DIGEORGE SYNDROME – IMPORTANCE OF THE EARLY FETAL ANATOMY ASSESSMENT AND MULTIDISCIPLINARY WORK-UP IN PREGNATAL DIAGNOSIS. A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Objective: To report a first trimester (FT) suspicion of minor abnormality of great vessels with normal fetal heart. In the second trimester a 22q11.2 deletion syndrome was diagnosed. Extensive review of the literature is presented in relation to our findings. Case Report: A 26-year-old woman, gravida 9, para 0, was referred to our Prenatal Diagnostic Unit for the FT genetic, structural sonographic evaluation and genetic counselling. The ultrasound (US) revealed a singleton fetus with normal heart and right aortic arch (RAA) - left ductus arteriosus (LD), and no additional structural anomalies. The chorionic villus sampling was offered to the patient, but the parents declined the procedure and decided to undergo early second-trimester (ST) evaluation. The ST US confirmed the great vessels abnormality described in the late FT scan. Amniocentesis was performed. Conventional cytogenetic analysis of cultured amniocytes revealed a normal female karyotype 46, XX. Metaphase fluorescence in situ hybridization (FISH) analysis on cultured amniocytes confirmed the 22q11.2 deletion. After multidisciplinary counselling, the couple requested termination, and the institution ethics board approved the therapeutic medical termination of pregnancy. The conventional autopsy confirmed all antenatally suspected morphological abnormalities. Conclusion: The FT suspicion of congenital anomalies raise the operators’ awareness and has the potential to increase detection rates in the ST. The prenatal US finding of congenital heart/great vessels defects indicate a fetus with an increased risk for chromosomal abnormalities. Studies for 22q11 deletion syndrome should be considered an adjunct to conventional karyotyping. FISH analysis is a valuable test for the diagnosis of 22q11 deletion syndrome.

KEYWORDS: DiGeorge syndrome, prenatal diagnosis, right aortic arch, first trimester, anomaly scan.

INTRODUCTION

Chromosome 22q11.2 deletion syndrome occur in approximately one in 4000 live births, and it is the most common human deletion syndrome. It encompasses a wide spectrum of abnormalities including DiGeorge syndrome (DGS) (or velocardiofacial syndrome). Fetuses with 22q11.2 deletion syndrome may suffer from congenital heart diseases, palatal abnormalities, thymic hypoplasia, learning difficulties, immune deficiency, characteristic facial features, psychiatric disorders, and hypoparathyroidism. Individuals with this syndrome have an estimate high rate of 74% of congenital heart disease, including tetralogy of Fallot, ventricular septal defect, interrupted aortic arch, and truncus arteriosus.\textsuperscript{[1,2]} Chromosome 22 microdeletion occurs de novo in most cases (93%), familial occurrence being rare.\textsuperscript{[3,4]} The microdeletion at chromosome 22q11.2 can be detected by fluorescence in situ hybridization, multiplex ligation-dependent probe amplification (MLPA), or chromosomal microarray. Inheritance is autosomal dominant. The gene, TBX1, found within the deleted region, is thought to be responsible for many of the typical features including cardiac anomalies. Penetrance of the disorder is complete with marked variability in phenotype.

With the advent of US and molecular genetics technology, many cases with 22q11.2 deletion have been diagnosed in the prenatal period.\textsuperscript{[5-12]} We report a case with congenital heart disease (RAA-LD, vascular ring around the trachea and esophagus) in which microdeletion of chromosome 22q11 was diagnosed prenatally by fluorescence in situ hybridization (FISH). In this case report, the early diagnosis of DGS confirms...
the importance of interdisciplinary work-up in a prenatal diagnosis setting.

Also, the case underlines the importance of the early screening for heart and great vessels anomalies in late FT, increasing the chances for an early complete (US and genetic) ST diagnosis.

CASE PRESENTATION

A 26-year-old woman, gravida 9, para 0, was referred to our Prenatal Diagnostic Unit at the 12 week of amenorrhea (WA) for the FT genetic scan, extended structural US assessment, and genetic counselling. Her husband was 28 years old. The parents were healthy and non-consanguineous. There was no family history of congenital malformations. She denied any recent infections or exposure to teratogens during this pregnancy. The patient had seven FT spontaneous pregnancy losses, and a late ST miscarriage. Following the tests results for thrombophilia performed before pregnancy, the haematology department board decided the FT low molecular weight heparin therapy initiation. The common pregnancy FT tests’ results were within normal limits and the evolution of the pregnancy has been uneventful until presentation in the Unit.

