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COMBINED TREATMENT OF DIGEORGE SYNDROME

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Keywords:
DiGeorge syndrome, thymic hypo/aplasia, tetralogy of Fallot, thymus transplantation.

Annotation

Background. DiGeorge syndrome is a rare congenital disease associated with a deletion of chromosome 22q11.2, which is characterized by the occurrence of various anomalies, such as hypo/aplasia of the thymus and parathyroid glands, which leads to T-cell immunodeficiency and hypoparathyroidism; this syndrome is also characterized by congenital heart disease (tetralogy of Fallot), anomalies in the development of craniofacial structures are observed, in the form of non-fusion of the hard palate and upper lip (cleft palate and cleft lip).

Results. This article will examine a clinical case of DiGeorge syndrome in a child, with the classic triad characteristic of this condition (immunodeficiency, hypoparathyroidism and congenital heart disease). The patient underwent the first stage of correction of a combined heart defect against the background of constant (monthly) immunocorrection. Due to the COVID-19 pandemic, our patient was unable to receive scheduled hospitalization for blood replacement and immunocorrective therapy in a timely manner. The key to increasing the survival rate of patients with DiGeorge syndrome is prenatal screening, timely correction of the anomaly and immunoreplacement therapy, which are actively used in foreign countries. Also, incomplete treatment of DiGeorge syndrome can subsequently lead to various other manifestations, such as autoimmune diseases, infectious diseases, etc.

Conclusion. The prognosis of DiGeorge syndrome is that this disease has various clinical manifestations, is combined with other variants of the anomaly that are incompatible with life and lead to delayed psychomotor development and have an unfavorable prognosis.

Ди Джорджи синдромын біріктірілген емдеу

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Мүдделер қақтығысы:
авторлар мүдделер қақтығысының жоқтығын мәдімдейді

Түйінді сөздер:
Ди Джорджи синдромы, тимус гипо/аплазиясы, Фалло тетралогиясы, тимус трансплантациясы.

Түйіндеме

Өзектідігі. Ди Джорджи синдромы – 22q11.2 хромосомасының жойылуымен байланысты сиректуа біткен ауру, ол тимус және қалқаншамаңы бездерінің гипо/аплазиясы сияқты әртүр-

лі ауытқулардың пайда болуымен сипатталады, бұл Т-жасушалық иммунтапшылығына және гипопаратиреозға әкеледі; Бұл синдром сонымен қатар туабіткен жүрек ақауымен (Фалло тетралогиясы) сипатталады, ал бас-жаққұрылымдарының даму аномалиялары қаттытаңдай мен жоғарғы еріннің біріктірілмеуі түрінде байқалады (жарықтаңдай және ерін жырығы).

Нәтижелер. Мақалада осы жағдайға тән классикалық триада (иммунитет тапшылығы, гипопаратиреоз және туа біткен жүрек ақауы) бар баладағы Ди Джорджи синдромының клиникалық жағдайы қарастырылады. Науқасқа тұрақты (ай сайынғы) иммунокоррекция фонында қатар жүретін жүрек ауруын түзетудің бірінші кезеңі өтті. COVID-19 пандемиясына байланысты біздің пациент қан алмастыру және иммунокоррекциялық терапия үшін жоспарлы госпитализацияны уақтылы ала алмады. Ди Джорджи синдромы бар науқастар дың өмірсүру деңгейі нарттырудың кілті - пренаталды скрининг, аномалияны дер кезінде түзету және шетелдерде белсенді түрде қолданылатын иммунорыналмастыру терапиясы. Сондай-ақ, Ди Джорджи синдромын толықем демеу кейіннен аутоиммундық аурулар, жұқпалы аурулар және т.б. сияқты басқа да көріністерге әкелуі мүмкін.

Қорытынды. Ди Джорджи синдромының болжамы – бұл аурудың әртүрлі клиникалық көріністері бар, аномалияның өмірге сәйкес келмейтін басқа нұсқаларымен біріктіріліп, психомоторлы дамудың кешігуіне әкелетін және нашар болжамға әкеледі.

