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CONTENT

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EBSTEIN'S ANOMALY IS A RARE CONGENITAL HEART DEFECT

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Absract. The lecture presents the history, epidemiology, etiology and pathogenesis, classification, clinic, methods of surgical treatment and rehabilitation of patients with Ebstein's anomaly — a rare congenital heart defect of the "blue" type, the incidence of which is 5.2 cases per 100 thousand newborns, which is about 1% of all congenital heart defects. The schemes of hemodynamics in this defect, the results of the examination, including visualization methods, the stages of surgical treatment are given.

Key words: *congenital heart defects; Ebstein's anomaly; children; tricuspid valve plastic surgery.*

АНОМАЛИЯ ЭБШТЕЙНА — РЕДКИЙ ВРОЖДЕННЫЙ ПОРОК СЕРДЦА

© Виталий Владимирович Суворов, Данила Александрович Фоменко

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Резюме. В лекции представлены история, эпидемиология, этиология и патогенез, классификация, клиника, методы хирургического лечения и реабилитации пациентов с аномалией Эбштейна — редкого врожденного порока сердца «синего» типа, частота встречаемости которого — 5,2 случая на 100 тыс. новорожденных, что составляет около 1% от всех врожденных пороков сердца. Приведены схемы гемодинамики при этом пороке, результаты обследования, в том числе визуализирующими методами, этапы оперативного лечения.

Ключевые слова: *аномалия Эбштейна; дети; пластика трикуспидального клапана; врожденные пороки сердца.*

Congenital heart diseases (CHD) are structural developmental anomalies of heart or great vessels that develop in an early intrauterine period [1]. CHDs are the second most common ones after congenital malformations of the nervous system [2]. About 17,500 children with various heart anomalies are born annually in the Russian Federation, which accounts for 249 in 100,000 infants. Congenital malformations are caused by exogenous factors in 89%, they include radiation, viral infections, maternal diseases during pregnancy, drugs and chemicals, and heavy metals. 10% of congenital heart diseases are due to inherited chromosomal abnormalities or may be the result of monogenic mutations. The diseases lead to heart dysfunction, blood stasis in veins, tissues and organs [3].

Ebstein malformation (EM) is a rare congenital cardiovascular defect, usually involving the tricuspid valve and right ventricle, with a wide range of anatomical and pathophysiologic manifestations [4]. This pathology is caused by incomplete delamination of the septal and posterior tricuspid valvar (TV) leaflets from the endocardium of the right ventricle (RV) at the stage of embryonic development. In turn, it leads to characteristic changes in

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Fig. 1. Wilhelm Ebstein, 1885 (© Städtisches Museum; Goettingen, Germany) [6].

Рис. 1. Вильгельм Эбштейн, ок. 1885 года (© Städtisches Museum; Геттинген, Германия) [6]

the valve apparatus: shortening and/or absence of TV chordae, apical displacement of the leaflets and coaptation zone, dilatation of the tricuspid valve. Moreover, EM reduces the functional part of the RV due to atrialization and progressive formation of myocardial fibrosis in the LV myocardium [5]. The incidence rate is 5.2 in 100,000 newborns, which is about 1% of all congenital heart defects. According to various authors, the average life expectancy in the natural course of the disease is up to 50 years, with 80–87% of fatal outcomes at the age of 30–40 years [6]. Since the pathology was first described by Wilhelm Ebstein (Fig. 1) in 1866, the malformation was named in his honor.

On June 28, 1864, a 19-year-old laborer was admitted to Dr. Ebstein's hospital, the patient had dyspnea and palpitations since childhood, which had increased with age. The patient's attending physician distinguished the patient's cachexia, marked cyanosis, jugular veins pulsing synchronously with the heart rate, a systolic heart murmur, and an enlarged cardiac silhouette detected during the percussion. The clinical picture indicated a congenital heart disease. Eight days later, the patient died. In 1866, Wilhelm Ebstein published his report, "A very rare case of tricuspid regurgitation caused by a congenital defect" [7].

ETIOLOGY

The exact causes of Ebstein's anomaly are unknown. The inheritability of Ebstein's anomaly is believed to obey Mendel's laws. The pathogenetic theory explaining the development of the desease is the concept of the abnormal cell death. There are observations that mothers using lithium gave birth to children with this anomaly. Lithium is known to be a toxic inducer leading to the birth of children with pathologic accessory conduction pathways. The use of benzodiazepines during pregnancy is another factor associated with a higher incidence of children born with this malformation. The risk is also higher in white families who have been exposed to paint products and have a history of miscarriage [8].

CLASSIFICATION

Currently, there are two main classifications widely used in cardiac surgical practice: anatomic and echocardiographic ones.

Troshkintsev, Podoksenov et al. cite Alain Carpentier's anatomic classification of Ebstein's malformation, according to which four types were distinguished (presented in Fig. 2).

The echocardiographic classification, for the first time proposed by Selermeier et al. is based on the correlation between the degree of the atrialized part of the LV and its functional part, as well as the LV in the four-chamber position at the end of diastole [9]. This correlation has four gradations depending on the degree of severity:

ratio 0.5 — I degree;
ratio 0.5 to 0.99 — II degree;
ratio from 1 to 1.49 — III degree;
ratio of more than 1.5 — IV degree.

Such gradation allows predicting the natural course of the malformation in patients: in case the ratio is more than 1.5, the probability of lethal outcome is 100%; the ratio from 1 to 1.4 corresponds with the lower probability of early lethal outcome and, as a rule, is up to 10%, however the mortality rate in the early childhood can reach 45%; in case the ratio is less than 1, the probability of lethal outcome is lower, the survival rate in patients reaches 92% [9].

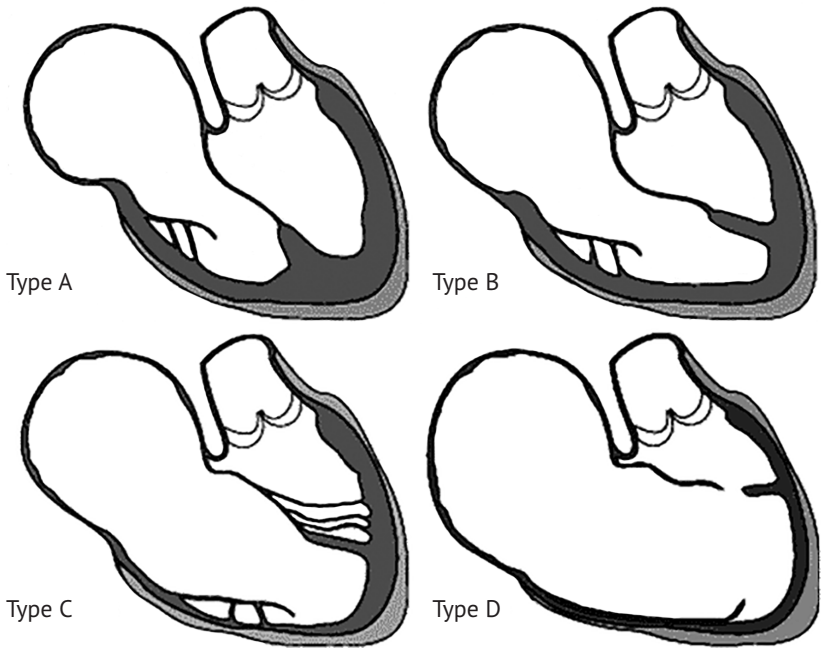

Fig. 2. Types of Ebstein malformation: type A — the volume of the true right ventricle (RV) is satisfactory; type B — there is a large atrialized component of the RV, and the anterior leaflet of the TV moves freely; type C — the anterior leaflet of the TV is limited in its movement and may cause obstruction in the RV outflow tract; type D — almost complete atrialization of the ventricle excepting a small part of the LV outflow tract [7]

Рис. 2. Типы аномалии Эбштейна: тип А — объем истинного ПЖ удовлетворительный; тип В — имеется большой атриализованный компонент ПЖ, а передняя створка ТК свободно перемещается; тип С — передняя створка ТК ограничена в своем движении и может служить причиной обструкции в выводном отделе ПЖ; тип D — почти полная атриализация желудочка за исключением небольшой части выводного отдела ПЖ [7]

PATHOLOGICAL ANATOMY

With respect to the norm, the tricuspid valve consists of three leaflets: anterior, posterior, and septal. Ebstein's malformation include following features (Fig. 3):

- There is insufficient detachment of the tricuspid valve leaflets which results in an anterior and apical rotational displacement of the functional valve ring. Downward displacement of the septal and posterior leaflets into the right ventricle is the main feature of this malformation.
- The anterior leaflet is usually attached to the TV but is enlarged or sail-like. In addition, the leaflet has multiple perforations and is fixed by chordae to the parietal wall of the ventricle.
- The part of the RV above the functional valve («atrialized right ventricle») is dilated, dysplastic, thin, with areas of hypertrophy. The tricuspid valve is almost always enlarged.
- The RV cavity behind the "atrialized" part is reduced ("functional right ventricle"), the inflow part is absent with preservation of the trabecular section.
- The right ventricular outflow tract is often obstructed by excess tissue of the anterior

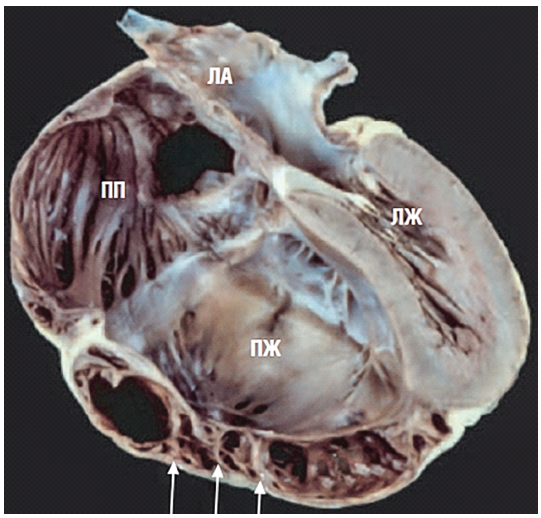

Fig. 3. Macropreparation of the heart in Ebstein's malformation. There is marked dystopia of the tricuspid valve leaflets with dilatation of the right ventricle at the expense of the atrialized part. LV — left ventricle; LA — left atrium; RV — right ventricle; RA — right atrium. The arrows show the obstruction of the right ventricular outflow tract [9].

Рис. 3. Макропрепарат сердца при аномалии Эбштейна. Отмечается выраженная дистопия створок трикуспидального клапана с дилатацией правого желудочка за счет атриализованной части. ЛЖ — левый желудочек; ЛП — левое предсердие; ПЖ — правый желудочек; ПП — правое предсердие. Стрелками изображена обструкция выводного отдела правого желудочка [9]

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leaflet and its chordal attachments, causing true anatomic obstruction. The obstruction is sometimes functional as a result of extremely poor contractility of the right ventricle [10].

PATHOPHYSIOLOGY

The degree of hemodynamic impairment in Ebstein's malformation is determined by the severity of anatomo-morphologic changes in the tricuspid valve and the RV. During systole of the right atrium, the atrialized chamber of the right ventricle is in the diastole phase. These discordant contractions lead to hindrance of blood flow in the atrialized chamber of the RV, causing decreased efficiency of atrial systole. Deformation of displaced tricuspid valve leaflets and dilated fibrous ring leads to its pronounced insufficiency. A large volume of venous blood during systole returns to the right atrium. Impeded outflow of blood from the right atrium leads to venous stasis in the great circulation circle and venous blood discharge into the left atrium through the open oval window or the atrial septal defect (ASD). The discharge of venous blood into the left heart causes arterial hypoxemia, which is directly proportional to pressure gradient between the atria. The blood flow into the left atrium through the ASD can be considered as a compensatory mechanism delaying the development of systemic venous insufficiency. The closer the tricuspid valvar leaflets are displaced to the apex of the RV and the smaller the diameter of the interatrial junction is, the more severe hemodynamic disorders develop in the patient [11].

CLINICAL PICTURE

Clinically, Ebstein's malformation can be manifested by dyspnea, skin cyanosis, pronounced cardiomegaly, decreased tolerance to physical exertion and the development of heart failure. However, the symptoms of the malformation might be absent and manifest themselves in a later period.

The clinical heterogeneity of patients with EM varies according to the severity of tricuspid valve pathology, the size of the functioning RV, the speed of the blood flow due to obstruction between the inflow and outflow tracts of the RV, the ammount of blood discharge at the atrial level, the presence of cardiac rhythm disturbances and concomitant heart defects [12, 13].

Clinical severity often correlates with the age when a patient is admitted to the hospital for the first time. Intrauterine, neonatal and infantile age are more often accompanied with additional diagnoses and more severe manifestations with cyanosis, right ventricular failure and high mortality. Dyspnea, fatigue, ascites, edema, exercise intolerance, and cyanosis might be present in children, adolescents and adults, which correlates with disease severity, but most of the symptoms attract attention when atrial arrhythmias appear [14]. Interatrial communication significantly increases the risks of paradoxical embolism, brain abscess and sudden death along with decreased exercise tolerance, which is determined by the volume of the intracardiac shunt and the degree of blood oxygenation in the systemic blood flow [9]. Increasingly, deformation of the terminal phalanges of fingers in the form of "drumsticks" (in children older than 1 year) is noted.

Jugular vein pulsation during examination which occurs as a result of marked regurgitation of the tricuspid valve and large volume overload of the right atrium is rarely observed. The third and fourth cardiac tones are regularly present in the act of auscultation [15–17]. Additionally, the first and second heart tones are often split due to delayed tricuspid and pulmonary components. Patients with EM often have a holosystolic murmur [15–17]. Thickening of the phalanges of the fingers in Ebstein's malformation depends on cyanosis and is caused by the degree of hypoxia.

ELECTROCARDIOGRAPHY

Supraventricular tachycardia (SVT) is the most frequent rhythm disturbance. It occurs in 7–30% of patients. This type of arrhythmia is due to the presence of additional conduction pathways (ACP) or additional atrial-ventricular junctions (AVJs) such as Wolff-Parkinson-White (WPW) syndrome. Other various types of tachycardia are also found in patients with the Ebstein's malformation: atrial ectopic tachycardia (AET), atrial flutter (AF), atrial reentry tachycardia (ART), atrial fibrillation and ventricular tachycardia [18]. Complete atrioventricular heart block is rare in the Ebstein's malformation, but I degree atrioventricular block is reported in 42% of patients due to dilatation of the right atrium [19, 20]. The atrioventricular node in the Ebstein's malformation may be prone to compression due to abnormal formation of the central fibrous body. Anomalies of the right bundle branch of Hiss and fibrosis of this part of the conducting system may be noted [21–23]. Between 6 and 36% of patients with Ebstein's malformation have at least one accessory conduction pathway [24–28], most

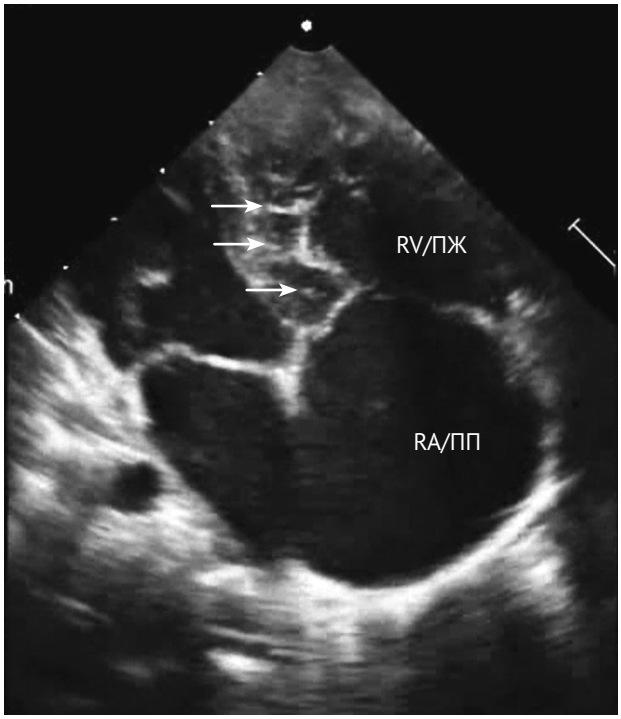

Fig. 4. Displacement of the right atrioventricular ring into the right ventricle (RV). Dilated RV and right atrium (RA). Delamination disorder of the septal leaflet of the TV (arrows)

Рис. 4. Смещение правого атриовентрикулярного кольца в правый желудочек (ПЖ). Дилатированный ПЖ и правое предсердие (ПП). Нарушение деламинации септальной створки ТК (стрелки)

of the accessory pathways are located around the open atrioventricular opening of the tricuspid valve [29–31]. Tachycardia with a wide QRS complex is due to supraventricular and septal accessory conduction pathways, which may cause ventricular tachycardia and flutter, ectopic atrial tachycardia, and atrial fibrillation [26, 27].

ECHOCARDIOGRAPHY

Diagnostic criteria:

- one or more TV leaflets are displaced to the apex of the RV;
- The point of closure of the TV leaflets is displaced to the apex by more than 8 mm;
- Signs of atrialization of the LV;
- Lengthening of one or more TV leaflets;
- TV dysfunction;
- Atrial septal defect (ASD) [32].

When pulmonary artery and aortic valve motion are simultaneously reordered, aortic valve closure occurs significantly earlier than pulmonary artery valve closes. Late pulmonary valve closure can be explained by reduced pumping function of the right ventricle due to its reduced size, high residual diastolic pressure and low compliance.

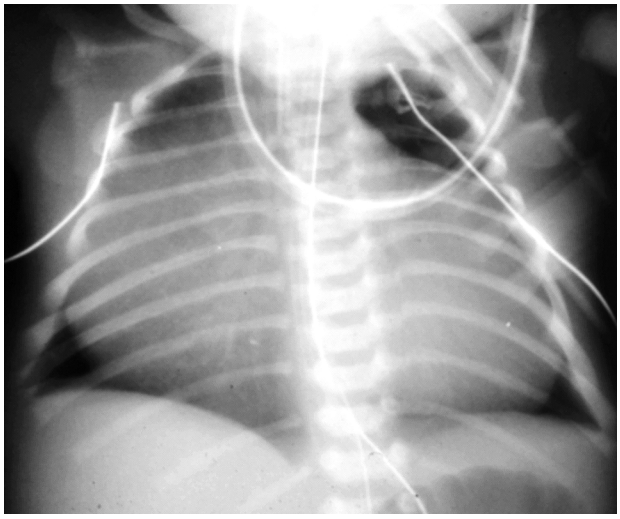

Fig. 5. Preoperative chest X-ray of a patient with Ebstein's malformation. A globular configuration of the heart with a pronounced expansion of borders in the cross-section is observed

Рис. 5. Обзорная рентгенография грудной клетки пациента с аномалией Эбштейна до операции. Отмечается шаровидная конфигурация сердца с выраженным расширением границ в поперечнике

The interatrial septum may displace into the left atrial cavity. The functional part of the right ventricle may compensatory enlarge and compress the left ventricle with further obstruction of the outflow tract.

2D-echocardiography is the most informative. Displacement of the right atrioventricular annulus is well visualized in a four-chamber view. The displacement can have varying degrees. With minimal displacement, the Ebstein's malformation is detected incidentally because there are no significant hemodynamic abnormalities [33] (Fig. 4).

RADIOLOGIC EXAMINATION

The cardiac shadow may vary from a nearly normal configuration to the globular cardiac configuration typical for Ebstein's malformation. There are signs of right atrial enlargement (upward shift of the right cardiovasal angle) [9]. Narrow vascular plexus and depression of the pulmonary artery segment. The left heart sections are not enlarged. Blood supply of the pulmonary fields may be normal or reduced. When cardiothoracic index is more than 65% it is considered as a prognostically unfavorable sign. There may be marked cardiomegaly (a box heart) with the heart silhouette almost filling the entire chest [10] (Fig. 5).

CARDIAC CAVITY CATHETERIZATION

Many patients with Ebstein's malformation may develop complex cardiac rhythm abnorma-

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lities during invasive cardiac testing that can result in cardiac arrest [34]. Diagnostic cardiac cavity catheterization is rarely required in patients with Ebstein's malformation and is mainly performed preoperatively for the purpose of coronary angiography. The pressure in the right ventricular and pulmonary artery in patients with Ebstein's malformation is usually normal, the right ventricle may have specifically increased end-diastolic pressure. Right atrial pressure may be normal despite severe regurgitation at the tricuspid valve, especially when the right atrium is discernibly dilated. Decreased systemic arterial oxygenation may be noted in the presence of interatrial communication and a marked right-to-left blood shunt during oxyhemometry.

TREATMENT

Peculiarities of drug therapy

Patients with Ebstein's malformation and heart failure who do not require surgical treatment are treated with standard therapeutic tactics for heart failure. The efficacy of angiotensin-converting enzyme (ACE) inhibitors in patients with Ebstein's malformation who have right ventricular heart failure has not been proven. Drug treatment of arrhythmias should be individualized and combined with surgical or endovascular methods of treatment when indicated [9].

Peculiarities of surgical treatment

Indications for surgery concerning EM are:

- the presence of a clinical picture in the neonatal period;
- at older age, surgical treatment is indicated in case of:
  - decreased tolerance to exercise;
  - right ventricular heart failure (NYHA class III–IV);
  - cyanosis on exercise;
  - arrhythmias uncontrolled by drug therapy occur;
  - decreased LV function due to its compression by the interventricular septum since the LV is dilatated [32].

The main goal of surgical intervention is to restore the closing function of the tricuspid valve, as well as to increase the volume of the RV, reduce the volume of the right atrium cavity and close the interatrial septum.

Treatment of severe Ebstein's malformation in newborns includes the use of prostaglandin E to prevent closure of the ductus arteriosus and administration of vasodilators. In case of insufficient interatrial communication, endovascular dilatation of the open oval window or the atrial septal defect is indicated (Rashkind procedure).

Relative contraindications for correction: age over 50 years; severe pulmonary hypertension; significant decrease in left ventricular function (ejection fraction less than 30%); complete impairment of delamination of septal and posterior tricuspid valve leaflets, with less than 50% delamination of the anterior leaflet [35].

There are two concepts for surgical treatment of Ebstein's malformation:

- univentricular correction;
- biventricular correction.

Single ventricle correction

The aim is to exclude the right ventricle from the bloodstream with further Fontaine surgery. Indication for univentricular correction of the defect is a severe clinical manifestation of Ebstein's malformation in a newborn, when the prognosis for life during the first month without surgery is unfavorable.

It is considered that main advantages of including the hypoplastic (pulmonary) ventricle for partial support of pulmonary circulation are [36]:

1) the possibility to increase cardiac output;
2) adaptation to exercise;
3) maintenance of pulsatile flow in the pulmonary circulation.

Patients who have safely survived the neonatal period need dynamic monitoring in the absence of surgical treatment indications [32].

Biventricular correction (cone reconstruction)

In most cases of biventricular correction, operative treatment consists of:

1) tricuspid valve repair;
2) plication of the atrialized part of the LV;
3) the right atrium repair [32];
4) the atrial septal defect repair or open oval window (OOW) repair (in case of moderate RV insufficiency with the fistula remaining about 3 mm);
5) elimination of previously performed systemic-pulmonary shunts and correction of concomitant anomalies such as ventricular septal defect (VSD), stenosis or open aortic duct (OAD) in accordance with the principles of their isolated correction;
6) performing various antiarrhythmic procedures when indicated (radiofrequency ablation or surgical dissection of accessory conduction

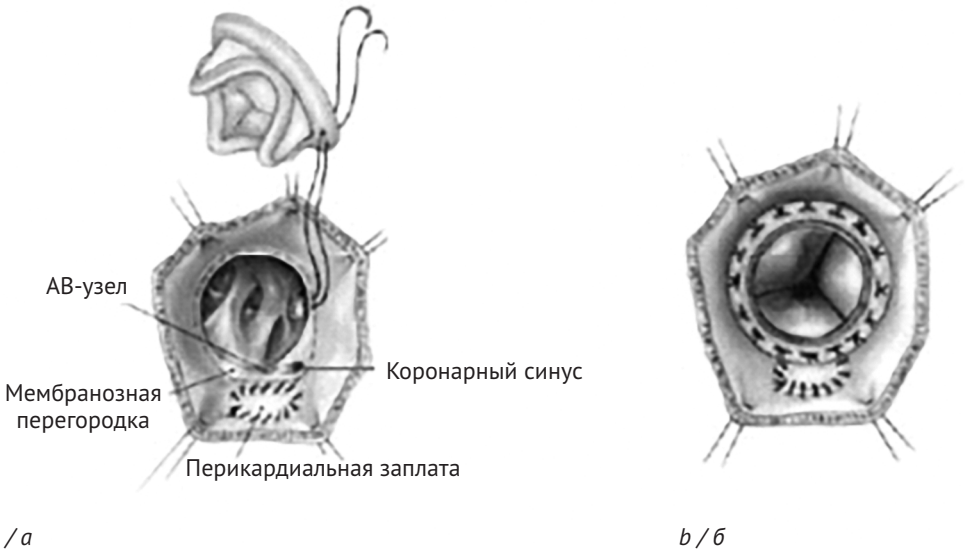

Fig. 6. Schematic representation of bioprosthetic tricuspid valve replacement in Ebstein's malformation. Along with the implantation of the bioprosthesis, the atrial septal defect is closed with a pericardial patch: *a* — the process of tricuspid valve replacement; *b* — the result of tricuspid valve replacement [9]

Рис. 6. Схематическое изображение биопротезирования трикуспидального клапана при аномалии Эбштейна. Наряду с имплантацией биопротеза осуществляют закрытие дефекта межпредсердной перегородки перикардиальной заплатой: *а* — процесс биопротезирования трикуспидального клапана; *б* — результат биопротезирования трикуспидального клапана [9]

pathways, cryoablation of the atrioventricular junction, right-sided MAZE procedure).

Biventricular correction of Ebstein's malformation always raise the issue of preserving the native valve and performing reconstructive surgery or prosthetic valve replacement. Some authors report the possibility of plastic surgery in virtually any anatomy of the malformation, while others recommend replacing the native valve with an artificial one if there is the slightest doubt, moreover the latter have not completely managed the issue of choosing an artificial valve, although most cardiac surgeons prefer biological prostheses.

Valve replacement is possible with the use of biological or mechanical prosthesis (Fig. 6) [37]. The prosthetic valve replacement is specific since the valve is located above the true fibrous ring of the TV. The tissue of leaflets causing obstruction of the RV outflow tract should be necessarily excised, and the true fibrous ring should be narrowed to the size of the prosthesis. The atrialized portion of the RV is reduced as well. The posterolateral wall tissue is usually thinner, so the suture line should be closer to the atrium to avoid injury to the right coronary artery. In order to avoid damage of the atrioventricular plexus, the suture line is placed above the coronary sinus, so that venous blood drainage will be in the RV.

Bioprostheses should be favored in prosthetic issues, but the use of mechanical prostheses is also justified in patients taking anticoagulants for unrelated reasons [38]. The technique of TV replacement currently performed is presented in Fig. 6.

However, most authors agree on the preference for reconstructive interventions on the TV [37, 39, 40], as they demonstrate a more durable and physiologic result and avoid potential complications inherent to valve replacement.

The surgical technique is carried out as follows. The operation is performed from the midline access. Access to the TV is performed through the right atriotomy after connection of the artificial circulation apparatus. The anterior leaflet of the TV is cut off from the true fibrous ring of the TV in the zone of «10 o'clock», the incision continues clockwise to the posterior leaflet. The leaflets are detached from the right ventricular myocardium by sharp and blunt routes, all secondary chordae fixing the leaflets are crossed, and leaflet delamination is performed. In case the anterior leaflet edge is fused with the right ventricular myocardium, fenestrating incisions are performed to allow blood flow from the RA into the RV. Delamination of the septal leaflet is performed. The holes in the leaflets are sutured, the edges of the formed flaps are sutured. The cut off edge of the posterior leaflet is rotated clockwise by 180° and fixed to the edge of the septal leaflet. The reconstructed tricuspid valve has a cone shape. Excision or plication of the atrialized part of the right ventricle is performed, as well as plication of the TV fibrous

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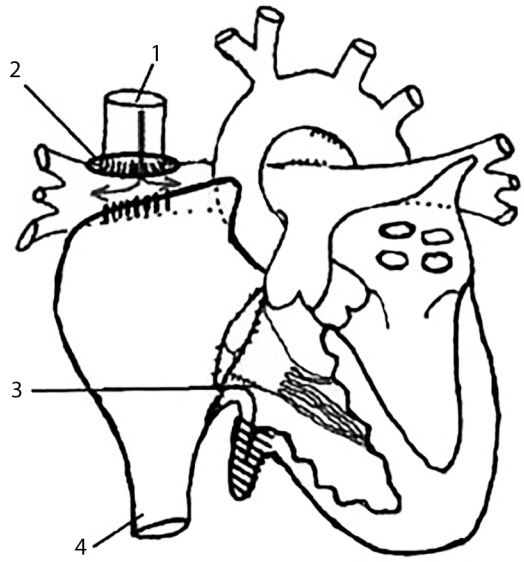

Fig. 7. Bidirectional cavapulmonary anastomosis combined with " cone" reconstruction of the tricuspid valve: 1 — superior vena cava; 2 — bidirectional cavapulmonary anastomosis; 3 — cone reconstruction of the tricuspid valve; 4 — inferior vena cava [7]

Рис. 7. Двунаправленный кавапульмональный анастомоз в сочетании с «конусной» реконструкцией трикуспидального клапана: 1 — верхняя полая вена; 2 — двунаправленный кавапульмональный анастомоз; 3 — конусная реконструкция трикуспидального клапана; 4 — нижняя полая вена [7]

ring is carried out, after which the cone is fixed to the true TV fibrous ring with a continuous single-row curling suture. In order to prevent atrioventricular conduction disturbance, sutures in the area of the membranous part of the interventricular septum are shifted towards the right atrium and superficially applied. If necessary, resection and plication of the RA are performed [41].

"Cone" reconstruction makes it possible to restore the valve closure function and can be applied to a wide variety of anatomical variants of pathology encountered in Ebstein's malformation [42]. In Russia, this technique is actively used in cardiac surgery clinics in Tomsk, St. Petersburg, and Samara.

Bidirectional cavapulmonary anastomosis is indicated in case of reduced LV function and inability to adequately provide pulmonary blood flow. The method is performed as follows: the superior vena cava is cut off from the right atrium 0.5–1 cm above its orifice (to exclude damage to the sinus node), the right atrium is sutured. The right pulmonary artery is dissected along, strictly above the superior vena cava, and sutured with the severed superior vena cava [43, 44]. The main objectives of this operation are to decrease the right ventricular preload (in childhood about 1/2 of venous return and 1/3 in adulthood) and to increase the left ventricular preload (Fig. 7).

ELECTROCARDIOSTIMULATION

BAbout 3.7% of patients with Ebstein's malformation require permanent electrocardiostimulation. The most common indication for pacemaker implantation is a complete form of atrioventricular block, and less frequently it is sinus node weakness syndrome [45]. In cases of artificial tricuspid valve replacement, the most expedient is to carry the electrode outside the cuff of the prosthesis. In cases of bioprosthetic tricuspid valve replacement, the electrode can be placed through the valve orifice, but this method is undesirable as the electrode may interfere with the normal mobility of the bioprosthetic leaflets and cause regurgitation.

TREATMENT OF ARRHYTHMIAS

Accessory conduction pathways or accessory atrial-ventricular junctions are noted in approximately 50% of cases [46–48] in EM patients. In addition, atrial flutter or fibrillation are frequent findings [49]. In the presence of premature ventricular excitation, there is a high risk of life-threatening ventricular arrhythmias. Prior tricuspid valve surgery may complicate catheter ablation of accessory pathways. Thus, even if preexcitation on ECG and history of supraventricular tachycardia are absent, it is reasonable to perform electrophysiologic study (EPS) before surgery to correct Ebstein's malformation and, if necessary, to perform catheter ablation before tricuspid valve surgery [50–52]. Although 3D mapping [53] and other advances in catheter technology are improving outcomes [53], recurrence rates remain high [54].

POSTOPERATIVE FOLLOW-UP

1. The duration and frequency of follow-up of patients with corrected Ebstein's malformation is determined individually. Hemodynamic status and the presence of arrhythmias should be evaluated regularly.

2. Prevention of bacterial endocarditis is necessary when indicated.

3. In the absence of signs of heart failure, it is acceptable to engage patients in physical training and sports after correction of the malformation [32].

FUTURE PROSPECTS

In most patients, right ventricular function improves postoperatively after an initial decline, regardless of the surgical strategy [55, 56]. In addition,

there is a tendency for gradual reduction of RV volume [55]. However, even early tricuspid valve repair fails to restore normal RV function in some cases.

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PROBIOTICS. USE OF THE L. RHAMNOSUS STRAIN IN NON-INFECTIOUS DISEASES OF THE GASTROINTESTINAL TRACT

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Abstract. Probiotics are living, apatogenic bacteria for humans that have antagonistic activity against pathogenic and conditionally pathogenic bacteria that ensure the restoration of normal microbiota. Not every microorganism can be assigned the status of "probiotic", but only those that are considered safe and meet certain criteria. Despite the fact that most of the probiotics are represented by isolates of the indigenous microbiota, the mechanism of their action in human bionishes is not equivalent to endogenous microorganisms. Functional gastrointestinal disorders (FGID) are widespread among children of any age. Changes in the "passport" of the intestinal microbiome can affect the key mechanisms associated with the symptoms of FGIR. Very often, the causes of digestive discomfort (abdominal pain, bloating, flatulence, flatulence and diarrhea) are associated with lactose intolerance (NL). Inflammatory bowel diseases (IBD) are characterized by bidirectional mutual.

