangements for delivery and postnatal surgical care, planning the immediate neonatal medical care, detecting other affected family members, and considering a cesarean section in case of fetal distress. These discussions and decisions are difficult when the diagnosis of a major anomaly requiring emergency care is established after birth.

These findings highlight the importance of performing FISH for suspected chromosome 22q11 deletion during pregnancy when ultrasound studies show a conotruncal cardiac anomaly. However, the counseling remains difficult in view of the clinical variability described in DGS, where the phenotype cannot be accurately predicted from the genotype. In our opinion, the knowledge of the fetal status with regard to the 22q11 microdeletion remains useful. It could help the decision making process of obstetricians, pediatric cardiologists, and surgeons in the perinatal period. In conclusion, prenatally detected tetralogy of Fallot may be considered for 22q11 microdeletion.

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