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CASE PRESENTATION

Tetralogy of Fallot and pulmonary valve agenesis in *22q11* deletion syndrome

Tetralogía de Fallot y síndrome de agenesia valvular pulmonar en el síndrome de deleción 22q11

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Abstract

The 22q11 deletion syndrome, also called DiGeorge syndrome, has a wide variety of symptoms and signs, the most prevalent being conotruncal cardiac alterations, hypoplastic thymus and hypocalcemia. We present the clinical case of a 15-day-old newborn who at her first minute of life presented clinical signs of respiratory failure, hypotonia and flaccidity, which required the use of invasive mechanical ventilation and hospitalization in the neonatal intensive care unit. Based on the clinical manifestations, imaging findings, and cytogenetic and molecular analyses, she was diagnosed with 22q11 microdeletion or DiGeorge syndrome. Given the rarity of this disease, with a diagnostically challenging presentation, the multidisciplinary diagnostic approach used in this case allowed us to obtain an early diagnosis and guide the necessary treatment. This is one of the first case reports of 22q11 microdeletion syndrome in Ecuador.

Keywords: 22q11 deletion syndrome. Phenotypic abnormalities. Complex congenital heart disease. Cytogenetics.

Resumen

El síndrome de deleción 22q11 o también llamado síndrome de DiGeorge, tiene una amplia variedad de síntomas y signos, siendo las de mayor prevalencia las alteraciones cardiacas conotruncales, timo hipoplásico e hipocalcemia. Se presenta el caso clínico de una recién nacida de quince días de vida, quien, al primer minuto, presentó datos clínicos de insuficiencia respiratoria, hipotonía y flacidez, por lo que fue necesario el uso de ventilación mecánica invasiva y hospitalización en la unidad de neonatología. Con base en las manifestaciones clínicas, los hallazgos imagenológicos, y los análisis citogenéticos y moleculares se planteó el diagnóstico de síndrome de microdeleción 22q11 o síndrome de DiGeorge. Al ser una enfermedad rara, cuya presentación clínica representa un reto diagnóstico para el equipo médico, el abordaje diagnóstico multidisciplinar llevado a cabo en este caso permitió obtener un diagnóstico precoz y orientar la conducta terapéutica necesaria. Este es uno de los primeros reportes de casos de síndrome de microdeleción 22q11 que se realizan en Ecuador.

***Palabras clave:** Síndrome de deleción 22q11. Anomalías fenotípicas. Cardiopatía congénita compleja. Citogenética.*

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Introduction

22q11 microdeletion syndrome (*22q11* DS) is caused by a hemizygous deletion of the long arm of chromosome 22 and was first described by Angelo DiGeorge in 1965. It is the most common microdeletion syndrome in the world, with a prevalence of 1 in 4,000-6,000 live births, and approximately 1 in 1,000 fetuses. However, there may be a higher prevalence of cases which are underdiagnosed due to a wide variety of clinical expression. *22q11* DS may be diagnosed at birth or later during childhood or even adolescence[1]. Approximately 70 to 80% of cases present with some type of congenital heart disease; the most common of these, with approximately 20%, is tetralogy of Fallot. Three to six percent of these patients have concomitant pulmonary valve agenesis; other congenital heart diseases found include ventricular septal defects (VSDs), truncus arteriosus, right aortic arch and other aortic arch anomalies[2,3]. In 90% of cases, the chromosomal disorder is caused by a de novo deletion, and in the other 10% it is transmitted as an autosomal dominant trait[2,4], which means that people with the chromosomal abnormality have a 50% chance of having an affected child in each pregnancy[5]. Historically, various syndromes, like DiGeorge, velocardiofacial or Shprintzen, conotruncal anomaly face, and autosomal dominant Optiz G/BBB syndromes have been described separately[6]. However, cytogenetic and molecular analysis using the fluorescence in situ hybridization (FISH) technique revealed that the common genetic cause in 90% of these patients was chromosome *22q11* microdeletion[1].

Depending on the age group, certain clinical characteristics like congenital heart disease, palate anomalies, typical facial features and immunodeficiency caused by thymic aplasia and hypoplasia[1] lead to a suspicion of *22q11* deletion.

The treatment of *22q11* DS is initially aimed at saving the patient's life, overcoming the emergency caused by the form of presentation and, subsequently, trying to improve the quality of life.

The goal of this article is to report a clinical case of *22q11* DS associated with tetralogy of Fallot with pulmonary valve agenesis in a 15-day-old newborn cared for at Hospital Vicente Corral Moscoso, Cuenca, Ecuador. The CARE guidelines for reporting clinical cases were followed for this report.

