Prenatally diagnosed case of 22q11.2 deletion syndrome associated with pulmonary artery aneurysm

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Here, we report a new case with chromosome 22q11 deletion and cardiac anomaly diagnosed prenatally by echocardiography. Fluorescence in situ hybridization (FISH) analysis demonstrated a heterozygous deletion at 22q11.2. Echocardiography revealed ventricular septal defect, pulmonary atresia, and aneurysm of the main pulmonary artery and its branches. Pulmonary artery aneurysm (PAA) is rarely seen in patients with 22q11.2 deletion syndrome (22qDS). In this case, PAA was found by prenatal echocardiographic examination at the 25th week of gestation. To date, no prenatally diagnosed case of 22qDS with PAA has been reported. This is the first 22qDS case with PAA that was detected prenatally by FISH analysis.

Key words: prenatal diagnosis, 22q11.2 microdeletion, fetal echocardiography, congenital heart disease, DiGeorge syndrome, pulmonary artery aneurysm.

Congenital heart diseases are the most commonly seen fatal birth defects associated with chromosomal abnormalities, specifically with trisomy 21 and 22q11.2 microdeletion/ DiGeorge syndrome (DGS)[1,2]. The incidence of chromosomal abnormalities among fetuses with congenital heart diseases is between 22-54%[2]. Microdeletion of 22q11 is responsible for DGS, velocardiofacial syndrome (VCFS), congenital conotruncal heart defects, and related disorders[1-5]. The estimated incidence of deletion of chromosome 22q11 is 1 in 4,000 live births[2,3,6]. Chromosome 22 microdeletion occurs de novo in most cases, with only 8% of deletions being familial[3,7]. A large number of clinical findings have been reported in affected patients, including cardiac defects, characteristic facial features, thymic hypoplasia, cleft palate, hypoparathyroidism, learning difficulties, and psychiatric disorders[1,8]. We report a new case with congenital heart disease (ventricular septal defect, pulmonary atresia, aneurysm of the main pulmonary artery and its branches), in which microdeletion of chromosome 22q11 was diagnosed prenatally by fluorescence in situ hybridization (FISH).

Case Report

A 23-year-old woman gravida 1 para 0 was referred to our center at the 25th week of gestation because of ultrasonographic (USG) and fetal echocardiographic findings (Fig. 1). Prenatal screening tests were not performed because the family decided not to undergo prenatal screening. Fetal echocardiographic examination revealed ventricular septal defect, pulmonary atresia and aneurysm of the main pulmonary artery and its branches. Branches of the pulmonary artery were enlarged and pulmonary valve tissue could not be observed. Pulmonary valvular flow was increased (1.87 m/sn).

Obstetric USG examination revealed that the patient was at 25 weeks of gestation. Fetal biometric measurements were: femur length (FL): 41 mm (2.7%), humerus length (HL): 37 mm (<5%), and estimated fetal weight (EFW): 679 g (12.2%). According to fetal USG examination, micrognathia was noted. FISH analysis was performed to the interphase stage amniocyte cells directly. Locus-specific FISH probes for the DiGeorge region were used (Vysis, Abbott, USA) and a heterozygous deletion was detected at 22q11.2. We applied

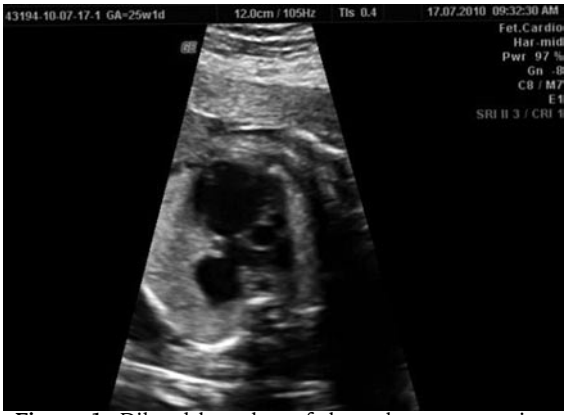

Figure 1. Dilated branches of the pulmonary arteries.

FISH to metaphase spreads and confirmed the previous interphase FISH results (Fig. 2). According to cytogenetic analysis, the fetus had a 46, XX normal karyotype. The family was informed about the 22q deletion syndrome phenotype, and after genetic counseling, decided to terminate this pregnancy. The family was informed about the familial inheritance of 22q deletion syndrome. FISH analysis of the parents was recommended to the family but was refused.

