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Case Report

Rare and Complex Cardiac Anomalies Associated with 22q11.2 Deletion: An Ultrasonographic Visual Trip from Diagnosis until Delivery

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Abstract: The 22q11.2 deletion syndrome (22q11.2DS) is the most common chromosomal microdeletion disorder caused by hemizygous microdeletion of the long arm of chromosome 22. It is now known to have a heterogeneous presentation that includes multiple additional congenital anomalies and later-onset conditions, such as gastrointestinal and renal abnormalities, autoimmune disease, variable cognitive delays, behavioral phenotypes and psychiatric illness. The purpose of our paper is to present the case of a fetus diagnosed with a rare and complex cardiac malformation (interrupted aortic arch (IAA) type B, large malalignment-type ventricular septal defect (VSD), pulmonary valve dysplasia, aberrant right subclavian artery (ARSA). The result of the genetic testing revealed 22q11.2 deletion and after genetic counselling the patient decided to continue the pregnancy. She was regularly followed until delivery which took place in Germany so that neonatal cardiac surgery could be performed in an experienced center for cardiac malformations. We emphasize on the ultrasound aspects regarding the cardiac anomaly and specific features of 22q11.2DS in a continuous manner from diagnosis until delivery.

Keywords: interrupted aortic arch; 22q11.2DS; ultrasound; genetic tests

1. Introduction

Interrupted aortic arch (IAA) is a rare, severe form of congenital heart defect (CHD) characterized by complete anatomical discontinuity between two adjacent segments of the aortic arch [1]. IAA occurs in about 1% of CHD and is classified as type A, B and C based on the anatomic location of the interruption in relation to the brachiocephalic vessels, being rarely diagnosed in fetal series [2].

Although clinically under-recognized, 22q11.2DS is the most common microdeletion syndrome with an estimated prevalence of 1 in 4000 live births [3,4]. The first description in the English literature of the constellation of findings now known to be due to this chromosomal difference was made in the 1960s in children with DiGeorge syndrome, who presented with the clinical triad of immunodeficiency, hypoparathyroidism and congenital heart disease [5]. The phenotypic spectrum of the 22q11.2DS includes a wide variety of malformations and abnormalities occurring in different combinations and with widely differing severity [4].

In 20% of malformations of the outflow tract and IAA type B 22q11.2DS occurs and this association is significantly predicted by the presence of associated ultrasound findings: thymic hypo/aplasia, intrauterine growth restriction (IUGR) and additional aortic arch anomalies [6]. This shows that IAA type A and type B are distinct entities and while in IAA type B in more than 50% of cases 22q11.2DS may be expected, type A is not commonly associated with 22q11 hemizygosity [7].

Screening options for 22q11.2DS include noninvasive prenatal testing (NIPT) and imaging. NIPT has a 70-83% detection rate and a 40-50% positive predictive value and prenatal imaging, usually by ultrasound, aims to detect several physical features associated with the syndrome [8]. Definitive diagnosis is made by genetic testing of chorionic villi or amniocytes using a chromosomal microarray.

About 85-90% of 22q11.2 microdeletions arise as de novo events and, in contrast to trisomies, are not related to parental age. The 22q11.2 region of the human genome facilitates the potential for non-allelic unequal homologous crossover (recombination) during meiosis, which can result in microdeletions [8].

2. Case Report

We present the case of a 34-years old IGIP who obtained a spontaneous pregnancy while starting diagnostic work-up for infertility and was examined in our department for the second trimester anomaly scan. The first trimester anomaly scan was reported as normal and she had a low-risk NIPT result for trisomies 21, 18 and 13. Her medical and family history was uneventful. At 22 weeks the ultrasound differential diagnosis of CHD was made between severe aortic coarctation and tubular hypoplasia with VSD and IAA. A dilated pulmonary artery was also revealed. The fetal echocardiography performed by a pediatric cardiologist established the final diagnosis as IAA type B with VSD, pulmonary valve dysplasia and ARSA.

The four-chamber view showed a slightly ventricular disproportion with a narrow left ventricle when compared to the right ventricle, similar to findings in fetuses with aortic coarctation and the ventricular septal defect. The five-chamber view shows a VSD and a small descending aorta (Figure 1).

