ISSN 2079-7850 (Print)
ISSN 2587-6252 (Online)

Педиатр

Научно-практический журнал для врачей

https://journals.eco-vector.com/pediatr

Pediatrician (St. Petersburg)

Том (Volume) 12
Выпуск (Issue) 2
2021

2021
ТОМ 12 Volume
Выпуск 2 Issue

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Рецензируемый научно-практический журнал

ПЕДИАТР

Pediatrician (St. Petersburg)

Основан в 2010 году в Санкт-Петербурге

ISSN 2079-7850

eISSN 2587-6252

Key title: Pediatr (Saint Petersburg)
Abbreviated key title: Pediatr (St.-Peterbg.)

Выходит 6 раз в год

Журнал реферируется РЖ ВИНИТИ

Учредители:

ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России,

ООО «Эко-Вектор»

Журнал зарегистрирован Федеральной службой по надзору в сфере массовых коммуникаций, связи и охраны культурного наследия ПИ № ФС77-69634 от 05 мая 2017 г.

Журнал входит в Перечень ведущих научных журналов и изданий ВАК, в которых должны быть опубликованы основные результаты диссертаций на соискание ученых степеней кандидата и доктора наук.

Распространяется по подписке.

Электронная версия —
http://www.pediatr.gpma.ru
http://elibrary.ru
http://journals.eco-vector.com/index.php/pediatr
Печатная версия по катологу агентства «Роспечать» **70 479**

Издатель, учредитель:

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2, Litovskaya St., St. Petersburg, 194100,
Russia. Tel/Fax: +7 (812) 784-97-51.

Формат 60 × 90/8. Усл.-печ. л. 12.
Тираж 500 экз. Цена свободная.
Оригинал-макет изготовлен
ООО «Эко-Вектор»

Отпечатано в ООО «Типография Фурсова».
196105, Санкт-Петербург, ул. Благодатная, д. 69.
Тел.: +7(812) 646-33-77.
Заказ 1-4602-Е. Подписано в печать 30.04.2021.

На обложке — фрагмент скульптуры «Доктор и больной», автор — академик И.Я. Гинцбург (1859–1939), добрый друг Юлии Ароновны Менделевой (ректора ЛПМИ с 01.04.1925 по 1949 г.) и ее семьи.

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DOI: https://doi.org/10.17816/PED1225-12

CYTOKINE STATUS IN MIDDLE-AGED MEN WITH ACUTE CORONARY SYNDROME AFTER CORONARY ARTERY STENTING

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For citation: Gostimskiy VA, Vasilenko VS, Kurnikova EA, Shenderov SV, Gurina OP. Cytokine status in middle-aged men with acute coronary syndrome after coronary artery stenting. *Pediatrician (St. Petersburg)*. 2021;12(2):5-12. https://doi.org/10.17816/PED1225-12

Received: 05.02.2021 Revised: 22.03.2021 Accepted: 23.04.2021

Background. Inflammatory cytokines and growth factors are involved in various mechanisms of coronary artery disease. Clinical studies have shown the correlation between the increase in the level of proinflammatory cytokines and the severity of coronary artery disease, while the data on the role of proinflammatory interleukin IL-8 and anti-inflammatory interleukin IL-4 are contradictory.

The aim of the study is to assess the levels of proinflammatory cytokines (IL-8, TNF-α) and anti-inflammatory interleukin (IL-4) in patients with various forms of coronary artery disease who underwent coronary artery stenting.

Materials and methods. By the method of enzyme-linked immunosorbent assay, the levels of cytokines were determined in 30 patients with acute coronary syndrome who underwent primary stenting of the coronary arteries and in 24 patients with chronic coronary syndrome who had previously had myocardial infarction with stenting of an infarction-associated artery, who were admitted to the clinic for staged stenting of the coronary arteries.

Results. In patients with chronic coronary syndrome the levels of IL-4 a do not exceed the reference values, in patients with acute coronary syndrome the levels of IL-4 there was an increase 3,70 ± 0,24 and 240,85 ± 49,25 pg/ml, $p \leqslant 0{,}001$. In patients with chronic coronary syndrome the levels of IL-8 a do not exceed the reference values, in patients with acute coronary syndrome the levels of IL-8 there was an increase 7,34 ± 1,29 and 110,33 ± 27,67 pg/ml, $p \leqslant 0{,}001$.

Conclusion. Most likely the increase in the level of IL-4 has a compensatory character and, along with a slight increase in TNF-α, can be considered as a positive factor stabilizing the course of the disease. There may be some relationship between of the increase in the level of interleukins in patients with acute coronary syndrome on the degree of stenosis of the coronary arteries (90–95%) and impaired myocardial contractility was established.

Keywords: acute coronary syndrome; chronic coronary syndrome; stenting of coronary arteries; interleukin-4; interleukin-8; tumor necrosis factor alpha; myocardial infarction.

ЦИТОКИНОВЫЙ СТАТУС У МУЖЧИН СРЕДНЕГО ВОЗРАСТА С ОСТРЫМ КОРОНАРНЫМ СИНДРОМОМ ПОСЛЕ СТЕНТИРОВАНИЯ КОРОНАРНЫХ АРТЕРИЙ

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Для цитирования: Гостимский В.А., Василенко В.С., Курникова Е.А., Шендеров С.В., Гурина О.П. Цитокиновый статус у мужчин среднего возраста с острым коронарным синдромом после стентирования коронарных артерий // Педиатр. – 2021. – Т. 12. – № 2. – С. 5–12. https://doi.org/10.17816/PED1225-12

Поступила: 05.02.2021 Одобрена: 22.03.2021 Принята к печати: 23.04.2021

Актуальность. Воспалительные цитокины и факторы роста участвуют в различных механизмах развития ишемической болезни сердца. Клинические исследования показали корреляцию повышения уровня провоспалительных цитокинов с тяжестью ишемической болезни сердца, при этом данные о роли провоспалительного интерлейкина IL-8 и противовоспалительного интерлейкина IL-4 противоречивы.

Цель исследования — оценить уровни провоспалительных цитокинов (IL-8, TNF-α) и противовоспалительного интерлейкина (IL-4) у пациентов, страдающих различными формами ишемической болезни сердца, которым было выполнено стентирование коронарных артерий.

Материалы и методы. Методом твердофазного иммуноферментного анализа определены уровни цитокинов у 30 пациентов с острым коронарным синдромом, которым было выполнено первичное стентирование коронарных артерий, и у 24 — с хроническим коронарным синдромом, ранее перенесших инфаркт миокарда со стентированием инфаркт-связанной артерии, которые поступили в клинику для этапного стентирования коронарных артерий.

Результаты. Уровень IL-4 у больных хроническим коронарным синдромом находился в пределах референсных значений, в то время как у пациентов с острым коронарным синдромом отмечалось его повышение — 3,70 ± 0,24 и 240,85 ± 49,25 пг/мл, при $p \leqslant 0{,}001$. Уровень IL-8 у пациентов с хроническим коронарным синдромом также находился в пределах референсных значений, тогда как в группе с острым коронарным синдромом отмечалось его повышение — 7,34 ± 1,29 и 110,33 ± 27,67 пг/мл, при $p \leqslant 0{,}001$.

Заключение. Вероятнее всего повышение уровня IL-4 имеет компенсаторный характер и, наряду с незначительным повышением TNF-α, может рассматриваться как положительный фактор, стабилизирующий течение заболевания. Может существовать определенная зависимость между повышением уровня интерлейкинов у пациентов с острым коронарным синдромом от степени стенозирования коронарных артерий (90–95 %) и нарушения сократимости миокарда.

Ключевые слова: острый коронарный синдром; хронический коронарный синдром; стентирование коронарных артерий; интерлейкин-4; интерлейкин-8; фактор некроза опухоли альфа; инфаркт миокарда.

BACKGROUND

Cardiovascular system diseases currently rank first in mortality and disability in all economically developed countries [2, 4, 16].

Coronary heart disease (CHD) affects a large proportion of the population in industrialized countries and causes more than a third of deaths among people aged >35 years [14]. According to Federal State Statistics Service, as of June 22, 2019, in the structure of mortality from diseases of the blood circulatory system, more than half (52.6%) of the cases accounted for CHD in 2018 [24]. In the same year, myocardial infarction as the cause of death was recorded in 54,427 people (6.5% in the structure of mortality in diseases of the blood circulatory system). With the widespread introduction of invasive treatment for patients with CHD, mortality from myocardial infarction is decreasing [5]; however, its indicators in Russia exceed those in Europe and North America [4].

Risk factors for CHD include obesity, diabetes, hypertension, high levels of low-density lipoprotein (LDL), tobacco smoking, cocaine or amphetamine abuse, family history, chronic kidney disease, human immunodeficiency virus infection, autoimmune disorders, and anemia [11]. The main etiological factors in the CHD development include atherosclerosis, chronic inflammatory lesion with infiltration of mononuclear leukocytes, proliferation of vascular smooth muscle cells, and accumulation of extracellular matrix [13, 23].

Acute coronary pathology includes unstable angina, myocardial infarction (acute coronary syndrome, ACS) with and without ST segment elevation, and acute myocardial infarction, which differ in the degree of myocardial damage and level of cardiac markers [5].

Acute coronary pathology is most commonly caused by atherothrombosis, which is triggered by damage to the atherosclerotic plaque. Moreover, the initial degree of coronary artery stenosis can be different, in some cases not reaching hemodynamic significance. A less common cause is coronary artery vasospasm (a variant of Prinzmetal angina pectoris) caused by endothelial or vascular dysfunction [12].

Multivessel coronary artery disease (MVCAD) is defined as significant stenosis (>70%) of two or more large coronary arteries (≥2.5 mm in diameter) [8]. Approximately 40%–60% of patients with ST-segment elevation myocardial infarction have multivessel coronary disease [21, 22]. However, the strategy of myocardial revascularization in patients with MVCAD has not yet been ultimately determined. Simultaneous stenting of all hemodynamically significant stenoses of the coronary arteries or only infarction-related artery with subsequent stenting of hemodynamically significant stenoses within

the same hospitalization or staged revascularization continues to be a subject of discussion [7, 9]. A recent meta-analysis (which included 7423 patients from 10 randomized trials) confirmed a significant reduction in the incidence of major adverse cardiovascular events in patients with a history of complete coronary revascularization (CR) compared with infarction-related arterial revascularization. The significant decrease was mainly caused by the low rate of repeated revascularization in the CR group, and a decrease was more pronounced when CR was performed during ST-segment elevation myocardial infarction rather than in stages [20].

Inflammatory cytokines and growth factors are involved in various pathways of CHD, including transcription activator, mitogen-activated protein kinase, and SMAD (transcription factor family) [1, 10, 18]. Clinical studies have shown a direct correlation between an increase in the level of proinflammatory cytokines (interferon-γ, tumor necrosis factor [TNF]-α, and interleukin [IL]-2, IL-6, IL-9, and IL-17) and CHD severity, determined by coronary angiography. Data on the level of anti-inflammatory IL-4 in patients with CHD are contradictory [17]. Various studies have highlighted the ambiguous role of IL-8 as an indicator of CHD risk. IL-8 is a leukocyte chemoattractant that is also present in atherosclerotic plaque and can contribute to the development of plaque instability by increasing leukocyte extravasation and endothelial cell adhesion [3, 15]. Moreover, in ischemic tissues, IL-8 accelerates neovascularization and promotes angiogenesis. Some authors have reported that high levels of IL-8 cannot be considered a marker of the risk of cardiovascular diseases in the future, while they are associated with an increased risk of death, regardless of the underlying cause. The main properties of IL-8, i.e., being pro-inflammatory and anti-ischemic, noted in experimental studies may partially explain the discordant association of IL-8 with the risk of cardiovascular diseases associated with atherosclerosis [6, 19].

Thus, inflammatory biomarkers, in particular pro- and anti-inflammatory cytokines, play essential roles in the initiation and development of CHD. Their analysis can provide a better understanding of the mechanism of vascular lesions and offer the most objective markers for predicting outcomes of CHD treatment.

The study aimed to assess the levels of pro-inflammatory cytokines (IL-8 and TNF-α) and anti-inflammatory cytokines (IL-4) in patients with various forms of CHD, who underwent coronary artery stenting.

MATERIALS AND METHODS

The study was performed in accordance with Good Clinical Practice and the principles of the World Medical Association Declaration of Helsinki on Ethical Principles for Scientific Medical Research Involving Human Subjects, as amended in 2000. The study protocol was approved by the Ethics Committees of all participating centers. Written informed consent was obtained from all patients before inclusion in the study.

The study enrolled 54 male patients aged 52–59 years (ACS group) and those aged 45–59 years (chronic coronary syndrome [CCS] group). The exclusion criteria were type I and II diabetes mellitus, chronic kidney disease requiring renal replacement therapy, ongoing inflammatory diseases that could affect an additional change in the cytokine status, as well as vasospastic and non-coronarogenic CHD.

All patients examined were distributed into two groups. The ACS group included 30 (55.6%) male patients admitted to the clinic with a diagnosis of ACS that subsequently progressed to unstable angina pectoris, without a history of myocardial infarction, with a single-vessel coronary artery disease, who underwent primary stenting of the coronary arteries. The CCS group consisted of 24 (44.4%) male patients who were admitted to the clinic with CCS and had a history of ST-segment elevation myocardial infarction with revascularization of the infarct-dependent artery with drug-eluting stents within the previous 2–6 months. This group underwent staged (planned) stenting of hemodynamically significant stenoses.

All patients underwent a comprehensive clinical examination. Before coronary angiography, the blood levels of pro-inflammatory cytokines (TNF-α and IL-8) and anti-inflammatory interleukin (IL-4) were measured. The enzyme-linked immunosorbent

assay with the use of reagents (indirect fluorescent antibody [IFA]-IL-4, IFA-IL-8, and IFA-TNF-α] produced by Cytokin (St. Petersburg) was applied on the Uniplan apparatus (CJSC Picon, Russia). The degree of stenosis of the coronary arteries was assessed using the standard Stenosis Analysis software installed on GE Healthcare angiography (Chicago, IL, USA). The ejection fraction was calculated with a two-dimensional Echo-CG according to the Simpson method.

Obtained data were processed on a personal computer using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA). Student's *t*-test was used to assess the differences between the two groups of values of indicators with normal distribution. Differences were considered significant at $p \leq 0.01$.

RESULTS AND DISCUSSION

Patients from both groups were distributed according to the degree of stenosis and localization of coronary artery lesions. Circumflex artery stenosis was recorded more often in the CCS group than in the ACS group ($p \leq 0.01$). Moreover, 80%–90% stenosis of the coronary artery was diagnosed in 83% of the cases ($p \leq 0.01$). In the ACS group, 90%–95% stenosis of the coronary artery ($p \leq 0.01$) was revealed in 60%, anterior interventricular artery in 40%, and right coronary artery in 50% of all cases (Table 1).

The degree of stenosis was higher in patients with ACS and single-vessel coronary artery disease, who underwent primary stenting of the coronary arteries, than in patients with CCS having a history of ST-segment elevation myocardial infarction with revascularization of the infarction-dependent artery with drug-eluting stents within the previous 2–6 months (Table 1). Moreover, circumflex artery lesion was noted less often in the ACS group.

Left ventricular ejection fraction was preserved in all patients of the CCS group (54%–63%). The ACS group had preserved and an intermediate left ventricular ejection fraction (48%–62%). The average group value of the ejection fraction in the ACS group with unstable angina pectoris was significantly lower than in the CCS group with stable angina pectoris (50.5 ± 0.7 versus $59 \pm 0.6\%$) ($p \leq 0.001$). Impaired myocardial contractility was recorded in 18 (60%) patients of the ACS group

Table 1 / Таблица 1

The degree of stenosis coronary arteries in different patients groups with acute coronary syndrome and chronic coronary syndrome

Степень стеноза коронарных артерий в группах пациентов с острым коронарным синдромом и хроническим коронарным синдромом

The degree of stenosis coronary arteries / Степень стеноза коронарных артерий	Group / Группа	Left anterior descending artery / Передняя межжелудочковая артерия	Left circumflex artery / Огибающая артерия	Right coronary artery / Правая коронарная артерия	Outcome / Итого
70–80%	1	3 (10%)	0	3 (10%)	6 (20%)
	2	0	0	0	0
80–90%	1	3 (10%)	3 (10%)	0	6 (20%)
	2	4 (17%)	12 * (50%)	4 (17%)	20 * (83%)
90–95%	1	6 (20%)	0	12 (40%)	18 (60%)
	2	0	0	4 (17%)	4 * (17%)
Total / Всего	1	12 (40%)	3 (10%)	15 (50%)	30 (100%)
	2	4 (17%)	12 * (50%)	8 (33%)	24 (100%)

* Differences with group 1 are statistically valid at $p \leq 0.01$.

* Различия относительно 1-й группы статистически значимы при $p \leq 0{,}01$.

Table 2 / Таблица 2

Risk Factors CAD in different patients groups with acute coronary syndrome and chronic coronary syndrome
Факторы риска ишемической болезни сердца в группах пациентов с острым коронарным синдромом и хроническим коронарным синдромом

Indication / Показатели	Group 1 / 1-я группа (n = 30)		Group 2 / 2-я группа (n = 24)		Statistics significance of differences (t) / Статистическая значимость различий (t)
	n	%	n	%	
Hyperlipidemia (LDL > 1.8 mmol/L) / Гиперлипидемия (ЛПНП > 1,8 ммоль/л)	24	80	6	25	$p \leq 0.001$ (4.7)
Hypertensive disease 3 stage / Гипертоническая болезнь 3-й стадии	5	16.7	24	100	$p \leq 0.001$ (4.4)
Chronic obstructive pulmonary disease / Хроническая обструктивная болезнь легких	7	23	3	12.5	$p > 0.05$ (1.0)
Smoking / Табакокурение	23	76.7	10	41.7	$p \leq 0.05$ (2.7)
Obesity I–II stage / Ожирение I–II степени	14	46.7	6	25	$p > 0.05$ (1.7)

Note. LDL – low density lipoproteins.
Примечание. ЛПНП — липопротеиды низкой плотности.

