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Case report

Velocardiofacial syndrome with complex congenital heart disease

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Abstract

Velocardiofacial syndrome, or DiGeorge syndrome, is characterized by an association of congenital heart defects, facial anomalies, thymus hypoplasia, hypocalcaemia, and cleft palate. The most prevalent cardiac anomalies in this association are tetralogy of Fallot, pulmonary atresia with ventricular septal defect, double-outlet right ventricle, and truncus arteriosus.

The aim of this paper is to report a case of velocardiofacial syndrome associated with complex heart disease (pulmonary atresia with ventricular septal defect) and demonstrate the importance of the suspicion of this genetic syndrome when facial anomalies are present in the physical examination.

This is the case of a full-term newborn who presented central cyanosis with 74% oxygen saturation and heart murmur at 21 hours of life. A cyanogenic heart disease (pulmonary atresia with ventricular septal defect) was identified on performing cardiological evaluation. At follow-up, this genetic syndrome was suspected due to the presence of hypertelorism, thin lips, and prominent forehead. Consequently, the diagnosis was confirmed by fluorescence in-situ hybridization.

DiGeorge syndrome may be associated with heart diseases; of which, the cyanogenic group of heart diseases is more prevalent. Their identification is essential, and it may have a negative impact on the evolution of the case.

Key words: velocardiofacial syndrome, congenital heart diseases, hypoxaemia.

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Introduction

Three types of the so-called "CATCH-22" phenotypes (a mnemonic derived from **c**ardiac abnormalities, **a**bnormal face, **t**hymus aplasia, **c**left palate, and **h**ypocalcaemia plus chromosome number 22) can be observed in patients with 22q11 deletion – 1) patients with Takao syndrome in whom cardiovascular changes are predominant; 2) those with DiGeorge syndrome in which hypocalcaemia and T lymphocyte deficiency (thymus hypoplasia/aplasia) predominate; and 3) those with Shprintzen syndrome in which the dominant phenotypic characteristic is a nasal voice related to palate defects [1]. Shprintzen syndrome or velocardiofacial syndrome (VCFS) is caused by the loss of a submicroscopic segment of DNA in the 22q11.2 region. This loss also occurs in patients with DiGeorge syndrome. Most cases are a new expression in the patient's family, but there may be inherited cases. These phenotypes have a prevalence of 1 case in 2000-5000 live births [2, 3]. They include a broad spectrum of presentations, which often makes early diagnosis

difficult, and they can be confused with the clinical diagnosis of DiGeorge syndrome (heterogenicity). The signs found include facial dysmorphia, aplasia, hypoplasia of the thymus, hypoparathyroidism, renal anomalies, palatine abnormalities, learning disabilities, and congenital heart diseases (CHDs). The most prevalent CHDs occur in the conus arteriosus and are hence called conotruncal. They include tetralogy of Fallot, pulmonary atresia with ventricular septal defect (VSD), double-outlet right ventricle, and truncus arteriosus [4].

Conotruncal and outflow cardiac defects can be prenatally diagnosed by ultrasonography (US). However, the evaluation of outflow tracts should be added to the 4-chamber view during routine US cardiac screening. The measurement of the thymic-thoracic ratio (TT-ratio) is a feasible and useful tool in fetuses with cardiac defects associated with CATCH-22q11delections (facial abnormalities, absent or hypoplastic thymus, cardiac defects and hypocalcaemia) [5]. The antenatal diagnosis may enable delivery planning strategies for fetuses with CHD, especially fetuses who will need to undergo an invasive cardiologic treatment or a cardiologic surgery within the first hours of postnatal life [6].