Key words: *probiotic; strain-specificity; L. rhamnosus (LGG); functional gastrointestinal disorders; constipation; colic; regurgitation; abdominal pain; lactose intolerance; inflammatory bowel diseases; Crohn's disease; nonspecific enterocolitis.*

ПРОБИОТИКИ. ИСПОЛЬЗОВАНИЕ ШТАММА *L. RHAMNOSUS* ПРИ НЕИНФЕКЦИОННЫХ ПОРАЖЕНИЯХ ГАСТРОИНТЕСТИНАЛЬНОГО ТРАКТА

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Резюме. Пробиотики — это живые, апатогенные для человека бактерии, обладающие антагонистической активностью в отношении патогенных и условно-патогенных бактерий и обеспечивающие восстановление нормальной микробиоты. Не любому микроорганизму может быть присвоен статус «пробиотик», а только тем, которые считаются безопасными и соответствуют определенным критериям. Несмотря на то что большая часть пробиотиков представлена изолятами индигенной микробиоты, механизм их действия в бионишах человека не эквивалентен эндогенным микроорганизмам. Функциональные гастроинтестинальные расстройства (ФГИР) широко распространены среди детей любого возраста. Изменения в «паспорте» микробиома кишечника способны затронуть ключевые механизмы, связанные с симптомами ФГИР. Очень часто причины пищеварительного дискомфорта (абдоминальная боль, вздутие живота, метеоризм, флатуленция и диарея) связаны с непереносимостью лактозы (НЛ). Воспалительные заболевания кишечника (ВЗК) характеризуются двунаправленной взаимосвязью между дисбиозом кишечника, хроническим воспалением и прогрессированием заболевания. В настоящее время мало клинических научных исследований с высокой степенью доказательности, что прием штаммоспецифичных пробиотиков обеспечивает должный биопрофилактический и биотерапевтический эффект при неинфекционных заболеваниях пищеварительного тракта. Хотя присутствуют как экспериментальные, так и клинические работы, в которых показано, что назначение *LGG* может оказать положительный эффект при этих нарушениях.

Ключевые слова: *пробиотик; штаммоспецифичность; L. rhamnosus (LGG), функциональные гастроинтестинальные расстройства; запор; колики; срыгивание; абдоминальная боль; непереносимость лактозы; воспалительные заболевания кишечника; болезнь Крона; неспецифический энтероколит.*

HISTORY OF PROBIOTICS

The beginning of the probiotic era can be considered the mid-19th century, when French microbiologist Louis Pasteur proved that food spoilage is caused by microorganisms [1–3], and British scientist Joseph Lister isolated *Streptococcus lactis* (now known as *Lactococcus lactis*) from rancid milk [4–7].

Nobel Prize winner I.I. Mechnikov made a huge contribution to the study of probiotics. While traveling in Bulgaria, he discovered that yogurt, which is everyday food of Bulgarians, contains specific bacteria and suggested that "health and longevity can be achieved by manipulating the intestinal microbiota, meaning the replacement of harmful microbes with beneficial ones" [8–12]. He identified that lactic acid bacteria found in yogurt, create an acidic environment entering the intestine, thus preventing the development of putrefactive bacteria, which cause the degradation of food proteins to indole, scatol, and other substances that are poisonous. These substances disrupt the vital functions of the body after being absorbed into the bloodstream.

In 1954, German scientist Ferdinand Vergin used the term «probiotic» to describe "active substances essential for health" and also emphasized the adverse effects of antibiotics on the beneficial gut microbiota [13, 14]. Later, American scientists D.M. Lilly and R.H. Stillwell (1965) introduced the term "probiotic" as opposed to the term antibiotic and characterized it as a microbial factor that stimulates the proliferative growth of other microorganisms [15].

In 1974, R. Parker described probiotics as «organisms and substances that promote intestinal microbial balance» [16]. Then R. Fuller (1980) emphasized the need for the viability of probiotics and put forward the idea of their positive impact on the health of patients [17, 18]. And finally, in 2014, the International Scientific Association for Probiotics and Prebiotics (ISAPP) confirmed R. Fuller's assumption and defined probiotics as «"live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [19].

According to the WHO (2005) definition, probiotics are live, apathogenic bacteria with antagonistic activity against pathogenic and opportunistic bacteria providing restoration of normal microbiota.

Studies in recent years demonstrate the effectiveness of not only live microbes, but also certain components of microorganisms, in particular, their DNA [20].

Commensal microorganisms inhabiting the intestines of healthy people (bifidobacteria, lactobacilli), as well as bacteria actively used in the food industry (lactococci, lactic acid streptococci, propionic acid bacteria and saccharomycetes (brewer's and baker's yeast)) are selected for further production. That is why their delivery matrix is not only in pharmaceutical forms, dietary supplements, but also in various types of food products, such as dairy products, ice cream, cheese, bakery products, etc. Taking into account the above-mentioned, the European Food Safety Authority (EFSA) recommends whole genome sequence (WGS) analysis of microorganisms intended for use in the food chain [21].

Only those species (genera) of microbes that meet certain criteria can be granted the status of "probiotic".

SELECTION CRITERIA FOR PROBIOTICS DEVELOPED FOR HUMAN USE

1. The origin of the probiotic strain must be consistent with its habitat in the host. Only isolates of human origin, namely isolates from the small and/or large intestine and breast milk are approved for the production of probiotics for human use [22].

2. Isolates should be carefully characterized and examined for their beneficial effects [19, 22].

3. According to the European Food Safety Authority (EFSA) guidelines, all microorganisms should have levels of taxonomic identification of genus, species and strain [19, 21, 23, 24].

4. Any strain should undergo a strict safety assessment [19, 22, 25–27].

5. Whole genome sequence (WGS) of candidate strains is required for further preparation of probiotics [21].

6. Selection of candidate strains requires evaluation of their mechanisms of action under simulated gastrointestinal tract conditions (*in vitro*). Probiotic candidates should have acid and bile tolerance, as well as withstand osmotic fluctuations to remain viable during their transit through the gastrointestinal tract [28].

7. Candidate strains for probiotic production require validation by means of preclinical trials followed by double-blind and randomized human clinical trials [29].

8. The recommended probiotic dose is between 10^8 (one hundred million) and 10^{11} (one hundred billion) viable colony forming units (CFU/mL/g) per day [29].

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Although most probiotics are represented by isolates of indigeneous microbiota, their mechanism of action in the human microfrola is not equivalent to endogenous microorganisms. This is most likely due to the fact that exogenous "alien" microbes are incompatible with the resident bacteria of the macroorganism [30].

PROBIOTIC MECHANISMS FOR THE MAINTENANCE OF A HEALTH PHENOTYPE

1. Competition for nutrients that would otherwise be consumed by enteropathogenic microorganisms [31–33].

2. Synthesis of antimicrobial compounds [34]. Different species of *Bifidobacteria* and *Lactobacilli* produce different types of bacteriocins and other antimicrobial compounds that inhibit the multiplication of pathogens [35, 36].

3. Modification (fermentation) of substrates in favor of the host [35–39], i.e. formation of large amounts of organic and volatile fatty acids [40]. Probiotic-mediated bioconversion of metabolites has been reported to have antimicrobial, anticancer, anti-inflammatory and antioxidant properties.

4. Immune stimulation. Probiotics demonstrate immunomodulatory activity by suppressing inflammatory responses, activating NK (natural killer) and DC (dendritic cells), modulating TLR (Toll-like receptors) expression, secretion of specific immunoglobulin A (IgA), regulating lymphocyte proliferation and balancing the ratio of T-helper (Th1/Th2) cells [41]. Structural components of the gut microbiota are extremelly important for biological prevention and biotherapeutic approaches because they have immunostimulatory effects and can be used instead of antibiotics, as vaccine adjuvants, as well as they can improve cognitive functions [42].

5. Strengthening the intestinal mucosal barrier by [43–45]:

- probiotic bacteria competing for cell adhesion sites;
- improving transepithelial electrical resistance (TEER);
- increasing butyrate levels;
- upregulation of tight junction (TJ) proteins (ZO-1, occludin and claudin-1);
- increasing mucus secretion (by upregulating MUC1, MUC2 and MUC3 in colonic epithelial cells);
- modulation of the gut microbiota.

Many studies have demonstrated that probiotics regulate inflammatory pathways, stimulate the expression of immune-related genes, and modulate the levels of immunologic markers [46, 47].

Despite the ever-growing spectrum of probiotic-based products, microbiome-targeted therapies, and related literature, the efficacy of specific probiotic strains in many diseases is not fully understood.

LACTOBACILLUS RHAMNOSUS (LGG) IN PREVENTION AND TREATMENT OF FUNCTIONAL GASTROINTESTINAL DISORDERS

Functional gastrointestinal disorders (FGID) are widespread, affecting about one third of the population. The incidence of FGID is 20–30% even in infants of the first year of life [48]. The estimated incidence and popularity of this problem varies according to diagnostic criteria and conditions.

The etiology of these disorders is not fully clarified. Factors influencing the pathogenesis of FGIDs include: impaired motor function, visceral hypersensitivity, minimal inflammatory modifications in the intestinal mucosa and immune function. Recently, FGID has been considered as a product of interaction between psychosocial factors and altered gastrointestinal physiology via the microbiota-gut-brain axis (MGBA).

The gut microcosm has been found to influence the development and function of both the enteric nervous system (ENS) and the brain, via pattern recognition receptors (PRRs) and Toll-like receptors (TLRs), products of bacterial metabolism (short-chain fatty acids (SCFAs), tryptophan metabolic products), synthesis and release of neurotransmitters (gamma-aminobutyric acid (GABA), serotonin, acetylcholine, dopamine, etc.), which penetrate the intestinal wall and cross the blood-brain barrier (BBB) not only under increased permeability but also under normal conditions [49].

Thus, an imbalance in the intestinal microbiota leads to damage in the MGB axis and further formation of a vicious circle developing FGIDs. It is believed that administration of strain-specific probiotics *Escherichia coli DSM17252, Bifidobacterium animalis DN-173, Saccharomyces boulardii CNCM I-745, Bifidobacterium infantis 35624, Lactobacillus rhamnosus NCIMB 30174, Lactobacillus plantarum NCIMB 30173, Lactobacillus acidophilus NCIMB 30175, Enterococcus faecium NCIMB 30176* help to restore the function along the MGB axis [50, 51].

The cost-effectiveness of probiotic strain *Lactobacillus rhamnosus GG (LGG)* in FGID patients was studied at the Department of Pediatric Gastroenterology and Nutrition, Warsaw Medical University. The patients met the Rome II diagnostic criteria. The total number of participants was 104 children aged 6–16 years. For 4 weeks, one part of the children received *LGG* 3×109 CFU twice daily, while the other part received placebo [52].

Overall, 18 of 104 (17%) respondents reported successful treatment. Patients in the *LGG* group were more likely to have treatment success than those in the placebo group (25% vs. 9.6%; RB 2.6; 95% CI 1.05–6.6, NNT 7, 95% CI 4–123). Disappearance of pain attacks at the end of therapy was considered a criterion for treatment success. The authors found no significant differences between groups for any other outcome criterion [52].

In 2018, a meta-analysis evaluating the efficacy of different approaches in the treatment of patients with functional abdominal pain (FAP) was conducted [53].

A promising method for treating FAB, according to the meta-analysis, was the administration of probiotics containing *L. rhamnosus GG* and a multibiotic (VSL#3). The multibiotic includes eight strains: *Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus bulgaris, Streptococcus thermophiles* [54, 55].

Analysis of 15 studies involving 1123 children suffering from different FGID syndromes showed that the following probiotic isolates were most commonly used: *Lactobacillus rhamnosus GG* (5 trials); Lactobacillus reuteri DSM 17938 (5 trials); significantly less frequently, *Bacillus coagulans* with fructo- and oligosaccharides (FOGS) (2 trials); VSL#3 multiprobiotic (1 trial); a combination of three *Bifidobacterium strains: B. longum BB536, B infantis M-63* and *B. breve M-16 V* (1 trial) and in another case *L. plantarum LP299*. The duration of treatment ranged from 4 to 12 weeks. Most studies evaluated short-term results — in the first 3 months after the intervention. 9 studies reported a reduction in the frequency and intensity of pain episodes with the use of probiotics [56–62].

One of the first European randomized scientific trials, supervised by N. Pedersen (2014) at Herlev Hospital, University of Copenhagen, Denmark, examined the effect of a diet containing low amounts of fermentable oligosaccharides, disaccharides, monosaccharides, polyols (FODMAP). In addition to that *L. rhamnosus GG (LGG)* was administered at a dose of 1×10^{11} CFU in irritable bowel syndrome (IBS). IBS was manifested by recurrent abdominal pain (IBS-A), constipation (IBS-C), or diarrhea (IBS-D). The study included 123 patients, predominantly female, 90 (73%). The mean age of the patients was 37 years, ranging from 18 to 74 years. All patients met Rome III diagnostic criteria prior to the study. They had a negative colonoscopy result, had no antibodies to transglutaminase and no lactose intolerance gene. The study continued for 6 weeks. Consequently, it was concluded that dietary adherence as well as LGG administration are effective in the treatment of patients with IBS, especially in IBS-D and IBS-A subtypes.

The efficacy of the isolate of *L. rhamnosus GG* might be explained by its ability to reduce acetylcholine-stimulated colonic contractions and to regulate the serotoninergic system, providing a prokinetic effect [63]. The way *Lactobacillus* effecting serotonin receptors and serotonin uptake mechanisms may play a key role in facilitating effective treatments of FGIDs associated with visceral hypersensitivity [64].

Thus, changes in the gut microbiome "passport" are able to affect key mechanisms associated with FGID symptoms: intestinal barrier permeability, impaired intestinal motility and visceral hypersensitivity. However, it is necessary to evaluate adherence to a FODMAP diet, satisfaction with dietitian recommendations, and improvement of symptoms in short and long term perspectives [65].

A 2015 meta-analysis of previous single studies confirmed that probiotic intervention reduces IBS symptoms [66]. Further studies revealed the efficacy of probiotic isolates such as *L. rhamnosus, L. acidophilus, S. thermophile, L. casei, L. bulgaricus, L. plantarum, L. salivarius, B. bifidum, B. longum (L. casei W56, L. acidophilus W22, L. paracasei W20, L. salivarius W24, L. plantarum W62, L. lactis W19, B. lactis W51, W52, B. bifidum W23)* in the therapy of IBS [67, 68].

A different opinion is traced in the works of C. Hill (2014) and H. Szajewska (2020). The authors mention that grouping several types of probiotics in such an analysis provides little information about the efficacy of individual strains, as they tend to have specific clinical effects [19, 69].

Lactic acid bacteria are thought to accelerate intestinal transit and improve stool consistency in constipation because they can modulate intes-

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tinal motility by stimulating epithelial cells or directly affecting the enteric nervous system.

Experimental studies have shown that unidentified fermentation metabolites produced by *Lactobacillus*- and *Bifidobacterium* can ameliorate postinfectious intestinal motility disorders. However, a published systematic review concluded that the available evidence on the use of *Lactobacillus rhamnosus, Lactobacillus reuteri, Lactobacillus casei, B. lactis and Bifidobacterium longum* is insufficient to support the use of probiotics in the treatment of constipation in children [70]. According to international clinical guidelines and ESPGHAN and NASPGHAN documents, no strain has received reliable evidence of satisfactory efficacy in functional constipation [71, 72].

FGIDs in infants, especially in the first year of life, are characterized by a distinctive feature: the appearance of clinical symptoms occurs without the involvement of a psychosocial factor. The most common conditions are regurgitation, intestinal colic and functional constipation.

Lactobacillus reuteri DSM 17938 is the most studied and promising strain in the prevention and correction of FGID [73–76].

Literature on the cost-effectiveness of probiotic isolates in infants with regurgitation syndrome was performed with the help of MEDLINE, CINAHL and the Cochrane Central Register of Controlled Trials. As a result, six randomized controlled trials (RCTs) were identified which investigated the prevention or treatment of regurgitation in infants in the first months of life with probiotics. A meta-analysis of three RCTs showed a statistically significant reduction in regurgitation episodes in the probiotic group compared to the placebo group. However, the study sample was small and had high heterogeneity (96%). The researchers' conclusion suggests that probiotic therapy appears promising for regurgitation in infants with some evidence of benefit [77].

Colic is considered to be the equivalent of functional abdominal pain in infants. The results of a developmental study involving 89 infants aged 7–12 weeks are based on an attempt to link the composition of the gut microbiota, anxiety and duration of crying. In a double-blind RCT, the children received *LGG* for two months: the first month at a dose of 10^9 CFU/day, the second month at a dose of 2×10^9 CFU/day, and were subsequently followed up for the entire first year of life. Children who were assigned to the «excessive crying» group were significantly less frequent in the *LGG* group than in the placebo group. According to the data of fecal microbiological studies, *Clostridium hydrolyticum* was detected significantly more often in children in the placebo group than in children receiving *LGG* (p=0,05).

Thus, the administration of *LGG*, as well as *L. reuteri*, may have a positive effect on such disorders as abdominal pain and intestinal discomfort in infants [78].

LACTOBACILLUS RHAMNOSUS (*LGG*) *AND LACTOSE INTOLERANCE*

Symptoms of digestive discomfort (abdominal pain, abdominal bloating, meteorism, flatulence and diarrhea) are very often associated with lactose intolerance (LI) and occur as a result of bacterial fermentation of the disaccharide in the colon [79]. The causes leading to gastrointestinal disorders are attributed to the influence of both acquired and congenital factors. About 70% of the world's population has been determined to suffer from lactase deficiency due to a genetically programmed gradual decrease in lactase gene expression after weaning [80, 81].

In addition to gastrointestinal problems, individuals with LI have an increased risk of developing extraintestinal diseases, including cancer [82]. The clinical features can be modified by several predictors, including the dose of the disaccharide consumed, residual expression of the lactase enzyme, concurrent intake of other food components, the time of carbohydrate transit through the intestine, and the composition of the intestinal microbiome [79]. For this reason, it is pathogenetically validated that probiotic bacteria will help to alleviate the clinical symptoms of LI with the help of heterogeneous delivery matrices (dosage form, dietary supplements, fermented and non-fermented dairy products) [83].

The efficacy of probiotics in the treatment of LI was evaluated using MEDLINE (via PUBMED) and SCOPUS databases according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and included 15 randomized double-blind studies.

The risk of systematic error was determined for each selected study according to the Cochrane Collaboration methodology.

The presented studies examined eight probiotic strains with the greatest number of proven benefits, namely heat tolerance during production, high proteolytic and peptidolytic properties as they pass through the host digestive tract, re-

lease of smaller molecules of bioactive peptides during bacterial fermentation and other processes that stimulate the enzyme lactase to help humans digest the milk sugar, lactose.

Lactic acid bacteria (LAB) are among probiotic isolates possessing these properties: *Lactobacillus delbrueckii sub sp. bulgaricus, Streptococcus thermophilus, L. casea, L. rhamnosus (GG)* and some species of bifidobacteria [84]. The results of studies demonstrate heterogeneity in efficacy, however there is a generally positive correlation between probiotics and LI with respect to specific strains and concentrations [85, 86].

The research conducted at Clinica Medica «A. Murri», Department of *Biomedical Sciences* and Human Oncology, University of Bari Medical School, Italy (2019), proved the hypothesis that therapy with *Bifidobacterium longum BB536* and *Lactobacillus rhamnosus HN001* in combination with vitamin B6 alleviates LI symptoms through positive modulation of gut microbial composition and metabolism.

Twenty-three patients with persistent symptoms of LI were included in a crossover randomized double-blind study. The patients followed a lactose-free diet. Clinical manifestations, microbiome and metabolome were evaluated at bathe beginning of the study and after 30 days. Probiotic and vitamin B_6 administration significantly reduced abdominal bloating (p=0.028) and constipation (p=0.045) compared to placebo. The fecal microbiome differed between the groups. Administration of a probiotic with vitamin B6 promoted the enrichment of several genera of microbes involved in lactose digestion, including Bifidobacerium. In addition, the relative content of acetic acid, 2-methylpropanoic acid, nonenal (a chemical compound subsumed into unsaturated fatty aldehydes that naturally occurs in the form of cis- and trans-isomers) and indolizin-3-methyl increased, while phenol decreased.

Thus, the results emphasized the importance of considering the composition of probiotics prescribed to alleviate symptoms and normalize gut dysbiosis in patients with HL and persistent functional gastrointestinal disorders [87].

LACTOBACILLUS RHAMNOSUS (LGG) AND PREVENTION OF INFLAMMATORY BOWEL DISEASES (CROHN'S DISEASE, NECROTISING ENTEROCOLITIS)

Inflammatory bowel diseases (IBD) are caused by a wide range of disorders characterized by intestinal dysbiosis, chronic inflammation, mucosal ulceration and ultimate loss of intestinal function [88, 89].

Recent achievements demonstrate a bidirectional relationship between gut dysbiosis and disease progression [89].

The molecular mechanisms by which probiotics induce an anti-inflammatory response have been studied. One of these studies identified a protective mechanism of breast milk and probiotics in necrotising enterocolitis (NEC) [90].

NEC is a serious gastrointestinal disease in preterm infants caused by invasion of pathogenic bacteria, followed by inflammation in the colon, which accelerates perforation and permeability of the intestine, leading to generalization of infection and death.

Prevention of the pathology is challenging, however, it has been observed that feeding a preterm infant with decanted native breast milk together with probiotics provides the best protection [91, 92]. The mechanism of protection is provided by indole-3-lactic acid (ILA), which is a tryptophan metabolite of breast milk. ILA has been identified as an anti-inflammatory molecule that induces an anti-inflammatory response through interaction with the aryl hydrocarbon transcription factor receptor (AHR) and suppresses IL-1β-induced transcription of IL-8, i.e., attenuates the synthesis of the pro-inflammatory cytokine IL-8 [90].

Clinical trials have demonstrated that a combination of *Lactobacillus* spp. and *Bifidobacterium spp. (L. rhamnosus ATCC 53103* and *B. longum subsp. infantis; or L. casei* and *B. breve; or L. rhamnosus, L. acidophilus, L. casei, B. longum subsp. infantis, B. bifidum* and *B. longum subsp. longum; or L. acidophilus* and *B. longum subsp. infantis; or L acidophilus* and *B. bifidum; or L. rhamnosus ATCC 53103* and *B. longum Reuter ATCC BAAA. longum Reuter ATCC BAA-999; or L. acidophilus, B. bifidum, B. animalis subsp. lactis,* and *B. longum subsp. longum); or B. animalis subsp. lactis (including DSM 15954) or L. reuteri (DSM 17938 or ATCC 55730); or L. rhamnosus (ATCC 53103 or ATC A07FA or LCR 35)* prevents NEC (medium to high level of evidence) in preterm infants (gestational age less than 37 weeks) and infants with low weight. A systematic review of RCTs also showed a reduced risk of death in groups of preterm infants treated with probiotics [93].

The effectiveness of probiotics in maintaining remission of Crohn's disease (CD) was searched in the electronic databases MEDLINE (from the creation to July 6, 2020), Embase (from the creation

to July 6, 2020), the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Register of Specialized Trials IBD Review Group, the World Health Organization (WHO) International Clinical Trials Registry Platform, and ClinicalTrials.gov.

There were found only two RCTs which comparing probiotics with placebo or any other non-biotic intervention for inducing remission in Crohn's disease (CD).

One study, conducted in Germany, involved 11 adults with mild to moderate CD who were treated with a week-long course of corticosteroids and antibiotics (ciprofloxacin 500 mg twice daily and metronidazole 250 mg three times daily) followed by randomized group assignment: *Lactobacillus rhamnosus* strain GG or placebo.

In another study conducted in the United Kingdom (UK), 35 adult participants with active CD (CDAI score between 150 and 450) were randomized to receive a synbiotic treatment consisting of lyophilized Bifidobacterium longum and a commercial product or placebo.

Cumulatively, both studies presented (n=46) showed no difference between probiotic and placebo use in inducing remission of BC after 6 months (OR 1.06; 95% CI 0.65–1.71), as well as no difference in the development of adverse events (OR 2.55; 95% CI 0.11–58.60).

Thus, the available evidence is very uncertain regarding the efficacy or safety of probiotics compared to placebo for inducing remission of Crohn's disease. Although, there are works supporting the high anti-inflammatory potential of probiotics and their efficacy in restoring the microbial landscape, with preservation of intestinal barrier integrity and reduction of intestinal inflammation. Further strain-specific RCTs are needed to understand the efficacy of probiotics in Crohn's disease [94].

CONCLUSIONS

The history of probiotic development spans over 170 years. The ultimate breakthrough in this field started from the middle of the twentieth century. At present, the production of probiotics continues to grow steadily as the demand for them is high both as prescription and over-the-counter drugs. However, the constantly expanding base of probiotic products is often mislabeled by industry and misunderstood by consumers. Inconsistencies must be avoided in the probiotic industry, including proper product labeling, safety and efficacy. In addition, probiotic strains must be able to withstand manufacturing processes and environmental factors to remain viable and retain the ability to colonize the gastrointestinal tract.

It is worth remembering that probiotic microorganisms are both strain and disease specific, meaning that each probiotic strain contains its own unique set of functional genes. Therefore, a particular product cannot be comprehensive for every condition when it comes to the functionality of probiotics.

The selection of an appropriate probiotic must be based on probiotic and host specific factors for successful treatment. Probiotic-specific factors include: origin of a strain, strain-specific genetic markers of a probiotic, type of formulation, viability of a strain, and amount of dose prescribed. Host-specific factors include: type of disease or indication, composition of a gut microflora, diet, age, anthropometric measurements and host lifestyle. Only after taking all these aspects into account it is possible to expect positive effects of probiotics.

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GASTROENTEROLOGICAL PROBLEMS OF PSORIASIS

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Abstract. The presented article is devoted to the association of psoriasis with gastroenterological diseases. The authors report on the most significant comorbidities of gastrointestinal pathology in psoriasis. The article emphasizes the role of an interdisciplinary approach to managing patients.

Key words: *psoriasis; inflammatory bowel disease; celiac disease; Helicobacter pylori; liver pathology.*

ГАСТРОЭНТЕРОЛОГИЧЕСКИЕ ПРОБЛЕМЫ ПСОРИАЗА

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Резюме. Представленная статья посвящена ассоциации псориаза с гастроэнтерологическими заболеваниями. Авторы сообщают о наиболее значимых коморбидностях патологии желудочно-кишечного тракта при псориазе. В статье подчеркивается роль междисциплинарного подхода ведения пациентов.

Ключевые слова: *псориаз; воспалительные заболевания кишечника; целиакия; Helicobacter pylori; патология печени.*

Psoriasis is a systemic immune-associated disease of multifactorial nature with dominating genetic factors. It is characterized by accelerated proliferation of epidermocytes and impaired differentiation, immune reactions in the dermis and synovial membranes, imbalance between proinflammatory and anti-inflammatory cytokines, chemokines; frequent pathological changes in the musculoskeletal system [1].

Psoriasis is among the most common skin diseases, it occurs in 1–2% of the population in developed countries [1, 2].

In most cases, psoriasis manifestation occurs at a young socially active age, which adversely affects the quality of life of a patient. According to several studies, dermatosis has a moderate to severe course among 35–50% of patients. Genetic factors, immune system disorders and environmental factors are considered the most significant in the etiology of psoriasis [1–4]. It should be noted that patients with psoriasis have an increased risk of comorbidity, which is especially relevant in conditions of demographic aging of the population. Cardiovascular diseases are the most prevalent comorbidity, the second place is held by the pathology of digestive organs, followed by endocrine system problems, etc. [4, 5]. N. Al-Mutairi et al. analyzed the structure of comorbid pathology in 1835 patients with various forms of psoriasis and showed that the incidence of concomitant pathology increases significantly in a severe variant of the disease [6].

A number of authors note the role of metabolic processes, functional state of the stomach, in-

testines, pancreas and hepatobiliary system in the development of psoriasis [2, 3, 5]. Y.Y. Milyutin examined 136 patients with psoriasis and found that they had disorders of acid-forming and pepsin-forming function of the stomach [7]. A.V. Bogatyreva found that patients with severe and long-lasting psoriasis have significant disorders of gastric secretory function, expressed in decreased secretion of gastric juice and hydrochloric acid and increased secretion of mucoproteins [8]. Such changes may be associated with autoimmune gastritis [9].

PSORIASIS AND INFLAMMATORY INTESTINAL DISEASES

Inflammatory bowel disease (IBD) is one of the widely discussed gastroenterologic comorbidities of psoriasis.

Such IBDs as Crohn's disease (CD) and ulcerative colitis (UC) are frequently associated with psoriasis. These pathologies are more frequent (3–4 times) in children compared to adults. Genetic predisposition and peculiarities of the immune response are distinguished among the causes of IBDs in patients with psoriasis. It was established that the incidence of psoriasis in patients with Crohn's disease is significantly higher than in the population — 9.6% [10, 11].

A.B. Gottlieb et al. summarized the data of systematic literature reviews and metaanalysis of 79 studies: CD and nonspecific ulcerative colitis (NUC) were among the most frequent comorbid conditions in psoriasis [12].

Cohen et al. found that psoriasis was more commonly associated with Crohn's disease than with NUC [13]. Multivariate analysis of two nurses' health studies (Nurses' Health Study I and II) including follow-up periods of 1996–2008 and 1991–2005 showed that psoriasis in women increased the risk of developing Crohn's disease by 3.5 times, regardless of body mass index, age, physical activity, habitual intoxication, use of oral contraceptives and postmenopausal hormone therapy [14].

Another large-scale prospective observation of 5661 patients with psoriasis and psoriatic arthritis showed that their risk of DC is 6.8 times higher, especially in patients with early onset of the disease, as well as in the presence of an active skin process for 10 years [15]. However, the study did not demonstrate the correlation between the risk of CD development and the severity of psoriasis, as 87% of patients suffered from the mild form of psoriasis. The obtained data corresponded to international studies of genome screening, which revealed the interleukin-23 gene that is common for psoriasis and inflammatory bowel diseases.

Possible explanations for the identified association between psoriasis and IBDs include genetic abnormalities, immune dysfunction, systemic inflammation, and dysregulation of the gut microbiota. Several studies have examined the genetic link between psoriasis and GCD. The chromosomal locus 6p21, a region involving genes related to the major compatibility complex (MHC), is the most extensively studied genetic region. Psoriasis and IBDs share the same genetic susceptibility loci on chromosome 6p21, which corresponds to PSORS1 in psoriasis and IBD. It is known that genes that are not associated with the major compatibility complex, including *IL23R* and *IL12B*, have also been identified in the pathogenesis of both psoriasis and IBD. The *IL23R* gene encodes a subunit of the IL-23 receptor and affects IL-23 binding ability. Interleukin-23 is necessary for differentiation and activation of Th17 lymphocytes, which produce IL-17 [16, 17]. IL-17 binding to its receptor stimulates hyperproliferation and differentiation of keratinocytes, maturation of myeloid dendritic cells, and recruitment of neutrophils and macrophages in psoriatic lesions. Increased expression of IL-17 was detected in the intestinal mucosa and serum of patients with IBD compared to the control group. IL-17-producing T lymphocytes in the intestine appeared be involved not in disease formation, but in elimination of infection and protection of the immune barrier. The *IL12B* gene encodes the p40 subunit, which is involved in both IL-12 and IL-23 signaling pathways; therefore, IL-12B can be suggested as an important cytokine subunit in the pathogenesis of both psoriasis and IBD [16, 17].

In addition, the skin and intestine in IBD and psoriasis share similarities regarding their great microbial diversity and abundant blood supply. The microbiota influences the physiology and immune response of the skin and gut epithelium by regulating biological metabolites. Among other things, the microbiota can lead to the expression of antimicrobial particles, increased levels of cytokines and consequently regulation of T cell activity and differentiation. Thus, microbiota dysfunction may cause systemic immune dysregulation [18]. Current evidence supports the gut-skin axis theory, which describes a close relationship between gut dysbiosis and skin manifestations. It was found that patients with psoriasis have a reduced diversity and abundance of gut microbiota, which is also observed in patients with IBD [19].

A study by Scher et al. [19] indicates a significant reduction ($p < 0.05$) of bacterial diversity in the

gut of patients with psoriasis and psoriatic arthritis. Another study found a reduction in *Akkermansia muciniphila* in psoriasis patients; this species plays a protective role against inflammation and is involved in strengthening the intestinal barrier. Further studies showed that an increased ratio of *Firmicutes* to Bacteroidetes in patients with psoriasis correlates with the presence of greater inflammation [20]. On the contrary, the work of Codoner et al. [21] showed an enhanced bacterial diversity with increased representation of *Faecalibacterium, Akkermansia* and *Ruminococcus* and decreased *Bacteroides*. The latter genus produces polysaccharide A and activates regulatory T cells, so its reduction may be associated with an altered immune response. However, the increase in Faecali bacterium did not correspond to an increase of F. praunitzii, which was found in low concentrations in both psoriasis and Crohn's disease patients. This species produces butyrate, which can inhibit the NF-κB pathway and therefore block the inflammatory response.

Gut dysbiosis has been extensively studied in patients with IBD and, particularly, in patients with BC. Most studies reported a decrease in *Bacteroides* and *Firmicutes* bacteria belonging to *Clostridium* species (17 strains of groups IV and XIVa and butyricum) and an increase in *Gammaproteobacteria* and *Actinobacteria*. In addition, patients with CD demonstrated a relative increase in Proteobacteria, mainly *E. coli*, concentrated in the mucosal-associated microbiota compared to fecal samples [21, 22].

Taking into account the fact that both psoriasis and Crohn's disease are associated with persistent immune dysfunction caused by dysbacteriosis of the gut microbiota, which can negatively affect immunologic homeostasis, restoring normal microbiota composition is crucial for disease therapy, even when genetic, epigenetic, and environmental risk factors are involved.

PSORIASIS AND *HELICOBACTER PYLORI*

Helicobacter pylori infection plays an important role in a number of extraintestinal pathologies, including metabolic, autoimmune, hematologic, cardiovascular, neurologic and skin diseases [23, 24]. On average, this chronic infection affects about 4.4 billion people worldwide. *H. pylori* infection is usually asymptomatic, however, as a frequent cause of peptic ulcer disease, chronic gastritis and gastric cancer, it might include such symptoms as nausea, vomiting and abdominal pain. There are numerous testing methods available for the diagnosis of *H. pylori* infection. They are characterised by high specificity and sensitivity, namely the urea breath test (UDT), which is the most popular and accurate non-invasive method [25].

Several studies have documented that seropositivity to *H. pylori* is associated with elevated levels of C-reactive protein (CRP) and platelet activation factors [26].