Table 3 / Таблица 3

Level of cytokine in different patients groups with acute coronary syndrome and chronic coronary syndrome
Уровень цитокинов в группах пациентов с острым коронарным синдромом и хроническим коронарным синдромом

Indication / Показатели	Group 1 / 1-я группа (n = 30)	Group 2 / 2-я группа (n = 24)	Statistics significance of differences (t) / Статистическая значимость различий (t)
IL-4 (0–4 pg/ml / пг/мл)*	240.85 ± 49.25	3.70 ± 0.24	$p \leq 0.001$ (4.8)
IL-8 (0–10 pg/ml / пг/мл)*	110.33 ± 27.67	7.34 ± 1.29	$p \leq 0.01$ (3.7)
TNF-α (0–6 pg/ml / пг/мл)*	0.81 ± 0.45	0.04 ± 0.004	$p > 0.05$ (1.7)

Note. * Reference interval according to laboratory data.
Примечание. * Референсный интервал по данным лаборатории.

and only in 4 (17%) patients of the CCS group ($p \leq 0.01$).

According to the anamnesis, the risk factors for CHD were established in patients with ACS and CCS (Table 2).

Hyperlipidemia and tobacco smoking significantly more often occurred in the ACS group ($p \leq$ 0.05–0.001). In the CCS group, the stage 3 hypertensive disease was noted in all patients with CCS ($p \leq 0.001$). The presence of chronic obstructive pulmonary disease and obesity grades I–II was not significantly different between the groups, and a tendency to their increase was only found in the ACS group (Table 2).

In the CCS group, a more favorable situation with regard to hyperlipidemia was associated with maintenance therapy with statins, which included in the complex treatment of myocardial infarction complications.

The CCS group had no significant change in the level of both pro-inflammatory and anti-inflammatory cytokines (Table 3). Their IL-4, IL-8, and TNF-α levels were within the reference interval. By contrast, the ACS group had very high mean group indicators of both pro-inflammatory IL-8 and anti-inflammatory IL-4 (Table 3).

As a result, the differences in the IL-8 and IL-4 levels between the groups were significant ($p \leq 0.01$–0.001) with an increase in the IL level

in the ACS group. Moreover, in 18 (60%) patients with ACS, the levels of IL-4 and IL-8 were higher than the reference values. The increase in the IL-4 level was probably of a compensatory property to proinflammatory cytokines and can be considered a positive factor in stabilizing the disease course. No significant change was noted in the levels of TNF-α in patients with ACS, which can also be considered a factor that facilitates the course of ACS.

According to echocardiography data, all patients with increased IL levels had 90%–95% coronary artery stenosis and impaired myocardial contractility. By contrast, IL levels in patients with ACS having 70%–90% stenosis did not increase. In the clinical analysis of blood in patients with increased IL levels, the erythrocyte sedimentation rate was higher in patients with ACS having normal IL level than in those with CCS.

CONCLUSIONS

1. In patients with ACS, levels of both pro-inflammatory IL-8 and anti-inflammatory IL-4 were increased. The increase in IL-4 level was most probably of a compensatory nature. In patients with CCS, the levels of IL-4 and IL-8 were within the reference values.
2. In patients with ACS, which subsequently progressed into unstable angina pectoris, and in patients with CCS, the level of TNF-α was not increased.
3. A higher degree of stenosis of the coronary arteries in combination with a disorder of local myocardial contractility leads to higher levels of IL-4 and IL-8, which may indicate a more extensive inflammatory response that resulted in the development of ACS.

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DOI: https://doi.org/10.17816/PED12219-27

A COMPARATIVE ANALYSIS OF THE RELATIONSHIP BETWEEN STATURE AND ULTRASOUND DIMENSIONS OF INTERNAL ORGANS IN ADOLESCENTS

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For citation: Yerkudov VO, Pugovkin AP, Volkov AJ, Musaeva OI, Volkov DJ, Rogozin SS, Chistjakova MV, Kochubeev AV, Pakhomova MA, Brus TV, Zabezhinsky MM. A comparative analysis of the relationship between stature and ultrasound dimensions of internal organs in adolescents. *Pediatrician (St. Petersburg).* 2021;12(2):19-27. https://doi.org/10.17816/PED12219-27

Received: 04.02.2021 Revised: 25.03.2021 Accepted: 23.04.2021

The *aim* of the study was a comparative characteristic of the size of internal organs according to ultrasonography data in subjects with various deviations in stature, determined using international standardized norms.

Materials and methods. The stature was measured in 93 adolescents, aged 13 to 17 years. Based on the measurements, the *Z*-score of body length was calculated according to the WHO Growth Reference, 2007 and three groups were formed for comparing the sizes of internal organs: "average", "above average", "below average". Ultrasonography data of the internal organs dimensions and thyroid gland was performed using a Toshiba Aplio 500 ultrasound scanner.

Results. There were statistically significantly lower values of the liver span and the longitudinal size of the gallbladder in the examined subjects from the "below average" group compared to the rest of the subjects. The length of the spleen and the total volume of the thyroid gland were statistically significantly different in subjects from all three groups, with the highest values in volunteers from the "above average" group. A weak direct correlation was shown between the *Z*-score of body length and liver span, the length of the cauda of the pancreas, and the width of the spleen. An average direct statistical relationship was found between the *Z*-score of stature and the length of the spleen, as well as the total volume of the thyroid gland.

Conclusion. To a greater extent, body length is associated with the size of the parenchymal organs with a pronounced connective tissue frame - the liver and spleen, as well as the thyroid gland due to the relationship of its volume with hormones that regulate growth and development. Clinical substantiation of the relationship between the structure of the body and internal organs opens up the possibility of creating anatomical standards that allow ultrasound morphometric assessment of internal organs, taking into account the individual characteristics of the patient's body size.

Keywords: *Z*-score; adolescents; body length; dimensions of internal organs; thyroid gland volume.

СОПОСТАВИТЕЛЬНЫЙ АНАЛИЗ ВЗАИМООТНОШЕНИЙ ДЛИНЫ ТЕЛА И РАЗМЕРОВ ВНУТРЕННИХ ОРГАНОВ У ПОДРОСТКОВ

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Для цитирования: Еркудов В.О., Пуговкин А.П., Волков А.Я., Мусаева О.И., Волков Д.Я., Рогозин С.С., Чистякова М.В., Кочубеев А.В., Пахомова М.А., Брус Т.В., Забежинский М.М. Сопоставительный анализ взаимоотношений длины тела и размеров внутренних органов у подростков // Педиатр. – 2021. – Т. 12. – № 2. – С. 19–27. https://doi.org/10.17816/PED12219-27

Поступила: 04.02.2021 Одобрена: 25.03.2021 Принята к печати: 23.04.2021

Цель работы — провести сравнительную характеристику размеров внутренних органов по данным ультрасонографии у испытуемых с различными отклонениями длины тела, определяемых с применением международных стандартизированных норм.

Материалы и методы. Проведено измерение верхушечной длины тела у 93 подростков, юношей в возрасте от 13 до 17 лет. На основании измерений рассчитан *Z*-индекс длины тела по стандартам WHO Growth Reference, 2007, и были сформированы три группы сравнения размеров внутренних органов: «средние», «выше средних», «ниже средних». Исследование органов брюшной полости и щитовидной железы проводили с использованием ультразвукового сканера Toshiba Aplio 500.

Результаты. Выявлены статистически значимо меньшие значения косого вертикального размера правой доли печени и продольного размера желчного пузыря у обследованных субъектов из группы «ниже средних» по сравнению с остальными испытуемыми. Длина селезенки и общий размер щитовидной железы статистически значимо отличались у испытуемых из всех трех групп с наибольшими значениями у добровольцев из группы «выше средних». Показана слабая прямая корреляция *Z*-индекса длины тела и косого вертикального размера печени, длины хвоста поджелудочной железы, ширины селезенки. Обнаружена средняя прямая статистическая связь *Z*-индекса длины тела и длины селезенки, а также общего объема щитовидной железы.

Выводы. В большей степени длина тела связана с размерами паренхиматозных органов с выраженным соединительнотканным каркасом — печенью и селезенкой, а также щитовидной железой в силу взаимосвязи ее объема с гормонами, регулирующим рост и развитие. Клиническое обоснование взаимоотношений строения тела и внутренних органов открывает возможность создания анатомических стандартов, позволяющих вести ультразвуковую морфометрическую оценку внутренних органов с учетом индивидуальных особенностей размеров тела пациента.

Ключевые слова: *Z*-индекс; подростки; длина тела; размеры внутренних органов; размеры щитовидной железы.

INTRODUCTION

The regulation of the growth and development of the skeleton and internal organs is a single humoral mechanism [33]. Thus, it becomes possible to use physical development parameters as predictors of the deviations in the size of internal organs from the standards during ultrasound (US) examination [20, 24, 26, 28, 31, 34].

The anatomical dimension of internal organs is a constant value; therefore, they may be considered as signs that determine the characteristics of a person's somatotype [8]. Studies have discussed the relationship between individual typological characteristics of internal organs, namely, the size of the liver, gallbladder, pancreas, and thyroid, and their relationship with a person's somatotype to create standards for the US assessment of these parameters [9, 18, 19].

Many studies have identified a mosaic distribution of differences in the size of internal organs in children with different somatotypes [3–5]. Thus, the focus on the constitutional characteristics of the organism as a factor capable of influencing the results of US morphometry of internal organs should be optional until the mechanisms and structure of these characteristics are clarified in detail. However, the results of these studies were less meaningful in the clinic because of the limited use of somatotyping in routine healthcare practice, that is, even if specialists determine the somatotype, they often do it by guesswork, without using special techniques [8]. Thus, comparing the dimensions of internal organs in individuals with different levels of physical development, that is, a certain length and body weight, ranked according to some generally accepted classifications, becomes necessary. The literature provides no unequivocal opinion on the problem of which approach to assess physical development should be considered a reference [6, 10, 11]. Several experts insist on the creation of updated standards in Russia, taking into account the ethnic, regional, and constitutional characteristics of the physical development of the population [6], and consider the method of centile tables by Mazurin and Vorontsov obsolete because of the accelerated development of children [10]. However, most authors [10, 11] suggest following the recommendations of the World Health Organization (WHO) for these purposes [25]. This method is easy to use, and the materials for its application are publicly available [11].

Reference values of US dimensions of the liver, spleen, kidneys, and thyroid gland, normalized for the length and body weight, were obtained when examining children living in Europe, Asia, and North America [20–24, 26–28, 31, 34]. In Russian scientific publications, such information is nearly nonexistent.

This study aimed to compare characteristics of the dimensions of internal organs according to US data in individuals with various deviations in body length, determined using international standardized norms.

MATERIALS AND METHODS

The study was performed during a routine preventive examination of children, which was conducted according to Order No. 27-O* in the Children's Polyclinic Department No. 3 of the Saint Petersburg City Polyclinic No. 109. All study participants signed voluntary informed consent for preventive examinations and processing of personal data. In total, 93 adolescent boys aged 13–17 years participated in the study. Apical body length was measured using a floor-standing medical stadiometer PM-2 Diakoms (Diakoms, Russia) with a measurement accuracy of up to 5 mm. The *Z*-index of body length was calculated according to the WHO Growth Reference standards (2007) using the WHO AnthroPlus program [25]. The body length of each participant was assessed not only by determining the significance of differences from the *Z*-indices in the indicated groups but also individually. If the *Z*-scores were within the range of –1 SD to +1 SD, body length values were qualified as "average," and their correspondence to ranges of less than –1 SD or more than +1 SD was accepted as "below-average" and "above-average" deviations, respectively [25]. Thus, three groups were formed for the comparison of US measurements of internal organs.

For US examination of the thyroid gland, a Toshiba Aplio 500 US scanner with a linear probe was used with a central frequency of 8.0 MHz (Toshiba Medical System Corporation, Japan). The volume of each lobe was estimated according to a generally accepted method by measuring the width, thickness, and length of each lobe, followed by calculating the lobe volume by multiplying its width, thickness, and length with an ellipsoidal correction factor, K = 0.479. The total volume of the thyroid gland was calculated by adding the volumes of the two lobes. Abdominal organs were examined using a Toshiba Aplio 500 US scanner with a convex probe with a central frequency of 3.75 MHz (Toshiba Medical System Corporation). Oblique vertical dimensions of the right liver lobe, longitudinal and transverse dimensions of the gallbladder, length of the head, body, and tail of the pancreas, as well as the length and width of the spleen, were measured.

The significance of the differences in the *Z*-index of the body length and size of internal organs in groups with different levels of deviations in body length ("below-average values," "average values," and "above-average values") was tested using the Kruskal–Wallis test. If the three samples demonstrated significant differences, pairwise comparison was performed using the Mann–Whitney test, with the Bonferroni correction for the multiplicity of comparisons. The ratio of the *Z*-index of the length and size of internal organs was assessed by calculating the Spearman correlation coefficient (ρ). When the ρ value was equal to 0, the relationship was considered absent; 0.01–0.29 (–0.01 to –0.29), weak direct correlation (reverse); 0.3–0.69 (–0.3 to –0.69), average direct correlation (reverse); 0.7–0.99 (–0.7 to –0.99), strong direct correlation (reverse); and 1 (–1), full direct correlation (reverse) [16]. The results were considered significant at $p < 0.05$. Calculations were performed using built-in Excel functions from the Microsoft Office 2010 application package, past version 2.17 (Norway, Oslo, 2012) software, and StatXact-8 statistical data processing algorithm with Cytel Studio version 8.0.0 software shell. Values are presented as mean (μ) of the *Z*-index of body length or size of the internal organ as well as the lower and upper bounds of the 95% confidence interval.

RESULTS AND DISCUSSION

In the comparison of the values of the *Z*-index of body length, significant differences were revealed in all participants from all three comparison groups (Table 1).

Data analysis showed significantly lower values of the oblique vertical size of the right lobe of the liver and the longitudinal size of the gallbladder from the group with "below-average" deviations in body length compared with groups with "above-average" and "average" deviations in body length. In addition, the length of the spleen and the total size of the thyroid gland were significantly different in all three groups, and their values were the greatest in the group with "above-average" deviations in body length, and the smallest values were noted in the group with "below-average" deviations in body length (Table).

Data analysis revealed no significant differences in the transverse size of the gallbladder, all dimensions of the pancreas, and width of the spleen in all three groups, as well as the oblique vertical dimension of the liver and longitudinal size of the gallbladder in the groups with "above-average" and "average" deviations in body length.

Analysis of the relationship between the size of internal organs and physical development revealed a weak direct correlation between the *Z*-index of

* Order No. 27-O "On the organization of work to fulfill the order of the Ministry of Health of the Russian Federation of August 10, 2017 No. 514-n "On the procedure for conducting preventive medical examinations of minor children" in the children's polyclinic department No. 3 of the St. Petersburg City Polyclinic No. 109."

Table / Таблица

Ultrasound dimensions of internal organs and *Z*-scores of body length in adolescents from three comparison groups (μ; 95% CI)

Размеры внутренних органов и значений *Z*-индекса длины тела у подростков из трех групп сравнения (μ; 95% CI)

Parameter / Параметр	"Above average" / «Выше средних»	"Average" / «Средние»	"Below average" / «Ниже средних»	*p*-value / *p*-значения			
				Kruskal–Wallis test / тест Краскелла–Уоллиса	pairwise comparisons / попарные сравнения		
					"above average"–"average" / «выше средних»–«средние»	"above average"–"below average" / «выше средних»–«ниже средних»	"average"–"below average" / «средние»–«ниже средних»
Z-score / *Z*-индекс длины тела	1.59 (1.40; 1.75)	0.33 (0.20; 0.46)	–1.20 (–1.66; –0.74)	$1.64 \cdot 10^{-16}$	$1.839 \cdot 10^{-13}$	$3.852 \cdot 10^{-13}$	$7.015 \cdot 10^{-7}$
Liver span, cm / Косой вертикальный размер правой доли печени, см	12.95 (12.61; 13.30)	12.88 (12.64; 13.11)	12.07 (11.68; 12.46)	0.00646	1	0.01376	0.006353
Longitudinal dimension of the gall bladder, cm / Продольный размер желчного пузыря, см	6.26 (5.75; 6.76)	6.34 (5.97; 6.72)	5.04 (4.28; 5.81)	0.0154	1	0.03536	0.01487
Transversal dimension of the gall bladder, cm / Поперечный размер желчного пузыря, см	2.25 (1.96; 2.53)	2.27 (2.15; 2.40)	2.09 (1.78; 2.40)	0.1394	0.06766	1	0.1824
Dimension of the pancreas caput, cm / Длина головки поджелудочной железы, см	2.20 (1.04; 3.35)	1.60 (1.54; 1.65)	1.54 (1.39; 1.70)	0.489	1	0.6529	1
Dimension of the pancreas corpus, cm / Длина тела поджелудочной железы, см	1.01 (0.94; 1.08)	1.22 (0.87; 1.58)	0.98 (0.88; 1.09)	0.3597	0.8878	1	0.6505
Dimension of the pancreas cauda, cm / Длина хвоста поджелудочной железы, см	1.79 (1.66; 1.91)	1.71 (1.65; 1.78)	1.66 (1.54; 1.79)	0.4952	1	0.8095	1
Spleen length, cm / Длина селезенки, см	11.50 (11.07; 11.93)	9.82 (9.56; 10.07)	8.99 (8.60; 9.40)	$3.243 \cdot 10^{-10}$	$3.26 \cdot 10^{-8}$	$6.879 \cdot 10^{-6}$	0.01494
Spleen width, cm / Ширина селезенки, см	4.08 (3.84; 4.32)	4.04 (3.86; 4.23)	3.81 (3.65; 3.97)	0.3907	1	0.4098	1
Thyroid gland volume, cm^3 / Общий объем щитовидной железы, $см^3$	9.95 (8.85; 11.05)	8.15 (7.59; 8.71)	6.89 (6.31; 7.47)	0.000124	0.00516	0.001725	0.04273

body length and oblique vertical size of the liver ($p = 0.22$; $p = 0.029325$), length of the pancreatic tail ($p = 0.21$; $p = 0.042216$), and spleen width ($p = 0.24$; $p = 0.018383$). An average significant relationship was found between the *Z*-index of body length and spleen length ($p = 0.37$; $p = 0.00030704$), as well as the total volume of the thyroid gland ($p = 0.44$; $p = 1.0462 \cdot 10^{-5}$). The correlation coefficient between the *Z*-index of body length, longitudinal ($p = 0.14$; $p = 0.19191$) and transverse ($p = –0.01$; $p = 0.85438$) dimensions of the gallbladder, as well as the head ($p = 0.09$; $p = 0.38561$) and body ($p = 0.07$; $p = 0.48775$) of the pancreas were not significantly different from zero.

