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Chromosomal abnormalities in children as a predictor of the development of congenital heart and vascular diseases

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Congenital heart defects (CHDs) are the most common of all congenital abnormalities in children and cover a wide range of lesions. They can manifest as minor defects and very complex combined lesions that are incompatible with life. CHDs occur on average in 8–10 cases per 100 live births. The complexity and diversity of cardiovascular defects is traditionally explained by multifactorial etiology, due to the interaction between several genes and environmental factors (the so-called «polygenic model»), but chromosomal abnormalities are often the leading factor in the occurrence of CHDs. The importance of studying chromosomal pathology in the context of CHD lies in the possibility of identifying specific genetic markers that are predictors of the development of these conditions.
The aim — to analyze the current research data on the frequency of CHDs in children with chromosomal pathology; find out the structural features and possibilities of correction of these defects; evaluate the prognostic possibilities of genetic counseling in the prevention and early detection of congenital cardiovascular system pathology in children with chromosomal defects.
The most common chromosomal abnormalities and their impact on the development of the child's cardiovascular system are considered, and the current state of research in this area is reflected. Clinical signs of the main types of chromosomal abnormalities, their cardiac and extracardiac manifestations are presented. It is established that the largest proportion of CHDs in patients with chromosomal abnormalities are septal defects, which are usually associated with impaired development of endocardial cushions due to an imbalance in the expression of genes located on the affected chromosomes. Genetic testing for congenital cardiovascular abnormality can potentially improve prognosis by providing valuable information on personalized health care, confidence in clinical diagnosis, and patient follow-up.
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Keywords: congenital heart defects, chromosomal pathology, early diagnosis, prognosis, children.

Хромосомні аномалії в дітей — предиктор розвитку вроджених вад серця та судин

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Вроджені вади серця (ВВС) є найпоширенішими серед усіх вроджених патологій у дітей і охоплюють широкий спектр уражень. Вони можуть проявлятися як незначними дефектами, так і дуже складними комбінованими ураженнями, несумісними з життям. ВВС зустрічаються в середньому в 8–10 випадках на 100 живонароджених немовлят. Складність і різноманітність вад серцево-судинної системи традиційно пояснюється мультифакторною етіологією внаслідок взаємодії між кількома генами та факторами навколишнього середовища (так звана «полігенна модель»), однак часто провідним чинником виникнення ВВС є хромосомні аномалії. Важливість вивчення хромосомної патології в контексті ВВС полягає в можливості виявлення конкретних генетичних маркерів, які є предикторами розвитку цих станів.
Мета: проаналізувати сучасні дані досліджень щодо частоти ВВС у дітей із хромосомною патологією; з'ясувати структурні особливості та можливості корекції цих вад; оцінити прогностичні можливості генетичного консультування у профілактиці та ранньому виявленні вродженої патології серцево-судинної системи в дітей із хромосомними дефектами.
Розглянуто найбільш поширені хромосомні аномалії, їхній вплив на розвиток серцево-судинної системи дитини, висвітлено поточний стан досліджень у цій області. Наведено клінічні ознаки основних видів хромосомних аномалій, їхні серцеві та позасерцеві прояви. Встановлено, що найбільшу частку серед ВВС у пацієнтів із хромосомними аномаліями становлять септальні дефекти, які зазвичай пов'язані з порушенням розвитку ендокардіальних подушок унаслідок дисбалансу експресії генів, розташованих на уражених хромосомах. Генетичне дослідження при вродженій патології серцево-судинної системи може потенційно покращити прогноз, надаючи цінну інформацію щодо персоналізованого медичного обслуговування, впевненості у клінічному діагнозі та спостереження за пацієнтом. Автори заявляють про відсутність конфлікту інтересів.
Ключові слова: вроджені вади серця, хромосомна патологія, рання діагностика, прогноз, діти.

Introduction

In recent decades, increased attention has been paid to the relationship between genetic factors and the development of congenital heart defects (CHDs) in children. CHDs can be either isolated or part of more complex syndromes associated with chromosomal abnormalities [8,11,13]. Understanding the genetic basis of CHDs not only contributes to a better understanding of these disorders but also opens up new horizons for the development of individualized approaches to the treatment and care of children with such conditions, helping to improve their overall health and quality of life.

The importance of studying chromosomal abnormalities in the context of CHDs lies in the possibility of identifying specific genetic markers that can serve as predictors of the risk of developing these conditions [34].

Turner syndrome is a disease of the female body caused by the complete or partial absence of one of the X chromosomes, the main manifestations of which can be short stature, hypogonadism, fertility disorders, and developmental defects, including CHDs. Turner syndrome is the most common chromosomal

abnormality affecting women: the incidence is 1 in every 2,500 live births. The incidence of CHDs in women with Turner syndrome is 23–50%, and it is the leading cause of early mortality of such patients [41]. The most commonly described CHDs in Turner syndrome are as follows: elongation of the transverse aortic arch (30–49%), aortic dilatation (23%), aortic coarctation (3.4–15.7%), bicuspid aortic valve (6.8–39.2%), abnormal connections of the great vessels (13–18%), persistent left superior vena cava (13%), aberrant right subclavian artery (8%) [17,32]. Turner syndrome can occur in several karyotypes: 45X0 — full monosomy, 45X0/47XX — mosaicism, and several structural abnormalities of the X chromosome (ring X chromosome, deletion of the short or long arm). The karyotype causing Turner synrdome is associated with the incidence of CHDs. Thus, in a retrospective cohort study conducted in Taiwan, a statistically significant difference was found in the frequency of aortic dilatation (32.5% in the group of full monosomy vs. 6.2% in the group of other karyotypes) and bicuspid aortic valve (15% vs. 0%, respectively) [13].

