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СИНДРОМ ДАУНА И СЕРДЕЧНО-СОСУДИСТАЯ ПАТОЛОГИЯ: КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ И ОБЗОР ЛИТЕРАТУРЫ

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АННОТАЦИЯ

Полная или частичная трисомия по 21-й хромосоме (синдром Дауна) является самой частой среди анеуплоидий, совместимых с жизнью, и встречается приблизительно у 1:800 новорожденных. Синдром Дауна также является самым частым наследственным заболеванием, ассоциированным с врожденными пороками сердца (ВПС). Не менее половины всех пациентов с синдромом Дауна имеют ВПС. Средняя продолжительность жизни при этом заболевании существенно возросла — с 25 до 53–58 лет, однако осложнения со стороны сердечно-сосудистой системы по-прежнему являются основным фактором, ограничивающим продолжительность жизни этих пациентов как в детстве, так и в более поздние периоды жизни. В настоящей работе мы представляем клиническое наблюдение пациентки 59 лет с синдромом Дауна, нарушениями проводимости (атриовентрикулярной блокадой 3-й степени, имплантированным электрокардиостимулятором) и выраженными проявлениями мультисистемных заболеваний, а также представляем обзор по спектру и патогенезу сердечно-сосудистых нарушений при этом заболевании. Понимание мультисистемного характера заболевания, особенностей клинических проявлений синдрома и своевременное лечение сердечно-сосудистой патологии могут значительно улучшить качество и увеличить продолжительность жизни этих больных.

Ключевые слова: синдром Дауна, врожденные пороки сердца, умственная отсталость, трисомия 21, химеризм, дефект атриовентрикулярной перегородки, приобретенные сердечно-сосудистые заболевания, пролапс митрального клапана, аортальная регургитация, преждевременное старение, атеросклероз, артериальная гипертензия, ишемическая болезнь сердца, легочная гипертензия, аритмия.

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DOWN SYNDROME AND CARDIOVASCULAR PATHOLOGY: CLINICAL OBSERVATION AND LITERATURE REVIEW

ANNOTATION

Complete or partial trisomy of chromosome 21 (Down syndrome) is the most common aneuploidy compatible with life, occurring in approximately 1:800 live births. Down syndrome is also the most common inherited disorder associated with congenital heart defects (CHD). At least half of all patients with Down syndrome have CHD. The average life expectancy for this disorder has increased significantly, from 25 to 53–58 years, but cardiovascular complications remain the major factor limiting the life expectancy of these patients both in childhood and later in life. In this paper, we present a clinical observation of a 59-year-old patient with Down syndrome, conduction disorders (third-degree atrioventricular block, implanted pacemaker) and severe manifestations of multisystem diseases, and also provide an overview of the spectrum and pathogenesis of cardiovascular disorders in this disease. Understanding the multisystem nature of the disease, the features of the clinical manifestations of the syndrome and timely treatment of cardiovascular pathology can significantly improve the quality of life and increase the life expectancy of these patients.

Keywords: Down syndrome, congenital heart defects, mental retardation, trisomy 21, chimerism, atrioventricular septal defect, acquired cardiovascular diseases, mitral valve prolapse, aortic regurgitation, premature aging, atherosclerosis, arterial hypertension, coronary heart disease, pulmonary hypertension, arrhythmia.

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DAUN SINDROMI VA YURAK-QON TOMIR PATOLOGIYASI: KLINIK KUZATISH VA ADABIYOTLARNI KO'RIB CHIQISH

