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A DiGeorge Syndrome Case Report—Challenges of Diagnosis and Management

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Abstract

Background: DiGeorge syndrome (also known as velo-cardio-facial syndrome) is a rare multisystem genetic disorder occurring in approximately 1 in 4000 to 1 in 6000 live births [1]. Although advances in genetic screening have improved diagnosis in developed countries, the condition remains underdiagnosed in developing nations such as the Republic of Moldova, where access to genetic testing and family planning services is limited. Routine prenatal screening usually includes regular ultrasounds, monitoring of blood pressure, complete blood counts, coagulation studies, glucose, urine protein, and urine culture. Current ultrasound techniques have limitations in detecting this syndrome due to variability in interpretation, and genetic testing is often performed based on clinical discretion. The ultrasound could potentially point towards a genetic problem, as in DiGeorge, if multiple cardiac malformations are spotted in utero, but most cases such as this one are diagnosed after birth while being described as totally normal on prenatal ultrasound. **Purpose:** This study aims to highlight the diagnostic challenges and the need for comprehensive evaluation in identifying DiGeorge syndrome, emphasizing the importance of considering the syndrome as a whole rather than focusing on isolated organ system issues. **Method:** We present a case report of a 6-month-old girl who, after an uneventful pregnancy and normal prenatal ultrasound, presented with cardiac insufficiency. Following extensive investigations and multiple surgical interventions, DiGeorge syndrome was diagnosed at 9 months of age. **Results:** The patient's diagnosis was delayed due to the lack of prenatal markers and the reliance on separate investigations of affected organ systems. Despite several interventions aimed at managing her symptoms, the final diagnosis was made after observing the association of multiple clinical features and conducting comprehensive genetic testing. **Conclusions:** This case underscores the importance of a holistic approach to diagnosis, which involves a thorough patient history, integration of diverse diagnostic tests, and recognition of the syndrome's multi-system nature. It

highlights the necessity for improved diagnostic protocols and increased awareness in regions with limited access to advanced genetic testing to prevent delays in identifying DiGeorge syndrome and to facilitate timely and appropriate management.

Keywords

DiGeorge, Velo-Cardio-Facial, TBX-1 Gene, Chromosome 22, 22q11.2 Deletion, Septal Defect, Immunodeficiency, Thymic Shadow, Congenital Cardiac Abnormalities, Prenatal Screening

1. Introduction

DiGeorge syndrome (DGS), also known as velo-cardio-facial syndrome, is a genetic disorder resulting from a microdeletion on chromosome 22q11.2. This syndrome presents with a diverse range of clinical manifestations affecting multiple organ systems, including congenital heart defects, immune system deficiencies, hypoparathyroidism, and distinctive craniofacial anomalies. While advances in genetic testing and prenatal screening have improved the detection of DiGeorge syndrome in developed countries, the disorder remains underdiagnosed in many developing regions due to limited access to comprehensive diagnostic resources due to their high cost, poorly-defined clinical protocols and limited understanding of their importance by primary-care physicians.

In developed countries, prenatal imaging and genetic screening can sometimes identify potential cases of DiGeorge syndrome. However, its variable presentation and overlap with other conditions often lead to delayed or missed diagnoses, as not all features may be evident at birth or through routine screening methods. In regions with fewer healthcare resources, such as the Republic of Moldova, the challenges are exacerbated by the limited availability of genetic testing and family planning services.

The clinical manifestations of DiGeorge syndrome can be subtle and diverse, making diagnosis particularly challenging. Common symptoms such as cardiac anomalies, recurrent infections, and endocrine disorders may initially be addressed in isolation, delaying the recognition of the syndrome as a whole. This often leads to a fragmented approach to diagnosis and management, impacting patient outcomes.

This case report aims to illustrate the diagnostic complexities associated with DiGeorge syndrome by detailing the experience of a patient in a setting with inappropriate prenatal and diagnostic resources. By highlighting the patient's path from symptom onset to diagnosis, we emphasize the need for a holistic approach to evaluation and increased awareness of the syndrome's diverse manifestations. This report seeks to contribute to the understanding of DiGeorge syndrome, particularly in under-resourced settings, and to advocate for improved diagnostic and management strategies.

