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BRIEF COMMUNICATION

Familial 22q11.2 Deletion: Pregnancy Options and Management

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Abstract DiGeorge syndrome (DGS) is caused by a submicroscopic deletion on the long arm of chromosome 22 and affects approximately 1 in 4000 persons. This report describes a familial 22q11.2 deletion diagnosed during pregnancy using an emerging technology, Bacterial artificial chromosome on Beads (BoBs). We discuss the implications of prenatally detected DGS and future options to prevent the recurrence.

Keywords DiGeorge syndrome · Prenatal diagnosis · Prenatal BoBs

Introduction

DiGeorge syndrome (DGS) is caused by a 1.5–3 Mb hemizygous deletion in chromosome 22q11.2, spanning approximately 0.7–3 million base pairs [1]. Most cases of DGS are sporadic; however, in about 10% of the cases, the deletion is inherited in an autosomal dominant pattern where there is a 50% risk of getting an affected child in each pregnancy [2]. The phenotypic expression shows wide variability which will give less reason to suspect and test. Thus, familial cases of DGS may often be underestimated [3].

In the last few decades, different methods for the detection of this syndrome have been developed and include the array comparative genomic hybridization (aCGH), fluorescent in situ hybridization (FISH) and multiplex ligation-dependent probe amplification (MLPA) [4]. aCGH has the added benefit of detecting large or submicroscopic chromosomal deletions/duplications on all chromosomes in addition to the classic chromosome 22q11.2 deletion. If aCGH is not possible, a FISH or MLPA study can be requested [4]. In this report, we discuss a case of familial DGS in pregnancy and the utility of a relatively new technology, prenatal Bacterial artificial chromosome on Beads (BoBs) in the diagnosis of this syndrome.

Case Report

A 21-year-old primigravida, whose fetus was diagnosed with a congenital heart defect (CHD) at 22 weeks of gestation during the fetal anatomy scan, was referred for further management at 33 weeks of gestation. Fetal echocardiogram showed Tetralogy of Fallot (ToF) with pulmonary atresia and major aortopulmonary collaterals. When she delivered at term, the prenatal diagnosis of ToF was confirmed by postnatal echo. Genetic evaluation of the baby by FISH confirmed the 22q11.2 deletion (Fig. 1). However, the baby died on postnatal day 40 due to septicemia. Subsequently, a pedigree chart of the family was constructed (Fig. 2) and the parents were evaluated by FISH and the mother was detected to have the 22q11.2 deletion. In the following year, for her second pregnancy, prenatal invasive testing by chorionic villus sampling was done at 11 weeks of gestation and the presence of 22q11.2 microdeletion was detected using BoB's technique. At 16 weeks, the antenatal scan revealed fetal hydrops with bilateral pleural effusion and ascites and the pregnancy

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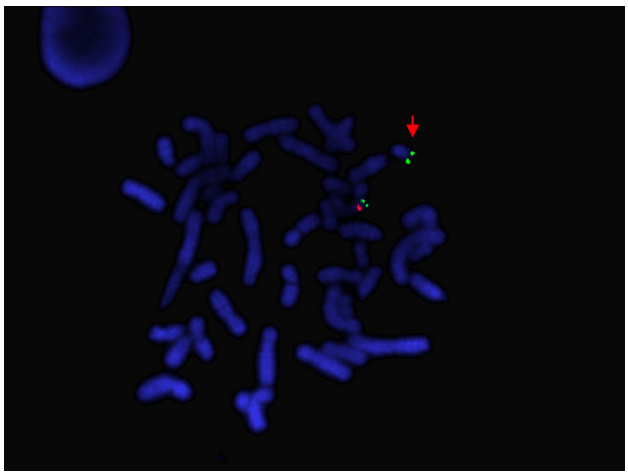

Fig. 1 Representative metaphase of the patient with the 22q11.2 deletion detected by FISH. The red signal indicates the 22q11.2 (*TUPLE1*) region and the green signal the terminal chromosome 22 (*ARSA*) control region. The arrow indicates the deleted chromosome 22, showing the presence of the control region only

ended in a miscarriage. There were no structural or functional cardiac problems detected in the 2D echocardiogram of the mother. Her facial features were normal besides a long face, broad nasal bridge and narrow palpebral fissures.