АННОТАЦИЯ

21-xromosomaning to'liq yoki qisman trisomiyasi (Daun sindromi) hayotga mos keladigan eng keng tarqalgan anevlodiya bo'lib, taxminan 1:800 tirik tug'ilgan chaqaloqlarda uchraydi. Down sindromi, shuningdek, tug'ma yurak nuqsonlari (CHD) bilan bog'liq eng keng tarqalgan irsiy kasallikdir. Daun sindromi bilan og'rigan bemorlarning kamida yarmida yurak-qon tomir kasalliklari mavjud. Ushbu buzuqlik uchun o'rtacha umr ko'rish sezilarli darajada oshdi, 25 dan 53-58 yilgacha, ammo yurak-qon tomir asoratlari bu bemorlarning bolalik davrida ham, keyingi hayotlarida ham umr ko'rishni cheklovchi asosiy omil bo'lib qolmoqda. Ushbu maqolada biz Daun sindromi, o'tkazuvchanlik buzilishi (uchinchi darajali atrioventrikulyar blokada, implantatsiya qilingan yurak stimulyatori) va ko'p tizimli kasalliklarning og'ir ko'rinishlari bo'lgan 59 yoshli bemorning klinik kuzatuvini taqdim etamiz, shuningdek, ushbu kasallikdagi yurak-qon tomir kasalliklarining spektri va patogenezi haqida umumiy ma'lumot beramiz. Kasallikning ko'p tizimli tabiatini tushunish, sindromning klinik ko'rinishlarining xususiyatlari va yurak-qon tomir patologiyasini o'z vaqtida davolash ushbu bemorlarning hayot sifatini sezilarli darajada yaxshilaydi va umr ko'rish davomiyligini oshiradi.

Kalit so'zlar: Daun sindromi, tug'ma yurak nuqsonlari, aqliy zaiflik, trisomiya 21, kimerizm, atrioventrikulyar septal nuqson, orttirilgan yurak-qon tomir kasalliklari, mitral qopqoq prolapsasi, aorta etishmovchiligi, erta qarish, ateroskleroz, arterial gipertenziya, o'pka gipertenziyasi, o'pka gipertenziyasi

Down syndrome is one of the most common chromosomal abnormalities, resulting from a mutation of the 21st pair of chromosomes, resulting in the formation of an extra copy in the human genome. This syndrome was first described by D. Down in 1866. Chromosome 21 is the smallest human chromosome, containing 200–300 genes (127 known genes, 98 predicted genes, and 59 pseudogenes) [1]. Patients with Down syndrome have a larger number of copies of genes on chromosome 21. The genes themselves are normal; the anomaly consists of the production of an increased number of gene products on this chromosome as a result of excessive expression in cells and tissues, which leads to the formation of phenotypic abnormalities [2].

The incidence rate is 1 in 800 live births [3]. The prevalence of the syndrome does not depend on race, nationality, or socioeconomic status. In Russia, the overall incidence of Down syndrome increased from 15.53 per 10,000 in 2011 to 19.93 per 10,000 in 2017. At the same time, the incidence of Down syndrome among newborns alone decreased over this period from 9.91 to 7.54 per 10,000 births [4].

Recently, thanks to improved care and early treatment of complications, the overall life expectancy of patients with Down syndrome has increased significantly, and they are beginning to come to the attention of physicians and cardiologists. This article presents a clinical case of a 59-year-old patient with Down syndrome who developed an acquired heart defect and severe conduction disturbances, leading to death.

Clinical observation

A 59-year-old female patient with critical depletion of the pacemaker's power supply was admitted to the cardiac intensive care unit of a multidisciplinary hospital. Upon admission, she had no complaints regarding the severity of her condition.

According to medical records, the patient had a history of hypertension, coronary artery disease, and angina, complicated by chronic heart failure, for over 10 years. In 2023 , a pacemaker was implanted for third-degree atrioventricular block. She also had a history of chronic pyelonephritis, C4 chronic kidney disease, Child-Pugh class B liver cirrhosis (9 points), and metal osteosynthesis for a closed fracture of the left femur.

At the pre-hospital stage, depletion of the power supply was detected, as a result of which the patient was hospitalized by an ambulance team in the intensive care unit.

On admission, the general condition is serious. Coma I. The skin is pale. Swelling of the shins and feet. The respiratory rate is 5 per 1 min, the rhythm is irregular. Percussion sound is clear pulmonary. On auscultation, breath sounds are weakened over the lower parts of the lungs, no wheezing. Tracheal intubation with an 8 mm tube was performed, artificial ventilation of the lungs was started with a Drager apparatus in Bipap mode. Heart sounds are muffled, a systolic murmur is heard over the projection point of the aortic valve, radiating to the vessels of the neck. The rhythm is irregular. Heart rate (HR) is 12-20 per 1 min with pauses of up to 15 s (Morgagni-Adams-Stokes attacks). There is no pulse deficit. Blood pressure is undetectable. The tongue is clean, enlarged. The abdomen is normal in shape, soft, painless. There are no symptoms of peritoneal irritation. The liver is painless to palpation, enlarged by 3 cm, and exhibits the "caput medusae" sign. The spleen is not enlarged to percussion, is not palpable, and is painless. Urination is free.