2. Case Presentation

A 6-month-old infant was brought to the family doctor's office by her parents due to symptoms of persistent cough, difficulty breathing, and swelling in the legs. Parents also reported that the patient had frequent infections and was not gaining weight as expected.

The child was born at 41 weeks gestation via spontaneous vaginal delivery to a gravida 2, para 1, aborta 1. The mother's previous pregnancy ended in a spontaneous abortion at 7 weeks gestation. The pregnancy was uncomplicated, with a slight toxicosis between 12 and 14 weeks of gestation. The mother received appropriate prenatal care, with regular screening ultrasounds at 6 - 7 weeks intervals. The child was born weighing 3140 g, with an Apgar score of 8 at 1 and 5 minutes.

At 11 days postpartum, the entire family was diagnosed with COVID-19. The mother and the 11-day-old child were hospitalized at the Mother and Child Care Center, in the Infectious Diseases section. While the child was being administered IV fluids, the mother noticed that the child's forehead became a dark blue color. This observation was not recorded by the nurse or the doctor.

At the family doctor's visit, the patient presented with a history of multiple infections since birth—sinusitis at 1 month, pneumonia treated with antibiotics at 2 months, with recurrences at 3 and 4 months.

Upon further clinical investigation, the patient was found to have a blowing, holosystolic murmur along the left sternal border, which prompted referral for an echocardiogram, which pointed out multiple cardiac malformations—atrial septal defect, ventricular septal defect, dextroposition of the aorta, a low ejection fraction and pulmonary hypertension. No further testing was done at the time. The patient was referred to a tertiary care center for a planned surgical intervention to correct the multiple congenital cardiac anomalies. The patient was admitted to a tertiary care at 9 months of age. Upon admission, the diagnosis of multiple congenital cardiac anomalies was confirmed. The surgery was conducted a few days later, after an appropriate evaluation by the anesthesiologist.

The surgery was done under general anesthesia. It included the correction and closure of the ventricular septal defect and suturing of the atrial septal defect, with suturing of the ductus arteriosus.

After the intervention, the patient was transferred to the Intensive Care Unit and was placed on mechanical ventilatory support due to respiratory insufficiency. Multiple pulmonary radiographs showed lobar pneumonia and atelectasis of the lower segments of both lungs. The oropharyngeal cultures identified Escherichia Coli. The patient remained on ventilatory support for a period of 10 days. Over this period, the patient was given intravenous antibiotics—Meropenem for 15 days and Amikacin for 10 days, according to the pathogen sensitivity to antibiotics. After 8 - 10 days, the radiographs began to show a resolution of the pneumonia and improvements in respiratory functioning, so the patient was successfully removed from ventilatory support. The right upper lobe remained

atelectatic, with progression to pneumofibrosis at the end of the patient's hospital stay.

The patient was discharged from the hospital 1 month after admission, with instructions to the Family Doctor for ongoing monitoring. The post-discharge care protocol included:

- Captopril powder 1.5 mg × 3 times/day, daily for 1 month
- Spironolactone powder 6.25 mg in the morning, daily for 1 month
- Propranolol powder 5 mg × 3 times/day, daily for 1 month
- Treatment of infections based on antibiotic sensitivity

Due to this constellation of symptoms and postoperative complications, the parents began to question if this could be related to a congenital disease, which prompted them to get a genetical consult in our private clinic. The patient's physical exam pointed out hypertelorism, a small philtrum and a bony defect in the palate of the patient, never mentioned before by the previous specialists. After a careful review of the patient's history, further lab and genetic testing was deemed necessary in order to integrate the cardiac abnormalities into the diagnosis of DiGeorge syndrome.

Lab studies of the patient's immune phenotypes pointed out deficiencies across multiple lymphocyte cell lines, such as the total number and percentage of T-cells, CD4+ T-cells and CD19+ B-cells (Refer to Table 1).

Table 1. Patient lymphocyte immunophenotyping.