Discussion

DGS is one of the most clinically variable syndromes and atypical or mild clinical presentations may go unnoticed until adulthood [1]. In our case scenario, the proband had no clinical symptoms of DGS, other than subtle facial features. She received her diagnosis after the birth of a severely affected child, confirmed as 22q11.2 micro-deletion. Thus, it appears that the severity within a given family can range from asymptomatic individuals to severely affected children [5].

The syndrome can be detected prenatally, which is of a great importance for all preventive and therapeutic measures. Indications for prenatal testing include previous child with a 22q11.2 deletion, an affected parent with a 22q11.2 deletion or in utero detection of a fetus with a conotruncal cardiac defect. Our case had TOF, one of the common DGS associated CHD, which highlights the importance of fetal echocardiogram in the prenatal detection of this syndrome. A fetus at risk should undergo a level II ultrasound with fetal echocardiogram to evaluate for the following anomalies: congenital heart disease; airway, palate, swallowing, and gastrointestinal defects possibly leading to polyhydramnios (congenital diaphragmatic hernia, tracheoesophageal fistula, subglottic stenosis, vascular ring, laryngeal web, and cleft palate/cleft lip/palate); renal anomalies; skeletal differences such as club foot and craniosynostosis; and umbilical and inguinal hernia [6]. Vora et al. [7] support the notion that the level of suspicion for the 22q11.2 DGS should be very high if any one of the minor signs on USG (cleft lip/palate, polyhydramnios, intrauterine growth restriction, renal abnormalities, absent or hypoplastic thymus) is present along with a heart defect or in conjunction with cleft palate or polyhydramnios. This study has also demonstrated the utility of prenatal-BoBs in the rapid detection of DGS. This is a multiplex, bead-based suspension array using microspheres that are internally dyed with a combination of two spectrally distinct infrared and red fluorochromes, which can produce more than 100 specific spectrums. Each bead is coupled to DNA amplified from BACs and analyzed using a Luminex cytometric acquisition system with two separate lasers [8].

Counseling a couple who have a child with DGS depends on whether either parent has a deletion. If any one of the parent has a deletion, each subsequent child has a possibility of 50% inheritance of the deletion and having physical and developmental problems associated with this condition. One study that tested asymptomatic parents for the presence of the mutation; estimated that mutations are

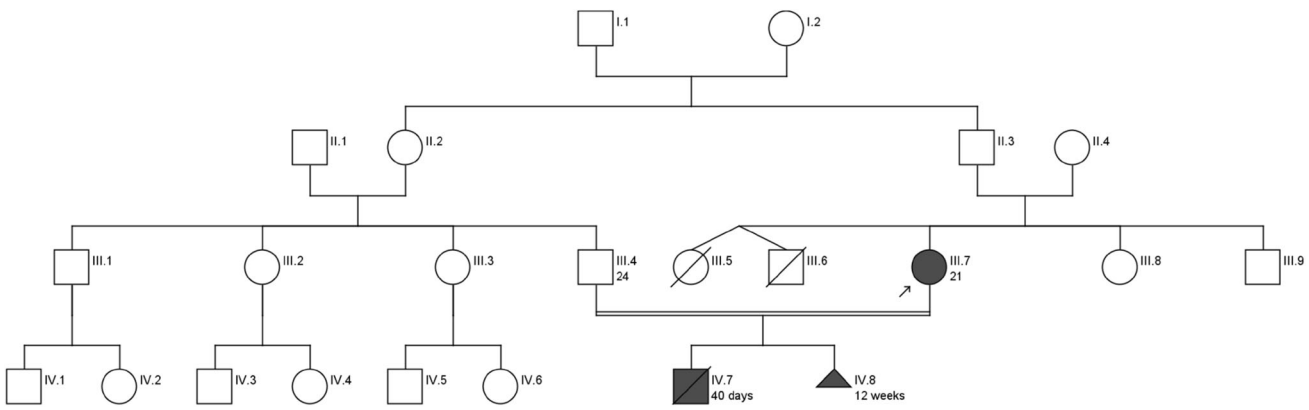

Fig. 2 Pedigree chart of the family

inherited from a parent are between 8 and 28% [9]. Thus, genetic counseling, evaluation of parents with an affected offspring, and the option of PGD/donor gametes using assisted reproductive technology will help the affected couples. We feel that counseling patients with this deletion to pursue PGD outweighs the risks and emotional stress, which is imposed by pregnancy terminations.

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