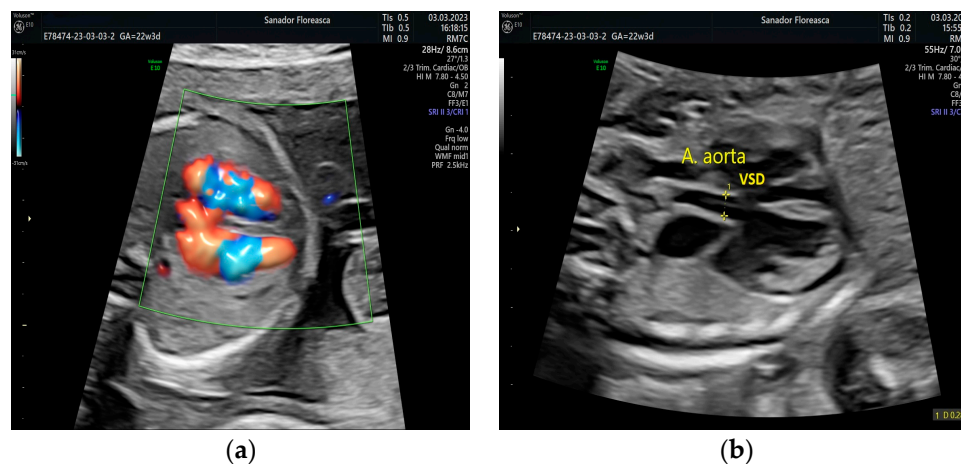


Figure 1. Four-chamber view in Color Doppler (a) and five-chamber view (b). The four-chamber view shows a slight ventricular disproportion and the VSD and the five-chamber view shows, in addition to the VSD, a small ascending aorta. VSD, ventricular septal defect.

The three-vessel-trachea view revealed one of the main diagnostic features of IAA which is the lack of continuity of the aortic arch; moreover, the trachea appeared in close proximity with the pulmonary artery because of the absence of the medially located aortic arch and the pulmonary trunk was dilated (Figure 2).

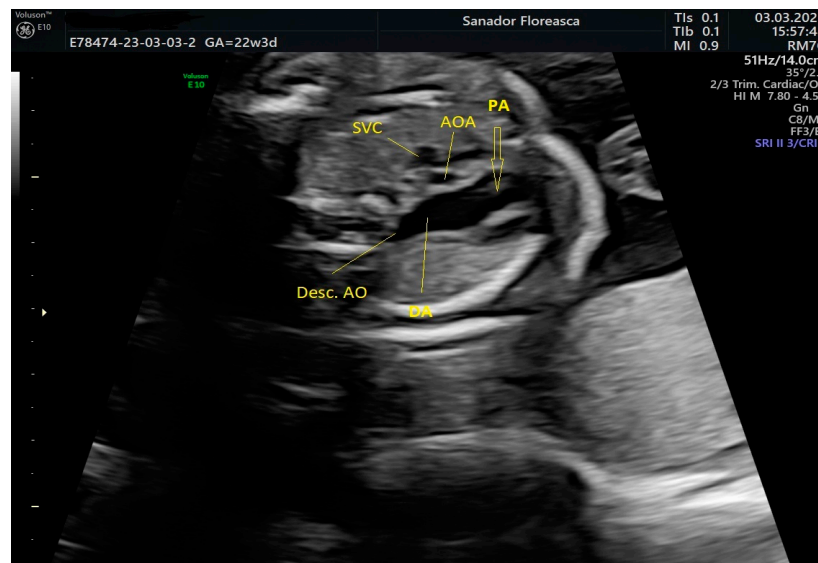


Figure 2. Three-vessel-trachea view. The continuity of the ascending aortic arch (AoA) toward a transverse aortic arch cannot be seen and the trachea is adjacent to the dilated pulmonary artery (PA) and ductus arteriosus (DA). PA, pulmonary artery; AoA, ascending aortic arch; SVC, superior vena cava; Desc AO, descending aorta; DA, ductus arteriosus.

The thymus appeared to be at least hypoplastic and, in consequence, the pulmonary artery was noted to be in close proximity to the sternum anteriorly (Figure 3). The thymic-to-thoracic ratio was 0.3.