According to the French national protocol for the diagnosis and treatment of Turner syndrome, the following identified symptoms enable to suspect this pathology in the antenatal period: thick neck, anasarca, coarctation of the aorta, left heart abnormalities, renal abnormalities, brachycephaly, moderate intrauterine growth retardation, hydroamnion/oligoamnion. The symptoms suggestive of Turner syndrome in newborns are as follows: lymphedema of the extremities, thick neck, orbito-palpebral abnormalities, strabismus, low-set or abnormal ears, frequent otitis, deafness, cubitus valgus, shortening of the 4th metacarpal bone, genu valgum, kyphosis, scoliosis, delayed ossification, thyroid chest, autoimmune thyroiditis, multiple nevi, vitiligo, alopecia. The symptoms that may indicate Turner syndrome in children and adults are as follows: short stature, primary ovarian failure, micrognathia, dental anomalies, domed palate, short and winged neck (which is a predictor of CHDs as well as large vessel anomalies), celiac disease, inflammatory gastrointestinal diseases, horseshoe, double, ectopic kidney or renal agenesis, learning difficulties, neurocognitive deficits, psychological immaturity [18].

One of the important causes of death in Turner's syndrome is aortic dissection; its incidence in this disease is 40 per 10,000 patients, which is higher than the incidence in the general population. The risk factors for aortic dissection in Turner syndrome have not been researched well enough, and the proposed variants include bicuspid aortic valve, aortic dilatation, and coarctation [17,29]. Aortic dilatation is observed in 23% of patients with Turner syndrome, although this condition in this pathology and the methods for its detection are not generally accepted. The American Heart Association (AHA) recommends transthoracic echocardiography and cardiac MRI with contrast [41]. To assess the risk of aortic dissection, it is recommended to use the aortic size index (ASI), which is calculated as the diameter of the ascending aorta divided by the body surface area. The ASI value of more than 2.5 cm/m^2 is considered to be associated with an increased risk of aortic dissection, but only in patients aged ⩾15 years. For younger patients, graphs of diameter distribution according to body area are used; values above 2 standard deviations from the median are defined as aortic enlargement [15].

The AHA sets the following indications for surgical treatment: ASI ⩾2.5 cm/m^2 in patients 15 years of age and older who have additional risk factors, such as arterial hypertension and bicuspid aortic valve; in their absence, however, surgical treatment may also be considered. In patients younger than 15 years of age, surgery should be considered if the expected diameter of the ascending aorta is deviated by 4 standard deviations or more. An increase in aortic diameter constituting 0.5 cm per year or an increase of one standard deviation over the same time is an indication for optimization of medical treatment (including blood pressure control, beta-blockers and angiotensin-converting enzyme (ACE) inhibitors, cardiac surgery consultations [15,17,41].

According to various studies, bicuspid aortic valve in Turner syndrome occurs in 25% to 39.2% of cases [29,35]. Its presence constitutes a risk factor for the development of aortic aneurysm, aortic valve insufficiency, stenosis due to accelerated calcification and infective endocarditis. Bicuspid aortic valve in the population of women with Turner syndrome is 30–60 times more common than in the general population. According to the AHA recommendation, if a female patient is diagnosed with a bicuspid aortic valve, she should be recommended for genetic testing to eliminate Turner syndrome [41].

The AHA recommends the following approaches to classifying patients with Turner syndrome into risk groups and their further management:

1) for patients under than 15 years of age, in the absence of aortic coarctation, bicuspid aortic valve or arterial hypertension, if the aortic diameter deviates from the expected one by 3 or fewer standard deviations, the patient is in the low-risk group, re-examination by a family doctor or pediatric cardiologist and echocardiography or magnetic resonance imaging (MRI) every 5 years is recommended;

— if the aortic diameter deviates from the expected one by more than 3 standard deviations — a moderate risk group, re-examination by a pediatric cardiologist and echocardiography or MRI is recommended every year; in the presence of coarctation of the aorta or bicuspid aortic valve or arterial hypertension, if the aortic diameter deviates from the expected one by 3 or fewer standard deviations — moderate risk group, re-examination by a pediatric cardiologist and echocardiography or MRI is recommended every 1–2 years; if the deviation of the aortic diameter from the expected one is more than 3 standard deviations — a high-risk group, repeated examination by a pediatric cardiologist and echocardiography or MRI every 6–12 months is recommended;

2) for patients ⩾15 years of age: in the absence of aortic coarctation, bicuspid aortic valve or arterial hypertension, with an ASI of less than 2 cm/m^2, the patient is considered to be at low risk, and repeated cardiologic examination and echocardiography or MRI every 5 to 10 years is recommended; with ASI within the range of 2–2.3 cm/m^2 — a moderate risk group, it is recommended to repeat the examination by a cardiologist and echocardiography or MRI every 3–5 years; with ASI of more than 2.3 cm/m^2 — a moderate risk group, it is recommended to repeat the examination by a cardiologist and echocardiography or MRI every year. In the presence of aortic coarctation or bicuspid aortic valve or arterial hypertension, if the ASI is less than or equal to 2.3 cm/m^2 — the patient belongs to the moderate risk group, it is recommended to repeat the examination by a cardiologist and echocardiography or MRI every 2–3 years; if ASI is more than 2.3 cm/m^2 — high risk group, it is recommended to repeat the examination by a cardiologist and MRI every 6–12 months [23,35,41].