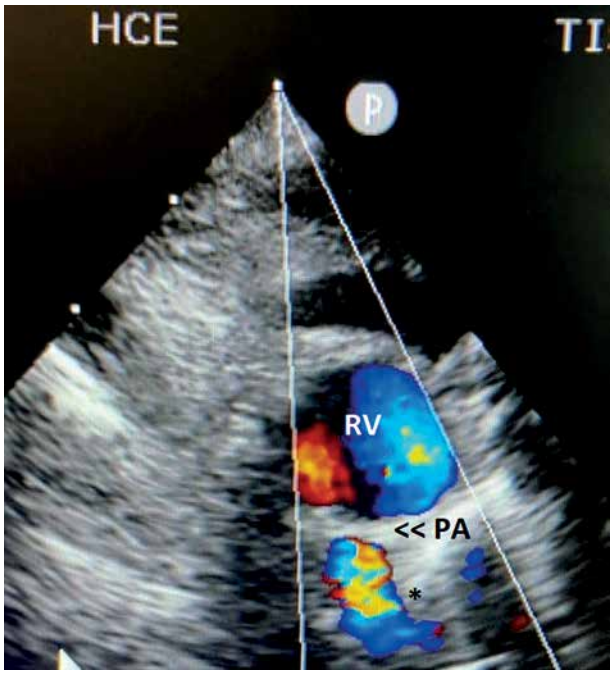

Figure 1. Transthoracic echocardiogram shows a large VSD at the 4-chamber view and the atresia of the pulmonary valve with the absence of the anterograde flow in the PA (parasternal short axis)

RV – right ventricle, PA – pulmonary artery.

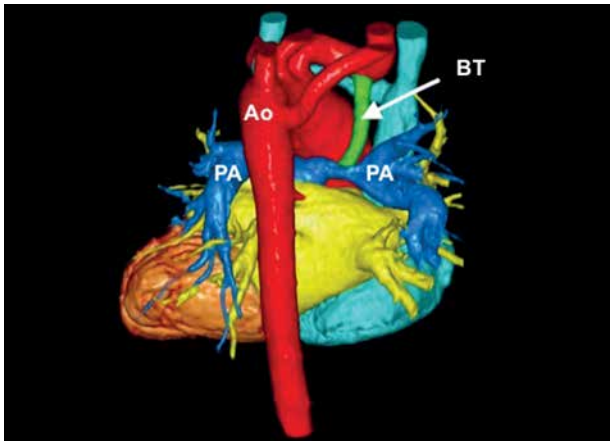

Figure 2. 3D reconstructed computed tomography angiography (CTA) shows the presence of the pulmonary arteries confluence and the Blalock-Taussig shunt (systemic-pulmonary anastomosis) (Courtesy of Prof. Aurea L. de A. Grippa de Souza)

Ao – aorta, PA – pulmonary artery, BT – Blalock-Taussig shunt.

Case description

The case patient was a full-term newborn female born via vaginal delivery having an Apgar score of 8/9, a gestational age of (Capurro) 38 weeks and 2 days, and birth weight of 2510 g (gestational history: maternal age 18 years, $G_2P_2A_0$, antenatal tests without changes). A morphological ultrasound was performed, which did not show signs of CHD, and the pregnant women was not referred to perform fetal echocardiography (low-risk mother). The newborn presented significant central cyanosis at 21 hours of life, with a systolic murmur of 4 ±6, oxygen saturation of 74%, respiratory rate of 56 breaths per minute, heart rate of 147 bpm, and blood pressure of 84/10 mm Hg. She was then transferred to the neonatal intensive care unit, and prostaglandin E2 was administered intravenously for patent ductus arteriosus maintenance. An echocardiogram was performed, which identified a cyanogenic CHD: pulmonary atresia with VSD. The right ventricle size was normal, and patent ductus arteriosus was observed (Figure 1). A chest X-ray was performed, which showed a borderline-sized cardiac area with an excavated medial arch and reduced pulmonary flow.

On the 7th day of life, the patient underwent palliative heart surgery with aortopulmonary anastomosis (Blalock–Taussig shunt) at the Brazilian Army Central Hospital (HCE) in Rio de Janeiro, Brazil (the hospital where she was born). However, performing surgical ligation of the ductus arteriosus was not possible.

The patient presented good evolution in the postoperative period, and the echocardiogram showed a functioning aortopulmonary anastomosis with good flow. Ventricular function was normal. Furthermore, the ductus arteriosus was patent, measuring 3 mm. The patient was discharged and prescribed aspirin (10 mg/kg/day) and furosemide (1.5 mg/kg/day). During outpatient follow-up, the patient was referred for genetic evaluation due to the presence of hypertelorism, thin lips, and prominent forehead. Consequently, the suspected clinical diagnosis of VCFS was confirmed via fluorescent in-situ hybridization (FISH). Computed tomography angiography (CTA) imaging was performed to schedule the corrective surgery (Rastelli procedure). It showed confluent pulmonary arteries with normal diameters (Figure 2, 🎥). The patient underwent the Rastelli procedure (closure of the VSD and placement of a tube containing a valve to direct the blood of the right ventricle to the main pulmonary artery) at 25 months of age, without complications. She is currently stable and under observation via outpatient follow-up.