The electrocardiogram (see figure) revealed complete atrioventricular block with pauses on the monitor of up to 15 seconds. Insertion of a temporary pacemaker was unsuccessful. The permanent pacemaker was replaced as an emergency measure.

A complete blood count revealed moderate normochromic normocytic anemia: hemoglobin concentration 84 g/L (normal 112–153 g/L), red blood cell count 2.94×10 12 /L (normal 3.8–5.15×10 12 /L), hematocrit 30% (normal 34.9–45.6%), mean corpuscular volume 86 fl (normal 82–98 fl), mean corpuscular hemoglobin content 28.0 pg (normal 26.7–33 pg), mean corpuscular hemoglobin concentration 325 g/L (normal 314–349 g/L), color index 0.86 (normal 0.82–1.1), leukocytes 12×10 9 /L (normal 4.5–11×10 9 /L), neutrophils 10.84×10 9 /L (normal 1.8–6.98×10 9 /L). The data of the biochemical blood test and coagulogram upon admission and over time are presented in Table 1.

A CT scan of the brain revealed no evidence of acute cerebrovascular accident. A chest X-ray revealed congestion and bilateral hydrothorax.

According to echocardiography (EchoCG), the aortic root is compacted and calcified, the aortic pulsation is rhythmic, the aortic diameter at the level of the sinuses of Valsalva is 26 mm. Calcification of the aortic valve with the formation of stenosis of the aortic orifice of mild severity (gradient 33/17 mm Hg, blood flow velocity through the aortic valve 2.91 m/s) [5] and mild insufficiency (small central

regurgitant flow, weak density, regurgitant jet width 2 mm) [6], the number of cusps is not reliably determined. Mitral valve prolapse: systolic prolapse of the anterior leaflet up to 2 mm, opening is not impaired. Left ventricular myocardial hypertrophy (144 g/m2) : interventricular septum (IVS) thickness in diastole is 11 mm, left ventricular (LV) posterior wall thickness in diastole is 11 mm. Left atrial cavity expansion: maximum anteroposterior dimension of the left atrium is 43 mm, volume is 74 ml. LV is not dilated: LV end-diastolic dimension is 38 mm, LV end-diastolic volume is 60 ml. LV ejection fraction is 50%. Local contractility is not impaired. IVS dyssynchrony. Right ventricle is not dilated: end-diastolic dimension is 34 mm, right atrium area is 16 cm2 . Pericardial leaflets are separated by up to 6 mm behind the posterior and lateral walls of the LV. There is a pacemaker electrode in the right sections. Estimated pulmonary artery systolic pressure is 30 mmHg.

Despite the therapy administered (including inotropic and respiratory support, and a change of pacemaker as needed), on the 8th day of hospitalization, ineffective cardiac pacing and asystole were recorded, resuscitation measures were carried out without effect, and biological death was confirmed.

The pathological diagnosis coincided with the clinical one:

“Underlying disease: valvular aortic stenosis: aortic valve perimeter 6.5 cm, orifice diameter 0.8 cm, calcification of the aortic valve leaflets, myocardial hypertrophy (heart weight 381 g, left ventricular wall thickness 1.7 cm).

Underlying disease: Down syndrome: hydronephrosis of the kidneys on both sides, hypoplasia of the left kidney.

Complications: cardiac conduction disorder: atrioventricular block grade 2–3. Implantation of the dual-chamber pacemaker "EKS-460-DR" in 2013. Critical depletion of the pacemaker power source. Replacement of the pacemaker "EKS-460-DR" with the pacemaker "EKS-460-DR" on October 15, 2020. Pulmonary edema. Bilateral hydrothorax (left 300 ml, right 800 ml). Ascites 200 ml. Acute venous congestion. Necrosis of the epithelium of the convoluted tubules of the kidneys. Cerebral edema.

Resuscitation and intensive care: puncture and catheterization of the right jugular vein on October 15, 2020. Orotracheal intubation on October 15, 2020. Artificial ventilation from October 15, 2020 to October 23, 2020.