According N.V. Pavlenk and E.N. Makhnovets, 76% of 50 patients suffering from the vulgar form of psoriasis were infected with *H. rulori*. As a result of the study, the following clinical features were revealed in the vulgar form of psoriasis with chronic helicobacteriosis: severe exudative component, more frequent deformation of nail plates with a «thimble» type [27]. The studies of S. Qayoom, Q.M. Ahmad showed 50 patients with psoriasis were infected with *H. pylori* significantly more often than the control group [28]. Some authors reported remission of psoriasis after *Hp* eradication therapy. [26]. Moreover, N. Onsun et al. demonstrated a correlative relationship between *Hp* infection and the severity of psoriasis course in the largest research ion this issue in 2014. Moreover, they emphasized that *Hp* eradication accelerates the resolution of psoriasis [29].

Campanati et al. demonstrated that *Hp*-positive patients with psoriasis had more severe clinical forms which rapidly regressed during eradication therapy [30]. Mesquita et al. demonstrated that the prevalence of anti-Hp antibodies was significantly higher in patients with psoriasis compared to healthy individuals [31].

A large meta-analysis conducted in Saudi Arabia in 2019 confirmed the correlation between *H. pylori* infection and psoriasis. The study reported a significant reduction in psoriasis area and severity index (PASI) in patients treated for *H. pylori* infection compared to the control group. The authors suggested that *H. pylori* treatment may reduce the severity of psoriasis and improve the effectiveness of treatment. The study revealed that psoriasis patients had a statistically significant attenuation of platelet P-selectin and CRP levels, CD4/CD8 ratio and percentage of lymphocytes after treatment of *H. pylori* infection compared to psoriasis patients without *H. pylori* eradication [32]. In addition, haptoglobin levels were substantially reduced in psoriasis patients treated for *H. pylori* infection compared to patients without therapy. The authors recommended the use of haptoglobin as a biomarker of psoriasis with a threshold value of 1.95 g/L and routine screening for *Hp*. The findings are consistent with the study of Onsul. Thus, the researchers concluded that *Hp* may be a trigger for psoriasis as well as a possible marker of its severity.

At the same time, according to E. Dauden et al. the most virulent strains of *H. pylori*, CagA+, have no significant influence on the course of psoriasis [33]. Conflicting literature data concerning the role of *H. pylori* in the development of psoriasis requires further scientific research and development.

PSORIASIS AND CELIAC DISEASE

Celiac disease, or gluten-sensitive enteropathy (GSEP), is a disease of the small intestine caused by an immune response to the plant protein gluten. The difficulties in diagnosing GSEP are related to the extreme variety of clinical manifestations — from extremely severe absorption disorders with chronic diarrhea to asymptomatic course or manifestation of extraintestinal symptoms, including psoriasis [34, 35]. Psoriasis and celiac disease are associated with dysregulation of Th1- and Th17-cell pathways, gamma-delta T cells and increased intestinal permeability, vitamin D deficiency, as its absorption is reduced by gluten enteropathy [36].

A recent retrospective cohort study conducted in California revealed that psoriatic patients have a 2.2-fold increased risk of being diagnosed with celiac disease compared to healthy individuals.

The meta-analysis showed that IgA AGAs were positive in about 14% of psoriatic patients compared to 5% of matched controls. Moreover, there was a correlation between celiac antibody positivity and severity of psoriatic manifestations [37].

At the same time, increased antibodies which are specific for celiac disease did not always lead to histologic markers of intestinal mucosa damage in psoriasis patients. However, adherence to a gluten-free diet resulted in rapid resolution of the clinical picture of the disease.

There is also an Italian multicenter study showing that 7 out of 8 patients with celiac disease and psoriasis who underwent a gluten-free diet had a significant improvement in psoriasis area and severity index (PASI), suggesting a role of gluten in the pathogenesis of both diseases [38].

PSORIASIS AND LIVER PATHOLOGY

In recent years, a significant number of publications indicate the relationship between psoriasis and pathology of the hepatobiliary system, particularly nonalcoholic fatty liver disease (NAFLD) and cholelithiasis. It corresponds to modern ideas of psoriasis pathogenesis. The development of NAFLD is based on excessive accumulation of triglycerides in the liver tissue. The disease begins with fatty hepatosis, and then progresses to steatohepatitis and, in case of further progression, to fibrosis and cirrhosis [39, 40].

NAFLD is considered to be one of the metabolic syndrome components and might be regarded as its hepatic manifestation [41].

The prevalence of NAFLD and metabolic syndrome among psoriasis patients is 10–25% which is higher than in the general population [40].

NAFLD includes a wide range of liver diseases with two main histological forms: simple hepatic steatosis (fat deposition without liver cell damage) and non-alcoholic steatohepatitis (NASH), which is characterized by liver inflammation, liver cell damage and fibrotic changes. A distinctive feature of NASH is excessive accumulation of fat in the liver associated with insulin resistance (IR). NASH is determined by the presence of fatty hepatosis (steatosis) in more than 5% of hepatocytes according to histological analysis or proton density of fat fraction (determined by the proportion of adipose tissue in the liver). Fat fraction which amounts to more than 5, 6% assessed by proton magnetic resonance spectroscopy (H-MRS) or quantification of the fat/water ratio by selective magnetic resonance imaging (MRI) is also specific for NASH [42].

The aberrant pathophysiologic processes underlying the progression of NASH are not fully understood, although they are assumed to include imbalances in fatty acid metabolism and cytokine production, increased inflammatory response as a result of oxidative or metabolic stress, leading to steatosis thereafter. In terms of clinical presentation, most cases of NAFLD are either asymptomatic or present with nonspecific symptoms such as fatigue and abdominal pain, and/or abnormal liver function test results [40, 41, 42].

The first data devoted to the association between psoriasis and NAFLD was published in 2001, it involved three patients with overweight/obesity and NASH, which was confirmed by liver biopsy [39, 40, 43]. Since then, various observational and controlled studies have revealed an increased prevalence of NASH in patients with psoriasis. In a large Dutch population-based study (2292 participants aged ≥55 years), the incidence of NAFLD was 46% in 118 patients with psoriasis and 33% in patients without psoriasis. Moreover, elderly patients with psoriasis were 70% more likely to develop NAFLD than those without psoriasis [44].

Patients with both NAFLD and psoriasis have an increased risk of developing more severe fibrotic changes in liver tissue compared to patients with NAFLD without psoriasis. In a case-con-

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trol study conducted by P. Gisondi et al. NAFLD was diagnosed in approximately half of patients with psoriasis [45]. At the same time, the majority of patients had NAFLD combined with metabolic syndrome and higher levels of inflammatory markers (C-reactive protein).

At the same time, the majority of patients have a combination of NAFLD with metabolic syndrome and higher levels of inflammatory markers (C-reactive protein). It is important to note that the presence of NAFLD correlates with the prevalence and severity of psoriasis index (PASI). Similar data were obtained in a large cohort study by E.A. Van der Voort et al. Psoriasis was recognized as one of the independent risk factors for the development of NAFLD [46].

A study in Taiwan confirms a bidirectional association between NAFLD and psoriasis, especially in patients under 40 y.o. [47].

A recent single-center cross-sectional study conducted in Spain identified that 52% of patients among 71 patients diagnosed with psoriasis suffered from NAFLD. It is worth mentioning that 14% of patients had hepatic fibrosis diagnosed by transient fibro-controlled elastography [48].

Several foreign studies indicate that the presence and severity of psoriasis correspond to higher prevalence and greater severity of NAFLD, as well as NAFLD is a strong predictor of higher Psoriasis Area and Severity Index (PASI) [49, 50]. Using an attenuation control parameter to assess the extent of fatty liver disease and the severity of psoriasis on body surface area, Candia et al. confirmed a positive correlation between the two diseases [49]. In addition, progression to more severe forms of liver disease was higher in patients with psoriasis. Roberts et al. reported that 48 of 103 (47%) patients with psoriasis had NASH and 23 of 103 (22%) had biopsy-confirmed NASH, 35% of which had stage II-III fibrosis [50]. The prevalence of NASH was markedly higher than 12%. This amount was registered at the same medical center among patients with similar demographic characteristics but without psoriasis. In addition, concomitant NAFLD in patients with psoriasis may lead to a higher 10-year cardiovascular risk compared to patients without psoriasis [50].

One of the key factors in the development of NAFLD is obesity and metabolic syndrome. Obesity also predisposes to the development of psoriasis, and simultaneously, the presence of psoriasis increases the risk of obesity. The risk factor for developing obesity in patients with psoriasis is 1.18. In addition, obesity directly correlates with the severity of psoriasis manifestations [48, 50].

Chronic moderate inflammation is noted in both NAFLD and psoriasis. Adipose tissue produces a complex of biologically active substances that affect different metabolic parameters and the activity of inflammatory reactions. As the mass of adipose tissue increases, the production of adipokines and cytokines such as leptin, tumor necrosis factor alpha (TNF-alpha), interleukin (IL)-6, -17 and resistin is induced, which have proinflammatory properties and play a key role in the pathogenesis of metabolic syndrom. At the same time, synthesis of such anti-inflammatory substances as adipocytokine and adiponectin, is decreased in adipocytes. NAFLD and psoriasis are characterized by an imbalance of pro- and anti-inflammatory cytokines [51, 52]. The content of TNF-alpha, which regulates immune and inflammatory reactions, is determined by body mass index, percentage of adipose tissue, and hyperinsulinemia. Its level is elevated in patients with NAFLD. In addition to obesity, insulin resistance, hyperinsulinemia, dyslipidemia are considered as factors provoking NAFLD. TNF-alpha inhibits the phosphorylation of tyrosine and substrate 1 of the insulin receptor, which lead to a reduced biological response of tissues and impaired glucose transport into cells. The development of insulin resistance is one of the first steps towards NAFLD. On the contrary, reduction of body weight contributes to the reduction of TNF-alpha levels and insulin resistance [53].

The proinflammatory cytokines IL-6 and IL-17 are involved in immunoinflammatory reactions in both psoriasis and NAFLD. IL-17 is supposed to influence the progression of steatohepatosis to steatohepatitis in NAFLD. Consequently, IL-17 stimulates the production of IL-6 by keratinocytes in psoriasis. In turn, IL-6 induces Th migration into the skin and regulates proliferation and differentiation of dermal and epidermal cells [52, 53].

The degree of cutaneous manifestations of psoriasis positively correlates with serum levels of IL-6 and IL-17 [53, 54].

Adiponectin produced by adipose tissue belongs to the anti-inflammatory adipocytokines. It has an opposite effect on metabolism. Its content in the blood is inversely proportional to body mass index and is significantly reduced in patients with obesity, type 2 diabetes mellitus and NAFLD. Adiponectin promotes tissue sensitivity to insulin [54]. Its anti-inflammatory effect in both psoriasis and NAFLD is realized through suppression of Th1-immune response. This effect consists of inhibition of the synthesis of proinflammatory cytokines TNF-alpha, IL-6, decreased production of vascular endothelial adhe-

sion molecules, reactive oxygen species and the expression of anti-inflammatory cytokine IL-8 [53–55]. Adiponectin production is suppressed by high concentrations of proinflammatory agents, and its level is inversely proportional to the levels of TNF-alpha and IL-6 both in psoriasis and NAFLD [55]. It is noteworthy that patients suffering from psoriasis combined with NAFLD have lower serum adiponectin levels than psoriasis patients without liver lesions.

Thus, the relationship between psoriasis and NAFLD is due to disorders of carbohydrate and fat metabolism, as well as a complex of local and systemic immune disorders that support persistent inflammation.

The study of L.X. Tong et al. presents noteworthy data regarding the increased risk of psoriasis development in individuals with cholelithiasis [56]. The grounds are not completely clear. However, a recent study found that hypercholesterolemia is one of the risk factors for the development of psoriasis. Hence, it may be a common pathogenetic link between psoriasis and cholelithiasis. It was found that long-term (more than seven years) hypercholesterolemia significantly increases the probability of psoriasis development.

Summarizing all the above mentioned, it is possible to conclude that liver pathology is an increasingly common and clinically important comorbidity, occurring in up to 65% of patients with psoriasis. Liver impairment supports systemic inflammation, contributes to disease progression and often develops tolerance to therapy.

Conflict of interest. The author declares that there is no conflict of interest.

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IODINE DEFICIENCY IN CHILDHOOD: THE CURRENT STATE OF THE ISSUE

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Abstract. The aim of the work was based on the results of a number of clinical studies to study the prevalence of iodine deficiency, its diagnosis and impact on the health of the child, as well as to consider possible ways to correct this condition. The geographical location of the Russian Federation, the peculiarities of the nature of nutrition of the majority of the child population at the present stage, the low level of use of iodized salt by the population causes a high prevalence of iodine deficiency among traditionally fed children. Compliance with restrictive types of nutrition by children without supervision of such a child by a pediatrician or a nutritionist may underlie the development of trace element imbalance and, as a consequence, the formation of iodine deficiency. The study of the prevalence of iodine provision in children who observe restrictive types of nutrition, as well as the study of modern possibilities for correcting the identified violations is an urgent issue of modern pediatrics, which is given little attention at the present stage.

Key words: *iodine; iodine deficiency; iodine deficiency diseases; supplementation; children.*

ЙОДНЫЙ ДЕФИЦИТ В ДЕТСКОМ ВОЗРАСТЕ: СОВРЕМЕННОЕ СОСТОЯНИЕ ВОПРОСА

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Резюме. Целью работы было на основании результатов ряда клинических исследований изучить распространенность йодного дефицита, его диагностику и влияние на здоровье ребенка, а также рассмотреть возможные способы коррекции данного состояния. Географическое расположение Российской Федерации, особенности характера питания большей части детского населения на современном этапе, низкий уровень использования йодированной соли населением обусловливает высокую распространенность йодного дефицита среди традиционно питающихся детей. Соблюдение ограничительных типов питания детьми без наблюдения за таким ребенком педиатра или диетолога может лежать в основе развития микроэлементного дисбаланса и как следствие — формирование йодного дефицита. Изучение распространенности йодной обеспеченности детей, соблюдающих ограничительные типы питания, а также изучение современных возможностей коррекции выявленных нарушений является актуальным вопросом современной педиатрии, которому уделяется достаточно мало внимания на современном этапе.

Ключевые слова: *йод; йодный дефицит; йоддефицитные заболевания; сапплементация; дети.*

Optimal supply of vitamins, essential macro- and microelements determines a child's normal growth, mental and physical development [1]. Iodine is an essential micronutrient. Ehe normal functioning of the human body is impossible without it. Regular iodine intake with food is a great importance for maintaining health, since the human body is unable to produce this trace element on its own [2]. Iodine is an obligatory structural component of thyroid hormones — thyroxine (T_4) and triiodothyronine (T_3), which determine the activity of most metabolic processes in our body. Physiological synthesis and secretion of thyroid hormones requires adequate intake of this trace element into the body.

The aim of the work was to study the prevalence of iodine deficiency (ID), its diagnosis and impact on child health, as well as to consider possible ways to correct this condition based on the results of a number of clinical studies.

The main natural sources of iodine for humans are products of plant and animal origin, drinking water. Most of the natural iodine reserves are located in sea water, where it was washed away during the formation of our planet from the soil surface by rains, glaciers, snow. At the same time, a significant part of land and fresh water is depleted of this trace element [3].

According to the results of epidemiological studies aimed at determining the prevalence of iodine deficiency diseases (IDD), it has been established that more than two billion inhabitants of our planet live in areas with IDD. At the same time, about one billion people have clinical manifestations of IDD: 740 million people have endemic goitre and 43 million suffer from mental retardation up to cretinism as a result of iodine deficiency [4]. According to the literature, about 50% of the European population has mild ID [5]. The most endemic regions for ID are considered to be mountainous areas, areas with frequent rainfall that washes iodine from the soil surface, and regions far from the ocean. Based on this information, a large part of the Russian Federation can be considered as endemic for ID.

According to the Iodine Global Network, the Russian Federation belongs to the areas with moderate ID. According to the literature it is known that this condition is detected practically on the entire territory of the post-Soviet states. In the Russian Federation, there are practically no territories whose population would not be at risk of developing IDD [6]. Thus, more than 50% of the territories of the subjects of our state are affected by naturally occurring IDD. About 60% of the population of our country lives in these territories [7]. Natural ID is aggravated by low consumption of food products that are sources of iodine (the fish, seafood and the algae). The most pronounced ID is observed among the inhabitants of foothill and mountainous areas (North Caucasus, Urals, Altai, Far East), in the territories of the Upper and Middle Volga region, Transbaikalia, in the population of Western and Eastern Siberia [8, 9, 10].

The food is the main source of iodine intake because the iodine content in drinking water is low (less than 2 μg/litre). Marine fish, seafood and seaweed are considered to be the main sources of iodine. Seaweed (kelp) is the richest product in terms of the content of this trace element (up to 1 % of dry weight). Eating 20–90 mg of dried seaweed provides its daily intake. However, this product is very rarely used in the nutrition of the child population in our country. In this case, the reaction of the child to the use of seaweed in food in most cases remains negative. Much less iodine is contained in the products on which the daily diet of most children is based — these are dairy products, cereals, potatoes and others. The iodine content in products of plant origin depends on its content in the soils on which they are grown, and in products of animal origin — on the content of the trace element in the animal feed used. It should be borne in mind that during heat treatment and storage of the product, the concentration of iodine in it decreases significantly, which significantly reduces the value of this product and dishes prepared from it as a source of iodine [11, 12].

Iodine enters the body in both inorganic and organic forms. After ingestion, it is almost completely absorbed in the small intestine, accumulating in the thyroid, which is the main depot of the trace element; kidneys; stomach; mammary and salivary glands. The concentration of iodine in breast milk, saliva and gastric juice is 30 times higher than its concentration in plasma. In the blood the trace element circulates as iodide and in the protein-bound state. The concentration of iodine in blood plasma at normal intake is about 10–15 μg/l. About 2/3 of iodine intake is excreted by kidneys (the iodine can also be excreted by mammary, salivary and sweat glands). Data on iodine concentration in the thyroid fluctuate widely. The human value is believed to be approximately 0.6 mg/l.

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The daily iodine requirement depends on age and physiological state. According to WHO data, for different population groups the daily dose of iodine differs and is: for children from birth to 6 years — 90 μg; for children from 6 to 12 years — 120 μg; for children from 12 years and adults — 150 μg; for pregnant and lactating women — 250 μg [13].

The chemical composition of food products and nutritional culture of the population of the Russian Federation indicate that it is impossible to ensure the recommended standards of iodine consumption using traditional products. To cover the need of the growing organism for this trace element, it is necessary to include a sufficiently large amount (about 100 g) of sea fish and seafood with high iodine content in the child's diet every day. Consequently, in modern conditions, a child's diet composed of natural products and quite adequate to the age-specific energy requirements is not able to provide the body with the necessary amount of iodine. This problem is especially acute among children who follow restrictive types of diet (includ vegetarianism) and don't like iodisation of food [13, 14].

Insufficient iodine intake into the body leads to the activation of successive adaptive processes aimed at maintaining normal synthesis and secretion of thyroid hormones. With a prolonged deficiency of this trace element occurs failure of adaptation mechanisms with the subsequent development of iodine deficiency.

It is known that the greatest danger is insufficient iodine intake into the body at the stage of intrauterine development and early childhood. Changes caused by iodine during these periods of life are manifested by irreversible defects in the intellectual and physical development of the child. Thyroid hormones play an important role in the formation of the brain during intrauterine development, and insufficient iodine supply in the pregnant woman can cause irreversible damage to the fetal brain [12, 15]. Among possible adverse effects of iodine deficiency in children are the development of hypothyroidism, goitre, mental retardation (up to cretinism), impaired cognitive function, lag in neuropsychiatric and physical development, and increased absorption of radioactive iodine in nuclear disasters.

Now control of iodine intake by the population, prevention of ID and IDD are urgent medical and social tasks. All IDD can be prevented, whereas the changes caused by iodine deficiency at the stage of intrauterine development and in early childhood are irreversible and practically cannot be treated and rehabilitated, leading to disability of the patient.

The severity of IDD is usually assessed by the level of excretion of iodine in the urine, which adequately reflects its intake, given that 90% of iodine consumed with food is excreted with urine. The urinary iodine level of an individual is known to vary throughout the day. Therefore, these measurements can only be used to estimate iodine availability in the general population in epidemiological researches.

Currently, the median urinary iodine concentration and the proportion of urine samples with iodine levels less than 50 μg/litre are the two main statistical indicators needed to assess iodine status worldwide. The main indicator of the degree of iodine stress in the population is ioduria — the level of urinary iodine excretion in a representative group of the population living in a particular region. The representative group is usually considered to be children of primary school age (6–12 years old), as this age period excludes the influence of occupation and working conditions, as well as hormonal shifts and other changes characteristic of puberty. The collection of the material itself is carried out directly in schools, which ensures the necessary random of selection. After determining the levels of iodine excretion in individual urine portions, an integral indicator is calculated — the median concentration of iodine in urine, according to which the level of iodine supply of the whole population is determined. With optimal iodine supply, no more than 20% of urine samples should have an iodine level of less than 50 μg/l [16].

For school students normal iodine availability in the region where the study is conducted is considered to be at a median ioduria of 100–200 μg/day. In mild ID, the median ioduria is 50–99 μg/day, in moderate ID it is 20–49 μg/day, and in severe ID it is less than 20 μg/day [4].

All measures to prevent IDD are based on the norms of physiological iodine intake. Today world experts have formed the main strategy for overcoming ID based on three main types of iodine prophylaxis: mass, individual and group. Mass prophylaxis is considered to be the most effective. The preference in mass iodine prophylaxis is given to iodisation of food salt, despite the fact that

there is an experience in iodisation of other products (milk, butter, bread).

The salt iodisation is recommended by WHO as a universal, highly effective method of mass iodine prophylaxis, according to which all salt for human consumption (i.e. the salt sold in shops and used in food processing) should be iodised [13]. To achieve optimal iodine intake (150 μg/day), WHO and the International Council for the Control of IDD recommend the addition of an average of 20–40 mg iodine per 1 kg of salt. Potassium iodate has been recommended as an iodising supplement [15]. The choice of salt as an iodine "carrier" is also due to the fact that it is used by the population regardless of social and economic characteristics. The average daily dose of salt consumption is 5–10 g and may vary depending on age, sex, and season. Unlike other foodstuffs, iodine from which isn't fully assimilated (10–50%), it is assimilated almost completely (85–90%) from iodised salt. Modern salt iodisation technologies are reliable and low-cost. At the same time, it has been found that mass iodine prophylaxis methods are effective if more than 90% of the participants in the process use iodised salt at home. Iodine overdose is practically impossible with proper salt iodisation. All of the above has led more than 120 countries around the world to choose this method of iodine prophylaxis as a national strategy for overcoming ID and preventing IDD.

It is estimated that the average daily iodine intake with iodised salt is about 150 μg, which corresponds to the daily norm and is safe for humans. Even if this amount of iodine (150 μg) is added to the average daily amount in the diet (40–80 μg), it will be only 20–25% of the maximum safe amount of iodine intake, which for a school-age child is 500 μg/day.

In the 1980s, the prevention of ID in the USSR was discontinued, resulting in a gradual increase in the prevalence and severity of ID among the population in the post-Soviet countries. In the Russian Federation, the use of iodised salt as the main method of mass prevention of IDD was introduced by the Russian government in 1999. However, in contrast to a number of near and far abroad countries (USA, Australia, Armenia, Belarus), where the law on universal salt iodisation was adopted and IDD was practically eliminated. In our country the use of iodised salt is voluntary, and only about 30–40% of families use it [12].

Control is quite important in the prevention of ID, which is organised by continuous monitoring of iodine supply to the population. The effectiveness of iodine prophylaxis is also assessed by the level of median ioduria, use of iodised salt and compliance of its samples with state standards. Iodine prophylaxis is considered effective when the median ioduria in the population ranges from 100–199 μg/l, and in pregnant women — 150–249 μg/l; prophylaxis is also considered effective when iodised salt is used in 90% of households (when 95% of salt samples comply with state standards for iodine content GOST R 51575–2000 «Iodised table salt. Methods of determination of iodine and sodium thiosulphate».) [15].

However, in certain periods of life (children under two years of age, pregnant and lactating women) physiological need for iodine increases, and the body needs additional amounts of this element. In such cases, individual and group iodine prophylaxis is carried out by taking pharmacological products containing a physiological (standardised) dose of potassium iodide. In these population groups, the prevalence of IDD is particularly high, and therefore the administration of medicines with an accurate dose of potassium iodide has not only preventive but also therapeutic value. The use of pharmacological preparations of iodine with its specific level allows to individually select the necessary dose of iodine and to control the effectiveness of the conducted prophylaxis [6].

For group and individual iodine prophylaxis, it is customary to use potassium iodide preparations in accordance with age norms. For the region of mild iodine deficiency it is recommended to use: for young children — 50–100 μg/day; for children of primary school age (6–12 years) — 100 μg/day; for adolescents — 200 μg/day; for pregnant and lactating women — 250 μg/day.

Iodine metabolism directly depends not only on the amount of iodine supplied to the body, but also on the supply of other micronutrients from which cofactors involved in iodine metabolism are synthesised. Thus, for the synthesis of thyroid hormones it is important to get enough tyrosine amino acid in the body, in this regard, the level of consumption of protein products (meat, fish, dairy products) is of particular importance. The structure of thyroperoxidase includes iron, and the activity of the enzyme depends on the level of cobalt and copper. Selenium is part of the deiodinases that convert T_4 to T_3. The synthesis of thy-

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roid hormones is impossible without superoxide dismutase, which is possessed by manganese, copper and zinc. That is why trace element imbalance is the basis for the decrease in the activity of metalloenzymes, aggravates iodine metabolism disorder, reduces the synthesis of thyroid hormones, increases its sensitivity to the stimulating effect of thyroid-stimulating hormone, increases the level of autocrine growth factors, activates apoptosis and autoimmune processes, which causes the development of goitre [7, 17, 18]. Probably, one of the reasons for the development of such trace element imbalance in a child may be the observance of vegetarian type of diet without medical supervision and without supplementation with trace elements and vitamins [19]. In this connection, the study of iodine supply in children following restrictive types of diet, as well as the functional state of the thyroid gland, is an urgent issue of modern paediatrics, especially in areas endemic for ID [20].

Thus, in a research conducted in Norway — a country with a high level of marine fish consumption, the iodine supply of adult vegans, vegetarians and pascetarians was studied. It was found that the median ioduria in vegans corresponded to mild-to-moderate ID, and in vegetarians and pascetarians to mild ID [21].

Low dietary iodine intake among vegans and vegetarians relative to traditionally eating people was also found in a study conducted in the Great Britain. The authors also point to the fact that people who follow restrictive diets, in most cases, do not control the level of micronutrient intake and do not perform their supplementation [22].

Along with inadequate iodine supply, a number of substances capable of impairing thyroid function — disruptors — have recently received increasing attention. These substances include thiocinates found in the cabbage, radish, rapeseed, horseradish, beans, potatoes and maize. Thiocinates inhibit the capture of iodine by the thyroid and stimulate its excretion from the body. Some flavonoids found in plant extracts and millet are also considered disruptors. They affect the binding of thyroid hormones by transport proteins. The qualitative and quantitative composition of anthropogenic disruptors in the modern environment is continuously changing and increasing. Road transport is an important source of such substances in the environment. These disruptors weaken the function of oxidases, which take part in the oxidation of iodide to elemental iodine. In addition, detergents and cleaning agents, dyes, degradation products of polymeric materials, the use of which in modern society is very common, have a negative impact on the thyroid gland.

Thus, the problem of studying the iodine supply of the child population of our country and further prevention of ID and development of IDD are urgent issues of modern paediatrics. The geographical location of the Russian Federation, the iodine content of foodstuffs for the majority of the child population at the present stage, and the low level of iodised salt use by the population cause a high prevalence of ID among traditionally nourished children. The absence in Russia of a state strategy aimed at the elimination of ID continues to have a negative impact on the health of the entire population of the country. In this regard, it is of current importance to popularise preventive measures using iodised salt, as well as group and individual prophylaxis with potassium iodide preparations in the most vulnerable population groups, which include pregnant women, lactating women and infants. Observance of restrictive types of nutrition by children without supervision of such a child by a paediatrician or nutritionist may underlie the development of microelement imbalance and, as a consequence, the formation of ID. Children living in our country who follow restrictive diets, including vegetarianism, should probably be considered as a risk group for ID and further development of IDD. The study of the prevalence of iodine availability in children following restrictive types of diet, as well as the study of modern possibilities of correction of the revealed disorders, is currently relevant and requires more attention.

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FEATURES OF ZINC METABOLISM IN NEWBORN AND INFANT CHILDREN

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Abstract. The child's body is in the process of continuous growth and development, and the violation of its normal course is regarded as an indicator of ill health. An important role is given to the deficiency of essential micronutrients, among which zinc is of particular importance. This trace element is necessary in the antenatal and postnatal periods, since it affects cell division and differentiation, neurogenesis, osteogenesis, is involved in cell metabolism, is an antioxidant protection factor, and also maintains homeostasis in the body. Zinc deficiency is associated with the development of immunopathological reactions that underlie the development of allergies, a decrease in the regenerative capabilities of the skin and mucous membranes. This article will consider the main aspects of the clinical significance of the trace element in newborns and young children.

Key words: *newborn; zinc; microelementoses.*

ОСОБЕННОСТИ ОБМЕНА ЦИНКА У НОВОРОЖДЕННЫХ И ДЕТЕЙ РАННЕГО ВОЗРАСТА

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Резюме. Организм ребенка находится в процессе непрерывного роста и развития, и нарушение его нормального хода расценивается как показатель неблагополучия в состоянии здоровья. Важная роль при этом придается дефициту эссенциальных микронутриентов, среди которых особое значение отводится цинку. Данный микроэлемент необходим в антенатальный и постнатальный периоды, поскольку он оказывает влияние на деление и дифференцировку клеток, нейрогенез, остеогенез, участвует в обеспечении клеточного метаболизма, является фактором антиоксидантной защиты, а также поддерживает гомеостаз в организме. С дефицитом цинка связано развитие иммунопатологических реакций, лежащих в основе развития аллергии, снижения регенераторных возможностей кожи и слизистых оболочек. В данной статье будут рассмотрены основные аспекты клинического значения цинка у новорожденных и детей раннего возраста.

Ключевые слова: *новорожденный; цинк; микроэлементозы.*

LONG-TERM EFFECTS OF ZINC DEFICIENCY DURING PREGNANCY

In recent years, the problem of macro- and microelementosis in various pathological conditions remains very controversial. This is due to the fact that most of these elements are part of biologically active substances or influence them, thus participating in most metabolic and immune processes in the child's body and determining the functional state of its various organs and systems [1]. Micronutrient deficiencies are dangerous because they do not clinically mani-

fest for a long time, thus causing a period of «hidden hunger». In addition, it should be noted that deficiency of essential elements, such as zinc, has the most severe consequences for health [2].

Unbalanced nutrition, considered by the World Health Organisation (WHO) as a problem of starvation, and, in particular, mineral deficiencies are often observed in the majority of the population (including pregnant women and lactating mothers), which, in turn, has a direct impact on morbidity and mortality. In addition, during pregnancy, the need for minerals increases significantly, and nutrition determines both the health of the mother and the full health and development of her future baby. In foreign studies it is noted that zinc deficiency increases the risk of pathological course of pregnancy and childbirth, uteroplacental circulation disorders, which, in turn, can cause chronic placental insufficiency, which leads to impaired nutrition of the foetus, the emergence of chronic hypoxia and delay in its intrauterine development. The impact of malnutrition during pregnancy may be comparable to the role of genetic factors and active chemical or infectious teratogens.

Normally zinc is actively transported through the placenta and accumulates in the organs and tissues of the fetus, mainly in the brain, liver, pancreas and bone tissue. Disturbances in homeostasis in the intrauterine and antenatal period can lead to the development of malformations, signs of dysadaptation, hypothorphy, anaemia and other nutrient-dependent diseases, disorders of physical and psychomotor development of the baby, as they and the mother represent a single biological system in which changes in the state of one of the links are reflected in the functional activity of the other. Analysis of zinc content in umbilical cord blood revealed zinc deficiency in preterm newborns compared to term infants. At the same time, in about one in ten of very low birth weight infants the concentration of zinc in cord blood did not differ from that in preterm infants with normal body weight. It was found that newborns with zinc deficiency more often had an unfavourable course of the period of early neonatal adaptation. Such indicators as the child's condition at birth, Apgar score, degree of weight loss, severity of borderline conditions and morbidity were significantly different [3, 4].

EFFECT OF TRACE ELEMENTAL NUTRITION ON METABOLIC PROCESSES IN A CHILDREN

Children with zinc deficiency are significantly more likely to have dry skin, perioral and periorbital dermatitis, pathological changes in skin derivatives in the form of dystrophic changes in the nail plate, hyperkeratosis of the nail bed, impaired hair growth and structure, as well as the development of eczema, psoriasis and furunculosis [5, 6]. Skin injuries in children with microelementosis heal much slower than in healthy babies. Atopic dermatitis is accompanied by more pronounced hyperproduction of IgE, increased number of eosinophils, decreased number of lymphocytes in peripheral blood, increased ratio of CD4+/CD8+ immunophenotypes of lymphocytes in blood. The obtained data are probably related to the fact that the deficiency of zink leads to atrophy of the thymic-lymphatic system (manifested by atrophy of thymus, tonsils, lymph nodes, spleen), decreased function of macrophages and T-lymphocytes, and, consequently, to depression of cellular immunity, decreased level of immunoglobulins and formation of allergic reactions of the reactive type. In childhood, at the stage of formation of specific defence mechanisms, these changes may contribute to the development of allergic reactions of both general and local nature [7].

The deficiency of zink in early childhood undermines the healthy functioning of the circulatory system and disrupts hematopoiesis [8]. The trace element is part of the enzyme carboanhydrase, which is found mainly in erythrocytes and is directly involved in the transfer of carbon dioxide to the lungs. In addition, the fact that the development of iron deficiency anaemia in zinc deficiency has been established. Zinc-dependent anaemia, the main symptoms of which are taste perversion and muscular hypotonia of the child, has been described. Since zinc is involved in the formation of antioxidant status as a protector of free-radical reactions [9], its deficiency adversely affects the morphofunctional state of the endocrine and reproductive systems and may cause late puberty and pathological disorders in the development of the child's reproductive organs: uterus in girls and testicles in boys.