Lymphocyte markers	Lymphocytes	Result	Reference range	Measurement units
CD3+CD45+	T-lymphocytes	64.7	45.0 - 79.0	%
CD3+CD45+	T-lymphocytes	**1342.0**	2280.0 - 6450.0	Cells/microliter
CD3+CD4+CD45+	T-helper cells	**29.8**	36.0 - 61.0	%
CD3+CD4+CD45+	T-helper cells	**606.0**	690.0 - 4460.0	Cells/microliter
CD3+CD8+CD45+	Cytotoxic T-cells	31.0	16.0 - 34.0	%
CD3+CD8+CD45+	Cytotoxic T-cells	**632.0**	720.0 - 2490.0	Cells/microliter
T-helper/cytotoxic T-cell index	CD3+CD4+/CD3+CD8+	1.0		
CD3-CD56+CD45+	NK cells	**14.2**	2.0 - 13.0	%
CD3-CD56+CD45+	NK cells	295.0		Cells/microliter
CD19+CD3-	B-lymphocytes	**14.3**	19.0 - 31.0	%
CD19+CD3-	B-lymphocytes	**296.0**	500.0 - 1500.0	Cells/microliter

Due to hypocalcemia due to hypoparathyroidism being a common feature of DiGeorge syndrome, the patient was referred for a serum hormone testing, which pointed out a slight decrease in the parathyroid hormone levels (Refer to Table 2).

Table 2. Normal serum thyroid with slightly decreased parathyroid hormone levels.

Hormone	Result	Reference range	Measurement units
TSH, Thyroid stimulatory hormone	2.24	0.27 - 4.20	Microunits/milliliter
FT4, Free T4	1.28	0.93 - 1.7	Nanograms/deciliter
PTH, Parathyroid hormone	7.8	8.0 - 51.0	Picograms/milliliter

After obtaining the immune phenotype, the patient was referred for an ultrasound, which revealed thymic hypoplasia (small, separate lobules instead of a clear organ).

After that, a genetic evaluation revealed a complete deletion of 22q11.2, which confirmed the diagnosis of DiGeorge syndrome (Refer to Table 3).

Table 3. QF-PCR investigation of the patient's chromosome 22q11.2 pointed out a complete deletion.

Gene	Number of copies in the patient	Normal number of copies	Locus	Explanation
GADPH	2	2	12p13.31	Reference gene
CRKL	1	2	22q11.21 (distal part)	Gene from the DiGeorge locus, distal to the centromere
PRODH	1	2	22q11.21 (proximal part)	Gene from the DiGeorge locus, proximal to the centromere

On the parents' genetic exam, chromosome 22 proved to be completely normal, which confirmed a de novo mutation, leading to the disease in the child (Refer to Table 4).

Table 4. QF-PCR investigation of the patient's parents' chromosome 22q11.2 showed 2 copies of the gene.

Gene	Number of copies in the patient	Normal number of copies	Locus	Explanation
GADPH	2	2	12p13.31	Reference gene
CRKL	2	2	22q11.21 (distal part)	Gene from the DiGeorge locus, distal to the centromere
PRODH	2	2	22q11.21 (proximal part)	Gene from the DiGeorge locus, proximal to the centromere

The diagnosis of DiGeorge syndrome was made 4 months after the initial patient referral to the family doctor. Further disease management includes treatment of infections according to pathogen sensitivity. Due to a complete deletion of the gene, the prognosis of this patient remains poor, with no actual treatment options available.

3. Discussions

DiGeorge syndrome, also known as the velo-cardio-facial syndrome, is a complex genetic syndrome, affecting multiple organs and systems. It most commonly affects the facial features (hypertelorism, palatal dysgenesis, small philtrum) [2], the heart (atrial septal defects, ventricular septal defects, pulmonary artery stenosis, transposition of the great vessels), the immune system (absence or hypoplasia of the thymus, decreased number and function of T helper cells) and calcium homeostasis (since it affects the evolution of the parathyroids). The heart defects, which required surgical correction, were the first identifying feature of the disease in the case described. Upon further investigation, deficiencies of the immune system, in the form of low B and T cells [3], and hypoparathyroidism have completed the clinical picture of DiGeorge syndrome.

It is caused by a partial or complete deletion in the long arm (Q) of chromosome 22, at locus 11.2 (22q11.2) [1] [4]. In this case, a complete deletion was identified. Multiple genes have been identified on the locus, the most studied is the T-box transcription factor 1 (TBX1), which is known to correlate (in mouse models) with severe defects in the development of the heart, thymus, and parathyroid glands. The described gene is also known to correlate with neurovascular abnormalities, which could explain the abnormal behaviour and development of the central nervous system of children with DiGeorge syndrome [5]-[7].