Concomitant conditions: aortic atherosclerosis (grade 1, stage II). Chronic pyelonephritis. Chronic simple bronchitis. Diffuse pneumosclerosis. Bilateral pleural adhesions. Child-Pugh class B liver cirrhosis (9 points). Moderate normochromic normocytic anemia."

Down syndrome

Down syndrome is caused by a mutation in the 21st pair of chromosomes, resulting in the formation of an extra copy in the human genome. Factors that increase the risk of having a child with trisomy 21 include maternal age. A woman has a 1:1925 risk at age 20, 1:885 at age 30, 1:365 at age 35, 1:110 at age 40, and 1:50 at age 45. Heredity and impaired gamete formation also play a role [7].

There are three forms of Down syndrome: simple trisomy 21, translocation trisomy 21, and mosaic trisomy 21. In simple trisomy 21, the genome consists of 47 chromosomes, including three chromosomes in the 21st pair. This type most often occurs during the formation of reproductive cells (oocytes in 95% of cases, and sperm less frequently) and is associated with a disruption in chromosome separation during the first or second meiotic cell division, resulting in an extra copy of chromosome 21. The karyotypes of children are as follows: females: 47, XX, +21; males: 47, XY, +21. It occurs in 90–95% of cases. The translocation variant involves the transfer of a chromosome fragment to another (usually between the 14th and 21st, 21st and 22nd, 22nd and 21st chromosomes) and accounts for 5–6% of all cases of Down syndrome. The karyotypes for girls are 46, XX, der (21, 21) +21 or 46, XX, der (14, 21) +21, for boys — 46, XY, der (21, 21) +21 or 46, XY, der (14, 21) +21. The mosaic form affects only some cells of the body, and is therefore the most difficult to diagnose. The frequency of occurrence is 2–3% of all cases of Down syndrome [8]. There are several types of mosaic trisomy: cellular, tissue, and chimerism. In the first case, it is represented by an alternation of normal and trisomic cells, in the second case, by tissues affected by trisomy; the latter variant is formed by the fusion of two fertilized eggs, one or both of which are affected by mosaicism, with the formation of one embryo [4, 5].

In Down syndrome, birth weight is typically low, and height, weight, and head circumference are below normal due to hypotonia, a small oral cavity, and associated gastrointestinal and cardiovascular diseases. With age, patients tend to gain weight due to hypothyroidism, high leptin levels, and a low basal metabolic rate. Variable degrees of mental retardation are also observed in patients. Intelligence Quotient (IQ) ranges from moderate (50–70) to low (35–50). Such children are less well-adjusted to life and adapt slowly. The typical behavioral pattern of such patients suggests an affectionate, caring, and fairly sociable person, but autistic personality traits are increasingly common among them, observed as early as 2–3 years of age [6, 7].

The "gold standard" for diagnosing the disease is chromosomal analysis, which can detect an extra copy of the chromosome. Molecular genetic methods, such as quantitative fluorescence polymerase chain reaction and interphase in situ hybridization, provide rapid diagnosis and can be used in premature infants [9].

Antenatal screening for Down syndrome allows us to determine the probability of having a child with this pathology and is recommended for women of all ages in the first and second trimesters of pregnancy. Screening in the first trimester is performed using statistical programs (Astraia, etc.) and includes an assessment of three components: the age risk of the parents, the biochemical risk (serum human gonadotropin + PAPP protein + PIGF), and the ultrasound risk (based on the nuchal translucency thickness), after which the total risk is calculated. The detection rate of the syndrome during screening is 80–82% with a false-positive rate of 3% [10]. Currently, only ultrasound screening is performed in the second trimester; more than 10 markers of Down syndrome are assessed at 19–21 weeks of pregnancy. Second trimester screening, previously performed as a triple or quadruple test (including determination of serum human gonadotropin, unconjugated estriol, alpha-fetoprotein, and inhibin A or 17-hydroxyprogesterone levels at 15–19 weeks), has now been discontinued due to low cost-effectiveness and clinical efficacy. Down syndrome was detected in 80% of cases [11]. If the threshold level of the total risk based on the results of the first screening exceeds 1:250, chorionic villus sampling at 11–12 weeks or safer and no less reliable amniocentesis at 16–18 weeks of pregnancy [10] is used for accurate verification of the diagnosis.