Комбинированное лечение синдрома Ди Джожди

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Ключевые слова:
синдром Ди Джорджи, гипо/аплазия тимуса, тетрада Фалло, трансплантация тимуса, COVID-19.

Аннотация

Синдром Ди Джорджи — редкое врожденное заболевание, связанное с делецией хромосомы 22q11.2, которое характеризуется возникновением различных аномалий, таких как гипо/аплазия тимуса и паращитовидных желез, что приводит к Т-клеточному иммунодефициту и гипопаратиреозу; данный синдром ассоциирован с врожденными пороками сердца, такими как тетрада Фалло, наблюдаются аномалии развития черепно-лицевых структур в виде несращения твердого неба и верхней губы (расщелина неба и заячья губа).

В статье представлен клинический случай синдрома Ди Джорджи у ребенка 2 лет, и рассмотрена предложенная схема комбинированного хирургического лечения и иммунокоррегирующей терапии. У пациента с классической триадой, характерной для этого состояния (иммунодефицит, гипопаратиреоз и врожденный порок сердца). верифицирован синдромом Ди Джорджи, подтвержденный лабораторными и инструментальными методами диагностики. Особенностью данного клинического случая явилось то, что ребенку были успешно проведены два этапа открытой хирургической коррекции сочетанного порока сердца на фоне постоянной (ежемесячной) иммунокоррекции, однако, в связи ограниченным доступом к госпитальной медицинской помощи пациентам с иммунодефицитными состояниями в период пандемии COVID-19, пациент не смог своевременно получить плановую иммунокоррекцию в условиях стационара. По мнению авторов, данные ограничения спровоцировали развитие тяжелых инфекционных осложнений, приведших в итоге к летальному исходу. Залогом повышения выживаемости больных синдромом Ди Джорджи являются пренатальный скрининг, а также комбинация своевременной

хирургической коррекции аномалий и иммунозаместительной терапии, которые активно применяются в зарубежных странах. Также неполный курс лечения синдрома Ди Джорджи может быть ассоциирован с развитием серьезных осложнений.

Introduction

DiGeorge syndrome, or velocardiofascial syndrome, is associated with a deletion of chromosome 22q11.2 and is one of the most common deletions in the human genome, second only to Down syndrome, which is associated with a trisomy on chromosome 21. The prevalence of DiGeorge syndrome ranges from 1:1000 to 1:4000 - 1:6000 newborns according to different literature data. The chromosomal deletion 22q11.2 results in impaired development of the pharyngeal gut, which gives rise to the posterior part of the oral cavity, tongue, salivary glands, palatine tonsils, glands derived from the epithelium of the pharyngeal pockets (thyroid, parathyroid, thymus) and the cardiac outflow tract.

Clinically, full DiGeorge syndrome can be observed, which includes the full range of typical manifestations, namely congenital anomalies and severe immunodeficiency. It is also possible to observe partial DiGeorge syndrome, which includes only some of the manifestations without evidence of marked immunodeficiency. A diagnostic criterion to distinguish between complete and incomplete DiGeorge syndrome is the determination of the number of native T cells (CD4+CD45RA+ T cells). T-cell deficiency is often associated with B-cell deficiency and hypogammaglobulinemia.

DiGeorge syndrome was first described as a clinical triad: immunodeficiency, hypoparathyroidism and congenital heart disease (conotruncal anomalies). Further study of DiGeorge syndrome has led to the identification of a variety of clinical manifestations of the disease, including many congenital anomalies and pathological conditions, such as non-enlargement of the hard palate and upper lip (wolf's mouth and harelip), as well as later manifestations, such as gastrointestinal or renal anomalies, autoimmune diseases, and various manifestations of cognitive retardation.

Objective: To discuss the complexities of combination treatment of DiGeorge syndrome within the constraints of the COVID-19 pandemic.