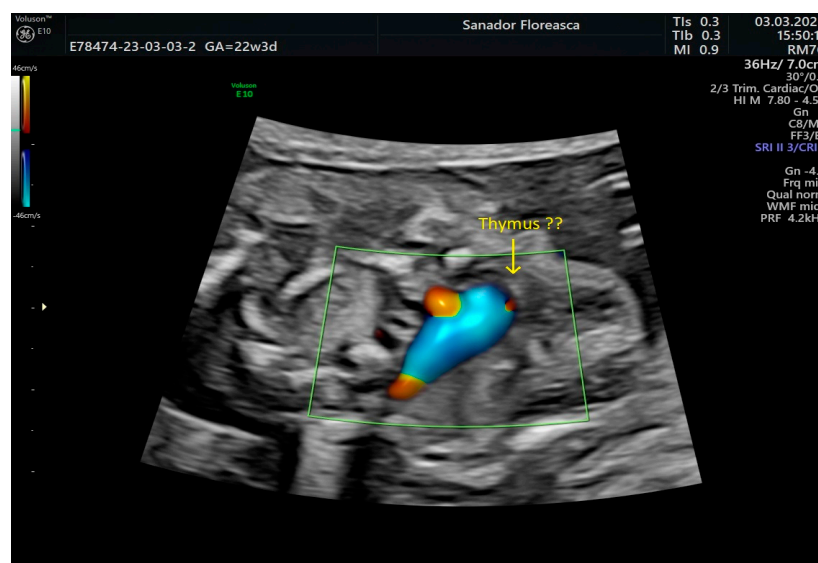


Figure 3. Three-vessel-trachea view in Color Doppler. Again, the continuity of the ascending aortic arch with the descending aorta cannot be demonstrated and the trachea is close to the dilated pulmonary artery. Note the presence of the hypoplastic thymus.

Invasive genetic testing revealed 22q11.2 microdeletion and genetic counselling was offered to the patient who decided to continue the pregnancy. She had regular follow-ups with ultrasound scans every 2-3 weeks to monitor fetal growth and condition and amniotic fluid volume.

In the second half of gestation, we observed an enlarged cavum septum pellucidum (CSP) and polyhydramnios. Extracardiac findings included typical facial features, such as a bulbous nose (Figure 4).



Figure 4. Fetal profile at different gestational ages showing the typical bulbous nose.

Although it is known that facial dysmorphism is typical in infants with this microdeletion, the prenatal ultrasound signs are not specific and can be subjective. The 3D reconstruction of fetal did not show any particular features throughout the gestation (Figure 5).



Figure 5. 3D reconstruction of fetal face at different gestational ages.

The patient delivered vaginally at 40 weeks in a tertiary center with immediate availability of pediatric cardiology services. The female newborn weighed 3420 g and measured 48 cm. After 7 days the baby underwent complex cardiac surgery and biventricular circulation was maintained. She

remained in the hospital under surveillance and the recovery was uneventful, so that after 2 weeks she was discharged.

At 7 weeks after birth the baby's evolution is favorable and she is undergoing follow-up in a multidisciplinary team (pediatrician, pediatric cardiologist, genetics specialist, family physician).

3. Discussion

Despite widely available genetic testing for nearly 30 years, 22q11.2DS remains under-diagnosed, in part due to its multisystem nature and variable severity of associated features [5,8,9]. Although common, lack of recognition of the condition and/ or lack of familiarity with genetic testing options, together with the wide variability of clinical presentation, delays diagnosis. Early diagnosis, preferably established prenatally could improve outcome and prognosis, thus stressing the importance of universal screening.

Significant progress has been made in understanding the complex molecular genetic etiology of 22q11.2DS underpinning the heterogeneity of clinical manifestations. The deletion is caused by chromosomal rearrangements in meiosis and is mediated by non-allelic homologous recombination events between low copy repeats or segmental duplications in the 22q11.2 region. A range of genetic modifiers and environmental factors, as well as the impact of hemizyosity on the remaining allele contribute to the intricate genotype-phenotype relationships [10].

For couples with no history of 22q11.2 microdeletion diagnosis in either parent, there are several possible routes to prenatal diagnostic testing that could identify a fetus with 22q11.2DS [8]. Although the diagnosis of this microdeletion has been traditionally based on the recognition of clinical features and cytogenetic testing using the fluorescence in situ hybridization (FISH) technique, poor clinical accuracy, the low confirmatory rate in the screening of suspected microdeletions and failure to detect other than the targeted microdeletion are the major drawbacks of this method [10]. So the golden standard method for detecting 22q11.2 microdeletions remains chromosomal microarray performed in invasively obtained prenatal samples, such as chorionic villi and amniotic fluid, as it was in our case.