Discussion

Heart diseases are the most common congenital malformations, and as per the literature, their incidence is between 0.5% and 2% of all live births, depending on the population studied [1-3]. Conotruncal congenital heart diseases are characterized by abnormalities of the great vessels and represent 25-30% of all CHDs. The most prevalent abnormalities are tetralogy of Fallot, transposition of the great arteries, pulmonary atresia with interventricular septal defect, and double-outlet right ventricle [2]. The literature reports an association of these anomalies with gestational diabetes and maternal exposure to teratogenic agents such as alcohol, rodenticides, and herbicides [7]. Conotruncal heart diseases are also associated with genetic syndromes (8%) and extracardiac anomalies (< 10%). The syndromes that are most frequently associated with tetralogy of Fallot, pulmonary atresia with interventricular septal defect, and double-outlet right ventricle are DiGeorge syndrome/velocardiofacial syndrome/CATCH-22/deletion of 22q11* and VATER, CHARGE, Alagille, cat-eye, and Down syndromes [8].

Assef et al. [9] recently studied a group of 4050 paediatric patients and found that tetralogy of Fallot was the most common cyanogenic CHD (approximately 5.2%), followed by the transposition of the great arteries, pulmonary atresia with VSD, and truncus arteriosus (1.3%, 0.62%, and 0.25%, respectively). Liu et al. conducted a systematic review and meta-analysis on the prevalence of CHD, which included 260 studies. Those authors also found a low prevalence of pulmonary atresia (1.3%), but the study did not provide details on the presence or absence of VSD [10].

The main anatomical feature of this CHD encompasses pulmonary valve atresia, which when associated with infundibular atresia represents the most severe forms in 70% of the cases. Pulmonary valve atresia (PA) can be found in rare instances due to the existence of only one imperforated membrane. The main pulmonary artery may be present and of reasonable size or markedly hypoplastic, the latter being more common. Another classic anatomical aspect of this CHD in association with VCFS, as in the case reported, is the association of PA with multiple collateral arteries that originate mainly from the descending aorta, subclavian arteries, or more rarely from the coronary arteries (Figure 3). The role of this network of collateral arteries is to provide better pulmonary blood supply.

A right-positioned aortic arch and defects of pulmonary branching (discontinuity between the pulmonary arteries, with pulmonary flow supplementation due to systemic–pulmonary collateral circulation) are prevalent findings in 22q11 deletion, and they have been described in several studies [11-13]. Marino et al. described the spectrum of the most prevalent cardiac malformations (anomalies of the aortic arch, pulmonary arteries, and pulmonary flow supplementation and defects of the infundibular septum and semilunar valves) in 88 patients with 22q.11 deletion [11]. Momma et al. [13] studied 49 patients with 22q11 deletion; of whom 23 had pulmonary atresia with VSD. Additional cardiac defects were demonstrated in that study, with a negative impact on the evolution of these cases. The identified cardiac anomalies were as follows: right-positioned aortic arch (70%), aberrant left subclavian artery (35%), absence of ductus arteriosus (83%), presence of aortopulmonary collateral arteries (91%), and absence of pulmonary arteries confluence (48%).

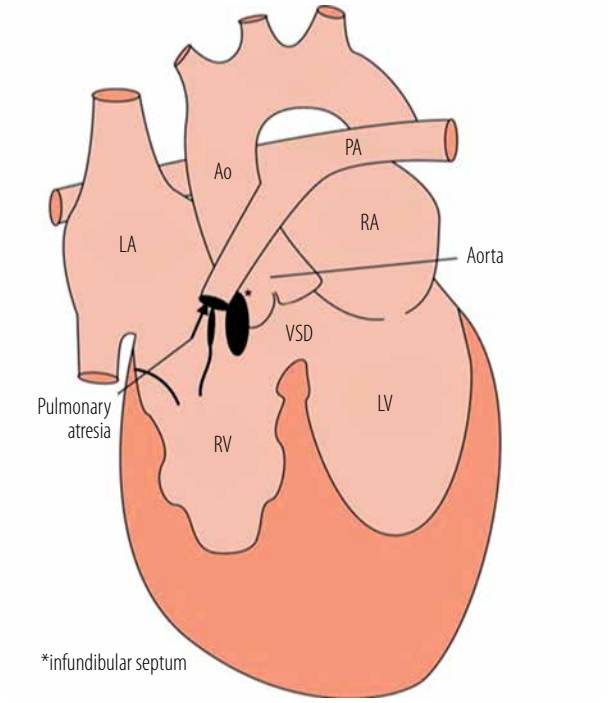

Figure 3. Schematic representation of pulmonary atresia with ventricular septal defect and nonconfluent pulmonary arteries with pulmonary circulation supplemented by collateral vessels

LA – left atrium, RA – right atrium, VSD – ventricular septal defect, RV – right ventricle, LV – left ventricle, Ao – aorta, PA – pulmonary artery.