Case presentation

A child, a boy aged 4.5 months, G4P4 uncomplicated pregnancy, with a birth weight of 2500g, with no family history of facial dysmorphism and other congenital anomalies, was admitted to a children's city clinical infectious disease hospital in September 2019 with signs of respiratory failure, rapid breathing, increased body temperature, cough, runny nose. The initial physical examination revealed skin cyanosis, decreased skin turgor, increased body temperature to 37.4°C, tachycardia 146 per minute, tachypnea 54 per minute. The child's weight at the time of the examination was 3500 g, which is below the age norm, and he was artificially fed, sucking weakly. The child's psychomotor development was also delayed.

In the cardiac region, a "heart hump" type bulge was visualized, and systolic tremor with widening of the cardiac borders in the cross section was noted on palpation. Auscultation of the lungs revealed dyspnea and dry wheezing rales. Auxiliary muscles were involved in breathing. Heart sounds were muffled and a coarse systolic "machine murmur" was noted at all sites. On initial physical examination, oxygen saturation was 85%, blood pressure was 72/46 mmHg, and heart rate was 150 beats/min. On the ECG, the cardiac axis was 100° to the right and there was evidence of hypertrophy of both ventricles.

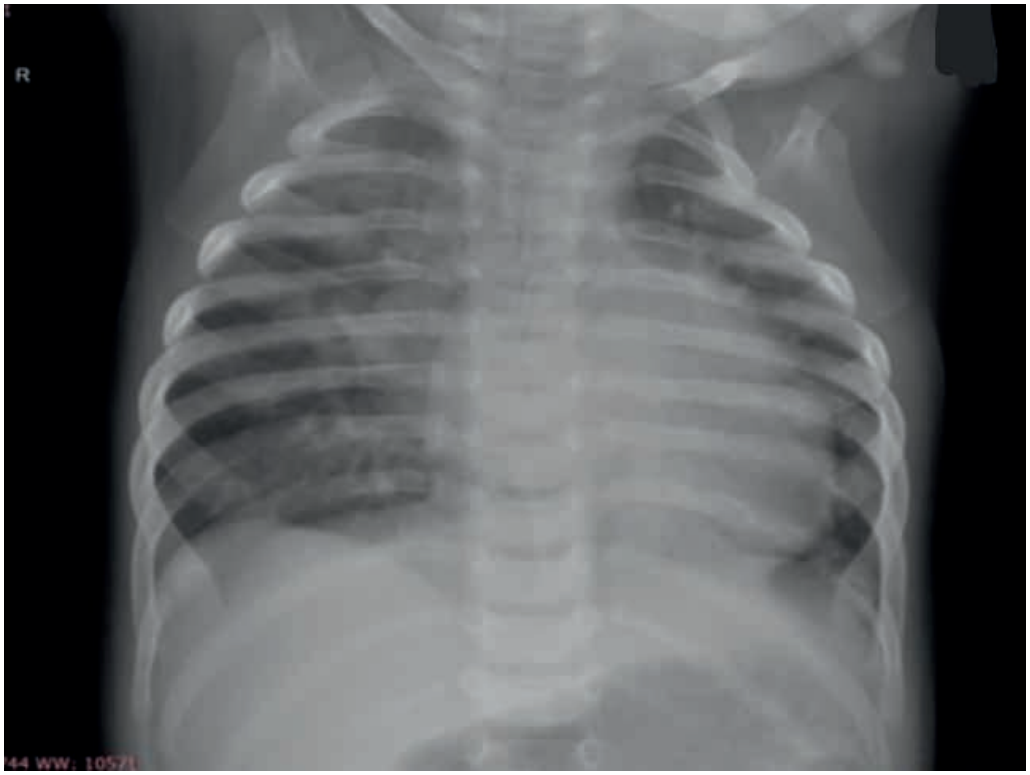


Figure 1.
X-ray shows signs of bilateral focal pneumonia. Cardiomegaly. Hypo/aplasia of the thymus gland.