Children with Down syndrome often have malformations of the cardiovascular, respiratory, nervous, immune, endocrine, genitourinary, and musculoskeletal systems. Congenital heart defects (CHDs) and vascular defects are of particular interest because they are the leading cause of death in people with Down syndrome. According to statistics, 13% of children and 24% of adults die from cardiac causes among these patients [12]. In addition to CHDs, respiratory infections and leukemia reduce patient survival. Recently, thanks to improved care and early treatment of complications, the overall life expectancy of patients with Down syndrome has increased significantly [12].

Congenital heart defects in Down syndrome

40–50% of newborns with Down syndrome have congenital heart defects [9, 10, 13–15]. They are the main cause of death in the first 2 years of life [16]. The most common congenital heart defects are complete or incomplete atrioventricular canal (or so-called atrioventricular septal defect (AVSD)), ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus (ductus arteriosus), and tetralogy of Fallot [10, 15]. AVSD and VSD are typical malformations in Down syndrome [17]. The most common defect in newborns is AVSD, accounting for 40% of all cases of congenital heart defects. The second most common is VSD, accounting for 35% of all cases of congenital heart defects [9, 13].

The mutation that contributes to the development of AVSD in Down syndrome is located on chromosome 21 [18]. To date, two specific genetic loci for AVSD have been identified. One of them is the AVSD1 locus, present on chromosome 1p31-p21 [19]. The other locus is present on chromosome 3p25 and the corresponding cysteine-rich gene, EGF-like domain 1 (CRELD1) [20, 21]. AVSD is a congenital heart defect in which the VSD and ASD are fused and there is pathology of the atrioventricular valves [22]. A distinction is made between complete and incomplete AVSD [23]. Incomplete AVSD is characterized by the

presence of separate atrioventricular valves, ostium primum ASD, inlet VSD, and mitral valve cleft. It is caused by incomplete fusion of the endocardial cushions [24].

Complete AVSD is characterized by a common atrioventricular valve, an ostium primum ASD, and an inlet VSD. It is caused by a complete nonfusion of the endocardial cushions [25]. In complete AVSD, the common atrioventricular valve has 5 large leaflets: 3 lateral (adjacent to the free walls) and 2 bridging (septal) [26]. In AVSD, a disproportion between the outlet and inlet sizes of the left ventricle is observed, with the former being larger than the latter compared to a normal heart, where they are equal.

In routine antenatal ultrasound scanning, AVSD is best visualized in the four-chamber view of the heart as a common atrioventricular valve [27]. However, the sensitivity of antenatal ultrasound for AVSD is very low [28]. Postnatal diagnosis of AVSD is made using electrocardiography, chest radiography, and echocardiography. Echocardiographic findings include abnormal atrioventricular valve configuration, loss of normal atrioventricular valve displacement, abnormal papillary muscle position, LV inlet-outlet disproportion, ostium primum ASD, inlet VSD, and other associated congenital heart defects [19, 22].

This is usually a severe, hemodynamically significant defect; however, it is compatible with life, and with mild impairments, patients can survive for up to 20 years or more [22]. AVSD is subject to surgical correction. The goal is to close the VSD, ASD, and restore the atrioventricular valves [27]. Patients who have undergone surgical treatment have a 15-year survival rate of approximately 90%. Between 9% and 10% of them require reoperation within 15 years [29].

VSD is a congenital heart defect characterized by a communication (hole) between the left and right ventricles, resulting in left-to-right shunting and pulmonary hypertension [22, 30]. Color Doppler mapping with transthoracic echocardiography is the most sensitive diagnostic method. Approximately 85% to 90% of small isolated VSDs spontaneously close within the first year of life. Surgical closure of VSD is indicated for moderate to large defects with LV dysfunction, in cases of progressive aortic insufficiency, or after an episode of endocarditis [31].

ASD is a congenital heart defect (CHD) in which there is a communication (hole) between the left and right atria, through which blood is shunted [22, 32]. ASD often does not cause clinical symptoms [33]. Diagnostic imaging is important to determine the size of the defect and is crucial for determining management tactics. Transthoracic echocardiography is the "gold standard" of imaging [32]. ASDs smaller than 5 mm often close spontaneously within the first year of life. ASDs larger than 1 cm most often require surgical closure of the defect [34].