ROLE OF ZINC IN THE FORMATION MUSCULOSKELETAL SYSTEM OF THE CHILD

When assessing the structure of musculoskeletal system pathology in children with zinc deficiency, it was found to be represented [10]:

- posture disorders — 39%;
- scoliosis — 19%;
- flat feet — 31%;
- flat-valgus or varus position of feet — 42%;
- valgus of knee joints — 22%.

At the same time, more severe forms of these diseases were observed in zinc-deficient young children.

This is explained by the fact that zinc is one of the cofactors of enzymes responsible for the synthesis of collagen and glycosaminoglycans, and participates in the performance of bone-forming cells (osteoblasts) of their main function — the synthesis of bone matrix. Moreover, the trace element is part of bone alkaline phosphatase and is associated with skeletal calcification, formation of hydroxyapatite, which determines its role in the maturation of the bone system.

ZINC IN THE DEVELOPMENT OF CNS STRUCTURES

The unique role of zinc in the development and activity of the central nervous system and behaviour has been proven. Compared to other organs in the baby's body, the highest zinc content is found in the brain (150 μmol/L), ten fold higher than its concentration in serum. The highest concentration is found in the neocortex, hippocampus, striatum and amygdala [11–14]. In zinc deficiency, conditioned reflexes are produced more slowly and learning ability is reduced. It is believed that in conditions of hypocincaemia the nuclear-cytoplasmic ratio of brain cells changes, brain development and structural maturation of the cerebellum are delayed. Deficiency of the mineral is especially dangerous during critical periods of brain development (antenatal stage, age from birth to three years). The child becomes more often ill, capricious, quickly tired [15]. In neglected cases, this can lead to the development of intellectual disability or serious mental illness. Autism spectrum disorders are one of the most complex types of child psychopathology in terms of etiopathogenesis and clinical and diagnostic differentiation. The peculiarity of autism spectrum disorders is the violation of the status of microelements, in particular, zinc deficiency. Intrauterine deficiency of this mineral occupies a key place among the causes of hypocyncaemia in autism spectrum disorders, which contributes not only to complications in pregnancy, but also to defects in fetal development and disruption of the functioning of organs and systems [16, 17].

It is important to note that the metabolism of zinc and vitamin A are closely related. It has been experimentally established that impaired absorption of zinc in the intestine worsens with vitamin A deficiency. In addition, all steps of the vitamin A enzymatic cascade are served by zinc-dependent enzymes. There is evidence that protein and zinc deficiency inhibits the synthesis of retinoic acid-binding protein. Thus, hypocincaemia also affects the baby's vision and may cause the development of myopia.

THE RELATIONSHIP BETWEEN GASTROINTESTINAL PATHOLOGIES AND HYPOCYCAEMIA

The importance of zinc for the normal functioning of the gastrointestinal tract lies in modulating the concentration of intracellular cyclic adenosine monophosphate (cyclic AMP), stimulation of absorption processes in enterocytes, and regulation of intestinal neurons. In addition, zinc as a component of the zinc ring takes part in the formation, migration and specification of cells in the neural crest, which are derived from the enteric nervous system [18].

In animal experiments, it has been proved that hypocincaemia causes the following disorders: significant reduction in the length of the small intestine, morphological changes in the jejunum, shortening and narrowing of villi, decreased absorptive surface, inhibition of mucosal cell proliferation and slower migration, decreased proliferation of crypt cells, ultrastructural changes at the cellular level, such as the appearance of membrane-bound autophagic vacuoles, pycnotic nuclei and enlarged nucleus periphery, as well as impaired intestinal mucin composition, which is accompanied by dysfunction of mucin-secreting goblet cells. Chronic zinc deficiency reduces the activity of disaccharidases, the full functioning of which is necessary for carbohydrate digestion and absorption of saccharides. Thus, zinc deficiency has a negative effect on the structure and function of the intestinal epithelium, characterized by impaired absorption of essential nutrients, malnutrition, diarrhoea and inflammation in the immature gut of the newborn.

Inflammation in the gastrointestinal tract can cause intestinal permeability, commonly referred to as «leaky gut» [19]. Gaps between cells in the small intestine can result in food and other toxins not being fully broken down as they enter the bloodstream, which can trigger an immune system response that triggers antibody production, thereby promoting chronic inflammation. Prolonged inflammation can affect microbial proliferation in the gastrointestinal tract and cause vitamin and mineral deficiencies, food allergies, and the development of autoimmune diseases such as celiac disease [20, 21].

In addition, zinc ions as a cofactor not only participate in insulin processing and storage, but also serve as a signalling molecule for α-cells, being released into the extracellular space after insulin secretion [22]. The discovery of zinc-finger sites in proteins has shown the structural function of zinc. Zinc stimulates insulin synthesis and is a part of its crystals, which are localized in secretory granules of pancreatic islet cells.

Thus, in children with serum zinc deficiency at birth, the deficiency of this trace element persists in early childhood, having a negative impact on growth processes and a harmony of physical and neuropsychiatric development, an allergopathology (among which atopic dermatitis takes the leading place), as well as diseases of the gastrointestinal tract, musculoskeletal and immune systems of the body [23].

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THE PLACE OF JEJUNOSTOMY IN PALLIATIVE CARE. LITERATURE REVIEW

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Abstract. The most common type of palliative care for dysphagia is the imposition of artificial nutritional fistulas. In this case, the operation of choice is considered to be gastrostomy, to which a large number of publications are devoted. Jejunostomy is performed much less frequently and is less covered in the literature. The article presents a review of the literature reflecting the evolution of jejunostomy as a palliative operation to provide enteral nutrition for dysphagia.

Key words: *jejunostomy; gastrostomy; dysphagia; palliative care.*

МЕСТО ЕЮНОСТОМИИ В ПАЛЛИАТИВНОЙ ПОМОЩИ. ОБЗОР ЛИТЕРАТУРЫ

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Резюме. Наиболее распространенным видом паллиативной помощи при дисфагии является наложение искусственных питательных свищей. При этом операцией выбора считается гастростомия, которой посвящено большое количество публикаций. Еюностомия выполняется значительно реже и меньше освещена в литературе. В статье представлен обзор литературы, отражающий эволюцию еюностомии как паллиативной операции для обеспечения энтеральным питанием при дисфагии.

Ключевые слова: *еюностомия; гастростомия; дисфагия; паллиативная помощь.*

A common type of palliative intervention for prolonged dysphagia is a nutritional fistula for enteral feeding [1–3]. Gastrostomy is considered the operation of choice, where the gastric stage of digestion is preserved. This is more physiological and reduces the risk of dumping syndrome and metabolic disorders that may develop when nutrition is introduced into the jejunum [4, 5]. For this reason, a jejunostomy is used when gastrostomy is technically impossible due to gastric lesions or in cases of gastric motility disorders and marked gastroesophageal reflux [4, 6–9].

The first feeding jejunostomy was applied by W. Busch to a patient with inoperable gastric cancer in 1858 [5] 9 years after the first gastrostomy [10]. Emerging new gastrostomy techniques have traditionally been adapted for eunostomy.

At present, the feeding jejunostomy with a U-shaped interintestinal anastomosis performed by K. Maydl in 1883 year remains relevant [11]. After laparotomy, the small intestine is crossed 30 cm from the ligament of Treitz. The proximal end of the intestine is anastomosed end-to-end with the small intestine 20 cm below the cross-

ing point. The distal end is passed obliquely, removed through a separate incision in the anterior abdominal wall, and fixed to the skin [12].

Another used operation is the O. Witzel jejunostomy with interintestinal anastomosis, which was proposed by A.F. Eiselberg in 1895 [7, 13]. Eiselberg in 1895 [7, 13]. After upper laparotomy the first loop of jejunum 40–50 cm long from the ligament of Treitz is taken out. An interintestinal anastomosis is applied between the driving and the withdrawing part of the intestine. A feeding tube is placed on the diverting loop proximal to the anastomosis, which is immersed in the intestinal wall with knotted sutures. The inner end of the tube is immersed through the opening in the intestinal lumen and is inserted proximal to the anastomosis area. The hole in the intestine is sutured with knotted or cicatellar sutures. Thus, the canal is formed according to O. Witzel. The tube is fixed with additional sutures to the intestinal wall and withdrawn through a separate incision of the anterior abdominal wall. The intestinal wall in the area of exit from the canal is sutured to the parietal peritoneum, and the tube is sutured to the skin with knotted sutures [14].

In addition to an independent palliative operation, the jejunostomy can be applied as a temporary step before or after another operation [7, 15, 16]. For example, nutritional eunostomy in reconstructive oesophageal surgery as a stage of small intestinal plasty according to Roux-Hertzen-Yudin, needle catheterisation of the small intestine according to H.M. Delany after abdominal operations [5, 13, 17].

Shortly after the advent of percutaneous endoscopic gastrostomy (PEG) in the 1980s, reports on the performance of direct percutaneous endoscopic eunostomy (PEE) appeared [5, 18, 19]. PEE is rarely used due to technical difficulty. As experience is gained, the success rate of the operation increases from 68 to 95% [20–22]. Possible complications are similar to those after PEG, with a lower risk of aspiration pneumonia. The mortality rate reaches 35%, but it is explained by the severity of the pathology [22].

The emergence of experience in puncture gastrostomy under X-ray, ultrasound and CT guidance has led to the adaptation of these techniques for eunostomy, but the number of observations is still small [9, 23, 24].

Naturally, the development of laparoscopic techniques has allowed traditional uninostomies to be applied laparoscopically [5, 16, 25]. In 1990, O'Regan et al. reported the first laparoscopically-assisted percutaneous eunostomy [19, 26].

There is no proven difference in the incidence of complications after different methods of eunostomy [5]. This is due to the small number of operations and difficulties in comparing data from heterogeneous groups of observations published by different institutions. The complication rate after traditional laparotomy jejunostomies can be as high as 56.7% [27], after needle catheterisation of the jejunum performed during another laparotomy, a complication rate of up to 3% is described [28], and complications in laparoscopic jejunostomies have been described in 9.8–17.0% of cases [29, 30]. As the PEE technique is being developed, there are reports about its advantage due to its low invasiveness, comparability in success rate (96%) and number of complications (5%) with laparoscopic eunostomy [31].

Different classifications of complications after eunostomy are used. By analogy with gastrostomy, major and minor complications are distinguished [32, 33]. There is a division of complications into the mechanical, infectious, gastrointestinal, and metabolic complications [5].

Mechanical complications are caused by the technique of the operation. Obstruction of the intestinal lumen is possible when using balloon-type tubes. In the case of O. Witzel tube jejunostomy — reflux of intestinal contents due to ischaemia and mucosal erosions from the tube pressure. In the puncture eunostomy, catheter prolapse or obstruction, intestinal pneumatisation, formation of intestinal fistulas and abscesses near the catheter are common. Laparoscopic eunostomy is additionally at risk of complications due to increased intra-abdominal pressure and deeper anaesthesia [5].

Infectious complications in the form of aspiration pneumonia may result from improper placement of the jejunostomy which leads to reflux [5].

Gastrointestinal complications are manifested as nausea, vomiting, diarrhoea, abdominal bloating, attacks of spastic abdominal pain. Their severity is strongly influenced by the diet used [5].

Metabolic disorders are manifested as hypokalaemia, hyperglycaemia and acid-base balance disorders. This may be due to improper positioning of the tube in the jejunum, administration of inappropriate nutrition. Due to the disconnection of the stomach and duodenum from digestion, there is a possibility of vitamin B12 and iron deficiency. Initiation of tube feeding after a period of fasting may lead to the development of hypokalaemia, hypophosphatemia and hypomagnesaemia. The pathophysiology is thought to be related to the release of insulin from the pancreas when feeding is

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initiated. This often manifests in patients in the intensive care unit as haemodynamic instability, respiratory failure and other non-specific features [5].

Thus, at present, for palliative care of dysphagia, eunostomy is rarely used, mainly when gastrostomy is not possible or its complications. In addition, an intermediate option between gastrostomy and eunostomy has emerged. This is the insertion of a feeding tube into the jejunum through a gastrostomy. In the case of PEG, this method is called "PEG with a jejunal extension tube (PEG-J)", i.e. PEG with a jejunal tube. The advantage of this technique is the simpler technique of gastric fistula formation, and the delivery of nutrition through the probe into the jejunum allows solving the problem of gastrostasis and gastroesophageal reflux [6, 7, 34, 35].

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INTESTINAL MICROBIOME ACTIVITY AND FORMATION IN CHILDREN IN INFANTS BORN FROM MOTHERS WITH GESTATIONAL DIABETES MELLITUS

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Abstract. The article presents the results of studies of gut microbiocenosis, as well as its metabolic features in young children born to mothers with gestational diabetes mellitus. The article examined the characteristics of gut microbiocenosis, as well as its metabolic features in early children born to mothers with gestational diabetes mellitus. The presence of intestinal microbiota balance disorders and its functional activity in the studied cohort of children is shown. Modern methods of gut microbiota investigation have been carried out and described. The gut microbiocenosis metabolite indices in the study groups of children were analyzed. It was concluded that the obtained results in the study groups of children have reliable deviations. Which makes experts pay attention to the possibility of the influence of the dysbiotic community of bacteria on the protective functions of biofilm and the impact on the health of the child as a whole.

Key words: *gut microbiocenosis; gestational diabetes mellitus; young children.*

ОСОБЕННОСТИ ФОРМИРОВАНИЯ МИКРОБИОТЫ КИШЕЧНИКА У ДЕТЕЙ РАННЕГО ВОЗРАСТА, РОЖДЕННЫХ ОТ МАТЕРЕЙ С ГЕСТАЦИОННЫМ САХАРНЫМ ДИАБЕТОМ

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Резюме. В статье приведены результаты исследований микробиоценоза кишечника у детей раннего возраста, рожденных от матерей с гестационным сахарным диабетом. Показано наличие нарушений баланса микробиома кишечника и его функциональной активности у исследуемой когорты детей. Проведены и описаны современные методы исследования микробиома кишечника. Статья заставляет обратить внимание специалистов на возможность влияния дисбиотического сообщества бактерий на защитные функции биопленки и воздействия на здоровье организма ребенка в целом.

Ключевые слова: *микробиом кишечника; гестационный сахарный диабет; дети раннего возраста.*

INTRODUCTION

In recent decades there is a large number of studies on the human gut microbiota in the medical community. Studies investigating the relationship between the structure of the gut microbiome and the presence of diabetes mellitus (DM) deserve special attention. In 2018, L. Zhou and X. Xiao conducted a study that found that altering a mother's microbiota prior to delivery has impact on her metabolism of carbohydrates and fats, which may negatively affect the structure of the child's gut microbiota. In this regard, the study of

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the state of intestinal microbiota in children born to mothers with diabetes mellitus is not only relevant, but also necessary.

AIM

The aim is to improve the diagnosis of gut microbial composition disorders in infants born to mothers with the gestational diabetes mellitus by determining the species composition and metabolic activity of the gut microbiome.

MATERIALS AND METHODS

The study of gut microbiome (GM) included 105 children aged 1–3 years among with 33 children from mothers with the gestational diabetes mellitus on insulin therapy (GDM IT), 42 children from mothers with the gestational diabetes mellitus on diet therapy (GDM DT), 30 children from mothers without the GDM (control group — CG) was carried out.

We studied: species composition of the intestinal microbiome; its functional state by concentrations of short-chain fatty acids (SCFA). The species composition was studied by ngs sequencing of faeces. The concentration of short-chain fatty acids was analyzed by gas-liquid chromatography of acidified supernatant of faeces. The biodiversity of the microbial community was taken as a measure of intestinal dysbiosis, which in biology is quantified by the Shannon index, corresponds to the number of microbial species in the intestinal microbial community and is calculated according to the formula:

$$H = -\sum_{i=1}^{n} p_i \log_2 p_i,$$

where

$$p_i = \frac{x_i}{\sum_{i=1}^{n} x_i}$$

The normalised Shannon index has a range of values from 0 to 1, which is suitable for interpreting the state of microbiocenosis. The data obtained during the study were statistically processed using Statistica 8.0 and MS Office Excel 2010 software packages.

RESEARCH FINDINGS

The study determined the distribution of microorganisms in the intestine of infants born to mothers with the GDM with a detailed breakdown by class and type using the 16s rRNA sequencing method (Table 1).

Table 1. Species of intestinal microorganisms in young children in the study groups, n=105, (Me [min; max])

Таблица 1. Типы микроорганизмов кишечника у детей раннего возраста в исследуемых группах, n=105 (Me [min; max])

Типы микроорганизмов	ГСД ИТ, n=33	ГСД ДТ, n=42	КГ, n=30
Euryarchaeota	0 [0–0]	0 [0–0]	0 [0–0]
Actinobacteria	33,78** [17,29–42,05]	42,11 [38,24–56,08]	48,92 [32,8–69,15]
Bacteroidetes	0,37 [0,04–0,68]	0,11 [0,03–0,29]	0,17 [0,07–0,78]
Cyanobacteria	0 [0–0]	0 [0–0]	0 [0–0]
Firmicutes	63,25 [55,13–77,72]	57,62** [43,89–60,94]	48,99 [28,57–62,96]
Proteobacteria	0,33 [0,08–2,51]	0,17 [0,01–0,39]	0,51 [0,18–2,17]
Tenericutes	0 [0–0]	0 [0–0]	0 [0–0]
Verrucomicrobia	0 [0–0,02]	0 [0–0,02]	0 [0–0,19]

Notes.
GDM DT — the gestational diabetes mellitus, diet therapy; GDM IT — the gestational diabetes mellitus, insulin therapy; CG — control group; n – the number of children.
The Mann-Whitney U-criterion, p<0.05, was used to assess the statistical significance of the frequencies of occurrence: * in the GDM group; ** in the CG..

Примечания.
ГСД ДТ — гестационный сахарный диабет, диетотерапия; ГСД ИТ — гестационный сахарный диабет, инсулинотерапия; КГ — контрольная группа; *n* — количество детей.
Для оценки статистической значимости частот встречаемости использован U-критерий Манна–Уитни p<0,05: * в группе ГСД; ** в КГ

According to the data obtained (Table 1), children from mothers with GDM IT and GDM DT showed no statistically significant differences between each other. In general, *Actinobacteria* and *Firmicutes* are more frequently represented in the microbial landscape of young children. The *Firmicutes* is represented by obligate and facultative anaerobic bacteria and is the most common type of bacteria in the human intestine in the norm. Most representatives of the type are Gram-positive bacteria and are capable of forming endospores, which helps bacteria of this type to survive in unfavourable conditions and restore their population [1]. Actinobacteria type consists of both aerobic and anaerobic Gram-positive bacteria, but contains more guanine and cytosine in its DNA structure than *Firmicutes [2]. Bifidobacteria spp.* — are the most common bacteria within this type in young children in the colonic microbiota [3]. But *Actinobacteria* in children from mothers with GDM IT were isolated in lower numbers than in children from CG (p=0.03). More intensive growth of *Firmicutes* type bacteria was ob-

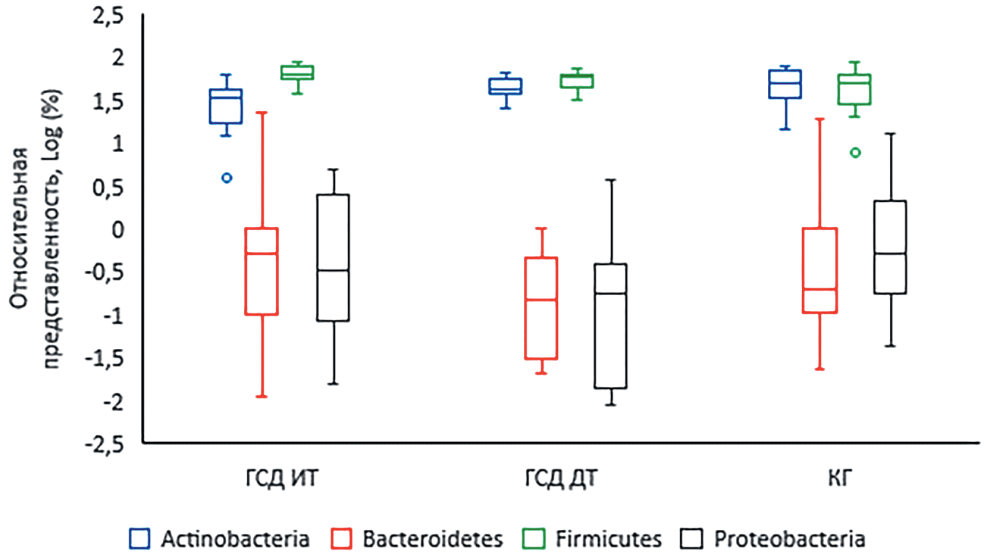

Fig. 1. Distribution of intestinal microorganism types in young children study groups
Рис. 1. Распределение типов микроорганизмов в кишечнике у детей раннего возраста исследуемых групп

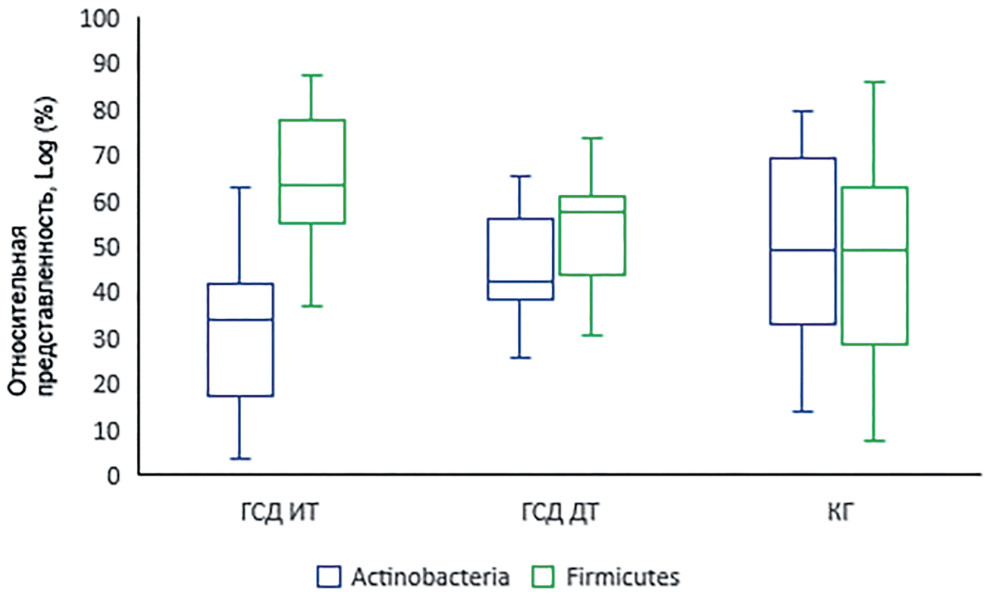

Fig. 2. Ratio of Actinobacteria and Firmicutes in the intestines of young children study groups
Рис. 2. Отношение *Actinobacteria* и *Firmicutes* в кишечнике детей раннего возраста исследуемых групп

served in children from mothers with GDM DT in early childhood than in CG (p=0.04), which may indicate the presence of favourable conditions for uncontrolled growth of opportunistic and pathogenic bacteria, disturbance of balance within the microbial community and formation of dysbiosis. *Proteobacteria* and *Bacteroidetes* are inferior in number to *Actinobacteria* and *Firmicutes*, which corresponds to the structure of differentiated gut microbiome of young children [4]. *Verrucomicrobia, Euryarchaeota, Tenericutes* and *Cyanobacteria* are isolated in smaller numbers.

Let us consider the Figure 1 in order to illustrate the quantitative distribution of intestinal microorganism types in children of the studied groups.

Thus, Figure 1 clearly depicts the obtained data: *Actinobacteria* and *Firmicutes* have the highest representation among other types of microorganisms. It can be noted that for all the studied groups of children at early age, the ratio of *Proteobacteria* and *Bacteroidetes* has no statistical significance or a pronounced tendency to favour one or the other type of bacteria.

We were interested to study the ratio between *Actinobacteria* and *Firmicutes* bacterial types, which is presented in Figure 2.

Based on the data obtained (Figure 2), it can be assumed that in children from mothers with GDM in general there is a tendency to decrease the relative representation of *Actinobacteria* to *Firmicutes*. The median values and variation of the relative representation of *Actinobacteria* and *Firmicutes* in children from mothers with GDM are significantly different from those in the CG. This indicates that the balance in the microbial community is disturbed, which may lead to increased risks of pathological processes associated with dysbiosis starting in the early age in children of the experimental groups.

The revealed peculiarities of the ratio of dominant types of bacteria are associated with changes in gut microbiome biodiversity. It is known that changes in biodiversity are characterised by the Shannon alpha biodiversity index, which increases with the number of species representation [5]. Changes in the Shannon index in the studied groups of children are presented in Figure 3.

According to the results (Fig. 3), there is a tendency to increase the degree of biodiversity from KG to GDM DT and further to GDM IT, which once again indicates a violation of get microbiome formation and the presence of dysbiotic changes in children of this cohort.

Table 2. Species composition of the gut microbiome of young children study groups, n=105 (Me [min; max])

Таблица 2. Видовой состав микробиома кишечника детей раннего возраста исследуемых групп, n=105 (Me [min; max])

Species of microorganisms / Виды микроорганизмов	GDM IT, n=33 / ГСД ИТ, n=33	GDM DT, n=42 / ГСД ДТ, n=42	CG, n=30 / КГ, n=30
Actinobacteria			
Actinomyces spp.	4,57** [0–14,8]	0 [0–17,7]	0 [0–0,1]
Bifidobacterium bifidum	0 [0–0]	0 [0–0]	0 [0–0]
Bifidobacterium spp.	2,4 [0–7,8]	0,07 [0–0,73]	0,17 [0–3,13]
Varibaculum spp.	0 [0–0]	0 [0–0,03]	0 [0–0]
Adlercreutzia spp.	0 [0–0,13]	0 [0–0,37]	0 [0–0]
Rothiamucilaginosa	1,9 [0,43–6]	0,77 [0,33–1,63]	0,5 [0–2,47]
Eggerthella spp.	0,03 [0–0,2]	0,2** [0,03–0,67]	0 [0–0,07]
Collinsella stercoris	0 [0–0,07]	0 [0–0]	0 [0–0,03]
Eggerthella lenta	0 [0–0,07]	0 [0–0]	0 [0–0]
Bifidobacterium adolescentis	0,13 [0,03–2,2]	0,07 [0–0,5]	0,37 [0,1–2,53]
Bacteroidetes			
Sediminibacterium spp.	0 [0–0]	0 [0–0,03]	0 [0–0,17]
Bacteroideso vatus	0 [0–0,53]	0 [0–0]	0 [0–0,4]
Bacteroides caccae	0 [0–0,07]	0,03 [0–0,13]	0 [0–0]

Continuation of the Table 2 / Продолжение табл. 2

Species of microorganisms / Виды микроорганизмов	GDM IT, n=33 / ГСД ИТ, n=33	GDM DT, n=42 / ГСД ДТ, n=42	CG, n=30 / КГ, n=30
Prevotella copri	0 [0–0,03]	0 [0–0,03]	0 [0–0]
Parabacteroides spp.	0 [0–0,03]	0 [0–0,07]	0 [0–0]
Bacteroides uniformis	0 [0–0,03]	0 [0–0,07]	0,03 [0–0,9]
Bacteroides spp.	0 [0–0,17]	0,03 [0–0,1]	0 [0–0,07]
Firmicutes			
Coprococcus catus	0,07** [0,03–0,07]	0,03 [0–0,1]	0 [0–0,03]
Clostridiales	0,03 [0–3,8]	1,6 [0–3,4]	0 [0–8,7]
Dialister spp.	0,47 [0–5,7]	0 [0–8,73]	0 [0–4,3]
Bulleidiamoorei	9,77 [2,8–33,8]	21,4 [13,2–37,7]	45,8 [24,5–56,8]**
Lactococcus spp.	0 [0–0]	0 [0–0]	0 [0–0]
Lachnospira spp.	0 [0–0,07]	0 [0–0]	0 [0–0]
Veillonella spp.	0 [0–0]	0 [0–0]	0 [0–0]
Ruminococcus spp.	0 [0–0]	0 [0–0]	0 [0–0]
Turicibacter spp.	0,27 [0–0,5]	0,13 [0–0,53]	0,13 [0–0,73]
Coprococcus spp.	0 [0–0]	0 [0–0]	0 [0–0]
Anaerostipes spp.	0 [0–0,47]	0,03 [0–1,4]	0 [0–0,07]
Clostridium neonatale	0 [0–0,03]	0,03 [0–0,13]	0,07 [0–0,47]
Peptoniphilus spp.	1,83 [0,23–7,27]	1,43 [0,17–6,1]	0,67 [0,2–1,17]
Clostridium butyricum	0 [0–0,2]	0 [0–0,03]	0 [0–0]
Ruminococcus bromii	0 [0–0]	0 [0–0,03]	0 [0–0]
Peptostreptococcus anaerobius	0,07 [0–1,67]	0 [0–1,37]	0,03 [0–0,3]
Clostridium hiranonis	8,4 [1,97–12,3]	4,2 [0,57–8,5]	0,43 [0–2,33]**
Lactobacillales	0 [0–0]	0 [0–0]	0 [0–0]
Dorea formicigenerans	0 [0–0,03]	0 [0–0]	0 [0–0]
*Peptostreptococcus*spp.	0,1 [0–0,2]	0 [0–0,1]	0 [0–0,03]
Lachnospiraceae	0,07 [0–1,83]	0 [0–0,03]	0 [0–0]
Anaerococcus spp.	0 [0–0]	0 [0–0]	0 [0–0]
Ruminococcus spp.	0 [0–0]	0 [0–0,03]	0 [0–0]
Roseburia spp.	0 [0–0,2]	0 [0–1,03]	0 [0–0]
Veillonellaceae	0 [0–1,77] **	0 [0–0]	0 [0–0]
Blautia producta	0,5 [0–0,8] *	0 [0–0,13]	0 [0–0,37]
Ruminococcus torques	0 [0–0,03]	0 [0–0,03]	0 [0–0,03]
Lactobacilluszeae	0 [0–0]	0 [0–0,03]	0 [0–0]
Lachnobacterium spp.	0 [0–0,03]	0 [0–0,03]	0 [0–0,03]
Enterococcaceae	0 [0–0]	0 [0–0]	0 [0–0]
Dorea spp.	0,03** [0–0,3]	0,17 [0,03–0,5]	0,5 [0,07–1,83]
Clostridium perfringens	0 [0–0,03]	0 [0–0]	0 [0–0]
Streptococcus spp.	16,4 [2,57–25,5]	16,8 [8,03–24,7]	10,2 [0,13–22,4]
Staphylococcus spp.	0 [0–0]	0 [0–0]	0 [0–0]

Ending of the table 2 / Окончание табл. 2

Species of microorganisms / Виды микроорганизмов	GDM IT, n=33 / ГСД ИТ, n=33	GDM DT, n=42 / ГСД ДТ, n=42	CG, n=30 / КГ, n=30
Streptococcus agalactiae	0,33 [0,03–1,1]	0,23 [0,1–3,17]	0,07 [0–0,37]
Lactobacillus spp.	0 [0–0]	0 [0–0]	0 [0–0]
Lactobacillaceae	0,03 [0–0,07]	0 [0–0,03]	0 [0–0,03]
Eubacterium spp.	0 [0–0]	0 [0–0]	0 [0–0]
Coprobacillus spp.	0 [0–0]	0 [0–0]	0 [0–0]
Blautia spp.	0 [0–0]	0 [0–0]	0 [0–0]
SMB53 spp.	0 [0–0]	0 [0–0]	0 [0–0,03]
Bacillus spp.	0 [0–0]	0 [0–0]	0 [0–0]
Erysipelotrichaceae	0 [0–0]	0 [0–0]	0 [0–0,3]
Proteobacteria			
Alphaproteobacteria	0 [0–0]	0 [0–0]	0 [0–0]
Acetobacteraceae	0 [0–0]	0 [0–0]	0 [0–0]
Vibrionaceae	0 [0–0,07]	0 [0–0]	0 [0–0,17]
Burkholderiabryophila	0 [0–0,03]	0 [0–0]	0 [0–0]
Proteobacteria	0 [0–0]	0 [0–0]	0 [0–0]
Sutterella spp.	0 [0–0]	0 [0–0]	0 [0–0]
Bilophila spp.	0,13 [0,03–0,5]	0,03 [0–0,47]	0,07 [0–0,5]
Nitrosomonadaceae	0,83 [0,17–6,6]	2,3 [0,2–3,83]	0,43 [0–2,9]
Thiotrichaceae	0 [0–0]	0 [0–0,07]	0 [0–0]
Acinetobacter spp.	2,37 [0,87–6,63]	2,13 [1,07–6,9]	3,5 [0,67–12,3]
Hydrocarboniphaga spp.	0,03 [0–0,43]	0,2 [0–0,33]	0 [0–0,2]
Enterobacteriaceae	0 [0–0]	0 [0–0]	0 [0–0]
Xanthobacteraceae	1,77** [0,87–3,93]	0,33 [0,07–4,7]	0,53 [0–1,1]
Tenericutes			
RF39	0 [0–0]	0 [0–0]	0 [0–0]
Verrucomicrobia			
Akkermansia muciniphila	0 [0–0]	0 [0–0]	0 [0–0]
Cyanobacteria			
Streptophyta	0 [0–0]	0 [0–0]	0 [0–0]
Euryarchaeota			
ANME-1	0 [0–0]	0 [0–0]	0 [0–0]
Bacteria			
Bacteria	0,27 [0–2,77]	0,63 [0,03–3,93]	0,17 [0–1,07]

Notes.
GDM DT — the gestational diabetes mellitus, diet therapy; GDM IT — the gestational diabetes mellitus, insulin therapy; CG — control group; n – the number of children.
The Mann-Whitney U-criterion, $p<0.05$, was used to assess the statistical significance of the frequencies of occurrence: * in the GDM group; ** in the CG..