In this study, the dimensions of the internal organs have the expected characteristic differences, as participants with low *Z*-index values for body length have smaller dimensions of the liver, spleen, and thyroid gland than participants with deviations in body length toward a higher dimension. The liver and spleen are parenchymal organs with a rigid tissue framework; therefore, in this study, stable and expected differences in their dimensions were revealed, which is in good agreement with the data from Russian [9, 18, 19] and international [20, 24, 26, 28, 31, 34] literatures. The obtained patterns of relationships between the volume of the thyroid gland and physical development were also representative [21–23, 27]. Body length and weight have a direct correlation not only with the thyroid gland volume but also with the concentration of insulin-like growth factor 1 in the blood [21–23], as well as protein and calorie supply in adolescents [22]. In addition, the formation of various physique and organ dimensions is partially regulated by thyroid hormones [12], since they can inhibit the proliferation of fibroblasts and the synthesis of collagen by these cells [29, 32]. Children with smaller body dimensions than their peers with body lengths above the average have an increased concentration of thyroid hormones [12].

Based on the data presented, these mechanisms may play important roles in the development of individual characteristics of the dimensions of the thyroid gland and other organs in participants with different levels of physical development.

In the present study, conflicting results were obtained regarding the relationship between physical development and the size of the pancreas. Significant differences were noted only in the gallbladder longitudinal size, not in all comparison groups. The dimensions of the head, tail, and body of the pancreas were not significantly different in adolescents with various deviations in body length as determined by the *Z*-index. The weak direct correlation of the *Z*-index of body length and length of the pancreatic tail cannot be regarded as a cause-and-effect relationship [16].

Methodological errors of the US morphometry of the pancreas and gallbladder dimensions in children with individual typological features of physical development are widely discussed [1, 2, 15, 14, 17]. The dependence of the pancreatic anatomical location on the size of the abdominal cavity [1], its abundant vascularization, deterioration of the US signal [2, 17], and abdominal obesity in children with increased body mass index [2, 17] lead to "blurring" of the image and appearance of optical illusions [2] when visualizing dimensions. Therefore, US data on the length of the head, body, and tail of the pancreas are very contradictory, unstable, and operator-dependent and correlate with the organization of the body [1, 2, 17].

As a result of computer modeling of the topographic location of the gallbladder based on spiral tomography data, significant individual differences were revealed in people with different anthropometric parameters [15]. This leads to the variabilities in the determination of its longitudinal and transverse US dimensions in children with different levels of physical development [2, 15]. The pancreas and gallbladder function continuously, changing constantly the exocrine and tonic activities, even in the "cerebral" phase of the regulation of these processes, which undoubtedly affects their size [7]. Therefore, the methodological organization of experiments to finally resolve the issue of the relationship between the somatotype and size of the pancreas and gallbladder should consider the standardization of nutritional conditions of the individuals examined and determination of the functional activity of these organs [13].

CONCLUSION

This study substantiates the relationship between deviations in body length, determined using international standardized norms, and the size of internal organs. To a greater extent, body length is associated with the size of parenchymal organs with a pronounced connective tissue framework, namely, the liver, spleen, as well as thyroid gland due to the relationship of its volume with hormones that regulate growth and development. Clinical substantiation of the relationship between the organization of the body and internal organs opens up the possibility of creating anatomical standards that enable US morphometric assessment of internal organs, taking into account the individual characteristics of the patient's

body size. The application of these standards in clinical practice will help limit erroneous positive and negative conclusions about hypotrophy and hypertrophy of internal organs.

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DOI: https://doi.org/10.17816/PED12243-52

THE USE OF WHOLE-BODY CRYOTHERAPY FOR INCREASING THE STRESS RESISTANCE OF FEMALE ATHLETES IN GROUP TYPES OF GYMNASTICS

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For citation: Vasilenko VS, Mamiev ND, Semenova YuB, Karpovskaya EB. The use of whole-body cryotherapy for increasing the stress resistance of female athletes in group types of gymnastics. *Pediatrician (St. Petersburg)*. 2021;12(2):43-52. https://doi.org/10.17816/PED12243-52

Received: 05.02.2021 Revised: 23.03.2021 Accepted: 23.04.2021

Background. Representatives of complex coordination sports are most susceptible to psychoemotional stress, since they demonstrate high sports results already at a young age. The tightening of anti-doping control has significantly reduced the possibility of using pharmacological and biologically active drugs to speed up the recovery of athletes. Against this background, in sports medicine, more attention is paid to the use of non-drug methods to improve performance and recovery in athletes.

Aim – to study the efficiency of the introduction of whole-body cryotherapy in the training process of female athletes of complex coordination sports (for example, group gymnastics) to increase stress resistance and reduce violations of adaptation processes as a result of neuropsychiatric overstrain.

Materials and methods. During the academic-training year, 22 gymnasts received six ten-day courses of whole-body cryotherapy in the ICEQUEEN cryosauna. 19 athletes were included in the control group. The studies were conducted 3 times: before the start of the procedures, after the first course of procedures, at the end of the training year. The diagnosis of nocturnal bruxism and the definition of the "psychological component of health" were carried out. Total and effective albumin concentrations were determined in the blood serum with the calculation of the albumin binding reserve, helper T-lymphocytes and killer T-lymphocytes with the calculation of the immunoregulatory index.

Results. After one course, there was an increase in the functional activity of serum albumins, a decrease in the number of episodes of involuntary contractions of the masticatory muscles at night, and an increase in the "psychological component of health" according to SF-36. After six courses of cryotherapy, the functional activity of serum albumins and the initial values of the immunoregulatory index were preserved by the end of the season, and the "psychological component of health" according to SF-36 was increased, while these indicators decreased in the control group. There was also a decrease in the number of episodes of involuntary contractions of the masticatory muscles at night with an increase in their number in the control group of female athletes.

Conclusions. Considering the obtained results, it is possible to recommend the use of whole-body cryotherapy in gymnasts during the preparatory and recovery periods of the annual training cycle in order to increase stress tolerance and prevent psychoemotional overstrain.

Keywords: gymnast; psychoemotional stress; overexertion; prevention; whole-body cryotherapy.

ИСПОЛЬЗОВАНИЕ КРИОТЕРАПИИ ДЛЯ ПОВЫШЕНИЯ СТРЕССОУСТОЙЧИВОСТИ СПОРТСМЕНОК В ГРУППОВЫХ ВИДАХ ГИМНАСТИКИ

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Для цитирования: Василенко В.С., Мамиев Н.Д., Семенова Ю.Б., Карповская Е.Б. Использование криотерапии для повышения стрессоустойчивости спортсменок в групповых видах гимнастики // Педиатр. – 2021. – Т. 12. – № 2. – С. 43–52. https://doi.org/10.17816/PED12243-52

Поступила: 05.02.2021 Одобрена: 23.03.2021 Принята к печати: 23.04.2021

Введение. Представительницы сложнокоординационных видов спорта наиболее подвержены психоэмоциональному стрессу, так как высокие спортивные результаты они демонстрируют уже в юном возрасте. Ужесточение антидопингового контроля значительно снизило возможность применения фармакологических и биологически активных препаратов для ускорения восстановления спортсменов. На этом фоне в спортивной медицине все большее внимание уделяется использованию немедикаментозных методов повышения работоспособности и восстановления у спортсменов.

Цель исследования — изучить эффективность введения общей воздушной криотерапии в тренировочный процесс спортсменок сложнокоординационных видов спорта (на примере групповых видов гимнастики) для повышения стрессоустойчивости и снижения нарушений процессов адаптации в результате нервно-психического перенапряжения.

Материалы и методы. На протяжении учебно-тренировочного года 22 гимнасткам было проведено шесть десятидневных курсов общей воздушной криотерапии в криосауне ICEQUEEN. 19 спортсменок были включены в контрольную группу. Исследования проводились 3 раза: до начала процедур, после первого курса процедур, в конце учебно-тренировочного года. Проводилась диагностика ночного бруксизма и определение «психологического компонента здоровья». В сыворотке крови определялись: общая и эффективная концентрации альбуминов с расчетом резерва связывания альбуминов, Т-лимфоциты хелперы и Т-лимфоциты киллеры с расчетом иммунорегуляторного индекса.

Результаты. После одного курса установлено повышение функциональной активности сывороточных альбуминов, снижение количества эпизодов непроизвольных сокращений жевательных мышц ночью и повышение «психологического компонента здоровья» по SF-36. После прохождения шести курсов криотерапии было отмечено сохранение к концу сезона функциональной активности сывороточных альбуминов и исходных значений иммунорегуляторного индекса, повышение «психологического компонента здоровья» по SF-36 при снижении этих показателей в контрольной группе. Зафиксировано снижение количества эпизодов непроизвольных сокращений жевательных мышц ночью при увеличении их количества в контрольной группе спортсменок.

Заключение. Учитывая полученные результаты, можно рекомендовать применение у гимнасток общей воздушной криотерапии в подготовительный и восстановительный периоды годового тренировочного цикла с целью повышения стрессоустойчивости и профилактики психоэмоционального перенапряжения.

Ключевые слова: гимнастка; психоэмоциональный стресс; перенапряжение; профилактика; общая воздушная криотерапия.

BACKGROUND

The results demonstrated by athletes in competitions are now approaching the limits of human capabilities. An athlete is not always able to control his/her emotional experiences, which can cause excessive neuropsychic stress and chronic psychoemotional stress [1, 6].

The most pronounced psychoemotional stress is registered in female athletes in such complex coordination sports as rhythmic and aesthetic gymnastics, which is associated with the specifics of the selection of the most artistic and emotional girls. At the same time, group gymnastics is characterized by the high individual responsibility of each gymnast, which in presence of pronounced psychoemotional stress can cause chronic psychoemotional stress and thus affects adversely the health of the gymnasts, efficiency of the training process, and competitive activity. In this regard, an important task of recovery procedures at all stages of training athletes in complex coordination sports is an increase in mental stability.

According to the literature, sleep bruxism can be considered a traceable clinical symptom and is an indicator of stress [3, 14, 16] and anxiety [4, 21]. For objective diagnostics of sleep bruxism, hardware methods are used. A significant correlation was found between stress and sleep bruxism index, assessed using the Bruxo device [23]. The relationship between stress and degree of nocturnal bruxism in well-trained athletes was established by Russian authors using the BiteStrip device [6].

As prognostic criteria for the risk of the development of organic anxiety disorders at an early disease stage, along with other methods, the recommendation was to decrease the immunoregulatory index (IRI) as a result of a decrease in the number of T-helper inducers ($CD4^+$ phenotype) and an increase in the level of cytotoxic T-suppressors ($CD8^+$ phenotype) [10].

In patients diagnosed with endogenous intoxication, shifts in homeostasis characteristic of chronic stress were established [8, 12]. One of the universal mechanisms of the body's response to an increase in metabolic products is the formation of complexes of various compounds with blood plasma albumins. It has been hypothesized that endogenous intoxication is an integral component of the pathogenesis of mental disorders [11].

An adequate balance between stress (training and competition load, other vital needs) and recovery is important for athletes to consistently achieve high results. Recovery after training and competition is a complex process and usually depends on the nature of the exercise performed and external stressors [17].

We have to take into account that tightening of anti-doping control has significantly reduced the possibility of using pharmacological and biologically active drugs to accelerate the recovery of ath-

letes. In this situation, in sports medicine, increasing is paid to the use of non-drug methods to improve performance and recovery in athletes. However, this is not only a problem of sports medicine, but also a social problem of the nation's health improvement, to ensure a decrease in the pharmacological load through the use of non-drug means of health improvement. These methods include cryotherapy [18, 19], and its safety has also been established in children and adolescents [13].

Whole-body air cryotherapy (WBAC) in athletes is mainly investigated to restore physical performance and treating injuries.

After intense physical exertion, WBAC causes a decrease in the level of markers of muscle damage and a decrease in the concentration of myostatin with an increase in isokinetic muscle strength [15].

Under WBAC, the severity of tissue hypoxia decreases and aerobic metabolism of erythrocytes increases; thus, this method is recommended to increase endurance and resistance to the hypoxic factor. Microcirculation conditions are improved by restructuring the peripheral link of blood circulation due to a decrease in arterial blood flow and vascular tone. An increase in the lipid fluidity in plasma membranes of blood cells after a course of whole-body gas cryotherapy can affect the structure and function of membrane proteins, as well as lipid–protein interactions in the membrane. Moreover, the malondialdehyde level decreased. There is a long-term stimulation of the body's antioxidant defense systems and the intensity of metabolic processes during cryotherapy [7].

The beneficial effect of cryotherapy on the immune system and hormonal and metabolic status has been established [20]. The biological effect of cryotherapy is based on the phenomenon of cross adaptation, when adaptation to cold increases the body's resistance to other stressors [5]. A study reported the effect of WBAC on the reduction of the inflammatory process and oxidative stress [24]. WBAC was demonstrated to be effective as an adjunct therapy to pharmacological treatment for depression [22].

However, regarding the effect of cryotherapy on physical recovery, very few studies have extensively focused on the role of cryotherapy in increasing the psychological adaptation and stress resistance of athletes.

This study aimed to analyze the efficiency of WBAC introduction into the training process of female athletes of complex coordination sports (such as group gymnastics) to increase stress resistance and reduce disorders of adaptation processes following a neuropsychic overstrain.

MATERIALS AND METHODS

Practically healthy athletes aged 14–16 (14.8 ± 0.09) years, specializing in group gymnastics (aesthetic gymnastics, $n = 23$; group rhythmic gymnastics exercises, $n = 18$), were examined. According to the results of an annual medical examination, all athletes were engaged in sports.

The study fulfilled the requirements of the World Medical Association Declaration of Helsinki on Ethical Principles for Scientific Medical Research Involving Human Subjects as amended in 2000 and Rules of Good Clinical Practice in the Russian Federation approved by order of the Ministry of Health of the Russian Federation (No. 200n* dated 01.04.2016). The study was approved by the ethical committee of the Saint Petersburg State Pediatric Medical University. Informed consent was obtained from the parents, coach, and athletes themselves for the publication of the data obtained without personal identification.

The randomization procedure for distributing the gymnasts into experimental and control groups was performed by the closed-envelope method. The experimental group included 22 athletes, and the control group included 19 participants.

The work design consisted of three studies in two phases:

Stage 1 (start of the academic and training year) included the following:

1) Special preparatory period 1 before exposure to WBAC.

2) Special preparatory period 1 after exposure to a 10-day course of WBAC.

Stage 2 (end of the academic and training year) included the following:

3) The recovery period at the end of the competition.

The experimental group received six courses of WBAC (cryosauna ICEQUEEN, GRAND-CRYO, Russia) in one academic and training year (two courses in two special preparatory periods before major competitions and four courses in four recovery periods). A conventional procedure was used. For 15 s, the temperature of the gas around the body was fixed at 110°C–120°C, and the procedure was performed for 120 s. The control group did not receive the WBAC.

To diagnose neuropsychic overstrain, a complex of studies was performed, including psychological, dental, immunological, and biochemical methods.

* https://cdnimg.rg.ru/pril/130/47/73/43357.pdf.

1. Determination of the psychological component of health. The method of the subjective assessment of the health-related quality of life (SF-36) in Russian was created and recommended by the Multinational Center for Quality of Life Research [9].

2. Episodes of involuntary contractions of the masticatory muscles at night (nocturnal bruxism) were considered one of the markers of psychoemotional stress in athletes [6, 23]. To diagnose nocturnal bruxism, the BiteStrip device ("Up 2 dent") was attached to the cheek (motor point of the lower jaw) by the athlete herself before going to sleep. In the morning, after removing the device, the number of involuntary contractions corresponding to a certain disease severity was recorded, and degree 1 of nocturnal bruxism occurs if there are 74–100 contractions [2].