In addition, it is necessary to note the possibility of developing cardiovascular complications of congenital heart disease in patients with Down syndrome, including pulmonary hypertension, arrhythmia and conduction disturbances, the presence of which is a predictor of an unfavorable prognosis for the patient [35].

Acquired CVD in patients with Down syndrome

The cardiac anatomy of individuals with trisomy 21 without overt CHD is not entirely normal. Shortening of the IVS and enlargement of its membranous portion have been reported in neonates with Down syndrome without CHD [36]. In addition, valvular dysplasia was detected in 64% of cases. Also, when evaluating the cardiac status of a random group of adults with Down syndrome, a large number of patients with mitral valve prolapse or aortic regurgitation were found [37–39]. Systolic function in adolescents with Down syndrome without CHD [40] and cardiorespiratory test results (treadmill test with assessment of external pulmonary function) [41] were adequate, suggesting the possibility of normal physical activity, although reduced performance was noted [42].

Premature aging and a tendency toward obesity have been described in patients with Down syndrome. Not only do degenerative changes in appearance, such as skin and hair, appear earlier than in mentally retarded individuals without Down syndrome, but symptoms of Alzheimer's disease are also noted earlier than in the general population. By the age of 45, almost all people with Down syndrome develop senile plaques, neurofibrillary tangles, and granulovacuolar degeneration of nerve cells. People with Down syndrome have a shorter life expectancy than the general population [43]. People with Down syndrome are also more likely to be overweight and obese than people without the disease, and have a higher incidence of thyroid and parathyroid disease, osteoporosis, metabolic syndrome, and type 2 diabetes [44–46]. Obesity is more common among women with Down syndrome than among men. Probable determinants of obesity included elevated leptin levels, decreased resting energy expenditure, comorbidities, poor diet, and low levels of physical activity. Obesity was positively associated with obstructive sleep apnea, dyslipidemia, hyperinsulinemia, and gait disturbance [47, 48].

According to E. Vianello et al. [49], adults with Down syndrome rarely develop atherosclerosis, arterial hypertension, and coronary heart disease (Table 2). The study [50] found that adults with Down syndrome have lower carotid intima-media thickness, systolic and diastolic blood pressure, and higher levels of C-reactive protein, triglycerides, and total body fat than the control group. Adults with Down syndrome may be protected from atherosclerosis despite higher levels of total body fat and increased CVD risk factors. This trend is explained by overexpression of protective anti-atherosclerotic factors through genes located on chromosome 21 [51]. Furthermore, it has been suggested that higher levels of adiponectin [52] and fatty acid binding proteins [49] may play a role in protecting adults with Down syndrome from atherosclerosis.

The cardiovascular system of patients with Down syndrome has also been reported to be characterized by altered autonomic control of cardiac activity and autonomic dysfunction. Patients with Down syndrome without congenital heart disease demonstrate decreased heart rate and blood pressure in response to isometric grip exercises, tilt testing, and cold press testing [54, 55]. Patients with Down syndrome exhibit less parasympathetic inhibition and sympathetic excitation in response to passive vertical tilt. These effects may be mediated by a smaller change in baroreflex sensitivity in individuals with Down syndrome [55]. Autonomic dysfunction may also partially explain the lack of increase in heart rate during the maximal treadmill test in these patients [54].

There are no statistics on the life expectancy of patients with Down syndrome in our country. According to international data [3], the average life expectancy for this condition has increased in recent years from 25 to 53–58 years. In the present case, the patient lived to age 59 and died of multiple organ failure due to untimely pacemaker replacement and acute decompensation of heart failure.

In the clinical observation we presented, a patient with a diagnosis of Down syndrome confirmed in childhood had no data for the presence of congenital heart disease; at 52 years of age, severe conduction disturbances developed, requiring the installation of a pacemaker; at 59 years of age, mild degenerative stenosis of the aortic orifice and aortic valve insufficiency were diagnosed.

Thus, as life expectancy increases, patients with Down syndrome are beginning to come to the attention of physicians, cardiologists, and intensive care specialists caring for adults. Currently, the management of these patients is guided by general guidelines. It is necessary to study the specific features of cardiovascular disease in this category of patients to provide them with adequate medical care. In the future, it is possible to develop specific clinical guidelines or include specific sections within general guidelines on the specific management of these patients

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