Примечания.
ГСД ДТ — гестационный сахарный диабет, диетотерапия; ГСД ИТ — гестационный сахарный диабет, инсулинотерапия; КГ — контрольная группа; n — количество детей.
Для оценки статистической значимости частот встречаемости использован U-критерий Манна–Уитни $p<0,05$.
Достоверные различия обозначены в таблице: * — между ГСД ИТ и ГСД ДТ; ** — между ГСД и КГ.

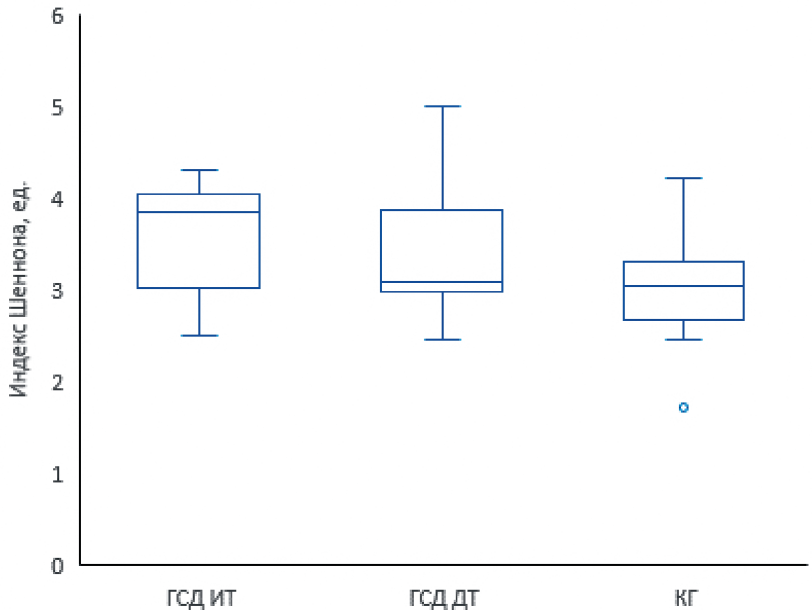

Fig. 3. Gut microbial community biodiversity index in young children study groups
Рис. 3. Индекс биоразнообразия микробного сообщества кишечника у детей раннего возраста исследуемых групп

To assess in detail the changes in gut microbiome composition in the studied groups of children, the species composition of microorganisms was studied (Table 2).

The data presented in Table 2 confirmed that the largest number of microbial species determined by NGS sequencing were Firmicutes. The number of represented bacterial species of this type decreases in a row:

- in the GDM IT group: *Streptococcus* spp. — 16%, *Bulleidiamoorei* — 10%, *Clostridium hiranonis* — 8%, *Actinomyces* spp. — 5%, *Bifidobacterium* spp. — 2%, *Acinetobacter* spp. — 2%, *Rothiamuci laginosa* — 2%, *Peptoniphilus* spp. — 2%, *Xanthobacteraceae* — 2%;
- in the GDM DT group:: *Bulleidiamoorei* — 21%, *Streptococcus* spp. — 17%, *Clostridium hiranonis* — 4%, *Nitrosomonadaceae* — 2%, *Acinetobacter* spp. — 2%, *Clostridiales* — 2%, *Peptoniphilus* spp. — 1%;
- in the control group: *Bulleidiamoorei* — 46%, *Streptococcus* spp. — 10%, *Acinetobacter* spp. — 3%.

Thus, 9 dominant microorganism species were detected in children born to mothers with the GDM IT, 7 microorganism species in the GDM DT group, and 5 microorganism species in the CG group. In the GDM IT group *Streptococcus* spp. was the dominant microorganism, but among other dominant opportunist species *Bifidobacterium* spp. were identified. *Bulleidiamoorei* dominates in the GDM DT and in the CG. But *Bulleidiamoorei* was significantly less frequent in children from mothers with the GDM IT (9.77 Lg/KOU ($p<0.01$)) and the GDM DT (21.4 Lg/KOU ($p=0.033$)) than in CG (45.8 Lg/KOU). *Clostridium hiranonis* was isolated in higher numbers in children from mothers with the GDM IT (8.4 Lg/COE ($p=0.023$)) and the GDM DT (4.2 Lg/COE ($p=0.041$)), relative to the CG (0.43 Lg/COE). *Clostridium hiranonis* belong to cluster XI of the genus *Clostridium* (a cluster including pathogens such as *C. difficile*) and can cause infectious diseases under favourable conditions [6]. Increased representation of *Actinomyces* spp. was observed in the GDM IT group, which was not observed in the CG ($p=0.023$). Representatives of the Actinomyces are saprophytes of humans, can cause actinomycosis, but their ability to secrete biologically active substances capable of selectively inhibiting the viability of other bacteria has also been established [7]. Eggerthella spp. (which associated with lipid metabolism, is a representative of the wall-adhered microbiota, a representative of normal flora, but in immunocompromised people causes bacteraemia [8, 9]), in greater numbers isolated in children from mothers with the GDM DT than in the CG ($p=0.029$). *Coprococcus catus* (which can switch from butyrate to propionate production, is a representative of resident microflora, but under certain conditions can cause inflammation in the intestine [10]), more isolated

in children from mothers with the GDM IT than in the CG (p=0.045). *Veillonellaceae* (is a representative of resident microflora, but under certain conditions can cause inflammation in the intestine [11]), more isolated in children from mothers with the GDM IT than in the CG (p=0.04). Blautia producta (the representative of resident microflora, elevated levels observed in irritable bowel syndrome, now identified as potentially probiotic for humans [12]), more isolated in children from mothers with the GDM IT than in the GDM DT (p=0.049). *Dorea* spp. (which associated with flatulence syndrome [13]), isolated in lower numbers in children from mothers with the GDM IT than in the CG (p=0.037). *Xanthobacteraceae* (which incompletely studied) was isolated in higher numbers in children from mothers with the GDM IT than in the CG (p=0.025).

Thus, in children born to mothers with the GDM, an increase in dysbiotic changes and biodiversity of potentially pathogenic bacteria in the intestine is noted. But in children from mothers with GDM IT also revealed an increase in beneficial bacteria and microorganisms capable of competing with pathogens for nutrient substrate and restrain their growth in the gut microbiota.

Despite the fact that compensatory mechanisms of gut microbiota regulation are presented both in children from mothers with GDM IT and in children from mothers with GDM DT, changes in the microbiocenosis may lead to disorders of digestion (malassimilation) and absorption (malabsorption). Nutrient deficiencies, the predominance of catabolism over anabolism, metabolic disorders in the future will have a negative impact on the growth and development of children from mothers with GDM.

The authors of the article state that there are no conflicts of interest.

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NUTRITIONAL STATUS AND INTESTINAL MICROBIOCENOSIS IN COMPLETE FASTING IN YOUNG VOLUNTEER

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Absract. Nowadays, it is becoming more and more popular among people to refuse to eat for a limited time. However, information about the impact of fasting on human health at the present time continues to be controversial. In our experiment, on the example of a young volunteer, changes in the nutritional status, metabolic profile and intestinal microbiocenosis were shown against the background of complete starvation for 15 days.

Key words: *fasting; metabolic profile; intestinal microbiota; bioimpedancemetry; young volunteer.*

СОСТОЯНИЕ НУТРИТИВНОГО СТАТУСА И МИКРОБИОЦЕНОЗА КИШЕЧНИКА ПРИ ПОЛНОМ ГОЛОДАНИИ У ДОБРОВОЛЬЦА МОЛОДОГО ВОЗРАСТА

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Резюме. В настоящее время все больше приобретает популярность среди людей отказ от приема пищи в течение ограниченного времени. Однако сведения о воздействии голодания на состояние здоровья человека в настоящее время продолжают оставаться противоречивыми. В нашем эксперименте на примере молодого добровольца были показаны изменения нутритивного статуса, метаболического профиля и микробиоценоза кишечника на фоне полного голодания в течение 15 дней.

Ключевые слова: *голодание; метаболический профиль; микробиота кишечника; биоимпедансометрия; молодой доброволец.*

INTRODUCTION

The popularity of following restrictive diets has a tendency to increase in most countries of the world [1]. In recent years, the issues of periodic fasting and its effect on the human body have been more frequently discussed at scientific medical forums [2–4]. Among the most common reasons for changing to an unconventional type of diet are usually considered the idea of health improvement and prevention of various somatic and infectious pathologies, ethical, religious, social and environmental aspects [1].

Various types of therapeutic fasting are traditionally used both in folk and Oriental medicine in the treatment of metabolic diseases, gastrointestinal and cardiovascular systems, respiratory organs and musculoskeletal system [5–7]. In classical medicine therapeutic fasting has been used since the time of Hippocrates. The founder of medicine wrote "when a patient is fed too abundantly, his disease is also fed. Sometimes it is more useful to take food away from a sick person for a while" [3].

In the USSR, the problem of therapeutic fasting was dealt with by such famous scientists as academicians P.K. Anokhin, A.A. Pokrovsky, N.A. Fedorov, L.N. Bakulev. Doctor of Medical Sciences, Professor Y.S. Nikolaev made a significant contribution to the scientific substantiation of treatment of a number of diseases by the method of unloading-diet therapy (UDT) [3]. In the XXI century, the topic of periodic fasting again came to the forefront in 2016 after the world scientific community recognised the merits of the Japanese scientist, molecular biologist Yoshinori Ohsumi. Dr Ohsumi, a professor of the Tokyo Institute of Technology, received the Nobel Award in Physiology and Medicine for his research into the poorly understood mechanisms of autophagy — regeneration processes occurring at the cellular level. In particular, Osumi discovered the genes that control this process; he was able to describe how the organism adapts to fasting, as well as the response of cells to the penetration of pathogens into the body. In autophagy, cells break down and recycle damaged organelles, in other words, they self-renew. It has been shown that failure of this regenerative process can lead to neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's syndrome, some forms of dementia and cancer. It has also been argued that it is possible to trigger autophagy in cells by adhering to various schemes of periodic fasting [8, 9].

Fasting is a pathological process that develops due to the deficiency of nutrients that enter the internal environment of the body during the processes of cavity, membrane hydrolysis and absorption of nutrients from the intestinal lumen [10–12]. Despite the fact that the organism is deprived of the main source of nutrition, it continues to receive energy and necessary substances, as it is forced to switch to active utilisation of already existing reserves. This is confirmed by blood glucose level which is an important indicator. Certain molecular and cellular mechanisms responsible for defence functions are also switched on, which can allow the organism to survive even in conditions of complete or partial absence of food sources with minimal damage. This process provokes adaptive cellular stress responses that lead to an increased ability to cope with stress and neutralise disease processes. The body begins to actively get rid of nitrates and other harmful substances that came with food. Lack of food forces the body to activate the search for an alternative source of nutrition and forces it to spend fat and carbohydrate reserves. First of all, the body starts to spend its dead cells, followed by diseased cells, which are not suitable for maintaining normal activity. As a result, only healthy tissues remainInternal self-purification takes place. This is due to the fact that the reserve forces restore the disturbed metabolism at the molecular, cellular and tissue levels. At the same time the process of destruction of infected and malignant molecules and cells begins, after which they are replaced by new and healthy ones. At the moment of transition to fasting and it's ending, the organism feels stress. It is worth giving up food gradually. The duration of recovery should coincide with the period of fasting. The stabilisation phase occurs after the end of the recovery period [13, 14].

Complete fasting is divided into periods of emergency adaptation, long-term stable adaptation, and decompensation. The initial period of emergency adaptation consists in activation of glycogenolysis, full use of its reserves, and stimulation of gluconeogenesis, with normal blood glucose levels during 12 to 24 h of fasting being ensured by glycogen reserves in the liver. Already after 24 hours from the beginning of fasting, glycogen stores in the liver are depleted, so the level of glucose in the blood is maintained by its formation from glycerol, glucogenic amino acids and free fatty acids during gluconeogenesis. After 24 h from the beginning of exogenous fasting, the organism starts to use proteins as energy sources and intensify the processes of gluconeogenesis. Starvation for more than 72 h leads to a decrease in the processes of amino acid utilisation, which is clinically manifested by a decrease in nitrogen excretion with urine. Glucose formation from amino acids by this time does not correspond to the energy needs using only or mainly glucose of brain cells, erythrocytes, brain matter of kidneys, other tissues and organs. With prolonged starvation, gluconeogenesis moves from the liver to the kidneys, where deamination occurs. In addition,

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there is a transformation of ketones into glucose through the acetone; the brain also begins to use ketone bodies as energy sources, but only after a certain reorganisation — by the 10th–12th day. As soon as the transition to a different energy supply of the nervous tissue occurs, the 2nd period of adaptation occurs — stable long-term adaptation to complete fasting. This period starts from the 2nd week of complete fasting and lasts until the 8th week of fasting and longer — depending on the volume of fat reserves. Glucose deficiency in the body, which occurs during prolonged fasting, is replenished by other energy substrates such as ketone bodies. The most important consequence of this neuroendocrine restructuring is the redirection of energy resources to those consumers that have exclusively or predominantly non-insulin-dependent glucose transporters inside cells (the brain, retina, gonads, adrenal glands, diaphragmatic muscle, myocardium, partly liver and kidneys). The cells where glucose transporters are exclusively insulin-dependent (connective tissue in all its types, lipocytes, bones, cartilage and ligaments, bone marrow, cells of blood and lymphoid organs, vascular walls, etc.) are on «starvation rations». The result of activation of the neuroendocrine catabolic system is the suppression of hunger, intestinal peristalsis. The supply of amino acids and lipolysis products into the blood increases due to adaptive intensification of catabolism. At full prolonged fasting only neurons of the brain and spinal cord use glucose as an energy substrate; cells of all other tissues utilise free fatty acids and ketone bodies for biological oxidation. The terminal period of decompensation occurs at a loss of 40–50% of the initial body weight, characterised by the loss of 100% of fat depots, almost 97% of visceral adipose tissue, increased protein breakdown in organs and tissues, and not only insulin-dependent, but also those whose metabolic interests were preserved for some time. Because of the mass apoptosis of cells, the nucleic acids are destroyed, and the excretion of non-urea nitrogen increases. During fasting there is a stepwise change in metabolism with characteristic stages of endocrine and metabolic changes and change of the main energy substrates [5, 6, 8, 13].

Researches confirm that changing caloric intake can have long-term positive effects on the body. Individual pilot intervention trials and several randomised studies in this direction have been carried out in experiments on sick people for therapeutic purposes [3, 5, 10, 11, 15]. Observations on healthy people in order to reveal the effect of fasting on healthy people and their physical capabilities are few and not widely studied.

AIM

To evaluate nutritional status, metabolic profile and gut microbiocenosis during complete fasting in a young human.

MATERIALS AND METHODS

The young volunteer was a young woman, 31 years old, married, with children. She is a 2nd year student of the Faculty of Paediatrics of the Federal State Budgetary Educational Institution of Higher Professional Education SPbGPMU of the Ministry of Health of the Russian Federation. The examination included determination of anthropometric and laboratory-instrumental indicators (clinical blood analysis, biochemical blood analysis, immunological status, determination of blood gas composition, gut microbiota composition by chromatography-mass spectrometry, assessment of the component body composition by bioimpedanceometry). The examination was carried out on the 1st, 4th, 9th, 15th days of complete fasting and 1 month after.

Statistical processing of the obtained data was performed using XL Statistica 7 (StatSoft, Russian version) and Microsoft Excel 2017 software packages.

The subject started the practice of therapeutic fasting in 2013 after a case of generalised acute arthritis of unclear aetiology. After discharge from the hospital and taking a course of sulfasalazine (for 3 months) in summer of 2013, the subject performed a course of therapeutic fasting on water for 10 days. As a result of it, her general condition significantly improved, swelling decreased, mobility improved, and subjective pain sensations in the area of large and small joints decreased. After that the subject periodically returned to the practice of spring annual fastings with the purpose of detoxification, improvement of general condition, reduction of pollen sensitisation in the spring-summer period. The present course of therapeutic fasting took place for 14 days from the end of April to the beginning of May 2022. This author's method was a compilation of different practical and theoretical materials on therapeutic fasting; the subject made additions to the fasting method based on empirical experience of past sessions [16, 17]. Before fasting, a bowel cleansing procedure was carried out, which was repeated once every two

or three days in order to empty the intestine and improve its peristalsis. Drinking regime included water at will (mineral or boiled) not less than 1.5 litres per day. Every day for 14 days the subject was engaged in sports (swimming, jogging, functional training, walking at least 6 km per day). Physical activity was monitored using a fitness bracelet. Once every five days the subject received 15 g of magnesium sulphate per 150 ml of water for gallbladder emptying. «Withdrawal» from the fasting period was continued gradually over two weeks with citrus (orange, lemon, grapefruit, tangerine) juice diluted 1:1 with water. On the first day — 500 ml of pure juice, from the second to the fifth day — 1 litre of juice per day. From the fourth day the juice was not diluted. From the fifth day the subject started eating whole fruits up to 1.5 kg per day. From the eighth day the subject started eating raw and heat-treated vegetables, from the 11th day — porridge with a small amount of vegetable oil (buckwheat porridge, rice), from the 15th day — a small amount of animal protein, nuts and gradually returned to the normal diet.

RESULTS

The young volunteers height was 170 cm, the body mass was 67 kg, BMI 22.4 kg/m2, waist circumference (WC) 63 cm, hip circumference (HC) 95 cm. No pathological changes were detected in clinical and biochemical blood tests. Immunological status: hyperimmunoglobulinaemia M and E, presence of circulating immune complexes (CIC) in blood serum were noted. A decrease in the absolute and relative number of CD25+ T-cells, HLA-DR T-cells, γδ T-cells was revealed. Gas composition was characterised as respiratory acidosis, which was associated with the presence of exacerbation of seasonal pollinosis in the volunteer.

According to the results of the gut microbiocenosis study, a higher ratio of representatives of the genus *Firmicutes* over the genus *Bacteroidetes* was found.

The content of some opportunistic microorganisms was increased 2–3 times before the study, including *Actinomyces* spp., *Alcaligenes spp., Staphylococcus epidermidis* and *mutans, Streptococcus mutans* and *sanguis*, *Clostridium coccoides* and *perfringens, Rhodococcus spp. Before the beginning of fasting, the number of Bifidobacterium spp.* and *Lactobacillus* spp. was reduced by 1.5 times, *Clostridium ramosum* was reduced by 4.3 times, which probably indicated the vaginal dysbiosis.

When assessing body composition, the amount of fat mass (FM) and its fraction (FFM), lean mass (LM), active cell mass (ACM), skeletal muscle mass (SMM), total water (TW), extracellular fluid (EF) were within normal reference values. The value of active cell mass fraction (ACMF) was increased by 10%, the value of skeletal muscle mass fraction (SMMF) was increased by 6%, which was due to sufficient motor activity, good training and endurance of the subject's organism. The index of basic metabolism (BM) corresponded to 1509 kcal/day.

During the first two days of the fasting period, the volunteer's feeling was satisfactory, she led a relatively passive lifestyle. From the 3rd to the 6th day, the volunteer noticed the weakness and decreased concentration. Physical activity during these days was quite intensive (kilocalorie consumption according to the fitness bracelet was from 500 to 900 kcal/day). On the 7th day (the middle of the fasting period) the condition and

Table 1. Monitoring of anthropometric indicators
Таблица 1. Мониторинг антропометрических показателей

День наблюдения / Observation day	Масса тела, кг / Body weight, kg	Окружность талии, см / Waist circumference, cm	Окружность бедер, см / Hip circumference, cm
1	67	73	95
2	66	72	95
3	65	70	94
4	63	69	93
5	62,5	69	93
6	62	69	93
7	61	68	93
8	61	67	93
9	61	67	93
10	61	67	93
11	60,5	67	93
12	60	67	93
13	59	67	93
14	59	67	93
15	59	67	93
After 1 month / Через 1 месяц	67	67	93

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well-being of the subject sharply deteriorated, partial lethargy appeared, pallor of the skin was noted, efficiency decreased. Verbal contact with the volunteer was maintained, but she was sluggish and delayed in answering questions. She was offered hospitalisation but she refused. This condition persisted on the following day and the volunteer was forced to stay at home. On the 9th day, the subject's condition began to improve and she was able to return to an active lifestyle and sports activities. From day 12 to 15, the subject's general condition was satisfactory, and her condition was assessed as "excellent": there was vigour, a "burst of energy" and a "high spirits".

Changes in anthropometric parameters of the volunteer during the observation period are presented in Table 1.

During the whole period of fasting, the volunteer lost 9 kg, her WC decreased by 6 cm, and her HC decreased by 2 cm. The maximum decrease in body weight was observed on day 4 (–4 kg), from day 7 to day 10 body weight remained stable, from day 11 to day 14 the volunteer lost another 3 kg. Waist and hip circumference values decreased more evenly and reached maximum values on day 8 and day 4, respectively. One month after the end of fasting, body weight had recovered to baseline values, while WC and HC remained less than baseline.

According to the results of the clinical blood test, significant changes were recorded by day 15: the total number of leukocytes decreased by 20%, erythrocytes and platelets — by 14.5% ($p < 0.05$); the mean platelet volume decreased by 21% ($p < 0.05$), thrombocrit decreased by 39% ($p < 0.05$), platelet distribution index increased by 31% ($p < 0.05$). In the leucocytic formula, there was a 42% decrease in neutrophils ($p < 0.05$) and an 18% increase in lymphocytes ($p < 0.05$). All of the indices returned to baseline values, except for the values of platelet distribution index and mean platelet volume after 1 month.

Blood glucose remained stable at the level of 4–4.5 mmol/l during the whole period of observation of the volunteer. Changes in fat metabolism were characterised by a gradual increase in triglyceride levels and maintenance of this trend after 1 month (from 0.67 to 1.21 mmol/l). Low density lipoprotein (LDL) levels increased by 14.8% ($p < 0.05$) by day 15 and decreased by 11.5% ($p < 0.05$) from the baseline after 1 month. High-density lipoprotein (HDL) levels decreased by 55% ($p < 0.05$) by day 15, and recovered to the original value after 1 month. Alkaline phosphatase levels also decreased by half by the 14th day and recovered to the baseline after 1 month. Uric acid levels decreased by 23% ($p < 0.05$) but also recovered to the baseline after 1 month.

According to the results of immune status study the volunteer still had hyperimmunoglobulinaemia M and E, CIC in blood serum after 15 days. In 1 month after the end of observation on the background of hyperimmunoglobulinaemia M and E, CIC in blood serum there was a 2-fold decrease in immunoglobulin A, a 19-fold decrease in absolute and relative number of γδ T-cells.

According to the results of blood gas composition study, primary respiratory acidosis with renal compensation was registered by the 15th day: a partial pressure of carbon dioxide in blood plasma increased 1.08 times, partial pressure of oxygen in blood plasma decreased 1.2 times. There was an increase in the amount of potassium ions in the blood by 1.17 times. In 1 month after the end of fasting, the partial pressure of carbon dioxide

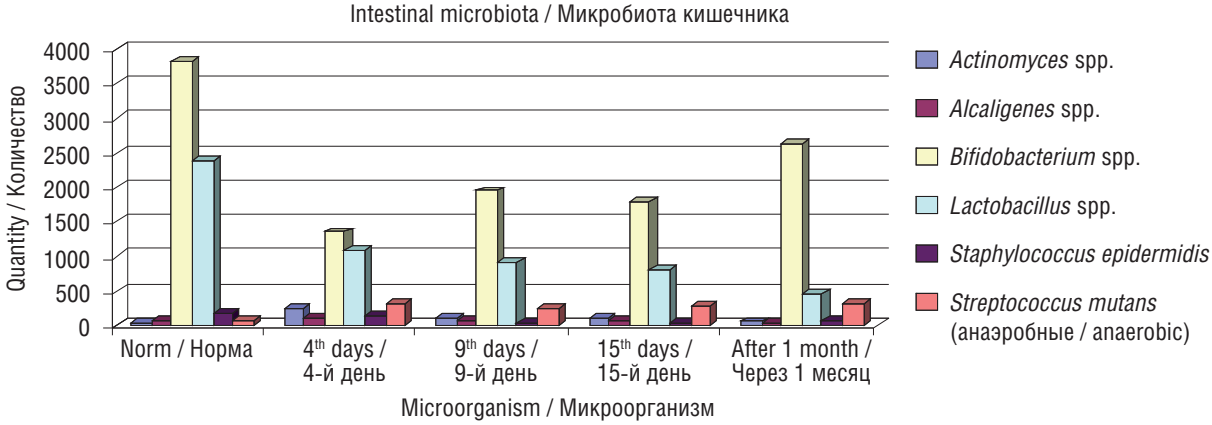

Fig. 1. Changes in the composition of the intestinal microbiota
Рис. 1. Изменение состава микробиоты кишечника

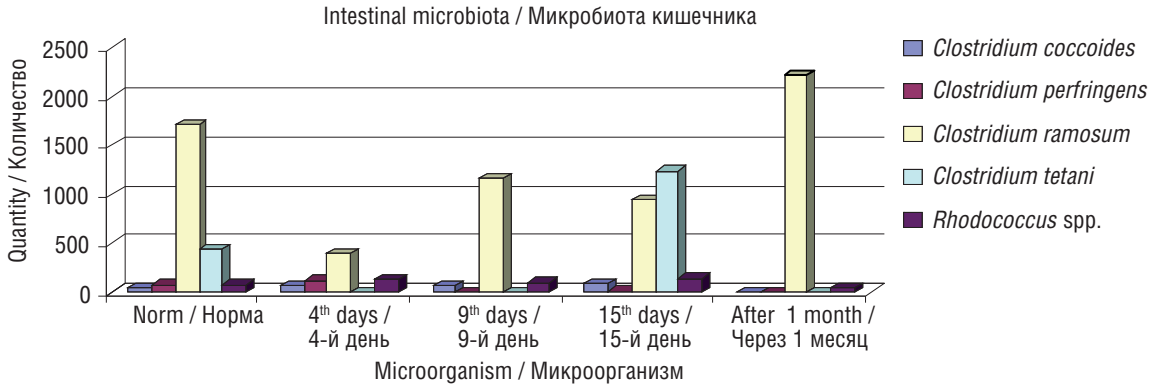

Fig. 2. Changes in the composition of the intestinal microbiota

Рис. 2. Изменение состава микробиоты кишечника

Table 2. Dynamics of indicators of nutritional status

Таблица 2. Динамика показателей состояния нутритивного статуса

День наблюдения / Observation day	ЖМ, кг / FM, kg	ДЖМ, % / FFM, %	ТМ, кг / LM, кг	АКМ, кг / ACM, кг	ДАКМ, % / ACMF, %	СММ, кг / SMM, кг	ДСММ, % / SMMF, %	ОВ, кг / BM, кг	ВЖ, кг / EF, кг
1	18,7	25,6	48,3	28,3	58,5	24,1	49,9	35,4	15
4	20,3	31,2	44,7	25,8	57,7	21,3	47,7	32,7	13,9
9	14,5	26	42,1	21,5	50,2	19,6	44	27,1	11,9
15	12	20	48	31,9	68,4	24,4	50,9	35,2	14,4
After 1 month / Через 1 месяц	18,4	25	48	29	63	24	50	36	14,5

Note: ACM — active cell mass; EF — extracellular fluid; ACMF — fraction of active cell mass; FFM — fraction of fat mass; SMMF — fraction of skeletal muscle mass; FM — fat mass; TW — total water; LM — lean mass.

Примечание: АКМ — активная клеточная масса; ВЖ — внеклеточная жидкость; ДАКМ — доля активной клеточной массы; ДЖМ — доля жировой массы; ДСММ — доля скелетно-мышечной массы; ЖМ — жировая масса; ОВ — общая вода; ТМ — тощая масса.

(45.5 mmHg) remained at the upper limit of normal, and oxygen (33.3 mmHg) was 2.5 times lower than the normal value.

Dynamics of changes in the number of representatives of gut microbiocenosis is presented in Figures 1 and 2.

On the background of fasting and in 1 month after the tendency to predominance of microorganisms of *Firmicutes* genus over *Bacteroidetes* genus remained. The number of *Actinomyces* spp., *Alcaligenes* spp., *Staphylococcus epidermidis* and *mutans, Streptococcus mutans* and *sanguis* decreased by the 14th day in 1,9–5 times. After 1 month it continued to decrease and reached normal values for the given sex and age of the subject. The number of *Clostridium coccoides* and *Perfringens, Rhodococcus* spp. normalised by the 14th day, and after 1 month they were not in blood samples.

The number of *Bifidobacterium* spp. increased 1.3 times after 15 days and 1.9 times after 1 month, but they did not reach the boundaries of normal reference values.

The amount of *Lactobacillus* spp., *Clostridium ramosum* on the background of fasting and in 1 month after its termination remained reduced by 50 and 25% respectively.

Changes in nutritional status according to the results of bioimpedanceometry are presented in Table 2.

On the 4th day the amount of FM increased by 1.5 kg, FFM — by 5%. The value of LM decreased by 3.6 kg, SMM — by 3 kg. The BM value decreased by 115 kcal/day. On day 9, the amount of FM decreased by 4 kg, but the FFM of the total body fat mass value recovered to the baseline value. The LM value decreased by another 2.5 kg, ACMF by 7 kg, SMM and TW by 2 and 3 kg, respectively. By day 15, the amount of FM had reached its minimum value, FFM decreased by 2.5%. The indices of LM, ACMF, SMM and TW were restored to the baseline values.

In 1 month after the end of follow-up, all investigated indices, including fat mass and its proportion, recovered to the initial ones. BM increased by 130 kcal/day and corresponded to 1624 kcal/day.

CONCLUSIONS

1. Reduction of human body weight is accompanied by loss of fat mass, reduction of active cell mass due to acceleration of basic metabolism and increased breakdown of proteins.

2. Prolonged fasting affects to a greater extent the change in the platelet link of homeostasis, which persists for a month after restoration of the dietary regime.

3. Changes in the metabolic profile during fasting are expressed in the violation of lipid metabolism in the form of an increase in triglycerides, LDL, and a decrease in HDL.

4. Starvation does not lead to significant changes in the state of cellular immunity and depends on the initial immunological reactivity of the organism.

5. During fasting, acidosis develops due to lack of carbohydrates, which, in turn, contributes to the mobilisation of fat from the depot.

6. Changes in the intestinal microbiota against the background of fasting are expressed by an increase in the number of bifidobacteria and a decrease in lactobacilli. After the cessation of fasting, this trend persists for a month. Fasting has a favourable effect on some representatives of opportunistic flora of microbiota (*Staphylococcus, Clostridium, Rhodococcus, Actinomyces, Alcaligenes*), which reduces the risk of development of diseases caused by them in the future.

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EXPERIENCE IN THE TREATMENT OF ALVEOLITIS IN ADOLESCENTS WITH THE USE OF DENTAL GEL WITH CHOLINE SALICYLATE AND CETALCONIUM CHLORIDE

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Abstract. Based on the analysis of the treatment of 47 adolescents (aged 15 to 18 years) who sought an appointment with a dentist-surgeon for alveolitis after the removal of various teeth for chronic periodontitis or its exacerbation, acute periostitis, as well as difficult eruption or retention of the tooth, the possibility was studied and the effectiveness of the use of domestic dental gel with choline salicylate and cetalconium chloride. It has been shown that the use of this drug for alveolitis is effective and allows to stop the pain syndrome 2 to 24 hours after medical care and its use, as well as to ensure that the wells are filled with granulation tissue for 8 to 15 days with an average number of visits of 1.6–2.6 per patient and an average period of disability of patients due to alveolitis of 1.4–2.3 days. It is concluded that dental gel with choline salicylate and cetalconium chloride is advisable to use in the clinical practice of dental surgeons for the treatment of alveolitis with high effectivity.

Key words: *adolescents; tooth extraction; alveolitis; treatment of alveolitis; dental gel with choline salicylate and cetalconium chloride; periodontitis; periostitis; tooth retention; complications of tooth extraction.*

ОПЫТ ЛЕЧЕНИЯ АЛЬВЕОЛИТА У ПОДРОСТКОВ С ПРИМЕНЕНИЕМ ГЕЛЯ СТОМАТОЛОГИЧЕСКОГО С ХОЛИНОМ САЛИЦИЛАТОМ И ЦЕТАЛКОНИЯ ХЛОРИДОМ

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Резюме. На основании анализа лечения 47 подростков (возраст от 15 до 18 лет), которые обратились на прием к врачу — стоматологу-хирургу по поводу альвеолита после удаления различных зубов, по поводу хронического периодонтита или его обострения, острого периостита, а также затрудненного прорезывания или ретенции зуба, изучена возможность и проведена оценка эффективности применения отечественного геля стоматологического с холином салицилатом и цеталкония хлоридом. Показано, что применение этого препарата при альвеолите эффективно и позволяет купировать болевой синдром через 2–24 часа после его использовании, а также обеспечить заполнение лунок грануляционной тканью на 8–15-е сутки при среднем числе посещений 1,6–2,6 на одного пациента и среднем сроке нетрудоспособности пациентов из-за альвеолита 1,4–2,3 суток. Сделан вывод, что гель стоматологический с холином салицилатом и цеталкония хлоридом целесообразно использовать в клинической практике врачей — стоматологов-хирургов для лечения альвеолита с высокой эффективностью.