3. A decrease in the IRI [10], which reflects the ratio of helper T-lymphocytes to killer T-lymphocytes, is used as prognostic criteria for the risk of anxiety disorders at an early stage. Counts of helper (CD4) and killer (CD8) lymphocytes were determined using a microlymphocytotoxic test with monoclonal antibodies to CD4 and CD8 antigens ("Ortho").

Chronic stress is accompanied by endogenous intoxication [11, 12]. One of the indicators of endogenous intoxication is a decrease in the functional activity of serum albumin. In this regard, to determine the adaptive capabilities of the organism, the total) and effective albumin concentrations (TAC and EAC, respectively) were determined (stationary fluorescence spectroscopy using a K-35 fluorescent probe) with the calculation of the albumin binding reserve (ABR) (ABR = EAC / TAC × 100).

For laboratory studies, blood samples were collected in the morning, before training, from a peripheral vein into a vacuum container. Statistical data processing was performed using nonparametric method of statistics (Wilcoxon *T*-test).

RESULTS AND DISCUSSION

High physical exertion causes an increase in the levels of metabolites. The body's ability to eliminate them characterizes the adaptive capabilities of the athlete. The functional activity of serum albumin determines the efficiency of cleansing the body from metabolites.

Endogenous intoxication disrupts the adaptive reactions of the body and can be triggered not only by physical but also by emotional stress [11]. To determine the disturbances in the disposal of metabolic products, an integrative indicator, ABR, was used, which characterizes the proportion of free albumin centers not blocked by metabolites.

During a 10-day WBAC course, ABR was increased in 19 female athletes. To establish the significance of the differences before and after the experiment, the Wilcoxon *T*-test was used. In this case, the empirical value of *T* was in the zone of significance with $T_{emp} < T_{cr}$ (0.01) (Table 1). Thus, a significant increase in ABR was recorded after a 10-day WBAC course.

In the control group, no significant decrease was found in the ABR value in six cases, and no significant increase was noted in five cases. In this case, the empirical value of *T* was in the zone of insignificance with $T_{emp} > T_{cr}$ (Table 1). Thus, the indicators tended to remain at the same level.

Table 1 / Таблица 1

Average values of the albumin binding reserve before and after a 10-day course of whole-body cryotherapy in the experimental group of female athletes relative to female athletes of the control group
Средние значения резерва связывания альбуминов до и после 10-дневного курса общей воздушной криотерапии в экспериментальной группе спортсменок относительно спортсменок контрольной группы

Group / Группа	Albumin binding reserve, % / Резерв связывания альбуминов, %		T_{emp} / $T_{эмп}$ ($\sum R_t$)	T_{cr} / $T_{кр}$ ($p \le 0.01$)	*p*
	examination 1 / 1-е обследование *M* (max–min)	examination 2 / 2-е обследование *M* (max–min)			
Experimental / Экспериментальная (*n* = 22)	90.45 (95–87)	92.52 (96–90)	17.5	55	<0.01
Control / Контрольная (*n* = 19)	91.36 (95–88)	91.31 (94–87)	70	37	>0.05

Note. *M* – average value; $\sum R_t$ – the sum of the ranks of atypical shifts; *T* – Wilcoxon test; T_{emp} – an empirical meaning; T_{cr} – critical value at $p < 0.01$ (in accordance with tables of critical values); *p* – statistical significance of differences.
Примечание. Здесь и в табл. 2–8. *M* — среднее значение; $\sum R_t$ — сумма рангов нетипичных сдвигов; *T* — критерий Вилкоксона; $T_{эмп}$ — эмпирическое значение; $T_{кр}$ — критическое значение при $p < 0{,}01$ (в соответствии с таблицами критических значений); *p* — статистическая значимость различий.

Table 2 / Таблица 2

Average values of the albumin binding reserve at the beginning and the end of the academic-training year in the gymnasts of the experimental group who underwent whole-body cryotherapy courses and the gymnasts of the control group
Средние значения резерва связывания альбуминов в начале и конце учебно-тренировочного года у гимнасток экспериментальной группы, проходивших курсы общей воздушной криотерапии, и гимнасток контрольной группы

Group / Группа	Albumin binding reserve, % / Резерв связывания альбуминов, %		T_{emp} / $T_{эмп}$ ($\sum R_i$)	T_{cr} / $T_{кр}$ ($p \le 0.01$)	p
	examination 1 / 1-е обследование M (max–min)	examination 3 / 3-е обследование M (max–min)			
Experimental / Экспериментальная (n = 22)	90.45 (95–87)	90.8 (93–89)	79	75	>0.05
Control / Контрольная (n = 19)	91.36 (95–88)	89.5 (94–86)	19	37	<0.01

Table 3 / Таблица 3

Average values of the immunoregulatory index in the gymnasts of the experimental group before and after a 10-day course of whole-body cryotherapy relative to the control group of gymnasts
Средние значения иммунорегуляторного индекса у гимнасток экспериментальной группы до и после 10-дневного курса общей воздушной криотерапии относительно контрольной группы гимнасток

Group / Группа	Albumin binding reserve, % / Резерв связывания альбуминов, %		T_{emp} / $T_{эмп}$ ($\sum R_i$)	T_{cr} / $T_{кр}$ ($p \le 0.01$)	p
	examination 1 / 1-е обследование M (max–min)	examination 2 / 2-е обследование M (max–min)			
Experimental / Экспериментальная (n = 22)	1.18 (1.5–0.9)	1.17 (1.5–1)	89.5	55	>0.05
Control / Контрольная (n = 19)	1.15(1.5–1.0)	1.16 (1.4–1.0)	75	37	>0.05

As no ABR changes occurred in the control group after a 10-day follow-up period, an increase in the ABR was noted in the experimental group, which was influenced by the WBAC course.

During the third examination in the experimental group at the end of the academic and training year, no significant decrease in ABR was noted in five female gymnasts. The empirical value of T was in the zone of insignificance with $T_{emp} > T_{cr}$ (Table 2). A possible conclusion is that the indicators tended to remain at the same level. Thus, in the experimental group, the ABR was not decreased at the end of the academic and training year.

In the control group, the third examination revealed a decrease in ABR in 12 gymnasts and an increase in only two gymnasts. The obtained empirical value T was in the zone of significance with $T_{emp} < T_{cr}$ (0.01) (Table 2). Accordingly, at the end of the academic and training year, the control group had a decrease in ABR, indicating an impairment of functioning of the serum albumin system.

Thus, after one WBAC course, there was a decrease in the level of metabolites and an acceleration of detoxification processes in athletes [4], which leads to the release of a high number of free centers of albumin and, accordingly, to their greater functional activity, which is expressed in an increase in the ABR index.

WBAC courses throughout the annual training cycle not only reduce the level of psychoemotional stress but also maintain the functional activity of the serum albumin system, preventing it from decreasing below the initial level.

The study of the effect of a 10-day WBAC course on the IRI showed its increase in six cases and a decrease in 10 cases. The empirical value of T was in the zone of insignificance with $T_{emp} > T_{cr}$ (Table 3). No significant decrease in IRI was found in the experimental group. In the control group, significant changes in IRI were also not found ($T_{emp} > T_{cr}$) (Table 3).

Table 4 / Таблица 4

Average values of the immunoregulatory index at the beginning and the end of the academic-training year in gymnasts of the experimental group who underwent whole-body cryotherapy courses and gymnasts of the control group

Средние значения иммунорегуляторного индекса в начале и конце учебно-тренировочного года у гимнасток экспериментальной группы, проходивших курсы общей воздушной криотерапии, и гимнасток контрольной группы

Group / Группа	Albumin binding reserve, % / Резерв связывания альбуминов, %		T_{emp} / $T_{эмп}$ ($\sum R_i$)	T_{cr} / $T_{кр}$ ($p \le 0.01$)	p
	examination 1 / 1-е обследование M (max–min)	examination 3 / 3-е обследование M (max–min)			
Experimental / Экспериментальная (n = 22)	1.18 (1.5–0.9)	1.2 (1.5–1.0)	70	55	>0.05
Control / Контрольная (n = 19)	1.15 (1.5–1.0)	1.0 (1.3–0.8)	22	37	<0.01

Table 5 / Таблица 5

Average values of the number of episodes of involuntary contractions of the masticatory muscles at night in the gymnasts of the experimental group before and after a 10-day course of whole-body cryotherapy relative to the control group of gymnasts

Средние значения числа эпизодов непроизвольных сокращений жевательных мышц ночью у гимнасток экспериментальной группы до и после 10-дневного курса общей воздушной криотерапии относительно контрольной группы гимнасток

Group / Группа	Albumin binding reserve, % / Резерв связывания альбуминов, %		T_{emp} / $T_{эмп}$ ($\sum R_i$)	T_{cr} / $T_{кр}$ ($p \le 0.01$)	p
	examination 1 / 1-е обследование M (max–min)	examination 2 / 2-е обследование M (max–min)			
Experimental / Экспериментальная (n = 22)	32.6 (140–0)	23.3 (110–0)	16	55	<0.01
Control / Контрольная (n = 19)	40.1 (135–0)	38.5 (140–0)	67	37	>0.05

At the end of the academic and training year, the experimental group showed an insignificant decrease in IRI in four athletes. No significant ABR dynamics was found relative to the first examination in the experimental group (Table 4). However, at the third examination in the control group, a decrease in the IRI relative to the first examination was recorded in 16 gymnasts. The empirical T was in the zone of significance with $T_{emp} < T_{cr}$ (0.01) (Table 4), and a significant decrease in IRI in the control group can be considered caused by the survey results at the end of the academic and training year. This confirms the data of other researchers on the decrease in the IRI under the influence of stress [10].

The number of involuntary contractions of the masticatory muscles at night in the experimental group significantly decreased after one WBAC course. The empirical T obtained was in the zone of significance with $T_{emp} < T_{cr}$ (0.01) (Table 5). In the control group, no decrease was observed in the frequency of involuntary contractions of the masticatory muscles at night on average $T_{emp} > T_{cr}$ (Table 5).

The examination at the end of the academic and training years revealed a further decrease in the number of involuntary contractions of the masticatory muscles at night. Empirical T was in the zone of significance with $T_{emp} < T_{cr}$ (0.01). In the control group, the average number of involuntary contrac-

Table 6 / Таблица 6

Average values of the number of episodes of involuntary contractions of the masticatory muscles at night at the beginning and the end of the academic-training year in the gymnasts of the experimental group who underwent whole-body cryotherapy courses and gymnasts of the control group
Средние значения числа эпизодов непроизвольных сокращений жевательных мышц ночью в начале и конце учебно-тренировочного года у гимнасток экспериментальной группы, проходивших курсы общей воздушной криотерапии, и гимнасток контрольной группы

Group / Группа	Albumin binding reserve, % / Резерв связывания альбуминов, %		T_{emp} / $T_{эмп}$ ($\sum R_t$)	T_{cr} / $T_{кр}$ ($p \le 0.01$)	p
	examination 1 / 1-е обследование M (max–min)	examination 3 / 3-е обследование M (max–min)			
Experimental / Экспериментальная (n = 22)	32.6 (140–0)	21.3 (108–0)	24	55	<0.01
Control / Контрольная (n = 19)	40.1 (135–0)	50.4 (130–0)	11.5	37	<0.01

Table 7 / Таблица 7

Average values of the "psychological component of health" according to SF-36 in the gymnasts of the experimental group before and after a 10-day course of whole-body cryotherapy relative to the gymnasts of the control group
Средние значения показателя «психологический компонент здоровья» по SF-36 у гимнасток экспериментальной группы до и после 10-дневного курса общей воздушной криотерапии относительно гимнасток контрольной группы

Group / Группа	Albumin binding reserve, % / Резерв связывания альбуминов, %		T_{emp} / $T_{эмп}$ ($\sum R_t$)	T_{cr} / $T_{кр}$ ($p \le 0.01$)	p
	examination 1 / 1-е обследование M (max–min)	examination 2 / 2-е обследование M (max–min)			
Experimental / Экспериментальная (n = 22)	73.7 (84–58)	78.8 (88–69)	12	55	<0.01
Control / Контрольная (n = 19)	74.3 (84–61)	75.1 (82–65)	81	37	>0.05

tions of the masticatory muscles at night increased. Empirical T was in the zone of significance with $T_{emp} < T_{cr}$ (0.01) (Table 6).

Thus, by reducing the number of involuntary contractions of the masticatory muscles at night, the positive effect of WBAC courses on the emotional state of gymnasts and an increase in their stress resistance was confirmed. At the end of the year, based on this indicator, an unstable psychoemotional state was diagnosed in the control group.

When polling gymnasts, even one WBAC course improved the psychoemotional state, as the majority of the gymnasts (82%) noted an improvement in mood, a feeling of freshness, and easiness after the first visit to the cryosauna.

To diagnose psychoemotional overstrain, a nonspecific questionnaire for assessing the quality of life (i.e., SF-36) was used. Based on the responses of the athletes, the "psychological component of health" (mental health) was determined, including average scores on the mental health, role functioning due to the emotional state, social functioning, and vitality scales.

After one WBAC course, an insignificant decrease in the psychological component of health according to SF-36 was noted in two gymnasts. Empirical T was in the zone of significance $T_{emp} < T_{cr}$ (0.01) (Table 7), which indicates an increase in the psychological component of health in the quality of life questionnaire. At the same time, among the athletes of the control group, no significant change was found in the psychological component of health during these 10 days, $T_{emp} > T_{cr}$ (Table 7). This confirms that the cryotherapy procedure had

Table 8 / Таблица 8

Average values of the "psychological component of health" according to SF-36 at the beginning and the end of the training year in gymnasts of the experimental group who underwent courses of whole-body cryotherapy and gymnasts of the control group

Средние значения показателия «психологический компонент здоровья» по SF-36 в начале и конце учебно-тренировочного года у гимнасток экспериментальной группы, проходивших курсы общей воздушной криотерапии и гимнасток контрольной группы

Group / Группа	Albumin binding reserve, % / Резерв связывания альбуминов, %		T_{emp} / $T_{эмп}$ ($\sum R_i$)	T_{cr} / $T_{кр}$ ($p \le 0.01$)	p
	examination 1 / 1-е обследование M (max–min)	examination 3 / 3-е обследование M (max–min)			
Experimental / Экспериментальная (n = 22)	73.7 (84–58)	77.0 (83–60)	31.5	55	<0.01
Control / Контрольная (n = 19)	74.3 (84–61)	68.7 (80–55)	16	32	<0.01

a positive effect on the psychoemotional state of the gymnasts.

The questionnaire survey, conducted at the end of the academic and training years, showed that the psychological component of health increased significantly relative to the first survey in the experimental group but decreased in the control group (Table 8).

Thus, the positive influence of WBAC on psychological indicators of self-assessment of the quality of life, such as vitality, social functioning, influences of the emotional state on role functioning, and assessment of mental health, has been established. Moreover, a positive effect was established after the first WBAC course.

CONCLUSIONS

The study results revealed that an increase in stress resistance and a decrease in psychoemotional stress during the WBAC procedure in gymnasts manifested itself as an increase in the binding capacity of serum albumin, IRI stabilization, a decrease in the number of involuntary contractions of the masticatory muscles at night, and an increase in the "psychological component of health" according to the SF-36.

In this regard, the use of WBAC can be recommended for gymnasts in the preparatory and recovery periods of annual training cycle to increase stress resistance and prevent psychoemotional overstrain.

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DOI: https://doi.org/10.17816/PED12253-64

CUTANEOUS MANIFESTATIONS OF ENDOCRINE DISEASES IN CHILDREN

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For citation: Gorlanov IA, Leina LM, Skorodok YuL, Milyavskaya IR. Cutaneous manifestations of endocrine diseases in children. *Pediatrician (St. Petersburg)*. 2021;12(2):53-64. https://doi.org/10.17816/PED12253-64

Received: 02.02.2021 Revised: 22.03.2021 Accepted: 23.04.2021

Endocrine diseases such as obesity, diabetes mellitus, Cushing's syndrome, hypothyroidism and hyperthyroidism, acromegaly and hyperandrogenism in children and adolescents are often manifested by changes in the skin. Moreover, skin symptoms can be a marker of systemic, in this case, endocrine and metabolic diseases. Obesity and diabetes are chronic diseases that affect people all over the world, and their incidence is increasing in both children and adults. Clinically, they affect a number of organs, including the skin. The cutaneous manifestations caused or aggravated by obesity and diabetes are varied and usually bear some relation to the time that has elapsed since the onset of the disease. They include acrochordons, acanthosis nigricans, striae, xerosis, keratosis pilaris, plantar hyperkeratosis, fungal and bacterial skin infections, granuloma annulare, necrobiosis lipoidica. In obese patients, psoriasis and atopic dermatitis are more common than in the control group. With the pathology of the thyroid gland, diseases such as alopecia, pretibial myxedema, urticaria, and some others develop. Hyperandrogenism (polycystic ovary syndrome) is accompanied by skin lesions such as acne vulgaris, hirsutism, androgenic alopecia, acanthosis nigricans. This literature review focuses on the main skin syndromes accompanying endocrine pathology in children and adolescents. Information about such clinical associations can make it easier for pediatricians and endocrinologists to diagnose and treat endocrine diseases in a timely manner and, thereby, prevent long-term adverse consequences.

Keywords: obesity; diabetes mellitus; hypothyroidism; hyperthyroidism; Cushing's syndrome; hirsutism; skin manifestations.