Most mutations (around 90%) occur de novo, with no relationship to preexisting genetic abnormalities in the parents [1] [8]. This has proven to be the case in our study since the parents had 2 copies of the normal gene.

The National Clinical Protocol for "Primary Immune Deficiency, DiGeorge Syndrome" of the Republic of Moldova mostly describes the immune aspect of the disease, leaving out the importance of prenatal diagnosis and its association with severe cardiac malformations, specific facial abnormalities and its effects on calcium homeostasis. This leaves important gaps in suspecting and diagnosing the disease since the protocol advises to "first refer to the family doctor", who must have a clear set of criteria for screening [9]. In our case, the family doctor didn't take into account the other accompanying features of the disease and didn't refer the patient for further testing, focusing mainly on the correction of the cardiac problem.

A complete deletion in 22q11.2 is only present in 1% of cases of DiGeorge syndrome. According to research, most of the patients with a complete deletion have a poor prognosis, dying before 12 months of age without a thymic or hematopoietic stem cell transplant. Even with a thymic transplant, in a study of 50 infants with a complete deletion, only 36 of them survived to two years [10]. In

our case, the patient also has a complete deletion, already surviving past 2 years of age.

While there's no mainstay in the treatment of DiGeorge syndrome, the main goals of therapy involve:

- Surgical correction of congenital cardiac abnormalities
- Calcium supplementation for the treatment of hypoparathyroidism
- Treatment of infections based on antibiotic sensitivity
- Allogeneic thymic transplantation for severe immune deficiency [10]-[13]. This treatment is not available in the Republic of Moldova at the time of this study

4. Differential Diagnosis

- **Congenital rubella infection**—the course of pregnancy was uncomplicated by any maternal infections. The mother received all required vaccinations. Congenital rubella is known to cause congenital heart disease (patent ductus arteriosus, ventricular septal defect), along with low birth weight, hepatosplenomegaly, cataracts, sensorineural hearing loss and a characteristic "blueberry muffin" rash. DiGeorge is also known to cause congenital cardiac malformations, hearing loss and eye problems. Congenital rubella is not reported to affect the immune system or have characteristic facial features on physical exam.
- **Down's syndrome**—Down's syndrome is known to be associated with endocardial cushion defects, which lead to atrial septal defects and ventricular septal defects. Endocardial cushion defects may also be associated with Tetralogy of Fallot and Transposition of the Great Vessels. Down's syndrome is caused by trisomy 21 and has characteristic facial features that may overlap with some of the features of DiGeorge's syndrome. Down's syndrome is not known to affect the immune system.
- **Severe combined immunodeficiency (SCID)**—history of complicated bacterial infections, such as otitis media and pneumonia, may need a differential for congenital immune deficiencies, such as SCID. The lack of mature T-cells may present similarly in SCID and DiGeorge, but other specific features such as cardiac malformations and characteristic facial features are present only in DiGeorge. SCID may either be caused by the mutation of the interleukin 2 receptor gamma (ILR2G) gene, located on the X chromosome and passed on by the mother, or a lack of the ADA (adenosine deaminase) enzyme, which is coded for by a gene located on chromosome 20 [14]. About 90% of cases of DiGeorge syndrome are caused by deletion in chromosome 22, more specifically on the long arm (q) at the 11.2 locus (22q11.2) [15]. The mainstay of differential diagnosis is usually the multiorgan problems in DiGeorge (cardiac, hearing, eye, immune) and its characteristic facial features [1] [4] [8].

5. Conclusions

- Any patient with multiple congenital cardiac anomalies must undergo a careful and detailed physical and laboratory examination, to avoid delayed/incorrect

diagnoses and incorrect management of the condition.

- A combination of facial abnormalities, multiple congenital cardiac malformations and chronic/delayed immune responses should prompt an evaluation for a genetic disorder (e.g. DiGeorge syndrome).
- Prenatal screening techniques have made huge advancements in the last 10 - 15 years, so any risk factors (advanced maternal age, history of spontaneous abortions in the first trimester, history of genetic disorders in the family) should raise the need for a prenatal genetic consult and testing.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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