Down syndrome is a set of clinical manifestations resulting from the trisomy of 21 chromosomes. Trisomy of chromosome 21 is the most common chromosomal abnormality and, among all trisomies there is the greatest chance of long-term survival. CHDs occur in about half of patients with Down syndrome [30,39]; CHDs and their complications cause 13% of deaths in childhood and 23% of deaths in adulthood in patients with Down syndrome [34]. Characteristic features of newborns with Down syndrome include hypotension which can lead to problems with feeding and reduced activity; flattened nasal bridge, brachycephaly, eye slits slanted upward, epicanthus, large protruding tongue, wide hands, wide gap between the 1st and 2nd toe [3,8]. According to the AHA recommendations, the main screening method for prenatal diagnosis of Down syndrome is extracellular DNA testing: the study of free-floating small DNA fragments that enter the mother's bloodstream from the placenta [8]. There are 2 groups of causes that bind trisomy to chromosome 21 and the development of CHD: a direct increase in protein production due to the expression of genes located on chromosome 21 and dysregulation of gene expression on other chromosomes due to aneuploidy [3,30] .

The most common CHDs found in patients with Down syndrome are the following: ventricular septal defect (VSD), atrial septal defect (ASD), atrioventricular canal defects, patent ductus arteriosus, and Fallot's tetrad. All of them are related to abnormalities in the development of the endocardial cushion [1]. Genes located on chromosome 21 and considered to be related to the development of CHDs include: Down syndrome cell adhesion molecule (DSCAM), cell adhesion molecule; 2 of 3 chains of collagen VI, an excessive amount of which activates discoidine domain receptors that regulate the interaction between cells and collagen; dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) and regulator of calcineurin 1 (DSCR1), both molecules reduce the activity of the nuclear factor of activated T-cell (NFATc) signaling pathway, which leads to defects in the endocardial cushion; they also modulate the activity of Synaptojanin 1 (SYNJ1) which regulates the activity of endosomal transport, which is extremely important for myocardial function [30].

Atrioventricular septal defect (atrioventricular canal defect) is a CHD characterized by a combination of defects in the VSD and ASD and a common or partially divided atrioventricular opening. This defect is the result of impaired fusion of endocardial cushions during embryogenesis.

There are complete and incomplete defects of the atrioventricular canal. A complete atrioventricular septal defect includes the primary ASD, VSD, and common atrioventricular opening, and constitutes the result of a complete disruption of the fusion of the endocardial cushions. In this case, the common atrioventricular opening valve includes 5 leaflets: superior septal, inferior septal, left wall, right wall, and anterior-upper. In accordance with the anatomy of this anomalous valve, 3 types of complete atrioventricular canal defect can be distinguished: type A — the superior septal leaflet is attached to the surface of the left ventricle by means of a chord; type B — the superior septal leaflet is attached to the surface of the right ventricle by means of a chord; type C — the superior septal leaflet is not attached to the interventricular septum. Incomplete atrioventricular septal defect includes the primary ASD, VSD, separate atrioventricular openings and a gap in one of the mitral valve leaflets, which is a consequence of partial fusion of endocardial cushions [1]. Atrioventricular septal defect is the most common CHD observed in patients with Down syndrome — approximately 40% of patients with CHDs in the European population [3]. According to a multicenter retrospective study conducted in the Korean population, the prevalence of atrioventricular canal defect was 38% (89 out of 234 patients with Down syndrome who underwent total surgical correction of CHD) [26]. In a retrospective study conducted in Morocco, the prevalence of atrioventricular canal defect was 29% (54 out of 186 patients with CHD). At the same time, a complete atrioventricular septal defect was observed in 46 out of 54 patients; of these, 12 had Rastelli type A anatomy, 34 had type C, and type B was not observed. Incomplete atrioventricular septal defect was detected in 8 out of 54 patients. Surgical correction was performed in 60% of patients [6]. In another cohort study conducted in Turkey, atrioventricular septal defect was the 3rd most common after ASD, VSD and was observed in 23% of patients with CHD (211 out of 901 patients), of which 155 had a complete defect. Out of the 155 patients with complete atrioventricular canal defect, 107 had an isolated defect, 31 had a combination with secondary ASD, and 15 had an open arterial duct. Among the 56 patients with incomplete atrioventricular canal defect, 36 had an isolated defect, 14 had a combination with secondary ASD, and 5 had an unclosed arterial duct. Surgical correction was performed in 61.6% of patients (130 of 211) [2]. According to a Korean study, the proportion of VSD in the structure of CHD in patients with Down syndrome was the highest and amounted to 38.8% (91 out of 234 who underwent surgical correction) [26]. According to a study conducted in Morocco, the proportion of VSD was 21.5% (40 out of 186 patients), second only to the frequency of atrioventricular canal defect. Out of these 40 patients, 28 were diagnosed with perimembranous VSD, 4 — with subpulmonary, 4 — muscular, and 4 — with outflow tract defects. 68% out of patients with VSD underwent surgical correction [6]. According to a study conducted in Turkey, the proportion of VSD in the structure of CHD in patients with Down syndrome was 35% (315 out of 901 patients), which was also the highest rate. Out of these, 162 patients had an isolated VSD, 94 had a combination with a secondary VSD, 27 had a combination with a patent ductus arteriosus, and 29 had both a secondary VSD and a patent ductus arteriosus. In addition, 152 patients (48.2%) had perimembranous VSD, 67 (21.3%) had muscular VSD, 24 (7.6%) had an outflow tract defect, and in 72 patients (22.9%) the type of defect was unspecified. This study also analyzed the possibility of spontaneous closure of the VSD. In total, 56 defects underwent spontaneous closure, which is 17.8% of all VSDs. In the group of perimembranous VSDs, this phenomenon was observed in 14.4% out of cases, muscular one — in 32.8% out of cases, defect of the entrance tract — 16.7%, among unspecified ones were 11.1%. In the overall group, 123 out of 315 patients underwent surgical correction (39%) [2].