Ключевые слова: *подростки; удаление зуба; альвеолит; лечение альвеолита; гель стоматологический с холином салицилатом и цеталкония хлоридом; периодонтит; периостит; ретенция зуба; осложнения удаления зуба.*

BACKGROUND

Dental surgery is rarely performed among adolescents. It is associated with the routine oral cavity sanitation in them [1]. At the same time, the problem of treatment of alveolitis, which occurs after surgical tooth extraction in 2.7–17% of patients and accounts for up to 50% of all postoperative complications arising from this most frequent operation in medicine, remains relevant in the practice of dental surgeons [2]. A large number of methods for treatment as well as pharmacological agents have been described, which at different times have been used and are still used in the daily clinical work of physicians in departments and offices of dental surgery with varying effectiveness. For these purposes, gelevin, oxycelodex, solcoseryl jelly, dermazine, herpenox, argakol, and special pastes prepared immediately before applying them to the wound surface in case of infectious-inflammatory phenomena were used [3–5]. Effective treatment of alveolitis helps to reduce pain syndrom in patients suffering from this disease [6, 7], as well as to prevent atrophy of alveolar processes and arches of jaws in them [8–10]. In the last decade, with the exception of one domestic enterprise, the use of iodoform gauzes prepared in medical institutions for the treatment of alveolitis, which are very effective for this purpose in both outpatient and inpatient dental practices, has almost completely stopped, due to the special conditions needed for their production [2]. So, the search for new effective agents for the treatment of alveolitis remains relevant due to the fact that the incidence of this immediate complication of tooth extraction surgery is not decreasing [7, 9]. Recently, special attention paid to the use of ready-made dosage forms in medical practice, which is convenient for practical dentistry.

Also recently, the incidence of alveolitis has increased in adolescents. It is associated with tooth extraction for orthodontic aims, as well as in connection with preparation for orthodontic treatment [11–13]. Therefore, improving the treatment for alveolitis in adolescents is currently relevant.

AIM

To study the opportunity and evaluate the efficacy of dental gel with choline salicylate and cetalkonium chloride for the treatment of alveolitis in adolescents.

MATERIALS AND METHODS

47 adolescents aged from 15 to 18 years (29 (61.7%) boys and 18 (38.3%) girls) were observed. All of them was treated by dental surgeon for alveolitis after extracting teeth of the upper jaw (17 patients/36,17%) and teeth of the lower jaw (30 patients/63,83%) (Fig. 1). The main indications for tooth extraction were chronic periodontitis, exacerbation of chronic periodontitis, chronic pericoronitis, orthodontic indications, and acute purulent periostitis of the jaws, retention of wisdom teeth (Figure 2). When alveolitis was diagnosed, we used the generally accepted method of treatment for this disease [14].

If a blood clot was preserved at least for half of the well after tooth extraction when a patient visited the doctor, a person was included in the study. This wells after their treatment with antiseptic solutions with use of syringe, cleaning from free-lying fragments of the alveolus and tooth, food residues and decay products with the use of sharp surgical spoons or excavators № 3, were filled with dental gel with choline salicylate and cetalkonium chloride ("Holisal", Ulfa A.O., Poland). Then sterile balls of gauze were placed on the well for 15–20 minutes. It should be noted that the composition of this drug contains a number of useful substances for the local treatment of the infectious and inflammatory processes and healing of the well after tooth extraction. Choline salicylate affects pain receptors and has an anti-inflammatory effect, as well as peppermint oil, which reduces halitosis. The efficacy of the drug in treatment for alveolitis was evaluated accoding to the generally accepted method [7], taking into account the time of disappearance of a pain syndrome (in hours), the time of well replacement with granulation tissue (in days), the average time of temporary disability of patients (in days) and the number of visits required to relieve the main symptoms of alveolitis that impair the quality of life of patients [14].

The data was processed on a personal computer using a specialized package for statistical analysis Statistica for Windows v. 6.0. Differences between the compared groups were considered reliable at $p \leq 0.05$. If the probability values of "p" were in the range from 0.05 to 0.10, cases were considered as «presence of a trend».

RESULTS AND DISCUSSION

In clinical study, we took into account the peculiarities of postoperative wounds and the number of roots in extracted teeth (Fig. 3), because the size of the postoperative wound affects the safety of the blood clot in the well of the extracted tooth

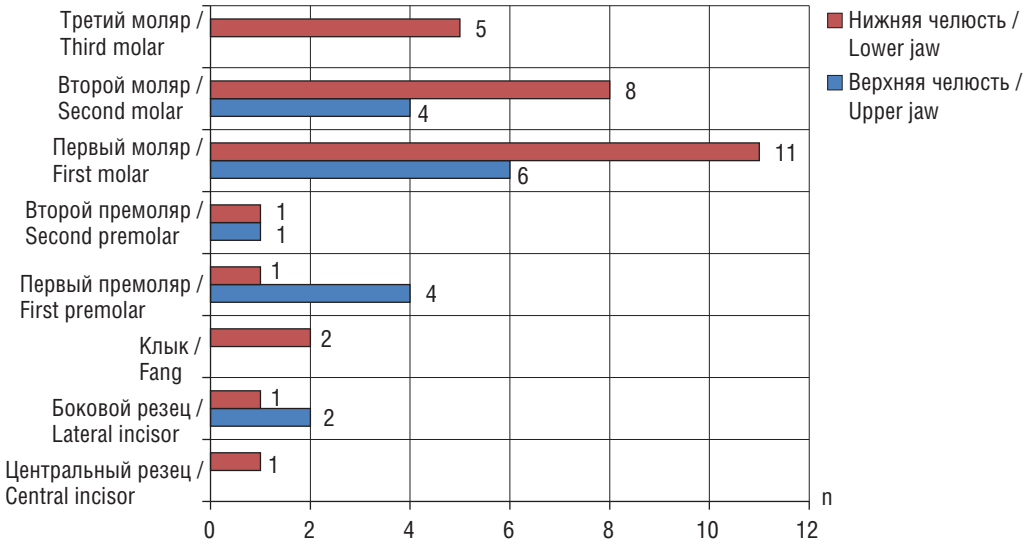

Fig. 1. Characteristics of teeth which extraction leaded to development of alveolitis in adolescents, *n*

Рис. 1. Характеристика зубов, после удаления которых у подростков возник альвеолит, *n*

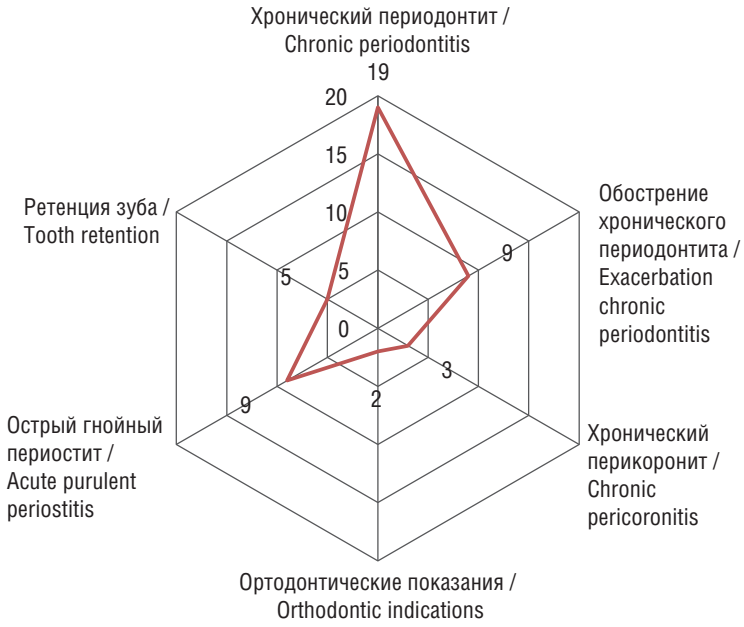

Fig. 2. Dental diseases, which leaded to consulting of adolescents by dentists and development of alveolitis after tooth extraction, n

Рис. 2. Заболевания зубов, в связи с которыми подростки обращались к врачу и после операции удаления которых возник альвеолит, *n*

and the terms of its healing. Analysis of the results of using dental gel with choline salicylate and cetalkonium chloride for treatment of alveolitis in adolescents showed that the disappearance of pain syndrome occurred within the period from 1 to 24 hours and significantly depended on the size of the well ($p \leq 0.05$). After providing medical care for alveolitis of the well after extraction of single-rooted teeth, with the same degree of severity of the course of disease, the pain syndrome was eliminated earlier (on average in 3–5 hours) than after extraction of two- (3–16) and three-rooted (4–24) teeth.

At a mild degree of alveolitis, the pain syndrome in adolescents resolved in 3.81±0.31 hours, filling of alveoli with granulation tissue occurred within 8–12 days. The average terms of their temporary disability (release from study or other pro-

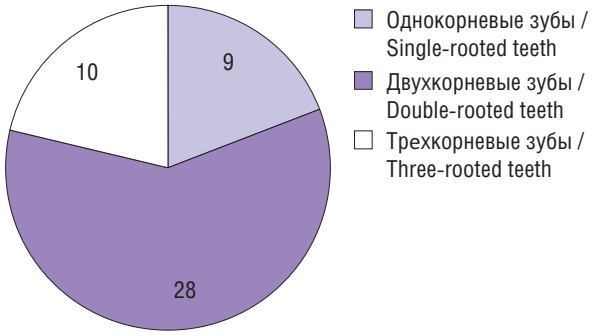

Fig. 3. Characteristics of teeth in light of the number of roots, which extraction leaded to alveolitis in adolescents, *n*

Рис. 3. Характеристика зубов с учетом количества корней, после удаления которых у подростков возник альвеолит, *n*

fessional activity) and number of visits amounted to 1.56±0.42 days and 1.44±0.31 visits, respectively (Figs. 4, 5). In case of moderate and severe alveolitis in adolescents, the pain syndrome disappeared in 8.25±0.42 and 11.82±0.48 hours, respectively, and filling of alveoli with granulation tissue occurred within 9–14 and 11–15 days, respectively. The mean time of temporary disability of adolescents and the number of visits in case of moderate and severe alveolitis were 2.13±0.44 and 2.57±0.63 days, 1.86±0.42 and 2.27±0.43 visits, respectively (Figs. 4, 5). There were no significant differences in the duration of temporary disability and the number of visits required to treat symptoms of alveolitis in adolescents depending on the number of roots of extracted tooth, which leaded to development of alveolitis ($p \geq 0.08$). Although there was a tendency to increase in number of visits and the duration of disability in patient with alveolitis after extraction of two- and three-rooted teeth. To a greater extent, these indicators depended on the severity of the course of alveolitis in adolescents ($p \leq 0.05$).

CONCLUSION

Comparison of the studied parameters of the treatment for alveolitis in adolescents using dental gel with choline salicylate and cetalkonium chloride with similar ones, obtained by other researchers, allowed us to conclude, that dental gel with choline salicylate and cetalkonium chloride is reasonable to use in the clinical practice of pediatric dentistry for treatment of alveolitis. The use of this drug was effective and allowed to eliminate pain syndrome in 2–24 hours after providing medical care and use of gel, as well as to ensure filling of the wells with granulation tissue on the 8–15th day with the average number of visits 1.56–2.57 per adolescent and the average period of their disability due to alveolitis 1.44–2.27 days. We think, that the use of dental gel with choline salicylate and cetalkonium chloride will be appropriate for adult patients with alveolitis and other inflammatory processes of the oral mucosa.

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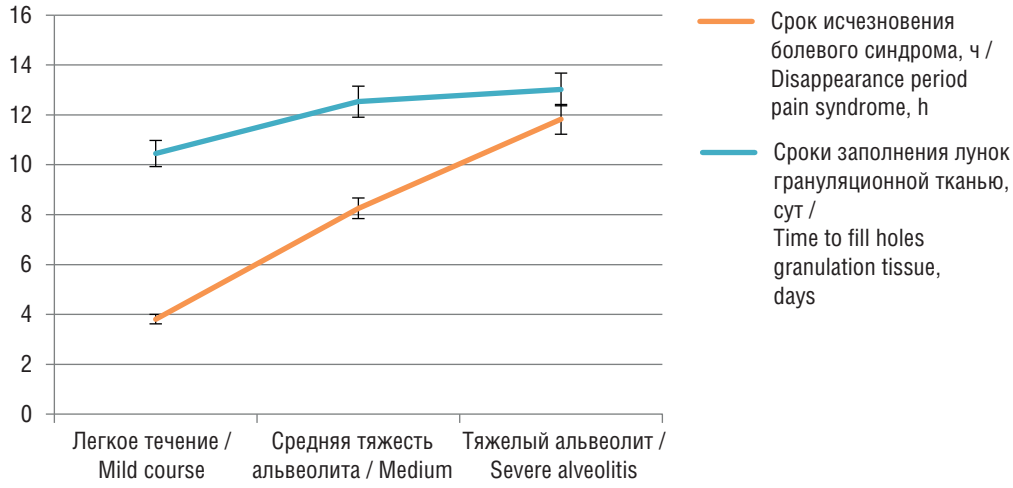

Fig. 4. Time of pain relief (hours) and filling of wells with granulation tissue (days) in adolescents during treatment of alveolitis using dental gel with choline salicylate and cetalkonium chloride ("Holisal", Ulfa A.O., Poland), n

Рис. 4. Сроки купирования болевого синдрома (часов) и заполнения лунок грануляционной тканью (суток) у подростков при лечении альвеолита с использованием геля стоматологического с холином салицилатом и цеталкония хлоридом (лекарственное средство «Холисал», Ульфа А.О., Польша), *n*

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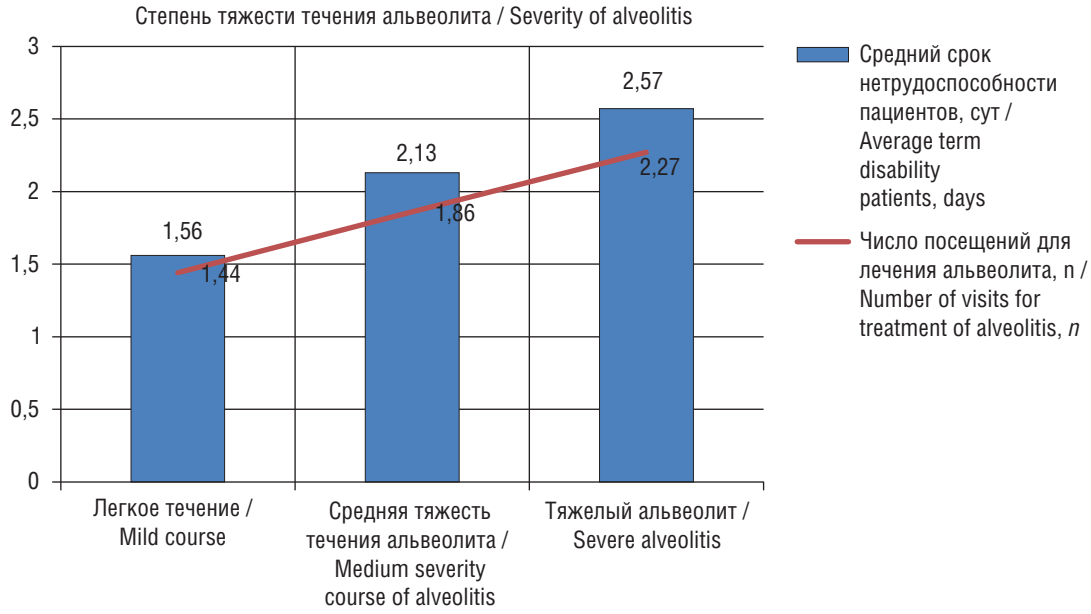

Fig. 5. Average periods of disability of adolescents (days) and number of visits required for relief symptoms of alveolitis (*n*) during treatment with dental gel with choline salicylate and cetalkonium chloride (drug "Holisal", Ulfa A.O., Poland)

Рис. 5. Средние сроки нетрудоспособности подростков (суток) и число посещений, необходимых для купирования симптомов альвеолита (*n*) при лечении с использованием геля стоматологического с холином салицилатом и цеталкония хлоридом (лекарственное средство «Холисал», Ульфа А.О., Польша)

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THE EFFECTIVENESS OF SURGICAL TREATMENT OF CHRONIC CONSTIPATION IN CHILDREN

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Abstract. Therapy of chronic constipation presents certain difficulties. Based on modern research methods and a large clinical material (3526 patients), it was shown that among patients with so-called functional constipation, anal achalasia is detected in 3.89% of children, and hypertrophy of the internal sphincter in 1.72%. The effectiveness of sphincterotomy of the internal sphincter of the anus has been proven, the immediate and long-term results of this operation have been studied. It was revealed that the restoration of normal defecation in patients with anal achalasia and hypertrophy of the internal sphincter of the anus, with conservative treatment, occurs in no more than 2–3% of cases, after sphincterotomy in 70–90%. However, this process is very slow, over several years.

Key words: *chronic constipation; children; anal achalasia; hypertrophy of the internal anal sphincter; sphincterotomy.*

ЭФФЕКТИВНОСТЬ ОПЕРАТИВНОГО ЛЕЧЕНИЯ ХРОНИЧЕСКИХ ЗАПОРОВ У ДЕТЕЙ

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Резюме. Терапия хронических запоров представляет определенные трудности. На основании современных методов исследования и большом клиническом материале (3526 пациентов) показано, что среди больных с так называемыми функциональными запорами у 3,89% детей выявляется анальная ахалазия, у 1,72% — гипертрофия внутреннего сфинктера. Доказана эффективность сфинктеротомии внутреннего сфинктера заднего прохода, изучены ближайшие и отдаленные результаты этой операции. Выявлено, что восстановление нормальной дефекации у пациентов с анальной ахалазией и гипертрофией внутреннего сфинктера заднего прохода при консервативном лечении происходит не более чем в 2–3% случаев, после сфинктеротомии — в 70–90%. Однако этот процесс происходит очень медленно, в течение нескольких лет.

Ключевые слова: *хронические запоры; дети; анальная ахалазия; гипертрофия внутреннего анального сфинктера; сфинктеротомия.*

Nowadays, chronic constipation is an urgent social problem due to significant prevalence and difficulties in therapy [1–4]. The causes of chronic fecal retention are observed in children with chronic constipations of organic or secondary etiology (surgical — in Hirschsprung's disease and after surgical treatment of anorectal malformations, neurogenic, systemic and metabolic disorders, toxic lesions) [5]. In the vast majority of cases, in more than ten thousand patients, the cause of defecation disorders is not established definitely, because the level of modern knowledge about this problem does not allow to do this, so the diagnosis of «functional constipation» is usually made and

treated conservatively [6–10]. At the same time, the studies of some scientists show, that an integral study with the use of radiodiagnosis and other methods to explain the colon [11–13], made it possible to identify patients with anal sphincter achalasia and hypertrophy of the internal anal sphincter in patients with functional constipation [14, 15]. Such patients were offered various methods of surgical treatment [16–18]. However, there is no data on the frequency of these diseases in the structure of patients with constipation in modern literature. There is contradictory information about the necessity and effectiveness of surgery, and the long-term results have not been studied.

AIM

To optimize the indications for surgical treatment and to make a comparative dynamic analysis of the long-term results of conservative and surgical treatment.

MATERIALS AND METHODS

The study is based on the retrospective analysis of case histories and observations of 3526 patients with chronic constipation in SPbSPMU and children's hospital № 22. All children were examined according to a unified program, including: clinical, radiological, colorectal examination, endorectal sonography, as well as histological and histochemical methods. **Clinical examination** included the study of anamnesis vitae according to a unified way, which included the age of patient when constipation and fecal impaction appeared, types of patient's complaints and examination data with the calculating of the Rome criteria.

Radiological methods. To assess the anatomical position of the colon, its contractility, and to exclude Hirschprung's disease, standard irrigography with barium suspension was performed without preliminary preparation before the start of conservative therapy. The emptying index [12] was used for objective assessment of emptying. This index was calculated according to the formula: I_0 = M op. / M zap. Where Io is the emptying index; M op. is the arithmetic mean of transverse dimensions of all colon sections after emptying in centimeters; M zap is the arithmetic mean of transverse dimensions of all colon sections during filling in centimeters. Emptying index from 0.1 to 0.4 was considered normal. Index values that exceeded 0.4 were considered as disorders of defecation. Three degrees were identified: I degree — I_0 from 0.4 to 0.65, which corresponded to a moderate delay in defecation and the possibility of independent defecation; II degree — I_0 from 0.65 to 0.8, corresponded to a significant delay in defecation (more than 50%), but it was possible to defecate independently; III degree — I_0 from 0.8 to 1, defecation was not possible without the use of laxatives or enemas.

Anorectal manometry was performed on the devices "Colodynamic 3" (manufacturer "Progress", Rostov-On-Don) and Menfis (Italy). This study allowed to diagnose the violation of reservoir and evacuator functions of the rectum (volume-threshold sensitivity — VTS), to measure the pressure in the anal canal. These indicators characterize the presence of the urge for defecation and its possibility. We separately studied the rectoanal reflex (RAR), which shows the neuroreflectory connection between the rectum and pelvic diaphragm and is a main importance for ensuring the normal act of defecation. Normally, when the pressure in the rectum increases, the pressure in the anal canal should decrease.

Endorectal ultrasonography allowed visualization and determination of the thickness of the internal anal sphincter (IASP); IASP sizes of 1.15±0.12 to 1.41±0.14 mm were considered normal.

Morphological and histochemical study. Biopsy of the rectum was performed according to Swenson's method. Signs of pathologic changes in ganglia were considered to be: agangliosis, hypogangliosis, ganglion dystrophy. A section of rectal mucosa with the dimensions of at least 0.3×0.5 cm was used as a material. Anticholinesterase (AChE) activity in the mucosa within the range of 1–11.0 μmol/mg per minute was considered normal.

To assess the degree of defecation disorder and the results of treatment,an evaluation system was created, which consisted of five sections (Table 1). Sections 1 and 3 assessed the ability to independent defecation, taking into account the frequency of stools and the Rome criteria. In the 2nd section, the presence and frequency of stools, and the 4th section included radiological data. According to the degree of pathology, the patient was given 3 points in each of these sections (0 — no pathology). Section 5 assessed the outcome of treatment.

A good result (0 points) was considered the possibility of independent defecation, when the diet was followed and the rules of defecation were taught, without need of use enemas or laxatives. Satisfactory (1–3 points) result — constipation which followed by the regular courses of conservative therapy (1–2 times a year) allowed

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Таблица 1. Оценка эффективности лечения детей с запором

Tab 1. Assessment of effectiveness of treatment for constipation in children

Part 1. Assessment of regularity of defecation / Раздел 1. Оценка регулярности опорожнения	
Regular defecation / Стул регулярныRegular defecation	0 point / 0 баллов
Defecation once in 2–3 days / Стул один раз в 2–3 дня	1 points / 1 балл
Defecation once in 4–6 days / Стул один раз в 4–6 дня	2 points / 2 балла
Defecation once in 10 days and rare / Стул один раз в 10 дней и реже	3 points / 3 балла
Part 2. Assessment of encopresis / Раздел 2. Оценка каломазания	
No encopresis / Каломазания нет	0 point / 0 баллов
Encopresis rare than 1–2 times a month / Каломазание не чаще 1–2 раз в месяц	1 points / 1 балл
Weekly encopresis / Каломазание еженедельно	2 points / 2 балла
Daily encopresis / Каломазание ежедневно	3 points / 3 балла
Part 3. Roma criteria / Раздел 3. Оценка Римских критериев	
Less than 3 criteria / Определяется менее 3 критериев	0 point / 0 баллов
3 criteria / Определяется 3 критерия	1 points / 1 балл
4 criteria / Определяется 4 критерияv	2 points / 2 балла
5 criteria / Определяется 5 критериев	3 points / 3 балла
Part 4. Assessment of defecation by irrigograms / Раздел 4. Оценка опорожнения по ирригограммам	
Normal defecation, I_o <0,4 / Опорожнение в норме, I_o <0,4	0 point / 0 баллов
1st degree of delay in emptying, I_o from 0.4 to 0.65 / 1-я степень задержки опорожнения, I_o от 0,4 до 0,65	1 points / 1 балл
2nd degree of delay in emptying, I_o from 0.65 to 0.8 / 2-я степень задержки опорожнения, I_o от 0,65 до 0,8	2 points / 2 балла
3rd degree of delay in emptying, I_o> 0.8 / 3-я степень задержки опорожнения, I_o> 0,8	3 points / 3 балла
Part 5. Assessment of treatment / Раздел 5. Оценка результата лечения	
Good result / Хороший результат	0 point / 0 баллов
Satisfactory result / Удовлетворительный результат	1–3 points / 1–3 балла
Unsatisfactory result / Неудовлетворительный результат	4–12 points / 4–12 баллов

to achieve long-term remissions. If there were unsatisfactory results (4–12 points), defecation was impossible without regular laxatives or enemas.

RESULTS

Due to the data of the integral study, three groups of patients were distinguished. The **1st group** consisted of 3330 patients (94.39%). In these children a slightly later appearance of constipation (after 2–3 years) and less severe clinical course of constipation were noted than in patients of the 2nd and 3rd groups. The average point of Rome criteria was 2.24±0.27, which indicated defecation disorder, but was not catastrophic. Markers of radiological methods in most cases indicated impaired motility of the colon and delayed emptying of the I–II degree. The severity of constipation on a 12-point scale was mostly 6–8 points. No specific features were revealed by the anorectal manometry, its results indicated decreased volume-threshold sensitivity, moderate increase in pressure in the anal canal, and normal rectoanal reflex. There were normal sizes of IASP, histologic changes of the rectal wall basically did not allow to draw any conclusions about the nature of constipation, it could be of primary or secondary etiology. However, the AChE value of the rectal mucosa was normal in all cases. It was an indirect sign of the absence of severe intramural conduction disturbance. These patients were diagnosed with **functional constipation**.

In patients of **groups 2** (136 children — 3.89%) and **3** (60 children — 1.72%) constipation appeared at an earlier age (up to two years) and was more severe. Their clinical picture was the same in both groups. In almost 80% of cases constipation was complicated by encopresis. More than 90% of patients suffered from

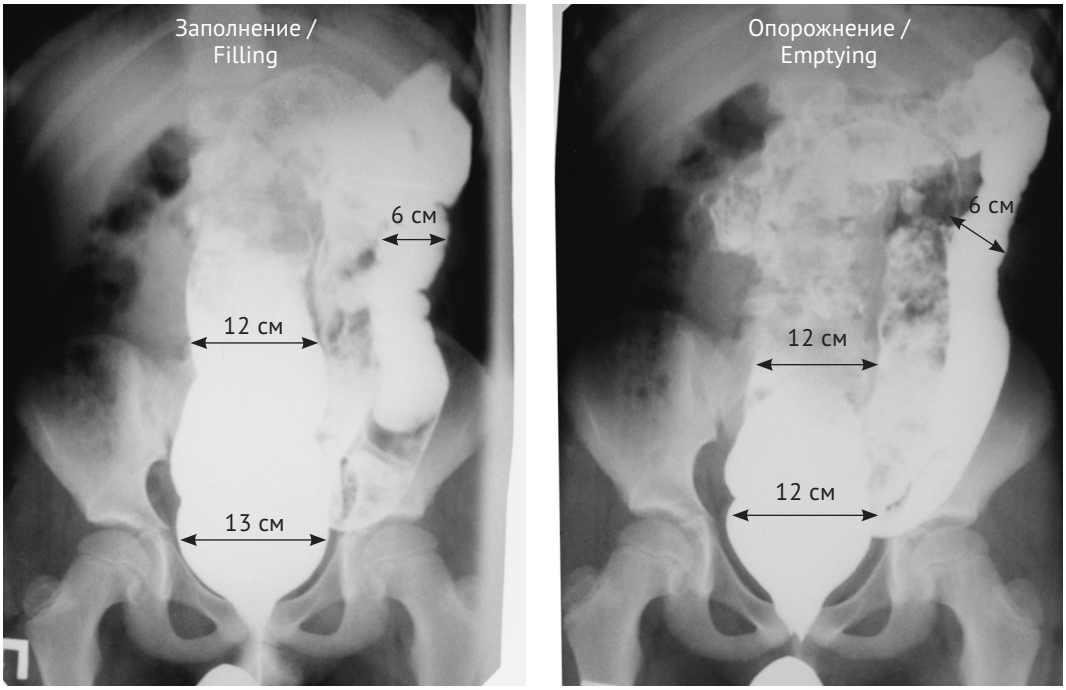

Fig. 1. Irrigograms of patient (group 2) with III degree of voiding disorder. Emptying index 0.96

Рис. 1. Ирриграммы пациента 2-й группы с нарушением опорожнения III степени. Индекс опорожнения 0,96

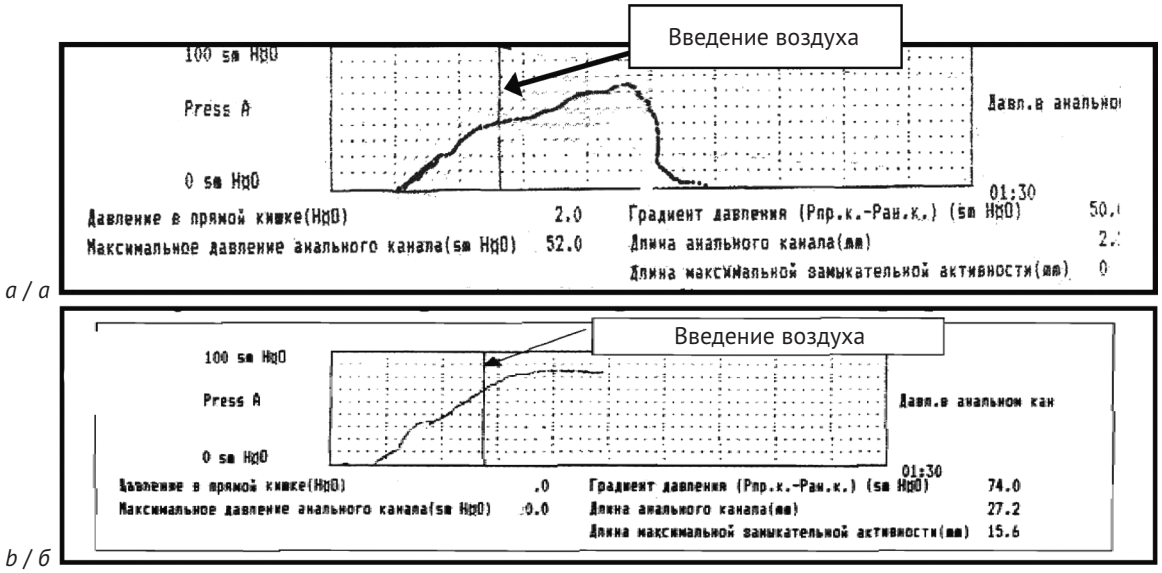

Fig. 2. Examination of rectoanal reflex in a child with anal achalasia: *a* — delayed RAR, after introduction of air into the rectum the decrease of pressure in the anal canal occurs with a significant delay; *b* — reverse "perverted" RAR, after introduction of air into the rectum the increase of pressure in the anal canal is determined

Рис. 2. Исследование ректоанального рефлекса у ребенка с анальной ахалазией: *а* — замедленный РАР, после введения воздуха в прямую кишку снижение давления в анальном канале происходит со значительной задержкой; *б* — обратный «извращенный» РАР, после введения воздуха в прямую кишку определяется повышение давления в анальном канале

delayed defecation longer than four days. The mean Rome criteria in group 2 was 4.47 and in group 3 was 4.19, indicating a very severe voiding disorder.

The radiological indicators (Fig. 1) showed a more pronounced decrease in the motility of colon (II and III degrees). The severity of constipation on a 12-point scale was more than 8 points.

Decreased volume-threshold sensitivity of the rectum, increased pressure in the anal canal, and histological changes were also more pronounced. However, according to these indicators it was impossible to differentiate these patients from children with functional constipation and from each other, since the noted factors were mostly individual for each patient.

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At the same time, only patients of **2nd** group in all cases had impaired rectoanal reflex (Fig. 2) and increased AChE activity of the mucosa (more than 18 μmol/L/g protein per hour). The developing of constipation in them can be explained by the violation of the defecation due to partial insufficiency of the intramural nervous system of the rectum and incomplete relaxation of the internal anal sphincter.

The cause of constipation can be considered as **anal achalasia**, because there was not any patient who had the zone of agangliosis at irrigograms, i.e. Hirschprung's disease.

In children of the 3rd group, normal rectoanal reflex and normal AChE values of the mucous membrane (2–10 μmol/mL per minute) were noted in all cases, so these changes were the same to those in patients with functional constipation (group 1). However, endorectal sonography in all cases revealed thickening of the internal anal sphincter (1.5–2 times) relative to normal age values, which constantly maintained high pressure in the anal canal and prevented the normal act of defecation (Table 2, Fig. 3). The degree of thickening was independent of duration of the disease. This allowed us to assume that **hypertrophy of the internal anal sphincter** is a primary pathological process, i.e., an independent disease and not a consequence of constipation.

The differential diagnosis table was created due to data of the research to identify «surgical» causes of functional constipation (Table 3).

All patients with constipation on admission to the hospital were prescribed complex conservative treatment, which included laxatives, enemas, and biofeedback lessons. The majority of children with functional constipation showed stable positive dynamics after the first course of conservative therapy. After 2–5 courses of inpatient treatment and following the doctor's recommendations at home, the number of points did not exceed 6, and the condition of more than 60% of patients was evaluated as 0–4 points. The results of therapy were good or satisfactory.

At the same time, after the similar conservative therapy, more than 60% of children with anal achalasia and hypertrophy of internal anal sphincter had regular defecation only after enema. In 20–30% of children constipation persisted for 2 to 4 days, and almost 10% of patients needed periodic cleansing enema to empty the colon. Only 14 (10.3%) patients had temporary (3–6 months)

Table 2. Thickness of internal anal sphincter in patients with its hypertrophy and in healthy children, mm

Таблица 2. Толщина ВСЗП у пациентов с гипертрофией ВСЗП и в норме, мм

	Age / Возраст		
	4–7 years old / 4–7 лет	8–12 years old / 8–12 лет	12–16 years old / 12–16 лет
Patients (group 3) / Больные 3-й группы	1,8±0,1*	2,00±0,1*	2,20±0,1*
Normal values / Нормальные возрастные показатели	1,15±0,12	1,28 ±0,16	1,41±0,14

*p <0,05.