Clinical case

We present the case of a 15-day-old female infant from Chaucha, Azuay Province, Ecuador. Significant medical history included a 29-year-old mother, G5P5L5, with five prenatal visits and iron and folic acid supplementation beginning in the fifth month of pregnancy. As a risk factor, the mother reported vaginosis in her sixth month of pregnancy, treated with vaginal suppositories.

The patient was a singleton live neonate born vaginally, weighing 2,710 grams, with a length of 47 cm, head circumference of 33 cm (standard deviation: -1, -2) and a Ballard gestational age assessment of 38 weeks. Her Apgar scores were 5 and 7 at 1 and 10 minutes, respectively. During the first minute, she was flaccid and hypotonic with poor respiratory effort, generalized pallor and a heart rate of less than 100 bpm; therefore, positive pressure ventilation was begun for two cycles. In light of a persistent heart rate under 100 bpm, pallor and poor respiratory effort, endotracheal intubation was performed, which improved the heart rate; however, the poor respiratory effort continued with poor ventilatory mechanics, intercostal retractions and oxygen saturation > 90%. She experienced three episodes of gaze deviation and tonic movements and was therefore admitted to the neonatal intensive care unit.

A physical exam of the head showed malar hypoplasia, a bulbous nose, a broad nasal bridge, an intact palate, a weak cry, low-set ears, and micrognathia. Her lung fields were ventilated with preserved breath sounds; on heart auscultation she had a II/IV systo-diastolic murmur at the base and tricuspid; on the spine, she had a tuft of hair in the sacral region, suggesting spina bifida occulta. On neurological exam she was alert, with sucking and plantar reflexes present. The exam of her extremities showed axial polydactyly of the left foot (Fig. 1).

Laboratory tests on admission showed hypoproteinemia (5.9 g/dl), elevated LDH (704 U/L), hypercalcemia (12 mg/dl), and elevated CK-MB (142.1 U/l), creatine phosphokinase (CPK) (1,809 U/L) and troponin T (51.4 pg/ml).

Transfontanellar, renal and abdominal ultrasound tests were normal. Spinal ultrasound showed findings suggestive of a possible cystic lesion in the distal spinal canal.

A transthoracic echocardiogram showed normal biventricular function (87% LVEF); a 3 mm patent foramen ovale, tetralogy of Fallot with a 5 mm subaortic ventricular septal defect, a stenotic pulmonary valve annulus (z score: 0) with absent semilunar cusps and severe pulmonary regurgitation, and right (z score: +2.7) and left (z score: +3.9) pulmonary artery branch dilation. She also had a right aortic arch. A cardiac

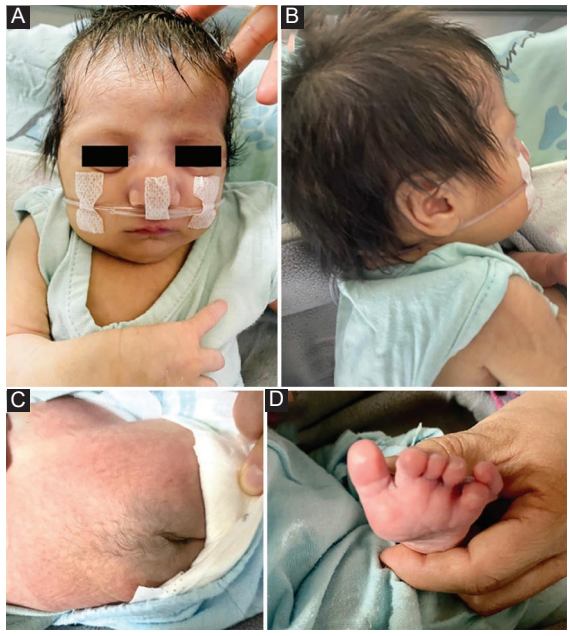

Figure 1. Clinical manifestations. **A:** a broad nasal base, malar hypoplasia, and micrognathia. **B:** low-set ears. **C:** a tuft of hair in the sacral region of the spinal column, suggesting spina bifida occulta. **D:** axial polydactyly of the left foot. *[Cuenca, Azuay, Ecuador; 17/01/2023]*.

tomography angiography confirmed the echocardiographic findings, pulmonary artery branch dilations and tetralogy of Fallot, plus right aortic arch and bronchomalacia (Fig. 2).