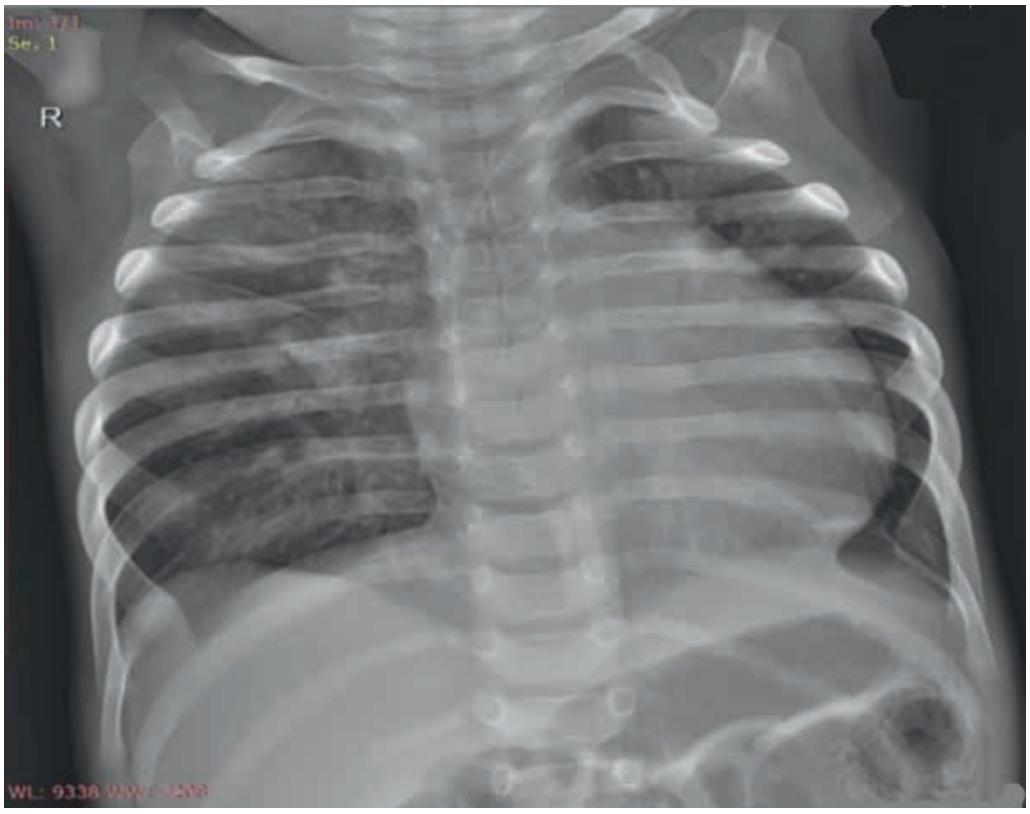
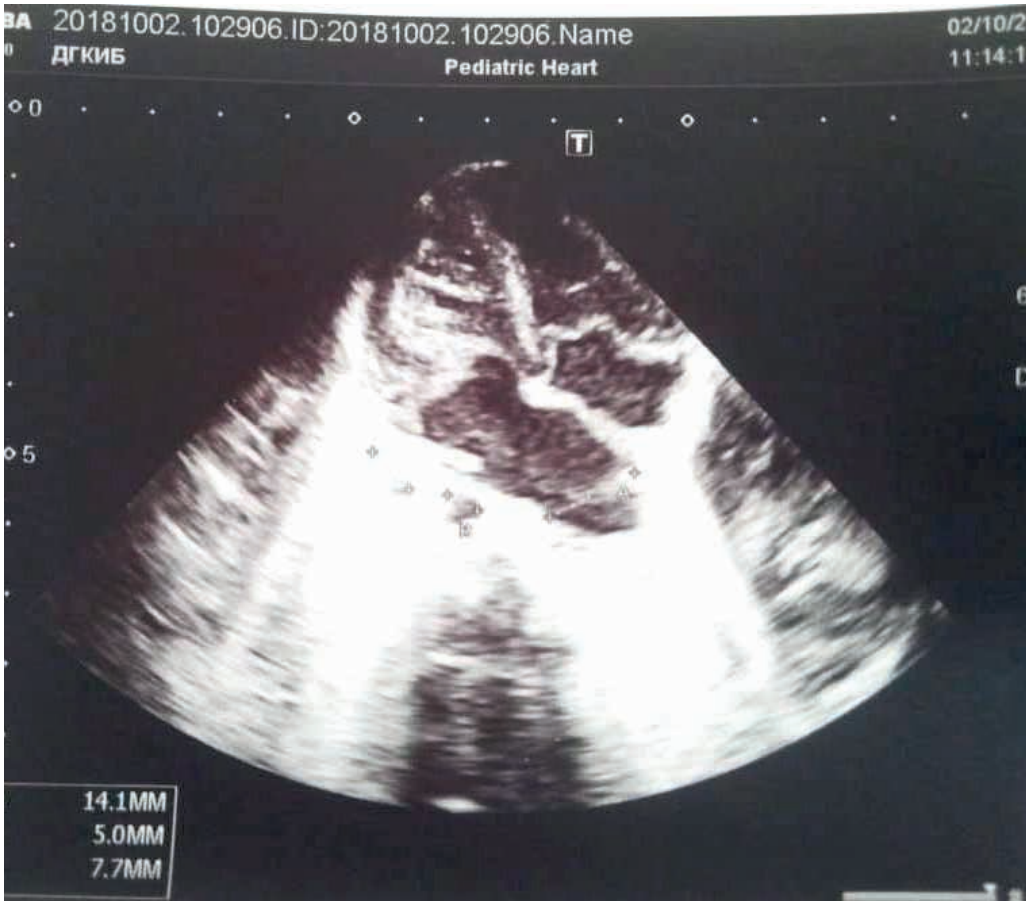