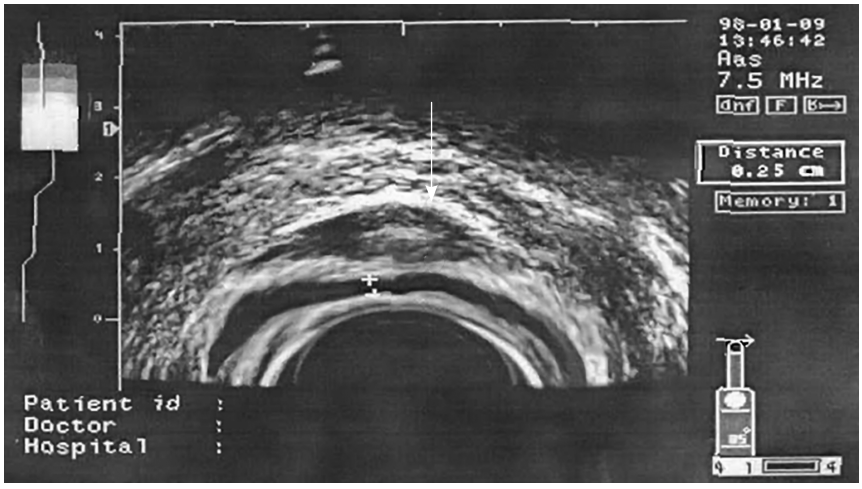

Fig. 3. Endosonogram of the anal canal of a child with hypertrophy of internal anal sphincter, internal sphincter thickness – 2.5 mm
Рис. 3. Эндосонограмма анального канала ребенка с гипертрофией ВСЗП, толщина внутреннего сфинктера – 2,5 мм

Table 3. Differential diagnosis to identify "surgical" causes of functional constipation

Таблица 3. Дифференциально-диагностическая таблица для выявления «хирургических» причин функциональных запоров

Group of patient's / Группы пациентов	Main diagnostics markers / Главные диагностические признаки	Diagnosis / Диагноз
1st group — 3330 patients (94,39%) / 1-я группа — 3330 пациентов (94,39%)	I_o >0,4, normal rectoanal reflex, AChE activity <11 μmol/L/g protein per hour, thickness of internal anal spincter <1.5 mm I_o >0,4, нормальный РАР, активность АХЭ <11 мкмоль/л/г белка в час, толщина ВСЗП <1,5 мм	Functional constipation / Функциональный запор
2nd group — 136 patients (3,89%) / 2-я группа — 136 пациентов (3,89%)	I_o >0,65, delayed or reversed rectoanal reflex, AChE activity >12 μmol/L/g protein per hour, thickness of internal anal spincter <1,5 mm / I_o >0,65, замедленный или обратный РАР, активность АХЭ >12 мкмоль/л/г белка в час, толщина ВСЗП <1,5 мм	Anal sphincter achalasia / Анальная ахалазия
3rd group — 60 patients (1,72%) / 3-я группа — 60 пациентов (1,72%)	I_o >0,65, normal rectoanal reflex, AChE activity <11 μmol/L/g protein per hour, thickness of internal anal spincter >1,6 мм / I_o >0,65, нормальный РАР, активность АХЭ <11 мкмоль/л/г белка в час, толщина ВСЗП >1,6 мм	Hypertrophy of internal anal sphincter / Гипертрофия ВСЗП

recovery of independent defecation. The number of points on a 12-point scale in all cases exceeded 7, so the results of treatment were unsatisfactory.

Thus, patients with anal sphincter achalasia and hypertrophy of the internal anal sphincter were very limited to conservative treatment, and its results were not reliable. This was the cause for the use of surgical treatment — sphincterotomy of the internal anal sphincter.

On the basis of these results we developed indications for surgical treatment of chronic constipation in children. In our opinion, there must be three factors out of five (the first two are mandatory):

1. Ineffectiveness of long-term (at least 1.5–2 years) complex and regular conservative therapy.
2. Presence on irrigograms of dilated, in the form of a poorly contracting balloon, distal colon with an emptying index of more than 0.65.
3. Increase in the tone of the anal canal above 50 cm of aqueous pressure (in anal sphincter achalasia and hypertrophy of internal anal sphincter). Reverse ("perverted") or delayed rectoanal reflex (in anal sphincter achalasia).
4. Increased activity of acetylcholinesterase of rectal mucosa more than 12 μmol/L/g protein per hour (in anal sphincter achalasia).
5. he thickness of the internal anal sphincter exceeding 1.6 mm (in hypertrophy of the internal anal sphincter).

SURGICAL TECHNIQUE

In the position, while the patient was lying on his back, as in lithotomy, the anal canal mucosa was fixed with «holders» along the posterior semicircle. 2–3 ml of 0.25% novocaine solution for "hydropreparation" was injected under it. The mucosa was dissected at 1/3 of the posterior semicircle of the anal canal in the transverse direction, on the border with the perianal skin. The anal canal and the distal part of the rectum were separated from the mucous membrane for 3–4 cm. A smooth muscle plate 2.5–3.5 cm long, 0.3–0.4 cm wide, and 1–2 mm thick was dissected along the posterior surface of the anal canal. The proximal end of the dissected section was the distal part of the smooth muscle layer of the rectum. Then the mucous membrane was sutured to the wound bottom. A swab with oil was left in the rectum for one day.

Table 4. Number of patients both with anal achalasia and without it examined in different times after surgical treatment

Таблица 4. Количество детей с анальной ахалазией, обследованных в разные сроки после операции, и пациентов контрольной группы

Time after surgery / Срок после операции	Number of patients / Количество детей	
	after internal sphincterotomy / после внутренней сфинктеротомии	control group / контрольная группа
1–2 years / 1–2 года	93	43
3–5 years / 3–5 лет	60	31
7–10 years 7–10 лет	43	18

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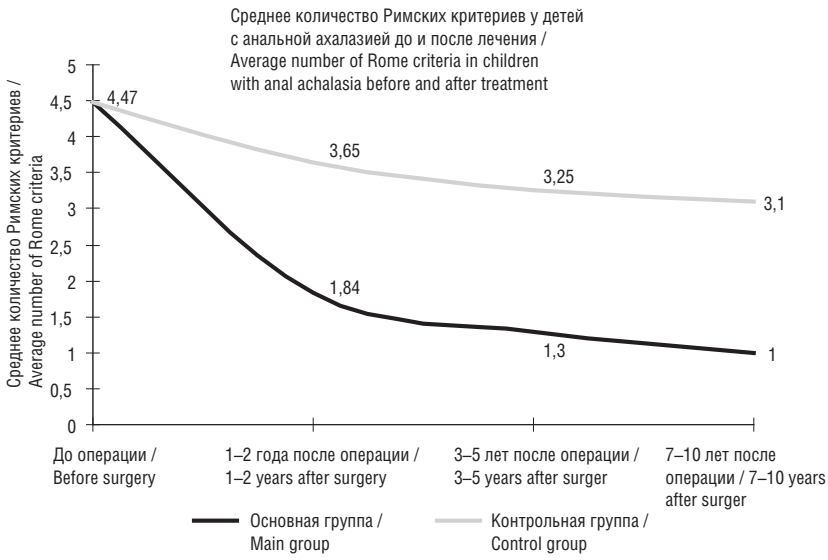

Fig. 4. Dynamics of changes in the number of Roma criteria in patients after surgery and control group

Рис. 4. Динамика изменения количества Римских критериев у больных после операции и контрольной группы

A total of 134 sphincterotomies were performed in children with anal sphincter achalasia and hypertrophy of the internal anal sphincter. 62 patients with the same diagnoses who were not operated on for various reasons have formed a control group and received conservative therapy.

Table 4 shows the number of children with anal sphincter achalasia examined at different times after surgery and patients of the control group who received only conservative therapy.

Before surgery, the majority of patients (93.81%) had stool retention for more than 4 days. In 1–2 years after internal sphincterotomy the number of patients with such a pronounced voiding delay decreased to 13.98% ($p < 0.05$). However, it should be noted that the recovery process was very slow. Thus, in 1–2 years after the operation independent defecation was noted only in 38.7% of cases, in 3–5 years — in 50% ($p < 0.05$), and in 7–10 years — in 60.47% of patients ($p < 0.05$).

The similar dynamics was observed in the study of fecal impaction. The disappearance of this unpleasant symptom occurred slowly and in the same time with the restoration of independent defecation. In the control group as a result of long-term conservative treatment there were no cases of complete restoration of independent defecation, although some patients showed some improvement. Figure 4 shows the comparative dynamics of changes in the number of Roma criteria in patients after surgery and in the control group.

The figure shows that before treatment, the average number of Roma criteria in both groups was similar and exceeded 4, indicating a serious degree of voiding impairment. After surgical treatment, we observed their constant decrease (on average to 1 after 7–10 years). At the same time in patients of the control group the decrease was less significant and amounted to 3.1 after 7–10 years. The differences were statistically significant ($p < 0.05$).

Similar dynamics was noted when comparing radiological parameters. Figure 5 shows that the contractile function of the colon in patients after sphincterotomy improved more than 2-fold, and in 3–5 years after surgery the emptying index approached normal values. In children of the control group every time this index indicated a serious delay in emptying of the colon (0.69 with a norm of 0.4).

Figures 6 and 7 show the dynamics of the main parameters of the gastrointestinal manometry — volume-threshold sensitivity and pressure in the anal canal. In both groups there was a tendency toward improvement of volume-threshold sensitivity. However, in patients who received surgery its values were close to normal, whereas in patients after conservative treatment a much larger volume of liquid was needed for the urge to defecate. The tone of anal canal after sphincterotomy, in contrast to the patients in the control group, also decreased and reached normal values.

The differences between the groups were statistically significant ($p < 0.05$). At the same time, it should be taken into account that these indicators are conditional and cannot always be associated with each specific patient, but they clearly demonstrate the general trend of the clinical course of the disease and changes in the data of various methods of investigation.

Table 5 summarizes the general data on the efficacy of internal sphincterotomy for anal achalasia.

The table shows that the effectiveness of surgical treatment increased depending on the time

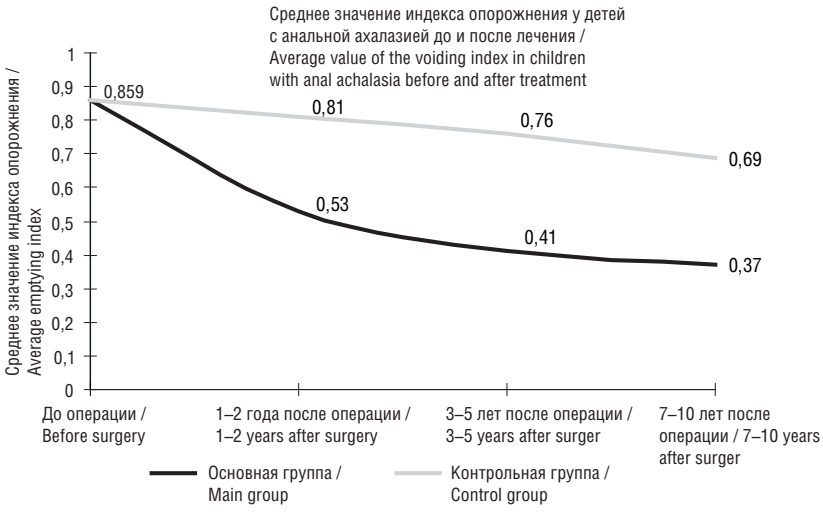

Fig. 5. Dynamics of changes in the mean values of the emptying index in patients after surgical treatment and in children of control group

Рис. 5. Динамика изменения средних значений индекса опорожнения у больных после операции и контрольной группы

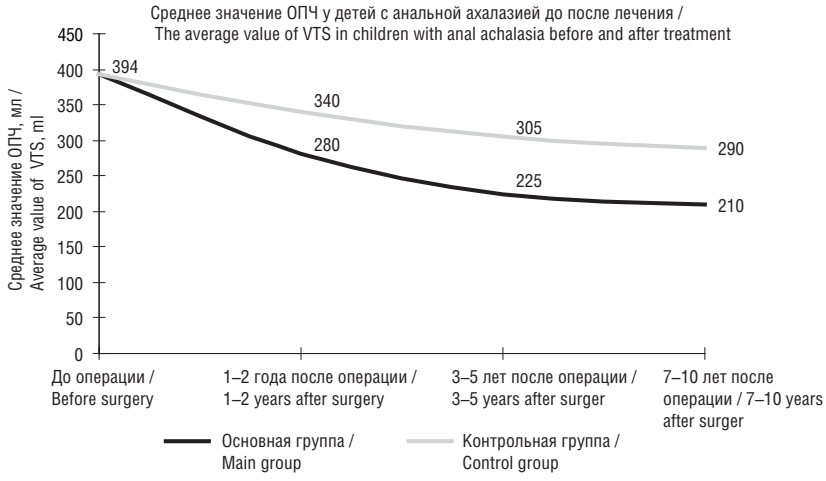

Fig. 6. Dynamics of changes in the average indices of volume-threshold sensitivity (VTS) in patients after surgical treatment and in children of control group

Рис. 6. Динамика изменения средних показателей объемно-пороговой чувствительности (ОПЧ) у больных после операции и контрольной группы

after its performance, but this process was very slow. In patients of the control group, the effectiveness of conservative treatment was unsatisfactory in all cases.

It should also be noted that in more than 23% of patients there was no improvement at all after surgical intervention. This is probably due to the fact that the current state of the problem does not always allow to determine the cause of constipation, and patients may need other methods of conservative or surgical treatment (transrectal resection of the rectum, Soave's or Duhamel operation).

Table 6 demonstrates the number of children with hypertrophy of internal anal sphincter examined in different times after surgery and patients of control group with the same diagnosis who received only conservative therapy.

The dynamics of clinical picture, radiologic data and results of gastrointestinal manometry at different terms after surgery in children with hypertrophy of internal anal sphincter was the same as in patients with anal achalasia. Only a slight difference in quantitative parameters was noted.

Table 7 presents general data on the efficacy of sphincterotomy of the internal anal sphincter if it was hypertrophied.

The table shows that the effectiveness of surgical treatment, as well as in children with anal achalasia, increased very slowly. In both groups of children, the maximum clinical improvement after sphincterotomy occurred within 3–5 years after surgery, and then the recovery of voiding function was sharply delayed.

CONCLUSION

In conclusion, it should be noted that, although anal achalasia and hypertrophy of the internal anal sphincter are different diseases, but the clinical manifestations and course of the disease, as well as the recovery process after sphincterotomy, were the same, because the pathogenetic mechanism in these conditions is identical — pathologically high pressure in the anal canal, which prevents the full

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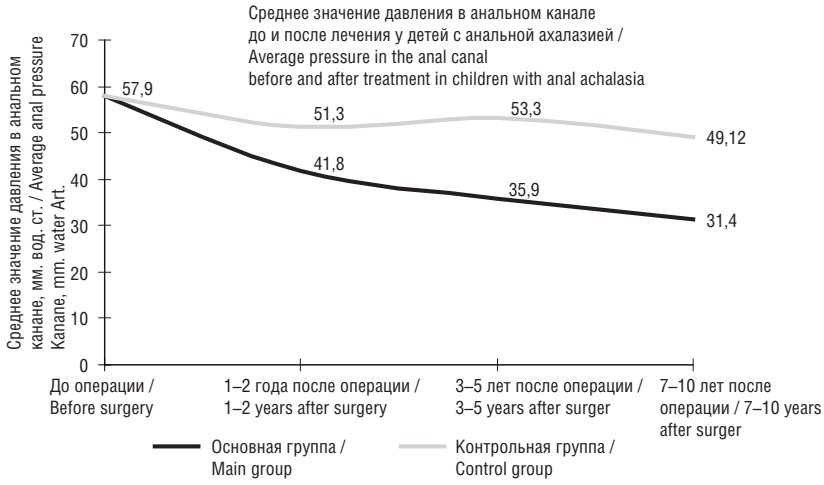

Fig. 7. Dynamics of changes in the mean data of pressure of anal canal in patients after surgical treatment and in children of control group

Рис. 7. Динамика изменения средних показателей давления в анальном канале у больных после операции и контрольной группы

Table 5. Results of internal sphincterotomy in patients with anal achalasia at different terms after surgery (with use of a 12-point scale)

Таблица 5. Результаты внутренней сфинктеротомии у больных с анальной ахалазией в разные сроки после операции (по 12-балльной шкале)

Result / Результат	Years after surgical treatment / Сроки после операции		
	1–2 years / 1–2 года	3–5 years / 3–5 лет	7–10 years / 7–10 лет
Good (0 point) / Хороший (0 баллов)	2,15%	41,67%*	60,47%*
Satisfying (1–3 point) / Удовлетворительный (1–3 балла)	56,99%	28,33%*	16,28%*
Unsatisfying (4–12 point) / Плохой (4–12 баллов)	40,86%	30,00%	23,26%

* p<0,05.

Table 6: Children with hypertrophy of internal anal sphincter examined in different times after surgery

Таблица 6. Количество детей с гипертрофией ВСЗП, обследованных в разные сроки после операции

Time after surgical treatment / Срок после операции	Children, n / Количество детей, n	
	after internal sphincterotomy / после внутренней сфинктеротомии	control group / контрольная группа
1–2 years / 1–2 года	41	19
3–5 years / 3–5 лет	24	14
7–10 years / 7–10 лет	14	8

act of defecation. Sphincterotomy of the internal anal sphincter allows to reduce anal pressure and achieve more than 70–90% of cases of restoration of independent emptying. At the same time, it should be taken into account that it is not etiological treatment. After this treatment, only prerequisites for the restoration of defecation are created, and an indispensable condition for the success of the operation is a full and long-term conservative therapy in the postoperative period.

Thus, it has been proved that in functional constipation the only objective diagnostic criterion is an increased emptying index. In anal achalasia, with a high emptying index, there is an increase in pressure in the anal canal, pathological rectoanal reflex and an increase in the concentration of acetylcholinesterase of the rectal mucosa. Hypertrophy of the internal anal sphincter is characterized by a high emptying index, high pressure in the anal canal combined with an increase in the thickness of the smooth muscle layer of the anal canal. Children with anal achalasia account for 3.9%, with hypertrophy of an internal anal sphincter — 1.7% in all patients with chronic constipa-

Table 7. Results of internal sphincterotomy in patients with hypertrophy of internal anal sphincter at different terms after surgery (with use of a 12-point scale)

Таблица 7. Результаты внутренней сфинктеротомии у больных с гипертрофией ВСЗП в разные сроки после операции (по 12-балльной шкале)

Result / Результат	Time after surgical treatment / Сроки после операции		
	1–2 years / 1–2 года	3–5 years / 3–5 лет	7–10 years / 7–10 лет
Good (0 point) / Хороший (0 баллов)	4,87%	58,33%*	64,29,%*
Satisfying (1–3 points) / Удовлетворительный (1–3 балла)	58,54%	25,0%*	28,57%*
Unsatisfying (4–12 points) / Плохой (4–12 баллов)	36,59%	16,67%*	7,14%*

* $p<0,05$.

tion. Sphincterotomy of the internal anal sphincter is indicated only for patients with anal achalasia and its hypertrophy. It was found that the recovery of defecation, radiological and colodynamical parameters after sphincterotomy is very slow, within 3–5 years. Conservative therapy for chronic constipation in children with anal achalasia and hypertrophy of the internal anal sphincter is ineffective. Sphincterotomy, in turn, is an effective procedure and allows to restore independent defecation in more than 70–90% of cases.

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FEATURES OF PROFESSIONAL ORAL HYGIENE IN SCHOOL-AGE CHILDREN

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Abstract. Inflammatory periodontal diseases are characterized by an increase and a high frequency of occurrence in the population not only among the adult population, but also in children. The main principle of treatment and prevention of VZP is to reduce the contamination of microorganisms of dental plaque. Removal of soft dental deposits from the surfaces of teeth is most physiologically carried out with an air-abrasive technique. In the presented clinical study, a comparative analysis of air-abrasive agents of various generations used in the comprehensive prevention and conservative treatment of inflammatory periodontal diseases in school-age children was performed. It is shown that air-abrasive products based on erythritol, along with good cleansing properties, have more pleasant organoleptic qualities and to a lesser extent lead to increased sensitivity of tooth enamel after professional oral hygiene in school-age children.

Key words: *periodontitis; gingivitis; oral hygiene in children; air-abrasive agents; erythritol.*

ОСОБЕННОСТИ ПРОВЕДЕНИЯ ПРОФЕССИОНАЛЬНОЙ ГИГИЕНЫ ПОЛОСТИ РТА У ДЕТЕЙ ШКОЛЬНОГО ВОЗРАСТА

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Резюме. Воспалительные заболевания пародонта (ВЗП) характеризуются ростом и высокой частотой встречаемости в популяции не только среди взрослого населения, но и у детей. Главным принципом лечения и профилактики ВЗП является снижение контаминации микроорганизмов зубной бляшки. Удаление мягких зубных отложений с поверхностей зубов наиболее физиологично проводится при воздушно-абразивной методике. В представленном клиническом исследовании выполнен сравнительный анализ воздушно-абразивных средств различных поколений, применяемых в комплексной профилактике и консервативном лечении воспалительных заболеваний пародонта у детей школьного возраста. Показано, что воздушно-абразивные средства на основе эритритола наряду с хорошими очищающими свойствами обладают более приятными органолептическими качествами и в меньшей степени приводят к повышению чувствительности эмали зубов после проведения профессиональной гигиены полости рта у детей школьного возраста.

Ключевые слова: *пародонтит; гингивит; гигиена полости рта у детей; воздушно-абразивные средства; эритритол.*

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INTRODUCTION

Nowadays, inflammatory periodontal diseases are characterized by increase of such cases and high frequency of occurrence in the population both in adults and children. The prevalence of different forms of gingivitis in children is about 80%, periodontitis is about 3–5%. Periodontal diseases are most often detected by dentists in school-age children. In patients of 12–15 years old periodontal pathology, according to various authors, occurs in 92–100%, and bleeding gums observed in 25–39% of respondents, tooth tartar occurs in 40–82% of cases, periodontal pocket in 2–4%. Periodontal diseases are most often detected in children of 9–10 years [1–5].

The problem of inflammatory periodontal diseases in school-age children is often associated with the fact that periodontal tissues are in a long-term state of physiological restructuring: development, eruption, formation and resorption of the roots of temporary teeth and their subsequent replacement by permanent teeth. The main principle of treatment and prevention of inflammatory periodontal diseases is to educate the patient in oral hygiene and to take measures aimed at reducing the contamination of microorganisms of biofilm (polymicrobial community fixed on the tooth surface) in the oral cavity [1, 3, 4, 9]. In this regard, conducting a timely complex of preventive hygiene is a very important and relevant area of prevention and treatment for periodontal diseases in children.

The removal of soft dental deposits from tooth surfaces is most physiologically performed with the air-abrasive technique. Nowadays, the most common compositions for this method are agents based on sodium bicarbonate, calcium carbonate, and glycine [2–4]. Some of them are quite abrasive and form a rough surface not only on the tooth surface, but also on the soft tissues of the gingiva, which causes discomfort and dissatisfaction with the procedure [6–8, 10, 11]. Currently, a prophylactic system for air-abrasion based on an organic substance, erythritol carbohydrate, has appeared on the dental market [12].

AIM

To perform a comparative analysis of air-abrasive agents of different generations used in complex prophylaxis and conservative treatment of inflammatory periodontal diseases in school-age children.

MATERIALS AND METHODS

To realize the aim, clinical observation of 23 school-age children and adolescents with chronic generalized catarrhal gingivitis, who were treated in dental clinics, was performed. The average age of the patients was 12.2±4.5 years. The distribution of patients by sex in the groups was similar, so it was not taken into account further in the study.

Clinical observation of the patients was performed in two groups: Group 1–11 children, who received an oral hygiene with use of air-abrasive agent based on glycine; Group 2–12 children, who received the treatment with use of air-abrasive agent based on erythritol.

To assess the effectiveness of the selected agents objectively, the time spent on removal of soft and pigmented plaque was studied.

Dental hyperesthesia was analyzed using the dental sensitivity index (DSI) created by L.Y. Orekhova and S.B. Ulitovsky (2008). The condition of the mucous membrane and the deg-ree of bleeding were evaluated using the bleeding index (Muhlemann). Patients of both groups were examined according to the scheme: before the procedure and immediately after. All the results were recorded in the periodontal chart.

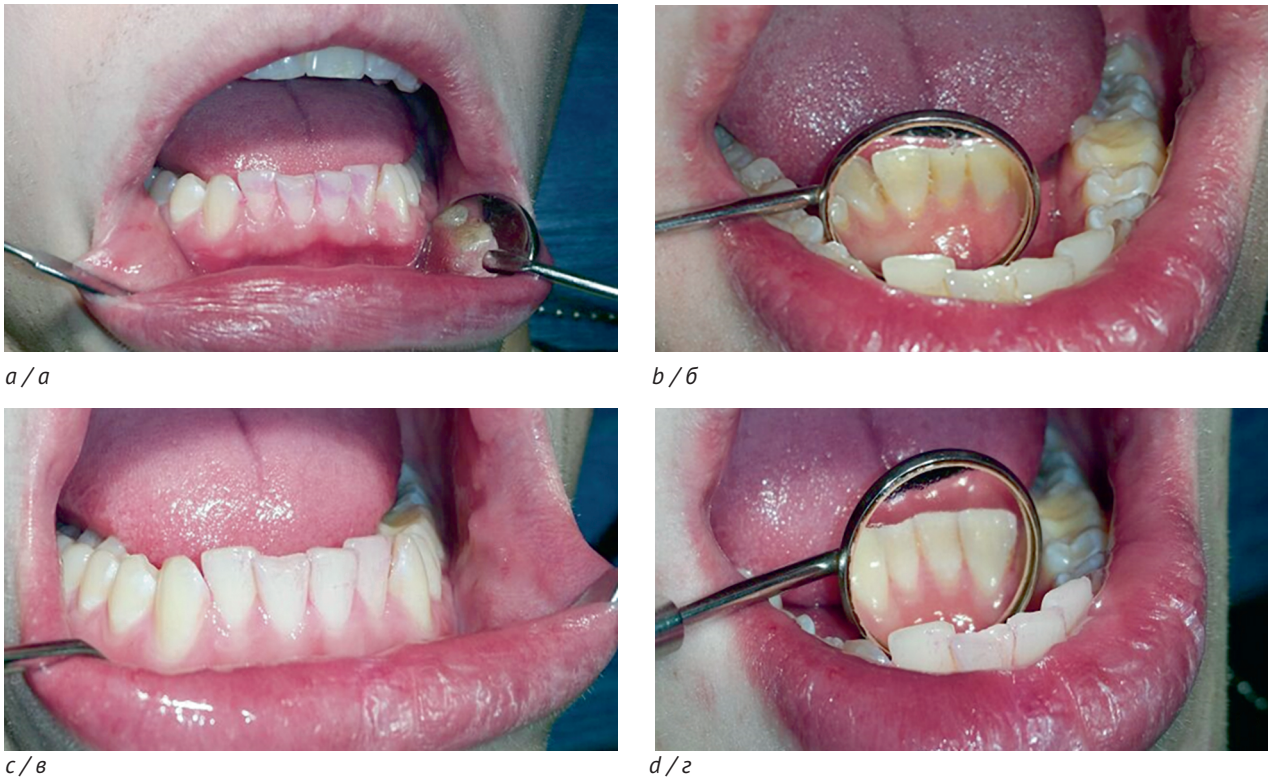
After professional hygiene each patient had to answer the questions of the questionnaire and evaluate the smoothness of teeth, taste of powder, general condition and satisfaction with the procedure.

Statistical processing of the results was performed using the software package STATISTICA 6. The mean (M) and standard error of the mean (m) were used to describe quantitative features. The Kraskell-Wallis H-criterion was used to compare the groups. The hypothesis of no differences between the indicators was rejected at $p < 0.05$.

RESULTS

No significant differences were obtained when we evaluated the time of occupational hygiene ($p > 0.05$). The mean time using the glycine-based product was 37.5+3.6 min, and using the erythritol-based product 38.4+3.8 min.

In Group 1, the mean value of tooth sensitivity was 44.7% (ranged from 41 to 60% — relatively compensated state of moderate tooth sensitivity); and in Group 2 – 29.9% (ranged from 21 to 40% — compensated state against the background of mild tooth sensitivity).



a / а *b / б*

c / в *d / г*

Fig. 1. Patient H., 15 years old: *a*, *b* — oral cavity before professional hygiene; *c*, *d* — oral cavity after professional hygiene using air-abrasive agent based on erythritol

Рис. 1. Пациент Х., 15 лет: *а*, *б* — полость рта до проведения профессиональной гигиены; *в*, *г* — полость рта после проведения профессиональной гигиены с использованием воздушно-абразивного средства на основе эритритола

The condition of the mucous membrane and the degree of bleeding were evaluated using the bleeding index before and after the air-abrasion procedure. When glycine was used, the index (Muhlemann) before the procedure was 0.9+0.16, and after — 1.5+0.19. When we used an erythritol-based product, the index value was 0.8+0.19 and 1.2+0.18, respectively.

An example of professional hygiene in a patient of the 1st group is presented in Figure 1.

The results of the children's questionnaires were comparable in both groups, but the more pleasant taste of erythritol-based powder and better overall feelings of comfort after the procedure were noted in patients of Group 2. In Group 1, despite the visible effect of professional hygiene, four people (36.3%) noted unpleasant sensations after the procedure.

CONCLUSION

The clinical study showed that the mean time spent on hygiene with use of air-abrasive technique in both groups of school-age children did not differ significantly ($p > 0.05$). The increase in tooth sensitivity was more pronounced with use of glycine-based products (44.7%) than with erythritol-based products (29.9%). The value of gingival bleeding index was higher after using glycine (1.5 ± 0.19) than erythritol (1.2 ± 0.18). The questionnaire survey showed a high level of satisfaction with the procedure when erythritol-based powder was used. First of all, respondents noted more pleasant taste qualities of this product.

Thus, it can be concluded that air-abrasive agents based on erythritol and good cleaning properties have more pleasant organoleptic qualities and less lead to increased sensitivity of tooth enamel after professional oral hygiene in school-age children.

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FOREIGN BODIES OF THE RESPIRATORY TRACT IN CHILDREN. RESULTS OF ENDOSCOPIC EXAMINATION IN CHILDREN OF THE REGIONAL CHILDREN'S HOSPITAL

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Abstract. The *purpose of the study* to describe the localization, nature and endoscopic picture of foreign bodies of the respiratory tract among children of different age groups. The medical histories and protocols of bronchoscopy of 46 patients (children 7 months — 14 years) were studied. The endoscopy department of the regional children's hospital of Saint Petersburg. Endoscopic examination was carried out with Pentax EB-1570K and Pentax EB-1170K videobronchoscopes; the extraction of foreign bodies was carried out using a Storz rigid bronchoscope. Out of 46 examined children with foreign bodies of the respiratory tract, 33 children were aged from 7 months to 3 years (71.7%), 8 children aged from 4 to 6 years (17.4%) and 5 children from 7 to 14 years (10.9%). Foreign bodies were most often food particles — in 47.8% of patients (apple, carrot, fish bone, nuts), small beads, toys or their fragments — 37.5% of patients, sharp objects (needles, pins, metal brackets) — 14.7% of patients. Foreign bodies of the respiratory tract can be found anywhere — nasal passages, larynx, trachea, bronchi, in the tissue of the lung itself. Foreign bodies were most often located in the right main bronchus in 17% of patients. Foreign bodies in the left main bronchus — 12.8% of cases; in the left lower lobe bronchus — 6.4%; in the right lower lobe bronchus — 4.3%. In 34% of the examined patients, foreign bodies were not visualized, which is due to their spontaneous evacuation. *Conclusion*. Foreign bodies of the respiratory tract are most often found in children under the age of 3 years. The most frequent localization is the right bronchus. A third of patients have complications in the form of tracheobronchitis.

Key words: *foreign body; respiratory tract; diagnosis; treatment; children.*

ИНОРОДНЫЕ ТЕЛА ДЫХАТЕЛЬНЫХ ПУТЕЙ У ДЕТЕЙ. РЕЗУЛЬТАТЫ ЭНДОСКОПИЧЕСКОГО ОБСЛЕДОВАНИЯ У ДЕТЕЙ ОБЛАСТНОЙ ДЕТСКОЙ БОЛЬНИЦЫ

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Резюме. *Цель исследования* — описать локализацию, характер и эндоскопическую картину при инородных телах дыхательных путей среди детей различных возрастных групп. Изучены истории болезней и протоколы бронхоскопии 46 пациентов (дети 7 месяцев — 14 лет) отделения эндоскопии ЛОГБУЗ «ДКБ» г. Санкт-Петербурга. Эндоскопическое исследование проведено видеобронхоскопами Pentax EB-1570K и Pentax EB-1170K; извлечение инородных тел проводилось с помощью ригибного бронхоскопа Storz. Из 46 обследованных детей с инородными телами дыхательных путей 33 ребенка были в возрасте от 7 меся-

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цев до 3 лет (71,7%), 8 детей в возрасте от 4 до 6 лет (17,4%) и 5 детей от 7 до 14 лет (10,9%). Инородными телами чаще всего являлись частицы пищи — у 47,8% пациентов (яблоко, морковь, рыбная кость, орехи), мелкие бусины, игрушки или их осколки — 37,5% пациентов, острые предметы (иглы, булавки, металлические скобки) — 14,7% пациентов. Инородные тела чаще всего находились в правом главном бронхе — у 17% пациентов. Инородные тела в левом главном бронхе — в 12,8% случаев; в левом нижнедолевом бронхе — в 6,4%; в правом нижнедолевом бронхе — в 4,3%. У 34% обследованных пациентов инородные тела не визуализировались, что связано с их самопроизвольной эвакуацией. *Заключение.* Чаще всего инородные тела дыхательных путей встречаются у детей в возрасте до трех лет. Самая частая локализация — правый бронх. Треть пациентов имеют осложнения в виде трахеобронхита.

Ключевые слова: *инородное тело; дыхательные пути; диагностика; лечение; дети.*

INTRODUCTION

Инородные тела в дыхательных путях детей являForeign bodies in the respiratory tract in children are a frequent pathology that threatens the child's life and requires immediate assistance [1–4]. The most dangerous localisaton is the larynx and trachea. Foreign bodies in this area can completely block air access. If immediate assistance is not rendered, death occurs within 1–2 minutes [5, 6].

Despite the progress made in the diagnostics and treatment of children with foreign bodies in the respiratory tract, this problem remains very urgent. Causes due to which foreign bodies can get into the respiratory tract are talking while eating, unexpected deep breathing when a child was frightened, sudden fell, laughing, scramming [1].