ПОРАЖЕНИЕ КОЖИ ПРИ ЭНДОКРИННЫХ ЗАБОЛЕВАНИЯХ У ДЕТЕЙ

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Для цитирования: Горланов И.А., Леина Л.М., Скородок Ю.Л., Милявская И.Р. Поражение кожи при эндокринных заболеваниях у детей // Педиатр. – 2021. – Т. 12. – № 2. – С. 53–64. https://doi.org/10.17816/PED12253-64

Поступила: 02.02.2021 Одобрена: 22.03.2021 Принята к печати: 23.04.2021

Эндокринные заболевания, такие как ожирение, сахарный диабет, синдром Кушинга, гипотиреоз и гипертиреоз, акромегалия и гиперандрогения, у детей и подростков нередко проявляются и изменениями со стороны кожи. Более того, кожные симптомы могут быть маркером системных, в данном случае эндокринных и метаболических, болезней. Ожирение и диабет — это хронические заболевания, которые распространены по всему миру и поражают несколько органов, включая кожу. Хотя оба заболевания чаще встречаются у взрослых, их распространенность среди детей возрастает. По данным Всемирной организации здравоохранения, 20 % детей и подростков в Европе имеют избыточный вес, а треть из них страдают ожирением. Кожные проявления, вызванные или усугубляемые ожирением и диабетом, разнообразны и обычно имеют некоторую связь со временем, прошедшим с начала заболевания. К дерматозам, ассоциированным с сахарным диабетом и ожирением, относятся мягкие фибромы, черный акантоз, стрии, ксероз, фолликулярный гиперкератоз, подошвенный гиперкератоз, грибковые и бактериальные инфекции кожи, кольцевидная гранулема, липоидный некробиоз. У больных ожирением чаще, чем в контрольной группе, встречается псориаз и атопический дерматит. При патологии щитовидной железы развиваются такие заболевания, как алопеция, претибиальная микседема, крапивница и некоторые другие. Гиперандрогения (синдром поликистозных яичников) сопровождается такими поражениями кожи, как вульгарные угри, гирсутизм, андрогенная алопеция, черный акантоз (acanthosis nigricans). Этот литературный обзор посвящен основным кожным синдромам,

сопровождающим эндокринную патологию у детей и подростков. Информация о подобных клинических ассоциациях может облегчить педиатрам и эндокринологам своевременную диагностику и лечение при эндокринных заболеваниях и тем самым предотвратить отдаленные неблагоприятные последствия.

Ключевые слова: ожирение; сахарный диабет; гипотиреоз; гипертиреоз; синдром Кушинга; гирсутизм; кожные проявления.

INTRODUCTION

Dermatologists often observe various skin changes that are characteristic of certain endocrine diseases. The identification of endocrinopathy is very important because patients will be able to receive pathogenetic rather than symptomatic treatment. Metabolism and endocrine gland disorders accompanied by skin lesions include obesity, diabetes mellitus (DM), hyperthyroidism, hypothyroidism, Cushing syndrome, acromegaly, and hyperandrogenism.

Cutaneous manifestations of DM and obesity are directly related to the onset age and duration and severity of the underlying disease.

Diabetes mellitus

DM represents a heterogeneous group of disorders characterized by high blood sugar levels and impaired lipid and carbohydrate metabolism. DM is classified according to pathogenesis as type 1 (T1DM) or type 2 (T2DM), and each type has particular clinical characteristics. Complications associated with DM are multifactorial in origin and result from biochemical, structural, and functional disorders. Approximately 30% of adult patients with DM will have cutaneous manifestations at some point in their lives; the timing varies depending on the DM type, patient's age, and disease duration. Children are not exempted. In the pediatric population, T1DM occurs predominantly with an average onset age of 8 years. Owing to the increasing prevalence of obesity and insulin resistance, the detection rate of T2DM has also increased, mainly in children aged >10 years [6, 7, 10, 26].

In 1985, a classification was proposed that distinguishes between skin diseases caused by DM, associated with DM or insulin therapy, and skin manifestations of insulin resistance [10] (Table 1).

Skin changes caused by DM. High blood glucose levels and damage to the vascular and nerve structures characteristic of DM cause skin changes and diseases such as xerosis, follicular hyperkeratosis, rubeosis, infections, limited joint mobility, microangiopathy, and neuropathy.

Xerosis, or dry skin, is one of the earliest and most common symptoms of DM and occurs in 22% of patients with type 1 DM [6, 44]. Interestingly, even in the absence of clinically evident xerosis, the skin of patients with DM exhibits abnormal desquamation and decreased elasticity, as well as an increase in thickness, which may contribute to a decrease in its elasticity.

Skin thickening is clinically divided into three categories, namely benign skin thickening, scleroderma-like syndrome, and Buschke scleredema. Thickening of the skin in DM is considered caused

Table / Таблица

Cutaneous manifestations in children with diabetes
Кожные проявления у детей с диабетом

Skin changes caused by diabetes / Изменения кожи, вызванные диабетом	Skin conditions associated with diabetes / Кожные заболевания, связанные с диабетом	Skin changes associated with insulin resistance / Изменения кожи, связанные с резистентностью к инсулину	Complications of insulin therapy/ Осложнения инсулинотерапии
• Xerosis / Ксероз • Follicular hyperkeratosis / Фолликулярный гиперкератоз • Fungal and bacterial infections / Инфекции грибковые и бактериальные • Microangiopathies and neuropathies / Микроангиопатии и нейропатии	• Granuloma annulare / Кольцевидная гранулема • Necrobiosis lipoidica / Липоидный некробиоз • Diabetic dermopathy / Диабетическая стопа • Onychodystrophy / Ониходистрофия • Vitiligo / Витилиго	• Acanthosis nigricans / Черный акантоз • Akrochordone / Акрохордоны • Acne, seborrhea / Угри, себорея	• Lipoatrophy and lipohypertrophy / Липоатрофия и липогипертрофия • Scarring / Рубцы • Blisters / Пузыри

by abnormal collagen glycation during episodes of hyperglycemia or collagen proliferation caused by excess insulin. The limbs appear to be the most vulnerable to benign skin thickening in patients with DM, which is closely related to the subsequent limitation of joint mobility. Even in the absence of visible changes, an increase in skin thickness can be confirmed by ultrasonography [10].

Hyperkeratosis follicularis (keratosis pilaris) is a common (11.7%) condition in patients with T1DM aged >10 years. Clinical manifestations include coarse follicular papules and erythema, located predominantly on the extensor surfaces of the arms and legs, sometimes on the face, buttocks, and trunk. Keratosis pilaris tends to be aggravated in winter and less severe in the summer months.

The so-called *face redness in patients with DM* (Rubeosis faciei diabeticorum) is a characteristic rash on the face noted in some patients, which is caused by dilatation of small vessels on the cheeks, probably as a result of diabetic microangiopathy [41]. The prevalence of this condition increases with the disease duration and is more common in patients with T2DM (51%) than in pediatric patients with T1DM (7%) [44].

Limited joint mobility, also called diabetic arthropathy, is the most clinically evident long-term complication of childhood T1DM [30]. It is characterized by asymptomatic bilateral contracture of the finger joints (chaeropathy) associated with waxy thickening of the skin. In more severe cases, the process involves the cervical spine, large joints of the limbs, and feet. This appears to be the result of non-enzymatic glycation of collagen, which leads to the formation of insoluble cross-linked collagen causing rigidity in the dermis and joints. The incidence rate of this complication (2.3%–30%) [10, 44] increases with the T1DM duration (>5 years), age (usually develops in prepubertal and pubertal age), and decreases due to improved glycemic control [5, 6]. Following the first manifestations, the disease progresses over several months or years, after which the pathological process is stabilized [41].

Patients with limited joint mobility are at increased risk of other microvascular complications of DM, especially retinopathy and neuropathy.

Infections. Patients with DM are prone to severe, recurrent, and atypical infections. DM causes changes in the immune system such as a decrease in the chemotaxis of leukocytes and phagocytosis, a significant deficit of the immune response due to impairment of the vascular reaction which contributes to the occurrence of infections and a delay in their resolution [36]. In children with DM, candidiasis is most common, and dermatophytosis is less often reported. Moreover, no association with viral skin diseases was noted. Candidal infection in the form of vulvovaginitis, balanitis, and angular cheilitis is reported more often in patients with DM than in the general population [6, 44]. Candidal vulvovaginitis accounts for up to 56% of infection cases of the external genital organs in girls with DM aged 2–15 years [10]. Among bacterial infections, staphyloderma and streptoderma infections are predominant, whereas staphylococcal infections occur more often in patients with T1DM than in those with T2DM [37, 38]. Folliculitis and impetigo are the most common infections in carriers of *Staphylococcus aureus*.

Microangiopathy and neuropathy. DM gradually affects the vascular and nervous system because it is associated with structural changes in tissues due to chronic hyperglycemia as well as ischemia. Microangiopathies are found more often in the second decade of life and associated with reduced elasticity and impaired endothelial function of peripheral arteries [6]. Lesions of the lower extremities include hypothermia, nail dystrophy, patchy skin color, and hair loss on the legs. Other manifestations are anhidrosis, which is a result of severe vascular or autonomic dysfunction, and poor wound healing due to vascular insufficiency and neuropathy. The most severe lesion of the lower extremities in DM, the so-called diabetic foot, is usually registered in older patients; however, in adolescents and young people, there can be changes that predispose to the development of a diabetic foot, namely helomas, ingrown nails, blisters, dryness, hypothermia, and skin dystrophy. These predisposing factors must be necessarily identified and preventive measures must be taken [30].

Skin diseases that are more common in patients with DM. There is a group of disorders of unknown etiology that are associated with DM or are more common in patients with DM. These are necrobiosis lipoidica, granuloma annulare, and diabetic dermopathy.

Necrobiosis lipoidica is a rare disease even among patients with DM, which is more common in women than in men and adults than in children (0.3% and 0.06%, respectively) [10].

Meanwhile, in 2007, M.D. Pavlović reported that necrobiosis lipoidica occurs in 2.3% of patients with T1DM and did not confirm a significant relationship among skin lesions, age, disease duration, and metabolic control [44]. Clinically, necrobiosis lipoidica manifests itself as bilateral,

asymptomatic, and yellow-orange or red-brown plaques located symmetrically on the lower extremities (often on the front of the lower leg) or in some cases on the upper extremities. Typical histological signs include neutrophilic necrotizing vasculitis in the early stages, amorphous degeneration, and hyalinization of cutaneous collagen (necrobiosis) in later stages. Treatment includes good blood glucose control.

Granuloma annulare is a benign inflammatory disease characterized by the degeneration of connective tissue and predominantly histiocytic inflammatory infiltration. Although the origin of this condition remains poorly understood, in adults, this condition is associated with several systemic diseases, especially rheumatic diseases and DM. In children, such associations were not noted, but the literature presents data on individual cases of granuloma annulare in children with DM [36]. Granuloma annulare can occur at any age, but it is generally more common in children and adolescents. In children, the most common clinical variants are localized and subcutaneous forms. Localized granuloma annulare appears as dense and smooth pale pink papules. Papules coalesce into one or more annular plaques around a slightly depressed pallid center [10, 36].

In some patients, granuloma annulare may coexist with necrobiosis lipoidica. Their histological similarity makes some researchers believe that granuloma annulare is an early phase of necrobiosis lipoidica. Treatment is often not required, as most rashes resolve spontaneously within 2 years.

Diabetic dermopathy is the most common cutaneous manifestation of DM in adults (9%–55%) and is relatively rare in children. It presents as clearly defined, slightly indented, light-brown atrophic spots, usually <1 cm in diameter. Lesions are usually localized on the anterior surface of the lower legs and lateral sides of the ankles and are less often on the thighs and arms. These lesions are usually bilateral or asymmetric. Although the etiology and pathogenesis of this condition are poorly understood, clinical manifestations are caused by hemosiderin and melanin deposits in the dermis. The histological pattern in the epidermis includes atrophy, moderate hyperkeratosis, and varying degrees of basal pigmentation. In the papillary dermis, telangiectasis, fibroblast proliferation, edema, hyaline microangiopathy, extravasated erythrocytes, hemosiderin deposits, and moderate perivascular infiltrate consisting of lymphocytes, histiocytes, and plasma cells are detected [10, 36].

Such dermopathy requires ruling out DM because it is closely related to DM and specific to it. The presence of dermopathy in patients with DM is an indicator that the disease is poorly controlled [37].

Vitiligo. According to the literature, vitiligo is registered in 1%–7% of patients with DM (and only in 0.2%–1% of the general population), and DM is diagnosed in 0.6% of patients with vitiligo [30, 35]. Vitiligo associated with DM often occurs in a generalized form that is resistant to treatment [30].

Cutaneous manifestations of insulin resistance syndrome. In recent years, the growing prevalence of insulin resistance syndrome and the worldwide increase in the incidence of T2DM are concerning. Insulin resistance is a condition when a certain amount of insulin does not elicit the expected biological response, followed by compensatory hyperinsulinemia to maintain normal glucose levels and lipid homeostasis [45]. Insulin resistance is a risk factor for DM and heart and central nervous system diseases. The most common cutaneous manifestations of insulin resistance are acrochordons and acanthosis nigricans. These disorders are reported in one-third of patients.

Acanthosis nigricans is the most common early sign of obesity and/or insulin resistance syndrome in children [10, 51, 53]. The etiology and pathogenesis of acanthosis nigricans have not been completely elucidated; however, data indicate the involvement of insulin in this process. Increased proliferation of epidermal cells in acanthosis nigricans is clearly associated with hyperinsulinemia and insulin resistance; an increased plasma insulin level was recorded in 74% of patients with obesity and acanthosis nigricans [25]. Acanthosis nigricans can develop under the influence of insulin-like growth factor-1 (IGF-1), which is overproduced by the liver due to hyperinsulinemia. IGF-1 receptors are expressed on basal keratinocytes and fibroblasts and are stimulated in similar proliferative conditions [36]. In the beginning, hyperpigmentation usually appears, later accompanied by hypertrophy of the skin, with a further intensification of its color, and papillomatosis. Most often, the process is localized in the armpits, on the rear and lateral surfaces of the neck, in the area of the external genital organs, and the inner surface of the thighs (Fig. 1).

Acrochordons (soft fibroma and fibroepithelial polyp) manifest as benign proliferative formations on the skin. They are represented by soft papules on pedicles of brownish or skin color, most often located in the armpits, groin areas, and neck. Me-

chanical friction, endocrine disorders, and human papillomavirus (HPV) are considered contributing factors. HPV infection begins with the inoculation of the virus into the viable epidermis at the sites of its damage, and infection further spreads because of autoinoculation [53].

Other skin manifestations include keratosis pilaris, hirsutism, and signs of hyperandrogenism such as acne and seborrhea, which are aggravated by obesity.

Skin disorders associated with insulin therapy. Information on the prevalence of skin complications caused by insulin injection varies; in one study, lipohypertrophy was detected in 1.8% of cases, but two other studies reported lipoatrophy and lipohypertrophy in 29% and 48% of the patients, respectively [10, 30]. Refusal to rotate injection sites is considered an independent risk factor for the development of lipohypertrophy [6].

Other post-injection skin changes can be redness, vesicular rashes, and local infection. In the literature, the most common complications of constant subcutaneous insulin infusion (insulin pump therapy) in children are scars (<3 mm), erythema, subcutaneous nodules, and lipohypertrophy.

Obesity

Obesity is a heterogeneous group of hereditary and acquired diseases associated with excessive accumulation of adipose tissues in the body. A study reported that the number of patients with obesity has increased in recent years [47]. Obesity is associated not only with an increased risk of such diseases serious as DM, atherosclerosis, and hypertension but also participates in the development of various dermatological diseases, in both adults and children [1, 2, 47, 49, 53]. Since the amount of adipose tissue is difficult to calculate, to diagnose obesity, body mass index (BMI) is used, which is the ratio of body weight in kilograms to the square of height in meters. BMI correlates with the amount of adipose tissue in the body in both adults and children (assessment in children should consider gender and age). A patient with BMI over the 95th percentile, or 2 standard deviation score (SDS), is diagnosed with obesity, and overweight is established with BMI corresponding to the 85–95th percentile, or 1–2 SDS [6]. Although the exact prevalence of cutaneous manifestations of obesity is unknown, they are directly related to the severity and duration of metabolic disorders. In addition, the combination of obesity with DM and/or insulin resistance syndrome increases the probability of dermatological diseases [10, 53].

Obesity affects the physiological processes in the skin, including the effect on its barrier function, functioning of the sebaceous and sweat glands, lymphatic and collagen structure of the skin, wound healing, microcirculation, and subcutaneous fat [33, 42].

Yosipovitch et al. [53] classified the skin changes in obesity (adapted for children).

Diseases associated with insulin resistance are as follows:

- Insulin resistance syndrome.
- Acanthosis nigricans.
- Acrochordons.
- Keratosis pilaris.
- Acne.
- Hirsutism.

