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PULMONARY ARTERY ATRESIA WITH THORACIC AORTIC COLLATERALS IN A PATIENT WITH 22Q11.2 DELETION SYNDROME

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Abstract: Introduction Pulmonary atresia with aortopulmonary collaterals is a rare congenital heart disease that may be associated with 22q11.2 deletion syndrome (DiGeorge syndrome), a chromosomal microdeletion with high phenotypic variability. Case report: We describe a female patient, the product of the first pregnancy of a mother with a history of thyroid cancer, bariatric surgery, and gestational diabetes. Prenatal diagnosis revealed tetralogy of Fallot with pulmonary atresia and aortopulmonary collaterals. At birth, she presented with micrognathia and cleft palate. Postnatal studies confirmed pulmonary atresia with non-confluent branches and pulmonary flow dependent on aortic collaterals. The karyotype showed a balanced translocation t(4;6)(q28;p25), and CGH-array analysis confirmed the 22q11.2 deletion. The patient developed infectious complications and required prolonged ventilatory support, subsequently being discharged with outpatient management and a palliative approach. Discussion: 22q11.2 deletion syndrome, which is autosomal dominant and has an estimated prevalence of between 1/2000 and 1/6395 live births, is associated with conotruncal heart defects, hypocalcemia, and cellular immunodeficiency. Balanced translocations, although phenotypically silent, may predispose offspring to unbalanced deletions. The combination of pulmonary atresia and aortic collaterals is more common in patients with 22q11.2 deletion. Conclusion: Timely genetic diagnosis is essential for comprehensive management and reproductive counseling of families, given the risk of recurrence and the clinical complexity of DiGeorge syndrome.

Keywords: Congenital heart disease, Translocation, Aneuploidy, Pulmonary atresia

Introduction

Congenital heart disease is a heart abnormality present at birth that can affect the structure or function of the heart. A rare form of this condition is pulmonary atresia, characterized by the absence or severe narrowing of the pulmonary valve, which causes obstruction of blood flow to the lungs . In addition, chromosomal translocation is a genetic disorder in which fragments of one chromosome fuse with other chromosomes.

In this case report, we describe a patient born to a mother with a history of thyroid cancer and bariatric surgery during her first pregnancy. Prenatal studies revealed several cardiac abnormalities, including pulmonary atresia, aortopulmonary collaterals, and a large ventricular septal defect. In addition, a 22q11.2 deletion syndrome associated with a balanced chromosomal translocation involving chromosomes 4 and 6 was identified.

The estimated prevalence of 22q11.2 deletion syndrome ranges from 1 in 2,000 to 6,395 live births, but this may be an underestimate due to underdiagnosis prior to the availability of confirmatory testing (1).

The characteristic phenotypic triad of 22q11.2 deletion, known as DiGeorge syndrome (DGS), is defined by conotruncal cardiac anomalies, hypocalcemia due to hypoparathyroidism, and T-cell deficiency due to thymic hypoplasia (3).

Case report:

Patient from the first pregnancy of a 31-year-old mother, with negative serology during pregnancy and 13 high-risk prenatal consultations due to a positive culture for group B streptococcus and a history of thyroid cancer and bariatric surgery. She also had diet-controlled gestational diabetes mellitus. Prenatal morphological ultrasounds identified tetralogy of Fallot with fetal pulmonary atresia. The results of the fetal echocardiograms were as follows:

- **May 11, 2022 (26 weeks):** Heart rate of 144 bpm, tetralogy of Fallot with pulmonary atresia, presence of aortic ride without visualization of the pulmonary artery outlet. In the three-vessel view, a 2.9 mm vessel was observed to the left of the aorta (pulmonary trunk) with reverse flow.
- **08/01/2022:** The pulmonary valve and pulmonary branches were not visualized. The study was hampered by gestational age and fetal statics. It was a duct-dependent heart defect, requiring further evaluation by cardiology after birth to determine the presence of the pulmonary artery.

A cesarean section was performed due to fetal heart disease. The female patient was born on 08/08/2022, with an APGAR score of 8/9 and respiratory distress requiring CPAP at 21%. Physical examination of the newborn revealed micrognathia and cleft palate, with the rest being normal. It was decided to transfer her to the neonatal intensive care unit for further management.

During hospitalization in the neonatal ICU of a referral center in Curitiba, Paraná, Brazil, several studies were performed as part of the malformation protocol, including:

- Normal abdominal ultrasound
- Normal ultrasound of the kidneys and urinary tract

- Transfontanellar ultrasound with grade I germinal matrix hemorrhage
- Transthoracic echocardiogram: Pulmonary atresia with non-visible pulmonary trunk, probably non-confluent branches; presence of systemic pulmonary collaterals originating in the thoracic aorta; preserved ventricular function, pulmonary flow maintained through collateral branches from the thoracic aorta with signs of restriction; wide interventricular communication (IVC)
- Chest angiotomography: Right aortic arch. The pulmonary artery trunk was not identified in this examination.
- Left heart catheterization: Pulmonary atresia with VSD and collaterals in the thoracic aorta. Pulmonary flow was maintained through collaterals from the thoracic aorta.
- Karyotype: 46, XX, t(4;6) (q28;p25), balanced translocation between the long arm of chromosome 4 and the short arm of chromosome 6 observed in all cells.
- CGH-ARRAY for analysis of chromosomal abnormalities: 22q11.2 deletion syndrome
- Bronchoscopy: Acute post-extubation laryngitis; extrinsic pulsatile compression of the lower right third of the trachea; acute traumatic injury to the main carina.