Detailed two-dimensional (2D), three-dimensional (3D) and four-dimensional (4D) US examination was performed, using a Voluson 730 machine (GE Healthcare, Zipf, Austria) at 12+2 weeks of amenorrhea. The fetal assessment was particularly challenging especially due to the large body mass index (of 41). A combined approach technique was used, by means of transabdominal and transvaginal routes (see figures 1 and 2).

We found an apparently normal fetus, with a normal amount of amniotic fluid and normal movements. The crown-rump length (CRL) was consistent with menstrual dates (58.6 mm). The normal profile was demonstrated, with normal nuchal translucency (NT) of 1.5 mm, and the nasal bone was classified as hypoplastic (see fig. 1). The cardiac sweep was consistent with a structurally normal heart and RAA-LD (see fig. 2). Spatial-temporal image correlation (STIC) datasets were acquired, in order to better assess the spatial arrangement of great arteries (see fig. 3). A thorough search for associated anomalies was performed, because RAA detected in fetal life was frequently associated with other cardiac/non-cardiac malformations, as heterotaxy syndromes and microdeletions 22q11.

The genetic (mandatory and additional) markers and structural features were found as follows: the spectral Doppler interrogation showed no regurgitation at the site of the tricuspid valve and normal “a” wave at the site of Arantius ductus venousus; normal intracranial translucency, choroid plexus symmetry, anterior bony palate, orbits, surface rendering face, abdominal insertion of umbilical cord, situs, stomach image, diaphragm, spine, bilateral limbs, bladder, three-vessels cord, cervical length, uterine arteries pulsatility index. A particularly large yolk sac was found (see fig. 1).

The calculated genetic risk at combined test results was low (free beta - human chorionic gonadotrophin = 0.948 MoM, pregnancy-associated plasma protein A = 1.626 MoM). However, the chorionic villus sampling had been offered to the patient. Being aware of the limits of screening, and of the FT scan in particular, and considering the difficult medical history, the couple declined the invasive manoeuvre. They decided an expectant management, with an early ST follow-up scan. A cervical cerclage was performed at 14 weeks (due to history, the tendency of the internal os to open, and the positive cervix stress test) with an uneventful postoperative evolution (see fig. 4). After the ST confirmation of isolated RAA-LD (16 weeks) the couple decided to undergo the ST amniocentesis in our centre, at 17 WA. The fetal conventional karyotype on cultured amniocytes (G-banding) was normal. The FISH test for chromosome 22q11 deletion, as the standard method for diagnosis of DiGeorge syndrome (DGS) was performed and the specific 22q11 deletion was confirmed (see fig. 5).

Congenital heart defects are the major cause of decease, and the general prognosis in DGS depends on the extent of anomalies. However, the developmental delay and intellectual disability are common in DGS. Autism spectrum disorders and schizophrenia are frequent (20% and 25%, respectively), and other psychiatric issues are common (such as attention deficit disorder and anxiety). The couple was counselled by a multidisciplinary team (obstetrician, geneticist, paediatrician, cardiologist, psychologist and public health) on all aspects of the postnatal care. The family requested the termination of the pregnancy.

After the medical abortion, the intact fetus (see fig. 6) was obtained and a conventional autopsy confirmed the antenatal finding of isolated RAA-LD, with the vascular ring surrounding the trachea and esophagus, and the facial dysmorphism (see fig. 7-9).

Both parents were tested (by means of conventional G-banding and FISH test) and the results were normal. Thus, our conclusion was that the confirmed deletion was de novo, and the couple faces a low recurrence risk.
Figure 1: FT assessment (12+2 WA).

A: normal fetal profile (evaluated by transvaginal route, 5-9 MHz probe). The hypoplastic nasal bone is observed and a normal fronto-maxillary-facial angle is measured.

B: enlarged yolk sac.

Figure 2: Details of cardiac morphology (12+2 WA).

A: normal four-chamber view with normal insertion and off-setting of the atroventricular valves, highlighted by red arrows. B: normal equal inflows in the two ventricles in high-definition power Doppler investigation. C: instead of a normal „V sign” confluence of on the left side of the spine, a “U sign” confluence of the two arterial arches is identified, behind the trachea and on the right side of the spine, characteristic for RAA-LD.

Fig 3: Details of cardiac morphology (12+2 WA) in 4D STIC dataset postprocessing in surface rendering mode, after applying high-definition power Doppler. A: atro-ventricular inflows at the level of five chamber view. B: venricular outflows and the abnormal confluence of the arterial arches.
Fig 4: Transvaginal cervical assessment at 14 WA, before the cerclage procedure. The dehiscent internal os is evident, with a remaining cervical length of 13 mm. Also, thin sludge above the membranes is seen (at the level of the opened internal os).