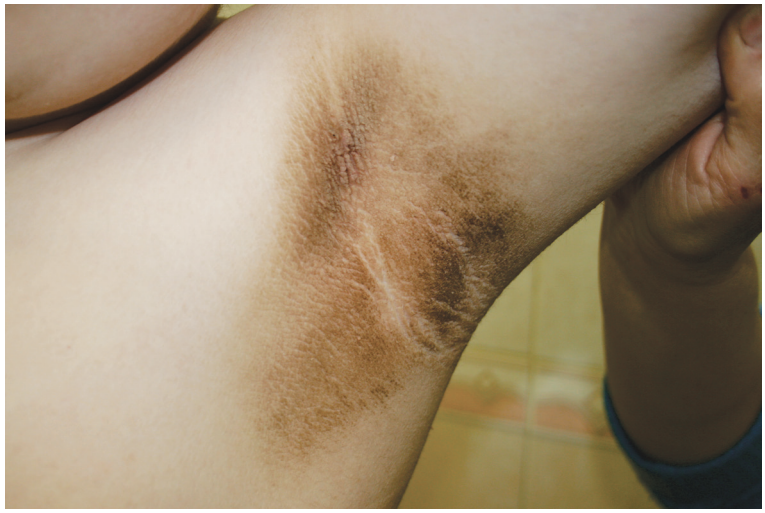

Fig. 1. Acanthosis nigricans in an obese patient

Рис. 1. Acanthosis nigricans (черный акантоз) у пациента с ожирением

Diseases associated with mechanical action on the skin:
- Plantar hyperkeratosis.
- Striae.

Infectious diseases
- Intertrigo.
- Candidiasis.
- Dermatophytosis.
- Folliculitis.

Inflammatory diseases:
- Psoriasis.
- Hydradenitis.

In recent studies, the majority of patients with obesity have plantar hyperkeratosis (47%), striae (68%), acrochordons (48%), intertrigo (44%), and less often acanthosis nigricans [12, 18]. Psoriasis in patients with obesity is detected five times more often than that in the control group [12, 21].

A recent study involved 40 patients with overweight and 25 with obesity aged 7–15 years; the control group consisted of 30 children with normal body weight. Acrochordons were detected in 40% of patients with obesity and in 2.5% patients with overweight, striae were registered in 32% and 22.5% patients, respectively, while plantar hyperkeratosis was noted only in patients with obesity (20%).

Horseshoe-shaped plantar hyperkeratosis, located on the posterior part of the sole, was the most frequent cutaneous manifestation in patients whose weight was excessive by more than 176%, and it can be considered a physiological response to mechanical trauma [11, 18].

Striae (stretch marks) are a particular form of skin atrophy, mainly in the places of its greatest stretching. Usually, striae are located symmetrically on the thighs (73%), shoulders (42%), and abdomen (30%) and less often on the chest and buttocks [24]. They have a length of 1–1.5 to 8–10 cm and a width of 1–2 to 5–6 mm, located flush with the skin, or have a retracted relief (Fig. 2).

The color of striae gradually, over several months, changes from bright pink, sometimes even purple, to whitish, with a pearlescent tint. Striae occur not only in obesity but also in conditions such as pregnancy and Cushing syndrome, and during treatment with topical corticosteroids. In the literature, striae in obese individuals are not as wide and atrophic as in patients with Cushing syndrome [8]. The exact pathogenesis of striae has not been elucidated; however, mechanical, hormonal, and genetic factors may play a role in their development [18].

Keratosis pilaris (hyperkeratosis follicularis) presents as small follicular papules (pinhead-sized, with vellus hair on the surface), usually localized on the extensor surfaces of the shoulders and hips. There may be a hyperemic corolla around the papules. When stroking the keratosis area, there is a symptom of "grater" or "sandpaper" [52]. In addition to obesity, follicular hyperkeratosis is noted in Cushing syndrome, DM, and hypothyroidism. Insulin resistance may play a role in the development of keratosis pilaris [53].

Additionally, hyperinsulinemia (as a consequence of insulin resistance) increases the production of androgens and decreases the production of sex hormone-binding globulin by the liver, which, in turn, may contribute to the development of acne, hirsutism, and androgenic alopecia [17, 47].

Obesity increases the incidence of skin infections such as candidiasis, dermatophytosis, and bacterial infections. Although infectious dermatoses are not specific to obesity, the incidence of skin infections

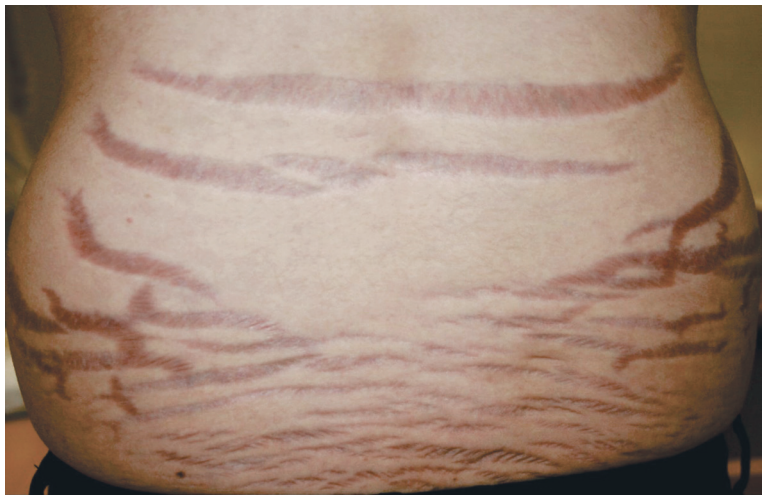

Fig. 2. Striae in a 14-year-old obese girl
Рис. 2. Стрии у девочки 14 лет с ожирением

in patients with overweight is higher than in those with normal body weight [18].

Skin folds become a preferable site of infections, where trivial intertrigo first occurs. Features of the skin of patients with obesity such as deep folds, hyperhidrosis, and mechanical friction, create a favorable environment for increasing maceration and subsequent infection [18].

Recent studies have presented a significantly higher prevalence of obesity in patients with psoriasis than in the general population [9, 13, 20, 32]. Moreover, the question of whether psoriasis or obesity is a precursor is still relevant. A study reported follow-up data of 557 patients with psoriasis and showed that the risk of developing psoriasis is not higher in patients with obesity aged <18 years than in patients without obesity, but obesity later appears in patients with psoriasis (Fig. 3) [22].

Studies have shown that the BMI value is directly related to the duration of psoriasis [46]. The lack of physical activity in patients with psoriasis, associated with a cosmetic defect or arthropathy, probably predisposes them to obesity. Studies have indicated that obesity, hyperlipidemia, hypertension, DM, metabolic syndrome, and polycystic ovary syndrome were more common in the families of patients with psoriasis than in the control group [34, 35, 50, 52]. A study showed that patients with psoriasis were more likely to be overweight than children in the control group (37.9 and 20.5%, respectively) [43]. Moreover, the onset of childhood obesity especially predisposes the patients to the development of psoriasis and psoriatic arthropathy, which probably reflects the influence of genetic factors [43]. Among children with obesity, the blood levels of cholesterol, low-density lipoproteins, and triglycerides were significantly higher in patients with psoriasis than in those without it [29]. Clinical cases confirm the presence of common signs in the pathogenesis of obesity and psoriasis. Macrophages in adipose tissue produce tumor necrosis factor (TNF)-α, as well as other cytokines (interleukin [IL]-1, IL-6, IL-17, and interferon-γ) involved in the development of psoriasis [3, 13, 19]. Adipocytes produce adipokines (adipocytokines), namely leptin, resistin, and adiponectin [4]. Cytokines and leptin accumulate in case of obesity and can have autocrine and paracrine effects on nearby skin. Leptin affects T-cell regulation and stimulates the release of pro-inflammatory cytokines [3]. The blood concentration of leptin correlates with the severity of psoriasis [14, 19]. The hormone resistin leads to insulin resistance and promotes the activation of inflammatory processes in the skin. The level of

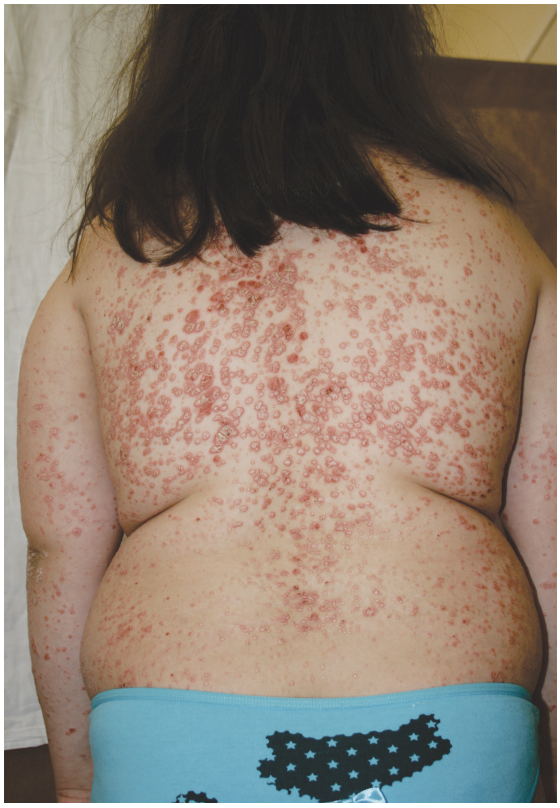

Fig. 3. Psoriasis in a 14-year-old obese girl
Рис. 3. Псориаз у девочки 14 лет с ожирением

resistin is increased in patients with psoriasis (directly dependent on the disease severity) and correlates with the BMI [24]. The level of the anti-inflammatory mediator adiponectin in patients with psoriasis and obesity is lower than that in patients with psoriasis and normal body weight [16]. Thus, immunological and metabolic disorders associated with obesity may be associated with the pathogenesis of psoriasis [14, 16, 19, 27]. The so-called inverse psoriasis (psoriasis in the folds) was recorded more often in the obese group than in the control group (11% and 5%, respectively) [22].

Studies have presented numerous data on the relationship between obesity and atopic dermatitis (AD) [15, 48, 52], and researchers revealed that the incidence of AD is significantly higher in patients with obesity, especially with manifestation at the age of up to 2 years, than in the control group. The duration of obesity (more than 2.5 years) also increased the probability of AD [39]. The association of AD with obesity is possibly due to various immune disorders detected in obesity, especially with the production of TNF-α and IL-6 by adipocytes. Leptin, which is produced by adipocytes, has a pro-inflammatory effect on the immune system, causing the proliferation and activation of monocytes

and CD4 and CD8 lymphocytes, and polarizing the T-cell response toward TH1 [17, 40].

Cushing syndrome

Cushing syndrome represents a combination of clinical symptoms caused by a chronic increase in the levels of cortisol or related corticosteroids in the blood. Although Cushing syndrome is predominant in female adolescents and adults, in the prepubertal period, boys are affected by it more often than girls. Most of the children with Cushing syndrome are obese in the trunk and have growth retardation [6]. Excessive glucocorticoid levels are believed to decrease the proliferation of keratinocytes and dermal fibroblasts, which in turn leads to decrease in the formation of collagen and other components of the extracellular matrix and ultimately contributes to skin atrophy and fragility. The catabolic effect of glucocorticoids extends to subcutaneous connective tissues. Cutaneous manifestations of Cushing syndrome are as follows [31]:

- Moonlike face.
- Striae.
- Cigarette paper atrophy of the skin on the elbows and dorsum of the hands.
- Slow wound healing.
- Steroid acne.
- Hyperpigmentation.
- Acanthosis nigricans.

Fatty tissue is often deposited on the face in the cheeks (moonlike face), on the posterior surface of the neck with the transition to the back (dorsocervical fat), above the collarbones (thick, short neck), and behind the orbit (exophthalmos). Cigarette paper skin on the elbows and the dorsal side of the hands is a result of epidermal and cutaneous atrophy. As body weight is redistributed and increased, the fragile skin stretches and subcutaneous blood vessels become more visible, looking like purple striae. In Cushing syndrome, the flaccid and wide (>1 cm in diameter) striae can be distinguished from the pinkish-silver thin striae seen in growth spurt, obesity, and pregnancy. Additional changes in the skin may appear in the form of acanthosis nigricans. An excess in the levels of endogenous or exogenous glucocorticoids can lead to steroid acne localized on the upper back, proximal upper limbs, neck, and face. Excess glucocorticoids can also lead to superficial dermatophytosis and malassezia infection.

Polycystic ovary syndrome

Polycystic ovary syndrome is characterized by the excessive production of androgens, which can manifest in adolescent girls as menstrual irregularities, android type obesity, and skin changes, such as acne and/or hirsutism [28, 31]. Initial screening for suspected androgen-associated disease is usually serum dehydroepiandrosterone sulfate, testosterone, and prolactin tests [31]. Cutaneous manifestations in hyperandrogenemia are as follows [28, 31]:

- Acne.
- Hirsutism.
- Androgenic alopecia.
- • Acanthosis nigricans.

Hirsutism is defined as excessive growth of terminal hairs in androgen-dependent areas, primarily the face, neck, back, chest, and lower abdomen [6, 28]. Hyperandrogenism promotes an increase in hair thickness and prolongs the phase of hair growth in the beard, armpits, and pubis. Acne vulgaris is an additional manifestation of polycystic ovary syndrome. The possibility of excess in androgen levels in patients with moderate to severe acne should be considered, especially acne that is resistant to traditional treatments or recurrence after the use of isotretinoin. Signs of severe hyperandrogenism are coarsening of the voice, muscle hypertrophy, breast size reduction, and androgenic alopecia. Patients with androgenic alopecia often notice a gradual thinning of the hair in the parietal region, while maintaining the front hair growth line [23, 27].

Hypothyroidism

Hypothyroidism can be congenital or acquired. Congenital hypothyroidism occurs in 1 per 2000–4000 newborns and is most often associated with thyroid dysgenesis. In the general population, autoimmune thyroiditis (AIT) is the most well-known cause of hypothyroidism worldwide. The incidence of AIT among schoolchildren reaches 1%–2%, and it affects girls 4–7 times more often than boys [6]. The clinical symptoms of hypothyroidism are of low specificity. Meanwhile, changes in the skin and its appendages as well as in the subcutaneous tissue require the exclusion of hypothyroidism, for which, in most cases, it is sufficient to determine the serum level of thyroid-stimulating hormone. Changes in the skin, subcutaneous tissue, and dermal appendages characteristic of hypothyroidism [6, 31] are as follows:

- Pale and subicteric skin.
- Dry, flaky, rough, and cold skin.
- Edematous face and tongue and edema in the area of the supraclavicular fossa and dorsum of the hands and feet.
- Loss of the lateral surfaces of the eyebrows.
- Dry and brittle hair or alopecia.

Hyperthyroidism

Hyperthyroidism is an integral sign of diffuse toxic goiter (DTG), or Graves' disease. In the pediatric population, the peak incidence is recorded at age 10–15 years, and similar to adults, DTG prevails in females. The main cutaneous manifestations of hyperthyroidism are as follows [31]:

- Warm moist thin skin.
- Erythema of the palms.
- Hyperhidrosis.
- Thin hair on the head.
- Onycholysis.
- Pretibial myxedema.
- General pruritus.
- Chronic urticaria.

The most common cutaneous manifestations of hyperthyroidism include facial flushing, palmar erythema, and hyperhidrosis of the palms and plantae. The hair on the head is thin and may fall out. Nails are thin; in rare cases (atypical for children), onycholysis (detachment of the nail plate from soft tissues) can be noted, when the proximal part of the plate remains pink, and the distal part becomes white or opaque (Plummer's nail). Pretibial myxedema is recorded in 4% of patients with Graves' disease (extremely rare in children). Indurations, deepened nodules, and plaques appear on the skin in the tibial area, with hyperpigmentation and desquamation.

Skin changes such as generalized pruritus and eczematous dermatitis are less common in hyperthyroidism. Chronic urticaria (as well as pretibial myxedema) should be considered a possible manifestation of autoimmune disease in DTG, not a consequence of hyperthyroidism.

Acromegaly

Excess growth hormone generates a cascade of clinical manifestations involving soft tissues and bones. Depending on whether hypersomatopinemia is registered before or after the fusion of the epiphyseal growth zones, the disease is defined as gigantism or acromegaly. Pituitary gigantism can be manifest by accelerated growth and tall stature at any age, and cases have been described from month 2 of life. Meanwhile, the incidence of gigantism is extremely low; one major study showed that hypersomatopinemia is found in 0.6% of pituitary adenomas in children and may be a consequence of neurofibromas of the central nervous system. Changes in the skin, as well as soft tissues and dermal appendages, typical for patients with closed growth zones, can also be seen in older adolescents with nearly complete growth and/or in controls in whom the growth hormone is no longer of the same significance [26, 31]:

- Macrocheilia.
- Macroglossia.
- Gingival hyperplasia.
- Coarse facial features.
- Hyperpigmentation.
- Acanthosis nigricans.
- Hyperhidrosis.
- Hypertrichosis.
- Nail changes.

CONCLUSIONS

Skin lesions are quite common in endocrine diseases. This fact must be kept in mind by pediatricians, dermatologists, and endocrinologists.