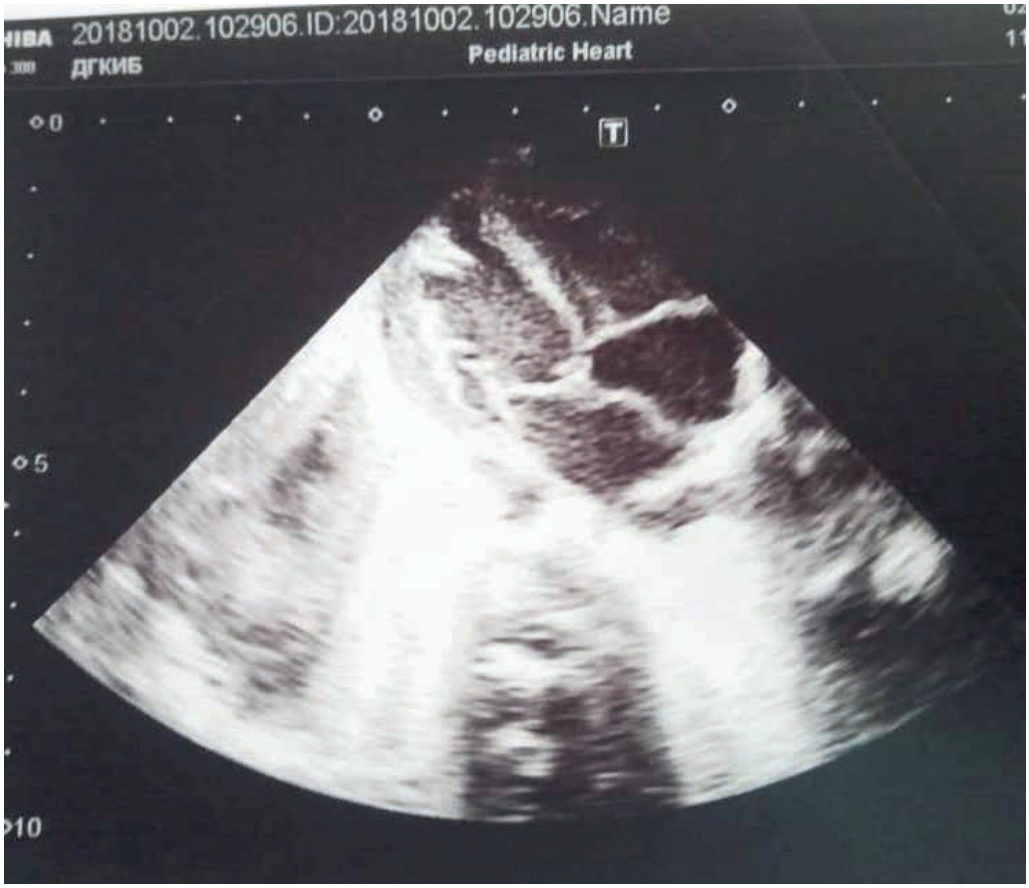
Figure 2.
Reconvalescence in dynamics after 10 days. Cardiomegaly, heart waist is smoothed.