According to a thorough study by S.B. Freeman et al., secondary ASD was one of the three most common CHDs in patients with Down syndrome, its share in the structure of defects was 10% [20]. In the group selected for the Korean population-based study, the proportion of ASD was only 5.5% (13 out of 234 patients), which can be explained by the selection features: the inclusion criterion was previous surgical correction of the CHD; ASD can close spontaneously without intervention, so it is less likely to be an indication for surgery [26]. According to the Moroccan study, the proportion of ASD in the structure of the CHD was 19.9% (37 out of 186 patients) and ranked 3rd after the atrioventricular canal defect and VSD. Surgical correction was performed in 87% of patients [6]. According to the Turkish study, frequent ASD

in the structure of the CHD was 31.8% (287 out of 901 patients), ranking 2nd in terms of frequency. 246 patients had isolated ASD, 36 had a combination with an open arterial duct, and 4 had a bicuspid aortic valve. In the cohort of this study, only 4.5% of patients (13 out of 287) underwent surgical correction; in 43.2% of patients (124 out of 287), the defect underwent spontaneous closure [2].

Fallot's tetrad, which is the most common cyanotic heart defect, is also thought to be associated with Down syndrome. One meta-analysis showed that Down syndrome is the most common genetic anomaly found in patients with Fallot's tetrad, with an average prevalence of 4.6% (137 different cohorts with a total of 21,427 patients analyzed) [37]. According to a Korean study, the proportion of Fallot's tetrad in the structure of CHD in patients with Down syndrome was 8.1% (19 out of 234 patients). According to a study conducted in Morocco, the proportion of Fallot's tetrad was 5.4% (10 out of 186 patients). According to a Turkish study, the proportion of Fallot's tetrad was 5% (45 out of 901 patients). Isolated Fallot's tetrad was observed in 23 patients, in 17 patients — it was combined with an atrioventricular canal defect, in 3 patients — with secondary ASD, in 2 patients — with an open arterial duct. Surgical correction was performed in 77.8% (35 out of 45 patients) [2,6,26].

Other trisomies. The other most common autosomal trisomies are Patau (trisomy 13) and Edwards (trisomy 18) syndromes. The frequency of both of these anomalies is 1 per 5,000 newborns [42]. The most frequent CHDs in Patau syndrome are VSD, ASD, and Fallot's tetrad; in Edwards syndrome — VSD, ASD, patent ductus arteriosus, and Fallot's tetrad. According to the analysis of the database of CHD-related operations, made by the American Society of Thoracic Surgeons, 21 out of 73 (28.8%) patients with Patau syndrome included in the analysis had VSD, 14 out of 73 (19.2%) had Fallot's tetrad, 5 (6.8%) had ASD, and 5 (6.8%) had aortic coarctation. The analysis included 270 patients with Edwards syndrome, of whom 146 (54.1%) had VSD, 20 (7.4%) had patent ductus arteriosus, 16 (5.9%) had Fallot's tetrad, and 15 had ASD and a combination with aortic coarctation or hypoplasia of the aortic arch [14]. It is worth noting that the registry included only patients who underwent surgery, which fact may affect the results. Another study also analyzed the structure of the CHDs in patients who were not recommended for surgical intervention for various reasons, such as cardiopulmonary insufficiency, central sleep apnea, and central nervous system (CNS) lesions. In the combined group of patients with Edwards and Patau syndromes, 23 out of 45 patients (51.1%) had VSD, 4 (8.9%) had pulmonary artery atresia in combination with VSD, 4 (8.9%) had VSD and pulmonary artery stenosis, and 3 (6.7%) had Fallot's tetrad [38]. Previously, it was believed that CHD was not the main cause of death in patients with these chromosomal abnormalities and that correction of CHD was not beneficial. However, recently, surgical interventions for Patau and Edwards syndromes have been considered as a component of aggressive life-prolonging therapy. Their safety has also been proven by numerous studies [10,31,43].

Trisomy on chromosome 22 is the most common trisomy identified in spontaneous abortions; cases of live birth are extremely rare. In most of these cases, mosaicism is observed. The median survival rate of such children is 4 days, and life expectancy is rarely longer than 2 weeks. The literature describes an extremely small number of cases of live-born children with non-mosaic trisomy on chromosome 22 and CHD, most of them had multiple defects. The most frequent of the CHDs was VSD (14 out of 22 cases) and ASD (12 out of 22 cases); there were also Fallot's tetrad, double branching of the great vessels from the right ventricle, and a number of other defects [24,33,44]. At present, only 2 cases of VSD correction in patients with complete trisomy on chromosome 22 have been described in the literature. In one of them, a patient with complete trisomy on chromosome 22 and double branching of the great arteries from the right ventricle, ASD, hypoplastic aortic valve, severe hypoplasia of the aortic arch and a large unclosed arterial duct was operated on in several stages; at the time of the case description, the patient was alive at the age of 16 months, her condition was satisfactory [24,33].

Trisomy on chromosome 9 is another chromosomal abnormality characterized by CHD. This syndrome was first described by Feingold and Atkins in 1973; to date, more than 200 cases of this abnormality (both complete trisomy and mosaicism) have been described [12]. The symptoms of mosaicism are considered to be similar, but less severe compared to full trisomy,

and people with mosaicism have a higher average life expectancy. Information on the long-term survival of such patients is limited; as of 2021, 3 adults (19, 24, and 24 years old) with trisomy 9 syndrome were described [28]. The main clinical features characteristic of trisomy 9 are: deformed, low-set ears, micrognathia, bulbous nose, hare lip and wolf mouth, missing or hypoplastic toes, their phalanges, tarsals and calcaneals, clinodactyly, breathing and feeding problems, congenital dislocation of the hip joint, microphthalmia and, in the vast majority of cases, developmental disorders of varying severity. The most typical CHDs in this pathology are VSD, ASP, patent ductus arteriosus, and valve dysplasia. Chenxia Xu et al., referring to the previously described cases of complete trisomy on chromosome 9 (including cases of pregnancy termination and fetuses that died in utero), provides the following data on the prevalence of these CHDs: VSD — 28/59 (47.46%), ASD — 8/59 (13.56%), patent ductus arteriosus — 7/59 (11.86%) [46]. Mindy Li et al. analyzing a cohort of 16 patients with complete or mosaic trisomy on chromosome 9 and referring to previously described cases, reported the following number of recorded CHDs: 28 previously described ASDs and 4 in their cohort, 27 previously described VSDs and 1 in their cohort, 22 previously described patent ductus arteriosus and 3 — in their cohort [28].