The classic clinical sign of pulmonary atresia with VSD in the neonatal period is hypoxaemia, which can be identified early using the neonatal pulse oximetry test. Murmurs are detected during cardiac auscultation due to associated lesions (patent ductus arteriosus and aortopulmonary collateral arteries). Chest X-rays usually demonstrate severely reduced pulmonary flow and an excavated middle arch. In some examinations, agenesis of the thymus may be suspected because this is a common finding in DiGeorge syndrome. Echocardiography enables the confirmation of CHD by the absence of anterograde flow through the pulmonary valve (pulmonary atresia) associated with a large VSD. A laterally positioned aortic arch, the presence of a patent ductus arteriosus or collateral vessels, and confluence or nonconfluence of the pulmonary arteries can be identified using echocardiography. The computed tomography pulmonary angiogram or cardiac catheterization may be required for detailing the pulmonary vascular anatomy.

In conotruncal anomalies, the 4-chamber view is expected to be normal. Therefore, the evaluation of the ventricular outflow views should be added to the 4-chamber view in order to enable this diagnosis in utero [5]. Fetal position and maternal characteristics may affect the prenatal diagnosis of the CHD during the routine US cardiac screening such in the current case. No fetal echocardiogram was performed due to this being a low-risk pregnancy. Because the patient was born in a hospi-

tal with paediatric cardiologists, neonatologists, and a cardiac surgery team, her postnatal outcome could be optimized.

Furthermore, the assessment of the thymus is important to detect cardiac defects associated with the CATCH-22q11 deletions. DiGeorge syndrome may also be suspected in utero when hypoplasia or agenesis of the thymus can be observed through ultrasound after a diagnosis of conotruncal CHD. The thymus can be visualized in the front of the 3 vessels as a less echogenic structure, and the measurement of the thymic-thoracic ratio (TT-ratio) is a feasible and useful tool to assess the absence or thymus hypoplasia [5]. Therefore, prenatal genetic diagnosis is highly recommended when these anomalies are found in association with polyhydramnios and extracardiac malformations such as cleft palate, lip vertebral anomalies, and polydactyly or when there is a family history of 22q.11 deletion [14]. In the postnatal examination of patients with DiGeorge syndrome, hypoplasia or agenesis of the thymus, in addition to cardiac and extracardiac malformations, can be observed on chest X-rays. Moreover, G-band karyotyping does not detect the deletion. This chromosomal abnormality can be detected in heterozygous cases via quantitative polymerase chain reaction (qPCR) or FISH analysis [15].

Because pulmonary atresia with VSD has a wide spectrum of presentations, clinical conduct must be individualized for each case. In newborns with ductus arteriosus-dependent pulmonary circulation, intravenous prostaglandin E1 should be administered while awaiting palliative surgery (systemic-pulmonary shunt). The modified Blalock-Taussig shunt using a Gore-Tex tube promotes anastomosis of the subclavian artery into the pulmonary artery.

Newborns with an extensive network of collateral arteries may have heart failure symptoms due to increased pulmonary flow. Thus, anticongestive therapy is indicated in such cases, and the surgical interruption of collateral vessels supplying pulmonary segments may be required.

The case reported herein had a favourable anatomy that allowed the closure of VSD and placement of a tube connecting the right ventricle with the pulmonary artery (Rastelli procedure). In complex cases with nonconfluent pulmonary arteries and multiple collateral vessels, the unifocalization of these arteries and reconstruction of the pulmonary circulation may require several surgical procedures [16].

Conclusions

In conclusion, this report describes a case of pulmonary atresia with VSD associated with the presence of facial dysmorphia, hypertelorism, thin lips, and prominent forehead. We emphasize the importance of clinical suspicion in the diagnosis of velocardiofacial syndrome in these cases and their frequent association with systemic-pulmonary collateral vessels, which can have a great impact on the prognosis of surgical correction due to the complexity of pulmonary circulation.

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Conflict of interest

The authors declare no conflict of interest.

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