The main signs of foreign body ingestion are cough, wheezing, skin cyanosis, dyspnea, etc. All these signs may be present as well as each of them separately [1].

Foreign bodies of the respiratory tract by its nature can be organic or inorganic — both nails, needles and fruit seeds and living organisms (leeches, worms, flies, wasps, etc.) [7, 8].

Foreign bodies in the trachea, as a rule, are mobile (balloting foreign bodies). Bronchial foreign bodies, if their size is smaller than the bronchial lumen, can migrate from one bronchus to another [9].

If a foreign body wedges into the main bronchus, it causes irritation of the mucous membrane and respiratory disturbance. Such foreign bodies cause inflammatory changes in the mucosa and bronchial wall — from catarrhal inflammation and edema to ulceration and perforation of the bronchial wall leading to mediastinal emphysema. Organic foreign bodies are the most aggressive with respect to the caused disorders and dysfunctions, which decompose, swell (e.g., beans, peas) and close the lumen of the bronchus, pushing the walls apart and breaking their integrity [1].

Diagnosis of foreign bodies in the bronchi is more difficult compared to the diagnosis of foreign bodies in the trachea. As the bronchial lumen decreases, the recognition of foreign bodies becomes more difficult. Sometimes foreign bodies in the respiratory tract may not manifest themselves at all. The main diagnostic tools are tracheobronchoscopy and X-ray [10, 11].

Treatment of foreign bodies in the bronchi consists in removal of foreign bodies [12–17].

Small foreign bodies of organic nature can disintegrate, liquefy and self-liquidate. Inflammatory complications are possible. Usually attempts to remove foreign bodies from trachea and bronchi are performed by tracheobronchoscopy. After removal of foreign bodies, some patients need rehabilitation measures, and after removal of complicated foreign bodies — in the prophylactic use of antimicrobial drugs [18].

The prognosis depends largely on the age of the patient. It is most serious in infants and children of the first years of life.

AIM

To describe the localization, nature and endoscopic pattern of foreign bodies in airway in children of different age groups.

MATERIALS AND METHODS

Case histories and bronchoscopy protocols of 46 patients of the endoscopy department of Leningrad regional state budgetary health care institution "Children's Clinical Hospital" (St. Petersburg) for the period from 2019 to 2021 were studied. The age of the children was from 7 months to 14 years. Endoscopic examination was performed with Pentax EB-1570K and Pentax-EB-1170K video bronchoscopes; retrieval of foreign body was performed with a Storz rigid bronchoscope.

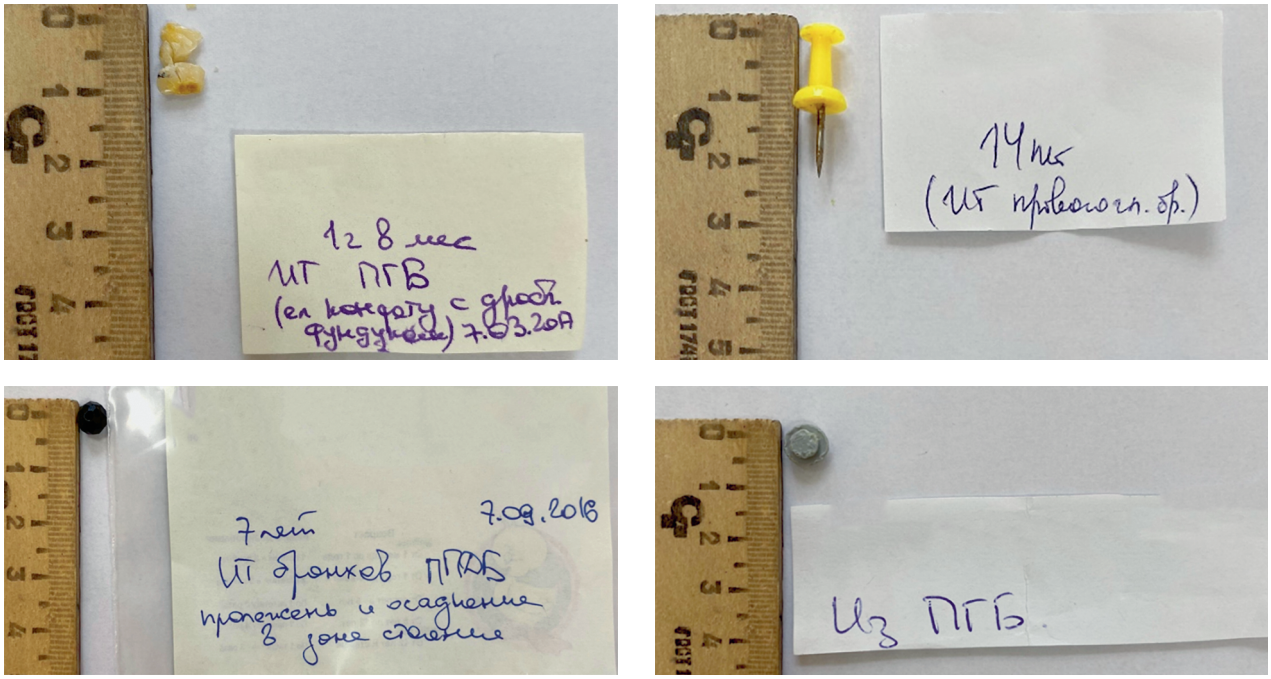

Fig. 1. Detection of foreign bodies during endoscopic examination
Рис. 1. Выявленные инородные тела при эндоскопическом исследовании

RESULTS

In 46 examined children with foreign bodies in the respiratory tract, 33 children were aged from 7 months to 3 years (71.7%), 8 children were aged from 4 to 6 years (17.4%) and 5 children were aged from 7 to 14 years (10.9%). Foreign bodies were most often food particles — in 47.8% of patients (apple, carrot, fish bone, nuts), small beads, toys or their fragments — in 37.5% of patients, sharp objects (needles, pins, metal staples) — in 14.7% of patients. The detected foreign bodies are presented in Figure 1.

Foreign bodies of the respiratory tract were located in various places: in the nasal passages, larynx, trachea, bronchi, and in the tissue of the lung. The most dangerous place was the larynx and trachea, when foreign bodies blocked air access and the patient was admitted for emergency care. Foreign bodies in the main and lobe bronchi are also very dangerous. In our study, foreign bodies were most often located in the right main bronchus — in 17% of patients, which is explained by the peculiarity of the bronchopulmonary system in children [19]. Foreign bodies in the left main bronchus were found in 12.8% of cases; in the left lower lobe bronchus — in 6.4%; in the right lower lobe bronchus — in 4.3%. In 34% of the examined patients foreign bodies were not visualized, which is associated with their spontaneous evacuation. The examination was most often performed in some time (days, weeks) after aspiration, when inflammation developed (32.6%): more often catarrhal, mucopurulent, purulent endobronchitis, which was the reason for bronchoscopy. This situation is rather typical, since it is known that foreign bodies may not manifest themselves at all during the first time after aspiration [20].

CONCLUSION

Prevention of aspiration of foreign body in young children is necessary.

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OBJECTIVE INDICATORS OF THE QUALITY OF MEDICAL CARE FOR PATIENTS WITH ACUTE APPENDICITIS

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Abstract. The article analyzes the timing of hospitalization, therapeutic and diagnostic measures in the hospital and morphological changes in remote appendix in patients with acute appendicitis treated at the St. Petersburg research Institute of emergency care I.I. Dzhanelidze in 2017. These indicators can serve as objective criteria for the quality of medical care in patients with acute appendicitis.

Key words: *quality of medical care; acute appendicitis; objective criteria of quality of medical care.*

ОБЪЕКТИВНЫЕ ПОКАЗАТЕЛИ КАЧЕСТВА ОКАЗАНИЯ МЕДИЦИНСКОЙ ПОМОЩИ БОЛЬНЫМ ОСТРЫМ АППЕНДИЦИТОМ

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Резюме. В статье проанализированы сроки госпитализации, проведения лечебно-диагностических мероприятий в стационаре и морфологические изменения удаленных червеобразных отростков у больных острым аппендицитом, пролеченных в Санкт-Петербургском научно-исследовательском институте скорой помощи им. И.И. Джанелидзе в 2017 году. Эти показатели могут служить объективными критериями качества оказания медицинской помощи у больных острым аппендицитом.

Ключевые слова: *качество оказания медицинской помощи; острый аппендицит; объективные критерии качества оказания медицинской помощи.*

INTRODUCTION

Nowadays, an assessment of the quality of medical care is carried out in a formalized way according to the data of medical records. It is difficult to separate the defects of records in the case history from the real defects of the treatment process. At the same time, there are objective criteria of the quality of medical care: terms of hospi-

talization, examination and treatment, results of histological examination of removed biomaterial and results of pathological and anatomical examination in case of lethal outcome. These criteria are especially relevant for assessing the quality of medical care in patients with acute appendicitis (AA), in whom active surgical tactics are used [1].

Improvement of the emergency medical service has reduced the time of hospitalization of patients with suspected AA. For example, in 2017, 4674 patients with AA were treated in St. Petersburg hospitals. Some of them, 1529 (32.7%) patients, were hospitalized in the first 6 hours from the onset of the disease [2]. There is a probability of an increase in the number of removed appendix with catarrhal changes due to the early terms of surgery from the onset of the disease [1].

AIM

To study the terms of hospitalization, therapeutic and diagnostic measures in hospital in patients with AA, to analyze morphological changes of the removed appendices, which can be used as objective criteria of the quality of medical care.

MATERIALS AND METHODS

We analyzed the electronic case histories of patients treated at the St. Petersburg research institute of emergency medicine named after I.I. Janelidze and discharged with diagnoses of appendix in 2017, which corresponded to ICD-10 codes K35.2, K35.3, K35.3, and K35.3. The required data were obtained using the medical information system "Ariadna".

The time of admission to the Research Institute from the onset of the disease was determined using the recorded anamnesis morbi. For statistical analysis, rates were presented in decimal system with rounding to tenths of an hour. If a time interval was specified in the electronic case history, the corresponding arithmetic mean was used.

The duration of examination and observation before surgery was determined based on the time of admission to the hospital and the time of the start of surgery. The time from the onset of the disease to the start of surgery was determined by summarizing the indicators described above. Information about complications of AA at the time of surgical treatment was obtained by studying operation protocols. The results of histological examination were obtained by studying the journals of the pathology department of the Research Institute.

RESULTS AND DISCUSSION

In 2017, 384 patients with suspected acute appendicitis were delivered to the Research Institute. All patients were hospitalized in the inpatient emergency department on admission. Subsequently, in 316 (82.3%) cases, diseases of appendix were verified. The patients were aged between 19 and 91 years, with a mean age of 36.2±13.63 years. The patients included 188 (59.5%) males and 128 (40.5%) females.

The time to hospitalization from onset ranged from 1.5 to 264.0 hours (11 days), with a median of 14.0 hours, a mode of 24.0 hours, a 75% persentile of 24.0 hours, and a 25% persentile of 7.0 hours.

The time from onset of disease to surgery ranged from 6.5 to 268.7 hours, median — 22.0 hours, mode 48.0 hours, 75% persentile — 35.9 hours, and 25% persentile — 15.5 hours.

Appendectomy was performed laparoscopically in 271 (85.8%) cases, in 20 (6.3%) cases diagnostic laparoscopy with subsequent access conversion was performed. 22 (7.0%) patients were operated immediately by open appendectomy. In 1 (0.3%) case diagnostic laparoscopy without appendectomy was performed due to appendiceal infiltration. Conservative therapy of appendiceal infiltration was performed in 2 (0.6%) cases.

Histological examination of the removed appendix revealed catarrhal appendicitis in 23 (7.3%) cases, phlegmonous appendicitis in 232 (73.4%) cases, gangrenous appendicitis in 48 (15.2%) cases, and chronic appendicitis in 1 (0.3%) case. Dense appendiceal infiltration were diagnosed in 3 (0.9%) cases, which were treated conservatively. Tumors were detected in 6 (1.9%) cases: carcinoid (3) and mucinous adenocarcinoma (1), sigmoid colon cancer with infiltrate formation (1), non-Hodgkin's lymphoma (1).

Catarrhal appendicitis was verified in 23 (7.3%) cases. There were 11 (47.8%) men and 12 (52.2%) women among the operated patients. Patients were aged from 19 to 63 years, with an average age of 32.7±11.83 years. The time from onset to hospitalization ranged from 2.75 to 120.0 hours, median — 14.0 hours, mode — 6.0 hours, 75% persentile — 24.0 hours, and 25% persentile — 6.0 hours. The duration of examination and follow-up from referral to surgery ranged from 2.68 to 35.0 hours, median — 7.0 hours, mode — none, 75% persentile — 10.9 hours, and 25% persentile — 4.5 hours. The time from disease onset to surgery was from 7.5 to 120 hours, median — 24.0 hours, mode — 36.0 hours, 75% persentile — 36.0 hours, 25% persentile — 16.8 hours.

Phlegmonous and phlegmonous-ulcerous appendicitis were verified by histological examination in 232 (73.4%) cases. The operated patients in this group were 141 (60.8%) males and 91 (39.2%) females. The patients were aged from 19 to 85 years, with an average age of 34.6±12.01 years.

Time of admission to the Research Institute ranged from 1.5 to 264 hours from onset, median — 12.8 hours, mode — 24.0, 75% persentile — 24.0 hours, and 25% persentile — 6.9 hours. Times of preoperative examination and observation ranged from 1.9 to 47.0 hours, median — 6.6 hours, mode — 4.0, 75% persentile — 10.3 hours, and 25% persentile — 4.6 hours.

Summary, operative time from onset ranged from 6.5 to 264.0 hours, median — 20.5 hours, mode — 48.0 hours, 75% pesentile — 31.0 hours, and 25% persentile — 15.0 hours.

Gangrenous appendicitis was verified with use of histological examination in 48 (15.2%) cases. There were 30 (62.5%) males and 18 (37.5%) females. The patients were aged from 19 to 80 years, with an average age of 43.1±16.53 years. The time of admission to the Research Institute from onset ranged from 3.0 to 168.0 hours, with a median of 27.0 hours, a mode of 48.0 hours, a 75% persentile of 48.0 hours, and a 25% persentile of 12.8 hours. The time from examination and follow-up to surgery ranged from 2.8 to 23.5 hours, median — 6.8 hours, mode — 9 hours, 75% persentile — 9.1 hours, and 25% persentile — 4.7 hours. The time from onset to surgery ranged from 10.0 to 176.0 hours, median — 33.3 hours, mode 48.0 — hours, 75% persentile — 52.0 hours, and 25% persentile — 23.0 hours. Complicated forms of gangrenous appendicitis were diagnosed intraoperatively in 41 (85.4%) cases.

Among 316 patients with diseases of appendix, 128 (40.5%) cases of intra-abdominal complications were diagnosed intraoperatively. In catarrhal appendicitis there were no intra-abdominal complications.

Localized unconfined peritonitis was a complication of gangrenous appendicitis in 13 cases, and phlegmonous appendicitis — in 46 cases, in total detected in 59 cases. The patients included 38 (64.4%) males and 21 (35.6%) females. The age of the patients ranged from 19 to 80 years, with an average age of 37.5±14.84 years. Hospitalization time from onset ranged from 2.0 to 120.0 hours, with a median of 21.5 hours, a mode of 24.0 hours, 75% persentile of 24.0 hours, and 25% persentile of 11.4 hours. Preoperative examination and follow-up times ranged from 1.9 to 22.8 hours, median — 6.4 hours, mode — 4.0 hours, 75% persentile — 9.4 hours, and 25% persentile — 4.4 hours. Thus, the time from onset to surgery ranged from 6.7 to 132.2 hours, median — 27.0 hours, mode — 72.0 hours, 75% persentile — 36.0 hours, and 25% persentile — 18.4 hours.

In gangrenous appendicitis localized peritonitis was serous in 9 cases, serous-fibrinous — in 2 cases, fibrinous-purulent — in 1 case and purulent — in 1 case. In phlegmonous appendicitis, serous localized unconfined peritonitis was detected in 34 cases, serous-fibrinous — in 8 cases, fibrinous-purulent — in 2 cases, purulent — in 1 case.

Thus, localized serous unconfined peritonitis was the most frequent — 43 cases, which amounted 33.6% of all complications in patients with AA. The majority of patients (37) were operated laparoscopically, in 5 cases the operation was performed by traditional access, in 4 cases — by laparotomy. In the postoperative period, there were 2 cases of local complications of the postoperative wound.

Diffuse peritonitis was diagnosed in 13 cases, including gangrenous appendicitis in 10 cases and phlegmonous appendicitis in 3 cases. Serous-fibrinous diffuse peritonitis was diagnosed in 4 cases, fibrinous-purulent — in 4 cases, purulent — in 6 cases and fecal — in 1 case. The age of patients was from 21 to 67 years, with a mean age of 44.5±13.84 years. The time of hospitalization from onset ranged from 6.0 to 96.0 hours, median — 31.0 hours, mode — 9 hours, 75% persentile — 48.0 hours, and 25% persentile — 9.0 hours. The time from admission to hospital to surgery was 2.6 to 11.2 hours, median — 4.9 hours, mode — no, 75% persentile — 6.6 hours, and 25% persentile — 4.3 hours. The time from onset to surgery ranged from 11.0 to 100.4 hours, median — 34.0 hours, mode — 48.0 hours, 75% persentile — 48.0 hours, and 25% persentile — 17.0 hours. Laparoscopic surgery was performed in 4 cases of diffuse peritonitis, and 1 case underwent sanation re-laparoscopy. Laparotomy was required in 9 cases.

Appendiceal infiltrates were diagnosed in 67 cases. The patients were aged from 20 to 80 years, with an average age of 43.2±15.5 years. Hospitalization time from onset ranged from 3.0 to 264 hours, median — 24.0 hours, mode — 48.0 hours, 75% persentile — 72.0 hours, 25% persentile — 11.4 hours. The time from hospitalization to surgery was 1.9 to 34 hours, median — 6.8 hours, mode — 5.8 hours, 75% persentile — 12.0 hours, and 25% persentile — 4.7 hours. The time to surgery from onset ranged from 6.5 to 268.7 hours, median — 30.8 hours, mode —

48 hours, 75% persentile — 56.7 hours, 25% persentile — 20.5 hours.

Conservative treatment without surgery was performed in 2 cases, diagnostic laparoscopy followed by conservative therapy in 1 case. In the remaining 64 cases infiltrate separation with appendectomy was performed: in 4 cases the operation was immediately performed by traditional access according to Diakonov-Volkovich-McBourney. In 13 cases laparoscopic operation with subsequent conversion to laparotomy was performed. Laparoscopic surgery was performed in 47 cases.

On the one hand, early hospitalization is an indicator of the success of the emergency medical service and reduces the risk of developing complicated forms of AA. On the other hand, early hospitalization complicates diagnostics and may lead to an increase in the number of removal appendices with catarrhal changes.

However, an observation in doubtful cases compensated for early hospitalization and reduced the proportion of operations for catarrhal appendicitis to 7.3%. At the same time, there was only 1 (0.3%) case of removal of appendix with signs of chronic appendicitis only. The number of appendectomies for catarrhal appendicitis is slightly higher than the average level of indicators, which reaches 1% in laparoscopic surgeries due to the active tactics adopted rather than the timing of hospitalization [3–5]. In addition, the total proportion of removed appendices with catarrhal and chronic changes corresponds to the literature data [3, 4].

CONCLUSION

The terms of hospitalization, performance of diagnostic and therapeutic measures, as well as the results of histological examination of removed appendices can be used as criteria of the quality of medical care in patients with AA. These criteria are objective and allow differentiating between defects in medical records and real defects in the process of medical care.

Early hospitalization of patients with suspected acute appendicitis does not increase the number of removed appendices with catarrhal and chronic changes. This is achieved due to the tactics of dynamic observation in patients with suspected acute appendicitis. Hospitalization of patients with suspected acute appendicitis to an inpatient emergency department for observation allows to avoid overloading specialized surgical departments with non-core patients.

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TRUKHMANOV MIKHAIL SERGEEVICH — 70 YEARS OLD

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ТРУХМАНОВУ МИХАИЛУ СЕРГЕЕВИЧУ — 70 ЛЕТ

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Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2

In 2022, Mikhail Sergeevich Trukhmanov, Candidate of Medical Sciences, Associate Professor of the Department of Propaedeutics of Chilhood Diseases with a course in general child care of St. Petersburg State Pediatric Medical University, turned 70 years old.

Mikhail Sergeevich is a talented pediatrician, experienced lecturer, dean and manager beloved by students.

Mikhail Sergeevich began his professional path after graduating from the Leningrad Pediatric Medical Institute in clinical residency, and then postgraduate studies at the Department of Children's Infectious Diseases in his alma mater. In 1981, after defending his PhD thesis, he was awarded the title of Candidate of Medical Sciences, and in 1995 — the academic title of Associate Professor.

After defending his PhD thesis, Mikhail Sergeevich worked as an assistant at the Department of Pathological Physiology of LPMI until 1985 year, then continued his work at the Department of Children's Diseases No. 1 of LPMI, firstly as an assistant and since 1993 as an associate professor of the department.

Mikhail Sergeevich approached his teaching work with extensive experience as a clinician. He successfully conducted practical classes with students of 4, 5, 6 courses on cycles "Hematology", "Clinic — hospital", "Maternity hospital", "Second stage of nursing premature" and with students of 5 and 6 courses on cycle "Work of pediatrician in children's city clinic", supervised practice of students of 5 courses, gave lectures for students of 5 and 6 courses, which were very popular among them.

In 2001–2008, he held the position of assistant professor at the Department of Polyclinic Pediatrics of St. Petersburg State Pediatric Medical Academy, where he conducted classes for 5th and 6th year students on the cycle «Work of a pediatrician in a children's city clinic», supervised the practice of 5th year students, and gave lectures for 6th year students. Since 2008, he has been an associate professor at the Department of Propaedeutics of Childhood Diseases with the course in general child care of St. Petersburg State Pediatric Medical University. He conducts practical classes with students of the 3rd year of pediatric faculty and students of the 5th year of general medical faculty.

Mikhail Sergeevich's clinical practice is extensive: since 1993 he has been conducting consultative appointments as a pediatrician on the basis of the Department in city clinics. For a long time, he cooperated with medical departments of insurance companies "Progress-Neva" and "Renaissance".

For many years he has been the Dean of the Faculty of Pediatrics. Several generations of pediatricians are grateful to Mikhail Sergeevich for his understanding, cordiality, attentive and sensitive attitude to solving issues that arose during the study. The staff of the department highly appreciates the professionalism, sensitivity and kind attitude of Mikhail Sergeevich and warmly congratulates talented teacher, pediatrician, brilliant manager and just a wonderful person on his anniversary.

ПРАВИЛА ДЛЯ АВТОРОВ

Утв. приказом ректора
ФГБОУ ВО СПбГПМУ Минздрава России от 15.03.2021 г.

НАСТОЯЩИЕ ПРАВИЛА ДЛЯ АВТОРОВ ЯВЛЯЮТСЯ ИЗДАТЕЛЬСКИМ ДОГОВОРОМ

Условия настоящего Договора (далее «Договор») являются публичной офертой в соответствии с п. 2 ст. 437 Гражданского кодекса Российской Федерации. Данный Договор определяет взаимоотношения между редакцией журнала «Children's medicine of the North-West (Детская медицина Северо-Запада)» (далее по тексту «Журнал»), зарегистрированного Федеральной службой по надзору в сфере связи, информационных технологий и массовых коммуникаций (РОСКОМНАДЗОР), Пи № ФС77-805334 от 1 марта 2021 г., именуемой в дальнейшем «Редакция» и являющейся структурным подразделением ФГБОУ ВО СПбГПМУ Минздрава России, и автором и/или авторским коллективом (или иным правообладателем), именуемым в дальнейшем «Автор», принявшим публичное предложение (оферту) о заключении Договора.

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Для всех статей, имеющих DOI, индекс необходимо указывать в конце библиографического описания.

По новым правилам, учитывающим требования международных систем цитирования, библиографические списки (References) входят в англоязычный блок статьи и, соответственно, должны даваться не только на языке оригинала, но и в латинице (романским алфавитом). Поэтому авторы статей должны давать список литературы в двух вариантах: один на языке оригинала (русскоязычные источники кириллицей, англоязычные латиницей), как было принято ранее, и отдельным блоком тот же список литературы (References) в романском алфавите для Scopus и других международных баз данных, повторяя в нем все источники литературы, независимо от того, имеются ли среди них иностранные. Если в списке есть ссылки на иностранные публикации, они полностью повторяются в списке, готовящемся в романском алфавите.

В романском алфавите для русскоязычных источников требуется следующая структура библиографической ссылки: автор(ы) (транслитерация), перевод названия книги или статьи на английский язык, название источника (транслитерация), выходные данные в цифровом формате, указание на язык статьи в скобках (in Russian).

Технология подготовки ссылок с использованием системы автоматической транслитерации и переводчика.

На сайте http://www.translit.ru можно бесплатно воспользоваться программой транслитерации русского текста в латиницу. Программа очень простая.

1. Входим в программу Translit.ru. В окошке «варианты» выбираем систему транслитерации BGN (Board of Geographic Names). Вставляем в специальное поле весь текст библиографии на русском языке и нажимаем кнопку «в транслит».

2. Копируем транслитерированный текст в готовящийся список References.

3. Переводим с помощью автоматического переводчика название книги, статьи, постановления и т.д. на английский язык, переносим его в готовящийся список. Перевод, безусловно, требует редактирования, поэтому данную часть необходимо готовить человеку, понимающему английский язык.

4. Объединяем описания в соответствии с принятыми правилами и редактируем список.

5. В конце ссылки в круглых скобках указывается (in Russian). Ссылка готова.

Примеры транслитерации русскоязычных источников литературы для англоязычного блока статьи

Книга: Avtor (y) Nazvanie knigi (znak tochka) [The title of the book in english] (znak tochka) Mesto izdaniya (dvoetochie) Nazvanie izdatel'stva (znak tochka s zapyatoy) god izdaniya.

Preobrazhenskiy B. S., Temkin Ya. S., Likhachev A. G. Bolezni ukha, gorla i nosa. [Diseases of the ear, nose and throat]. M.: Meditsina; 1968. (in Russian).

Radzinskiy V.E., ed. Perioneologiya: uchebnoe posobie. [Perineology tutorial]. M.: RUDN; 2008. (in Russian).

Глава из книги: Avtor (y) Nazvanie glavy (znak tochka) [The title of the article in english] (znak tochka) In: Avtor (y) Nazvanie knigi (znak tochka) Mesto izdaniya (dvoetochie) Nazvanie izdatel'stva (znak tochka s zapyatoy) god izdaniya]. (dvoetochie) stranisi ot i do.

Korobkov G. A. Temp rechi. [Rate of speech]. In.: Sovremennye problemy fiziologii i patologii rechi: sb. tr. T. 23. M.; 1989: 107–11. (in Russian).

Статья из журнала: Avtor (y) Nazvanie stat'I (znak tochka) [The title of the article in english] (znak tochka) Nazvanie zhurnala (znak tochka) god izdaniya (znak tochka s zapyatoy) tom (esli est' v kruglykh skobkakh nomer zhurnala) zatem (znak dvoetochie) stranitsy ot i do.

Kiryushchenkov A. P., Sovchi M. G., Ivanova P. S. Polikistoznye yaichniki. [Polycystic ovary]. Akusherstvo i ginekologiya. 1994; N 1: 11–4. (in Russian).

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Babiy A. I., Levashov M. M. Novyy algoritm nakhozhdeniya kul'minatsii eksperimental'nogo nistagma (minimetriya). [New algorithm of finding of the culmination experimental nystagmus (minimetriya)]. III s'ezd otorinolaringologov Resp. Belarus': tez. dokl. Minsk; 1992: 68–70. (in Russian).

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Petrov S. M. Vremya reaktsii i slukhovaya adaptatsiya v norme i pri perifericheskikh porazheniyakh slukha. [Time of reaction and acoustical adaptation in norm and at peripheral defeats of hearing]. PhD thesis. SPb.; 1993. (in Russian).

Описание Интернет-ресурса

Shcheglov I. Naskol'ko velika rol' mikroflory v biologii vida-khozyaina? [How great is the microflora role in type-owner biology?]. Zhivye sistemy: nauchnyy elektronnyy zhurnal. Available at: http://www.biorf.ru/catalog.aspx?cat_id=396&d_no=3576 (accessed 02.07.2012). (in Russian).

ОТВЕТСТВЕННОСТЬ ЗА ПРАВИЛЬНОСТЬ БИБЛИОГРАФИЧЕСКИХ ДАННЫХ НЕСЕТ АВТОР.

Остальные материалы предоставляются либо на русском, либо на английском языке, либо на обоих языках по желанию.

СТРУКТУРА ОСНОВНОГО ТЕКСТА СТАТЬИ

Введение, изложение основного материала, заключение, литература. Для оригинальных исследований — введение, методика, результаты исследования, обсуждение результатов, литература (IMRAD).

В разделе «методика» обязательно указываются сведения о статистической обработке экспериментального или клинического материала. Единицы измерения даются в соответствии с Международной системой единиц — СИ. Фамилии иностранных авторов, цитируемые в тексте рукописи, приводятся в оригинальной транскрипции.

Объем рукописей.

Объем рукописи обзора не должен превышать 25 стр. машинописного текста через два интервала, 12 кеглем (включая таблицы, список литературы, подписи к рисункам и резюме на английском языке), поля не менее 25 мм. Нумеруйте страницы последовательно, начиная с титульной. Объем рукописи статьи экспериментального характера не должен превышать 15 стр. машинописного текста; кратких сообщений (писем в редакцию) — 7 стр.; отчетов о конференциях — 3 стр.; рецензий на книги — 3 стр. Используйте колонтитул — сокращенный заголовок и нумерацию страниц, для помещения вверху или внизу всех страниц статьи.

Иллюстрации и таблицы. Число рисунков рекомендуется не более 5. В подписях под рисунками должны быть сделаны объяснения значений всех кривых, букв, цифр и прочих условных обозначений. Все графы в таблицах должны иметь заголовки. Повторять одни и те же данные в тексте, на рисунках и в таблицах не следует. **Все надписи на рисунках и в таблицахприводятся на русском и английском языках.**

Рисунки, схемы, фотографии должны быть представлены в точечных форматах tif, bmp (300–600 dpi), или в векторных форматах pdf, ai, eps, cdr. При оформлении графических материалов учитывайте размеры печатного поля Журнала (ширина иллюстрации в одну колонку — 90 мм, в 2 — 180 мм). Масштаб 1:1.

В конце каждой статьи обязательно указываются вклад авторов в написание статьи, источники финансирования (если имеются), отсутствие конфликта интересов, наличие согласия на публикацию со стороны пациентов.

РЕЦЕНЗИРОВАНИЕ

Статьи, поступившие в редакцию, обязательно рецензируются. Если у рецензента возникают вопросы, то статья с комментариями рецензента возвращается Автору. Датой поступления статьи считается дата получения Редакцией окончательного варианта статьи. Редакция оставляет за собой право внесения редакторских изменений в текст, не искажающих смысла статьи (литературная и технологическая правка).

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АДРЕС РЕДАКЦИИ

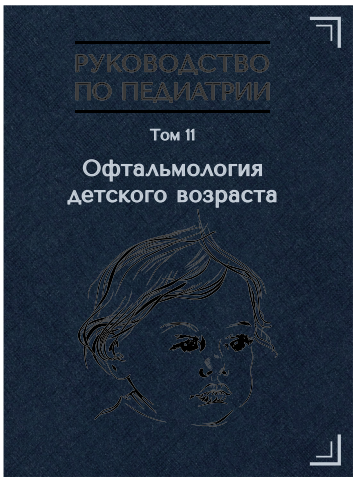
194100, Санкт-Петербург, Литовская ул., 2
e-mail: lt2007@inbox.ru.

Сайт журнала: http://ojs3.gpmu.org/index.php/childmed/index.

ИЗДАТЕЛЬСТВО ПЕДИАТРИЧЕСКОГО УНИВЕРСИТЕТА ПРЕДСТАВЛЯЕТ

Руководство по педиатрии. ОФТАЛЬМОЛОГИЯ ДЕТСКОГО ВОЗРАСТА

Редакционная коллегия тома: Д.О. Иванов, В.В. Бржеский



Том 11 «Руководства по педиатрии» отражает современный уровень развития офтальмологии детского возраста. Книга содержит актуальную информацию о современных методах диагностики и лечения заболеваний глаз у детей. Отдельные разделы посвящены клиническим рекомендациям по основным синдромам и заболеваниям.

Издание предназначено офтальмологам, педиатрам и представителям других медицинских дисциплин, а также студентам старших курсов медицинских вузов.

Твердый переплет, цветные иллюстрации, 344 страницы.

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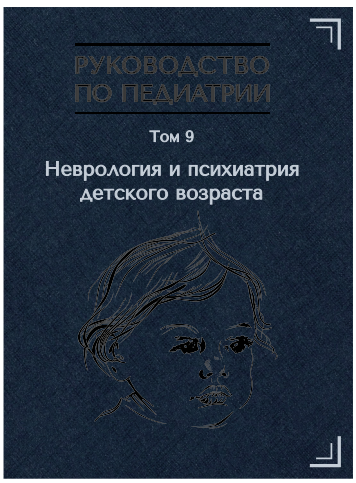
Руководство по педиатрии. НЕВРОЛОГИЯ И ПСИХИАТРИЯ ДЕТСКОГО ВОЗРАСТА

Редакционная коллегия тома: Д.О. Иванов, В.И. Гузева, С.В. Гречаный



Том 9 «Руководства по педиатрии» отражает современный уровень развития неврологии и психиатрии детского возраста. Книга содержит актуальную информацию о современных методах диагностики и лечения заболеваний нервной системы и психических расстройствах. Отдельные разделы посвящены клиническим рекомендациям по основным синдромам и заболеваниям.

Руководство предназначено неврологам, нейрохирургам, психиатрам, психотерапевтам и представителям других медицинских дисциплин, а также студентам старших курсов медицинских вузов.

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