Cat eye syndrome is a rare genetic defect, often characterized by iris coloboma, ear and anus malformation. The cause of this disease is a duplication or triplication of the long arm of chromosome 22. The incidence of cat eye syndrome is 1 in 150,000 newborns. Coloboma of the iris is detected in 50–60% of patients, fistulas or papillae in front of the ears — in 85% of cases, anus atresia — in 80% of cases, urogenital malformations (abnormalities of the male external genitalia, kidney agenesis, hydronephrosis) — in 70%, intellectual disability — in 50% of cases. Other craniofacial malformations are also possible (micrognathia, hypertelorism, hemifacial hypoplasia, antimongoloid eye incision, epicanthal folds, external auditory canal agenesis, microtia) [21]. Prenatal diagnosis of cat eye syndrome is difficult due to the nonspecific nature of the findings. In case of suspicion of this disease, the diagnosis is confirmed by karyotyping, fluorescent in situ hybridization (FISH), multiplex amplification of ligated probes [40]. CHD is observed in 50–63% of patients with cat eye syndrome. A number of studies have described the connection of cat's eye syndrome with such CHDs as VSD, Fallot's tetrad, persistent left superior vena cava, absence of inferior vena cava, and tricuspid valve atresia. Two rare CHDs that are particularly common for this chromosomal abnormality compared to the general population are complete anomalous pulmonary venous return and interrupted aortic arch, type B [22,40,45]. A complete anomalous pulmonary venous return is a condition in which blood from the pulmonary veins enters the right atrium rather than the left. The detection of complete anomalous pulmonary venous return should raise suspicion of a genetic anomaly and appropriate testing [11,22,40]. An interrupted aortic arch is an anomaly in which there is no lumen between the ascending and descending aorta. Type A of the interrupted aortic arch is diagnosed when the obstruction is detected distal to the origin of the left subclavian artery; Type B — obstruction between the left subclavian and left common carotid arteries; Type C — obstruction between the anonymous and left common carotid arteries [19]. Patients with cat eye syndrome usually have a good prognosis, including neurological, after correction of congenital abnormalities [22].

Klinefelter syndrome is a disease caused by the presence of 1 or more additional X chromosomes in the presence of a Y chromosome. 90% of cases have karyotype 47, XXY; the remaining 10% of cases constitute mosaicism (46XY/47XY) and multiple additional X chromosomes (48XXY, 49XXY). It is believed that Klinefelter syndrome occurs with a frequency of 1 per 600 newborn boys, but 64% of cases are never diagnosed during life [5]. The classical set of symptoms typical for Klinefelter syndrome includes tall stature, eunuchal physique, wide hips, little body hair, small testicular volume, and gynecomastia. Some sources believe that this syndrome is not characterized by the characteristic dysmorphic changes described classically, since the phenotype depends on the level of hypogonadism; the described manifestations occur only in extremely severe hypogonadism, which can lead to underdiagnosis of this pathology. Learning difficulties and speech disorders may also be observed. Severe cases of aneuploidy (49 XXXXXY) are characterized by impaired precision of movement and speech, with preserved visual perceptual and nonverbal skills [7]. The key feature of the syndrome is hypogonadism — biochemical, including low

testosterone levels, and clinical, including micropenis, slow virilization, gynecomastia, high body mass index, and poor muscle development. Reduced testicular volume is observed in almost all cases and is usually 2–5 ml after puberty [5,9]. The relationship between Klinefelter syndrome and CHD still requires further research, but there is evidence of a higher incidence of CHD in this pathology than in the general population. Thus, Adlyne R. Asirvatham et. al. examined a group of 44 patients with cytogenetically confirmed Klinefelter syndrome and found that CHDs were present in 10 patients (22.7%). Isolated CHDs were present in 6 of these patients: 2 cases of VSD, 2 cases of ASD, and 2 cases of patent ductus arteriosus. The remaining patients had a combination of CHDs such as: VSD and patent ductus arteriosus, VSD and transposition of great vessels, double transposition of great vessels from the right ventricle and VSD to ASD, and VACTERL anomaly (spinal defects, anus atresia, CHD, transesophageal fistula, renal anomalies, limb abnormalities) [4].

Cri du chat syndrome is a disease resulting from a deletion of the short arm of the 5th chromosome. The main manifestations in the neonatal period are a weak high monotonous cry, possibly caused by abnormalities of the epiglottis and larynx, which are often present in this pathology, low birth weight and height, sucking disorders, dysphagia, muscle hypotonia, gastroesophageal and nasal reflux, episodes of asphyxia, cyanosis and stridor; characteristic craniofacial abnormalities include microcephaly, facial asymmetry, moon face, epicanthal folds, tips of the mouth turned downward, broad (wide) nasal bridge, short groove, microretrognathia; deafness or, conversely, hypersensitivity to sounds are possible. Intellectual disabilities are also characteristic [36]. CHD is observed in 15–20% of patients with Cri du chat syndrome. The most common abnormalities are VSD, ASD, patent ductus arteriosus and Fallot's tetrad. An unbalanced translocation leading to the deletion of a part of chromosome 5 causes more severe CHD in a greater number of patients (up to 55% of cases). The mortality rate in the first month of life is 75%, in the first year — 90%. The main causes of death are aspiration pneumonia and CHD. After reaching the age of 1 year, patients reach a high survival rate and life expectancy: cases of reaching the age of 50 and 70 years have been described [16].