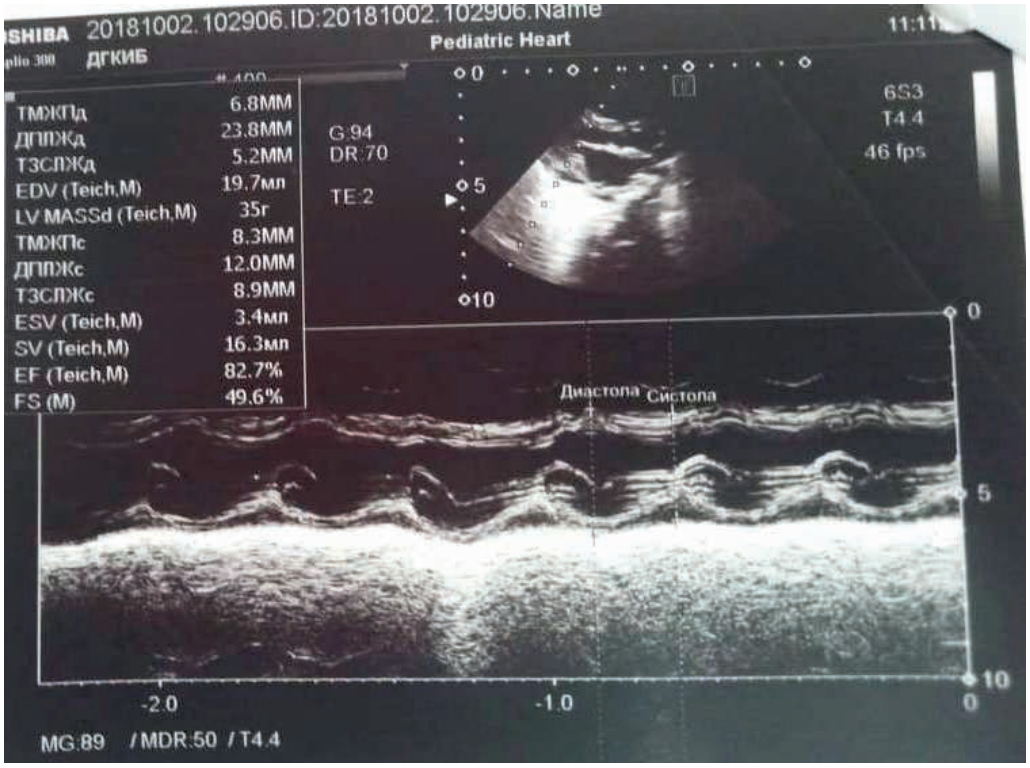
The patient was referred to a pediatric cardiac surgery center, where EchoCG revealed a wide open aortic duct, atrial septal aneurysm with an atrial septal defect, as well as an interventricular septal defect and left ventricular wall hypertrophy.