The clinical information and imaging characteristics led to a suspicion of *22q11* DS; therefore, a FISH test was performed which confirmed the *22q11* chromosome microdeletion and, thus, the clinical suspicion (Fig. 3).

Discussion

Congenital heart diseases have a frequency of 4 to 50 per 1,000 live births, worldwide, and can be associated with genetic abnormalities. Of these, 5 to 10% are caused by chromosome abnormalities, especially trisomy of chromosomes 13, 18 and 21. In 25% of cases, immediate intervention must be carried out within the first year of life, as the patients can progress to cardiogenic shock, cyanosis and pulmonary edema[7]. In Ecuador, the prevalence of congenital heart diseases in newborns has been determined to be 2.7 per 1,000 live births; the province of Azuay and the city of Cuenca were found to have incidence rates of 2.35 and 2.74 per 1,000 live births, respectively[8].

Tetralogy of Fallot and its association with pulmonary valve agenesis is a rare variant that occurs in 3 to 6% of these patients. In this condition, the valvular ring has rudimentary cusps and a stenosed annulus, leading to aneurysmal dilation of the pulmonary artery and its branches which compresses the anterior portion of the lower end of the trachea and the bronchi during fetal development, causing hypoplasia of the compressed airways and, consequently, respiratory failure, which is the main cause of death in these patients[4,9].

In this report, we present the clinical case of a newborn female patient with both clinical and imaging characteristics of *22q11* DS. The earliest clinical signs and symptoms were acute respiratory failure, generalized pallor, hypotonia and bradycardia. In addition, the physical exam revealed low-set ears, malar hypoplasia, micrognathia, a wide nasal bridge, a weak cry, a heart murmur and axial polydactyly of the left foot. From a radiological perspective, the echocardiography and cardiac tomography angiography findings were associated with a complex congenital heart disease, and therefore she was screened for *22q11* DS. Within the spectrum of clinical findings, a possible spina bifida occulta indicated by a tuft of hair in the sacral region and the ultrasound finding of a cystic lesion in the spinal canal were probably due to concomitant pathologies. As mentioned in the American Heart Association (AHA) congenital heart disease guidelines, screening for *22q11* DS was necessary due to the finding of a complex congenital heart disease; in this case, screening was done with the FISH technique, and a *22q11* microdeletion was diagnosed[10].

In the *22q11* deletion there is an alteration in the region containing the *TBX1* gene, which is one of the transcription factors involved in the development of the third and fourth pharyngeal arches, causing abnormal development of the thymus and parathyroid, the absence of features such as aplasia/hypoplasia of the thymus, hypoparathyroidism with hypocalcemia and nasopharyngeal reflux in a newborn is rare since these are usually the main clinical features that raise suspicion in the diagnosis and this has to do with the wide variability in the expression of genes that are part of the *22q11* region, so in this case the clinical suspicion starts from the phenotypic expressions and complex congenital heart disease[10].

The treatment of heart disease in patients with *22q11* DS has been greatly debated, but the consensus is that a rapid and timely diagnosis should be made, since the definitive treatment of the congenital heart disease is surgical. Tetralogy of Fallot repair must be done according to each patient's clinical and anatomical condition,