Williams syndrome (Williams–Beuren syndrome) is a multiorgan systemic disease caused by a deletion of a small part of chromosome 7, which usually occurs *de novo*. Its incidence varies, according to various data, from about 1 in 10,000 to 1 in 7,500 live births [25,48]. The main symptoms of Williams syndrome are craniofacial abnormalities (wide forehead, flat nose bridge, full cheeks, elongated upper lip groove, reduced and thinned cheekbones — the «elf face» phenotype; in adolescents and adults, the face lengthens, the bridge of the nose ceases to be flat, full lips and a widened mouth can be observed, especially when smiling), hypercalcemia (blood calcium >12 mg/dl is noted in 5–10% of children with Williams syndrome between 6 and 30 months of age), growth retardation and intellectual disabilities (70% of adults have an IQ<70, autism spectrum disorders are also common), and a number of CHDs. The diagnosis is confirmed by FISH, multiplex amplification of ligated probes, and chromosomal microarray analysis (the only method that does not require a suspecting the Williams syndrome to obtain a result). Unfortunately, there are no specific prenatal diagnostic and screening methods; the only non-specific finding may be fetal growth retardation during ultrasound diagnostics. The method of studying free-floating small DNA fragments is currently unable to detect the microdeletion that causes Williams syndrome. The direct factors affecting the pathogenesis of Williams syndrome are the loss of 25–27 genes on chromosome 7 and dysregulation of gene expression on other chromosomes. The most studied genes lost during microdeletion include, in particular, the elastin gene (ELN). The absence of elastin gene expression is observed in familial elastin-related aortic stenosis and Williams syndrome, and is accompanied by the following symptoms: focal or significant stenosis of large elastic arteries, most often — aortic and pulmonary stenosis, and also possible lesions of the descending aorta, renal, mesenteric and coronary arteries. The development of stenosis is explained by two possible mechanisms: excessive myocyte proliferation or development of media fibrosis. Deletion of the GTF2I and GTF2IRD1 genes in Williams syndrome leads to physical developmental delays, intellectual disabilities, and high sociality towards familiar people as well as lack of fear towards strangers (social dysinhibition) typical for this disease. Deletion of the BAZ1B gene is considered to be the cause of craniofacial abnormalities, the

LIMK1 gene — visual-spatial orientation disorders, the MLXIPL and STX1A genes — the cause of glucose and lipid metabolism disorders [25].

The cardiovascular defects that occur in Williams syndrome include supravalvular aortic stenosis, pulmonary artery stenosis, mitral valve prolapse, aortic coarctation, bicuspid aortic valve, aortic hypoplasia, and coronary artery stenosis. On average, various CHDs and their combinations affect 80% of patients with this genetic disease. The disease most commonly associated with Williams syndrome is supravalvular aortic stenosis. Its proportion among patients with Williams syndrome with CHD varies, according to various studies, it makes from 61 to 72% [47]. The manifestations of supravalvular aortic stenosis are similar to those of aortic valve stenosis: syncope, shortness of breath; a systolic murmur can be heard in the second intercostal space on the right, and possible asymmetry of the pulse in the radial arteries (weakened on the left). Stenosis leads to the development of hypertrophy of the left heart, the clinic develops mainly by the age of 20. There are differences in views on the natural course of supravalvular aortic stenosis in patients with Williams syndrome, which is explained by the small size of the cohorts and the difficulty in conducting prospective studies due to the rarity of the pathology. Some studies show that the severity of stenosis worsens over time, while others, on the contrary, indicate a greater likelihood of hemodynamic disorder being alleviated with age. For example, a study published in 2022 and conducted at a hospital in Taiwan analyzed a cohort of 30 patients with confirmed Williams syndrome who did not undergo surgical CHD correction. Out of the 30 patients, 15 (50%) had supravalvular aortic stenosis; of these, 7 (46.6%) had hemodynamically mild stenosis, 4 (26.7%) had moderate stenosis, and 4 (26.7%) had severe stenosis. At repeated echocardiography (median difference between measurements was 5.6 years), a significant increase in the peak pressure gradient was recorded only in the group of severe stenosis (from 55.4±3.5 to 65±4.0 mm Hg) [27]. Another typical feature of Williams syndrome is pulmonary artery stenosis, which accounts for 39–45% of the total structure; both pulmonary valve stenosis and stenosis of the pulmonary artery branches are possible [47]. It is believed that peripheral pulmonary artery stenosis tends to improve hemodynamically with age. According to the above-mentioned Taiwan study, peripheral pulmonary artery stenosis was detected in 11 out of 30 patients (36.7%). Out of these, 3 (27.2%) cases were classified as mild, 4 (36.4%) as moderate, and 4 (36.4%) as severe. In all severity groups, a significant decrease in the peak pressure gradient was noted during repeated echocardiography (median interval between measurements — 6 years) (from 38.4±16.5 to 25.3±13 mm Hg among all 15 patients). It is believed that only severe peripheral pulmonary artery stenosis can be an indication for balloon angioplasty [27].

Conclusions

1. Quite often, CHDs are part of genetic syndromes caused by chromosomal abnormalities. The largest proportion of CHDs in patients with chromosomal abnormalities are septal defects, which are usually associated with impaired development of endocardial cushions as a result of imbalance in the expression of genes located on the affected chromosomes.

2. An important component of the management of patients with chromosomal abnormalities is regular examination by a cardiologist for the purpose of early detection and correction of CHD.