Figure 5: FISH results in the presented case. This technique was used to identify the presence of specific chromosomes or chromosomal regions through hybridization (attachment) of fluorescently-labeled DNA probes to denatured chromosomal DNA. Examination under fluorescent lighting detects the presence of the hybridized fluorescent signal (and hence presence of the chromosome material) or absence of the hybridized fluorescent signal (and hence absence of the chromosome material). The images confirmed the 22q11 deletion.

Figure 6: The specimen assessment: profile and front view of craniofacial dismorphym in DGS. Main phenotypic features of patients with the 22q11.2 deletion syndrome may be observed: retrognathia/micrognathia, a long face, with high and broad nasal bridge, narrow palpebral fissure, asymmetrical crying face, downturned mouth, short philtrum, low-set ears, hypertelorism, and thin lips.
Figure 7: Images from the specimen conventional autopsy logbook: view from above (A) and lateral view (B). The vascular ring around the trachea and esophagus is present. Trachea is clamped in the forceps (A).

Figure 8: Image from the specimen conventional autopsy logbook. The right aortic arch location and branching. Normal head and neck vessels arising toward the cephalic extremity and the descending aorta lying in the right side of the thorax.

DISCUSSION

The incidence of DGS is 1 in 4000 to 1 in 6395 births, although this figure may be an underestimate. The incidence of chromosomal abnormalities among fetuses with congenital heart diseases is between 22-54%.\[^{13}\]

Although 22q11.2 deletion syndrome is usually characterized by multiple anomalies, the congenital heart disease being the most common, we report a particularly paucisymptomatic case in the prenatal period, having a normal heart and an isolated minor great vessels anomaly.

The improvements in routine US techniques are expected to increase significantly the number of cases with prenatally detected cardiac defects.\[^{11,17}\] Although there is no definite opinion for the prenatal diagnosis of 22q11.2 deletion, given the progress in US techniques and increasing awareness of physicians regarding 22q11.2 deletion syndrome appearance, there will probably be a dramatic increase in the demand for prenatal diagnosis.\[^{4}\] 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 US findings.\[^{4}\] Usually, anomalies such as cleft palate, polyhydramnios and renal or skeletal anomalies, in addition to cardiac defects, may raise the suspicion.\[^{13}\] In the case presented the patients had a negative family history and very few US features.

Prenatal US finding of congenital heart defects indicates that the fetuses are at increased risk for chromosome abnormalities. The 22q11 deletion is commonly found in patients with aortic arch malformation or an outflow tracts malformation. Interrupted aortic arch is seen in 50-80% of patients and truncus arteriosus is seen in 35% of the patients.\[^{3,13}\] Tetralogy of Fallot (15%), double-outlet
right ventricle and transposition of great vessels are seen less frequently in patients with 22q11.2 deletion.\[3,13]\n
The etiology of congenital heart defects diagnosed prenatally is still challenging to establish. Therefore, molecular and cytogenetic analysis for chromosomal abnormalities should be considered in these cases. Testing for chromosome 22q11.2 deletion is required especially in conotruncal heart defects.\[3,6,11,18]\n
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.\[3,13]\n
FISH analysis should be performed when fetal echocardiography shows the presence of cardiac defect.\[13,19]\n
US 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.\[20]\n
Prenatal detection of 22q11 deletion is very important for genetic counselling. 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 it is widely used for the detection of 22q11 deletion.

Children and adults with 22q11.2DS have high rates of behavioral, psychiatric, and communication disorders. In children, these include attention-deficit/hyperactivity disorder, anxiety, autism, and affective disorders. Adults have a high rate of psychotic disorders, particularly schizophrenia.

The first trimester (FT) cardiac scan started as a rank outsider for the prenatal care in the early years of the century.\[23]\n
The current guidelines still do not establish morphological protocols for the FT screening for congenital heart diseases (CHDs).\[20,25]\n
Yet, many recent reports provide proof that most of the major CHDs (MCHDs) may be identified in late FT.\[22-24]\n
Lower detection rates are achieved in isolated CHDs and in low-risk population, probably depending mainly on FT scan protocols. In our Unit such a high risk pregnancy is offered the extended genetic and anomaly scan, and the assessment of the fetal heart in early pregnancy is mandatory. In our view, if the approach would have been different, such a paucisymptomatic case, would have been easily missed. In our case, the 4D STIC acquisition and postprocessing was instrumental in confirming the FT abnormal spatial arrangement of the outflow tracts.

We previously showed that this technique is beneficial in confirming the most important landmarks of the FT normal heart.\[32]\n
Finally, this report presented a new prenatally diagnosed 22q11.2 deletion syndrome with fetal cardiac anomaly and the importance of a multidisciplinary approach in early prenatal diagnosis.

The case presented hereby emphasizes that a detailed US 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.

REFERENCES