Echocardiography revealed a combined congenital heart defect (CHD) - Tetralogy of Fallot.

Figure 3 and 4.
Cardiac ultrasound revealed a congenital heart defect: Small anomalies of cardiac development (SACD). Interventricular septal defect, multiple moderate dilations of the right and left ventricles. Severe hypertrophy of the right ventricular walls.







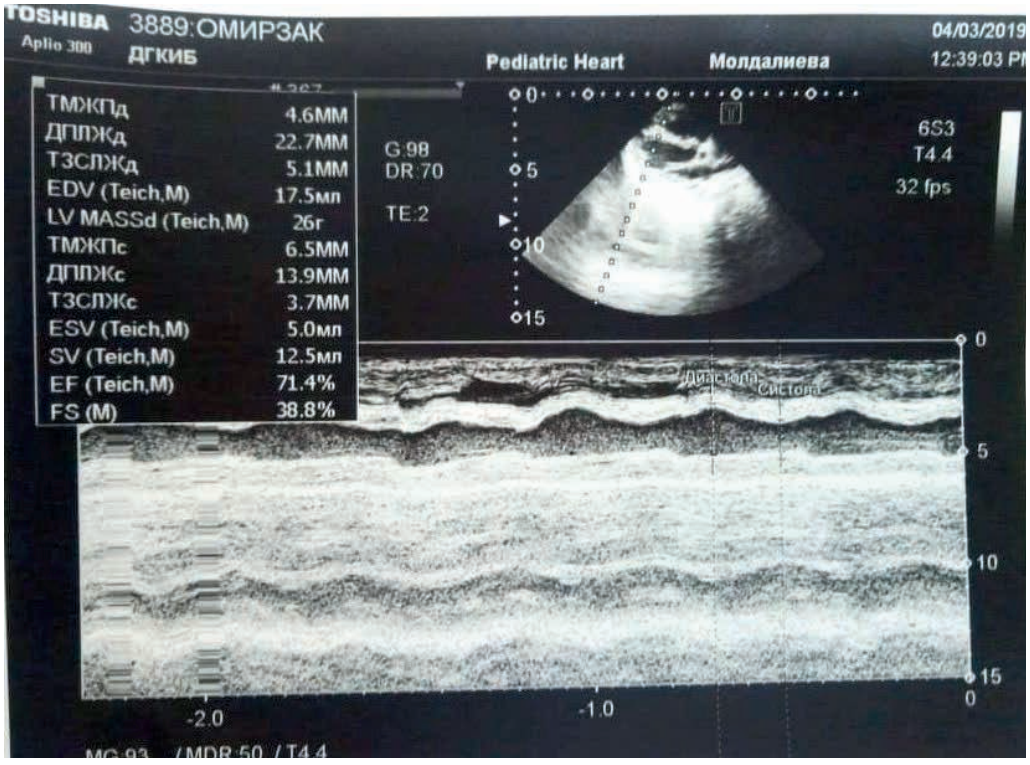


Figure 5 and 6.
Open ductus arteriosus. Signs of pulmonary hypertension. Additive papillary muscle group. Aneurysm of the sinuses of Valsava. Mitral and tricuspid valve insufficiency. Myocardial contractility is satisfactory.

Discussion

DiGeorge syndrome is caused by a chromosomal microdeletion 22q11.2 and is characterised by a wide range of clinical manifestations. Congenital heart disease occurs in 80% of cases, with the most common manifestations being coarctation of the aorta, common arterial trunk and tetralogy of Fallot. Lesions of the nasopharyngeal apparatus occur in about 70% of cases and manifest as velopharyngeal anomalies, cleft palate, cleft lip, cleft frenulum of the palate, nasal tone of voice, olfactory

dysfunction and hearing loss. There may be various signs of dysembryogenesis stigma, characteristic facial features such as elongated face, macrognathia, broad nasal bridge, small teeth. Delayed physical, speech and psychomotor development is observed in 70-90% and manifests itself with age. Immunological disorders occur in 77% of cases. Infections due to immunodeficiency occur not from birth but throughout the course of the disease. T-cell deficiency may predispose to autoimmune disease, which may be as high as 8.5%, especially in patients with CD4+ deficiency.[2]