3. Genetic testing in CHD can potentially improve prognosis by providing valuable information on personalized health care and accuracy of clinical diagnosis. In addition, genetic assessment can serve as a tool for predicting risks, determining the pattern of inheritance in the family and assessing the need for further family screening.

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REFERENCES/ЛІТЕРАТУРА

1. Ahmed I, Anjum F. (2023, Jan). Atrioventricular Septal Defect. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. URL: https://www.ncbi.nlm.nih.gov/books/NBK562194.
2. Alkaya DU, Öztürk B, Ülker AY, Bozlak S, Öztürk E, Dedeoğlu R et al. (2023). Congenital Heart Defects and Outcome in a Large Cohort of Down Syndrome: A Single-Center Experience from Turkey. Turkish Archives of Pediatrics. 58(5): 473.
3. Antonarakis SE, Skotko BG, Rafii MS, Strydom A, Pape SE, Bianchi DW et al. (2020). Down syndrome. Nature Reviews Disease Primers. 6(1): 9.
4. Asirvatham AR, Pavithran PV, Pankaj A, Bhavani N, Menon U, Menon A et al. (2019). Klinefelter syndrome: clinical spectrum based on 44 consecutive cases from a South Indian tertiary care center. Indian Journal of Endocrinology and Metabolism. 23(2): 263.

5. Bearelly P, Oates R. (2019). Recent advances in managing and understanding Klinefelter syndrome. F1000Research. 8. doi: 10.12688/f1000research.16747.1. PMID: 30755791; PMCID: PMC6352920.
6. Benhaourech S, Drighil A, Hammiri AE. (2016). Congenital heart disease and Down syndrome: various aspects of a confirmed association. Cardiovascular journal of Africa. 27(5): 287–290.
7. Bonomi M, Rochira V, Pasquali D, Balercia G, Jannini EA, Ferlin A. (2017). Klinefelter syndrome (KS): genetics, clinical phenotype and hypogonadism. Journal of endocrinological investigation. 40: 123–134.
8. Bull MJ, Trotter T, Santoro SL, Christensen C, Grout RW, Council on Genetics. (2022). Health supervision for children and adolescents with Down syndrome. Pediatrics. 149(5): e2022057010.
9. Butler G, Srirangalingam U, Faithfull J, Sangster P, Senniappan S, Mitchell R. (2023). Klinefelter syndrome: going beyond the diagnosis. Archives of disease in childhood. 108: 166–171.
10. Carey JC. (2021). Trisomy 18 and trisomy 13 syndromes. Cassidy and Allanson's management of genetic syndromes: 937–956.
11. Chen CP, Ko TM, Chen YY, Su JW, Wang W. (2013). Prenatal diagnosis and molecular cytogenetic characterization of mosaicism for a small supernumerary marker chromosome derived from chromosome 22 associated with cat eye syndrome. Gene. 527(1): 384–388.
12. Cho H, Heo JS, Ahn KH, Hong SC. (2021). Trisomy 9 Mosaicism in an Extremely Low Birth Weight Infant. Perinatology. 32(2): 100–103.
13. Chou YY, Wang CJ, Lin CH, Chung HT, Lo FS. (2020). Association between cardiovascular anomalies and karyotypes in Turner syndrome patients in Taiwan: A local cohort study. Pediatrics & Neonatology. 61(2): 188–194.
14. Cooper DS, Riggs KW, Zafar F, Jacobs JP, Hill KD, Pasquali SK et al. (2019). Cardiac surgery in patients with trisomy 13 and 18: an analysis of the society of thoracic surgeons congenital heart surgery database. Journal of the American Heart Association. 8(13): e012349.
15. Corbitt H, Maslen C, Prakash S, Morris SA, Silberbach M. (2018). Allometric considerations when assessing aortic aneurysms in Turner syndrome: Implications for activity recommendations and medical decision-making. American Journal of Medical Genetics Part A, 176(2): 277–282.
16. Davis C, Grischkan J, Tobias JD. (2020). Perioperative Care of a Child With Cri Du Chat Syndrome. Journal of Medical Cases. 11(9): 279.
17. Donato B, Ferreira MJ. (2018). Cardiovascular risk in Turner syndrome. Revista portuguesa de cardiologia. 37(7): 607–621.
18. Fiot E, Alauze B, Donadille B, Samara–Boustani D, Houang M, De Filippo G et al. (2022). Turner syndrome: French national diagnosis and care protocol (NDCP; national diagnosis and care protocol). Orphanet Journal of Rare Diseases. 17(1): 1–39.
19. Franconeri A, Ballati F, Pin M, Carone L, Danesino GM, Valentini A. (2020). Interrupted aortic arch: A case report. Indian Journal of Radiology and Imaging. 30(01): 81–83.
20. Freeman SB, Taft LF, Dooley KJ, Allran K, Sherman SL, Hassold TJ et al. (1998). Population-based study of congenital heart defects in Down syndrome. American journal of medical genetics. 80(3): 213–217.
21. Gaspar NS, Rocha G, Grangeia A, Soares HC. (2022). Cat-eye syndrome: a report of two cases and literature review. Cureus. 14(6).
22. Gözgeç E, Kantarci M, Guven F, Ogul H, Ceviz N, Eren S. (2021). Determination of anomalous pulmonary venous return with high-pitch low-dose computed tomography in paediatric patients. Folia Morphologica. 80(2): 336–343.
23. Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO et al. (2017). Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. European journal of endocrinology. 177(3): G1-G70.
24. Heinrich T, Nanda I, Rehn M, Zollner U, Frieauff E, Wirbelauer J et al. (2013). Live-born trisomy 22: patient report and review. Molecular Syndromology. 3(6): 262–269.
25. Kozel BA, Barak B, Kim CA, Mervis CB, Osborne LR, Porter M, Pober BR. (2021). Williams syndrome. Nature Reviews Disease Primers. 7(1): 42.
26. Kwak JH, Lee SW, Cha HR, Huh J, Kang IS, Jun TG et al. (2022). Long-Term Observational Outcomes after Total Correction of Congenital Heart Disease in Korean Patients with Down Syndrome: A National Cohort Study. Children. 9(9): 1329.
27. Lee CL, Lin SM, Chen MR, Chuang CK, Syu YM, Chiu HC et al. (2022). Long-term cardiovascular findings in Williams syndrome: a single medical center experience in Taiwan. Journal of Personalized Medicine. 12(5): 817.
28. Li M, Glass J, Du X, Dubbs H, Harr MH, Falk M et al. (2021). Trisomy 9 mosaic syndrome: sixteen additional patients with new and/or less commonly reported features, literature review, and suggested clinical guidelines. American Journal of Medical Genetics Part A. 185(8): 2374–2383.
29. Lin AE, Lippe BM, Geffner ME, Gomes A, Lois JF, Barton CW et al. (1986). Aortic dilation, dissection, and rupture in patients with Turner syndrome. The Journal of pediatrics. 109(5): 820–826.
30. Mollo N, Scognamiglio R, Conti A, Paladino S, Nitsch L, Izzo A. (2023). Genetics and Molecular Basis of Congenital Heart Defects in Down Syndrome: Role of Extracellular Matrix Regulation. International Journal of Molecular Sciences. 24(3): 2918.
31. Nelson KE, Rosella LC, Mahant S, Guttmann A. (2016). Survival and surgical interventions for children with trisomy 13 and 18. Jamaю 316(4): 420–428.
32. Noordman ID, Fejzic Z, Bos M, Duijnhouwer AL, Weijers G, Kempers M et al. (2021). Cardiac abnormalities in girls with Turner syndrome: ECG abnormalities, myocardial strain imaging, and karyotype–phenotype associations. American Journal of Medical Genetics Part A. 185(8): 2399–2408.
33. Phung V, Singh KE, Danon S, Tan CA, Dabagh S. (2023). Non-mosaic trisomy 22 and congenital heart surgery using the shared decision making model: a case report. BMC pediatrics. 23(1): 122.
34. Pierpont ME, Brueckner M, Chung WK, Garg V, Lacro RV, McGuire AL et al. (2018). Genetic basis for congenital heart disease: revisited: a scientific statement from the American Heart Association. Circulation. 138(21): e653–e711.
35. Quezada E, Lapidus J, Shaughnessy R, Chen Z, Silberbach M. (2015). Aortic dimensions in Turner syndrome. American Journal of Medical Genetics Part A. 167(11): 2527–2532.