The patient required multiple courses of antibiotics for healthcare-associated pneumonia, bloodstream infection, sepsis, and multiple transfusions for refractory anemia. There were two extubation failures after 66 days of mechanical ventilation, maintaining a good respiratory pattern with baseline saturation between 75-85% in ambient air.

Evaluation by pediatric palliative care in conjunction with pediatric cardiology

Patient with severe, progressive, and incurable heart disease, with no indication for surgery at this time. She was discharged after 118 days of hospitalization, on room air, with outpatient follow-up by speech therapy, ph r physical therapy, high-risk childcare, pediatric palliative care, pediatric pulmonology, pediatric neurology, and pediatric cardiology.

Discussion

The patient, with a maternal history of thyroid cancer, gestational diabetes, and bariatric surgery, presented with a heterozygous 22q11.2 deletion of approximately 2.1 Mb covering 43 coding genes, associated with a balanced translocation between heterologous chromosomes of groups B and C t(4;6).

The frequency of reciprocal translocation carriers in the newborn population is approximately 0.14%. Although balanced translocations do not usually cause symptoms in the carrier, they can generate reproductive risk of offspring with unbalanced deletions or duplications (8).

In a systematic review of reproductive counseling in cases of parental constitutional balanced translocation (9;22), it was found that the phenotypes of non-recipro-

cal translocation cases included cardiac and neurological abnormalities, cognitive delay, urogenital abnormalities, respiratory and immunological dysfunction, and facial or skeletal malformations. In this study, 5 of the 13 live births with this condition had cardiac anomalies, and of these, 3 were diagnosed with DiGeorge syndrome (9). Further research is needed to determine what proportion of deletions on chromosome 22q11.2 originate from parents who are carriers of balanced translocations.

22q11.2 deletion syndrome, known as DiGeorge syndrome, is one of the most common chromosomal microdeletion syndromes. Even so, this entity is underdiagnosed because genetic screening was not widely available until 1990 using the FISH technique (4).

The current estimated prevalence of DiGeorge syndrome ranges from 1 in 2,000 to 6,395 live births, with no gender predominance. It affects Hispanics more commonly than Caucasians, African Americans, or Asians (1).

The classic phenotypic triad of DiGeorge syndrome (DGS) is characterized by conotruncal heart defects, hypocalcemia caused by hypoparathyroidism, and T-cell deficiency due to thymic hypoplasia. This is explained by the common embryological origin of the heart, thymus, and parathyroid glands (3).

The clinical manifestations described occur in 35 to 90% of cases secondary to a hemiczygotic microdeletion on chromosome 22, such as s a result of an incorrect chromosomal rearrangement during meiosis. This rearrangement involves low-copy repeats (LCRs) scattered throughout a region of chromosome 22q11.2 (5). DGS can be inherited in an autosomal dominant manner, although 90% of cases are due to de novo microdeletions (4).

Cardiac abnormalities are present in up to 80% of patients. Before the age of 2, tetralogy of Fallot, truncus arteriosus, and interrupted aortic arch are commonly diagnosed; after the age of 2, ventricular septal defect, pulmonary atresia with VSD, and conotruncal defects are generally diagnosed (2).

The patient in the case report presented with severe heart disease due to pulmonary atresia, which was diagnosed during the fetal period. Although this is not the most common presentation of heart disease secondary to DiGeorge syndrome, atresia and the presence of aortopulmonary collaterals are more common in patients with tetralogy of Fallot and 22q11.2 deletion compared to those without the deletion (7).

Associated craniofacial manifestations have also been described, including bifid uvula, cleft palate, submucosal cleft palate, and rarely cleft palate and cleft lip (2). If these occur in association with heart disease, genetic screening is necessary.

Secondary to thymus hypoplasia, this syndrome is also associated with a deficit in cellular immune response. It presents different levels of T-cell lymphopenia that subsequently resemble healthy controls, due to thymus involution at 1 to 2 years of age (5).

As a result of the poor functioning of T cells, humoral deficits also occur, including low levels of gamma globulins, insufficient specific antibody responses, and impaired B cell maturation (5).

The patient required several courses of antibiotics due to healthcare-associated pneumonia, bloodstream infection, and

sepsis. This highlights the importance of timely diagnosis of DiGeorge syndrome, as it facilitates the appropriate choice of antibiotic treatment and its duration, considering the predisposition of these patients to recurrent infections.

Depending on the phenotype of patients with DGS, they may require isolation, prophylactic antibiotics, and in certain cases, hematopoietic or thymic cell transplantation. The management of cardiac abnormalities, palate malformations, or metabolic disorders such as hypocalcemia will require surgical intervention and specialized follow-up. The y occurrence of autoimmune diseases is also common, so it is important to evaluate them regularly. Speech therapy, psychiatric care, and early intervention are essential to promote the patient's proper neurodevelopment.

Genetic testing is also recommended for the patient's immediate family members, such as parents and siblings, especially if they show signs consistent with DiGeorge syndrome (DGS). Patients should be informed that there is a 50% risk of passing the disease on to their children, and the various diagnostic options available, such as prenatal testing and preimplantation alternatives, should be discussed. (4)

Conclusion

This case highlights the importance of balanced translocations in patients and their parents, as well as the relevance of early identification of SDG in order to select the most appropriate treatment, particularly with regard to infection management and cardiological follow-up. Heart defects, craniofacial malformations, and immune dysfunction require surgical interventions, specific therapies, and continuous monitoring to prevent patient deterioration. It is also recommended that close relatives undergo genetic testing and receive guidance on the risk of inheriting the disease, which is key to future reproductive planning. Early detection and appropriate treatment are essential to improve the prognosis and quality of life of patients with DGS.

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