A multicenter prospective observational study published recently evaluated the performance of single- nucleotide polymorphism (SNP)- based noninvasive prenatal testing (NIPT) for the 22q11.2 microdeletion in a large cohort of women. The results showed that noninvasive cell-free DNA prenatal screening can detect most affected cases, including smaller nested deletions, with a low false positive rate[11]. Other studies revealed also that prenatal screening for 22q11.2 deletion has become clinically feasible[12,13].

The most frequent association is made between 22q11.2DS and congenital heart disease and cleft palate [14]; moreover, cardiac anomalies reported include conotruncal anomalies such as interrupted aortic arch, common arterial trunk, absent pulmonary valve syndrome, pulmonary atresia with VSD, tetralogy of Fallot and conoventricular septal defects [15,16]. The presence of a right aortic arch, an aberrant right subclavian artery, especially in combination with a cardiac anomaly, a hypoplastic thymus or other extracardiac anomalies increases the risk for deletion of 22q11.2 [17,18].

We bring into discussion the case of a newborn with 22q11.2DS diagnosed prenatally with a complex cardiac anomaly who required postnatally major surgical repair in a tertiary center for pediatric cardiology. Our aim was to call attention to the paramount importance of a correct prenatal diagnosis which allows counselling of the patient, offering genetic testing and managing the case further in a multidisciplinary team.

In our case the final fetal cardiologic diagnosis was IAA type B with a large VSD, pulmonary valve dysplasia and ARSA. IAA is a rare form of critical neonatal heart disease and in the absence of prenatal diagnosis patients with IAA present in shock when the patent ductus arteriosus closes; thus, initiation of prostaglandin E1 infusion allows for adequate lower body perfusion prior to surgical repair [19]. As a result of accurate prenatal diagnosis our patient was admitted to a tertiary pediatric cardiology unit where the surgical intervention was performed successfully.

It is rare for patients with isolated IAA to survive to adulthood without operation; still, cases of isolated IAA diagnosed using CT angiography have been reported in literature [20–23]. In a

retrospective study published by Jiang et al. it was observed that in these cases the patients had extensive collateral vessels joining the descending aorta. Anti-hypertensive medical management with long-term follow-up appears to be a reasonable treatment option for these patients, although surgical intervention is a good choice [20]. This is not applicable in our case report considering that the fetus was diagnosed with complex IAA and also a genetic syndrome, thus warranting immediate surgical correction.

The age of the newborn to undergo the operation was in our case 7 days, which is consistent to the study reported by Onalan et al. [24]. Yet, 38% of their patients required reintervention due to aortic arch restenosis during the follow-up period. Preoperative aortic root size is a predictive factor for postoperative left ventricular outflow tract obstruction after single-stage repair of IAA with VSD [25]; if we take into consideration the cut-off value of 6.5 mm for the aortic root size our patient falls into the high-risk group and will require a close follow-up in order to promptly identify progressive obstruction.

Furthermore, a case of middle cerebral artery aneurysm rupture occurring at 2 weeks after undergoing congenital heart anomaly repair in a neonate with IAA has been published [26]. Also, another unusual complication following cardiac surgery for IAA was reported in an 8-year-old patient: giant aortic arch aneurysm [27], pointing to the fact that an extended period of follow-up is essential.

As expected, our patient had an association between 22q11.2DS and IAA type B, whereas IAA type A is found rarely in combination with this genetic deletion [28–30]; Paolo Volpe's study confirms that IAA type B is usually syndromic (66.7% of the cases analyzed were associated with 22q11.2DS), this suggesting that IAA type A and type B could be two separate pathogenetic entities [1]. One possible explanation might lie in the disparate embryological origin of the different segments composing the aortic arch.

5. Conclusions

22q11.2DS is quintessentially a multi-system syndrome with a remarkable variability in the severity and extent of expression in individuals, even in affected members of the same family [3]. In consequence, treatment must be targeted to best suit the individual, age or developmental stage and the particular constellation of associated features, severity and need for treatment.

We presented in this paper an interesting case of prenatally diagnosed 22q11.2DS in a fetus with severe and complex cardiac anomalies and other syndromic ultrasound features (enlarged CSP, hypoplastic thymus, bulbous nose, polyhydramnios). We emphasize the importance of early diagnosis and increased awareness of prenatal extended screening which provides the best opportunity for affecting the course of the illness and optimizing outcomes.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Video S1: Characteristic appearance of IAA, VSD, dilated pulmonary artery, ARSA and severe thymus hypoplasia.

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