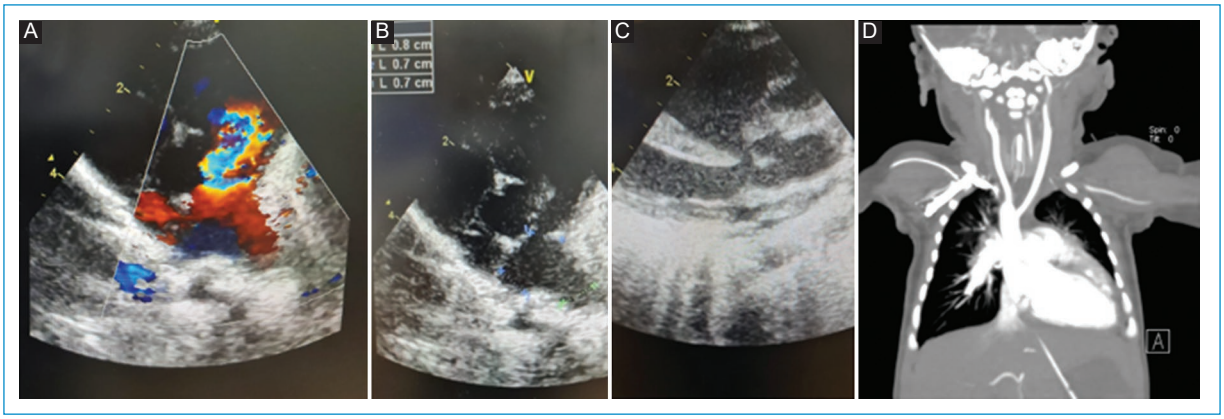

Figure 2. Echocardiography and tomography angiography findings. **A:** the pulmonary valve ring is shown, with aneurysmal dilation of the pulmonary artery branches and Doppler aliasing at the annulus. **B:** pulmonary artery branch dilation, with the right branch measuring 7 mm and the left branch 6 mm. **C:** the aortic annulus overriding the interventricular septum. **D:** enlarged right heart chambers with pulmonary stenosis; the main pulmonary trunk measures 10.5 mm, its right branch 11.4 mm and its left branch 9.6 mm. A 4 mm diameter atrial septal defect (ASD). The aorta is overriding the interventricular septum. A right aortic arch with an aberrant subclavian artery on the left *[Imaging and Radiology Service at Hospital «Vicente Corral Moscoso». Cuenca, Azuay, Ecuador; 04/01/2023].*

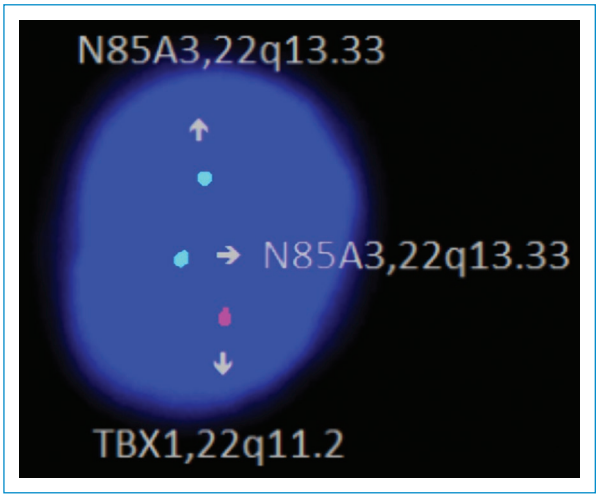

Figure 3. The fluorescence in situ hybridization (FISH) test, showing one signal for the *TBX1* gene and two signals for the N85A3 gene, compatible with a deletion in the *22q11.2* region in 25 analyzed cells. This result is consistent with the DiGeorge syndrome diagnosis *[Cuenca, Azuay, Ecuador; 11/01/2023].*

and therefore is recommended within the first year, between three and six months of age[11,12].

According to the literature, the treatment of patients with tetralogy of Fallot and pulmonary valve agenesis consists of primary complete repair of the VSD via a right ventriculotomy (through the pulmonary annulus) and replacement of the dysplastic pulmonary valve with a homograft or a conduit with a valve, along with repair of the pulmonary artery and its branches. This helps reduce the adverse effects of tissue hypoxia and decreases the progression of fibrosis and right ventricular hypertrophy, optimizing long-term ventricular function. Some surgeons propose sectioning the aorta to achieve proper exposure of the pulmonary artery and thus perform extensive pulmonary arterioplasties in both pulmonary hila. Surgical mortality occurs early and is greater than 20%; the one-year survival rate is 75%[12,13].

Conclusion

The main heart abnormality in *22q11* DS is tetralogy of Fallot, and its association with pulmonary valve agenesis is rare, but highly suggestive of *22q11* DS. Therefore, these findings should trigger a complete screening for neonatal genetic disorders.

22q11 DS can be diagnosed based on phenotypic findings of the characteristic elements in newborns. In this regard, the facial anomalies and heart abnormalities were key elements which led the medical team to suspect this syndrome. Finally, cytogenetic and molecular techniques, along with imaging findings, were essential for the definitive diagnosis of *22q11* DS.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of humans and animals. The authors declare that the procedures followed conformed to the ethical standards of the responsible human experimentation committee and were in accordance with the World Medical Association and the Declaration of Helsinki.

Data confidentiality. The authors declare that they have followed their center's protocols on the publication of patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patients and/or subjects referred to in the article. The corresponding author is in possession of this document.

Use of artificial intelligence to generate texts. The authors declare that they have not used any type of generative artificial intelligence in the writing of this manuscript or for the creation of figures, graphs, tables, or their corresponding captions or legends.

Consent

Written informed consent for publishing this case report and its accompanying images was obtained from the patient's legal guardian. A copy of the informed consent is available for review by the Editor in Chief of this journal.

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