DiGeorge syndrome is not uncommon in adults in the form of various variants of CHD: Tetralogy of Fallot, unilateral absence of the pulmonary artery, and others. Among patients with CHD, 55% had chromosomal abnormalities, 71% of patients with chromosomal abnormalities had cardiac CHD, four of whom had the triad: congenital laryngeal membrane, deletion of chromosome 22q11 and congenital cardiovascular anomalies.[3]

Surgical correction and complete repair of Tetralogy of Fallot consists of repair of the interventricular septal defect by patch placement, dilation of the right ventricular outflow tract by muscle resection, pulmonary valvuloplasty and, if necessary, enlargement of the pulmonary trunk patch. If there is significant hypoplasia of the pulmonary valve annulus, a transannular patch is placed. Surgery is usually elective at 2-6 months of age, but can be performed at any time if symptoms are present or if there is severe right ventricular outflow tract obstruction.[4]

Prophylaxis against infection is recommended for most patients with DiGeorge syndrome who are incompletely immunodeficient, and thymic transplantation (TT) is recommended for those who are fully immunodeficient.[5]

Therefore, the next important treatment tactic for DiGeorge syndrome is TT. TT is a promising treatment strategy for complete DiGeorge syndrome. According to the literature, 71 infants with complete DiGeorge anomaly were identified, of which 59 infants underwent TT. After TT, 12 (20%) infants required emergency admission to the intensive care unit (ICU). Of these, 7 (58%) of the 12 infants survived to discharge from ORIT and six survived 6 months after TT. 42 (71%) of the 59 infants who underwent TT had CHD, of whom 9 (75%) were treated in the ORIT. There was a correlation between days without mechanical ventilation and age at transplantation (R 0.17; p = 0.423). Age at transplantation and the presence of CAD were not associated with the risk of ORIT hospitalisation (odds ratio 0.95; 95% CI 0.78-1.15 and odds ratio 1.27; 95% CI 0.30-5.49, respectively) or ORIT mortality (odds ratio 0.98; 95% CI 0.73-1.31 and odds ratio 0.40; 95% CI 0.15-1.07, respectively).[6]

The causes of early post-transplant mortality were viral infections in the absence of thymopoiesis and late death due to autoimmune thrombocytopenia, septic shock with graft rejection and the need for repeat TT. Signs of thymopoiesis developed in 5-6 months, also at 12 and 24 months after TT in 10 patients there was observed a dynamic increase in the level of circulating naive CD4 and T cells. Although the age norm is not always reached, the risk of new infections is reduced. On average, prophylactic antimicrobials and immunoglobulin replacement therapy are discontinued after 49 months. Histological confirmation of thymopoiesis has been observed in patients who have undergone biopsy of the transplanted tissue, with complete maturation to the formation of terminal Hassall's corpuscles and expression of autoimmune regulators.[7,8]

However, autoimmune complications have occurred after TT. Untimely therapy, namely correction of cardiac CHD and TT of the thymus gland, may lead to an unfavourable outcome, as occurred in our clinical case.[9]

Recent studies following the COVID-19 pandemic have shown that many respiratory viruses are more severe in people with T-cell immunodeficiency. Patients with 22q11.2 deletion syndrome were at risk for a severe course of COVID-19.[10]

Conclusion

Patient A underwent the first stage of surgical correction of CHD. The presented clinical case coincided with the period of COVID-19 pandemic. Restrictive measures were introduced during the period

of disease incidence (May-June 2020), including limited planned hospitalisation of immunocompromised patients. As a result, Patient A was unable to receive planned monthly immune-replacement therapy to correct primary immunodeficiency, which led to the development of infectious complications of viral infection of unclear genesis during the COVID-19 outbreak and ultimately to death.

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