36. Rodríguez Caballero Á, Torres–Lagares D, Rodríguez Pérez A, Serrera Figallo MA, Hernández Guisado JM, Machuca Portillo G. (2010). Cri du chat syndrome: a critical review. Med Oral Patol Oral Cir Bucal. 15(3): 473–478.
37. Romeo JL, Etnel JR, Takkenberg JJ, Roos–Hesselink JW, Helbing WA, van de Woestijne P et al. (2020). Outcome after surgical repair of tetralogy of Fallot: a systematic review and meta-analysis. The Journal of Thoracic and Cardiovascular Surgery. 159(1): 220–236.
38. Rosenblum JM, Kanter KR, Shashidharan S, Shaw FR, Chai PJ. (2022). Cardiac surgery in children with trisomy 13 or trisomy 18: How safe is it? JTCVS open. 12: 364–371.
39. Santoro M, Coi A, Spadoni I, Bianchi F, Pierini A. (2018). Sex differences for major congenital heart defects in Down Syndrome: A population based study. European journal of medical genetics. 61(9): 546–550.
40. Sharma D, Murki S, Pratap T, Vasikarla M. (2014). Cat eye syndrome. Case Reports. 2014: bcr2014203923.
41. Silberbach M, Roos–Hesselink JW, Andersen NH, Braverman AC, Brown N, Collins RT et al. (2018). Cardiovascular health in Turner syndrome: a scientific statement from the American Heart Association. Circulation: Genomic and Precision Medicine. 11(10): e000048.
42. Springett A, Wellesley D, Greenlees R, Loane M, Addor MC, Arriola L et al. (2015). Congenital anomalies associated with trisomy 18 or trisomy 13: A registry-based study in 16 European countries, 2000–2011. American journal of medical genetics Part A. 167(12): 3062–3069.
43. Swanson SK, Schumacher KR, Ohye RG, Zampi JD. (2021). Impact of trisomy 13 and 18 on airway anomalies and pulmonary complications after cardiac surgery. The Journal of Thoracic and Cardiovascular Surgery. 162(1): 241–249.
44. Tinkle BT, Walker ME, Blough-Pfau RI, Saal HM, Hopkin RJ. (2003). Unexpected survival in a case of prenatally diagnosed non-mosaic trisomy 22: Clinical report and review of the natural history. American Journal of Medical Genetics Part A. 118(1): 90–95.
45. Williams JL, McDonald MT, Seifert BA, Deak KL, Rehder CW, Campbell MJ. (2020). An unusual association: total anomalous pulmonary venous return and aortic arch obstruction in patients with cat eye syndrome. Journal of Pediatric Genetics. 10(01): 035–038.
46. Xu C, Li M, Peng J, Zhang Y, Li H, Zheng G, Wang D. (2023). Case report: A case report and literature review of complete trisomy 9. Frontiers in Genetics. 14.
47. Yuan SM. (2017). Congenital heart defects in Williams syndrome. Turkish Journal of Pediatrics. 59(3).
48. Zucker EJ. (2018). Syndromes with aortic involvement: pictorial review. Cardiovascular Diagnosis and Therapy. 8; Suppl 1: S71.

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