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DOI: https://doi.org/10.17816/PED12273-83

CONGENITAL METABOLIC DISEASES. LYSOSOMAL STORAGE DISEASES

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For citation: Gorbunova VN. Congenital metabolic diseases. Lysosomal Storage Diseases. *Pediatrician (St. Petersburg)*. 2021;12(2):73-83. https://doi.org/10.17816/PED12273-83

Received: 04.02.2021 Revised: 26.03.2021 Accepted: 23.04.2021

The classification and epidemiology of hereditary metabolic disorders are presented. That is a large group consisting from more them 800 monogenic diseases, each of which caused by inherited deficiency of certain metabolic fate. Many of these disorders are extremely rare, but their total incidence in the population is close to 1:1000–5000. Lysosomal storage diseases (LSD) resulting from inherited deficiency in lysosomal functions occupy a special place among hereditary metabolic disorders. The defects of catabolism cause the accumulation of undigested or partially digested macromolecules in lysosomes (that is, 'storage'), which can result in cellular damage. About 60 diseases take part in this group with total incidence of about 1:7000–8000. LSDs typically present in infancy and childhood, although adult-onset forms also occur. Most of them have a progressive neurodegenerative clinical course, although symptoms in other organ systems are frequent. The etiology and pathogenetic aspects of their main clinical entities: mucopolysaccharidosis, glycolipidosis, mucolipidosis, glycoproteinosis, etc, are presented. Mucopolysaccharidoses caused by malfunctioning of lysosomal enzymes needed to break down glycosaminoglycans are more frequent among LSD. Sphingolipidoses caused by defects of lipid catabolism are second for frequency group of LSD. The state-of-art in field of newborn screening. clinical, biochemical and molecular diagnostics of these grave diseases are discussed. The main directions of modern lysosomal storage diseases therapy are characterized: transplantation of hematopoietic stem cells; enzyme replacement therapy; therapy with limitation of substrate synthesis (substrate-reducing therapy); pharmacological chaperone therapy. Perspective directions for LSD therapy are gene therapy and genome editing which are at advanced preclinical stages.

Keywords: inborn errors of metabolism; lysosomal storage disorders; diagnosis; newborn screening; enzyme replacement therapy.

НАСЛЕДСТВЕННЫЕ БОЛЕЗНИ ОБМЕНА. ЛИЗОСОМНЫЕ БОЛЕЗНИ НАКОПЛЕНИЯ

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Для цитирования: Горбунова В.Н. Наследственные болезни обмена. Лизосомные болезни накопления // Педиатр. – 2021. – Т. 12. – № 2. – С. 73–83. https://doi.org/10.17816/PED12273-83

Поступила: 04.02.2021 Одобрена: 26.03.2021 Принята к печати: 23.04.2021

В статье представлена классификация и эпидемиология наследственных болезней обмена (НБО). НБО — это большая группа из более чем 800 моногенных заболеваний, обусловленных наследственной недостаточностью определенного метаболического пути. Многие из этих болезней встречаются крайне редко, однако их общая частота в популяции приближается к 1 : 1000–5000. Среди НБО особое положение занимают лизосомные болезни накопления (ЛБН), обусловленные наследственной дисфункцией лизосом. Дефекты лизосомного катаболизма приводят к накоплению в лизосомах не расщепленных или частично расщепленных макромолекул, представляющих угрозу для клеток. В группу ЛБН входит более 60 заболеваний, их суммарная частота составляет 1 : 7000–8000. ЛБН чаще всего дебютируют в младенчестве или детстве, хотя описаны и взрослые формы заболевания. Для многих ЛБН характерно одновременное вовлечение в патологический процесс многих органов и систем, при этом частыми являются прогрессирующие нейродегенеративные расстройства. Обсуждается этиология и патогенез главных групп ЛБН, таких как мукополисахаридозы, сфинголипидозы, муколипидозы, гликопротеинозы и др.

Наиболее частыми среди ЛБН являются мукополисахаридозы — генетически гетерогенная группа заболеваний, обусловленных мутациями в генах ферментов, участвующих в деградации гликозаминогликанов. Вторые по значимости — сфинголипидозы, причиной развития которых становится нарушение катаболизма липидов. Обсуждается современное состояние в области неонатального скрининга, клинической, биохимической и молекулярной диагностики ЛБН. Охарактеризованы основные направления современной терапии этих тяжелых заболеваний: трансплантация гемопоэтических стволовых клеток, ферментная заместительная терапия; терапия с ограничением синтеза субстратов (субстратредуцирующая терапия); фармакологическая шаперонотерапия. Перспективными подходами для лечения ЛБН являются генная терапия и геномное редактирование, которые находятся на стадии преклинических испытаний.

Ключевые слова: наследственные болезни обмена; лизосомные болезни накопления; диагностика; неонатальный скрининг; ферментная заместительная терапия.

Hereditary metabolic diseases (HMD) are caused by disorders of the catalytic function of various enzymes. This is one of the most and well-studied groups of monogenic human diseases inherited most often in an autosomal recessive mode. Approximately 800 types of HMDs are identified [33, 37], and each disease is characterized by a set of specific biochemical disorders associated with hereditary insufficiency of a certain metabolic pathway. Most often, patients have inactivating mutations in the genes of the corresponding enzymes, and sometimes, other proteins are involved in their activation or transport. The pathogenetic mechanisms of HMDs are associated with either the accumulation of toxic concentrations of substances preceding the enzymatic block or a deficiency of the end products of the reaction. Additionally, blockage of the metabolic chain may be accompanied by pronounced "secondary" biochemical disorders.

Incidence rates of various nosological forms of HMDs vary from 1 : 10,000 newborns to $1:10^5$–10^6, and many of them are characterized by pronounced differences in this parameter in different ethnic groups and populations [7]. In some isolated populations, HMDs can occur in 1 per 3000–5000 newborns. The total incidence of HMD is 1 per 1000–5000 newborns.

Generally, HMDs represent serious conditions with quite diverse clinical manifestations. They often include psychomotor retardation, seizure syndrome, myopathy, skeletal abnormalities, recurrent coma, ketoacidosis, hepatosplenomegaly, malabsorption, ataxia, and sudden death syndrome. For most HMDs, neonatal, childhood, adult, and in some cases even asymptomatic disease forms have been described. Differences in disease onset and severity are determined by the enzyme residual activity, which in turn depends on the type of the corresponding mutation. In neonatal and childhood forms, which often end in early lethal outcomes, the enzyme activity is not determined or is significantly less than 1% of the norm; in juvenile forms, it varies from 0.5% to higher rates, and in the case of adult forms, it usually exceeds 5%, sometimes reaching several tens of percent with subclinical disease forms. However, in some cases, significant phenotypic polymorphism is registered in patients who are consanguineous and have identical mutations, which indicates the potential influence of the environmental and/or genotypic background on the manifestation of the mutation [10, 18].

HMDs are divided into 22 groups depending on the intracellular localization of the disorder (i.e., lysosomal, mitochondrial, and peroxisomal) or the type of the damaged metabolic pathway (aminoacidopathy, organic aciduria, metabolic disorders of carbohydrates, lipids, steroids and other hormones, purines and pyrimidines, bilirubin, porphyrin, among others). However, the classification of HMDs is not always unambiguous because some metabolic pathways intersect. The groups with numerous nosological forms are those that combine metabolic disorders of organic acids and amino acids, lysosomal storage diseases (LSDs), mitochondrial diseases, and disorders of carbohydrate and glycogen metabolism.

At the clinical level, HMDs can only be suspected. Biochemical methods are the first options in the diagnostics of HMD. At stage 1, the corresponding metabolites were analyzed, and at the next stage, the dysfunction of the mutant protein is identified by assessing its activity and/or amount. The determination of the concentration of metabolites in biological fluids, primarily in urine and blood, as well as their qualitative or semiquantitative analysis, often enables suspicion of a certain group of HMDs or even a nosological form with high accuracy. In this case, various spectrophotometry and chromatography types are usually used, such as primarily tandem mass spectrometry, which enable characterization of the structure within a few minutes, determine the

molecular weight, and quantify various substances. In biochemical diagnostics of HMD, approximately 50 compounds are determined in one sample.

The most complete biochemical diagnostics of HMD in Russia is performed at the Medical Genetic Scientific Center (MGSC) of the Russian Academy of Medical Sciences in the laboratory of HMDs, which was headed by K.D. Krasnopolskaya for many years. The laboratory has collected and characterized a large sample of patients. Throughout her life, Ksenia Dmitrievna has attracted the attention of doctors, medical geneticists, and specialists from other medical genetic centers of Russia to the problem of HMD, publishing articles and speaking at various conferences, meetings, and congresses. The results of this long-term work are summarized in a unique monograph by K.D. Krasnopolskaya [10], released by her students, who continue successfully the work started under the supervision of E.Yu. Zakharova [7].

Objective diagnosis of HMDs is achieved by identifying inactivating mutations in the corresponding genes. Currently, in several Russian molecular diagnostic centers, and, first of all, in the N.P. Bochkov MGSC, DNA diagnostics of HMDs is performed using "new-generation sequencing" methods. Another example is the GenoMed Center, created in the molecular pathology laboratory of the Moscow Medical Genetic Center, which offers a molecular diagnostic panel for the simultaneous assessment of the state of 500 HMD-associated genes.

LSDs hold a special place among HMDs, which represent a heterogeneous group of recessive diseases, including approximately 60 nosological forms [4, 33]. All LSDs are caused by genetic disorders of the functions of lysosomes that control intracellular cleavage processes of most biological macromolecules, such as glycolipids, glycosaminoglycans (GAGs), and glycoproteins. LSDs occur in 1 per 7–8 thousand newborns [7]. Each disease type occurs in 1 per 10,000–100,000 populations, but it can be much lower in most cases. In the laboratory of HMDs of the MGSC of the Russian Academy of Medical Sciences, from 1992 to 2009, more than 900 patients with 25 nosological forms of LSDs were identified and characterized, which enabled assessment of the range and incidence of these diseases in Russia [7, 10].

Primary lysosomes are formed from the Golgi apparatus. By merging with other membrane vesicles, secondary lysosomes are formed and contained materials that entered the cells as a result of endocytosis or are absorbed during autophagy. Lysosomes are a central component of the endosomal–lysosomal system which functions in conjunction with the chaperone-mediator system of autophagy.

Lysosomal enzymes belong to the class of acidic hydrolases which mainly break down macromolecules into their primary components, namely, amino acids, monosaccharides, and fatty and nucleic acids. Lysosomal enzymes include acid and alkaline phosphatases, glucose 6-phosphatase, lipase, cholinesterase, protease, urease, among others. Hydrolases are synthesized in the endoplasmic reticulum and then undergo post-translational processing when they are glycosylated by the addition of oligosaccharides and acquire the terminal residue of mannose 6-phosphate. In this form, hydrolases are transported to primary lysosomes. Genetic disorders at any stage of the synthesis and maturation of these enzymes lead to the accumulation of the corresponding specific substrates such as mucopolysaccharides, gangliosides, lipids, and glycoproteins, in the lysosomes. This increases the number of lysosomes, which is morphologically revealed in the appearance of so-called foam cells. The accumulation of non-cleaved macromolecules can reach significant amounts, especially in tissues and organs characterized by an increased rate of regeneration. Some LSDs are caused by genetic disorders of proteins involved in the biogenesis of lysosomes, as well as activator proteins that solubilize insoluble substrates (glycolipids), and proteins that control the vesicular transport of lysosomal enzymes or substrates subject to hydrolysis [5, 33].

Mononuclear phagocytic system cells are rich in lysosomes and thus are often involved in the pathological process in LSD. The target organs are the natural sites of the corresponding macromolecule destruction. Thus, when myelin catabolism is impaired, the white matter of the brain is involved in the process, and the accumulation of unsplit macromolecules in central nervous system (CNS) tissues generally stimulates the development of neurodegenerative processes and mental retardation. With the accumulation of metabolites in parenchymal organs, hepatosplenomegaly, anemia, and thrombocytopenia occur; the accumulation of pathological material in bone tissue contributes to the development of multiple dysostosis; and the accumulation of mucopolysaccharides present in most tissues leads to generalized damage to various organs and systems [33].

Neurological disorders are often combined with signs of dysmorphogenesis (such as coarse facial features and macroglossia), hepatosplenomegaly, skeletal disorders, contractures, umbilical hernia,

cardiovascular system pathologies (such as arrhythmia and cardiomegaly), and visual damage (corneal haze or cherry-red spot) [9, 11–14, 17]. Currently, several groups of LSDs are identified, namely mucopolysaccharidoses (MPS), lipidoses, mucolipidoses, oligosaccharidoses, neuronal ceroid lipofuscinosis [3, 6, 15].

MPS are the most common lysosomal diseases and represent a genetically heterogeneous group of recessive diseases with a high level of clinical polymorphism [9, 13, 14]. All MPS are caused by mutations in the genes of lysosomal enzymes involved in the degradation of GAGs or mucopolysaccharides. Owing to the deficiency of these enzymes in many organs and systems, an excessive amount of partially degraded GAGs (carbohydrate structures linked covalently to the core proteins of proteoglycans) accumulate. By chemical structure, GAGs are linear polymers containing amino sugar (N-acetylated or N-sulfated) and uronic or iduronic acid, which forms disaccharidase units specific for each type. GAGs include hyaluronic acid, type A, B, and C chondroitin sulfates, keratin sulfate, heparan sulfate, and heparin.

The most abundant chondroitin sulfate and dermatan sulfate proteoglycans are distributed in the extracellular space. Their interactions with collagen and elastic fibers provide the mechanical properties of many connective tissues. By contrast, heparan sulfate proteoglycans are transmembrane proteins and act as receptors for extracellular matrix proteins, growth factors, and angiogenic peptides.

GAG synthesis starts with transferring xylose to serine residues in the core protein of proteoglycans. When two residues of galactose and glucuronic acid are sequentially added, a common linked structure is formed, which is present in most types of proteoglycans. Alternative addition to this structure of N-acetylglucose or N-acetylgalactose residues leads to the formation of heparan sulfate or chondroitin sulfate, respectively. Proteoglycans degradation is a normal physiological process. It is implemented by two classes of enzymes, namely, proteinases (exo- and endopeptidases) that break down the core protein and glycosidases that break down GAG chains and oligosaccharides [33].

All MPSs are characterized by the multiplicity of lesions and simultaneous involvement of many organs and systems in the pathological process. The main clinical manifestations of MPS are considered coarse, grotesque facial features (gargoylism), significant growth retardation, multiple dysostosis, joint stiffness, hernias, hepatosplenomegaly, corneal opacity and glaucoma, hypertelorism, decreased intelligence, and bradyacuasia, and, in the cardiovascular system, hypertrophic cardiomyopathy and myxomatous degeneration of valves, more often aortic and mitral valves, with the development of their insufficiency or stenosis in the disease outcome. Typically, a clinical diagnosis cannot be established at birth. The disease manifestations are formed gradually during the first several months or even years of life and further progress. In clinical practice, MPS are often divided into two groups, namely, Hurler-like and Morquio-like phenotypes. There is a high genetic heterogeneity of the MPS. At present, genes mutated in 11 hereditary types of these diseases have been identified [15]. The Morquio-like phenotype is a characteristic of types A and B Morquio syndromes, and the remaining types constitute the MPS group with a Hurler-like phenotype.

Table 1 presents primary biochemical defects, mutant genes, and accumulation products in different MPS.

Worldwide, MPS occur in 1.56 per 100,000 newborns [24]. The most common type is MPS II which accounts for approximately 30% of all MPS cases in European countries and more than 50% in Japan. MPS types I, III, and IV account for 12%, 24%, and 24% in Europe and 15%, 16%, and 10% in Japan, respectively. MPS types VI and VII are less common; in Europe, they account for 7.3% and 2.4% of all MPS cases and in Japan 1.7% and 1.3%, respectively. The ratio of incidence of different types of MPS in Russia is approaching European values [7].

Hereditary **glycolipidoses** are caused by the deficiency of lysosomal enzymes involved in lipid catabolism, or a disorder of one of the stages of synthesis, transport, and degradation of lipoproteins, which include all the main plasma lipids, namely, triglycerides, phospholipids, cholesterol, and free fatty acids [1, 11, 12, 17]. These diseases are characterized by the abnormal deposition of large amounts of unsplit products of fat metabolism in various organs and tissues.