Discussion

The improvements in routine ultrasound techniques are expected to increase significantly the number of cases with prenatally detected cardiac defects[7,9,10]. Although there is no definite opinion for the prenatal diagnosis of 22q11.2 deletion, given the progress in USG techniques and increasing awareness of physicians about 22q11.2 deletion, there will be a dramatic increase in the demand for prenatal diagnosis[7]. Pregnancies at risk for the 22q11.2 deletion can be evaluated as two distinct groups: the first group is pregnancy with a family history of 22q11.2 deletion and the other group is pregnancy with abnormal fetal USG findings[7]. Several studies have shown that the indications for prenatal testing for the 22q11.2 deletion include a previous affected child with a 22q11.2 deletion or DGS/VCFS, an affected parent with a 22q11.2 deletion and in utero detection of a conotruncal cardiac defect. Fetal cardiac defects have been reported to be caused by a chromosomal anomaly at a rate of 20%[2,3]. The deletion is commonly found in patients with aortic arch malformation or an outflow tract malformation. Interrupted aortic arch is seen in 50-80% of patients and truncus arteriosus is seen in 35% of the patients[2,3]. Tetralogy of Fallot (15%), double-outlet right ventricle and transposition of great vessels are seen less frequently in patients with 22q11.2 deletion[2,3]. Pulmonary artery aneurysm (PAA) is a rare congenital cardiac malformation and can be congenital or acquired. Infections, Marfan syndrome, atherosclerosis, chronic pulmonary hypertension with or without congenital heart disease, and vasculitis can be considered as etiologic factors of PAA. Pulmonary artery anomalies are detected frequently in patients with chromosome 22q11 deletion, but only two cases with PAA have been reported to date in the literature[8]. The first observation was an autopsy case of a 46-day-old male infant with multiple dissecting PAAs distributed in both lungs and multiple jejunal atresias[9]. The other case was a male fetus (23 weeks of gestation) that had ductus Botalli atresia, PAA, ventricular septal defect, thymic hypoplasia, and dysmorphic face[9]. This pregnancy was terminated because of hydrops fetalis, and PAA was diagnosed on autopsy of this case[10]. To our knowledge, no prenatally diagnosed case of chromosome 22q11 deletion with PAA has been reported to date.

In addition to cardiac defects, anomalies such as cleft palate, polyhydramnios and renal or skeletal anomalies may raise the suspicion of a 22q11.2 deletion[2]. In our case, in addition to cardiac defects such as ventricular septal

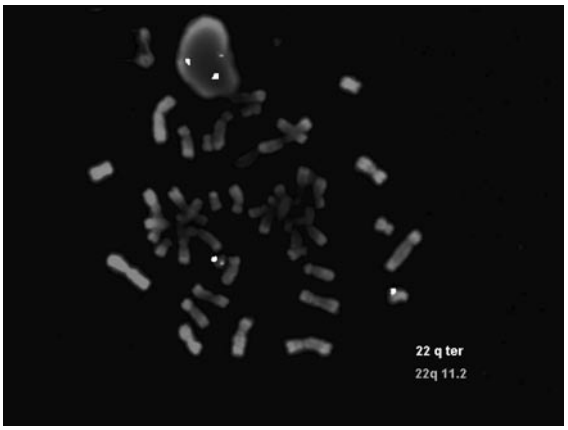

Figure 2. FISH analysis of the fetus showing 22q11.2 deletion. Red signals show 22q11.2 region and green signals show 22qter region as internal control. Heterozygous deletions can be seen on both metaphase and interphase.

defect, pulmonary atresia and aneurysm of the main pulmonary artery and its branches, micrognathia was also noted.

Among the pregnancies with prenatally detected heart defect, about 11.5% of the cases are reported to have 22q11.2 deletion[11,14]. Cardiac anomalies like ventricular septal defect and pulmonary atresia are important prenatal USG findings for DGS[15]. It has been reported that the decision for prenatal testing should be based on the finding of either a cardiac defect or two or more associated anomalies and family history[2]. Evaluation of the patients with 22q11.2 deletion by USG may reveal some anomalies. Although these anomalies are nonspecific findings, their combination with cardiac defect or other associated anomalies can support the presence of 22q11.2 deletion[2]. Several reports have recommended that 22q11.2 deletion by FISH analysis should be performed when fetal echocardiography shows the presence of cardiac defect[2,12]. USG and fetal echocardiography are not considered to be diagnostic tests, so they should be confirmed by FISH and cytogenetic analysis. The most appropriate method for detecting the 22q11.2 deletion is the FISH method[13]. Prenatal detection of 22q11 deletion is very important for genetic counseling. Early prenatal diagnosis is important for decision-making about the pregnancy and postnatal management and neonatal care. FISH is an efficient, quick and direct method for the detection of microdeletions and is widely used for the detection of 22q11 deletion.

Finally, this report presented a new prenatally diagnosed 22q11.2 deletion syndrome with fetal cardiac anomaly and aneurysm of the main pulmonary artery and its branches. This case emphasizes that a detailed USG examination has remarkable importance during early pregnancy to choose the specific genetic test as FISH analysis in addition to the routine cytogenetic tests for an early prenatal diagnosis. In this case, FISH analysis provided early detection of microdeletion at the Di George region of chromosome 22q from interphase stage amniotic cells.

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