The majority of glycolipids are represented by sphingolipids, mainly including sphingomyelins, cerebrosides, glycosphingolipids, gangliosides, and sulfatides. Sphingomyelins are composed of sphingosine that can be combined with phosphocholine or phosphoethanolamine. These phospholipids are located on the outside of the lipid layer of the cell membrane and are especially abundant in the myelin sheath of axons. Cerebrosides, or glycosphingolipids, are also components of cell membranes. They include sphingosines, fatty acids, and carbohydrates, which can be represented by galactose or, less often,

Table 1 / Таблица 1

Molecular genetic description of the mucopolysaccharidoses (MPS)
Молекулярно-генетическая характеристика мукополисахаридоза (МПС)

Syndrome / Синдром OMIM [37]	Protein, gene, localization / Белок, ген, локализация	Storage product / Продукт накопления
MPS type I: Hurler syndrome, 607014; Scheie syndrome, 607016; Hurler–Scheie syndrome, 607015 / МПС тип I: синдром Гурлера, 607014; синдром Шейе, 607016; синдром Гурлера–Шейе, 607015	Alpha-L-iduronidase / Альфа-L-идуронидаза *IDUA*; 4p16.3	Dermatan sulfate, heparan sulfate / Дерматансульфат, гепарансульфат
MPS type II Hunter syndrome МПС тип II: синдром Хантера / 309900	Iduronate 2-sulfatase / Идуронат-2-сульфатаза *IDS*; Xq28	Dermatan sulfate, heparan sulfate / Дерматансульфат, гепарансульфат
MPS type IIIA: Sanfilippo syndrome A / МПС тип IIIA: синдром Санфилиппо, тип A 252900	Heparan N-sulfatase, or sulfamidase / Гепаран-N-сульфатаза или сульфамидаза *SGSH*; 17q25.3	Heparan sulfate / Гепарансульфат
MPS type IIIB: Sanfilippo syndrome B / МПС тип IIIB: синдром Санфилиппо, тип B 252920	Alpha-N-acetylglucosaminidase / A-N-ацетил-глюкозаминидаза*NAGLU*; 17q21.1	Heparan sulfate / Гепарансульфат
MPS type IIIC: Sanfilippo syndrome C / МПС тип IIIC: синдром Санфилиппо, тип C 252930	Aacetyl CoA: alpha-glucosaminide acetyltransferase / Ацетил-КоА: α-глюкозаминидаза-N-ацетилтрансфераза *HGSNAT*; 8p11.1	Heparan sulfate / Гепарансульфат
MPS type IIID: Sanfilippo syndrome D / МПС тип IIID: синдром Санфилиппо, тип D 252940	N-acetylglucosamine-6-sulfatase / N-ацетилглюкозамин-6-сульфатаза *GNS*; 12q14	Heparan sulfate / Гепарансульфат
MPS type IVA: Morquio syndrome A / МПС тип IVA: синдром Моркио, тип A 253000	Galactosamine-6-sulfate sulfatase / Галактозамин-6-сульфат-сульфатаза *GALNS*; 16q24.3	Keratan sulfate, chondroitin-6-sulfate / Кератансульфат, хондроитин-6-сульфат
MPS type IVB: Morquio syndrome B / МПС тип IVB: синдром Моркио, тип B 253010	Beta-galactosidase-1 / Бета-галактозидаза-1 *GLBI*; 3p21.33	Keratan sulfate / Кератансульфат
MPS type VI: Maroteaux–Lamy syndrome / МПС тип VI: синдром Марото–Лами 253200	Arylsulfatase B / Арилсульфатаза B *ARSB*; 5q11-q13	Dermatan sulfate / Дерматансульфат
MPS type VII: Sly syndrome / МПС тип VII: синдром Слая 253220	Beta-glucuronidase / Бета-глюкуронидаза *GUSB*; 7q21.11	Heparan sulfate, dermatan sulfate / Гепарансульфат, дерматансульфат
MPS type IX / МПС тип IX 601492	Hyaluronidase / Гиалуронидаза *HYAL1*; 3p21.31	Keratan sulfate, heparan sulfate / Кератансульфат, гепарансульфат

glucose (galactocerebrosides and glucocerebrosides, respectively). Gangliosides (GM1, GM2, and GA2) are an integral part of glycosphingolipids located on the outer surface of most cell membranes. They are especially abundant in cells of the nervous system. Sulfatides are involved in the construction of the myelin sheath of nerve fibers [33].

Lysosomal diseases caused by hereditary insufficiency of sphingolipids are called **sphingolipidosis**. Sphingolipid catabolism occurs in lysosomes, where glycohydrolases degrade them by sequential separation of terminal sugars to the core ceramide. Sphingolipidoses include disease groups such as glycosphingolipidosis, cerebrozidosis, gangliosidosis, and leukodystrophy. Cerebrosidosis includes Fabry disease [17], glucosylceramide lipidosis (or Gaucher disease) [12], lipogranulomatosis (or Farber disease), and sphingomyelin lipidosis (or Niemann–Pick disease) [11].

Gangliosidosis includes GM1 gangliosidosis and three GM2 gangliosidoses, namely, types I and II (or Tay–Sachs disease and Sandhoff disease,

respectively), as well as type AB. Hereditary leukodystrophies include Krabbe disease (or globoid cell leukodystrophy), metachromatic leukodystrophy, combined deficiency of prosopasine, a precursor of sphingolipid hydrolysis activator proteins, and multiple sulfatase deficiency.

All sphingolipidoses are characterized by signs related to the intracellular accumulation of certain sphingolipids in the liver, spleen, lungs, bone marrow, and brain. Table 2 shows primary biochemical defects, mutant genes, and accumulation products in different types of glycolipidoses.

Mucolipidosis is based on the deficiency of enzymes involved in the processing of lysosomal hydrolases such as N-acetylglucosamine 1-phosphotransferase, which is an enzyme necessary for the attachment of mannose 6-phosphate to oligosaccharides of lysosomal enzymes. Without mannose 6-phosphate, enzymes cannot enter the lysosomes and are eliminated from the cell. The most famous mucolipidosis is I-cell disease, and its clinical presentation is largely reminiscent of Hurler's syndrome, and pseudo-Hurler polydystrophy, characterized by later onset and mild course. Table 3 presents primary biochemical defects, mutant genes, and accumulation products in different types of mucolipidosis.

Hereditary disorders of glycosidases involved in oligosaccharide breakdown can cause the development of **oligosaccharidoses**. Generally, the structure of glycoproteins represents a protein core and oligosaccharide chains attached to it in the process of movement from ribosomes to the Golgi apparatus. In this case, two metabolic pathways can be used, namely, monosaccharide–nucleotide and lipid (dolichol)-mediated pathways. Both pathways ensure attachment of fucose-rich oligosaccharide chains to proteins through the formation of an N-glycosidic bond between N-acetylglucosamine and asparagine and an O-glycosidic bond between N-acetylgalactosamine and serine or threonine. The dolichol-mediated metabolic pathway is used to attach mannose-rich and complex oligosaccharide chains to proteins through the formation of an N-glycosidic bond between N-acetylglucosamine and asparagines.

The catabolism of oligosaccharide chains is implemented by exoglycosidases in lysosomes such that the degradation product of one of the enzymes serves as a substrate for the other. Impairment of these processes leads to oligosaccharidoses, or glycoproteinosis, which include mannosidoses, fucosidosis, and aspartylglucosaminuria. Table 4 presents primary biochemical defects, mutant genes, and accumulation products in different types of glycoproteinoses.

Neuronal ceroid lipofuscinosis represents a group of autosomal recessive neurodegenerative diseases characterized by progressive visual impairment, myoclonus epilepsy, neurodegeneration, and accumulation of autofluorescent lipopigment in neurons and other cells. The neurodegenerative process is accompanied by ataxia, progressive mental retardation, and psychomotor disorders. In classical forms, the disease onset is registered at age 4–7 years. Depending on the time of emergence of the first symptoms and clinical signs, three main disease types are identified, namely, infantile, classic late infantile, and juvenile. Several atypical disease forms with onset in late infancy have also been described, including the "Finnish" variant. The genetic heterogeneity of neuronal ceroid lipofuscinosis is much greater. Currently, genes have been identified in 14 genetic forms of the disease.

Other LSDs have also been described, which biochemical characteristics do not fit into the described disease groups. These are type C Niemann–Pick disease, Wolman disease, cholesterol ester storage disease, cystinosis, Sahl's disease, pycnodysostosis, among others.

Recently, HMD and, especially, LSD has received increased attention worldwide, not only due to the development of effective methods for their early molecular diagnostics, including prenatal, but also the possibility of treating these severe conditions, which until recently were considered completely incurable [8, 15, 16]. The main therapeutic approaches among proposed ones include enzyme replacement therapy [21, 28], therapy with a limited synthesis of substrates (substrate-reducing therapy), pharmacological chaperone therapy, and hematopoietic stem cell transplantation [19, 23, 26, 34, 35]. For some diseases, gene therapy methods have been successfully tested in experimental models.

Enzyme replacement therapy is considered a priority approach in the treatment of patients with LSD, while the necessary drugs, the number of which has been rapidly increasing in recent years, are produced using genetic engineering methods. Experimental studies and clinical trials conducted in some cases have revealed that under the influence of such drugs, patients experience an improvement in the functions of many organs and systems, which pathological changes are the main cause of severe disability and lethal outcomes. The most successful enzyme replacement therapy has proven itself in the treatment of patients with type I Gaucher disease [12] and some forms of MPS [2, 9, 13, 14].

Table 2 / Таблица 2

Molecular genetic description of the lipid storage disorders
Молекулярно-генетическая характеристика болезней накопления липидов

Syndrome / Синдром OMIM [37]	Protein, gene, localization / Белок, ген, локализация	Storage product / Продукт накопления
Glycosphingolipidoses / Гликосфинголипидозы		
Fabry disease, alpha-galactosidase A deficiency / Болезнь Фабри, недостаточность α-галактозидазы, тип А 300644	Alpha-galactosidase A / α-Галактозидаза А *GLA*; Xq22.1	Globotriaoslyceramide (Gb3) / Глоботриаозилцерамид
Gaucher disease, types I, II, III / Болезнь Гоше, типы I, II, III 230800	Beta-glucocerebrosidase / β-Глюкоцереброзидаза *GBA*; 1q21	Glucocerebrosid (GlcCer) / Глюкоцереброзид
Sphingomyelin lipidosis, Niemann–Pick disease types A/B / Липидоз сфингомиелиновый, болезнь Ниманна–Пика, тип А/В 257200	Sphingomyelinase / Сфингомиелиназа *SMPD1*; 11p15.4-p15.1	Sphingomyelin / Сфингомиелин
Farber lipogranulomatosis / Болезнь Фарбера, липогранулематоз 228000	Acid ceramidase / Кислая церамидаза *ASAH1*; 8p22	Cerebrosides / Цереброзиды
Gangliosidoses / Ганглиозидозы		
GM1-gangliosidosis, mucopolysaccharidoses IVB / Ганглиозидоз GM1, мукополисахаридоз типа IVB 230500	Beta-galactosidase-1 / Галактозидаза, бета-1 *GLB1*; 3p21.33	GM_1-ganglioside / GM_1-ганглиозид
GM2-gangliosidosis, type I, B, B1 and pseudo-AB variantes, Tay–Sachs disease / GM2-ганглиозидоз тип I, варианты В, В1 и псевдо-АВ, болезнь Тея–Сакса 272800	Hexosaminidase A, alpha / Гексозаминидаза А, альфа *HEXA*; 15q23-q24	GM_2-ganglioside / GM_2-ганглиозид
GM2-gangliosidosis, variant AB / GM2-ганглиозидоз, вариант АВ 272750	Hexosaminidase activator / Активатор гексозаминидазы *GM2A*; 5q31.3-q33.1	GM_2-ganglioside / GM_2-ганглиозид
GM2-gangliosidosis, type II, Sandhoff disease/ GM2-ганглиозидоз, тип II, болезнь Зандхоффа 268800	Hexosaminidase B, beta / Гексозаминидаза В, бета *HEXB*; 5q13	GM_2-ganglioside / GM_2-ганглиозид
Leukodystrophies / Лейкодистрофии		
Vetachromatic leukodystrophy / Лейкодистрофия метахроматическая 250100	Arylsulfatase A / Арилсульфатаза А *ARSA*; 22q13	Sulfatides / Сульфатиды
Globoid cell leukodystrophy, Krabbe disease / Лейкодистрофия глобоидно-клеточная, болезнь Краббе 245200	Galactosylceramidase / Галактозилцерамидаза *GALC*; 14q31	Galactocerebroside / Галактоцереброзид (GalCer)
Combined prosaposin deficiency – precursor of sphingolipid activator proteins (SAPs) / Комбинированная недостаточность просапазина — предшественника сфинголипид-активаторных белков (SAPs) 611721	Prosaposin, Saposin B, C, A / Просапозин, сапозин В, С, А *PRSP*; 10q22.1	Lipides, sulfatides, galucocerebroside, galactocerebroside / Липиды, сульфатиды, глюкоцереброзид, галактоцереброзид
Multiple sulfatase deficiency, or juvenile sulfatidosis, Austin disease / Множественная сульфатазная недостаточность, или сульфатидоз юношеский, болезнь Аустина 272200	Sulfatase-modifying factor-1 / Сульфатазомодифицирующий фактор-1 *SUMF1*; 3p26.1	Sulfatides, dermatan sulfate, heparan sulfate, cholesterol sulfate / Сульфатиды, дерматансульфат, гепарансульфат, холестерилсульфат

Table 3 / Таблица 3

Molecular genetic description of the mucolipidoses
Молекулярно-генетическая характеристика муколипидозов

Syndrome / Синдром OMIM [37]	Protein, gene, localization / Белок, ген, локализация	Storage product / Продукт накопления
Sialidosis, mucolipidosis I / Сиалидоз, муколипидоз I 256550	Neuraminidase / Нейраминидаза *NEU1*; 6p21.33	Salylated glycopeptides, oligosaccharides / Сиалосодержащие гликопротеиды, олигосахариды
Mucolipidosis II alpha/beta, or I-cell disease / Муколипидоз II альфа/бета, или «I-клеточная» болезнь 252500 / Mucolipidosis III alpha/beta, or pseudo-Hurler polydystrophy / Муколипидоз III, альфа/бета, или полидистрофия псевдо-Гурлера 252600	N-acetylglucosamine-1-phosphotransferase, alpha and beta / N-ацетилглюкозаминил-1-фосфотрансфераза, альфа и бета *GNPTAB*; 12q23.2	Sialyl-hexasaccharide / Сиаловые гексосахариды
Mucolipidosis III, gamma / Муколипидоз III, гамма 252605	N-acetylglucosamine-1-phosphotransferase, gamma / N-ацетил-глюкозаминил-1-фосфотрансфераза, гамма *GNPTG*; 16p13.3	Oligosaccharides / Олигосахариды
Mucolipidosis IV, or sialolipidosis / Муколипидоз IV, или сиалолипидоз 252650	Mucolipin I / Муколипин-1 *MCOLN1*; 19p13.2	Phospholipides, sphyngolipides mucopolysacharides, gangliosides / Фосфолипиды, сфинголипиды, мукополисахариды, ганглиозиды

Table 4 / Таблица 4

Molecular genetic description of the glycoproteinoses
Молекулярно-генетическая характеристика гликопротеинозов

Syndrome / Синдром OMIM [37]	Protein, gene, localization / Белок, ген, локализация	Storage product / Продукт накопления
Alpha-mannosidosis / Альфа-маннозидоз 248500	Alpha-D-mannosidase / Альфа-D-маннозидаза *MAN2B1*; 19p13.2	Alpha-mannose 6-phosphate-containing oligosaccharides / Альфа-маннозо-6-фосфат-содержащие олигосахариды
Beta-mannosidosis / Бета-маннозидоз 248510	Beta-D-mannosidase / Бета-D-маннозидаза *MAN2B1*; 4q24	Beta-mannose-6-phosphate-containing oligosaccharides / Бета-маннозо-6-фосфат-содержащие олигосахариды
Fucosidosis / Фукозидоз 230000	Alpha-L-mannosidase / Альфа-L-маннозидаза *FUCA*; 1p36.11	Fucopolysaccharides, fucosphyngolipides / Фукополисахариды, фукосфинголипиды
Aspartylglucosaminuria / Аспартилглюкозаминурия 208400	Aspartylglucosaminidase / Аспартилглюкозаминидаза *AGA*; 4q34.3	Asparagine, aspartylglucosamin / Аспарагин, аспартилглюкозамин

However, it is an expensive drug, which patients usually need to take for life.

The most complete data on the efficacy, limitations, and safety of enzyme replacement therapy have been obtained in types I, II, IVA, VI, and VII MPS [28]. These studies have now passed phase III of clinical trials, and the corresponding drugs have been registered in the USA and some European countries, including Russia [2, 9, 13, 14]. The results of these trials, conducted in different centers, are often contradictory and depend on the disease severity, involvement of various organs and systems in the pathological process, patient's age at the start of treatment, and production of antidrug antibodies. Antidrug antibodies develop in all patients, but their role in resistance to enzyme replacement therapy is less investigated. In general, the therapy is effective in reducing the level of GAGs in the

urine and reducing the liver and spleen volumes. However, such a treatment has a relatively small effect on cardiological, skeletal, and bronchopulmonary manifestations of diseases as well as hearing and vision of patients, which is apparently due to the limited penetration of drugs into specific tissues. When administered intravenously, the drugs do not pass through the blood–brain barrier and are therefore not able to influence the pathological processes occurring in the CNS. To overcome these difficulties, methods are being developed for the administration of medicinal preparations into the cerebrospinal fluid and CNS, using viral vectors as carriers of genetically engineered enzyme preparations [8].

Substrate-reducing therapy is based on restricting the synthesis of metabolites that serve as a source of toxic compounds by selective suppression of the corresponding enzymes. This approach was proven successful in the treatment of patients with type C Niemann–Pick disease. Pharmacological chaperone therapy is based on the ability of certain chemical compounds to have a stabilizing effect on the residual activity of enzymes, the deficiency of which leads to HMD development. The work in this direction is still experimental in nature.

Umbilical cord blood transfusion from unrelated donors and hematopoietic stem cell transplantation for the treatment of patients with HMDs can be used only if they are diagnosed early, i.e., before the development of gross morphological changes in the brain and other organs and systems [30]. In this regard, the issues of including LSD in neonatal screening programs, which are already being introduced into the clinical practice in several countries, are essential [20, 25, 29, 36]. In this case, the most commonly used method is liquid chromatography and tandem mass spectrometry on dried blood stains of newborns. The results of biochemical screening require further confirmation by molecular genetic methods. This approach has already proved its effectiveness in the early diagnostics of types II, IIIB, IVA, VI, and VII MPS [22, 26, 31]. A similar strategy can be used to develop neonatal screening programs for Gaucher disease, Fabry disease, Pompe disease, Krabbe disease, type B Niemann–Pick disease, metachromatic leucodystrophy, and other lysosomal diseases [27, 32].

Thus, in recent years, significant progress has been made in the field of biochemical and molecular diagnostics of HMDs, including LSDs, as a basis for their prevention and prenatal diagnostics. Moreover, treatment algorithms for these severe diseases have been outlined, and the first successful clinical trials have been conducted. Although this work is still at the very beginning, its prospects inspire some optimism.

In further reviews, we will consider in more detail individual diseases included in various groups of LSDs.

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